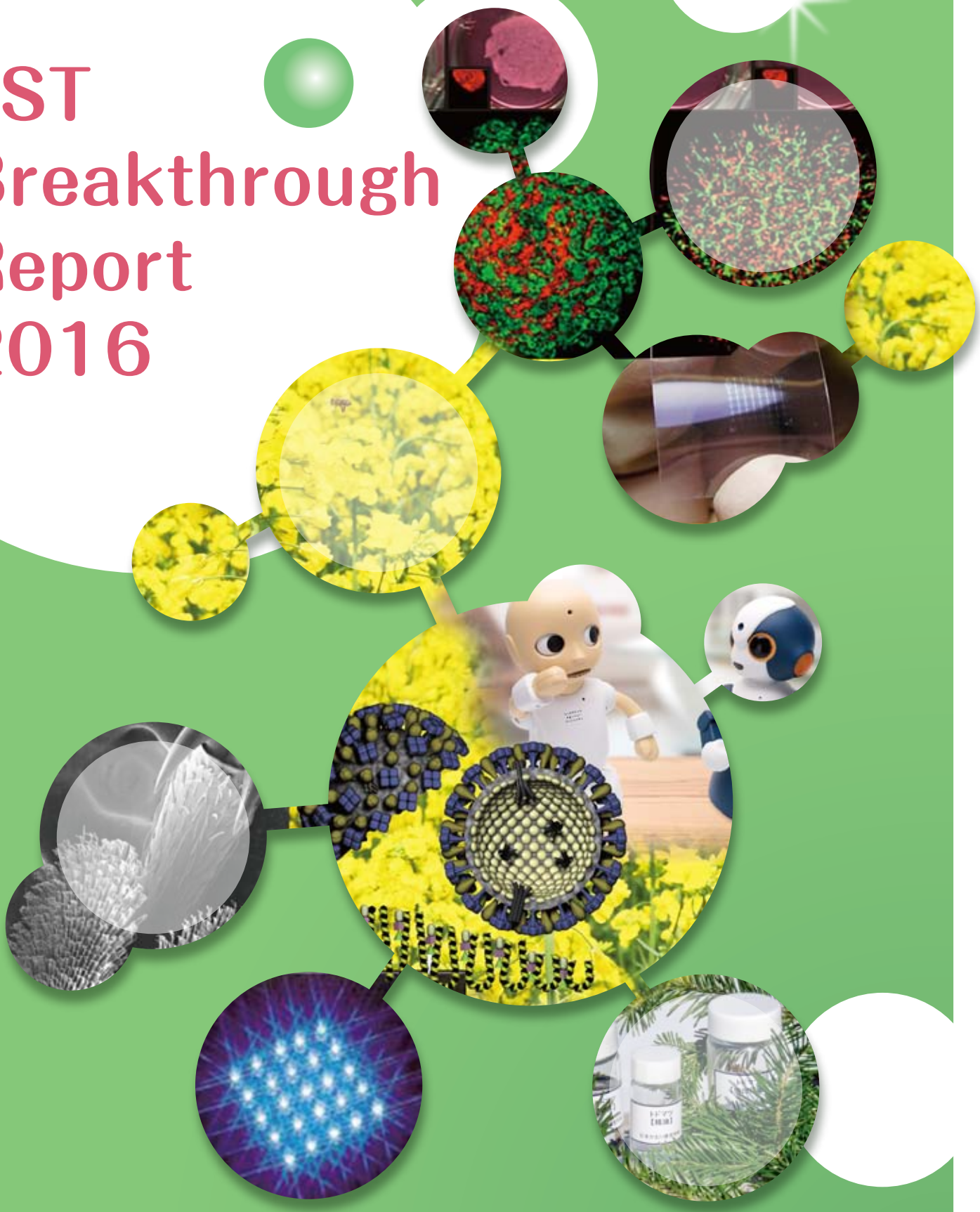
JST Breakthrough Report 2016



Japan Science and Technology Agency

CONTENTS

Green Innovation

Life Innovation

Nanotechnology and Materials

Information and Communications Technology

Science and Technology for Society and Social Infrastructure

Reconstruction from the Great East Japan Earthquake

Others

To solve energy problems

The biggest mystery of photosynthesis has been solved

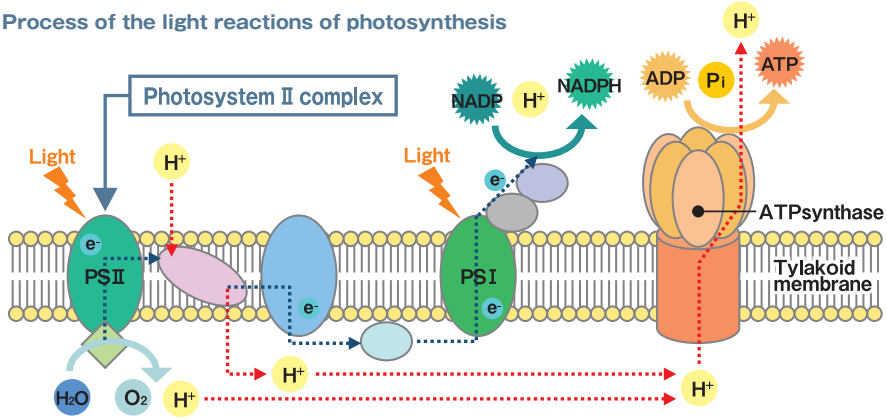
Jian-Ren Shen
(Professor, Graduate School of Natural Science and Technology, Okayama University)
PRESTO
Structure and Function of Biomolecules
"Molecular mechanisms of bioluminescent energy conversion: Crystal structure analysis of photosystem Ⅱ membrane protein complex" Researcher (2002-2005)

The great challenges too many mysteries of photosynthesis

Photosynthesis is a reaction that breaks down water, produces oxygen, and fixes carbon dioxide in organic compounds, using the energy of light. It is an essential function supporting biological activity on earth. Its fundamental composition was already understood by the late 18th century, but a great deal of research into photosynthesis was still conducted after this time, and by untangling these chemical reactions at the molecular level, we have now come to understand that extremely complex protein groups are responsible. At present, even elementary school students learn about "photosynthesis" in science class. However, **the composition of the protein groups responsible for the most important part of the chemical reaction of photosynthesis—the generation of oxygen— long remained an inexplicable mystery**.

Professor Jian-Ren Shen worked tirelessly for 20 years to unravel this mystery. **In 2011, he finally succeeded in discovering the structure of the photosystem Ⅱ membrane protein group (PS Ⅱ)**, the most significant component of photosynthesis. **The U.S. scientific journal "Science" selected this result as one of the greatest breakthrough of the year 2011, along with the Hayabusa asteroid probe**. This achievement represents a huge step toward the development of technology enabling the artificial control of photosynthesis, and it may even change the entire direction of research and development aimed at energy problem-solving in future.

Process of the light reactions of photosynthesis

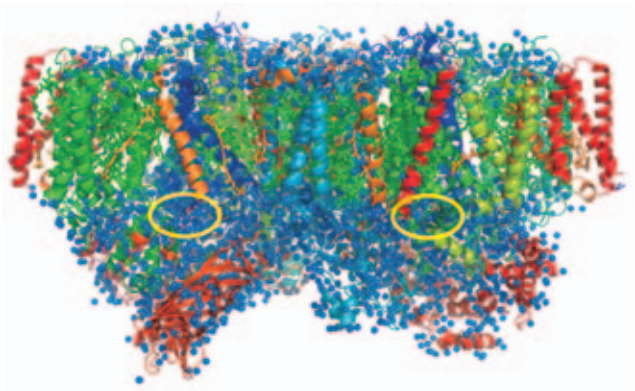


Photosynthesis consists of two phases, that is light reactions and dark reactions. In the first step of light reactions, PS Ⅱ makes catalytic, water is split to produce, oxygen is using a solar energy, synthesis reaction makes oxygen and life action energy.

A long fascination with PS II crystallization & the encounter with "PRESTO" (Sakigake)

In plants, the protein complex responsible for the initial photosynthetic reaction is known as PS Ⅱ, which breaks down water and generates oxygen using energy from light. To unlock the secret of how PS Ⅱ catalyzes* this reaction, it is first necessary to understand the structural subtleties of PS Ⅱ. However, to investigate its structure, it is necessary to extract the PS Ⅱ from the cell without destroying it, which requires an advanced technique for creating high quality crystals. This proved extremely difficult. Professor Shen, whose academic background was in agricultural science, had almost none of the chemistry knowledge or techniques required to achieve this crystallization process; however, he fell under the spell of the 200 year mystery, and over a 20- year period, devoted himself doggedly to research on crystallization. This was undeniably an ongoing period of extraordinary difficulty. In fact, confronting the impending dissolution of the laboratory to which he belonged, Professor Shen

even considered abandoning his crystallization research. Facing this dilemma, **in 2002 Professor Shen's work was adopted by the PRESTO, which subsequently led to robust support, both financial and mental**. Under the PRESTO (Sakigake) program, researchers are selected by a research supervisor, and they receive a great deal of encouragement for the duration of their research. Even when results were not immediately forthcoming during his research, Professor Shen received outstanding evaluations from the research supervisor, which he found very encouraging. Behind his eventual success lay the fundamental philosophy of PRESTO (Sakigake) : to support creative and forward-thinking individual-style research.



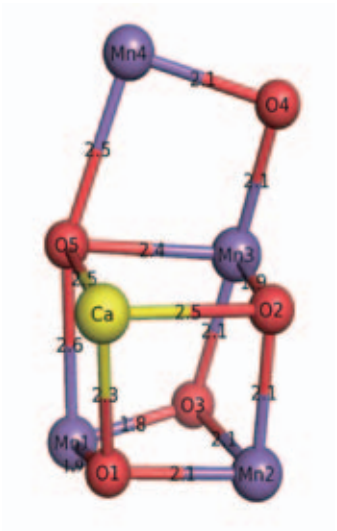
Overall structural diagram of PS Ⅱ
PSII consists of 19 proteins and there is a symmetrical axis at the center of PS Ⅱ. The yellow circles indicate the catalytic centers. It was considered to be composed by 4 manganese atoms; however structure of the PS Ⅱ was not clarified.

A world-level competitive struggle: 1.9Å resolution achieved!

There was tremendously fierce competition with German and English research institutions in the field of crystallization research. The leading edge of this research swung back and forth internationally. The PS Ⅱ structure was successfully resolved to a level of 3.8Å (Ångstroms. 1Å is 0.1 nanometer. The smaller the value, the more precise the analysis) by the German team in 2001, after which it was resolved by Professor Shen (during he participated in a project) to 3.7Å in 2003, then to 3.5Å by the U.K. in 2004, to 3.0Å by Germany in 2005, and to 2.9Å by Germany again in 2009. In the midst of this seemingly impossible situation, Professor Shen's hard work and dedication finally paid off in 2011, when **he rewrote the record books by resolving the structure to the 1.9Å level: a remarkable result indeed**.

This 1.9Å value is extremely significant. In truth, the structural layout at the atomic level was actually unknowable at all previous resolutions. However, **at the 1.9Å level, it became possible to investigate the type of every single atom, as well as the distance between each atom**. As a result of this analysis, it was discovered that the center of the PS Ⅱ enzyme evolution reaction formed an unstable structure resembling a deformed chair comprising four manganese atoms, one calcium atom, and five oxygen atoms. This moment of enlightenment was the breakthrough in 200 years of mystery in the field of photosynthesis research.

The oxygen-evolving catalytic center of "distorted chair structure"



Structure of the oxygen-evolving catalytic center of PS Ⅱ was revealed by Professor Shen. It was found that the catalytic center of PS Ⅱ consists of four manganese, one calcium, and five oxygen atoms have shape similar to a distorted chair.

Solving the world's energy problems: working toward artificial photosynthesis

The very instability of the structure at the center of the PS Ⅱ reaction is expected to be the long-pursued key to its oxygen generation mechanism. Professor Shen is proceeding further with his research in order to verify this hypothesis. If techniques for artificial photosynthesis can be established in future, then **instead of carbon dioxide-generating substances of petroleum and coal, we may be able to achieve clean energy in the truest sense of the words**.

Photosynthesis is the foundation and source of all life and activity, and countless organisms owe their existence to it. However, one day it may support our daily lives even further as the foundation stone of energy in the future.

* Substance that increases the speed of a chemical reaction but does not change itself or its action. It has specificity to create only the desired products.

Open a path to development of new energy conversion technology

Generating spin current by irradiating light on insulator

Ken-ichi Uchida

(Institute for Materials Research, Tohoku University, Associate Professor)

PRESTO Phase Interfaces for Highly Efficient Energy Utilization "Creation of Innovative Energy Device Technology Based on Spin Currents" Researcher (2012-2018)

Eiji Saitoh

(WPI Advanced Institute for Materials Research/Institute for Materials Research, Tohoku University, Professor)

PRESTO Materials and Processes for Innovative Next-generation Devices "Spintronics Based on Spin Currents and Spin-photon Coupling in Dielectrics" Researcher (2007-2011)

CREST Creation of Nanosystems with Novel Functions through Process Integration "Generation of Nanointegration of Heat, Electricity and Motion by Spin Current" Representative Researcher (2010-2015)

SICP Combination region combining the material field and other field "Development of Thin-film Thermoelectric Devices by Utilizing Magnetic Nanostructures for Ubiquitous Thermoelectrics" Researcher (2011-2014)

ERATO "SAITOH Spin Quantum Rectification Project" Research Director (2014-2020)

Birth of completely new energy conversion principle

We now see world-wide approaches for a solution to environmental and energy issues aiming at a sustainable society. Among them, one of the most feasible trials is the one to utilize quite familiar items, such as light, heat, vibration and electromagnetic wave as an energy source. Power generation utilizing solar cells and thermoelectric devices is focused as energy conversion technology, which also is clean and highly reliable, so that it is a quite popular research subject.

Associate Professor Ken-ichi Uchida has succeeded in the conversion of optical energy into a spin current (magnetic flow) for the first time in the world by irradiating visible light to an insulator magnet *1 in which specific metal particles are embedded in the research of PRESTO; Phase Interfaces for Highly Efficient Energy Utilization. His former supervisor, Professor Eiji Saitoh, was honored by awards in the fundamental discovery of spin currents, who is actually regarded as the PRESTO of the field. Associate Professor Uchida, who was the member of the Saitoh laboratory at Keio University, discovered the spin Seebeck effect (phenomenon to cause spin currents from the temperature difference in a magnetic substance) for the first time in the world under Professor Saitoh. This discovery was published as his faculty graduation thesis in Nature in 2008.

Light/spin-current conversion realized by strong electromagnetic field

The conceptual diagram (Figure 1 <a>) shows the concept of PRESTO research of Associate Professor Uchida. A powerful electromagnetic field is formed adjacent to metal particles (Figure 1 <b>) embedded in an insulator magnet using the collective motion of electrons, which is called the surface plasmon*2 generated by the stimulus from light with a specific wavelength (Figure 1 <c>). This electromagnetic field has effectively driven the motion of spin to realize the light/spin-current conversion by an insulator magnet.

Here, he uses a device that is formed by jointing a thin film of platinum (Pt) on the surface of an insulating thin film called the magnetic garnet ($BiY_2Fe_5O_{12}$). The magnetic garnet layer of this device has gold (Au) particles with the size of a nanometer (nm, 1 nm is a one billionth of 1 m) embedded in it (Figure 1 <b>).

Irradiating light on it forms a powerful electromagnetic field adjacent to the particles only when the wavelength of the incident light meets the surface plasmon resonance condition. This means that the gold particles function as an antenna for the light (Figure 2<a>), and as a result, the motion of spins has obtained an external energy due to the powerful electromagnetic field, and the spin current is generated in the top layer of the platinum thin film (Figure 2<b>),

The conventional research regarding a light-spin conversion has always used a semiconductor. This research is based on the completely different physical principle, which for the first time has enabled the light/spin-current conversion with an insulator magnet.

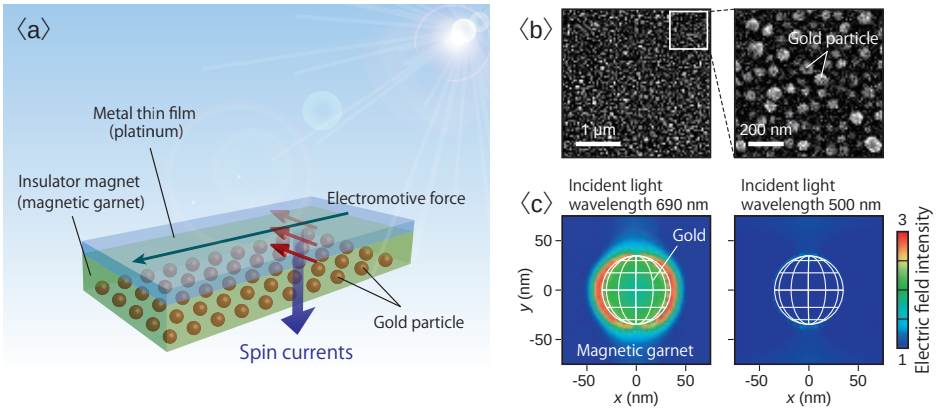


Figure 1 Light-spin conversion using surface plasmon

⟨a⟩ Conceptual diagram of research - Schematic diagram of the device used in this experiment

⟨b⟩ Gold particle captured by scanning electron microscope

⟨c⟩ Result of a simulation of electromagnetic field distribution adjacent to gold particles
On the left; a powerful electromagnetic field is formed; on the right, no reinforcing effect of the electromagnetic field.

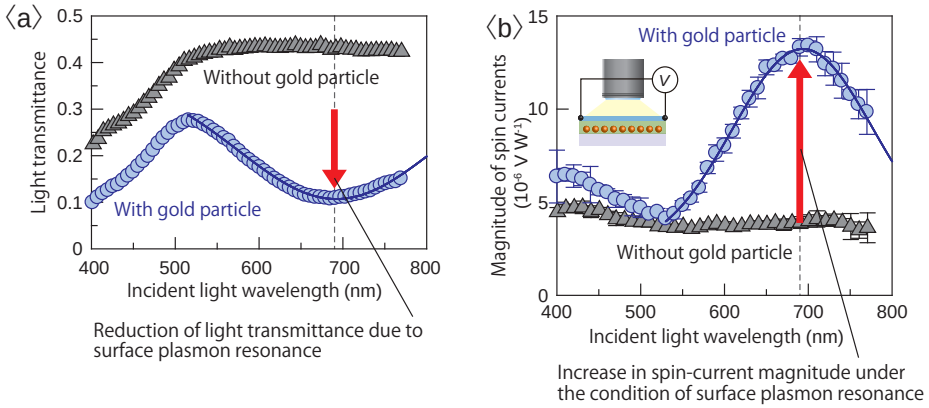


Figure 2 Wavelength dependency of the light transmittance and the spin-current magnitude for the device used in this experiment

Innovative characteristics such as a degree of freedom of device design and being enabled to utilize an insulator

The technology level of this energy conversion using spin currents has not reached the level of the existing energy conversion yet. However, it still has great characteristics compared to others, which includes a high degree of freedom for device design thanks to the simple thin film structure, being able to utilize an insulator that has been a mere substrate or container of devices, and being able to utilize various energy sources simultaneously. We see more and more increase in interest to the thermoelectric conversion technology with the new principle utilizing the spin Seebeck effect.

Expectation to contribution for formation and development of new fusion research field

The importance of this outcome is to indicate the possibility of converting various energy sources, such as light, heat, sound waves, and electromagnetic waves, into spin and electric currents, while we still have a subject to further increase efficiency.

The current critical subject is to secure a power source that is available full time in regards to the research development of the power source capable of a long-term energy provision without any need for recharging, exchanging, or refueling. The spin current capable of simultaneous utilization of various energy sources with a single device is a hope to pioneer in the future. This conversion principle that Associate Professor Uchida has discovered shall contribute greatly to the birth of a new research field fusing the surface plasmon and spin currents, and the research development of electric and magnetic devices without the need for any external power source.

*1 Collective term for substances that are not conductive. Professor Saitoh and his colleagues verified in 2010 that spins can flow in an insulator with the property of a magnet, such as a magnetic garnet.

*2 Free electrons' collective oscillation on the surface of a metal, excited by an optical electric field. A resonance phenomenon between an electric field excited by the oscillation of free electrons and an optical electric field is called surface plasmon resonance.

High performance and economic efficiency

Hydrogen is activated at room temperature and under atmospheric pressure

Seiji Ogo
(Professor, International Institute for Carbon-Neutral Energy Research /Faculty of Engineering, Kyushu University)

CREST
Development of the Foundation for Nano-Interface Technology
"Energy Conversion via the interface with Hydrogen Activation Aqua Catalysis" Representative Researcher (2008-2013)

Consistently investigating 'hydrogen' as an energy career

Recently, public and private sectors have paid attention to and discussed 'hydrogen' as a representative for an energy career (energy-storage media) for the next generation. The world has now begun to recognize, with the background, in mind that fossil fuels are depleting and the catastrophic accident took place in Fukushima. A safe, clean, and sustainable energy supply is one of the significant challenges in the 21st century.

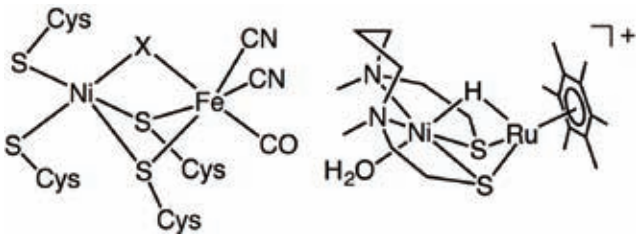
In light of this situation, the research group of Seiji Ogo has established the policy, and consistently focused on hydrogen, ascertaining the mechanism of hydrogen activation by an enzyme, and extracted electrons from hydrogen to develop energy utilization technologies. In 2007, the research group had already announced the first 'model compound' that operated similar to the 'hydrogen activating enzyme.' Later, they were selected as one of the representative researchers by CREST in 2008. They continued to work and finally succeeded in accomplishing the complete modeling of the hydrogen activating enzyme in February 2013.

Success of developing an artificial catalyst that does not use noble metals
(The Nikkan Kogyo Shimbun (News paper), February 8, 2013)

Launch for developing the artificial catalyst by modeling natural catalysts

The research by Professor Ogo et al. started with focusing on a protein that naturally acts as a catalyst*, in other words, a natural 'enzyme.' This hydrogen activating enzyme is called 'nickel-iron hydrogenase.' The enzyme catalyzes 'proton (H+) reduction' and 'hydrogen oxidation,' under mild conditions (in room temperature and under atmospheric pressure). When this enzyme functions, hydrogen molecules are burned and utilized as energy. It was also known that the hydrogen molecules are utilized freely as hydride ion (H-: hydrogen with minus charge) or electrons.

With that in mind, the research group paid attention to this function in terms of its application to the research and development in hydrogen energy, and was successful in synthesizing an artificial catalyst using the function mentioned above in 2007: it was 'nickel and ruthenium catalysts' which **used the noble metal of ruthenium (Ru) as a catalyst instead of iron (Fe)**. This was the best functional model in terms of safety and quality performance among many artificial catalysts developed at that time. The following year, the research group was also successful in deriving hydrogen in room temperature and under atmospheric pressure using this catalyst.



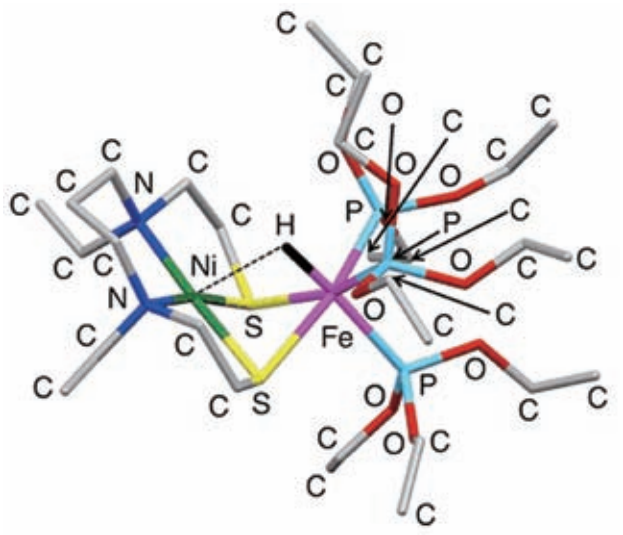
(Left) The structure of active center of Hydrogen Activating Enzyme "nickel-iron hydrogenase"
(Right) It was modeled structure of artificial Catalyst which synthesized "nickel and ruthenium catalysis"

The astonishing value of 'noble metal-free catalyst'

In February 2013, the research group of professor Ogo et.al. **developed an artificial catalyst 'nickel-iron catalyst' by modeling the 'nickel-iron hydrogenase,' which functioned similar to the hydrogenase**. Being different from the model that used the noble metal of ruthenium in 2007, the research group was successful in transferring electrons from hydrogen to electron acceptors (ferrocenium ion, methylviologen, etc.) by using a catalyst with iron in room temperature and under atmospheric pressure. After ascertaining the crystal architecture, the group also confirmed that the hydride ion (H-) that is generated after activating hydrogen bonds to iron, not to nickel. Previously, there was no one who was able to tell which one the hydride ion bonded to.

As a successful result the hydrogen activating using **the catalyst with iron instead of previous model of ruthenium, this produced another benefit that was realized other than for just academic purposes. This is the cost. As of in February 2013, the market price of the noble metal of ruthenium used in the previous model was 240 yen/g, whereas that of iron was one-four thousandth of the price of ruthenium, 0.06 yen/g**. It cannot be overstated that the ratio of metal price has a direct bearing on the complex catalyst price. This 'economic' value is significant since a large amount of catalysts is required for the use of fuel batteries, etc. In this sense it is a revolutionary development.

The crystal structure of 'nickel-iron catalyst'



To what extent are the 'three themes' achieved?

The artificial modeling of the hydrogen activating enzyme, which started in 2007, has almost completely been accomplished through the success of this development of 'nickel-iron catalyst.' **Subsequently, it can be said that the research of hydrogen activating with the 'noble-metal-free catalyst,' as well as the breakthrough of the mechanism for hydrogen activating of natural enzyme, 'nickeliron hydrogenase', has made great progress**.

As mentioned above, professor Ogo always emphasizes that following three themes have to be accomplished in order to solve energy problems in the 21st century: **1: Breakthrough function principle of life, 2: Developing the technique to abstract and apply the life function, 3: Overwhelming the life function**. The first one, has been accomplished to some degree, since the breakthrough of the mechanism for hydrogen activating of 'nickel-iron hydrogenase' has continued. As for the second has been realized by the success of deriving electrons from hydrogen with the 'noble metal-free catalyst.' No.3 has to be worked on continually. In this regard, we may develop 'platinum-free fuel battery' with 'nickel-iron catalyst.' It is necessary to use 'platinum' for electrode catalysts in fuel batteries. However platinum is expensive, what is more, it is limited in supply. Alternative catalysts are awaited, such as 'nickel' or 'iron' that are rich in the amount of the deposit and the price is cheap.

* Substance that increases the speed of a chemical reaction but does not change itself or its action. It has specificity to create only the desired products.

Definitive solar energy!

Everything made solar cells just be applying !

Eiichi Nakamura (Professor, The University of Tokyo)

ERATO

"Nakamura Functional Carbon Cluster Project" Research General Overview (2004-2009)

S-Innovation

Developing new electronics technologies based on organic materials

"Creating long-life organic solar cell coatings and developing basic technologies aimed at practical applications" Project manager (2009-)

Technology like magic: all kinds of things functioning as solar cells

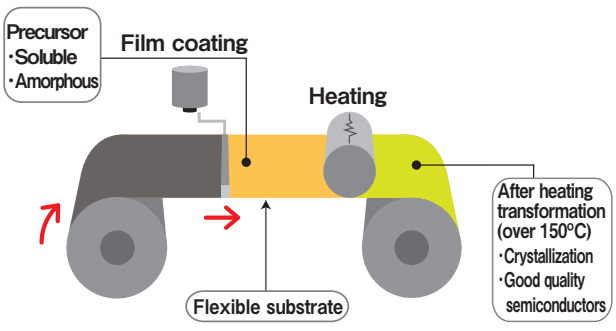
Quite some time has passed since the widespread call for conservation of electricity in the wake of the Great East Japan Earthquake, but during this time, the level of interest in natural energy has increased markedly. Natural energy includes non-exhaustible forms of energy such as solar power, hydropower, geothermal power, and wind power; of these, solar power is certainly the form of natural energy that most closely surrounds us. It's reasonable to suggest that solar power is the only form of natural energy that regular individuals are able to get their hands on. However, despite lowered costs, introducing this technology to residential houses remains difficult at the moment without national or municipal assistance.

Research on technology that may overturn our basic notions of solar power generation is currently being conducted by Professor Eiichi Nakamura, who also opened up fundamental research into fullerene compounds. Through an industry/academic liaison project with Mitsubishi Chemical Corporation, Professor Nakamura's work is moving one step closer to practical implementation. The technology known as 'organic thin-film solar cells,' **once mass production commences, will be able to provide significantly more control over production costs compared to current cheap silicon solar cells**. This alone would be an outstanding achievement, but its most remarkable attribute is the fact that with **a simple thin film coating, the material itself can generate electricity from sunlight**. This means that what was previously a dream has become possible; for example, roofing tiles coated with this process would remain unchanged in appearance, but would provide the household's entire energy needs. **In the near future, all sorts of unexpected objects— not only engineered products such as automobile bodies, but also things like curtains, walls, and so on— might be used to generate electricity**.

Manufacturing enabled with printing technology

Organic thin film solar cells are manufactured from a combination of two types of organic semiconductor: an electron donor material which donates electrons and an electron acceptor material which accepts electrons. **If the coating technology continues to improve, these two organic semiconductors will be able to be manufactured in a process just like printing. Since soft materials can also be coated, they can be bent and curved, and colors can be added**. If this technology can be properly implemented, it has the potential to change the world dramatically through green energy.

Diagram of continuous coating film application process

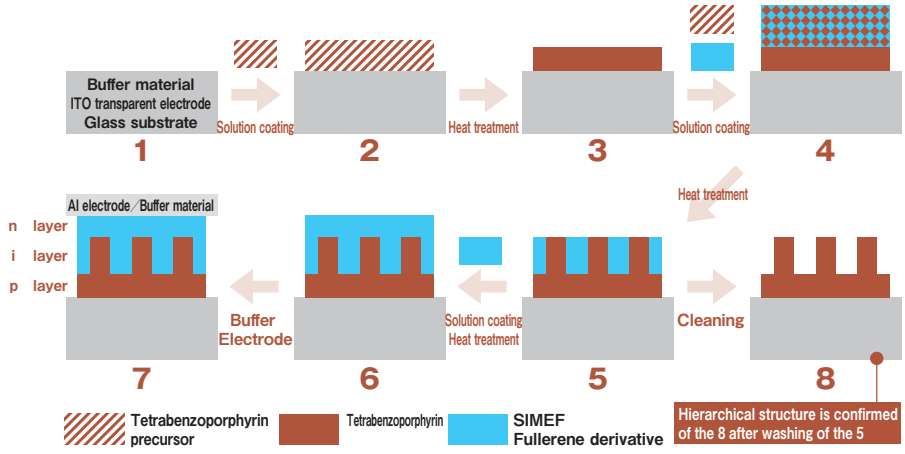


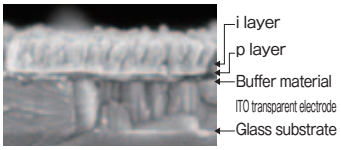
Successfully breaking all kinds of boundaries

The development of organic thin film solar cells was a laborious search for the ideal combination of electron donor material and electron acceptor material. After a great deal of repetitive trial-and- error experimentation, a new concept for combining these two elements was discovered. This was a combination of tetrabenzoporphyrin and the independently developed fullerene compound SIMEF. Tetrabenzoporphyrin was not originally developed for solar cell research, but rather for completely different applications. Combining tetrabenzoporphyrin with SIMEF gave clear indications of an ideal structural configuration known as the 'column/ canyon' structure. With that, Japan' s own unique printable low-molecular organic thin film solar cells were born. This combination increased conversion efficiency from just over 2% to 5.4%: a dramatic developmental leap.

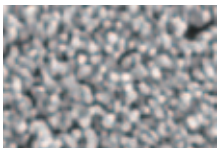
Collaborative research by materials physicists and chemists has almost never been undertaken in the field of solar cell research, until now. **The ERATO project enables research to take place beyond** organizational boundaries; the invention of organic thin film solar cells was born of precisely such a process of concept sharing between materials physicists and chemists. This research has also been **designated S-Innovation and has been gathering increased attention as a model case of collaborative development between industry and academia**. This outcome has been truly been achieved by breaking all kinds of boundaries.

Solution-processable three-layered p-i-n organic photovoltaic devices deposition process





Column/canyon structure viewed from side


Column/canyon structure viewed from above

Collaboration with Mitsubishi Chemical Corporation aims at practical applications

Organic thin film solar cells are indeed an amazing discovery, but there are still problems to be solved before these can see practical implementation. The first is energy conversion efficiency. Compared to conventional silicon solar cells, the conversion efficiency of organic thin film solar cells is quite low. In 2009, Professor Nakamura increased this to 5.4%— the world' s highest level at the time— but this figure was still rather low in comparison with the conversion efficiency of silicon solar cells. However, since they can be produced extremely efficiently compared to silicon solar cells —the "roll to roll" coating process enables continuous production— together with their module efficiency of about 7%, equivalent for amorphous silicon solar battery (10% cell efficiency), they were believed to have significant potential for market penetration. Subsequently, **in September 2012, Professor Nakamura' s development partner Mitsubishi Chemical Corporation announced that it had lifted the conversion efficiency of organic thin film solar cells to 11.7%**. With this announcement, the problem of conversion efficiency will move steadily towards resolution, making this a major step forward for practical implementation.

Durability is a further problem. Until now, organic thin film solar cells have been easy to manufacture but have had concomitant problems with durability. However, as **at 2011, they have been proven to possess more than 5 years of durability using plastic substrate and 10 years using glass. The technology has overcome** a significant barrier, and the future world of our dreams beckons. The industry/academic collaborative projects that JST promotes are demonstrating some outstanding outcomes.

Developing combined analysis system equipment for airborne minute substances

Contributing investigation of the actual conditions of PM 2.5

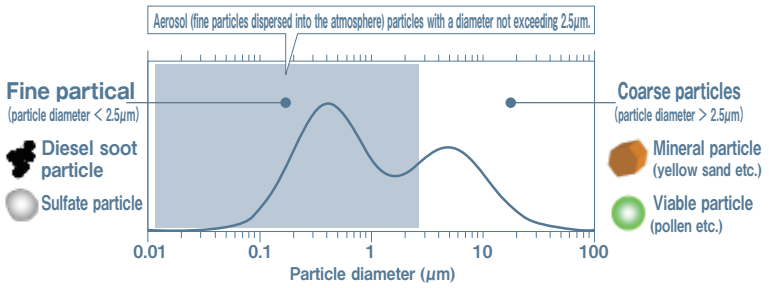
Nobuyuki Takegawa
(Professor at the Department of Chemistry, Graduate School of Science and Engineering, Tokyo Metropolitan University)
Development of Advanced Measurement and Analysis Systems
"System development: Development of an Online Aerosol Particle Combined Analysis System" team leader (2008-2012)

Particles, bringing about grave effects on health and climate, due to their small size, without allowing themselves to be observed.

M2.5 has been drawing attention as a causative agent of air pollution. PM2.5 is the general term for microscopic particulate matter (aerosol particles) with a diameter not exceeding 2.5 micrometers. It is considered that aerosol particles, due to their small size, are likely to become deposited in bronchi and lungs, thus constituting a major factor in respiratory disease. In addition, there is concern over their impact on weather change resulting from their causing sunlight to scatter and becoming nuclei for the generation of cloud as well as their serving as carriers of radioactive material. **Since PM2.5 is composed of a wide variety of chemical substances, the reality is that an analytical method to elucidate the actual conditions of PM2.5 has yet to be established.**

An aerosol combined analysis system to efficiently collect and analyze such complex PM 2.5 particles was developed. It was Professor Nobuyuki Takegawa (an assistant professor at the Research Center for Advanced Science and Technology of the University of Tokyo at the time development) who served as the team leader.

Typical particle size distribution of aerosol (mass concentration)



Not only their small size but also "variability" stands in the way of research progress

When Professor Takegawa started the research on aerosol, he was troubled with the "instability" of aerosol as well as its small size. Gas components contained in exhaust from factories or vehicles change into particles of nitrate, sulfate or organic substances due to chemical reactions. Such secondary particles constitute a large portion of aerosol. The way chemical reaction happens changes constantly depending on weather conditions and other factors.

Therefore, **to understand the actual conditions of aerosol, it is necessary to measure its chemical composition in real time**. However, since the concentration of aerosol particles in the atmosphere is very small, it is necessary to employ a special collecting and analyzing method. Professor Takegawa tried using the U.S.-made real-time analysis equipment, but there was a big problem in the efficiency of collecting particles.

With that, Professor Takegawa determined to construct observational equipment of his own. After forming a team with Fuji Electric Co., Ltd., which established an organized coordination with the Research Center for Advanced Science and Technology, and the Japan Agency for Marine-Earth Science and Technology (JAMSTEC), the research was adopted as part of the Development of Advanced Measurement and Analysis Systems. And finally, full-scale development of the observational equipment started.

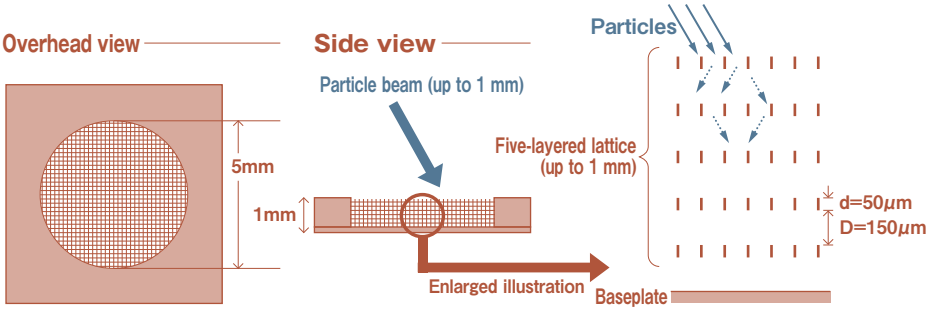
Real-time analysis made possible by a “particle trap” with a three-dimensional lattice structure

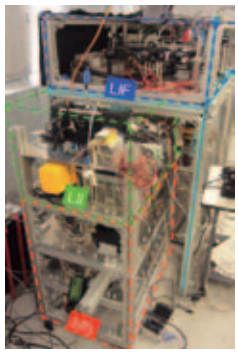
How could small aerosol particles be caught in their entirety in a short period of time? Professor Takegawa and his fellow researchers went through a long process of trial and error in order to find a solution to that biggest challenge, and finally arrived at a “particle trap.”

To analyze particles using the conventional method, they have to be vaporized by bouncing them off a heated plate. However, many of the particles don’ t rebound in a vaporized state. They came up with an idea of using a “lattice” as a trap for catching particles in their entirety. **Lattices are placed diagonally to a particle beam like blocking out sunshine with a window blind. Only one lattice is not enough, five are needed**. A microscopic and regularly structured three-dimensional lattice actualized by the processing technology of Fuji Electric succeeded in capturing particles with an efficiency of nearly 100%. Thus, **it became possible to collect aerosol wholly in a short time**.

Finally, an aerosol combined analysis system was completed. This analyzer is equipped with an instrument for “laser-induced fluorescence detection (LIF),” in which biological particles and soil particles are detected as well as an instrument for “laser-induced incandescence detection (LII),” in which particles derived from diesel engine exhaust are detected, in addition to an instrument for “mass spectrometry (MS),” in which chemical composition of sulfate, nitrate, etc. are quantitatively analyzed. Thus, **by combining various element technologies effectively, a new analysis method was established, with which a new analysis, which previously could not be performed only by a single method, became possible**.

Particle trap in the mass spectrometer





Test model

New multiple analysis techniques that should be shared among countries

The completed combined aerosol analysis system was immediately used for trial observations, thus the real-time monitoring of change in the concentration of PM2.5 constituents was brought to realization. Through the monitoring, the importance of measuring the components of fine particle was reconfirmed. For example, an extreme increase in PM2.5 concentration can cause reduced visibility; however, such a phenomenon is not always caused by harmful substances. Reduced visibility can be potentially caused by natural phenomenon such as dust. In the past, it was impossible to identify particles in real time, which now can be performed by using an analysis method in which multiple analysis methods are combined. It is expected that accumulating observational data and thereby advancing the research will lead to the establishment of reliable environmental standards, resulting in ensuring the safety and security of the people.

To that end, **much more extensive observation has to be conducted over a larger region**. Aerosol easily spreads beyond national boundaries. To understand its behavior precisely, it is necessary to conduct observations not only in Japan, but also in many other parts of the world. The combined aerosol analysis system is commercialized by Fuji Electric in 2015 after the verification test in Kawasaki-shi and other places. In future, it is expected that observational data will be accumulated. Aerosol is considered to be associated with global climate change as well as with air pollution. It is urgent to establish an international strategy with an eye on both widespread air pollution and climate change.

Commercialized Aerosol Particle Combined Analysis System

The Sahara Desert as a power plant for the Earth

High-temperature superconducting cable to cut transmission loss to zero

Sumitomo Electric Industries, Ltd.／late **Kazuo Fueki** (Emeritus professor, The University of Tokyo)／late **Koichi Kitazawa** (Emeritus professor, The University of Tokyo)／late **Hiroshi Maeda** (Emeritus fellow, National Institute for Material Science)

Development of Creative Technology Seeds, Contract development Manufacturing technology of oxide superconducting material "Bi-based superconducting wire" Developing and implementing Company/Representative Researcher (1991-1996)

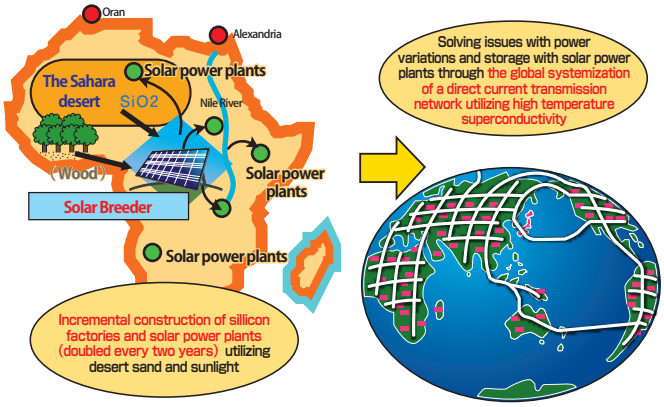
Late **Koichi Kitazawa** (Emeritus professor, The University of Tokyo)

CREST Phenomena of Extreme Conditions "High-resolution of phase and amplitude of electron waves" Chief Researcher (1995-2000)

SORST "Development and application of high-resolution microscopes for the imaging of phase and amplitude of electron waves" Chief Researcher (2000-2003)

High-temperature superconducting cable enables the transmission of electricity on a global scale

The Sahara Solar Breeder Project



Electrical resistance is a term expressing the difficulty of electricity flow. Generally speaking, all substances possess electrical resistance, and the resistance value increases in proportion to length. This means that whenever electrical power generated by a power plant is delivered to homes or businesses, there are various losses along the way. This transmission loss is understood to be around 5% in modern-day Japan. 5% may seem like a small amount, but over the **course of a year this amounts to around 45.807 billion kWh: equivalent to a 100 kWh power plant running at maximum operation for more than 5 years**. Cutting this transmission loss to zero would be a major step toward solving many of the world's energy problems.

One answer to this problem is superconducting cable using high-temperature superconductors. Superconductors are specific substances that possess zero electrical resistance when cooled to ultra-low temperatures; if this principle is properly utilized, then electrical cables with very low transmission loss can be constructed.

If we are able to utilize this technology, it might well bring about an electrical revolution on a global scale. The Sahara Solar Breeder Project is a **dream project involving construction of a massive solar power system in the Sahara Desert and transmission of the electrical power thus created around the world using high-temperature superconducting cable**. It has been calculated that around one-quarter of the Sahara Desert area could provide the world's entire electrical energy needs. If it was possible to transmit electricity over distances of several thousand kilometers, then this is certainly not an impossible dream.

Practical implementation through Contract Developmet

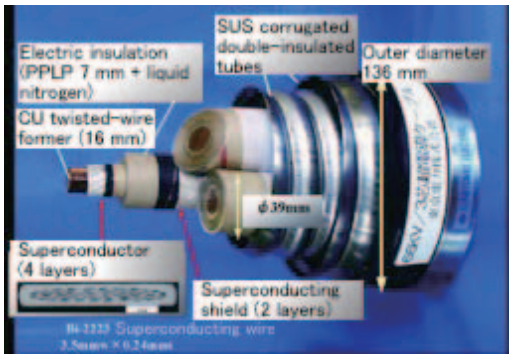
This research into high-temperature superconducting cable was conducted as a collaborative project by Professor Koichi Kitazawa, Professor Kazuo Fueki, Professor Mikio Takano, and Hiroshi Maeda. The research theme was "Manufacturing technology for oxide superconductors (bismuth superconductors), which was adopted by the 'Contract Developmet' system in 1990, with Sumitomo Electric Industries, Ltd. assisting the progress of research as the commissioning company.

Bismuth superconductors can sustain a superconductive state at temperatures at least 100°C higher than previously used metal superconductors; however, they are extremely difficult to engineer, and the road to their practical implementation is certainly not an easy one.

Seeking superconductivity at higher temperatures with bismuth cable materials

The temperature at which a superconductive state is entered varies greatly depending on the material in question. Metal superconductors, which were commonly used before the discovery of oxide superconductors, do not enter a superconductive state unless cooled to -269°C. For this reason, they required the use of extremely expensive liquid helium and thus the high running cost was a problem.

On the other hand, **bismuth oxide superconductors enter a superconductive state at -163°C**. It was believed that **if the use of comparatively inexpensive liquid nitrogen could be successfully developed instead of liquid helium, costs could be significantly reduced**. However, bismuth superconductors are composed of 5 elements in an extremely complex ceramic structure, making them difficult to engineer. They are hard and also brittle. So are most ceramics, generally speaking, **and practical implementation of this specific material took over 10 years**. The development of a bend- resistant long wire in lengths over 2 kilometers using this hard, brittle ceramic was only achievable with the engineering and manufacturing expertise of Sumitomo Electric Industries, Ltd., one of Japan's leaders in the field. **No other team could have implement this technology practically but these researchers and companies working in close collaborate**.



High-temperature superconducting cable (1)

First participation in US government project by Japanese corporation

High-temperature superconducting cable (2)

In 2001, massive blackouts occurred in the state of California, repeating again in 2003 across North America. Many reasons for this failure were given, such as system failure or deterioration of transmission cables, but the surprising thing here is that electrical blackouts, which almost never occur in Japan, are still experienced quite frequently across the USA. In response to this fact, as part of America's energy strategy, a project is underway to construct a power transmission network using superconducting cables across the entire USA by 2030. As part of this project, experiments were conducted on superconducting cable used for electrical transmission in the world's first practical implementation of this technology in the city of Albany, New York.

Sumitomo Electric Industries, Ltd. provided high-temperature superconducting cable developed under the Contract Developmet program, which represented the first participation in a US government project by a Japanese corporation.

In the international joint project, known as the Albany Project, although only 350 meters of superconducting cable was actually laid, it was demonstrated that this would stand up to the rigors of practical implementation. This superconducting cable was installed completely free of trouble, and is capable of continuous unattended operation. In 2012, Japan too commenced its first experimental trials of superconducting power transmission. It seems that this ideal of uniting the world with superconducting cable will soon no longer be a dream, but reality.

Successfully passed the global standard with half precious metal catalyst!

Emission gas purification system derived from paper making technology

F.C.C. Co., Ltd. / Takuya Kitaoka
(Professor of Graduate School of Faculty of Agriculture, Kyushu University)

Development of Creative Technology Seeds Contract Development
"Emission gas purification system using wet paper making method" Development and implementing company / Representative Researcher (2006-2010)

Paper making technology changes the future of emission gas purification

To control emission of greenhouse gas that contributes to global warming, emission control has been implemented on vehicles and motor cycles all over the world.

A conventional emission gas purification system is made of a honeycomb-structured ceramics or stainless steel coated with ternary catalyst using platinum, rhodium and palladium, that makes nitrogen oxide, carbon hydride and carbon monoxide contained in emission gas harmless. However, with many concerns, such as resource protection and stable supply, a new purification system is needed. Amid this, the Emission gas purification system using wet paper making method was developed on the Development of Creative Technology Seeds, Contract Development by Professor Takuya Kitaoka and F.C.C. Co., Ltd. This unique method is based on Japanese traditional technique called "kamisuki (paper making)".

There is an urgent need to develop a purification system with less quantity of precious metal

Production of vehicles and motorcycles has been expanding all over the world. Strengthening of emission gas control will continue in the future. A conventional purification system responded to strengthening of the control only by increasing the quantity of precious mental used as a catalyst. However, this method has reached its limit. It is impossible to continue to use limited resources such as platinum and rhodium at the current rate. It was an urgent issue to develop an effective emission gas purification system using less precious metal.

Production of an innovative new catalyst by wet paper making method

Professor Takuya Kitaoka had been exploring the possibilities of a new catalyst. He thought it possible to provide effective emission gas purification if he made a catalyst structure with many pores like paper. Then, he found a crutch maker, F.C.C. This company used paper-making technique to manufacture a friction material as the major component of a crutch. Can this technique be applied? Then, their innovative joint research started.

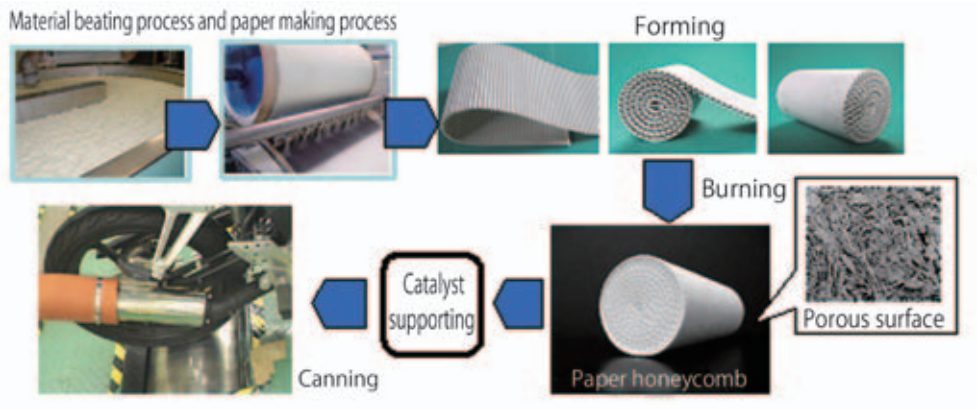
After many twists and turns, they reached a method called the "wet paper making method". In this method, a material containing powder of ceramics and pulp is sheeted like making thin hand-made Japanese paper. By rewinding it, it is shaped into a honeycomb-shaped structure. By highly heating it and adding palladium and rhodium as catalysts, they accomplished a new emission gas purification system.

What did the quantity of precious metal in it become? **Surprisingly, there was no need to use platinum**. Then, the system successfully passed the current global standard, EURO3 as a European emission standard for motorcycles (carbon monoxide: 2.0 g/km or lower, carbon hydride: 0.3 g/km or lower, nitrogen oxide: 0.15 g/km or lower) with around half the conventional quantity of precious metal. This improved the efficiency while achieving significant cost reduction. It has higher heat resistance, which a conventional system did not have,

and a conspicuous characteristic that its purification performance does not decrease even at 1000 degrees C.

F.C.C. had already commercialized paper catalyst. **They produced an innovative result using a conventional paper making technique**.

Production process of new system



(1) Material beating process and paper-making process: Paper is made from mainly ceramics powder and pulp and paper sheet is produced.
(2) Forming: Rewinding it into a corrugated shape after forming produces a honeycomb-shaped structure.
(3) Burning: It is burned at higher temperature (organic components are burnt/pores are formed).
(4) Catalyst supporting: Palladium-supported and rhodium-supported magnetoplumbite are coated and they are fired and fixed at lower temperature.
(5) Canning: A ceramics mat is used as a supporting material on the stainless steel pipe to press the honeycomb structure.

Emission gas purification system using wet paper making method

Development to hydrogen production catalysts and photocatalysts is expected

This system is light and easy crushable into small pieces for recycling of precious metal because the honeycomb structure is made of porous ceramics. Passing standards of strength enough to mount on a vehicle and purification performance, as the system is cost effective, it is greatly expected that it is used on general machines and motorcycles. In addition, development of the structure specific to paper by the new technique to hydrogen production catalysts and photocatalysts is expected. Anyway, the result of this R&D will continue to contribute to environmental problems that will get more acute in the future.

* Substance that increases the speed of the chemical reaction but does not change itself or its action. It has specificity to create only the desired products.

Depollution of nitrogen dioxide with Forest powers !

Air purification with tree essential oils

Japan Aroma Laboratory Co., Ltd /
Tatsuro Ohira (Chief of Wood Extractives laboratory, Forestry and Forest Products Research Institute, National Research and Development Agency)

Development of Creative Technology Seeds, Commercial Development by Innovative Venture Campanies
"Environmental depollution agents using tree essential oils"
Developing and implementing company / representive researcher (2007-2011)

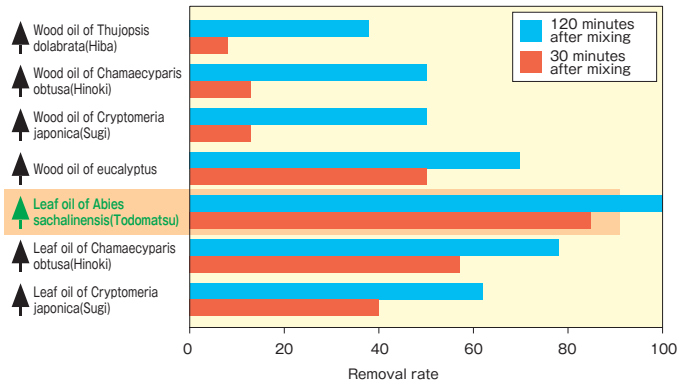
To improve the atmospheric environment of Japan The focus is on "forest air."

Nitrogen dioxide (NO_2), one of major causes of air pollution, also seriously affects human health. It increases the risk of diseases, such as bronchitis, pulmonary emphysema, and asthma. The symptom of hay fever from which many people are suffering tends to exacerbate when NO_2 is linked to the proteins of pollen.

Japan Aroma Laboratory and Forestry and Forest Products Research Institute(FFPRI) thus first paid attention to forest air. **"Can we improve the atmospheric environment of Japan using the forest air?" With such questions raised in these two research groups, the attempt started to use essential oil extracted from tree leaves**. FFPRI had already known that leaves contained more essential oil than trunks and that the essential oil depolluted a certain type of organic substance. They supposed that essential oils of trees would also have the effect of depolluting air pollutants. With this idea, they started a project to improve polluted urban air using unused forest resources with an aid of JST(Japan Science and Technology Agency).

Superior ability of essential oil from Abies sachalinensis to remove nitrogen dioxide

Comparison of the ability of tree essential oil gases (aromas) to remove nitrogen dioxide



$$\text{Removal rate (\%)} = \frac{(\text{NO}_2 \text{ concentration before mixing}) - (\text{NO}_2 \text{ concentration in a certain time after mixing})}{(\text{NO}_2 \text{ concentration before mixing})} \times 100$$

The essential oil from leaves of Abies sachalinensis expressed higher NO_2 removal ability compared to other tree oils.

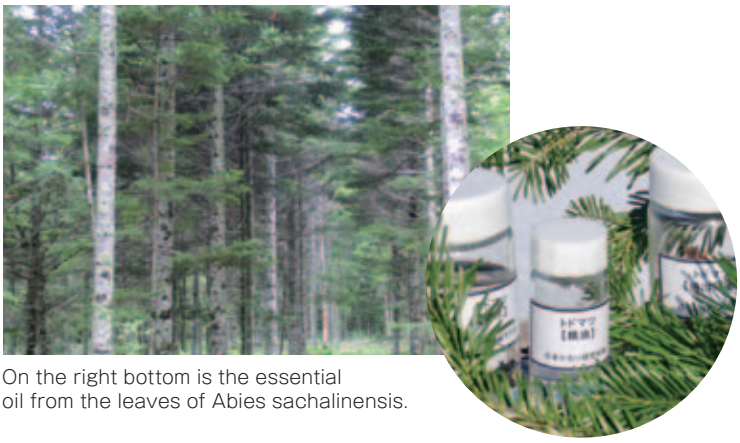
Two groups first studied the air purification ability of tree essential oils. **They found that the essential oil extracted from the leaves of Abies sachalinensis had an superior ability to remove NO_2**. Components such as β-phellandrene and myrcene, which are especially abundant in the leaves of Abies sachalinensis, worked effectively. How can the essential oil depollute NO_2? As a result of studies, **they found that the components of the essential oil attracted NO_2 in the air and coagulated it (particles coming together and forming a larger mass)**. NO_2 is depolluted in this way, and it is different from turning NO_2 into a different component as a result of a chemical reaction. Moreover, the effect did not change at all when exposed to ultraviolet rays or high temperature.

Hokkaido has more than 95% of the production of Abies sachalinensis in Japan, that means Hokkaido has high potential of NO_2 removal ability by huge storage of essential oil in leaves. The area was suitable for the creation of new industry.

Successful development of a new extraction system with energy efficient and low cost

"Clear Forest Project" was launched to utilize the power of essential oils. This is an innovative attempt to use unused forest resources which used to be discarded. The team first developed efficient system (from the collection of the leaves of Abies sachalinensis to the extraction), with the cooperation of local regions. The team first constructed a oil production facilities in Kushiro, Hokkaido. They then **successfully developed an extraction system (vaccume controlled microwave assisted extraction system) that was completely different from a conventional steam distillation system** in order to improve extraction efficiency of essential oil. This system shortens the duration of extraction, and the extraction temperature and pressure can be easily adjusted. It dose not produce extra waste water. It really is an energy efficient and low cost extraction system. The extraction residues after extracting essential oil also have deodorizing effects, and may be used as deodorants in the future.Using forest resources effectively and making full use of its power. This is a unique system that can also be a key to revitalize Japanese forests.

Abies sachalinensis forest in the Kushiro area, Hokkaido.



On the right bottom is the essential oil from the leaves of Abies sachalinensis.

Vaccume controlled Microwave assisted Extraction system

This system uses the water contained in plants without adding water. Thus, waste water in not produced after extraction. The vaccume control system enables selective extraction of components.

Business oparation has started and won several Prizes

S.T. Corporation has already started business oparation of the essential oil of Abies sachalinensis as a raw material and produced air purifier for interior of automobiles by the brand name "Clear Forest". Living environment can be improved by the use of this product. It can also be used as air purifying systems in public spaces including hospitals, nursing facilities, sports facilities, and government offices.

Examples of commercially available "Clear Forest" products using the essential oil of Abies sachalinensis

The Japan Aroma Laboratory and FFPRI won **the 12th Industry, Academia and Government Cooperation Contribution Award in the Minister's Prize, the Ministry of Agriculture, Forestry and Fisheries in 2014 that commemorated outstanding projects of industry-academia-government cooperation. They also won the 40th Inoue Harushige Award, a distinguished award in the field of technology in 2015**. These prizes recognized highly of the development of the new air purifier and also the establishment of the network of cooperation among private companies, public organizations, and municipalities including Hokkaido prefecture. In addition to businesses in Japan, they are expected to expand their businesses in China with its exacerbating environmental pollution and Asian countries with spreading deforestation.

Expectations towards regenerative medicine and drug development

Establishing induced pluripotent stem (iPS) cells

Shinya Yamanaka (Director, Center for iPS Cell Research and Application (CiRA), Kyoto University)

CREST
Translational Research for Intractable Immune Disorders and Infectious Diseases
"Generation of Ideal Pluripotent Stem Cells for Clinical Applications" Research Director (2003-2008)

Yamanaka iPS Cell Project
Research Director (2008-2012)

Core Center for iPS Cell Research
"Center of Excellence in Development of iPS Cell Stock for Regenerative Medicine" Center Director (2013-)*
*This research project has been transferred to the Japan Agency for Medical Research and Development as of April 1, 2015.

Toward realization of regenerative medicine

On November 20, 2007, Professor Shinya Yamanaka announced in the journal Cell his discovery of the phenomenon of initialization of mature cells, which enabled them to acquire pluripotentiality. This announcement took the world by storm, bringing with it high expectations for clinical applications such as regenerative medicine and treating intractable diseases. **In 2012, only 5 years later, in consideration of the discovery that shook the world in 2007, Professor Yamanaka was awarded the Nobel Prize in Physiology or Medicine.**

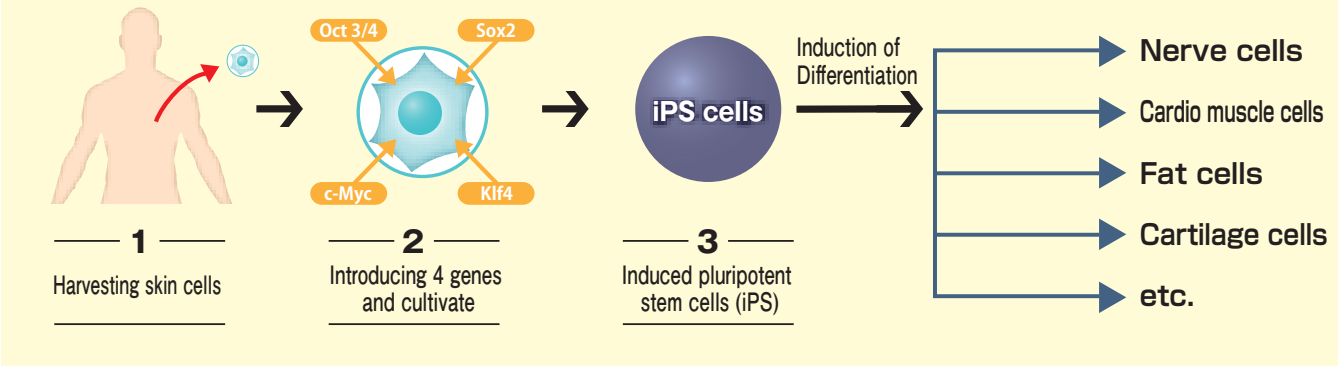
The establishment of iPS cells overturned the previous conventional understanding—that once differentiated, cells do not initialize again—and has also overcome the various ethical problems surrounding the use of embryonic stem cells (ES cells). This discovery continues to spark innovation worldwide. Moreover, **in September 2014, the project leader Masayo Takahashi and others at RIKEN performed the world's first clinical research of transplanting the pigment epithelium that derives from iPS cell to an exudative age-related macular degeneration patient.**

Creating bones, hearts, nerves, livers, blood, etc., from skin cells!

iPS cells are induced pluripotent stem cells. Pluripotent stem cells have **universal properties, and if properly cultivated, can be differentiated to grow into bones, hearts, nerves, livers, blood cells, and various other parts: all the cells that constitute the human body.** Previously, it was unthinkable that the cells that constitute the skin etc. could ever become pluripotent stem cells. This is because returning cells to the same pluripotent state as fertilized ova seemed to represent nothing less than winding back the clock, like some kind of time machine.

However, **by simply introduction of mere 4 genes into skin cells**, Professor Yamanaka's team achieved the seemingly impossible task of winding back the clock.

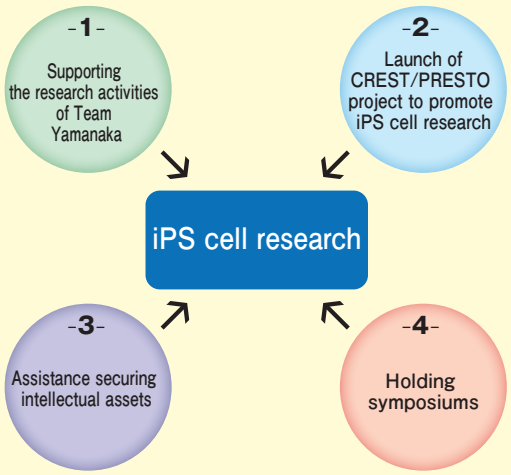
Producing human iPS cells (*initial method)



Overcoming major barriers to regenerative medicine!

Given current medical treatment, the only existing medical procedure for organ failure is a transplant from another individual. However, organ transplants involve the inherent risk of rejection, and have also been chronic donor shortage. Since embryonic stem cells, which possess the same pluripotentiality universal properties as iPS cells, require the use of fertilized human ova, it has been argued that they are ethically problematic. Fertilized ova could be a cell represents the original mechanism for creating human life. It is a telling fact that **in the USA, the creation of new embryonic human stem cells using public research funding was prohibited during the Bush administration**.

iPS cells, which can be readily created from human skin cells, represent nothing less than one of the most significant discoveries of the century, and can become the solution to all these problems. After the announcement of iPS cell research, so crucial to humanity's long-held dream of regenerative medicine, **JST quickly established the "Basic Strategic Research Program for Cellular Reprogramming using iPS Cells" to create an all-Japan research framework**. Under this rubric, Japan supports iPS research in many different ways: hosting international symposia, launching the Yamanaka iPS Cell Project (based upon the 2008 Strategic Sector "Creating fundamental technologies for advanced medicine through generation and regulation of stem cells, based on cellular reprogramming"), mandating new CREST/PRESTO research areas, and more. Moreover Research Center Network for Realization of Generative Medicine has established in 2012 as a core center is supporting iPS cell research of stock of iPS generative medicine.



Basic Strategic Research Program for Cellular Reprogramming using iPS Cells

New Medical Treatments Made Possible Through iPS cells

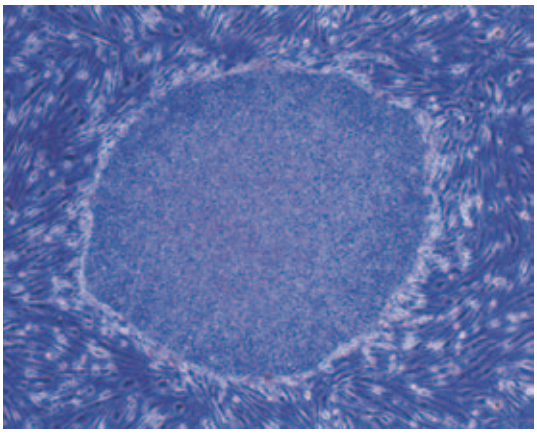
The possibilities of iPS cells are far more wide-ranging than just regenerative medicine. Major results are also expected in the creation of new pharmaceuticals.

For example, by differentiating iPS cells into the various cells of tissues for patients with rare and intractable diseases of unknown causes, and then comparing these with normal healthy cells, it will be possible to diagnose these pathologies and develop effective pharmaceuticals. In cases where physical examination of tissue structure is not possible, such as with the heart or central nervous system, it is expected that these cells can be recreated using iPS cells and used to find out the cause of the medical condition. The discovery of iPS also seems likely to bring about an end to the previous necessity of animal experimentation conducted in the biological sciences.

Kyoto University has been granted patents relating to this basic iPS cell technology in many countries Of these patents, the right for methods of establishing iPS cells extends to the use of the established iPS cells in medical treatments and drug development.

These influential patents **owned by public institutions licensing widely an environment is created that fosters and enables the participation of many companies in iPS cell research and development, screening for candidate drug substances**. We can expect that providing for curative medicine and medical cure by these companies enter into research and development for many people using iPS cell technology.

iPS cells derived from human skin cells



Provided by : Center for iPS Cell Research and Application

Momentous first step toward regenerative medicine using iPS cells!

Successful iPS cell transplant surgery on a human!

Masayo Takahashi

(Project Leader of the Laboratory for Retinal Regeneration, Riken Center for Developmental Biology)

Strategic Promotion of Innovative Research and Development (S-Innovation)
Construction of Medical Industry Using Cells with iPS at Its Core
"Retinal Regeneration by Cell Transplantation" Project manager (2009-2011)

Highway Program for Realization of Regenerative Medicine
"Development of Age-Related Macular Degeneration Treatment by the Transplantation if iPS Cell-Derived Retinal Pigment Epithelium Cells" Project leader (2011-2015) *
*This project has been transferred to the Japan Agency for Medical Research and Development as of April 1, 2015.

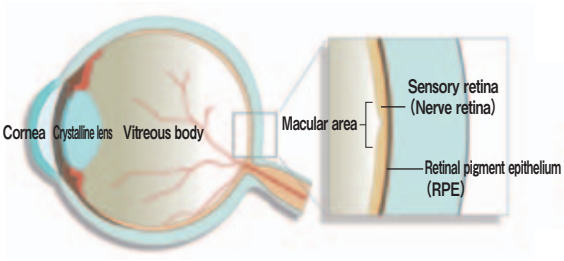
Seven years since stunning debut; milestone leading to practical application

It was on September 12 in 2014, seven years from when Professor Shinya Yamanaka sent shock waves through the world with the establishment of iPS cells, that the operation in which a patient's own iPS-cell derived retinal pigment epithelium (RPE) cells were transplanted into the same patient with exudative age-related macular degeneration was performed.

This was the world's first case where tissue produced from iPS cells was used in a transplant surgery on a human.

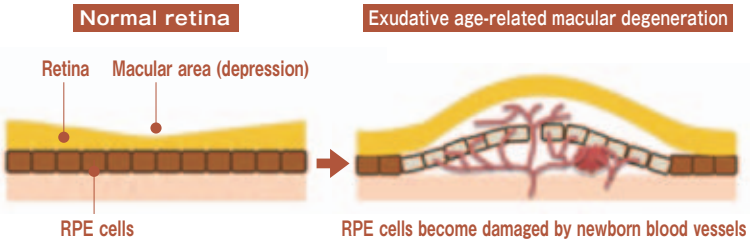
What is exudative age-related macular degeneration?

The basic structure of the human eye



The retina consists of the sensory retina containing visual cells (neural retina) and the retinal pigment epithelium(RPE). The RPE is responsible for nutritional support to nerve cells and the digestion of waste.

Exudative age-related macular degeneration



When the RPE and the sensory retina become damaged by abnormal blood vessels called choroidal neovasculars, the function of the macular area deteriorates.

Even a huge wall is to be overcome someday

The center of an eye retina is called the macula, which plays an important role when you see things. Exudative age-related macular degeneration is a disease in which abnormal blood vessels are newly generated under the retina in the macula area. This disease leads to the deterioration of vision, and before long, results in the loss of sight. Although the cause of the disease has yet to be understood in detail, this disease is considered to be associated with the aging of RPE cells. Therapeutic agents to suppress the development of blood vessels have been developed; **however, it is still impossible to undo the damage in RPE cells and tissue with such therapeutic agents. For a radical cure, the transplantation of RPE cells is necessary**.

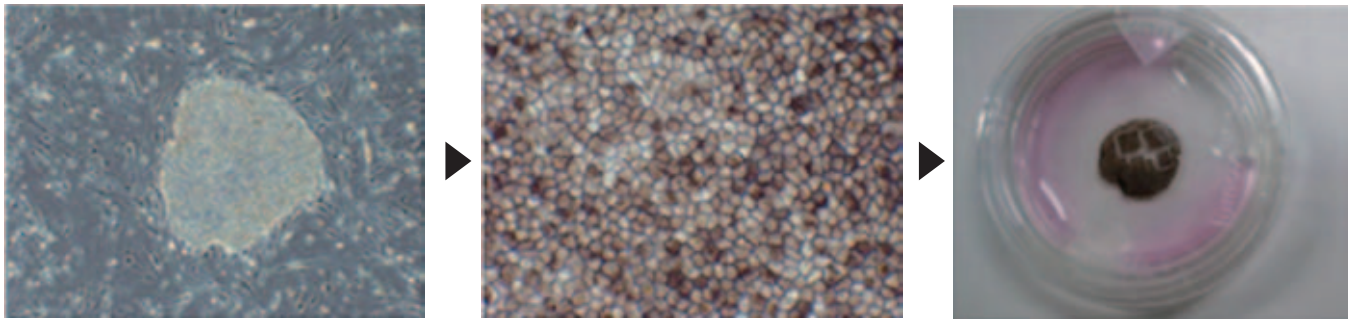
Project Leader Masayo Takahashi proceeded with the study of inducing differentiation of ES cells (embryonic stem cell), which are pluripotential stem cells derived from reproductive cells, into RPE cells, and produced good results; however, the use of ES cells was not approved in Japan due to problems associated with the regulations. Thus, the establishment of the technique to induce the differentiation of ES cells into RPE cells did not go far enough in opening the way to its practical use.

Becoming a frontrunner leading to the practical use of iPS cells

That was when iPS cells appeared like a savior. Since being able to be produced from a patient's own cells, the use of iPS cells doesn't pose grave ethical problems and doesn't carry a serious risk of rejection. Project Leader Takahashi says: "I felt like I had seen a ray of light in the darkness." Then she became a research leader of the Strategic Promotion of Innovative Research and Development, and since then, **started to work on the establishment of the technique to induce the differentiation of ES cells into RPE cells and its clinical application**. Fortunately, the differentiation-inducing method to be used for iPS cells was found to be not significantly different from that used for ES cells, so the research advanced steadily. Among the researches on regenerative medicine associated with iPS cells that started around the same time, the research conducted went one step further ahead of what the others were doing, attracting attention as a pioneer in the practical uses of iPS cells.

After the Highway Program for Realization of Regenerative Medicine that was based on the New Growth Strategy started in 2011, the research was adopted as the research subject for the aforementioned program under the name of the Development of Age-Related Macular Degeneration Treatment by the Transplantation of iPS Cell-Derived Retinal Pigment Epithelium Cells, thus the research further accelerated. In July 2013, the Ministry of Health, Labour and Welfare approved its clinical research implementation plan, and the clinical research finally started.

Producing RPE cells from iPS cells



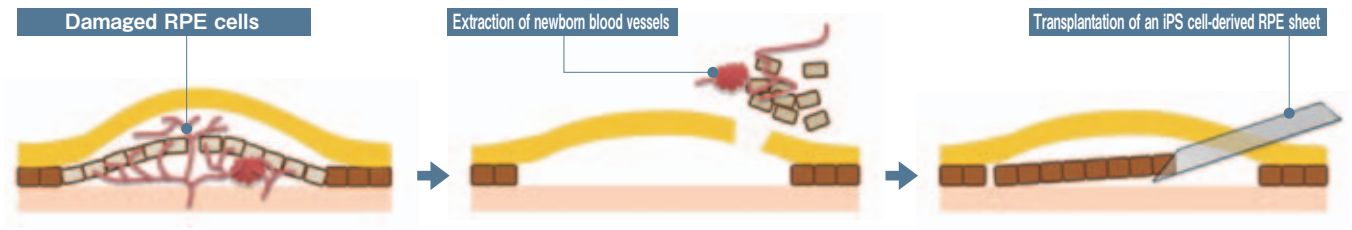
iPS cell　Producing RPE cells　RPE sheet for transplantation

Great significance of the "first step"

Prior to the transplant surgery, skin tissue was taken from the patient's arm, and then it was cultured to produce iPS cells. After that, the produced iPS cells were induced to differentiate into forming RPE cells, from which a sheet the size of 1.3 mm × 3 mm was produced. On the day of the surgery, the abnormal blood vessels that were constituting a factor for the deterioration of vision were removed and the sheet-liked RPC cells were transplanted. Now, a follow-up inspection is being carried out.

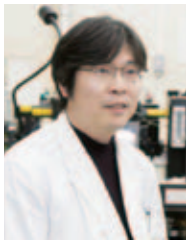
This surgery was performed as part of clinical **research at an early stage**. The main purpose lay in the confirmation of safety, rather than in achieving a remarkable therapeutic effect such as significant vision improvement. It is necessary to conduct prolonged further clinical research in the future until this therapeutic method is established as a new therapeutic method and becomes common. iPS cells, which sent shock waves through the world, thus took the first step toward bringing a blessing to mankind.

Transplantation of an iPS cell-derived retinal pigment epithelium (RPE) sheet



Contributing to R&D of medical products

Organ generation using iPS cells



Hideki Taniguchi (Professor, Graduate School of Medicine, Yokohama City University)

S-Innovation
"Constriction of human hepatic stem cell library for pharmaco-cellomics" Program manager (2009-2013)

Regeneration medicine realization hub network program
"Hub for development of generation of metabolic organs using iPS cells" manager (2013-)*
*This research project has been transferred to the Japan Agency for Medical Research and Development as of April 1, 2015.

iPS cell research - the next step in "clinical research" and "organ generation"

In November 2007, a research team (Professor Shinya Yamanaka et al., Kyoto University) generated "iPS cells" from cutaneous cells. This research surprised the world, because it had been generally believed in the medical world that it was impossible to reprogram cells once they differentiated. However, the "iPS cells" have pluripotency which allows them to differentiate into any type of cell.

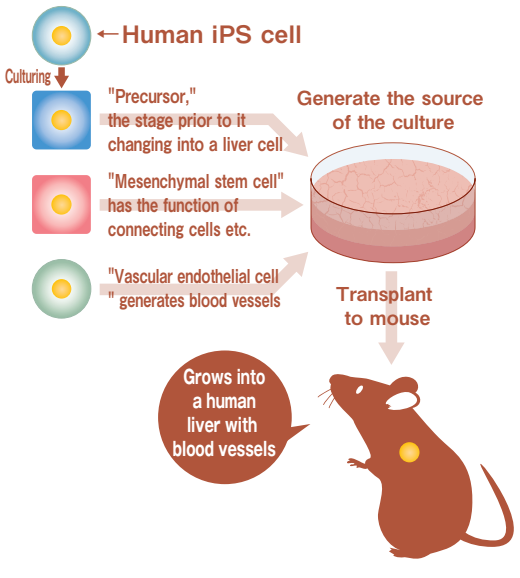
Now researchers have almost completed the research stage regarding what types of cells iPS cells can differentiate into. **The main themes presently being addressed are "Clinical research developed by the application of iPS cells" and "Organ generation." These two themes correspond with the application of the iPS cells in regenerative medicine, or medical treatment for regeneration of lost tissues and organs. In 2013, researchers made substantial progress** in these areas. As for the former theme, Project Leader Masayo Takahashi et al. in RIKEN, launched the first clinical research in the world in the regeneration medicine realization hub network program that took on the results of s-innovation in August 2013. As for the latter theme, Professor Hideki Taniguchi with his team members at Yokohama City University generated a human organ in s-innovation for the first time in the world in July.

Perceptional change "from cell induction to organ induction"

There is a disease that is called "terminal organ incompetence." If a person suffers from this disease, his/her specified organ fails to function. An effective medical treatment for this case is "organ transplantation", in which a healthy organ is replaced with a damaged organ. However, organs from donors are in extremely short supply while the number of patients who need an organ transplant are increasing year after year. Thus, in order to solve this problem, it is urgent and imperative to develop a medical treatment which will serve as a substitute for organ transplantation. For this reason, researchers have recently carried on the regenerative medical research, using differentiated and inducted organ cells from pluripotent stem cells (iPS cells, ES cells) with the aim of recovering damaged organ function.

In order to achieve this, **the research group of Professor Hideki Taniguchi et al. departed from the previous developmental notion of "cell differentiation induction."** Instead, the group aimed to realize "differentiation and induction based on organ reconstruction." Naturally, organs are constructed not only with cells that bear a specific function (functional cell), but also with multiple kinds of cells which are arranged three-dimensionally and interact with one another, both of which contribute to the proper function of the organ. Thus, the basic idea **can be described as follows: in order to acquire cells that function fully, it is imperative to "induce organs" (organ generation) that enable the reconstruction of three-dimensional tissues, in addition to inducing the differentiation of the functional cells.**

The way the iPS cells become human livers

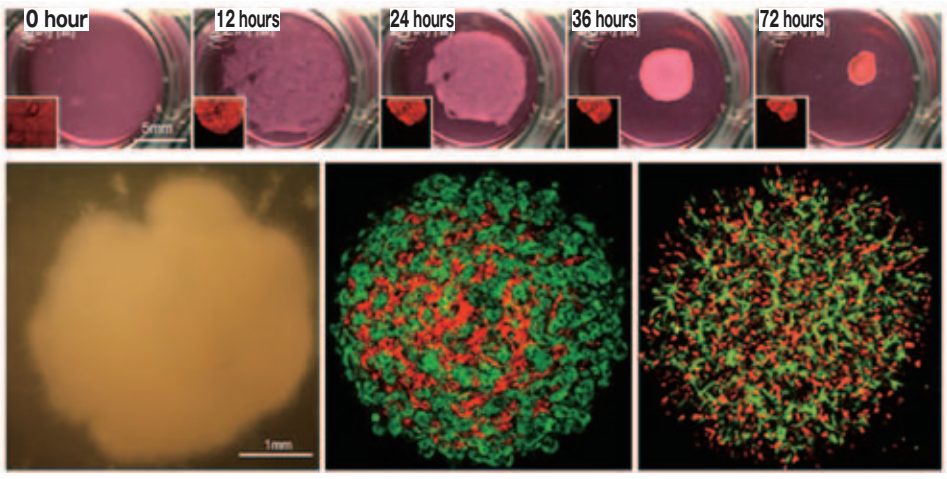


3 types of cells gathered together in a ball shape to create a "mini-liver"!

First of all, the research group developed a new cell culture handling technique in order to follow the process of "organ rudiment" (organ seed) formation that takes place in the womb in a test tube. After this, the research group added "vascular endothelial cells" (that generated blood vessels) and "mesenchymal stem cells" (that had the function to connect cells) to "endoderm cells" that were made of human iPS cells ("precursors" that are in the stage just before they differentiate into liver cells), then co-cultured in a test tube. As a result, **3 types of undifferentiated cells gathered together in a ball shape to form autonomously three-dimensional liver rudiments (what is called the human "mini-liver") in approximately 48 hours**. When they transplanted these rudiments to living organisms (immunosuppressed mice), vascular networks with bloodstreams were reconstructed, and finally it was found that the rudiments matured into tissue with features of human liver functions, such as synthesis of protein and drug metabolism. In addition, the survival rate of the mice group that had the hepatic failure, into which the rudiments had been transplanted, improved significantly compared to the mice group that didn' t received the transplantation. This indicates that human liver cells that were differentiated and inducted in living organisms were successful in performing a function as a liver, and the effectiveness of the treatment was observed.

Thus, this research group succeeded in creating a functional human liver with vascular networks from iPS cell-derived cells for the first time in the world.

Picture of the formation process for the human liver rudiment in three-dimension



By co-culturing 3 types of undifferentiated cells under special conditions, three-dimensional liver rudiments were formed autonomously (upper). It became obvious that iPS cell-derived endoderm cells can be differentiated and inducted into liver precursors effectively, and vascular cells can also form network-like structures (lower)

For alternate treatment of organ transplant and pharmaceutical screening

The research group of Professor Taniguchi et al. named this developmental technique as a "transplant remedy for organ rudiment," and proposed this remedy as an alternate treatment for organ transplants. If we can substantiate the treatment based on the technique, we will be able to save the lives of many patients. To that end, the research group is now working on mass producing technology, seeking the best way to transplant organ rudiments, trying to realize the regenerative medicine for patients with liver disorder, and thus accelerating the research for the application possibility for organs other than the liver.

On the other hand, the result of this research is likely to contribute largely to the development of the pharmaceutical industry in Japan. Human hepatic cells are regarded as highly marketable and the most important among the cells currently utilized for the development in the pharmaceutical industry. They have proved to be useful for screening (selection of new drug candidates) for pharmaceutical developments such as metabolic stability tests and enzyme induction, but unfortunately, almost 100% of the supply relies on Europe and the United States at present. Therefore, we believe that if we are able to produce iPS cell-derived human hepatic cells and hepatic tissues in large quantity and provide them for the screening using the technique developed through this research, we will make a further contribution to the development in the pharmaceutical industry in Japan.

Just sticking the sheet can be a cure!

Miraculous Cell Sheet

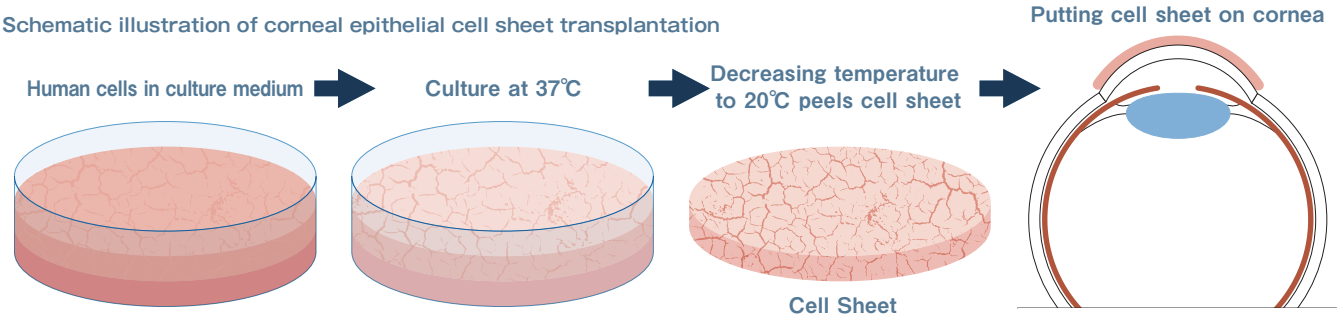
Teruo Okano
(Professor Emeritus/Project Professor at Institute of Advanced BioMedical Engineering and Science (ABMES), Tokyo Women's Medical University)
CREST
Creation of Bio-Devices and Bio-Systems with Chemical and Biological Molecules for Medical Use
"Development of a Novel Tissue Reconstruction Technique and Next Generation Biosensors" Research Director (2001-2006)
FIRST
"System Integration for Industrialization of Regenerative Medicine: Creation of Organ Factory" Core Researcher (2009-2013)

Technology described as a "treasure of humanity"

When human organs lose their function, it is difficult for them to recover on their own. Although the advent of organ transplantation has brought about the greatest progress in modern medicine, saving many lives, this procedure still faces some severe limitations. The **need for more donors**, and the collateral problems caused after transplantation, together with the ethical concerns encourage the search for new alternatives. If we could create artificial organs, many more patients could be saved. Prof. Teruo Okano has established a technology for the manufacture of cell sheets to produce artificial organs: a long-held dream of humanity.

These cell sheets represent a foundational technology that can be applied to the regenerative therapies of various tissues and organs. For example, a clinical trial using myoblast cell sheets to treat heart failure has recently been completed. This success has allowed the release of the myoblast sheet as the world's first marketed product of engineered tissue for heart failure treatment. In addition, other clinical studies and trials for the treatment of esophagus, inner ear, articular cartilage, periodontal membrane, and cornea are actually being conducted both in Japan and abroad. **Even when only considering the treatment of patients suffering from ischemic cardiac diseases (i.e. infarction), we could save several millions of patients worldwide** by using cell sheet technology.

Schematic illustration of corneal epithelial cell sheet transplantation

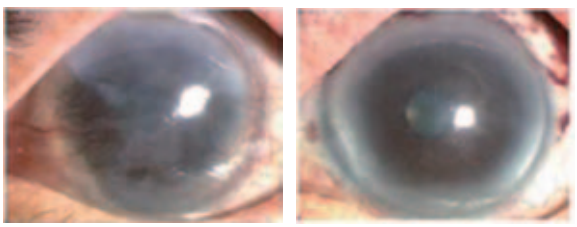


The miracle sheet: just stick it on the injured area!

The cell sheet technology possesses many marvelous advantages, but the most remarkable is the simplicity of manipulation and transplantation. This is a crucial aspect that improves the success of surgical procedures. **Essentially, the sheets can be stuck directly to the injured area**, avoiding any additional suturing, and reducing the difficulties for both doctor and patient. For example, in the case of the corneal treatment, the procedure just requires placing the sheet lightly in position onto the eyeball. Furthermore, severe cardiac infarctions, which previously could only be cured by heart transplantation, can be treated by just sticking the cell sheets on the necrotic area. In this sense, the cell sheet transplantation is an amazing therapy that is beyond our traditional knowledge.

Another important benefit of the cell sheet therapy is that it allows the use of autologous cells, avoiding immunological rejection. In addition, there is no need for allogeneic donors, so the patients can be treated immediately.

Transplantation of autologous oral mucosal cell sheet to treat ocular pemphigoid

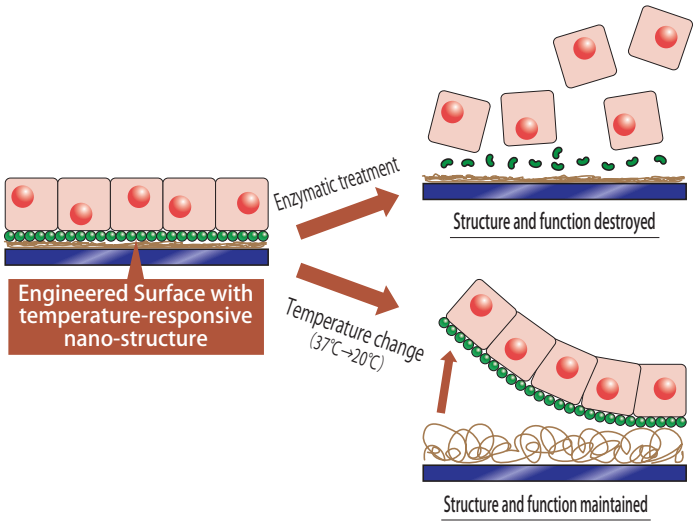


Before surgery　　2 months after surgery

Development of culture dishes to create cell sheets

The important point in creating cell sheets is, in fact, the development of culture dishes. Although the adhesiveness of the cell sheets is an advantage for transplantation, it also makes it very difficult to detach the cell sheets from culture dishes. Conventionally, cultured cells are harvested from culture dishes by enzymatic digestion to destroy cell-dish connections. However, this method can damage the cells.

Accordingly, Prof. Okano developed **novel culture dishes that allow detachment of cultured cells by temperature change, without destroying the cell membrane structure**. The surfaces of these novel culture dishes are coated with a 20-nanometer-thick layer of temperature-responsive polymer, which changes its molecular structure depending on the temperature. **The properties of this surface for cell attachment are similar to a normal culture surface at human body temperature around 37C, which is the standard temperature for cell culture. However, when the temperature decreases to 20C, the surface properties change to prevent cell attachment, allowing the cell sheet to detach from this surface without any damage**. The development of this special culture dishes allowed the creation of cell sheets and their clinical applications.



New world achieved by integration of medicine, science, and engineering

The advances in modern medical treatment are not anymore relying solely on medical knowledge, but requiring close collaboration of medicine, science, and engineering. Actually, the development of the above-mentioned culture dishes could not be achieved by medicine alone. Prof. Okano firmly believes that **new technologies developed through the fusion of medicine, science, and engineering will make it possible to save many patients regardless of the surgeon' s skills. At the moment, some of these patients can be saved only by a handful of extremely prominent surgeons**.

Following these beliefs and concepts, Tokyo Women' s Medical University and Waseda University have cooperated and established a joint institution for the research and education of advanced biomedical engineering and science. This multidisciplinary institution **accomplished the fusion of medicine, science, and engineering, where clinicians, chemists, biologists, and engineers are working together, creating a research environment that is unique and unparalleled in the world**.

'Self-eating' cells: An intracellular bulk degradation process

Fascinated by Autophagy

Noboru Mizushima
(Professor, Graduate School and Faculty of Medicine, The University of Tokyo)

PRESTO Unit Process and Combined Circuit
"Molecular mechanism of autophagy and its physiological role" Researcher (1999-2002)

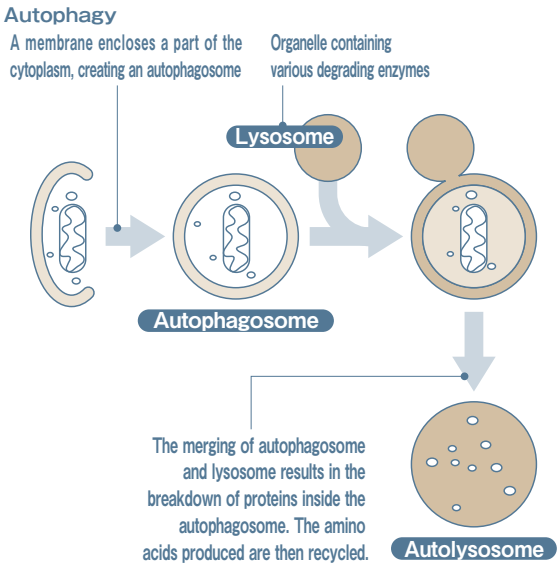
PRESTO Time's Arrow and Biosignaling
"The Role of Autophagy in Mammals and Its Control Mechanism" Researcher (2002-2005)

SORST "Intercellular Clearance Mechanism by Autophagy" Principal Researcher (2006-2007)

Autophagy research, which was limited in research methods

A cell eats itself. It was in the 1960s that this strange phenomenon was first discovered. Using an electron microscope, a cell eating the protein that was contained in the cell itself, and then breaking it down into amino acid was confirmed. A membrane encloses a part of the cytoplasm (autophagosome), which then becomes merged (autolysosome) with an organelle (lysosome) containing various degrading enzymes, causing the contained proteins to be broken down and becoming amino acids.

This phenomenon, named autophagy, was one that differed in nature compared to prior physiological knowledge. Tens of thousands of different protein types exist within our bodies, and these substances carry out various key functions. We eat every day, and the protein contained in these foods are broken down into as amino acids and absorbed. Then, the absorbed amino acids become components of protein synthesis, which is essential for life sustaining activities. Considering this common knowledge, it may seem like an unwise action of eating itself. There was speculation that this action involved metabolic action of transforming unnecessary protein into a different substance, but back then **the only method available to observe this was through an electron microscope. It was difficult to confirm when, where and how this was taking place**. As the years went by, autophagy would rarely be brought up by biologists researchers, and by the mid 90' s it had come to the point where only a few papers were published annually.



Development of a real-time observation technique using an animal cell

It was Professor Noboru Mizushima, who took an interest in autophagy at a time when few researchers addressed this subject. At that time he was still a graduate student at the Tokyo Medical and Dental University. It started out when he learned of the research by Professor Yoshinori Ohsumi of the National Institute for Basic Biology in Okazaki City (currently a Honorary Professor at the Tokyo Institute of Technology). Having confirmed the occurrence of autophagy in budding yeast, Professor Ohsumi had been carrying out his research. Professor Mizushima was drawn to this phenomenon called autophagy after coming across Professor Ohsumi's paper, and he became a part-time researcher at Ohsumi' s laboratory. This is how Professor Mizushima began his research.

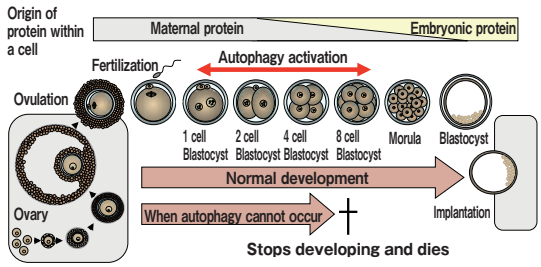
One year later, he was selected to the PRESTO 'Unit Process and Combined Circuit' project, and he accelerated his research. **He unraveled the mechanism of two proteins called the Apg12 and Apg5 bonding together to form an autophagosome. Even more ground-breaking was that he confirmed the occurrence of autophagy in tissues throughout the body even in mammals**, which he accomplished with a technique for visualization in cells that using GFP. Prior

to this, autophagosomes could only be captured with an electron microscope due to its small size. It had become possible to observe when, where and how autophagy is occurring in real-time. In the PRESTO 'Time s' Arrow and Biosignaling' project to which he was selected thereafter, he engaged in investigating the roles of autophagy and its control mechanism within mammals by creating a knockout mouse that deficient in genes involved in autophagy.

Clarification of its physiological roles in maintaining homeostasis and starvation state

With the real-time observation and development of the knockout mouse, autophagy research progressed rapidly. Based on the observations that autophagy becomes active in the entire body when starved, and that a knockout mouse deficient in Atg5, a gene critical required in autophagy, falls into a severely undernourished condition immediately after birth and dies, **it was found that autophagy plays an important alimentary role in starvation state**. Also, a movement disorder was seen in mice that were deficient in Atg5 genes specific to nerve cells. Based on the abnormal accumulation and aggregation of protein seen when observing the inside of the nerve cell, it was found that in addition to supplementing amino acid during a starvation state, **autophagy plays a housekeeping role intracellularly in removing misfolded or aggregated unnecessary proteins**.

After the completion of the PRESTO project, Professor Mizushima continued his research at the SORST program entitled 'Intracellular Clearance Mechanism by Autophagy' . Where he focused on autophagy s' role in removing unnecessary proteins, and studied their roles in various tissues. For instance, in the fertilized eggs of mice, it was confirmed that autophagy becomes unusually active within four hours from fertilization. As for mouse deficient in Atg5 genes specific to egg cells, ovulation and fertilization occurred normally, but development stopped prior to reaching implantation and died as a result. **In a normal mouse, the activation of autophagy immediately following fertilization allows the removal of unnecessary proteins that comes from the mother, as well as the securing of amino acids that are to become components of the new protein synthesis, prerequisite for the development process**.



In the fertilized egg of a mouse in which autophagy does not occur, the development terminates before implantation and results in death

The moment an autophagosome is formed, as captured by an electron microscope. The mitochondria (V-shape in the center), is about to be enclosed by the white-appearing isolation film (upper left part of center). (Photo: Chieko Kishi)

An emerging research field that is attracting worldwide attention

In this way, Professor Mizushima and his colleagues used a newly developed observation method to reveal that autophagy is evolutionarily conserved in eukaryotesfrom yeast to mammals, and they have continued to unravel its mechanism and role. This contributed to the promotion of autophagy research all over the world, and is about to lead us to treatment for diseases such as cancer and Alzheimer' s. In 2013, Professor Mizushima was jointly awarded with Honorary Professor Ohsumi and others as Highly Cited Researchers selected by Thomson Reuters. The selection criteria for this award is based on the number of times a researcher' s own paper was cited in others papers, and honorands are said to be leading candidates to receive a Nobel prize. Several decades have passed since the time when only a few related papers would be published each year. With the research results of Professor Mizushima and others who possess foresight as the impetus, autophagy is growing into a research area attracting the attention of the world.

Revolutionize the common knowledgeof immunology!

The role of innate immunity

Shizuo Akira (Professor/Director, WPI Immunology Frontier Research Center, Osaka University)

CREST
Host Defense Mechanism "Studies on Host Defense Mechanisms by Gene Targeting" Research Director (1995-1999)

SORST
"Elucidating the Molecular Mechanism of the Natural Immunity System" Core Researcher (2000-2001)

ERATO
"Akira Innate Immunity Project" Research Director (2002-2007)

An enduring contribution to the study of innate immunity

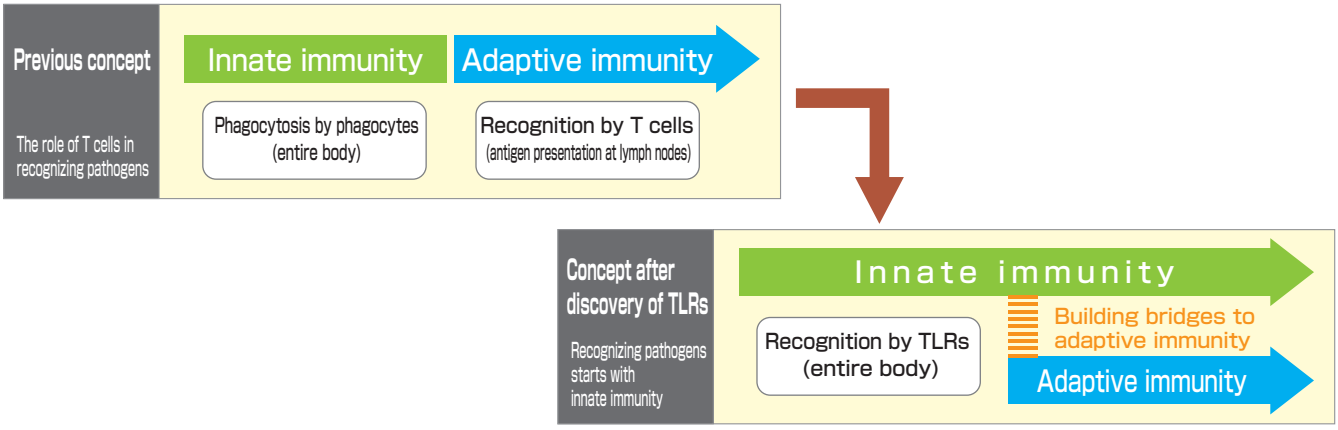
The 2011 Nobel Prize in Physiology or Medicine was awarded to 3 researchers in the field of immunology: French molecular biologist Jules A. Hoffmann, Bruce Alan Beutler of the Scripps Research Institute (USA), and Ralph M. Steinman of Rockefeller University (USA). All three share the distinction of having explicated the refined workings of innate immunity, which serves as a biological defense for living organisms but which had previously been considered primitive.

However, there is another researcher in this field whose contributions are no less impressive than the aforementioned three: Professor Shizuo Akira. **In addition to winning several prestigious international awards for medical science such as the Robert Koch-Prize, one of the best German medicine prize in 2004, andCanada Gaidner International award in 2011 Professor Akira has continuously appeared on the US Thomson Scientific (present Thomson Reuters) "World's Hottest Researchers" list, ranking 8th in 2004, 1st in 2005 and 2006, and 4th in 2007**, with his contributions to innate immunity research recognized on a world level.

The role that innate immunity plays in almost all living organisms

Immunity is known as the mechanism that protects our bodies against viruses and bacteria, but there are many details of the immune mechanism that remain unclear. Innate immunity, in particular, **is often dismissed as the body's most primitive immune response, which simply digests and fights off any pathogens that invade the body. On the other hand, adaptive immunity is a system found only in vertebrates (such as mammals) which boasts an advanced learning capability that remembers pathogens and immediately eliminates them if the same pathogen ever invades the body again**. Adaptive immunity has been the subject of exhaustive research, such as in vaccine development and more. Until the late 1990s, **adaptive immunity was widely considered to represent all immune function, with immunology textbooks even stating that while the term "innate immunity" contained the word "immunity," it did not actually represent an immune function.**

Changing of immune system concept

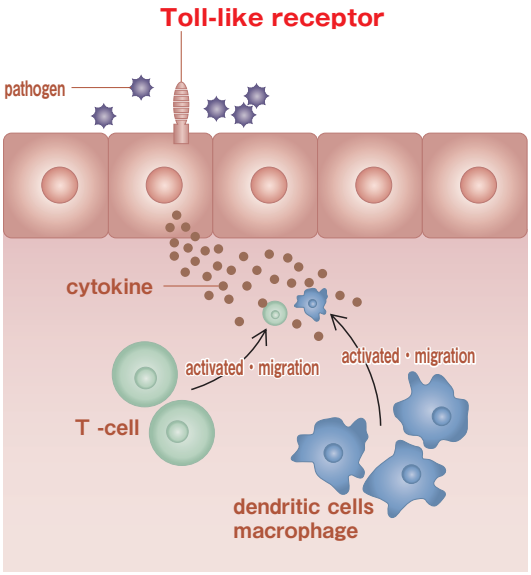


Could fruit fly immune receptors be relevant to humans?

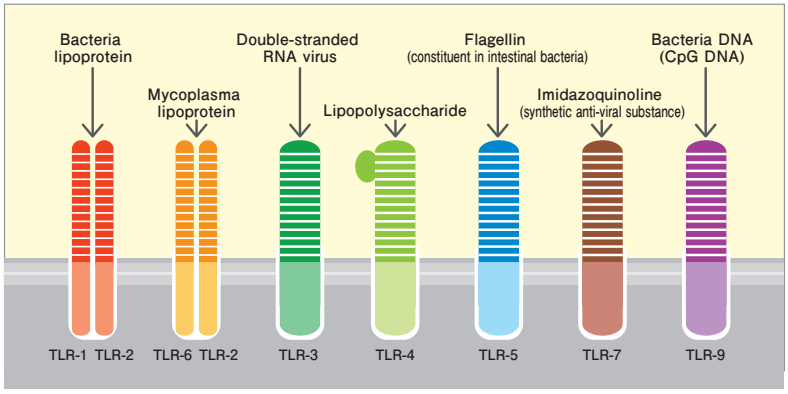
In 1996, the role of Toll receptors in the innate immunity of Drosophila fruit flies was discovered by French molecular biologist Jules Hoffmann's group at the Institut de Biologie Moléculaire et Cellulaire (IBMC). They reported that fruit flies lacking these Toll receptors had no innate immunity function, were overcome by fungus, and eventually died. Subsequently, Toll-like receptors were found to exist in all kinds of insects, with similar proteins also found to exist in the human body. Since these human proteins resemble the Toll receptors found in flies, they were given the name "Toll-like receptors." Professor Akira conducted repeated experiments on "knockout mice" * to find out what sort of action 12 kinds of Toll-like receptors have in the mammal body. **He finally discovered that all of Toll-like receptors were responsible for recognizing different bacteria or viruses**.

Professor Akira had discovered that these Toll-like receptors **played an important role in linking innate immunity and adaptive immunity, which had previously been considered two completely** separate systems; this completely overturned conventional wisdom in the field of immunology. Far from being just a primitive immune response, innate immunity has now been recognized as playing an essential role within adaptive immunity.

Induction of immune reaction



Cells detect pathogens through the toll-like receptors and inflammatory proteins called cytokine are secreted, which recruits and activates T-cell, dendritic cells and macrophage, leading to a multiple of immune reactions



Toll-like receptor (TLR) family and known active ingredients Antiviral synthetic compound

Helping develop pharmaceutical treatments for hayfever, etc.

Professor Akira's discovery has already **proven useful in the research and development of pharmaceuticals targeting innate immunity:** for example, in the development of drugs to treat hayfever, which with 20 million sufferers across Japan has been described as Japan's national disease, as well as atopic eczema and more.

It has also found partial practical applications in medication for infectious diseases such as herpes, among others. In the scant 10+ years since Professor Akira's discovery, the field of immunology has evolved at great speed. **In future, clearer understanding of immune mechanisms is expected to enable treatments not only for diseases linked to abnormal immune responses, but also for intractable diseases such as cancer**.

This research, which started with Toll receptors discovered in fruit flies, has garnered immense interest worldwide as research that could critically influence humanity's future.

Subsequent research has determined that toll receptors and toll-like receptors are structurally similar, but significantly different in function. There remains no doubt that a huge diversity of living creatures found on earth is protected by such advanced innate immunity systems.

*A gene knockout mouse of which a specific gene is artificially damaged so as not to function

Whole-body imaging at a single cell level !

A whole mouse made transparent

Hiroki Ueda (Professor at the Graduate School of Medicine, The University of Tokyo / Group Director at Quantitative Biology Center, Riken)

CREST

Innovation for Ideal Medical Treatment Based on the Understanding of Maintenance, Change and Breakdown Mechanisms of Homeostasis among Interacting Organ Systems

"Challenge to Reveal Dynamic Properties in Circadian Sleep-Wake Homeostasis" Research Director(2013-2018)

Challenge towards the dream of seeing every single cell in the body

Although about 350 years have passed since Robert Hooke of England discovered cells under a microscope, no-one in the world has seen and identified every single cell in the bodies of humans or mice as a high resolution image. The body of a mouse with body weight of 30 g is made up of about 30 billion cells, and complex cellular network spreads across the entire body. Even if we focus on brain as a critical organ, a brain with 0.5 g of weight contains nearly 500 million cells. Observing the individual cells is more difficult than observing individual persons from outside the islands of Japan. What is then needed to observe the individual cells in further detail? Collaborative research group led by Professor Hiroki Ueda has tackled this problem as a part of CREST "Innovation for Ideal Medical Treatment Based on the Understanding of Maintenance, Change and Breakdown Mechanisms of Homeostasis among Interacting Organ Systems" project. In order to comprehensively analyze the entire body as a single system, they have attempted to develop an **imaging technology to obtain the function of the cell network and genes across the body as a 3D image with single-cell level resolution**.

Figure 1
Entire mouse made transparent (the left figure shows the infant mouse, the right figure shows the adult mouse)

Image provide by Riken

Removal of endogenous pigments as requirement for transparency

In the observation of brain cells, the light is scattered by water, protein, and lipid in the cells, making it unclear to see. Professor Ueda thought that "if it cannot be seen, it should be made see-through." He has removed the lipid which causes the scattering of light and made the refractive index in the tissue uniform, and succeeded in obtaining a highly transparent brain sample.

However, **an effective method was needed for the removal of endogenous pigments that absorb lights in order to achieve transparency in organs with high content of endogenous pigments such as a heme in red blood cells, for example liver and spleen**. Many researchers have attempted to make the organs transparent in the past; however no efficient method was discovered for the removal of pigment in tissues containing endogenous pigments without disruption of proteins.

At last, the organs and the body is made entirely see-through!

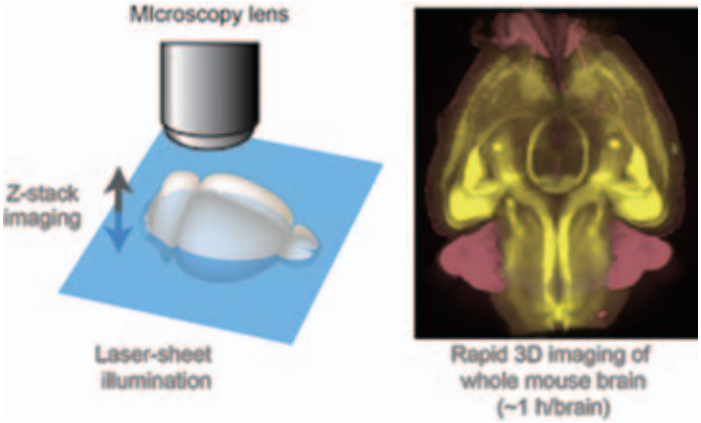
The solution to this problem was the transparency reagent (ScaleCUBIC reagent, hereinafter referred to as CUBIC reagent) used in CUBIC*, which Professor Ueda and his colleagues developed as whole-brain imaging and analyzing technology. This reagent was accidently **discovered to efficiently decolorize blood**. They have clarified the mechanism where aminoalcohol, a component in CUBIC reagent, efficiently dissolves the red pigment heme in the blood, resulting in decolorization of the blood.

Furthermore, **a new perfusion protocol using CUBIC reagent was developed** in order to obtain a sample with higher transparency. The procedures involved are as follows: Firstly, perfusion fixation is performed on the body of a mouse using 4% paraformaldehyde (typical method of fixation to maintain the components in the tissues in a state as close to the living state as possible). Following this, CUBIC reagent diluted to 1/2 concentration is circulated to the whole body via the vascular system. The heart, lung, kidneys, liver, pancreas, spleen, muscle, stomach, intestinal tract, and skin are immersed in the same reagent for 10 days. This process enables the entire organ to become transparent. If the body of a mouse with the skin removed is immersed in the reagent for 2 weeks, the whole body can be made transparent.

Using these transparent organ and body samples, and by using the light sheet fluorescence microscopy (microscope where laser ray is spread in a sheet-like manner and radiated from the side of the sample and the image is taken from the top to enable a certain plane in a sample in a single session (refer to Figure 2)), **it is possible to obtain a single-cell resolution 3D imaging data of an entire organ or body, showing the positions of the cells, etc., in a short period of 1 hour**. In previous methods, high resolution imaging of an entire brain required at least a day. Using this microscope where the radiating axis and observing axis cross orthogonally, a 2D image can be obtained quickly, and a 3D image can be obtained at high-speed by simply changing the sheet height.

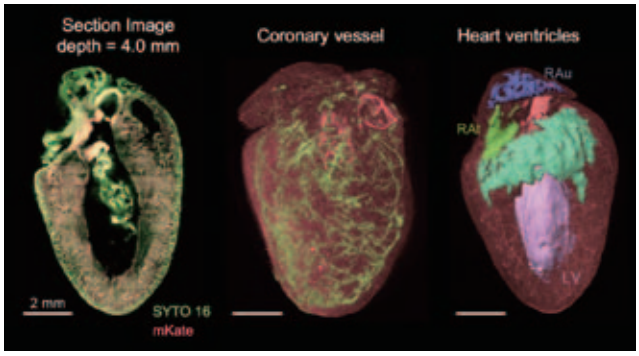
Adaptation of high-speed 3D imaging in Figure 2

Image provided by Riken



Use in biology and medicine, as well as elucidation of sleep-wake cycles

Figure 3 3D anatomy using CUBIC



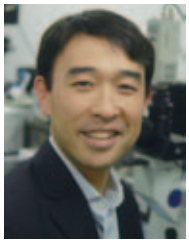
The characteristic structures of the organ can be extracted by image analysis. In the heart, internal structures such as ventricles and atria were extracted. Image provide by Riken

This technology by Professor Ueda and his colleagues **can be applied to 3D pathological analysis and 3D anatomy, as well as immunohistological analysis**. Since this technology enables the clarification of vital phenomenon and its operating principles on an individual body level, it is expected to contribute **not only in biology but also in the field of medicine**. This technology also plays an important role in Professor Ueda' s ongoing research on the sleep-wake cycles. It will help investigate the activity of individual cells important in the research, thereby assisting in clarifying the mechanisms involved. It is said to eventually **elucidate and treat the psychiatric disorders of depression and schizophrenia**. The collaborative research continues its challenges for dreams further ahead.

*Abbreviation of "Clear, Unobstructed Brain/Body Imaging Cocktails and Computational analysis." It is a combination of clearing reagents and protocols for whole-brain imaging, and computer image analysis.

The world's first success in photographing the division of a fertilized egg of a plant!

Real-time Observation of Plant Cells



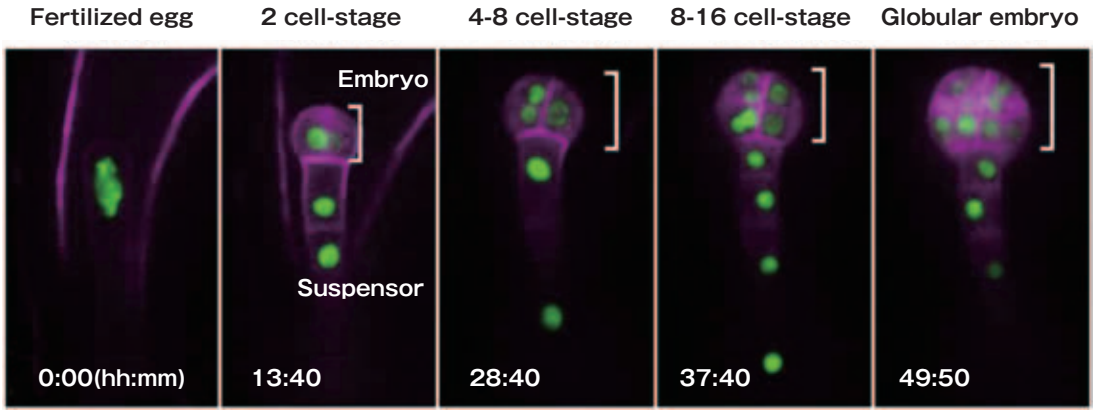
Tetsuya Higashiyama
(Professor, WPI Institute of Transformative Bio-Molecules, Nagoya University)
PRESTO
The Dynamic Mechanism of and Fundamental Technology for Biological System
"Dynamic System of Pollen Tube Guidance" Researcher (2007-2011)
ERATO
"HIGASHIYAMA Live-Holonics Project" Research Director (2010-2016)

The live imaging technology to observe the cell division process of a plant fertilized egg

A fertilized egg of an animal can be easily removed, and the process of cell division can be observed alive. However, a fertilized egg of a plant cannot be removed and observed alive since it lies deep inside of a pistil. No one has ever seen the fertilization process or the cell division process of an angiosperm, a flowering plant.

Professor Tetsuya Higashiyama **developed a system that enables the real-time observation (live imaging) of a living fertilized egg through the ERATO project, and succeeded in taking the world's first live images that clearly show the fertilized egg of a plant dividing to form an embryo**. The motto of this project is to establish the "live cell (living cell) biology", in which living cells and molecules of multicellular organisms can be flexibly manipulated and analyzed under a microscope Professor Tetsuya Higashiyama stated that it was his very big goal to observe and explore interactions between components and the whole of a living body with the live cell technology.

Live imaging of fertilized egg division and embryogenesis of *Arabidopsis thaliana*



A fertilized egg divides to form an embryo and a suspensor. The sections indicated in green represent the cell nucleus and those in pink represent the cell membrane. Embryonic cells divide to form globular tissue changing the direction of division, while suspensor cells divide along the longitudinal direction only to form a rod-shaped tissue.

Laser microscope and micro devices that support the study

The two main pillars, "laser microscope" and "micro devices", played an important role in the study. Professor Higashiyama organized a project team consisting of experts in various fields including optical equipment, engineering, and information science.

A laser microscope uses a laser beam with a shorter wavelength and higher rectilinearity than the visible light of an optical microscope, allowing the acquisition of sharper and more high-contrast images. This laser beam also enables cell manipulation; for example, it can destroy target cells or parts of cells, allowing the investigation of cell functions. The other main pillar is the application of new micro devices produced by micromachining technologies. **Micro devices, tiny devices called "tip," are produced by engineering technologies, and have made it possible to grow**

plant cells in a form that is appropriate for effective culture/observation. The latest micropillar arrays (a structure in which many tiny pillars are arranged at uniform distances) have a flexible structure, which enables the observation of delicate changes in the cells.

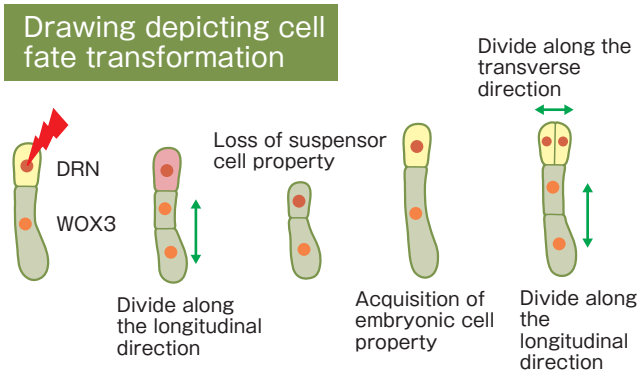
The discovery of the "cell regenerative ability" and "new cell fusion phenomenon" of plants

One of the remarkable achievements in this project is the elucidation of the "regenerative ability of cells." A fertilized egg of an angiosperm divides asymmetrically into apical cells (eventually developing into the plant body) and basal cells (responsible for supplying nutrients to the embryo). The research group destroyed apical cells with the laser technology described above, and observed the subsequent influence on the basal cells sequentially. As a result, surprising facts that had not been known to date were revealed. **When apical cells were damaged, "cell fate transformation" occurred where basal cells, which had already been developing into suspensor cells, played the role of apical cells to compensate for the damaged apical cells**. This is a proof of the surprising regenerative ability of plants.

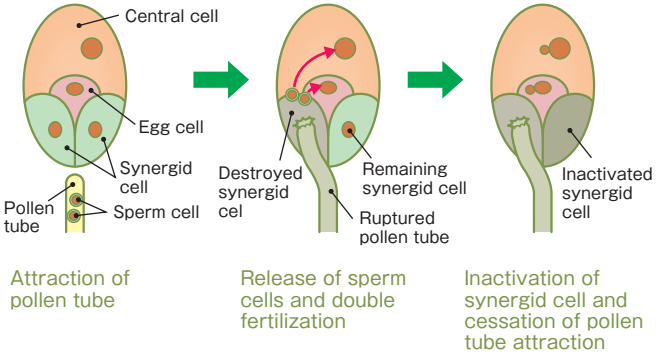
Furthermore, a completely new type of cell fusion phenomenon was discovered. In the development process of a seed of a plant, a pollen tube that extended from pollen is attracted by a tissue from which a seed is developed. At this time, what attract the pollen tube into the tissue are two synergid cells that lie adjacent to the egg cell. After the pollen tube reaches one of the synergid cells, two sperm cells gush out of the tip of the pollen tube, destroying the synergid cell. Then, one of the sperm cells is fertilized with the egg cell to develop into the embryo, while the other is fertilized with the central cell to develop into endosperm. Professor Higashiyama and his colleagues studied the changes that occurred in the remaining synergid cell by using *Arabidopsis thaliana*, a major model plant. As a result, **a cell fusion phenomenon was observed in which the synergid cell and endosperm were fused and their contents were mixed**. This phenomenon caused the rapid dispersion of the attractants in the synergid cell, suppressing the attraction of a pollen tube. This study elucidated the cessation mechanism of pollen tube attraction.

The cell fusion of plants has not been known to date except for fertilization, so this discovery not only greatly changed the perspective on plant cells, but also presented a new function of plant cells. It is no exaggeration to say that **this discovery will break out the paradigm**.

Changes in cells caused by the destruction of an apical cell



Double fertilization and cell fusion of synergid cell in an angiosperm



Contribution to the accelerated progresses of global embryogenesis study

The progresses of the global study of embryogenesis will accelerate as a result of the live imaging technology of plants. It is expected that the elucidation of the mechanism that enables cell fate transformation will contribute to the development of breeding/culture technologies associated with plants, including efficient tissue culture. The presence of the program that causes cell fusion other than fertilization was shown in plants, which will lead to the development of new cell fusion technologies of plants. In addition, Professor Higashiyama and his colleagues **succeeded in developing the reagent "ClearSee," which makes a plant transparent**, allowing detailed observation of the inner structure of a plant.

The series of studies described above greatly shocked the whole world. Due to the close cooperation among experts in imaging, engineering, and information science fields, the study is progressing further toward the identification of key molecules. Further achievements are expected in the future.

Visualize cancer cells by simple spraying

A light of hope for the improvement of residual breast cancer after surgery

Yasuteru Urano (Professor at the Graduate School of Pharmaceutical Sciences and Graduate School of Medicine, The University of Tokyo)

PRESTO Structure Function and Measurement Analysis "Development of advanced photo-functional probe molecules for elucidation of biological events in the living cells" Researcher (2004-2008)

Research Acceleration "In vivo tiny tumor detection project using light functional probe" Research Director (2010-2015)

CREST Creation of Innovative Technology for Medical Applications Based on the Global Analyses and Regulation of Disease-Related Metabolites "Creation of search techniques for disease-related metabolic activities based on live imaging of clinical specimen and its application to drug developments" Research Director (2014)*

*This project was transferred to the Japan Agency for Medical Research and Development from fiscal 2015.

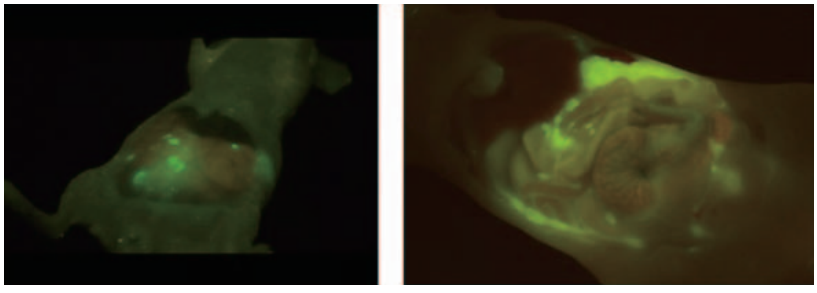
Development of the world's first fluorescent reagent that enables extremely rapid detection of cancer site

Early discovery and treatment is important in cancer. Prognosis can be improved dramatically if the primary lesion is removed before metastasis, and if the metastatic tiny tumor can be removed even after metastasis. In recent years, the treatment methods are shifting towards endoscopic or laparoscopic surgery to reduce the burden, creating a high demand for the establishment of methods that enable accurate detection of cancer location.

The limit of cancer detection is around 1 cm with the present method of cancer screening, and it is extremely difficult to detect cancer with the size of a few millimeters. In order to prevent the recurrence of cancer, there is a need to remove all metastatic tiny tumor around 1 mm in size, however this was previously dependent on the experience of the operating surgeon, and failure in detection and removal was an issue.

In Research Acceleration, Professor Yasuteru Urano and principal investigator Hisataka Kobayashi of the National Institutes of Health (US) conducted a joint research and **succeeded in a development of an innovational reagent which enables only cancer cells to be detected in a short period of time. By simply spraying a small amount of "organic small molecule fluorescent probe", a pigment that visualizes the substances in the living body, onto the affected area, fluorescence appears only in the area of the cancer.** This is the first technology in the world which enables the area of cancer to emit visible fluorescence by spraying locally, and it is a truly innovative technology.

Fluorescence detection image of the cancer sites



By spraying the probe reagent, the cancer sites emit a strong fluorescence after about 1 minute. It is possible to detect the area of tiny tumor by visual inspection (mouse model with peritoneal metastasis of ovarian cancer).

Tiny tumor at the size of 1 mm or smaller can be detected in a few tens of seconds to few minutes

In this research, **Professor Urano and his colleagues focused on "γ-glutamyl transpeptidase (GGT)", a protease whose activity is increased in many cancer cells, such as ovarian and lung cancer.** Based on the original fluorescent probe design established by the professor himself, the world's first fluorescent imaging reagent was successfully developed that detects the GGT activity of living cells as green fluorescence. **This reagent itself is colorless and dose not emit fluorescence, however it changes into molecules which emit strong green fluorescence when it comes in contact with GGT.** This enables fluorescent staining only for cells that have high GGT activity in a short period of time.

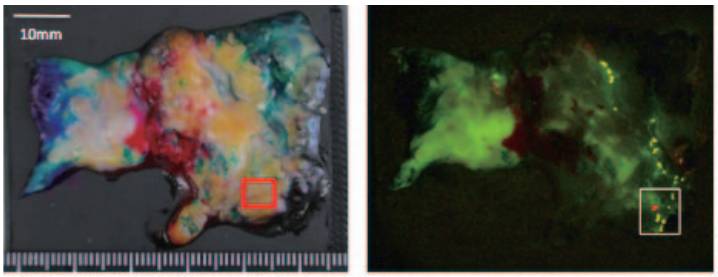
This reagent was tested in model mice, which revealed that tiny tumor at the size of 1 mm or smaller can be detected clearly in a few tens of seconds to a few minutes after spraying in the area of the suspected cancer. The strong fluorescence at the cancer site could be observed not only with a fluorescent endoscope but also by visual inspection. In addition, this reagent visualized the undetected very tiny tumor areas in the body of the model mice and succeeded in the mock surgery of removing these tumors with forceps.

Effective in the actual surgery for breast cancer

The effectiveness of the developed fluorescent imaging reagent was demonstrated in cancer model mice. However, the nature of cancer in human is highly diverse, and it was not known if the reagent would be effective for actual surgery. In a joint research with Professor Koshi Mimori of Kyushu University Beppu Hospital, Professor Urano has attempted to confirm efficacy in human cancer samples. **As a result, spraying of this reagent on the clinical sample resected in breast surgery has shown strong fluorescence in tiny tumor at the size of 1 mm or smaller after about 1 to 5 minutes of spraying,** enabling clear distinction of breast cancer from the surrounding health tissues such as mammary glands and fat. This method revealed that 1 mm or smaller size cancer tissues in small mammary ducts can be detected.

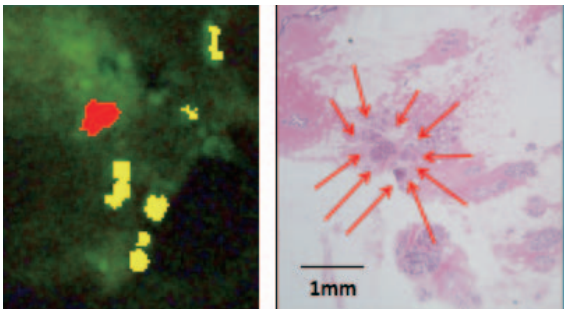
In the actual partial mastectomy of breast cancer, there is a need to detect small lesions (1 mm or smaller) in a sample the size of a few centimeters. In order to check whether the cancer cells have been completely removed, the cut end of the resected specimen must be checked for cancer cells during the surgery. However, in the present days where there is a shortage of pathologists, it is difficult to test all specimens, and the remaining cancer may be let undetected. This reagent is considered innovative in that it eliminates failure of detection in pathological diagnosis, thereby preventing the failure to remove cancer in surgery.

Detection of small cancer in the surgery specimen using the fluorescent reagent



In the large sample at the size of about 5 cm (left diagram) contains small hidden cancer in the area shown with a red rectangle in the right bottom corner. Although this cannot be seen with the naked eye, a few areas of strong fluorescence were detected about 5 minutes after spraying the reagent (right diagram). This section was subject to detailed pathological examinations.

Magnified diagram of the photograph above and the result of histopathological staining



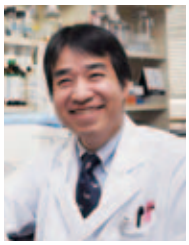
Success in detecting small cancer around 1 mm in size, which cannot be detected visually
(The areas with red and yellow in the left diagram shows strong fluorescence. Of these, the red area was proved by histopathological staining to be identical to the area of cancer in the right diagram).

Clinical evaluation conducted by industry-academia collaboration towards commercialization

Because of the rapid and convenient nature of fluorescent detection and the affordable cost, this technology has a high expectation for being used widely as a general method of cancer detection. **Currently, clinical evaluation is conducted by industry-academia collaboration to investigate the safety and efficacy of the reagent with the aim of commercialization as clinical pharmaceutical**. However, there are types of cancer that have almost no expression of GGT used as a target in this reagent (some cases of colon cancer, ovarian cancer, and gastric cancer), and the development of new reagents that visualize cancer tissues in these types of cancer is now on-going. It is expected that in future most cancer sites will be detected in a short period of time. In any case, development of this reagent is likely to be good news for many patients with cancer, and a brings dramatic change to the future of cancer as a disorder.

Targeting just the cancer cells !

Realization Through Molecular Target Therapy



Hiroyuki Mano
(Professor, Graduate school of medicine and facility of medicine, the University of Tokyo)

CREST Basic Technology to Establishing Tailor-Made Medicine by Utilizing Genome Information
"Characterization Human Disorders with a High-throughput Analysis of the Regulatory Mechanism for Gene Expression" Research Director (2002-2008)

Research Acceleration "Novel cancer gene identification project" Research Director (2009-2014)

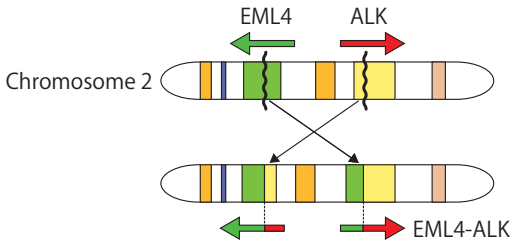
Research toward a long-held dream: an oral drug to cure cancer

Until around 40 years ago, the cancer overwhelmingly typical of the Japanese was stomach cancer. However, as times have changed, the incidence of lung cancer has risen dramatically, such that in 2009 lung cancer was the leading cause of cancer death among both men and women. The idea of an oral drug that might cure lung cancer sounds like a dream; however, recently announced research results seem likely to fulfill this dream. **This research has gained worldwide attention as an indicator of new possibilities; not only for lung cancer, but across the entire spectrum of cancer treatments**.

In order to discover cancer genes, Professor Hiroyuki Mano et al. developed a new screening method. **At CREST in 2007, Professor Mano discovered the EML4-ALK fusion gene; at Research Acceleration in 2012, he discovered the RET and ROSI fusion genes, which are all responsible for causing lung cancer. Moreover, he discovered RAC point mutation genes in 2013. These genes indicate possibility of causing breast cancer, melanoma, pancreas cancer, etc**. Simply put, by taking medication that suppresses the activation of these genes, we can now eliminate cancer caused by EML4-ALK. Actually, it has been confirmed that ALK fusion gene inhibitors are surprisingly effective in treating lung cancer possessing the EML4-ALK gene; **in August 2011, an ALK fusion gene inhibitor was approved in the USA as oral medication for EML4-ALK-positive lung cancer**. This was the world's fastest ever development of an anti-cancer agent, taking a mere 4 years from discovery of the therapeutic target to approval of medication. **It was also approved for manufacture and sale in Japan in March 2012, with sales of the medication commencing in May of that year. At present, it is used for more than 12,000 people across the world, and at least 2,500 people in Japan alone. Furthermore, ALK inhibitor Alectinib, which was developed domestically and approved for manufacture and sale in July 2014, proved to have incredible treatment effect with an efficiency of 93.5%. Close to 900 people in Japan have already been treated. It is expected to contribute further to the treatment for EML4-ALK-positive lung cancer in the future**.

Genetic breakdowns give rise to cancer

Our cells, of which we are said to possess around 60 trillion, are controlled by more than 200,000 genes. This genetic control functions as precisely as a computer; however, in extremely rare cases, a gene breaks down and an abnormal signal is sent in error. **This genetic breakdown causes the occurrence of cancer cells**. Genes break down for a wide range of reasons, including viruses, exposure to chemical substances, and errors during gene replication. In the case of the EML4-ALK fusion gene, this error results from part of the EML4 gene being switched with part of the ALK gene during the process of gene replication.



As a result of chromosome recombination, the genes EML4 and ALK combine to form the EML4-ALK fusion gene, which causes cancer.

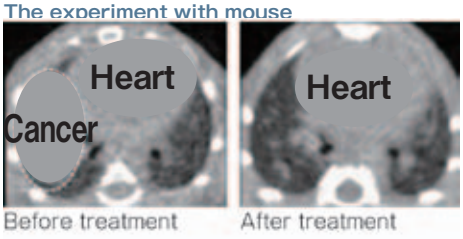
Are more potent genes actually easier to overcome?

When most people think about cancer treatments, they imagine anti-cancer drug therapy with strong side effects. Many conventional anti-cancer drugs are **used with the intention of impeding the process of cell division and proliferation**. Because the speed of proliferation of cancer cells is abnormally fast, they are more strongly affected by anti-cancer drugs in comparison to normal healthy cells. However, since healthy cells are also affected, strong side effects remain a problem. **A new method of treatment has now emerged that targets and attacks only the cancer cells, minimizing side effects: molecular target therapy**. This method distinguishes between cancer cells and normal healthy cells at both the genetic and the molecular levels, achieving treatment by fighting only the molecules required for the proliferation and metastasis of cancer. Believing molecular target therapy to be the "holy grail" of cancer treatment, Professor Mano embarked upon his research.

Although we often talk about "cancer" as a single disease, there are actually many different genes that may cause it. The lung cancer caused by the EML4-ALK gene discovered by Professor Mano represents no more than 5% of all cancer (30% or more for those aged under 50). However, the EML4-ALK gene is extremely strong in comparison to other types of cancer genes, and cancer progresses rapidly once it emerges, often to the point of death. However, although the fact was previously unknown to medical science, this very potency can actually be advantageous when it comes to cancer therapy.

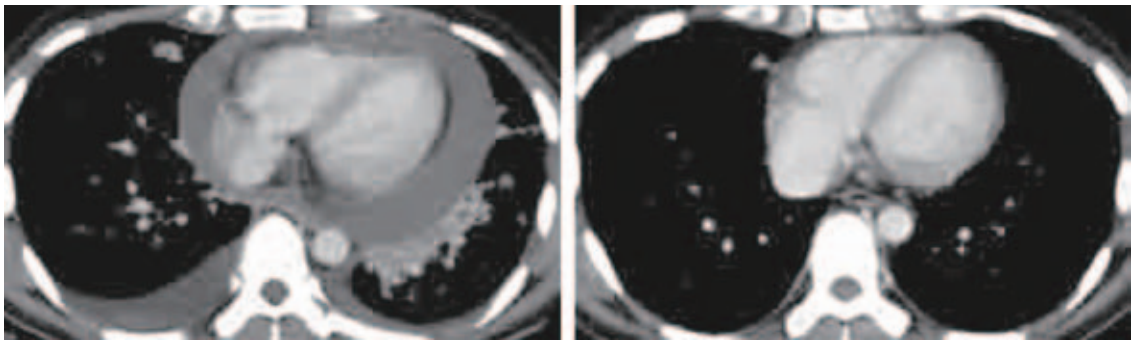
Due to its potency, the EML4-ALK gene causes cancer all by itself; thus, if this gene can be controlled with a single drug, the progress of cancer can be halted, offering the patient a chance for full recovery.

The experiment with mouse



A mouse with the expressed EML4-ALK gene had a large amount of cancer in both lungs, but with the ALK inhibitor, the lung cancer disappeared.

Clinical testing of cancer patient



Effect of treatment with an ALK inhibitor Crizotinib. Upon prescription of Crizotinib for a ALK-lung cancer patient, tumor and associated pericardial effusion disappeared rapidly (right).

Other cancer-related applications

We can safely say that Professor Mano's **discovery of cancer-causing genes such as EML4-ALK has greatly expanded the possibilities of molecular target therapy in treating cancer**. At present, few other genes are proven to singlehandedly cause cancer in the same way as the EML4-ALK gene, and we do not have detailed information about the abnormal genes in most types of cancer. However, moving forward, Professor Mano intends to pursue further research to shed light on the genes responsible for other cancers which claim many lives and for which effective treatment methods do not yet exist: such as liver cancer, pancreatic cancer, early-onset breast cancer and stomach cancer. Results are sure to follow.

Treatment with less fear of side effect and economic burden

Nano capsules allows the direct treatment of the affected parts of the body

Kazunori Kataoka
(Professor, Graduate Schools of Engineering and Medicine, The University of Tokyo)

CREST Creation of Bio-Devices and Bio-Systems with Chemical and Biological Molecules for Medical Use "Development of Novel Nano-structured Device for Gene and Drug Delivery" Research Director (2001-2006)

CREST Establishment of Innovative Manufacturing Technology Based on Nanoscience "Development of Manufacturing Processes of Supramolecular Nanodevices for Practical Gene Therapy" Research Director (2006-2011)

FIRST "Development of Innovative Diagnostic and Therapeutic Systems Based on Nanobiotechnology" Core Researcher (2009-2013)

Seeking to establish medical treatment using nano-biotechnology

In the film Fantastic Voyage, made in the USA in 1966, people are shrunk down and enter the human body with the aim of curing a patient's serious medical condition— at the time, a revolutionary idea. The film was highly acclaimed. Of course, Fantastic Voyage was intended as science fiction, but it seems that now a medical technology not too dissimilar to this science fiction movie is poised to become reality. Moreover, this new technology functions on the nano level: even smaller than the microscopic reality depicted in the film. Many people do not have an immediate grasp on how small the nano scale actually is. **The cells of the human body are around 6,000 to 25,000 nm in size, while the influenza virus is around 100 nm**. Clearly, this represents some remarkably small units.

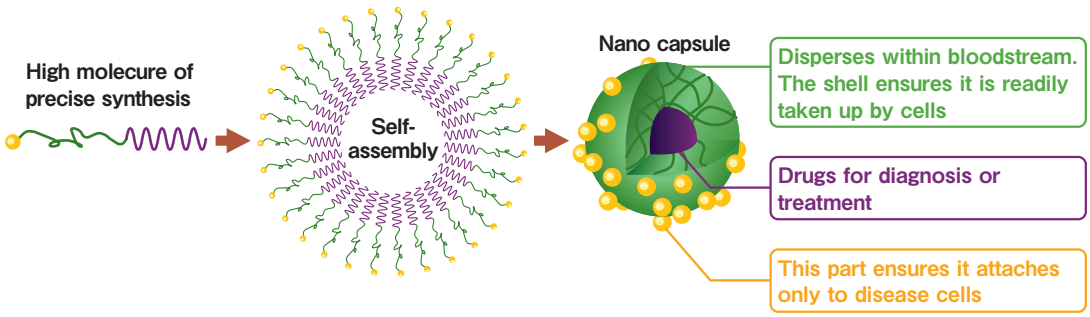
Professor Kazunori Kataoka is working to create nano-capsules on the atomic and molecular levels, and to establish drug delivery systems (DDS) and gene delivery systems capable of introducing drugs or genes directly into the diseased part. This research received the Humboldt Award in March 2012, and in July of the same year was awarded the 9th Leo Esaki Prize for outstanding world-acclaimed research contributions in the field of nanotechnology.

Nano-medicine: any time, any place, anyone

The aim of nano-biotechnology is not simply curing illness, but a rapid return to society with a minimum of burden placed on the patient. For this reason, researchers aim to construct a system based on 4 research strands: a **nano-diagnosis system** to diagnose illness, a **nano-DDS system** to deliver pharmacological agents to the affected areas of the body, a **minimally invasive nano-treatment system** for surgical treatment of affected areas using the nano-DDS, and a **nano-regenerative system** to regenerate body parts lost to disease.

By achieving all these, it will be possible to reduce **side effects and shrink overall medical care costs by reducing the costs of treatment and hospital stays, as well as cutting hospital stay time**. It seems that nano-medicine, one of the ultimate aims of nano-biotechnology therapy for anyone, any time, any place will soon reach viability.

Pieces of macromolecules were clustered together to form the capsule like a solid puzzle



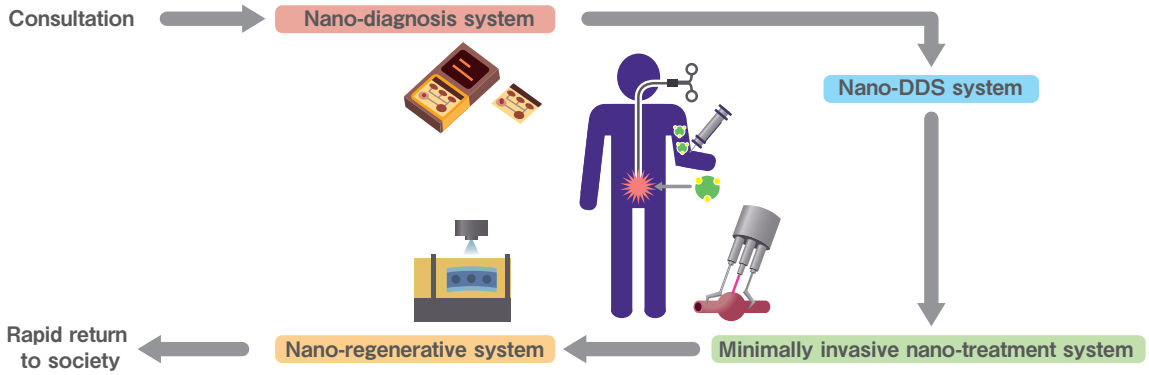
The nano-DDS: delivering drugs directly into the nucleus of cancer cells

Nano-biotechnology is extremely effective for treating cancer, which is the leading cause of death in Japan. Aside from surgery, prescription of anti-cancer drugs is the most common treatment for cancer at present, but since these drugs attack not only cancer cells but also healthy cells, they are accompanied by harsh side effects, which is a major drawback. Due to this, the patient is forced to forgo a normal lifestyle, and in addition to high medical expenses, these can also inflict significant damage.

On the other hand, with a nano-DDS, **not only are the drugs delivered to the cancer cells, but they are able to directly affect the nuclei of these cells, leading to a massive reduction of side-effects**. Moreover, since the effect is achieved using a far smaller quantity of the drug, the economic burden of treatment is also reduced.

Also, with this technology, since it is capable of carrying not only drugs but also genes, **it is possible to enable control of cell differentiation within the body when combined with regenerative medicine using iPS cells** (currently the focus of a great deal of attention). Aside from this, it also allows simple monitoring of what is occurring inside the body, enables surgery in regions where the human hand cannot reach, and so on. In short, this system is a long-held dream that will change the very fundamentals of medical treatment.

Ultra-early detection, precision diagnosis, and pinpoint treatment of cancer



Project to construct a system rather than make products

This project was first developed as CREST, which is led by Professor Kataoka, and has made substantial progress under the Funding Program for World-Leading Innovative R&D on Science and Technology program (the FIRST program) operated by Japan's Cabinet Office.

Moreover, he took this result step further under the COI program named "Development of a nanomachine brings a smart life care into reality" by MEXT. **In Professor Kataoka's opinion, the single most significant issue is the construction of system**.

Of course, development of molecules to carry drugs is important, but establishing a medical treatment system that uses these drugs is what we must aim for, he believes. In short, the objective is not construction of any of the respective components, but rather the creation of a system unifying all these parts.

If nano-biotechnology systems, techniques, know-how, and patents and so on (which possess the potential to become central to medical science) are dominated by various other countries, it is not unthinkable that Japan might be forced to pay vast compensation for these. Conversely, becoming a global leader in these technologies will enable Japan to assume a major leadership role. The project that Professor Kataoka is driving forward is nothing less than a state project.

Combines with the original bone in a short period after implantation!

Success in the development of sponge-textured artificial bone

HOYA Technosurgical Corporation / Junzo Tanaka
(Emeritus professor, Tokyo Institute of Technology)

Development of Creative Technology Seeds, Contract Development
"Manufacturing technology for biologically substituting organic-inorganic hybrid artificial bone"
Developing and implementing company/Representative Researcher (2003-2012)

Strong need for artificial bones with performance higher than autologous bones

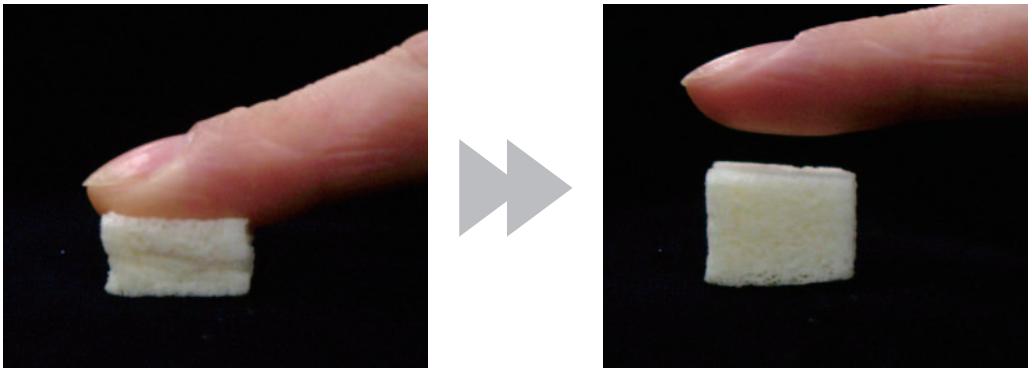
Bones support the human body and protect the brain and organs. In cases where a part of these bones is heavily damaged by disease or injury, the bone of the patients (autologous bone) was implanted as a replacement. Since autologous bones can be implanted while maintaining their activities, it is highly functional in bone regeneration, and are associated with significant advantages such as being free of problems related to immunity and infection. However, there is a limit to the amount of autologous bone which can be sampled, and surgeries are required in two locations for the procedure. In addition, there are large burdens on patients, including the frequent problems in the sampling location. For this reason, the idea of artificial bone was conceived.

The artificial bones currently in use are made of ceramic, and have been developed in the 1970' s. The percentage of use of artificial bones is around 40% as of 2009. **Why are autologous bones still being used? The main reason is that regeneration of bone with artificial bone is not nearly as effective as that of the autologous bone**. In Japan, an increasing number of cases require bone grafts (such as bone fracture and bone tumor) with the increased elderly population, and there is a heightened need for artificial bones with performance equal to or superior than the autologous bone. In response to this, **an artificial bone based on new ideas were realized by Hoya Corporation, New Ceramics Division (currently Hoya Technosurgical Corporation) based on the results of research by Emeritus Professor Tanaka Junzo and his colleagues, which utilized the Development of Creative Technology Seeds, Contract Development**.

Birth of new artificial bone which overcome the problems of operability and insufficient bone regeneration!

There have been previous developments of artificial bones made from various materials, which enable resorption and replacement by bone cells and eventually being regenerated to live bones. An artificial bone using β-type tricalcium phosphate is evaluated highly for the high effect of resorption and replacement; however, there are difficulties of operation during surgery due to its fragility. In addition, there are reports that in some cases only the resorption of the material progressed, resulting in insufficient bone regeneration, or the residual material cause the delay in regenerations. Artificial bone by Emeritus Professor Tanaka and his colleagues was developed to overcome these problems.

Elasticity of the new artificial bone



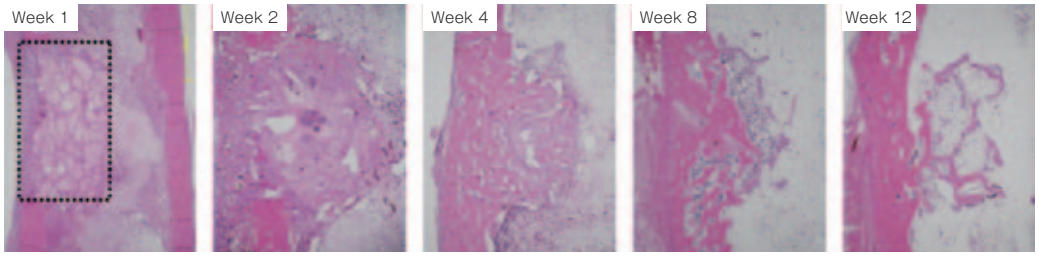
Elasticity never seem before facilitates the handling during surgery

Sponge-like texture with elasticity! Can be cut with a scalpel and integrates quickly with the surrounding bone

The artificial bone developed **is created by mixing collagen with thin crystals of hydroxyapatite at a ratio of 4:1, the ratio identical to the live bone, and made into fiber form, resulting in a sponge-like texture**. This enables the material to be readily absorbed by the body, and the conjugated fiber with collagen created elasticity that was not observed in conventional artificial bones. As a result, the artificial bone can be processed easily with scalpels and scissors during surgery, and even if the area of bone defect has a complex shape, the artificial bone itself changes shape to fill the area easily and with certainty.

Does this sponge-textured artificial bone function as intended in living bodies? Studies in animals were conducted to confirm the efficacy of the product. A defect at the diameter of 5 mm was created in the shin bone of rabbits, then the artificial bone at 5 mm in diameter and 3 mm in thickness was implanted into this defect, and the condition was observed up to 12 weeks. As a result, the developed artificial bone entered the bone metabolism cycle of the body, and was observed to simultaneously undergo both bone formation around and inside the artificial bone due to osteoblasts and **resorption of artificial bone due to osteoclasts, and eventually replaced by autologous bones**. The final results showed **complete recovery in 60% or more of the cases at 24 weeks after surgery**, and the artificial bones in the remaining cases had almost integrated to the surrounding bones. No notable safety problems were observed.

Result of efficacy confirmation study



The area shown with broken lines to the left is the area of artificial bone compensation. The artificial bone is resorbed with the passage of time and integrated with the surrounding bones, resulting in replacement by healthy bone by Week 12.

Actual use in human

Preoperative | Postoperative | 12 weeks postoperative | 24 weeks postoperative | 3 years postoperative

The area of the bone tumor lesion in the left fifth toe (shown with a circle) was surgically replaced with the new artificial bone. As a result, the artificial bone integrated with the surrounding bone and reduced the bone deformation caused by tumor.

Expectation for wide use in regenerative medicine and expansion of market

Because of reasons, such as the revision of Pharmaceutical Affairs Law during the clinical experiments, 10 years were spent in developing this material as a product. This **artificial bone gained market approval for medical devices in June 2012 under the proprietary name Refit and was covered by insurance since January 2013**. Currently, the use of the product in surgery has commenced in some medical institutions.

This artificial bone that had overcome the problems associated with conventional products is not only expected to substitute for the products but **also for use in a wide range of areas including regenerative medicine**. The scale of Japanese market for artificial bones used in bone transplant treatment is said to be 10 billion yen, however the **more widespread use of this new artificial bone is expected to increase the percentage of use, thereby accelerating the growth of the market**.

From medical devices to household items

MPC polymer; harmless to the human body

NOF Corporation /
Nobuo Nakabayashi (Emeritus Professor, Tokyo Medical and Dental University) /
Kazuhiko Ishihara (Professor, The University of Tokyo)

Development of Creative Technology Seeds, Contract Development
"Manufacturing technology of polymer with phospholipid polar group" Developing and implementing company/Representative Researcher (1994-1999)

Kyocera Medical Corporation (formerly Japan Medical Materials Corporation) /
Kozo Nakamura (President of National Rehabilitation Center for Persons with Disabilities) /
Kazuhiko Ishihara (Professor, The University of Tokyo)

Development of Creative Technology Seeds, Contract Development
"Long-life Artificial hip joint with high endurance by MPC treatment" Developing and implementing company/Representative Researcher (2006-2011)

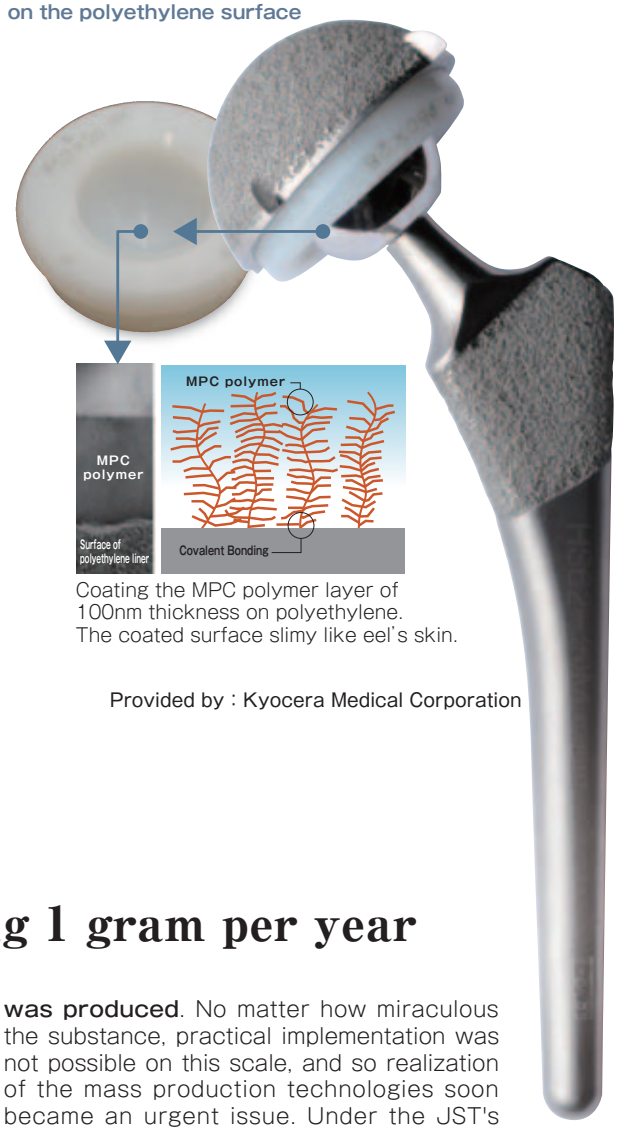
MPC polymers are changing medical science

Most people are aware of the word 'polymer,' but few are able to answer correctly when asked what a polymer is. In terms of items in daily use, the highly moisture-absorbent polymers used in paper diapers and bed sheets etc. and automotive polymer coatings are probably the best known. Although these both bear the name 'polymer,' their uses are completely different; ' polymer' is a chemical term referring generally to a molecular organic compound, and many types exist.

One such polymer plays an important role on the front line of medical treatment. This is MPC polymer (a polymer possessing phospholipid polar groups), which was the subject of long years of joint research by Emeritus Professor Nobuo Nakabayashi and Professor Kazuhiko Ishihara.

One major problem with the silicon and polyethylene used to manufacture medical tubes and catheters is that often when introduced into the human body, the body rejects it as foreign matter, causing rejection responses such as blood clotting etc. This problem has been solved by MPC polymer. **MPC polymer contains phospholipids, which constitute a major component of biological membranes (cell membranes); thus, simply coating silicon or polyethylene with MPC polymer makes it extremely difficult for proteins or blood cells to adhere.**

Artificial hip joint which formed the MPC polymer layer on the polyethylene surface



Coating the MPC polymer layer of 100nm thickness on polyethylene. The coated surface slimy like eel's skin.

Provided by : Kyocera Medical Corporation

The challenge from producing 1 gram per year

Before the development of MPC polymer, artificial blood vessels were between 10 mm and 20 mm in thickness. However, using MPC polymer, blood vessels can be made as small as 2 mm thick without obstructing blood flow. In this way, MPC polymer has brought a groundbreaking new innovation to the front line of medical treatment. However, synthesizing the polymer was extremely difficult; **in 1978, when the compound was initially synthesized, less than 1 gram per year was produced**. No matter how miraculous the substance, practical implementation was not possible on this scale, and so realization of the mass production technologies soon became an urgent issue. Under the JST's Contract Development, the NOF Corporation which JST invested 800 million yen as the development expenditure proceeded the mass production development. Finally the

development was highly successful, **as a result, it has become possible to produce pure high-grade MPC polymer in large quantities these days**.

The challenge of long-life artificial hip joints

With mass production now enabled, MPC polymer is currently meeting the new challenge of another medical issue: the longevity of artificial hip joints. We may not often hear about them, but there are actually 40,000 or more artificial hip joint replacement surgeries conducted in Japan alone each year. Although the causes of joint function disorder are diverse, in all cases this surgery involves replacing hip joints that have lost their normal function with artificial hip joints. However, there is one major problem with this surgery. With the passing of time, the components wear down, due to constantly grinding against each other, which causes the artificial joint to slacken and become loose. According to overseas data, around 10-20% of those receiving artificial hip replacements in the 1970s have subsequently undergone another hip replacement surgery.

This fact drove the medical community to seek development of a material that does not wear down, in order to ensure long-term use. Eventually, it was Japan Medical Materials Corporation (JMMC) that resolved this difficult issue, by utilizing the JST's Contract Development. By coating polyethylene components with MPC polymer, **the antiwear property of articular surfaces was improved, thus JMMC succeeded in developing artificial hip joints that are expected to have a longer service life.**

Friction experiments using hip joint simulator

Further expanding the possibilities of MPC polymers

"Using biocompatible materials, I want to create a bio-interface to build a bridge between the human body and artificial materials," says Professor Ishihara. A bio-interface refers to an interface that does not trigger a rejection response between a living body and artificial materials. MPC polymer, which is currently already in use for artificial hearts etc., certainly promises to be an effective material for creating bio-interfaces in future.

In order to further promote the many uses of MPC polymer, Professor Ishihara also provides samples of MPC polymer to interested researchers around the world. He hopes that by so doing, the potential uses for MPC polymer, originally developed for medical applications, will be greatly expanded. These efforts have ensured that MPC polymer is now utilized in a diverse range of fields beyond the medical profession, including **practical implementation in contact lens care products, cosmetics materials, textile processing agents, and much more**.

With further great leaps forward expected in the fields of medicine and engineering, MPC polymer is certain to become an essential part of our daily lives in future.

MPC polymers are used widely across a range of fields

Combining the optical microscope and the mass spectrometer

Imaging Mass Microscope

Mitsutoshi Setou
(Professor, Department of Cell biology and Anatomy, Hamamatsu University School of Medicine)
Development of Advanced Measurement and Analysis Systems
System Development "Development of mass microscope" Team leader (2004-2008)

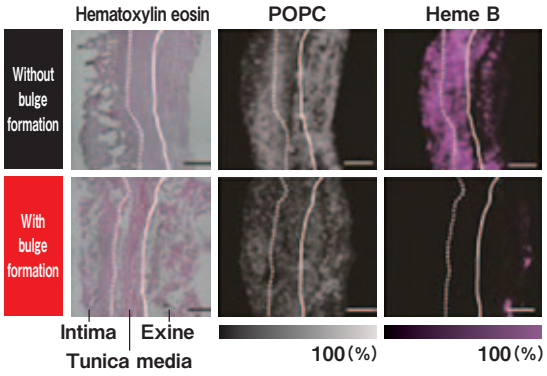
Kiyoshi Ogawa
(General manager of advanced technology development, Technology Research Laboratory, Shimadzu Corporation)
Development of Advanced Measurement and Analysis Systems
Practical Realization "Development and application of mass microscope" Team leader (2009-2011)

An innovative discovery about the pathological change of 'abdominal aortic aneurysm'

There is a disease called 'abdominal aortic aneurysm.' When someone suffers from this disease, part of the vascular wall becomes swollen and bulges in a part of their aorta that runs through their abdomen. Such a bulge is fragile and it can easily rupture. What is more, once it ruptures, it results in death from excessive bleeding in 80 percent of the patients. However, since the cause and the mechanism of the bulge formation is unknown, treatments are limited to surgical ones, such as removing lesions. No effective medical prevention or treatment method is known at this time.

In September 2012, a discovery that could lead to the breakthrough in learning how the formation of the abdominal aortic aneurysm occurs was reported from the research group of Professor Mitsutoshi Setou et al. As a result of analyzing a lesion section that had been removed through surgery, a **pathological change was confirmed; Blood vessels inside an aortic wall that formed a bulge became narrow and thus the blood volume decreased**. This indicates the possibility that vascular walls can become fragile when oxygen or nutrition does not reach them due to a decrease in blood flow inside the vascular walls.

It is the 'imaging mass microscope,' that helped derive this discovery. This microscope was created by combining an optical microscope and a mass spectrometer. This is a new measuring and analyzing apparatus developed by the group of Professor Setou and the project team of Mr. Kiyoshi Ogawa (General manager of advanced technology development) at the Shimadzu Corporation as part of the development of advanced measurement and analysis systems In April 2013, this imaging mass microscope was produced (and introduced) with the name 'iMScope.'



Left column) Pathological images by a pre-existing microscope
(Center and right column) Imaging pictures by mass microscope

As for the pathological images and POPC (distribution of lipid) images, no big difference was observed regardless of whether there was the existence of a bulge or not. On the other hand, a large amount of heme B (molecules that signify blood) existed where there was no bulge, whereas, it was rarely seen around the abdominal aorta wall where a bulge was formed.

Combination of the 'observation' of pathological tissues and the 'mass spectrometry' of molecules

According to Professor Setou, who has taken the lead in the development of mass microscopes since 2004 as a team leader of JST Development of Systems and Technologies for Advanced Measurement and Analysis, this development was based on a new concept of 'molecular biology' that was introduced in the medicine field in the 1990s. This biology explains life phenomenon from the viewpoint of molecules.

The world of medicine has been developing through systematically constructing enormous amounts of knowledge that is empirically gained, as well as with pathology that 'acknowledges patterns of lesion sections' using microscopes. In addition to these, the viewpoint that 'a human body is made from molecules' has been accepted. In other words, **a new method of 'specifying what kind of molecules make up a particular kind of tissue' is added to the pre-existing method of 'observing pathological tissues.'** In order to establish 'what kind of molecules make up a particular kind of tissue' or elucidate various types and properties of

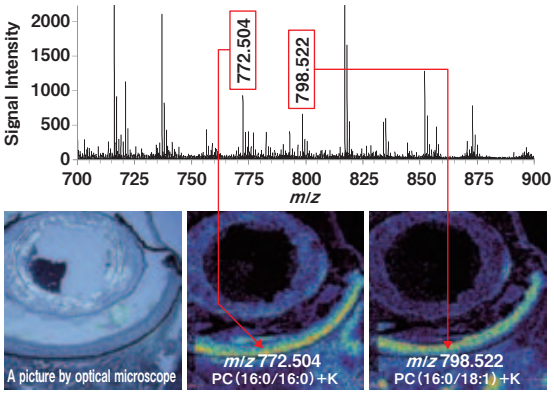
molecules included in samples, it is appropriate to use 'mass spectrometry,' which elicits the answer by measuring and analyzing the mass.

By combining this pathological 'observation' and 'mass spectrometry' that brings understanding from the viewpoint of molecular biology, this concept was born: Visualization like a map pertaining to the existence of molecules with the imaging mass microscope.

Analyzing molecules by ionization, and detecting distribution with images

In order to measure targeted molecules with the pre-existing mass spectrometry method, pre-treatments are needed; Samples should be ground down and isolated per component before analysis. If whole tissue is ground down for analysis, it is then impossible to know where the tissue originated from. That is to say, even if specific molecules accumulate at high-density on a specific section of a sample, we lose such information when we grind it down. It was difficult for researchers to perform 'image observation' and 'mass spectrometry' at the same time; They could not observe samples by leaving the molecules where they were originally located. The researchers must have been frustrated by this dilemma.

However, if a researcher uses a mass microscope using laser, it is capable of irradiating laser beams directly on an observation sample for ionizing and imaging molecules in order to analyze them. The development project adopts Matrix Assisted Laser Desorption/Ionization (MALDI) (the method which enhanced the technique developed by Mr. Koichi Tanaka at Shimadzu Corporation who won the Nobel Prize for Chemistry in 2002), **which can analyze by ionizing plural molecules with laser irradiation directly on the sample, and can even compare their distribution with one another using images. This can be called a 'molecule map.'**



Right-side two pictures show image data that indicates distribution of molecules with specific mass, or 'molecule maps.' Left-side picture is an image obtained by an optical microscope.

Increasing expectation as an analysis tool in various fields

The new measurement analysis apparatus 'iMScope' which is equipped with a high-performance optical microscope and provides pictures obtained by imaging mass analysis under atmospheric pressure has been contributing to researches especially in the field of basic medical sciences. **When it comes to the 'abdominal aortic aneurysm, the researchers discovered that blood volume had decreased where the lesion had formed. This result indicated the possibility below: Control advanced / relapsed aneurysm by improving the bloodstream. Prevent aneurysms with medicines that lessen inflammation and prevent blood vessels from being clogged.** Based on this knowledge, Hamamatsu University school of medicine has launched a clinical research for the treatment and prevention of the abdominal aortic aneurysm. Furthermore, this knowledge is now being utilized for the research and development of medical supplies, such as verification of the process of medicine metabolism and accumulation. The expectation as an innovative analysis tool is increasing in other fields like food safety, quality control of organic materials, and etc.

Imaging mass microscope 'iMScope'

Meeting the challenge of "impossible" technology

Succeeded in the practical implementation of blue light-emitting diode!

Research in the unattainable territory that won the Nobel Prize

The 2014 Nobel Physics Prize was presented to three researchers, Professor Isamu Akasaki, Professor Hiroshi Amano and Professor Shuji Nakamura for the invention of an efficient blue light-emitting diode (LED). Red LEDs and yellow-green LEDs were developed in the 1960s; however, practical implementation of blue LEDs was so difficult that it was even said that "it would be impossible to realize blue LEDs by the end of the 20th century." Amid such a circumstance, Professor Akasaki, Professor Amano and Professor Nakamura worked on the high-quality single crystallization and the p-type doping of gallium nitride (GaN), both of which had been given up by researchers around the world. Their efforts from the 1980s to the 1990s finally led to their success in the development and practical implementation of blue LED. The development of blue LED resulted in the commercialization of much brighter and energy-saving white light, thus contributing to energy conservation in the world and an improvement of people's lives in areas without sufficient electricity. In addition to their use as light sources, blue LEDs are now being widely applied in various fields such as information technology, transportation, medicine and agriculture. Additionally, the technology to put gallium nitride into practical implementation developed by the three researchers is expected to find various applications in the future, such as an application in power devices that serve as electric power converters in electric vehicles and smart grids, next-generation power distribution grids,.

Isamu Akasaki (Professor at Meijo University, Professor Emeritus and Distinguished Professor at Nagoya University)/**Toyoda Gosei Co., Ltd**

Development of Creative Technology Seeds, Contract Development

"Manufacturing technology of GaN blue light emitting diodes" Representative Researcher / Developing and implementing company (1987-1990)

Hiroshi Amano (Professor at Nagoya University)/**EL-Seed Corp.**

Development of Creative Technology Seeds, Contract Development

"Manufacturing technology for LED moth-eye structure" Representative Researcher / Developing and implementing company (2007-2010)

Commercialization of blue LEDs through by using the contract development

Many researchers withdrew from the development of blue LED one after another concluding that its realization was impossible, however, Professor Isamu Akasaki saw the possibility of its realization in gallium nitride. In 1986, Professor Akasaki used the MOVPE method (metal organic vapor phase epitaxy method) for the formation of a buffer layer such as aluminum nitride (AlN) deposited in low temperature. As a result, the layer filled the differences such as the lattice constant between a sapphire substrate and a gallium nitride. This attempt led to the creation of a high-quality single crystal of gallium nitride.

In 1987, Toyoda Gosei Co., Ltd. and Professor Akasaki decided to work together toward practical implementation of blue LEDs by utilizing the contract development provided from the Research Development Corporation of Japan (current JST). Finally, Professor Akasaki succeeded in the formulation of a p-n junction in gallium nitride, thus realizing the blue LED using gallium nitride for the first time in the world.

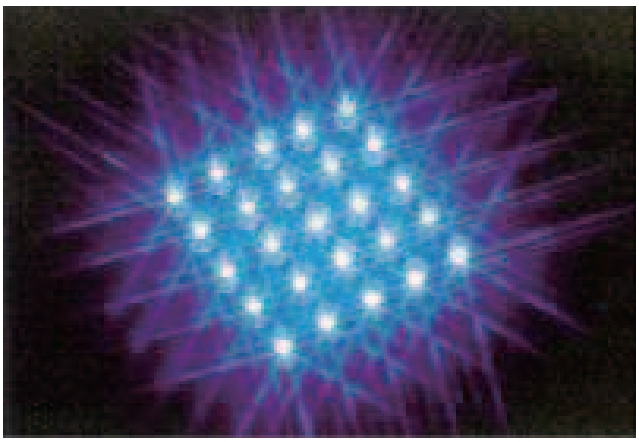
After this project was successful, the blue LEDs was commercialized. JST supported the company by providing a development cost of 550 million yen, and this business brought about an income of about 5.6 billion yen as license fee (as of 2013). Company' s enthusiasm and an effective support system, combined with outstanding technology, made the impossible possible.

LED development continues to the next generation

Hiroshi Amano was once a student of Professor Akasaki and was also involved in his blue LED research. Professor Amano is presently advancing his own LED research with the aim of improving the efficiency of LED. He is now making special efforts to enhance LED light efficiency, which is currently about 50%, to as close to 100% as possible and to develop a new yellow LED, thus spending every single day for the aim of developing the

ultimate light source that humanity could possibly create.

EL-Seed Corp. is a venture corporation that was established in 2006 by JST' s Supporting Program for Creating University-Initiated Ventures "Monolithic High-Output Color Rendered Large White LED Development." Mr. Satoshi Kamiyama, Chief Scientific Officer of the company, also used to learn from Professor Akasaki at his laboratory, being two years junior to Professor Amano. Based on Professor Amano' s research results, Mr. Kamiyama succeeded in the contract development "Manufacturing technology for LED moth-eye structure", that can greatly enhance the light output of LEDs
The LED research that started with Professor Akasaki will continue to be taken over by young researchers and produce great results.



Blue light-emitting diode

Shuji Nakamura

(Professor at the University of California, Santa Barbara)

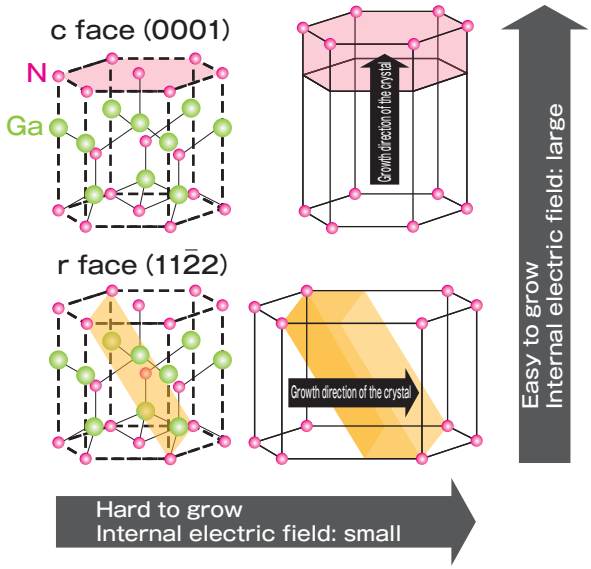
ERATO **"NAMAMURA Inhomogeneous Crystal project" Reserch Director (2001-2006)**

Further progress in the development of gallium nitride-based devices

After bright blue LEDs were put into practical use in 1993, further research and development aiming efficient and cost reducing technology were started For this goal, the ERATO "NAMAMURA Inhomogeneous Crystal project" had started and detailed research was conducted. The research group focused on "inhomogeneity," a special property of a nitride semiconductor, and attempted to improve the performance of devices by intentionally utilizing this property.

Indium gallium nitride (InGaN) used in the light-emitting layer of the conventional blue LED allows a minute electric field to be generated inside because of its structure, which was found to lead to a decrease in luminance efficiency. The realization of a blue LED with the luminous efficiency higher than that of conventional ones and a bluish-purple laser diode was achieved by making crystals grow toward the direction in which the generation of a minute electric field is less likely to occur. Additionally, utilizing an ammonothermal method, in which ammonia is used to produce crystals, opened the door to the bulk production of gallium nitride single crystals. At the same time, this project promoted the understanding of gallium nitride-based materials as the solid state physics through revealing the light-emitting mechanism of a gallium nitride blue LED, providing new guidelines for the designing of various semiconductor devices.

Growing faces of indium gallium nitride



Crystals tend to grow toward the face c (faces in pink), which allows an electric field to be generated inside. Therefore, the research group focused on the face r (faces in orange), in which electric field generated inside is small.

Triggered by the transparent oxide semiconductors IGZO-TFT

A Revolution in Flat Panel Displays

Hideo Hosono
(Professor, Materials and Structures Laboratory / Director, Materials Research Center for Element Strategy, Tokyo Institute of Technology)

ERATO "HOSONO Transparent ElectroActive Materials" Research Director (1999-2004)

SORST "Exploring and Developing Applications for Active Functions Utilizing Nanostructure Embedded in Transparent Oxides" Research Representative (2004-2010)

ACCEL "Materials Science and Application of Electrides" Research Director (2013-2018)

Breaking new ground with revolutionary new materials

Apresent, a great many PCs and televisions feature liquid crystal dis-A plays, and the world market for the TFT(Thin Film Transistor) panels used in these displays to be around 10 trillion yen. Howev-er, several problems exist with the amorphous silicon semiconductors cur-rently used as a main component in TFT liquid crystal displays. As technol-ogy continues to evolve toward more advanced functionality, the capabilities of these semiconductors will not be able to keep pace.

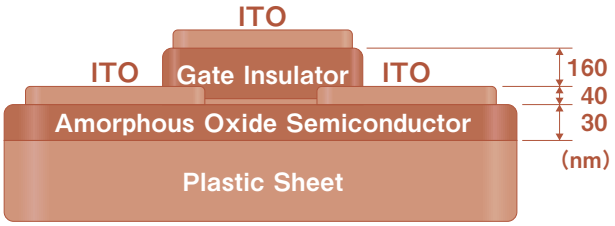
Consequently, one technology that has gained increasing attention is Transparent Amorphous Oxide Semiconductors (TAOS), developed by Professor Hideo Hosono at ERATO and SORST. One of its materials, TFT (hereinafter referred to as IGZO-TFT*), has been invented using In-Ga-Zn-O (an oxidized material consisting of indium, gallium and zinc) by Professor Hosono' s group. Development of these semiconductors has en-abled subsequent **accelerated research into their practical applications now underway by corporations both in Japan and overseas, thus taking development of TFT liquid crystal technology to a completely new level.**

In May 2011, Professor Hosono was commended for his outstanding achievement in the Jan Rajchman Prize by the Society for Information Display (SID) in recognition of his successful discovery of TAOS. More-over, he was given an honor the "Motto Lecture Award" by International Conference on Amorphous Semiconductor in 2013. Upon receiving the award, Professor Hosono commented, "It is revolutionary new materials that enable us to break new ground," emphasizing to the world the impor-tance of materials research. In 2016, Professor Hosono was recognized for his achievements in his "creation of unconventional inorganic materials with novel electronic functions based on nanostructure engineering" in the "Materials and Production" field, and was awarded the Japan Prize.

As semiconductors for next-generation TFT panels, TAOS gains worldwide attention!

TAOS have a range of advantages in comparison with conventional amorphous silicon semiconductors. Firstly, they possess electron mobility up to 50 times higher than previously possible. Conven-tional amorphous silicon semiconductors with lower electron mobility will be unable to handle the demanding requirements of future televisions, such as 3D and large screen functionality. Also, as the release of various new devices continues, the development of flexible TFT will also take on increasing sig-nificance. TAOS, which can be flexible on substrate, are particular effective in this regard. Moreover, **the TAOS thin film manufacturing process can be conducted at room temperature, which enables production at lower costs and reduced power consumption**, making it altogether a dream material that has garnered attention form companies worldwide.

Constitution of flexible thin film transistor

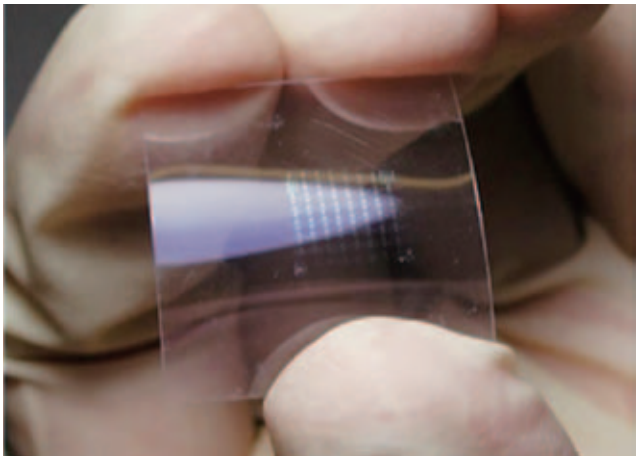


10 years after TAOS disclosed: the Professor's revenge!

"Light passes through it, but electricity will not." Until Profes-sor Hosono presented his paper on TAOS at the 16th National Amorphous Semiconductor Conference in Kobe in 1995, this was the general understanding of glass among scientists. In truth, it would be more accurate to say they had absolutely no interest in it. There was almost zero reaction to Professor Hosono's findings; even worse, some even mocked him by suggesting that the conference was no place for a glass scientist to attend.

However, Professor Hosono refused to give up. At the time, in 1995, cathode ray tubes were far more mainstream than liquid crystal technol-ogy; certainly, no-one had predicted the modern demand for liquid crys-tal that would later emerge. This was evidenced by the fact that in the 8 years following 1995, Professor Hosono's findings on TAOS were cited a scant 4 times (of which 2 were self-citations). However, the climate of the times changed dramatically, and the demand for flexible electronics skyrocketed.In 2004, Professor Hosono' s group successfully created a thin film transistor (TFT) on a plastic substrate using active layers of In-Ga-Zn-O, **capable of approximately 20 times the electron mobility than the amorphous silicon previously used for displays, as reported in the journal Nature**. (Also, crystal IGZO-TFT reported in the Science Journal in 2003) This paper was the first indication that a high performance TFT could be achieved using amorphous oxide semiconductors, and it made a major impact around the world (it has already been cited more than 2,500 times).

Moreover, in 2013, he was honored by that same conference bearing the name of one of its founders, Sir Nevil Mott, a Nobel laureate in physics. The originality of Professor Hosono was confirmed in both academic and technical aspects.



Since the thin film is manufactured onto a plastic substrate, it can be bent easily between the fingers.

Originality is the starting point of research

It is often said that apply materials research in a practical way takes at least10 years. The phrase "10 years" may roll off the tongue easily enough, but researching the same material for 10 year requires stubborn persistence. Up to this point in time, Professor Hosono has been **maintaining ongoing research into glass, iron, con-crete and all manner of mundane materials, having achieved signifi-cant results in each**.

The results that Professor Hosono has achieved so far in materials re-search have been most heavily influenced by his stance on research. In the environment of his graduate student days and even obtain employ-ment at lab, only research with a high degree of originality was ever properly recognized; thus, originality has always been Professor Hosono's starting point. In his earlier days, **Professor Hosono came to understand that original research is work that would clearly never be done if the right person was not around and recognized by the world; and that research was a isolated job, pursuing something that no-one else is doing**.

In 2012, high-precision displays driven by IGZO TFT technology were incorporated into new tablet PCs and low-energy smart phones, representing the long-awaited product launch of this technology. Then in 2014, this technology was also utilized in large-sized organic EL televisions.

*One type of TAOS. Named IGZO-TFT, formed by the initials of indium (In), gallium (Ga), zinc (Zn) and oxygen (O) used in this TFT.

Uncovering new functions hidden in as-yet unexplored materials

Spurring a New Boom in Iron-Based Superconductors !

Hideo Hosono

(Professor, Materials and Structures Laboratory / Director, Materials Research Center for Element Strategy, Tokyo Institute of Technology)

ERATO "HOSONO Transparent ElectroActive Materials" Research Director (1999-2004)

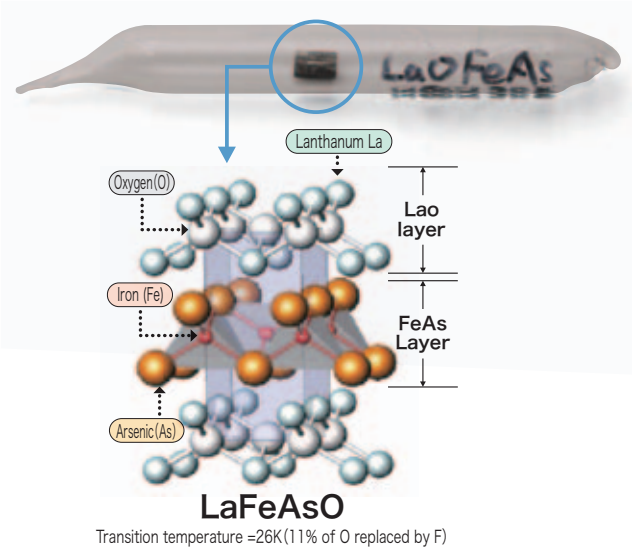
SORST "Exploring and Developing Applications for Active Functions Utilizing Nanostructure Embedded in Transparent Oxides" Research Representative (2004-2010)

ACCEL "Materials Science and Application of Electrides" Research Director (2013-2018)

A telling impact: "Thomson Reuters Citation Laureates"

Superconductivity research has always been performed using metallic materials or copper-oxide materials, but in 2008, a research paper on iron-based high-temperature superconductors published by Professor Hideo Hosono had a massive impact on the world of superconductivity. Magnetism and super-conductivity are compete, therefore, no one imagine that a substance that contains iron, which is also the symbolic element of magnetic material becomes superconducting, involved in superconductivity.

The impact of this discovery of the century can be easily judged by the fact that it **was dubbed one of "Breakthrough of the Year 2008" by Science magazine**, Additionally on September 2013, Professor Hosono was received that announced and selected the researcher of Nobel Prize class as known as "**Thomson Reuters citation Laureates.**" Accordingly, publication of this paper triggered huge research figures— nothing less than a worldwide iron-based superconductor boom— and demonstrated some exciting new possibilities for superconductors.



A serendipitous discovery overturns conventional wisdom in condensed matter physics

This amazing discovery of iron-based superconductors was actually a completely serendipitous discovery made during the course of a search for a new magnetic semiconductor at SORST. Professor Hosono, who made this discovery, had originally been conducting research on transparent semiconductors. During the research on p-type semiconductive property of lanthanum oxide copper selenide (LaCuSeO), Professor Hosono found that it possessed an extremely interesting crys-talline structure and electronic structure. Taking his p-type semicon-ductor research in a new direction, Professor Hosono started investigat-ing magnetic semiconductors possessing spin using this structure. In the course of this research, while examining the properties of lanthanum oxide iron phosphide (LaOFeP),which possess the same structure as LaCuSeO, **he serendipitously discovered the occurrence of a superconductivity phenomenon at temperatures around 4K (-269° C)**.

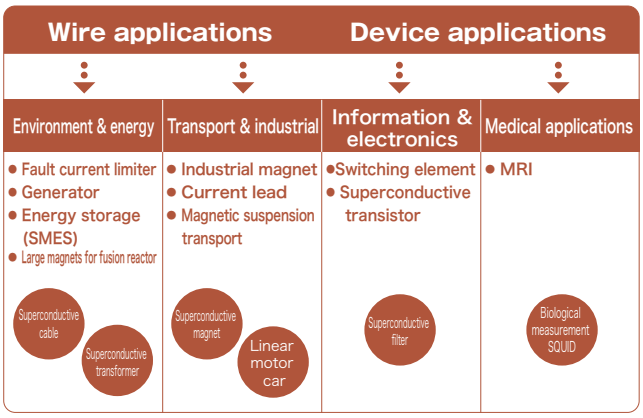
Since it was previously understood within the field of condensed matter physics that the superconductivity phenomenon does not occur in substances containing some magnetic element, conventional understanding within the field has been overturned by this discovery.

World market for the superconductor industry will be 2-3 trillion yen in 2020 !

Upon hearing the word "superconductor," many people may feel that these are something very far removed from us. But actually, superconductors are expected to have many applications in areas close to our daily lives; for example, in the fields of environment and energy, medicine, electronics, transport and industry, and more, with **the world market for superconductors expected to reach around 2-3 trillion yen in 2020**.

Thus, ongoing superconductor research holds the promise of chang-ing our daily lives in major ways. It is no exaggeration to say that su-perconductor technology will enable us to achieve the future we have dreamed of.

Superconductor applications



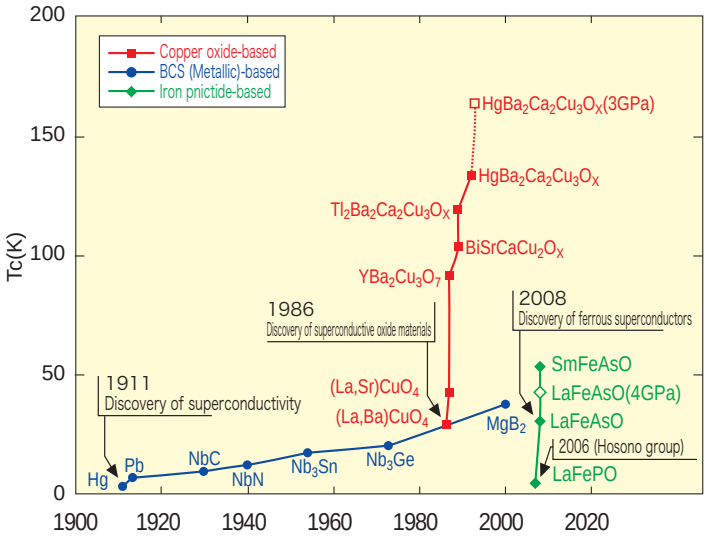
Toward a practical application of iron-based superconducting research

Discovered by Dr. Heike Kamerlingh Onnes in 1911, supercon-ductivity was long believed to be achievable only at ultra-low temperatures. However, in 1986, copper oxide materials broke the transition temperature barrier of 100K (− 173° C), and there was much excitement that a superconductive body capable of functioning at room temperature might exist. However, the subsequent 20 years passed without any great change, and it seemed that the possibilities of metallic-based and copper oxide–based superconductive materials had reached a plateau.

The announcement in 2008 that Professor Hosono had discovered iron-based superconductive materials, since then many researchers explore new super conductor mate-rials.

Although Iron-based superconductor transition tempera-ture announced that 50K has not been updated since 2008, a basic research of a application of wire rod showing the rapid progress. A wire rod is made by Iron-based super-conductor powder into a tube is easy method and critical current density became increase more than one-digit the last year of half, also it became more close in a value to a currently in a practical use Iron-based wire rod.

At present, among Japan (National Institute for Materials Science) , The United States (University of Florida) and China(Chinese Academy of Science) are competing the best record. Thus, Professor Hosono pioneer an Iron-based superconductor research launch into a new development round.



Control magnets by electricity!

Multiferroics Research

Yoshinori Tokura
(Professor, School of Engineering, The University of Tokyo)
ERATO
"TOKURA Spin Superstructure Project" Research Director (2001-2006)
ERATO
"TOKURA Multiferroics Project" Research Director (2006-2011)

Like magnets brought about the use of electricity, they having the potential to totally change the life of mankind

One day, while a shepherd named Magnes was herding his sheep, the iron tip of his staff and the nails in his sandals suddenly became firmly stuck to a large black rock—. This is a legend accounting for the discovery of magnets recorded about two thousand years ago by Pliny of ancient Rome in his book, Natural History. Mankind became intrigued by the mysterious properties of stone called a magnet, which is magnetism, and began to study it. Before long, magnetism became connected with electricity, which led to the development of 'electromagnetism' , as a result of which we came to be able to generate electricity of our own and use it. Magnetism is now used in hard disks or memories in computers.

Now, materials that have unique properties comparable to those of a magnet, which changed the history of mankind, and thus have the potential of greatly changing our lives have suddenly entered into the spotlight. Professor Yoshinori Tokura is taking the lead in advancing the research of 'multiferroics,' which are not materials found in nature by someone like Magnes, but materials produced by humans for themselves by utilizing the results of electromagnetism.

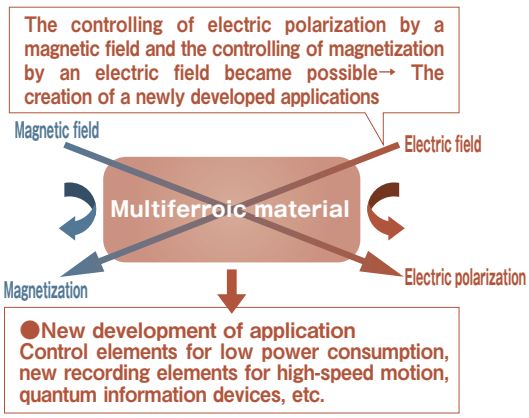
The practical application had not been achieved more than one hundred years after the "prediction" by Curie

Multiferroics are defined as materials that have the two properties of ferromagnetism and ferroelectricity. Electron behavior plays a key role.

An electron rotates itself or spins and thereby exhibits a magnetic property, thus becoming a kind of small magnet, so to speak. However, many of the materials do not exhibit a magnetic property as a whole. Since spin directions of a myriad of electrons in such materials vary, electrons cancel out each other' s magnetic property. Still, there is a material in which spin directions are aligned and thereby can exhibit a strong magnetic property as a whole. This is a magnet. Such phenomenon is called magnetization, **and the direction of the magnetization of a magnet-like ferromagnetic material can be controlled by applying a magnetic field from outside**.

On the other hand, an electron is also negatively charged. However, many of the materials are balanced as a whole, thus not being electrically-charged. Still, some materials are found to be electrically charged; one part is more negatively charged and the other side is more positively charged. This phenomenon is called electric polarization, in which the property called a dielectricity is exhibited, and **the direction of electric polarization in a ferroelectric can be controlled by applying an electric field from outside**.

Conceptual scheme of magnetoelectric effect



Magnetization and electric polarization were understood to be separate phenomena and materials having both ferromagnetism and ferroelectricity had not been identified. However, at the end of the 19th century, Pierre Curie **predicted the existence of a material that exhibits a 'magnetoelectric effect,' in which electric polarization occurs when a magnetic**

field is applied to it, and when an electric field is applied, magnetization occurs. As predicted, in the 1960s, materials that have both ferromagnetism and ferroelectricity and thus exhibit magnetoelectric effect were discovered, and the remarkably great extraordinary electromagnetic-force effect was named 'multiferroics' . If a great magnetoelectric effect is realized, it becomes theoretically possible to create an efficient and innovative electric magnet whose magnetic force can be turned on and off by using electricity like when you use a switch, without taking the trouble to wind a coil around an iron core. However, the magnetoelectric effects exhibited by the materials discovered at that time were so weak that time passed without that discovery leading to an application.

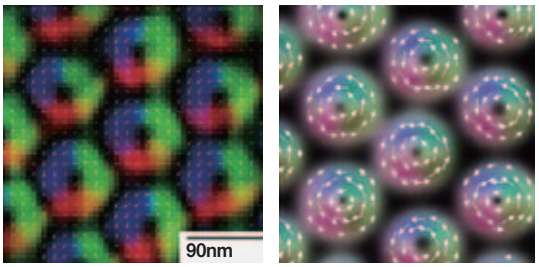
Succeeding in the creation of innovative materials whose *1electric permittivity can be magnified several hundred times when a magnetic field is applied

What drastically changed that situation was the ERATO 'TOKURA Spin Superstructure Project,' which started in 2001. With the emergence of high temperature superconducting materials*2, study on 'strongly-correlated electron systems' (the materials in which interactions working between electrons are remarkably strong), which were structural features of such materials, started to be advanced.

It was during that time that Professor Tokura succeeded in theoretically designing the spatial arrangement of electron spin and created a variety of strongly correlated electron systems, including an electronic-type high temperature superconductor.

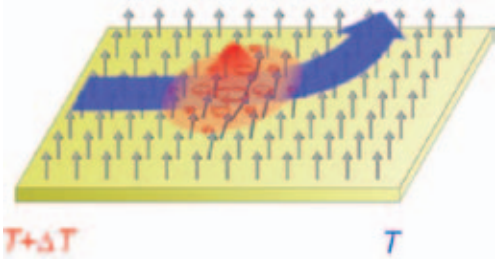
Professor Tokura engaged in a project aiming to clarify the properties of the strongly correlated electron systems and to develop their manufacturing method, in addition to creating new strongly correlated electron systems. In this project, Professor Tokura also worked on the creation of multiferroics, which had been an unresolved proposition over the years in electromagnetism. Finally, Professor Tokura **succeeded in the creation of materials in which electric permittivity suddenly becomes several hundred times greater by application of magnetic field**. The realization of a significant magnetoelectric effect, which is sufficiently brought into practical use, surprised the world.

After the ERATO TOKURA multiferroics Project started in 2006, the research proceeded at an accelerated pace. Professor Tokura discovered multiferroics in universal and versatile material systems, such as ferrite and perovskites, and succeeded in their modelization and theorization. Then, he succeeded in the observation and visualization of a skyrmion crystal, which is a helical structure of a spin formed in a material. It is thought that this helical structure produces significant physical interaction in the relationship between electricity and magnetism. Also, Professor Tokura successfully observed the topological Hall effect resulting from the rotational movement of electrons caused by a huge virtual magnetic field brought about by the skyrmion crystal. In addition, Professor Tokura successfully made an experimental observation of the magnon Hall effect, in which the traveling direction of magnon, which is a spin wave in magnetic material that is represented as particles, curved from the effect of magnetism. Furthermore, **other new discoveries associated with the correlation between electricity and magnetism in solids** were brought about one after another.



Two-dimensional skyrmion crystal obtained by Lorentz electron microscopy (left) and two-dimensional skyrmion crystallogram obtained by Monte Carlo simulation (right)

Conceptual scheme of magnon Hall effect



Opening of a door leading to the new scientific field of new science quantum science on strong correlation and its application

September 2014, **Professor Yoshinori Tokura was selected as one of the 27 'Thomson Reuters Citation Laureates'**, who are leading researchers selected by the Thomson Reuters Corporation for their achievements based on the data on the number of citations made over the past twenty years. Professor Tokura won his second award following his first Citation Laureates of 2002 in a different category.

The creation of multiferroics is receiving a great deal of attention, which is because their creation has led to the opening of a door leading to quantum science on strong correlation more than simply bringing about the creation of new materials. Like the discovery of magnets that led to the use of electricity, the great fruitage awaiting us beyond the door will surely change the history of mankind.

This research advanced by the ERATO Project was being promoted by the FIRST Project (Funding Program for World-Leading Innovative R&D on Science and Technology), and now it is promoted for the purpose of contributing to the establishment of a sustainable society through the realization of the ultimate functions of ultra-low power consumption electronics, ultra-low-loss energy transportation, and ultra-high efficiency energy conversion by conducting further research in the future.

*1 Electric permittivity is a coefficient that shows a relation between an electric charge and the power generated by the electric charge in a material, and each material has its specific coefficient value.

*2 The material showing the characteristics of superconductivity when the temperature is around 77K (-196℃) or higher than it in the superconductive materials (on page 13).

Increase the capacity of hard disk

Tunnel magnetoresistance (TMR)

Shinji Yuasa (Director, Spintronics Research Center, The National Institute of Advanced Industrial Science and Technology)

PRESTO Nanostructure and Material Property "Development of single-crystal TMR Devices for High-Density Magnetoresistive Random Access Memory" Researcher (2002-2006)

SORST "Development of high-performance MgO-based magnetic tunnel junction devices and their application to next-generation MRAM" Research representative (2006)

CREST Research of Innovative Material and Process for Creation of Next-generation Electronics Devices "Development of metal/oxide hybrid devices by novel deposition processes" Research Director (2009-2015)

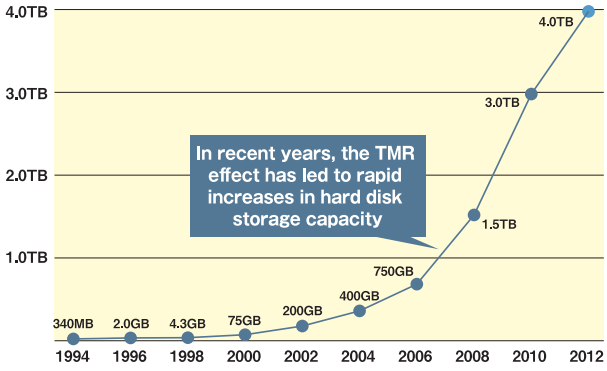
A prodigious invention with a worldwide 98.4% share!

In recent years, hard disk capacity has continued to increase rapidly, with 4TB hard disks generally available for sale in 2012.

If we consider that the largest hard disk on sale in 2000 was 75GB, we can see that storage capacity expanded nearly by a factor of 50 over this 12-year period.

The (giant) tunnel magnetoresistance (TMR) element, which was developed by Mr. Shinji Yuasa and his team at PRESTO and SORST, has been playing an important role in the achievement of this dramatic progress. It is no exaggeration to state that without this research, current large-capacity hard disks would not have been possible. In fact, **since around 2007, the number of commercially available large-capacity hard disks making practical use of TMR elements has skyrocketed.**

Changes in storage capacity of commercially available hard disks



A trump card for increasing hard disk capacity : advanced magnetic heads

One of the most significant technologies for large-capacity hard disks was the development of magnetic heads. These were an essential technology for increasing memory capacity without changing the physical size of the hard disk itself by enabling the writing and reading of recorded information at ultra high densities. The magnetoresistance effect[*1] is a physical phenomenon that magnetic heads use when reading information.

It can be argued that the evolution of magnetic heads represents the evolution of the magnetoresistance element. Each consecutive development of elements incorporating this new magnetoresistance effect has smashed the data storage barrier for hard disks.

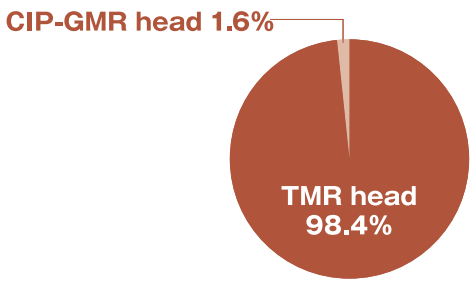
Internal structure of a hard disk

The TMR effect makes huge evolutionary leaps with support from JST

With the discovery of giant magnetoresistance (GMR) in 1988 by German researcher Peter Grünberg and French researcher Albert Fert, the magnetoresistance effect suddenly gained a great deal of attention. Subsequently, a magnetoresistance ratio (MR)*2 of 18% at room temperature an amazingly high value at the time was recorded in experiments in 1995 by Professor Terunobu Miyazaki of Tohoku
University, which further galvanized research in this area.

During the intense international competition **in 2004 Shinji Yuasa' s team was able to achieve a massive MR ratio of 230% at room temperature by using magnesium oxide (MgO): a phenomenon that he named TMR effect**. This far exceeded any previous values, and greatly changed the future of the large-capacity hard disk drive. In fact, this principle saw practical application in 2007 a scant 3 years after Professor Yuasa' s publication with this technology utilized in 98.4% of the 530 million hard disk units shipped around the world in the following year (2008).

Breakdown of magnetic head disks by material (2008)
Fuji Chimera Research Institute estimate



Only a few low-end models still use CIP-GMR. TMR is expected to reach almost 100% usage in future.

Anticipated role as key element in high-performance non-volatile MRAM memory

Hard disks are not the only media used for computer memory. There is also flash memory, best known as USB memory and SSD, as well as semiconductor memory such as DRAM, which is used as a temporary memory device inside computers. Just as with hard disks, global development of these technologies is also fiercely competitive.

Widely anticipated as the next generation of semiconductor memory is magnetoresistive random-access memory (MRAM). **As the name indicates, MRAM makes use of the magnetoresistance effect, utilizing an internal TMR element**. MRAM has some major advantages: it reads and writes data extremely quickly, and is capable of preserving stored memory even without a power supply (i.e. is non-volatile). In future, **the adoption of MRAM is expected to significantly reduce standby power consumption for computers, and to develop new memory that transcends the overwriting frequency constraints of flash memory**.

The giant TMR element developed by Professor Yuasa' s team brought about the aforementioned significant impact upon the hard disk market; moreover, it holds the promise of similar potential in the future. Not only contributing to our present-day technology, but also effective in developing the technologies of the future: this is TMR effect research.

State-of-the-art single-crystal TMR manufacturing facility

*1: The phenomenon whereby the electrical resistance of a material changes with magnetic fields.
*2: For elements using the magnetoresistance effect, the ratio between maximum resistance value and minimum resistance value when changing with the presence of magnetic fields.

Verification of the theory of relativity to the estimation of underground resources

Optical lattice clock changes our concept of time

Hidetoshi Katori
(Professor, University of Tokyo/Senior Research Engineer, RIKEN)
ERATO
"KATORI Innovative Space-Time Project" Research Director (2010-2016)

Precision of an optical lattice clock is 1,000 times higher than the current International Atomic Time

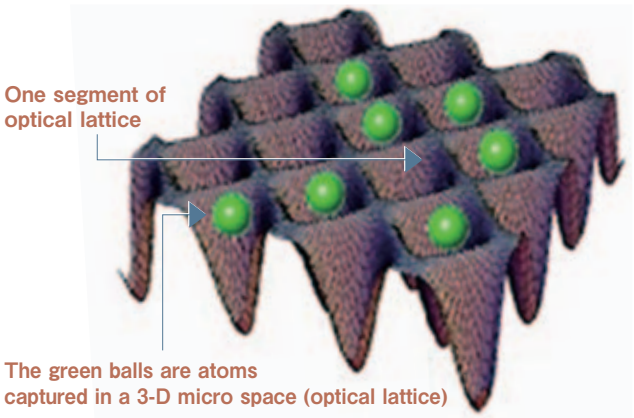
There is a clock called the "optical lattice clock." First, each atom cooled by laser is captured in a 3-D micro space (optical lattice), which is created by interference of laser beams with special wavelength called the "magic wavelength," to prevent interaction between the atoms. Next, these atoms are irradiated with another laser beams, and the frequency of the absorbed light (resonance frequency) is measured precisely to determine the length of a second. Since an optical lattice as a whole can capture approximately one million atoms, the time can be determined in a short time by measuring their resonance frequencies all at once, and then taking the average.

This optical lattice clock is a major candidate for the "definition of a second" of the next generation. The accuracy of the cesium atomic clock, which is the current universal time, has an uncertainty of 10^{-15}, or 1 second per 30 million years. Researchers across the world aim to improve this by approximately 1,000 times to achieve higher precision using the method mentioned above.

The research group led by Professor Hidetoshi Katori, an inventor of the optical lattice clock, developed the two optical lattice clocks, which perform the high-precision spectroscopy of strontium atoms under a low temperature environment through the research process of ERATO and proved the statistical agreement at a fractional uncertainty of 2×10^{-18} between those two clocks in May 2014. This research group newly developed the optical lattice clock based on mercury atoms and directly compared it with a low temperature operation strontium-based optical lattice clock, which has the world's best accuracy, in March 2015. The frequency ratio of mercury and strontium was obtained in a high accuracy significantly better than the second currently defined as unit of time. This achievement may accelerate the movement toward the future redefinition of a second.

In June 2014, the research group also has succeeded in high-precision spectroscopy of strontium atoms in a hollow optical fiber. This is a significant achievement that will be a new foundation technology toward downsizing the quantum measurement instrument. Their goal for the future is to develop the optical lattice clock in a small size.

Pattern diagram of optical lattice



Create an optical lattice in a hollow fiber to confine strontium atoms

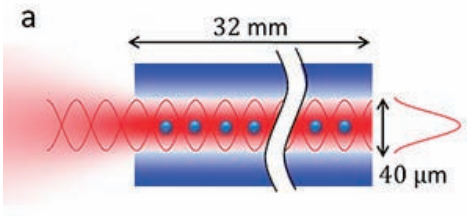
The research group, which has been advancing technological development of downsizing the optical lattice clock, focused their attention on a hollow core photonic crystal fiber (hereinafter referred to as "hollow core fiber"). **Since a hollow optical fiber can confine light and atoms in a hollow core, it was considered to be a prospective downsizing technology**.

However, in the previous expectation, because of interaction among atoms and between atoms and the hollow core fiber wall, resonance frequencies expanded to more than several MHz. Therefore, it was considered that obtaining narrow spectra close to natural linewidth was difficult in optical fibers.

The research group created an optical lattice with magic wavelength in the hollow core fiber, and captured each laser-cooled strontium atom into each segment of the lattice, in order not to broaden the linewidth of the atom's resonance spectra.

To create a high-precision optical lattice clock, there needs to be sufficient time for interrogating the clock transition. Thus, they attempted to prevent collision between strontium atoms and residual gas in the fiber. As a result of measuring the lifetime for capturing atoms in the fiber, it was confirmed that the trap lifetime was 350 to 500 milliseconds, which was sufficient to construct an optical lattice clock.

Overview of experiment apparatus



In a hollow fiber with a core diameter of 40 μm and length of 32 mm, create an optical lattice with magic wavelength (red wave line) and capture strontium atoms (blue ball). Constitute a 1-D optical lattice in the hollow core fiber. The distance between strontium atoms becomes half of the magic wavelength (approximately 0.4 μm).
A sectional view of the hollow fiber that was used. The central part is hollow.

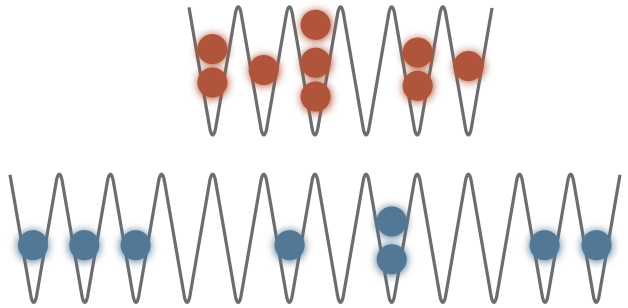
Reduce spectral linewidth to near 1/1,000

To reduce quantum noise of an atomic clock, it is important to increase the number of atoms that are observed. Since laser beam expands by diffraction in free space, atoms can be captured only in an area near its focal point. To the contrary, in a hollow core fiber, light can be transmitted without expanding its beam size inside the core. Therefore, it is possible to greatly increase the number of atoms that are captured in proportion to fiber length.

In this case, what should be considered is whether just one atom can be captured in one segment of an optical lattice to prevent interaction among atoms. Therefore, **after capturing atoms into an optical lattice and introducing them into a hollow core fiber, and the atoms are released from the optical lattice to freely expand in the hollow core fiber, then each atom is captured again. By doing so, the number of atoms in each segment of the optical lattice was reduced to one or less**. With this method, the number of atoms could be maintained, while interaction among atoms was reduced. As a result, the resonance spectrum of frequency linewidth of 7.8 kHz was obtained.

Previously, spectra of atoms and molecules measured in an optical fiber was approximately 5 MHz. However, by introducing the optical lattice with magic wavelength, the spectral linewidth was reduced to 1/1,000 than that of before. The obtained spectral linewidth is close to the atomic natural linewidth, and no interaction with the fiber wall is observed. However, it was estimated by calculation that the influence of the interaction between atoms and the fiber wall on the precision of a clock is 10^{-17} (uncertainty of 1 second per 3 billion years). These provide a foothold for constructing a compact and high-precision optical lattice clock using the hollow core fiber.

Expand atoms in 1-D lattice



The spread of atoms in transverse direction is small immediately after introducing atoms in the fiber, and multiple atoms are captured in a segment of the lattice (the upper diagram). Interaction among atoms broaden the atomic spectrum. By capturing atoms again in the optical lattice after releasing the atoms once from the optical lattice to diffuse them, the number of atoms in each segment of the optical lattice was reduced to one or less.

Uncertainty is only 0.4 seconds per 13.8 billion years, which is the age of the universe

In an ultra precise clock, the influence of Einstein's theory of relativity, "The stronger the gravitational potential, the slower time passes," can be measured. The goal of the research group is to attain the precision of 1×10^{-18} (uncertainty of only 0.4 seconds over 13.8 billion years from the Big Bang to today, which is the age of the universe). **They can detect the differences in the passage of time (according to the general theory of relativity) that is brought by gravity with an elevation difference of only 1 cm. In addition, time delay (according to the special theory of relativity) occurring at a person's walking speed can also be detected**.

The gravitational field is powerful when there is mineral vein underneath and time will move more slowly than that of its preferential area. The achievement of a compact optical lattice clock enables the search for mineral resources underground. It is expected that development of technology aiming for the downsizing and improved portability of the optical lattice clock will continue based on this achievement.

Molecular structure analysis without crystallization on the microgram scale

Crystalline sponge can solve the 100-year-old problem !

Makoto Fujita

(Professor, School of Engineering, The University of Tokyo)

CREST Single Molecule and Atom Level Reactions "Self-organizing Molecular Systems Utilizing Transition Metals" Research Director (1997-2003)

CREST Creation of Novel Nano-material/System Synthesized by Self-organization for Medical Use "Development of Self-organizing Molecular Systems for Chemical Translation of Biological Functions" Research Director (2002-2008)

CREST Development of the foundation for nano-interface technology "Chemical study on self-assembly finite nano-interface" Research Director (2007-2013)

ACCEL "Innovative Molecular Structure Analysis based on Self-Assembly Technology" Research Director (2014-2019)

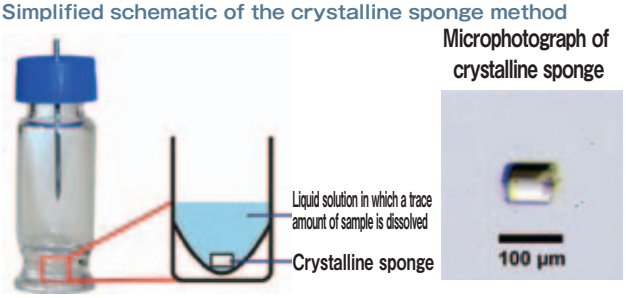
The "100-year-old problem" was finally solved !

In a crystal of material, molecules are arranged three-dimensionally in order. An "X-ray crystal structure analysis" is an analysis method for determining molecular structure by using the diffraction of an X-ray deriving from that regularity (diffraction pattern). The representative one among the methods for determining molecular structure is the "single-crystal X-ray structure analysis" that uses single crystals (crystals with a constant crystal axis) as a sample. The molecular structure you can obtain through a diffraction figure is so clear that you might feel as **if you were looking at molecules with your naked eyes**. Therefore, as a means for providing accurate and reliable structural information, this method has been widely used in various fields, ranging from basic research to industrial circles.

However, this method is under a remarkable restriction in which target samples have to be crystallized beforehand. Therefore, the single-crystal X-ray structure analysis can neither be applied to liquid compounds that originally don't have a property to crystallize nor to samples that you cannot get enough of for crystallization.

In March 2013, this problem, which had been even called the "100-year-old problem of X-ray crystal structure analysis," was finally solved. The research group, led by Professor Makoto Fujita, a Research Director of CREST, succeeded in performing the single-crystal X-ray structure analysis without crystallization by simply soaking a sample into the material, called a crystalline sponge, in a solution containing from only a few micrograms (one microgram is equal to one millionth of a gram) of the target sample.

Simplified schematic of the crystalline sponge method



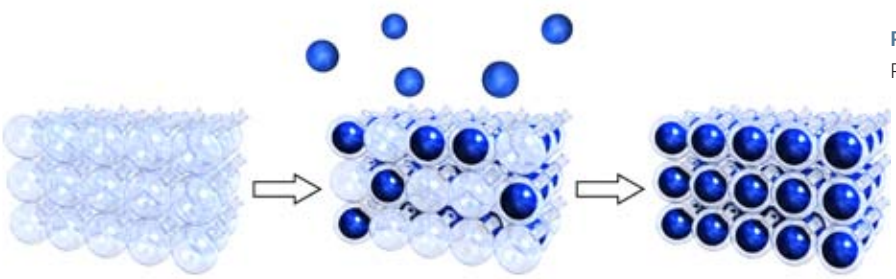
Dissolve a tiny amount of measurement sample in an appropriate solvent and pour the solution into a sample bottle containing a crystalline sponge. Allow the solvent to evaporate slowly, and the sample will become concentrated in the crystalline sponge. If you take the crystals out and conduct a normal X-ray crystal structure analysis on them, you will be able to observe the structure of the sample compound that has penetrated into the holes of the sponge as well as the framework of the sponge.

Analyzing structure with minimum amount without crystallization

A Crystal sponge consists of microporous complex crystalline material with countless holes (micropores) that have a diameter ranging from 0.5 to 1 nm (one nanometer is equal to one-billionth of a meter). The technique for storing molecules in pores has long been known; however, when a general microporous complex is used, guest molecules get packed into its holes randomly, from which you cannot obtain the periodicity that is needed for an X-ray crystal structure analysis. Therefore, by providing a microporous complex with **the "molecular-recognition faculty," which is the ability to stably capture guest molecules into an optimum positions according to the shape or properties of molecules,** his research team succeeded in arranging captured molecules in a periodic sequence. This is the principle of a crystalline sponge. Thus, it becomes possible to conduct a single-crystal X-ray structure analysis without crystallizing liquid compound at room temperature.

Moreover, **in this technique, you need only a 100 μm (micrometer; one μm is equal to one millionth of a meter) cube-sized single piece of crystalline sponge for one type of measurement sample**. The maximum

amount of molecules absorbed by this crystalline sponge is 5 μg and the minimum amount of molecules absorbed is only 80 ng (one nanogram; one ng is equal to one billionth of a gram). Surprisingly, the X-ray structure analysis makes it possible to determine the molecular structure with only such a small amount of sample.



Principle of crystalline sponge method
Pouring substrate into "crystallized space"

Breakthrough analysis technique "LC-SCD method"

Usually, many types of minor components extracted from plants and animals are separated and analyzed using a "liquid chromatography (LC)" method. When you use this method, you can isolate only less than a few micrograms of samples; therefore, it is extremely difficult to determine the molecular structure by means of the conventional technique.

With that, the research group **has established an "LC-SCD (Liquid Chromatography- Single Crystal Diffraction)" method, a revolutionary analysis technique that directly connects the LC method and the crystalline sponge method**. In this technique, a number of minor components isolated by means of the LC method are absorbed into the directly connected crystalline sponge, and then, the single-crystal X-ray structure analysis will be performed straightaway.

Meeting various needs, ranging from drug development to scientific crime investigation

As you might have noticed, the "crystalline sponge method" developed by the research group led by Professor Fujita is a technique that will exhibit a decisive power in the structural determination of minor compounds. Actually, the same group **has already succeeded in determining the structure of more than one hundred types of minor components, including natural compounds and synthetic components.**

But of course, that is only the beginning of what is to come. There are a lot of fields that call for the structural determination of minor compounds. For example, in the field of "drug development and process chemistry," the structural determination for metabolic compounds, the structural determination for the high-throughput synthesis of large amounts of samples and the impurity structural determination for the new process development and quality control, etc. need to be performed, and also, in the field of study of food science, the impurity structural determination of seasonings, processed foods and raw materials, the structural determination of natural health food lead compounds need to be performed. Actually, the needs for structural determination are increasing more and more in various fields, including the study of flagrance materials and scientific crime investigation associated with agricultural chemicals, cosmetics, and organic compounds. And without a doubt, the crystal sponge method will meet those needs and make a significant contribution in many fields.

Structural analysis was performed on the following compounds by means of the crystalline sponge method.

Absolute structural determination of natural products

Single-crystal structure of liquid crystal molecules

Structure determination of flexible carbohydrates

Selective gas adsorption and separation

Development of porous coordination polymers (PCP)

Susumu Kitagawa
(Director/Professor, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University)

ERATO
"KITAGAWA Integrated Pores Project" Research Director (2007-2014)

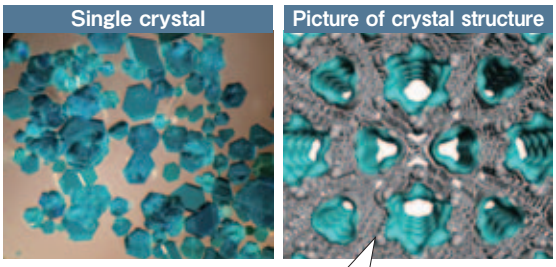
ACT-C
"Methanol Synthesis in Porous Coordination Polymers as Reaction Field" Principal Investigator (2012-)

ACCEL
"The Nanospace Science of PCP for Molecular Control" Research Director (2013-2018)

Collection of carbon dioxide generated from fossil fuel becomes possible

Gases, such as oxygen, carbon dioxide, methane, hydrogen, etc., are harder to deal with than solid substances and aqueous fluids. It is expected that **the development of technology that separates and stores gases selectively can lead to the breakthrough in various fields**. If carbon dioxide emitted from factories etc. can be captured and stored, it will greatly contribute in solving environmental problems. If hydrogen can be easily generated from water, dissemination of fuel battery would no doubt advance rapidly. The development of porous coordination polymers (PCP) by Professor Susumu Kitagawa has the potential to open the gate for such an innovation.

Porous coordination polymers (PCP)



Its structure consists of countless "holes." The portions with a gray color are frameworks and the portions with an aqua color are hole surfaces

Adsorption of gases with small molecule size - flexible designability to create various functions-

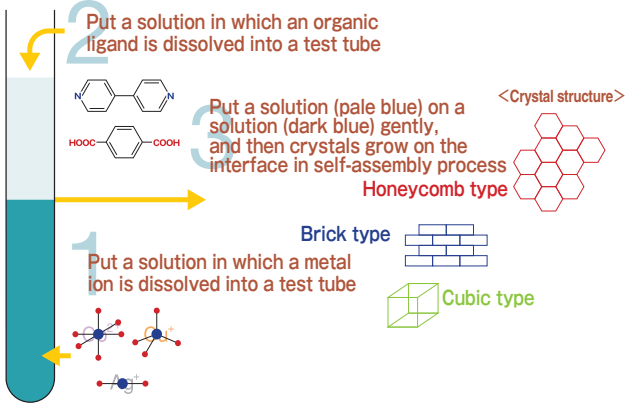
Previously, zeolite, which has a porous structure with countless "holes," was widely used as an adsorbent for gases. Since the surface area is large, it can adsorb a large amount of gas molecules. Carbon (activated carbon), which has been used as an air refresher since long before, also has this "porous" structure and adsorbs gas molecules in air which are the source of smelling. These materials are called "porous materials," and they have led to research on the adsorption of target molecules by changing their pore size.

Professor Kitagawa made a breakthrough in this situation even though he was not a researcher of porous materials. He majored in "coordination chemistry." Metal complex has the structure of bonding organic molecules (ligands) around a metal ion. **It can obtain various functions by changing the kind of metal ions and ligands. Thus, it has great potentiality as a new porous material**.

However, metal complexes including organic molecules are unstable in their structures, and they are extremely easy to break down. Professor Kitagawa was the first to demonstrate that a porous metal complex can adsorbs gases reversibly without collapse of the porous structure.

Furthermore, he achieved the production of a metal complex that changes its structure or its property in response to surrounding environments and external stimuli, which enables adsorption and desorption with high selectivity. The new material, which is named Porous Coordination Polymer (PCP), has been researched and developed for practical use across the world as an epoch-making adsorbent that **surpasses the previous limitation of conventional porous materials**.

Synthesis of PCP



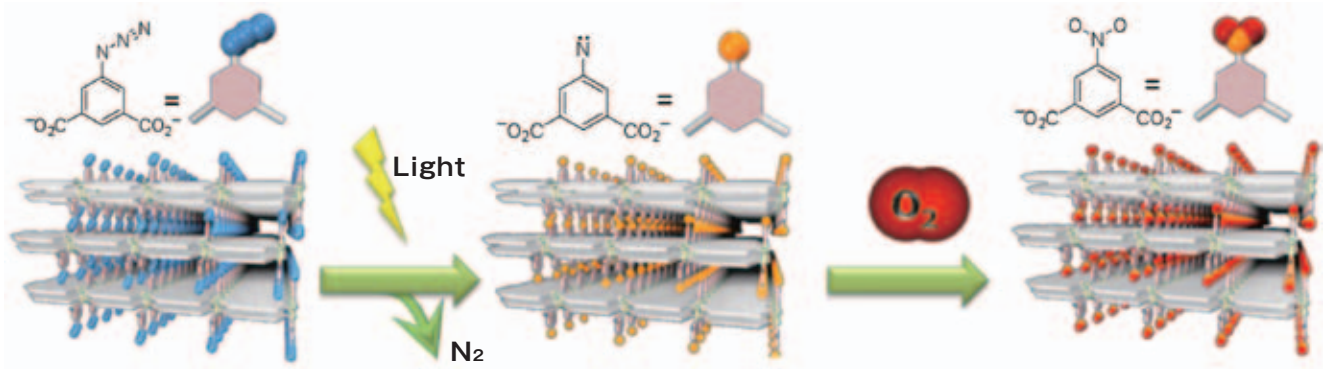
Looking into the structures and phenomena without making haste for actual use

Professor Kitagawa started ERATO "KITAGAWA Integrated Pores Project" in 2007, **and focused on bringing out new knowledge by looking into the PCP structure and property**, rather than advancing technological development that led to immediate practical realization.

He has investigated the unique property of the micropore in a PCP showing structural transformations to effectively accommodate target molecules and succeeded in controlling the strength of taking in molecules by downsizing the PCP particle size to the utmost limit. Furthermore, he paid attention to the difference in electronic properties between oxygen and nitrogen that are difficult to be separated due to the resemblance in size and shape. He then synthesized a PCP that shows a partial electron transfer between host and guest, and easily separated oxygen from the air that consists of 78% nitrogen and only 20% oxygen. He was also successful in selective adsorption oxygen, carbon monoxide, etc. by transformation of PCPs in response to the condition of pressure, light, and temperature. In addition, he is developing a PCP that discriminate super subtle difference in the structures of molecules that are taken in, and provides information with emission color.

These research achievements largely extend the potentials for practical use of PCPs, such as enhancing the selectivity of the adsorption and separation of targeted molecules, providing application for sensors, etc.

Capturing oxygen by activating PCP with irradiation



Release of nitrogen gas　　Selective trapping of oxygene

The time has come for practical realization based on the obtained knowledge

In 2013, ACCEL Research and Development Subject of "The Nanospace Science of PCP for Molecular Control" started. The aims of this research project are to further enhance separation performance, to elucidate its mechanism, and to develop its production method pertaining to the PCP of carbon monoxide adsorption that provides the highest performance of gas separation among PCPs, while advancing research. At the same time, it is also expected development of a potential use of PCP in the wide field of gas related applications such as gas separation, purification and conversion.

Although he did not majored in porous materials, Professor Kitagawa discovered the great potentials as porous materials based on his own research background in coordination chemistry, developed the new materials called PCP, sought for a new science in PCPs, and expanded the possibilities for practical use. He is attracting attention as a major candidate for the Nobel Prize in Chemistry.

Heat-release design crucial to Smartphones

High-quality graphite sheet

Susumu Yoshimura

(Visiting Professor, Nagasaki Institute of Applied Science)

Risk-Taking Fund for Technology Development

"Development of high-quality graphite manufacturing process" Team Leader (1988-1992)

ERATO

"Organic Electronic Materials Group in OGATA Fine Polymer Project" Group Leader (1981-1986)
"YOSHIMURA π-Electron Materials Project" Reserch Director (1991-1996)

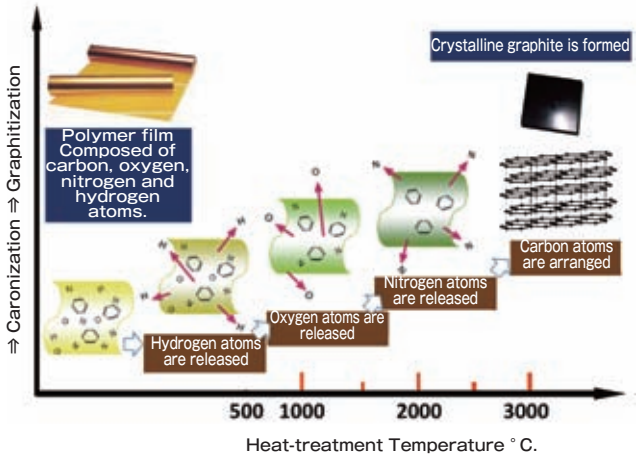
In search for innovative graphite manufacturing process

Graphite, a crystalline form of carbon, is an element mineral composed of carbon alone. Because it effectively diffract or transmit radiations such as x-rays, it is used as optical elements of radiation. Usually, natural graphite occurs in a powder form, and its crystalline form is rarely obtained. Instead, artificial graphite has been used for industrial applications. The material, however, **requires complex manufacturing processes, a considerable period of process time and is extremely expensive**. To develop a process for high-quality graphite in a less expensive way, Matsushita Electronic Components Corporation, one of the subsidiaries of Matsushita Electric Industrial, carried out the development project. Professor Susumu Yoshimura, then a researcher with Matsushita Research Institute Tokyo, headed the project team.

Prof. Yoshimura's team developed the technology for crystallizing carbon at 3000 ° C.

The key technology that enabled the breakthrough was a heat-treating process on polymeric materials containing carbon. The process was developed by the Organic Electronic Materials Group led by Prof. Yoshimura as a part of ERATO OGATA Fine Polymer Project. As polymeric materials are heated in an inactive gas atmosphere, hydrogen, oxygen and nitrogen atoms are successively released at 500°C, 1000°C, and 2000 °C, respectively, eventually leaving carbon alone. The carbonaceous material is crystallized into high-quality graphite through subsequent heat-treatment at over 3000°C temperatures. The development team investigated various polymer materials at different heat-treatment temperatures and eventually discovered that specific polymer materials (such as polyimides) **can be crystallized into graphite over 3000°C** (Figure 1). Since it can be manufactured at low cost and in a short process time, the crystalline material was put into **use in an industrial basis as optical elements**, such as neutron and x-ray monochromators.

Figure 1

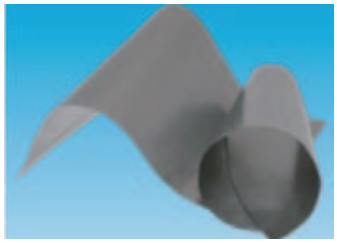


As polymeric materials are heated, hydrogen, oxygen and nitrogen atoms are successively released, eventually leaving carbon alone. The carbon is then heated at 3000°C to form crystalline graphite.

The graphite sheet is able to efficiently release the heat.

At the time when the novel manufacturing technology of graphite came into existence, **the mobile terminals including mobile phones had been rapidly gaining popularity and the devices had been underway toward miniaturization and sophistication**. Central processing units (CPUs), which drive those devices, tend to lose their performance due to the heat caused by their operation. **The challenge, therefore, was how to efficiently release the heat**. Graphite sheets provided a definitive solution to the issue (Figure 2).

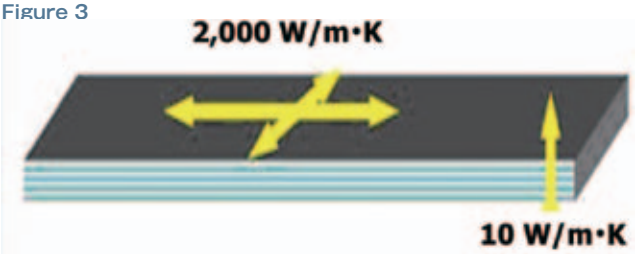
Figure 2



"Panasonic Graphite Sheet (PGS) 10μm-thick product," launched for Smartphones in September 2012.

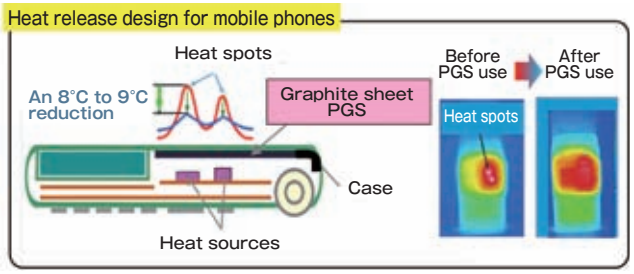
Graphite has a layered crystal structure. Its thermal conductivity is very high in the horizontal direction (when heat is transferred over a laminar plane), while it is approximately 200-fold lower in the perpendicular direction (when heat is transferred upward/downward) (Figure 3). **The graphite sheet came to be extensively used as materials that release heat once applied to devices**. It also has great flexibility and the characteristics allowed it to be used to cover heat sources with differences in level (Figure 4). In addition, it has lower specific gravity and higher strength than metal materials. The advantage also greatly contributed to miniaturization and higher durability. **As carbon crystals, graphite has extremely lower environmental burden**, which was another characteristics preferred by manufacturers. Now, the material has opened up a 100 billion-yen market globally, which is incredible as for the passive component.

Figure 3



Heat conductivity profile of graphite sheet: It has low heat conductivity in the thickness direction, while it exhibits very high heat conductivity in the surface direction.

Figure 4



Highly heat-conductive graphite sheet reduces heat spots

New carbon materials with innovative functions

Later, Prof. Yoshimura led the ERATO YOSHIMURA π -Electron Materials project as a reserch director in parallel with his continued efforts to develop new business frontiers for the high heat-conductivity graphite. The "π-electron" mentioned in the project title has an important role on characterizing properties and functions in organic materials. Prof. Yoshimura continued to work for new carbon-based materials and brought a lot of achievements, including **low-temperature synthesis of graphite thin-film and carbon nanotube**, synthesis of new intercalation compounds that contains alkali metals in graphite and their new quantum effects, development of carbon thin-film-based solar cells, development of polymerization-induced epitaxy process using graphite surfaces and luminescent phenomenon occurring in silica glass containing carbon intermediates. Notably, the technology for synthesizing graphite thin-film and carbon nanotube at low temperature enabled **synthesis at 600 °C to 1000°C** using chemical vapor deposition (CVD) method. The technology opened up a way to synthesizing graphite in conventional semiconductor manufacturing processes.

His scientific achievements on the conditions and control methods applied to CVD-based low-temperature synthesis of carbon nanotube found their successors in an international collaborative work, ICORP Nanotubulite Project, led by Prof. Sumio Iijima, Meijyo University. The project served as **seed bed for a new material, "carbon nanohorn." Works have been underway to use the material as an electrode material of fuel cells**. The technology will reportedly be coming out **soon in practical use**. Prof. Yoshimura' s achievements in ERATO are bearing fruit across different disciplines.

Versatile and economic polymerization method

Practical application of innovative, advanced color materials

Dainichiseika Color & Chemicals Mfg. Co., Ltd.

Atsushi Goto (Associate professor at Nanyang Technological University, Singapore)

A-STEP Seeds development type

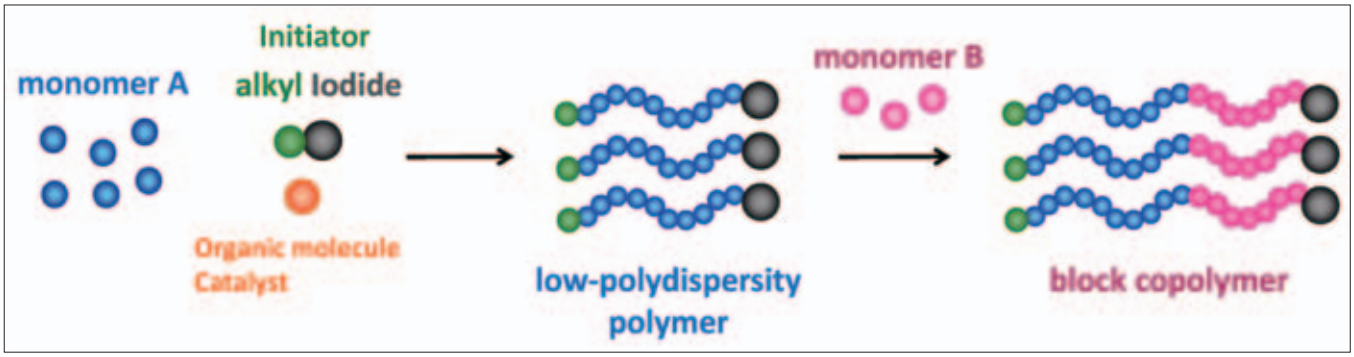
"Development of high performance color materials with advanced functions based on living radical polymerization with organic catalyst" (2011-2015)

Features of living radical polymerization

Polymerization refers to the process of connecting low molecular weight compounds (monomers) in chemical reactions to produce thread-like high molecular weight compounds (polymers). Industries often use a method called radical polymerization. However, the length of produced polymers (molecular weights*) is not uniform and the structures of polymers cannot be controlled. Living radical polymerization is a method to overcome this disadvantage. This method can offer polymers with nearly uniform molecular weights and controlled structures (structurally controlled polymers). Such structurally controlled polymers can provide advanced polymer materials which can enrich our daily lives. Living radical polymerization is thus expected to serve as a powerful method for manufacturing high-value polymer products in a wide variety of industrial applications.

Production of various functional polymers at low cost

Figure 1 Living radical polymerization with organic catalysts



Industry thus starts to use living radical polymerization. However, high cost is a significant problem among other problems. **One of the effective approaches that overcome this challenge is organocatalyzed living radical polymerization that Associate Professor Atsushi Goto (Kyoto University at that time) invented**. Figure 1 shows the concept of this method. This method can significantly cut down the production cost of such structurally controlled polymers because it uses only inexpensive organic compounds as controlling agents (catalysts and initiators). This method is applicable to various functional monomers that can afford various functions such as hydrophilicity and hydrophobicity onto the polymers. This method thus allows tailor-made design of polymers and has great **capability and versatility to industrial applications**. An example of the useful applications is block copolymer dispersants that are obtainable with this method. Such block copolymer dispersants can finely disperse small particles such as pigments in liquids and resins. Pigments are usually easy to aggregate and conventionally very difficult to disperse effectively.

Realization of practical application of innovative inventions with the cooperation of the industry, academia, and government

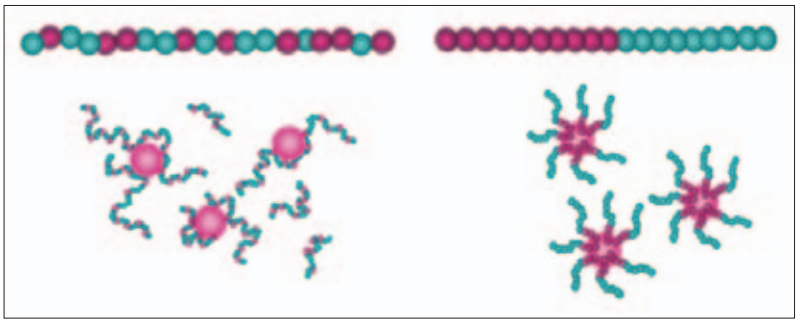
The journey to our successful commercial application of this polymerization started at a new technology briefing session of nano-materials of JST in 2008. Prof. Goto proposed **this method that he had just invented** to Dainichiseika Color & Chemicals Mfg. Co., Ltd. and a joint project among the industry, academia, and government began. Dainichiseika Color & Chemicals Mfg. Co., Ltd. **positioned this polymerization method as a core technology for developing color materials** and targeted color materials superior in the global market. They aimed to develop new advance color materials and also extend their markets to information technology (IT), environment, and energy, for example. They received a research funding of A-STEP from JST for seeking commercial applications of this polymerization to color and its related materials. In the A-STEP project, they improved the polymerization performance, installed a pilot plant in an industrial scale, developed a variety of new color and color-related materials, and eventually succeeded in commercial applications.

Successful production of high-performance dispersant (color material)

Dainichiseika Color & Chemicals Mfg. Co., Ltd. explored methods to uniformly disperse pigments in water and oil. Figure 2 shows the structures of pigment dispersants. A polymer dispersant consists of two different units. One unit can be adsorbed onto pigments (red dots in the figure) and the other unit can be dissolved in dispersive media such as water and oil (blue dots).

Conventional radical polymerization can provide only random copolymer dispersants (Figure 2, left) in which the mentioned two units (with different roles) are randomly distributed. In addition, the molecular weight is not uniform. On the other hand, our living radical polymerization method can provide block copolymer dispersants (Figure 2, right), in which the mentioned two units are separately distributed in two distinct segments. Random copolymer dispersants can attach onto pigments in a "dot-like" manner, because the pigment-attaching units (red dots) are randomly distributed in a chain. On the other hand, block copolymer dispersants can attach onto pigments in a "line-like" manner, because the pigment-attaching units form a segment. Therefore, block copolymer dispersants have strong adhesion to pigments. A similar concept is valid in the affinity to dispersive medium. Because of these two reasons, **the pigment dispersants synthesized with this technology enable more stable dispersion of pigment particles in various environments and conditions.** Along with these researches on product design, the company also installed a pilot plant suitable for this polymerization method (Figure 3). Through these researches and tests, they succeeded in the commercial production of dispersion materials in which nano-particles are finely dispersed in stable forms. Dainichiseika Color & Chemicals Mfg. Co., Ltd. is currently extending their commercial application to various color materials and other new materials.

Figure 2



An image of dispersions of dispersant with random copolymer <left> and dispersant with block copolymer<right>

Figure 3

A pilot plant for living radical polymerization method with organic catalyst

* The molecular weight is not uniform in synthetic polymer. Synthetic polymers usually have broad distribution of molecular weight.

High-speed full-automatic component analysis using supercritical fluids

Application for pesticide residue analysis and disease diagnosis

Takeshi Bamba
(Professor, Medical Institute of Bioregulation, Kyushu University)
Development of Advanced Measurement and Analysis Systems
"Development of supercritical fluid extraction–separation instrument for mass analysis" team leader (2012-2014)

The importance of sample pre-treatment technique

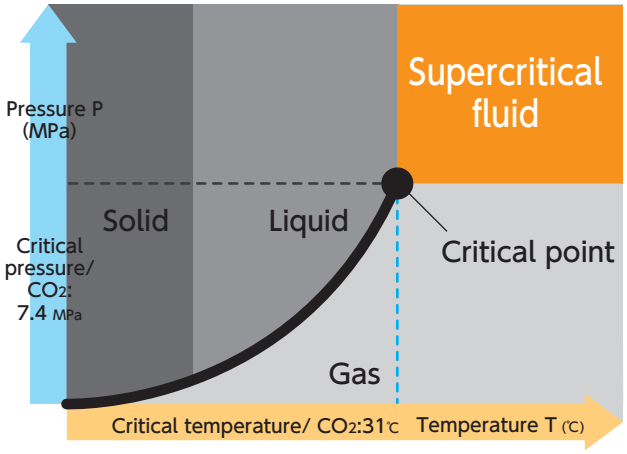
Rapid and accurate data acquisition is demanded in practical application for safety evaluation of agricultural commodities and disease diagnosis. Sample pre-treatment to extract target components serves as major challenge but indispensible in chemical analysis. Extraction and separation of target components, are tedious, required skillful operator and can produce variation in terms of recovery rate and extraction accuracy. In addition, some components are subject to oxidation or decomposition thus may require specific extraction method. The development team led by Professor Takeshi Bamba has successfully resolved this challenging issue employing supercritical fluid based instrument that allows simultaneous extraction and separation analysis. It enables rapid, accurate, and fully automated system for multicomponent analysis.

Features of SFE-SFC system

The supercritical fluid refers to any substance at a temperature and pressure beyond its critical point. It has properties such as low viscosity and high diffusivity thus suitable to dissolve substances as well as effuse effectively through solid and narrow material. By controlling temperature and pressure, the properties of supercritical fluid can be modulated to dissolve more diverse substances. **Supercritical Fluid Extraction (SFE)** is a technique applying the principle of supercritical fluid, allowing extraction of components that are not dissolved in normal temperature and pressure. It has been used to extract caffeine from coffee beans. On the other hand, **Supercritical Fluid Chromatography (SFC)** is widely applied for isomers analysis in pharmaceutical field due to its high separation performance. Professor Takeshi Bamba is SFC expert and has engaged in the research field of SFC for more than fifteen years.

Because the two techniques are based on same dissolving media, his breakthrough idea is to connect the instruments that enable full-automatic SFE-SFC system for extraction and separation of multicomponents. Furthermore, development of instrument with tight sealed interconnecting system to prevent exposure of ambient air and light facilitates component analyses that have been difficult to accomplish up to now. However, co-existence of SFE extraction and SFC separation in a single scheme is still problematic since development of switchable multi-extraction vessels and advance system of flow path are challenging thus SFE-SFC system capable of continuous analysis of multiple components has not been applied for practical use.

Figure 1 Phase diagram of carbon dioxide

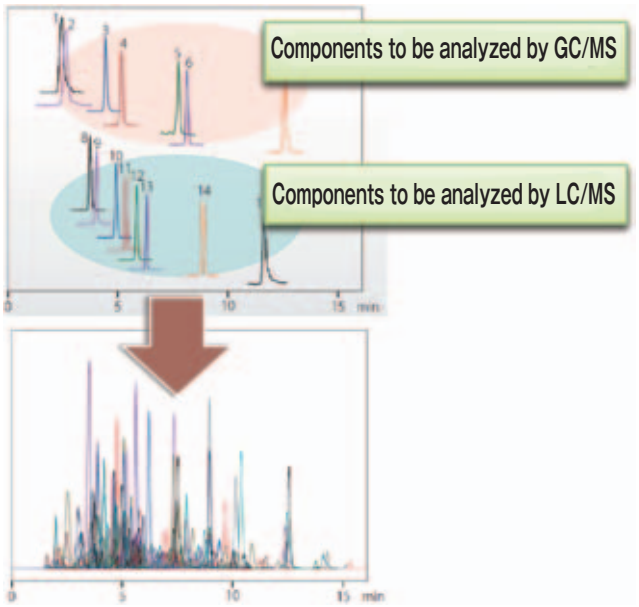


Development of simultaneous detection of 500 pesticide residues in a single analysis using SFE-SFC system

Professor Bamba had an opportunity **to be acquainted with a key-person** on the course of the SFE-SFC system development, Takashi Ando, **the director of Miyazaki agricultural research institute. Takashi Ando is a leading expert in the research of supercritical fluid extraction of analysis of pesticides**. He discovered the optimal condition of temperature and pressure for selective extraction of pesticide components. Professor Bamba and Takashi Ando established three-party project collaboration to develop SFE-SFC system with Shimadzu Corporation. The project was launched in 2012. Development of world' s first **full-automatic analysis system of SFE-SFC was successfully completed** in an extraordinary speed within two years. With effective collaborative work and strong will among the participants, the project was finalized earlier than the initial plan to produce new innovative analytical system.

This analysis system eliminated any complicated pre-treatment and solve the latent problems in the sample extraction, such as reduction of variations in the component extraction due to manual operation, improvement of analysis speed and prevention of oxidation and decomposition. For analysis of residual pesticides in foods, the pre-treatment that used to take approximately thirty-five minutes in the traditional method was shortened to just five minutes and reduce the amount of organic solvent to approximately one-tenth. Additionally, the SFE/SFC system could successfully **measure 500 pesticide components simultaneously that was conventionally achieved using multi-instruments. The applicability of SFE/SFC system was confirmed to seek blood biomarkers for early disease diagnosis** at the experiments by Masaru Yoshida, the associate professor at Kobe University School of Medicine.

Simultaneous analysis of 500 components of pesticide



Simultaneous analysis of broad range pesticide components using SFE/SFC system

Highly acclaimed analytical system in domestic and overseas

Shimadzu Corporation commercialized and launched sales of the SFE/SFC analysis system in 2015. It was received **Pittcon Editors' Gold Awards at Pittcon 2015** as the most innovative analysis product, **2015 R&D 100 Awards**, which is regarded as the "Academy Award of Technology Innovation", and the **2015 Nikkan Kogyo Shimbun' s Best 10 new product awards**. In the future, the application of SFE/SFC system is expected to expand in a number of fields including the medical and nutritional fields for early stage diagnosis of diseases and research of functional component in food and many others. In near future, development of advanced measurement technology launched from Japan has a promising prospect to create new industry.

SFE-SFC-MS system commercialized by Shimadzu Corporation (Nexera UC).

2015 Best 10 new product awards

2015 R&D 100 Awards from R&D magazine

2015 Pittcon Editors' Gold Award

Transcending the limitations of conventional X-ray imaging devices

Contributing early diagnoses with a Super X-ray

Atsushi Momose (Professor,Tohoku University)/ Konica Minolta,Inc.

Development of Advanced Measurement and Analysis Systems
Technology development (2004-2007), System development (2007-2011)
Practical Realization (2011-2013), Promotion for common use of outputs (2011-2013)
Developing an X-ray grating interferometer apparatus -Development of a diagnostic devise based on differential phase contrast by X-ray Talbot-Lau interferometry-; Team leader

Scanning soft tissue as well! Developing a revolutionary new X-ray apparatus

In conventional X-ray imaging used for bone examinations and so on, contrasting shades are obtained depending on the extent to which the object absorbs X-rays. **When examining tissues such as organs, for example, since contrasting shades cannot be sufficiently obtained with this method, X-ray photography is conducted after introducing a contrasting agent such as barium into the body; alternatively, advanced scanning technology such as the MRI must be used.** If some method could be developed to use X-rays to provide images of soft tissue, this would lighten the patient burden, and would also likely prove useful in the early detection of diseases.

For the last 20 years, Professor Atsushi Momose has been working on development of just such an X-ray imaging apparatus. In order to develop an apparatus useful for medical practice that transcends the limitations of conventional X-ray imaging devices, Professor Momose has been conducting various kinds of research.

This X-ray photography method, based on a completely new principle discovered by Prof Momose, is currently being developed for commercialization by medical equipment manufacturer Konica Minolta. **It has already been successfully used for early detection of breast cancer lesions and imaging of cartilage**, and it is expected to bring further benefits to the front line of medical practice.

Conventional method (Absorption image) | Differential phase image | Scattered image

A real radiography image of thumb took by a X-ray photography apparatus has succeeded in developing (middle: differential phase image, right: scattered image).
Tissues such as cartilage and tendons were taken by its apparatus use the traditional method.

Using slight X-ray refractions to enable the scanning of soft tissue

In 1836, the British scientist Henry Fox Talbot discovered the phenomenon known as the "Talbot effect," whereby waves of light passing through a substance with a regular structure such as a grating form self-images at specific distances. Just as with light, X-rays possess wave properties. **By applying the Talbot effect (brought to light almost 180 years previously) to X-rays**, Professor Momose believed he could realize a **new high-precision imaging technology**.

In the early 1990s, before becoming interested in the Talbot effect, Professor Momose detected X-ray refraction with an apparatus known as an X-ray interferometer using silicon crystals, thus proving that high sensitivity X-ray photography was possible. Using X-rays, this method was able to provide images of cancer tissue; however, it required a massive source of special X-rays and so was not adopted for immediate medical application. In the 2000s, Professor Momose started developing a "Talbot interferometer" using the Talbot effect, achieved by placing two gratings between the

X-ray detection device and the object scanned. With the Talbot interferometer, X-rays pass from the X-ray source through the object and then pass through the first grating. Since the speed of X-rays passing through the solid object changes, the wave' s position goes out of alignment and refraction occurs at around a ten-thousandth of 1 degree. As a result, the self-image that appears due to the Talbot effect is distorted. Subsequently, by placing a second grating corresponding to this self image, differences in the extent of X-ray penetration are created, depending on the distortion, which forms a moiré pattern that can be observed. **With analysis of this pattern, Professor Momose has successfully established a method for the imaging of soft tissue such as internal organs**.

In 2004, as part of the Development of Advanced Measurement and Analysis Systems,, development of X-ray imaging apparatus using the Talbot effect commenced.

In order to obtain the Talbot effect, it is necessary to form the X-rays into waves. In initial development, a light source capable of emitting X-ray formed in waves (a micro-focus X-ray source) was used, with practical use in hospitals expected. However, the X-rays emitted from the light source were weak and sufficiently good images could not be obtained given practical imaging times.

Prototype X-ray photography apparatus (vertical model)
(Provided by, Konica Minolta Inc.)

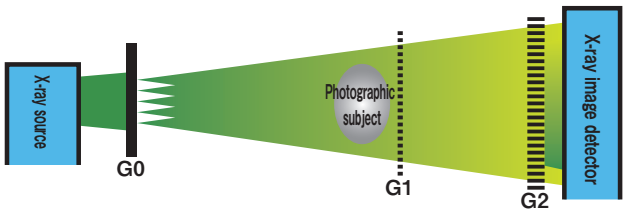
Utilizing the X-ray used in hospitals !

The X-rays used in hospitals are not formed into waves, which mean they cannot use the Talbot effect unmodified. This problem was solved by installing one more grating close to the general X-ray source. The newly added grating is designed to only allow X-rays formed into waves to pass through to the Talbot interferometer. With this solution, X-ray sources that have been successfully used in hospitals can be utilized for X-ray photography utilizing the Talbot effect; thus, the **Talbot low X-ray interferometer** was born, which also effectively cuts down photography time.

This revolutionary X-ray photography apparatus is capable of imaging of tissue with early stage breast cancer, soft cartilage and other conditions that are difficult to image with conventional methods, and it is expected to bring great results in medical practice. Furthermore, **with high spatial resolution and online testing equipment practical development of the three-dimensional imaging for the realization of the X-ray non-destructive testing for the possible precision testing equipment has begun. This device expands to use not only medical field also used for the purpose of safety and security and industrial production management such as organic materials and devices.**

Composition of X-ray Talbot-Lau interferometer

Using 2 plates (G1andG2) installed another plate close to close to light source of the X-ray Talbot-Law interferometer. It is possible to extract only x-ray coherent even the x ray-sourse used in the hospitals.



Flexible thinking brings about revolutionary results

"Researchers need to have a playful mentality. The way you use your brain when conducting research is more like arts and crafts or music than undergraduate study," says Professor Momose. **By incorporating flexible thinking with the Talbot effect, a 180-year old concept which had not been utilized in the world of X-ray technology, a new technology has been successfully created**. The revolutionary X-ray photograph apparatus developed in this way is expected to contribute greatly to the early detection of diseases.

Preventing the release of gas or water even in a high vacuum

Observing organisms in a living state with nano-suits

Takahiko Hariyama
(Professor, Department of biology, Hamamatsu University School of Medicine)
CREST
Establishment of innovative manufacturing technology based on nanoscience
"Novel Engineering of Hierarchically Structured Biomimetic Surfaces" Co-researcher (2008-2014)

A shift from the observation of "deformed and non-living organisms" to the observation of "actual living organisms"

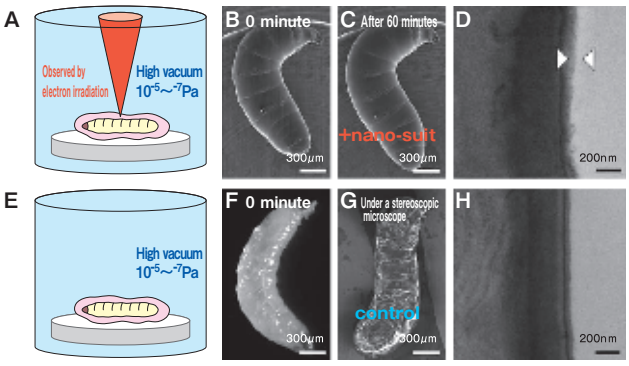
In order to observe the micro structure of the surface of an organism, it is necessary to arrange the sample in the high vacuum chamber of an electron microscope so that an electron beam can be sent to the sample easily. If you do so, however, what will happen to an organism of which water accounts for 80% of its body weight? In order to adjust to various environments, the body surface of an organism is covered with an extracellular substance (ECS: a substance formed by the accumulation of substances secreted from a cell); however, under an extreme situation like a high-vacuum state, the ECS is not able to prevent the release of gas or water. Understandably, the external structure of the organism will become significantly deformed due to volumetric shrinkage caused by dehydration, resulting in the death of the organism. Therefore, it' s still the case that when observing the micro structure of the surface of an organism with an electron microscope, researchers apply a drying treatment and surface metal coating to a "lifeless organism" after chemically fixing it, in order to keep the state of the organism as close to the living state as possible.

In April 2013, however, it became possible to observe a "living organism" with an electron microscope. The group led by Professor Takahiko Hariyama, a co-researcher of a project adopted in CREST in 2008 (chief researcher: Professor Masatsugu Shimomura at Chitose Institute of Science and Technology) succeeded in developing a **"nano-suit" (nano polymer membrane) that prevents the release of gas and liquid from an organism even in a high vacuum, thus protecting its life by irradiating a plasma or electron beam to the ECS or a thin liquid membrane mimicking it.**

A thin membrane was formed by means of an electron beam or plasma irradiation

First, the research team observed various organisms using a high-resolution scanning electron microscope (FE-SEM) and found that most of them died and their surface structure had become greatly deformed. However, **some organisms (including drosophila larvae) that have an ECS with a high viscosity in the outermost layer remained active in the microscope** (larvae A, B and C) without suffering neither shrinkage nor deformation of their micro structure. On the other hand, however, the larvae that were observed after being left to stand for one hour without receiving electron beam irradiation were found to have been squashed and dead due to dehydration (larvae E, F and G).

With that, the researchers observed the ultrathin cut section of the outermost layer of larva C with a transmission electron microscope, and found that a thin membrane with the thickness of 50 – 100 nanometers (nm: a nm is equal to one billionth of a meter) was formed (D). In contrast, a thin membrane was not found in the case of larva G (H). As a result, it was found that a thin membrane was formed on the outermost layer of the larvae by means of electron beam irradiation and this membrane was inhibiting the release of gas and liquid. The same result was also obtained in the experiment using plasma irradiation. Thus, it was confirmed that "**an ECS on the outermost layer of a larva forms a thin membrane with the thickness of 50 – 100 nanometers that can inhibit the release of internal substances under the electron beam or plasma irradiation, which brings the FE-SEM observation under high vacuum to realization.**" The research team named this thin membrane "nano-suit" (polymer membrane of nano-scale).

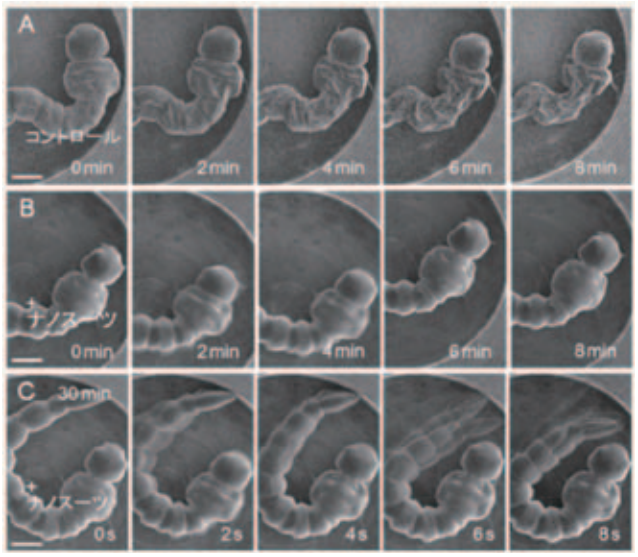


Drosophila larvae were directly put in the electron microscope and observed

Developing a nano-suit by irradiating a surfactant with plasma

The next step was the development of a "nano-suit." After analyzing the components in an ECS, the research team selected a solvent having a chemical functional group similar to that of an ECS and conducted a test on organisms that don't have an ECS to see if they would express the similar functions. What was selected was a surfactant "**Tween 20" which is designated as a food additive**. They applied this to mosquito larvae in a thin layer and then irradiated them with plasma for a few minutes (In a normal FE-SEM observation, mosquito larvae get squashed and die within a few minutes. larva A). Through the FE-SEM observation, it was found that the samples with a nano-suit were, however, staying active under a high vacuum without experiencing any morphological change (larva B). **A thin membrane with the thickness of 50 – 100 nm was formed on the outermost layer of the larva (wiggler) after the observation as in the case of the ECS of drosophila larvae**. The nano- suit created with Tween 20 was proved to be able to fulfill its function and bring the observation of microstructure of organisms in a living state to reality. The nano-suit method was developed in this way; subsequently, this method was proven be able to be performed with surfactants other than Tween 20.

The nano-suit method was applied to various organisms that are small enough to be put under an electron microscope, most of which could sustain their lives and keep active.



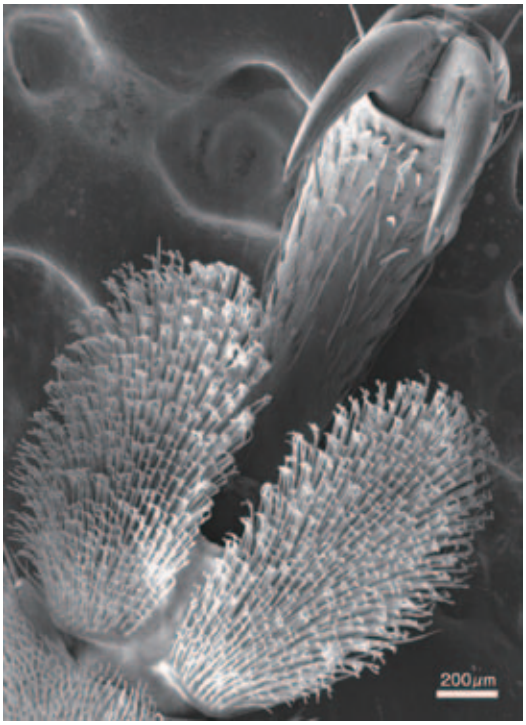
You can observe organisms covered with a nano-suit moving actively without experiencing a morphological change. C stayed active for more than 30 minutes.

From microscopic "biomimetics" to the immense world of "life science"

The "nano-suit method" developed by the research group led by Professor Hariyama has made it possible to observe the microstructure of organisms in a living state, which is sure to contribute to the advancement of research fields including **the fields of "monozukuri (manufacturing)," and especially the field of "biomimetics."** This is a technological field in which various studies are conducted with the aim of creating new materials or systems through learning and mimicking the functions and mechanisms that organisms have developed to survive in various environments. Increasing attention is paid to the development of materials that mimic the microstructure of organisms.

Some well-known areas might be studies on the super water repellency of lotus leaves, the structural color of butterfly wings and the low frictional properties of shark skin.

Meanwhile, the nano-suit method has made **it possible to directly observe the activities being done in extremely microscopic areas in small animals, cells, etc**. It is also expected that such observation will lead to understanding phenomena or behaviors relating to organisms that are not currently understood, in addition to revealing the interaction between tissues and cells. Thus, the creation of the nano-suit method will eventually lead to a contribution to the development of immense "life science" that includes biology, agriculture and medicine, etc.



High resolution photographs taken under a high vacuum state of the microstructure of the front leg of a leaf beetle to which nano-suit method was applied

Substantially reducing the number of operations in computing

Development of super high-speed algorithms

Shinichi Minato
(Professor, Graduate School of Information Science and Technology, Hokkaido University)
ERATO
"MINATO Discrete Structure Processing System Project" Research Director (2009-2014)

Super high-speed enumeration of a vast amount of combinations

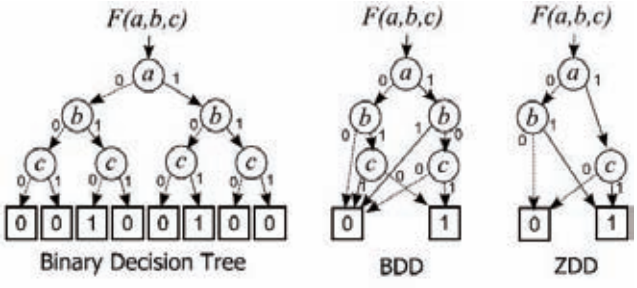
There is a unit called "mysterious" in Japan. It' s the unit of the number 10 to the power of 64. Actually, we are sometimes faced with **10 to the power of 64 alternatives in exploring the best combinatorial solution, for example, transfer in a train network, or switching an electric power distribution network**. What should be done to find the best solution by enumerating these combinations in a short time and low cost? **A key technique to this question is the "algorithm," description of the computation procedure and strategies for processing**.

Today, computers are used for processing information, including for optimization and analysis of industrial processes, marketing and bioinformatics. In recent years, **we need to process explosively growing Big Data, and the importance of algorithmic techniques has been** recognized more and more, as well as the hardware speed up. To contribute such problems, Professor Shinichi Minato, ERATO research director, has tackled the research of "discrete structure manipulation system," a state-of-the-art system for efficiently processing discrete structures (mathematical model represented by discrete symbols).

Reducing the number of operations in computing

The **basis of this study is the Zero-suppressed BDD (ZDD) devised by Professor Minato in 1993 and attracting worldwide attention** (Figure 1). Logic functions are one of the basic discrete structures. In general, a logic function can be expressed as a binary decision tree when we classify the results of the logic function for all possible patterns of the input variables. Replacing this by computer processing, the number of branches means the number of processing times. As a device to reduce the number of processing times, an algorithm using a data structure called a binary decision diagram (BDD) was contrived in the United States in 1986. The ZDD that Professor Minato devised evolves this BDD into processing of aggregated data and can **substantially compress the number of processing times in a case where, for example, an extremely small number is selected from a vast population, like selecting 10 items from 10,000 products**. Though it depends on the case, it is said that compression several tens to several hundreds of times higher than BDD can be achieved by using ZDD.

Figure 1



ZDD on the right is zero-suppressed BDD Professor Minato devised.

Succeeded in optimizing smart grid

Professor Minato et al. systematized a technique for comprehensively processing various discrete structures by developing the techniques of BDD and ZDD. They aimed at processing real cross-sector, large-scale problems, including system verification and optimization, data mining, and knowledge discovery. As one of their results, the **development of a technique called the Frontier method and its application** can be cited. The Frontier method is a technique that constructs ZDD and that enumerates all combinations that satisfy a constraint condition given in the form of a general graph structure, which has increasingly been applied to the analysis of various social infrastructures. As an example, analysis of a power network called a smart grid can be cited. They **succeeded for the first time in the world in comprehensively enumerating and indexing astronomically many combinations of switch configurations (ON/OFF) in a typical electrical power network consisting of 72 substations and 468 switches and obtaining the optimum configuration that minimizes transmission loss while meeting the given electrical power conditions**.

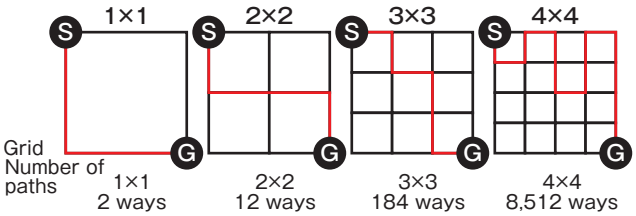
Development of software and publishing a technical guide

In ERATO, a **study of path enumeration problems (Figure 2)** of effectively counting the total number of paths between two diagonal points of an n × n grid graph without going through the same point more than once, though detouring is acceptable, was also conducted by using ZDD. **In November 2013, the total number of paths in a case of n = 26 was successfully counted for the first time in the world**. It took one week. If it were counted with a naive method, it is said that it would have taken 29 billion years even in the case of n = 11. The same problem, however, can be allegedly solved in several seconds by their algorithm.

Supplying the technique cultivated by the study in the form easy for researchers and industries to use is one of the objectives of Professor Minato. The research result of the path enumeration problem is supplied as **Graphillion, a software for super high-speed graph enumeration and indexing**. In addition, a **technical book** that describes how to use this software and summarizes the internal algorithm technique, **Super High-speed Graph Enumeration Algorithm**, was published in April 2015 (Morikita Publishing Co., Ltd.), rallying a lot of support and going through several editions. Moreover, an **electoral district allocation analysis program** based on the result of the study **was also developed**.

The result of ERATO is expected to be used widely because it **can be used in the analysis of various social infrastructures**, such as water services, gas, railroad, road, communication, and **shelter installation**, as well as smart grids and electoral district allocation.

Figure 2



The total number of paths will explosively increase as the number of grids of a graph increases. It will be 1,282,816 ways in the case of 5 × 5 and as many as 575,780,564 ways in the case of 6 × 6.

"The Art of 10^{64} -Understanding Vastness-" Time with class! Let's count!

Video produced for exhibition at the National Museum of Emerging Science and Innovation (Miraikan)

Art of 1064

Played back 1.75 million times on YouTube (as of January 2016)

Relationship Newly Developed Between Humans and Robots

Robot Technology for Improving Human-Robot Interaction

Hiroshi Ishiguro
(Professor, Department of Systems Science, Graduate School of Engineering Science, Osaka University / Visiting director and ATR fellow, Intelligent Robotics and Communication Laboratories of Advanced Telecommunications Research Institute International (ATR))

CREST
Studies on cellphone-type teleoperated androids transmitting human presence
"Creation of Human-Harmonized Information Technology for Convivial Society" Research Director (2010-2014)
ERATO
"ISHIGURO Symbiotic Human Robot Interaction Project" Research Director (2014-2019)

"Hugvie" enables users to strongly feel the presence of remote partner on a call

The lady is holding a human-shaped beaded cushion similar to the body pillow with happy face. She puts her ear on the head of the human-shaped pillow so she can hear the voice of the interaction partner in a distant location, and the partner hears the user talking. Now you know that the cushion is a human-shaped pillow phone. Hugvie is a new communication media that, **when holding it, can create a strong feeling as if the phone conversation partner in a distant location were beside the user, a feeling that cannot be attained via ordinary phones**.

Stress relieving effect by experiencing partner's presence while on a call

Hugvie was originally developed by Prof. Hiroshi Ishiguro. He has been working on the development of humanlike robots capable of successfully interacting with humans, including the humanlike androids not only in their appearance but also in their delicate movement and humanoids such as Robovie designed for natural communication with humans.

One of his study themes is creating **Geminoid (a portable teleoperated android robot) that enables users to show their presence even though they are in a distant location**. When a geminoid, which is created resembling the user, interacted with others by remote operation from a distance, it was confirmed that these people felt as if a familiar face were there and could have a natural conversation with the creature.

As a result of further study, the necessary features were carefully selected to simplify the functions. **The research showed that user could effectively feel the presence of the interaction partner when hugging or holding a simple object without humanlike fine movement or appearance while speaking to the partner**. Hugvie was developed based on this finding. It has a pocket in its head so the user can place the communication device, such as a mobile phone, inside. The user who hugs it while on a call can strongly sense the presence of the interaction partner by the simplest elements including the partner' s voice close to the ear and vibrations in synchronization with the voice tone of the partner. According to the effect evaluation, **the group who hugged the Hugvie during the conversation had lower levels of hormone cortisol in their blood, which is elevated with stress, compared to the other group who had a conversation using an ordinary cell phone**. The result showed that Hugvie was effective in relieving stress similar to what one might find in physical contact with another person.

The results obtained through the research provide new insight into the future design of communication media. The communication media, such as Hugvie, for talking in a hugging state can be effective for remote therapy by phone.

Social Conversation Robot CommU and Sota

The tabletop robot with big round eyes is talking to a fellow robot. I have joined their conversation as the robot talked to me. This could be quite weird. The name of this creation is CommU, which was inspired through the research for developing robots designed to naturally interact with people. This creature is the work of Prof. Ishiguro known from ERATO Ishiguro Symbiotic Human Robot Interaction Project and Associate Prof. Yuichiro Yoshikawa from the Graduate School of Engineering Science, Osaka University, in collaboration with a robot company Vstone.

CommU is about 30 cm in size, consisting of only the upper body. **The robot draws humans into conversation between other robots, thereby the participant feels the sense of conversation** that had been difficult to acquire. CommU is capable of demonstrating natural conversation by a natural facial expression and eye movement because of the plentiful degrees of freedom in its eyes, head, and body, which are not usually adopted to a small robot.

Sota is a robot inspired from the research results of CommU and developed by Vstone for the purpose of commercial products. It has a simple architecture whose eyes do not move and the limited degrees of freedom in physical movement. This creature was designed by a robot creator Tomotaka Takahashi.

Social Conversation Robot CommU on left and Sota on right

Toward the successful relationship between human and robot

The project group is now making effort to **exemplify the effectiveness of androids in therapy for elderly people or children with autism, as well as for the communication study and learning support**, using Erica, which was designed for natural conversation by the newly developed voice recognizer, and the baby sized android, Telenoid, which was developed by CREST. How will those robots be further developed and transformed into advanced unique creatures from now on? Are they able to provide the new insight on the future relationship between humans and robots?

▲Telenoid

◀Android Erica

Touching 3D images before our eyes

Realization of an alter-ego robot capable of transmitting haptic sensations

Susumu Tachi (Professor Emeritus, The University of Tokyo)

CREST
Advanced Media Technology for Everyday Living "Telexistence Communication Systems", Research Director (2000-2006)

CREST
Creation of Human-Harmonized Information Technology for Convivial Society "Construction and Utilization of Human-harmonized "Tangible" Information Environment", Research Director (2009-2015)

ACCEL
"Embodied Media Technology based on Haptic Primary Colors", Research Director (2014-2019)

Prevalence of 3D display and the problem its presents

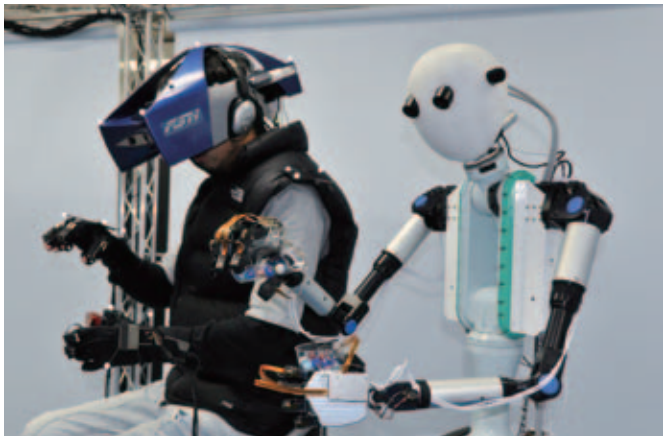
Technology only used to allow the relationship between information media and humans to involve the passive reception of audio-visual information; however, in recent years it has progressed to active audio-visual experiences via the body following the development of virtual reality (VR) and robotic technologies.

We experience full body movement and physical sensations, including cutaneous sensations, such as the sense of touch, holding, walking and running, and interaction, besides audio-visual sensations in our daily lives. Once platforms with the ability to record, transmit, and reproduce the above-mentioned sensations are developed, it would **allow us to experience and work remotely via a robot and virtual environment and would enable the creation of new haptic content**.

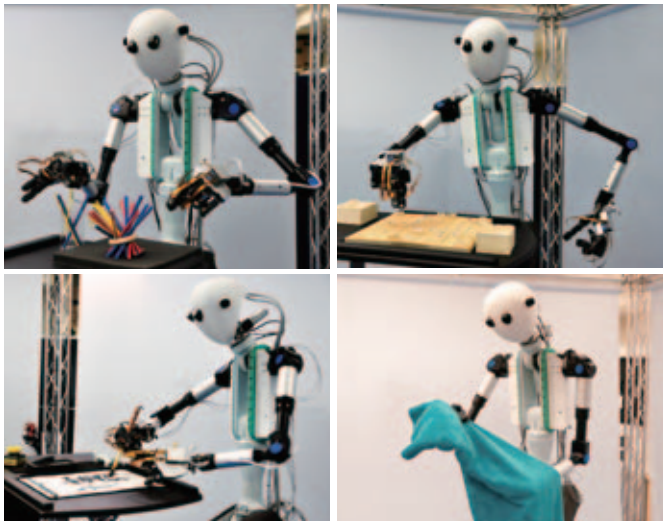
Revolutionary new media technologies, which overcame existing technical challenges, have been presented. These technologies include the telexistence system TELESAR V and HaptoMIRAGE equipped with autostereoscopic 3D display, which were developed by a research group led by Professor Susumu Tachi.

TELESAR V consists of an avatar robot that synchronizes with a human to mimic its motions and a cockpit that transmits the sense of sight, hearing, and touch. **The avatar enables a person to remotely experience interactions with others, perform manipulations of objects, and convey feelings of touch via the robot in a remote location that transmits sensations as though the other person were physically present**.

This system, known as telexistence, embodies an innovative concept that was proposed by Professor Tachi in 1980, namely interactive communication technology capable of transmitting the sense of a user' s existence as well as delivering a highly realistic experience in a remote environment without being there.



TELESAR V: The user on the left moves the robot on the right as an embodiment of him/herself. The telexistence effect is achieved by a camera and microphone that move in response to the user's movements and transmit the audio-visual information to the head-mounted-display (HMD) and headphones and also deliver the haptic sensation.



Examples of human activity using TELESAR V

Aiming for realization of the "tangible information environment"

Since 2009, Professor Susumu Tachi's team has aimed to develop a "tangible information environment" by developing a display that enables 3D content to be touched by hands to operate.

Enabling users to touch the 3D content required the 3D display to be constructed in a way such that no physical obstacles existed between the user and the 3D content. Previous methods included a glass surface between the user and the content, which prevented the content from being touched directly. As a result, the operation had to be conducted from a different location. One approach to overcoming the problem would have been to use an HMD to present the content; however, users would then be isolated from the real environment around them, which would cause alienation between the real space and the information space.

Thus, in 2010, Professor Tachi and his collaborators developed an autostereoscopic 3D display with multiple viewpoints, named "RePro3D." **This solved three of the problems associated with previous displays, namely "autostereoscopic 3D content with multiple viewpoints," "superimposing digital information in real space," and "tactile presentation in which a person can touch what they see at the exact location at which they find themselves."** This technology was augmented by a new method for presenting content, the HaptoMIRAGE, which is able to display 3D content that can be observed from within a wide area by multiple persons simultaneously.

Display example of the autostereoscopic 3D display with multiple viewpoints, "RePro3D"

Observation of natural 3D content

The HaptoMIRAGE provides an interactive experience in which real space is fused three dimensionally with the information environment; for example, a person can draw **a 3D sketch with a pen in mid-air**. It then becomes possible to project the 3D virtual object onto a real stand for interaction via the real object, that is to say, the 3D virtual object moves when the stand turns.

Enabling multiple users to observe a 3D virtual object autostereoscopically from each user's viewpoint would require a group of light beams to be provided for both of each user's eyes. These beams correspond to both binocular parallax (the perception of stereoscopic vision by content that is introduced to both the right and left eyes) and motion parallax (the perception of stereoscopic vision by changing the viewpoint according to the position of the user's head) in accordance with the user's standing position.

3D virtual drawing in real space

Introduction to the field of broadcasting, entertainment, telework, medicine, and welfare

In this way, an excellent autostereoscopic 3D display capable of projecting 3D content in mid-air was developed. This display is expected to find application in various fields, **such as in interactive exhibitions in museums, electronic signatures (digital signage) in public spaces, and entertainment systems (arcade games etc.).**

The research group has also developed the technology for the transmission of haptic sensation based on the principle of haptic primary colors that process haptic sensations as media similar to audiovisual sensations. The group has already launched a research and development project involving Embodied Media, which aims to realize virtual physical experience by integrating the above-described technologies. TELESAR V was first developed in 2012 and remains under further development. Future expectations are that anyone would be able to undertake an active role from anywhere by using their alter-ego robot via a network system irrespective of their location or time zone.

Everything around us can be a computer

Realization of a future type information environment

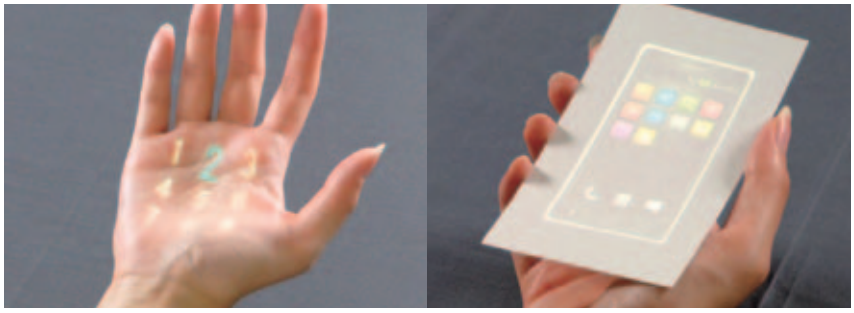
Masatoshi Ishikawa
(Professor, Graduate School of Information Science and Technology, The University of Tokyo)

CREST
Creation of Human-Harmonized Information Technology for Convivial Society "The construction of harmonized dynamic information space based on high-speed sensor technology" Principal Researcher (2009-2015)

"A palm" visual tactile display

The world is now rapidly shifting toward an advanced information oriented society due to the introduction of information communication technologies such as the Internet and smartphones. However, even though computers and smartphones have advanced and prevailed, further improvement is desired. For example, some electronic devices are not performing speedily because many functions are embedded. Plus, there is not a lot of flexibility for displays and input devices.

Therefore, the research group of Professor Masatoshi Ishikawa, principal researcher of CREST, largely changed their way of thinking regarding pre-existing computers and smartphones in order to develop a new system. **It is a system which rapidly tracks an object (a human palm, a sheet of paper, a ball, etc.) that is moving in a space without binding its movement, and it projects videos and produces tactile stimulation onto the object without delay**. If this system is used, everything around us can be transformed into a computer.

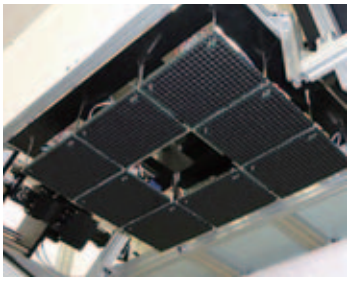


A picture displayed on moving paper (right), and a picture displayed on a moving palm (the tactile stimulation is also displayed).

Tracking objects quickly and presenting tactile stimulation

This is a new system which integrates two subsystems.

Firstly, "1ms Auto Pan/Tilt system;" It can track a moving object quickly and accurately. The research group developed this high speed image processing equipped with **"high-speed vision," which can extract a position of a moving object every 2ms (0.002 seconds), and a "high-speed gaze control device," which uses two mirrors**. By using these technologies, the direction of the mirrors can be maneuvered up and down and left and right (pan/tilt) so that the object is positioned on the center of the screen just as an autofocus device automatically focuses on its target.



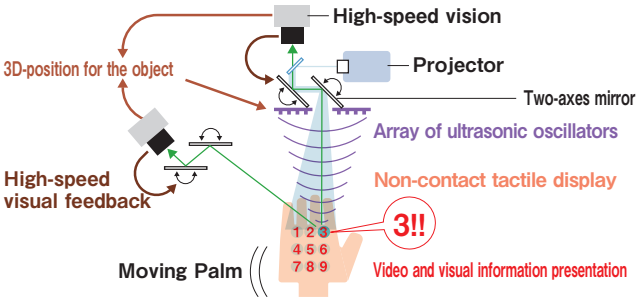
"1ms pan/Tilt system" and "Array of tactile display oscillators"

By connecting a projector in the same direction and angle as to this optical system, it becomes possible to project videos on objects that are moving at high speed. **As for the performance, it has a range of 60 degrees of pan/tilt at the most, and 40 degrees of the visual line direction change can be made in 3.5ms (0.0035 seconds)**.

On the other hand, the "non-contact tactile display" uses an array of ultrasonic wave oscillators which creates tactile sensation on an object (for example, "a palm") through radiation pressure of aerial ultrasonic waves. This was developed by the same research as well. The current system **can present 7.4 g-force (roughly the same weight as what would be felt when holding a 500 yen coin) at the most, focusing on a spot with approximately 1 cm diameter. In addition, the system can vary the degree of the force or vibration pattern by 1ms unit, and it can also move spotting positions at a high speed on the skin**.

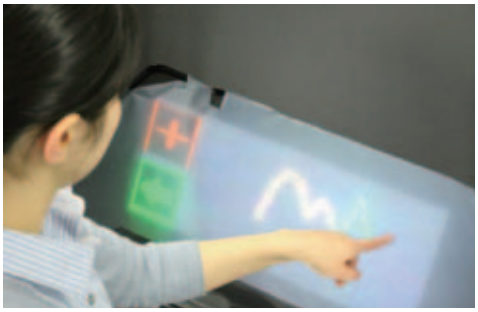
By integrating the "1ms auto pan/tilt system" and the "non-contact tactile display," we configured a system that can project information that was conventionally displayed on screens onto moving objects without positional displacement, together with tactile stimulation. In this sense, this system can be regarded as a moving object version and a tactile presentation version of projection mapping technology.。

Overview of experimental system



Operating aerial images by hand with the "next generation 3D display"

Additionally, the research group formed aerial images that are observable from a wide viewing area, and developed a next generation 3D display called "AIRR (Aerial Imaging by Retro-Reflection) Tablet" that is operatable by hand. This display integrates the "AIRR display technology" that forms a large aerial image with a wide viewing angle by use of retro-reflection sheeting, which possesses the property of reflecting light to the direction of incidence, with the "high-speed 3D gesture recognition" that recognizes the position and movement of an object (a fingertip etc.) within every 2ms using "1ms auto pan/tilt system" to make operation of aerial images possible. **Not only can aerial images be expanded and rotated using both hands, but they can also be made responsive to fast movements like punching**. Thus, the developed system demonstrates a future information environment in which aerial images are operatable by gestures.



Embedding information into existing objects and environments

Most of the research on current image processing and human interfaces is aimed at the "realization of human-like movement," whereas the research group of Professor Ishikawa is aimed at "**visual and tactile sense that exceeds human ability.**" When a human sees something and makes a decision to act, information transmission of "eye → brain → movement of his/her body" is needed, which takes approximately 60ms The system of Professor Ishikawa, at el. achieved overwhelmingly high-speed processing of "a high-speed vision sensor → information process by computer → a high-speed servomotor, " exceeding the limitations of the speed of human perception ability.

That this system embeds information onto/into existing objects/environments themselves, including moving objects such as a human palm or paper as well as empty space, to make intuitive operation possible is a totally new paradigm, while pre-existing information devices embed intelligent functions into objects such as tablets. It points the way toward future dramatic changes in our information environment. The information world and the physical world can become one in the future.

3D chip with wireless data link

Ultra low-power consumption high-speed data transmission!

Tadahiro Kuroda (Professor, Science and Technology, Keio University)

CREST Technology Innovation and Integration for Information Systems with Ultra Low Power "Generation of High-performance, Ultra-low-power, Short-range Wireless Mobile Information System" Research Director (2005-2011)

CREST Fundamental Technologies for Dependable VLSI System "Dependable Wireless Solid-State Drive (SSD)" Lead Joint Researcher (2009-2015)

ACCEL "Realization and development of innovative information processing system and application using near-field coupling integration technology" Research Director(2015 - 2020)

Data communication at low power consumption but at high speed

Since technologies advanced and computer processing power increased, vast amounts of data are now being exchanged. The higher the volume of data to be processed becomes, the more difficult the operation will be due to higher consumption power and heat generation. In recent years, the research has therefore been pursued to dramatically reduce power consumption, which attracts enormous attention. In order to catch up with the accelerating evolution of the information society, reduction of power consumption is definitely needed.

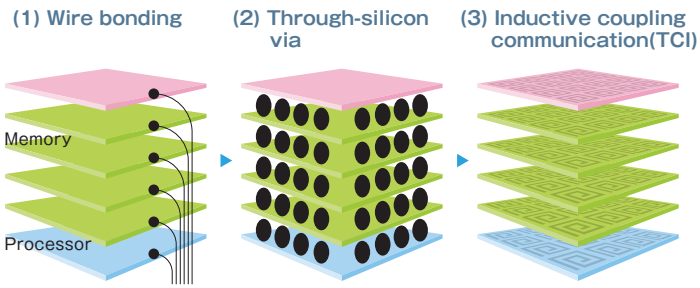
Ahead of any other teams in CREST, the team led by Professor Tadahiro Kuroda has **successfully reduced the consumption power straight to 1/1000 of the conventional level thanks to the short-range wireless data communication technology. That is the ThruChip Interface (TCI), which is one of the chip-to-chip wireless communication technologies utilizing near-field coupling (method of wireless communication for very short range using coils)**.

Specifically saying with concrete figures, the data of 6 million two-hour movies can be transmitted from chip to chip by only little electric power out of one button battery, which the amount of data is equivalent to a record of 1400 years of time. This is the epoch-making technology and the highly potential research to open up a new step, which the Professor Kuroda' s team only could accomplish through long-time researches on lower power consumption and wireless communication.

ThruChip Interface actually reduced the electric power to 1/1000

TCI is the technology that can reduce the consumption power to 1/1000. Then, how can TCI be described? To put it simply, this technology realizes wireless data communication from chip to chip stacked within a large-scale integrated circuit. The research on 3D implementation that pursues higher speed communication by stacking chips, not by laying chips on a flat surface, has been being conducted worldwide. However, there were major problems of low processing speed due to the wire bonding technology for connecting chip to chip, high manufacturing cost due to through-silicon via that drills a vertical hole to make a path for signal, and so on. (See Figure)

Evolution of the communication technology for stacked chips



ThruChip Interface =TCI is the technology that can solve these problems by wirelessly connecting chip to chip using a circuit technology, instead of drilling a hole that penetrates chips. Coils are made using a wiring on a chip. As a current flowing along the coil on one side is changed, the magnetic field running between the coils changes accordingly, which results in a voltage change in the other coil and then in data transmission. What is happening in this technology is quite simple - non-contact data communication between two coils as mentioned above. It is simple but absolutely unique in terms of the idea of using magnetic field coupling for inter-chip data transfer.

Unique development of non-contact connector applicable also to smartphones

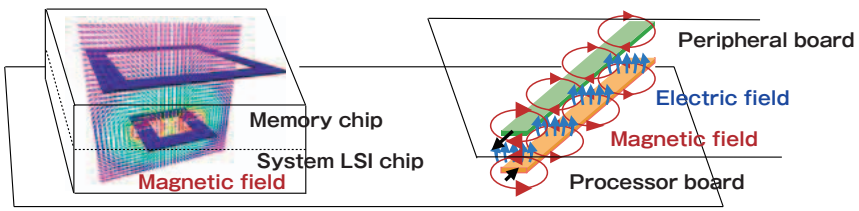
Speaking of the technologies uniquely developed by Professor Kuroda and his collaborators, **Transmission Line Coupler (TLC) - the non-contact connector technology using electromagnetic field coupling - is also important**. Normally, connector is to mechanically connect circuit boards and modules. **On the other hand, this non-contact connector is wireless type so that it hardly undergoes communication failures due to loose connection as compared to the conventional connectors that are to be mechanically connected, while it contributes to cost reduction due to lighter weight and is applicable to high-speed, power-saving and reliable systems**. In the most recent release, the non-contact connector became even smaller and the applicability to connections between small modules, such as smartphones, was verified.

Toward the realization of small, high performance, low power consumption and high reliability system

In 2015, Professor Kuroda and his collaborators have started the research and development for ACCEL toward the realization of the even lower power consumption and higher performance information processing integrated system. In this research and development, system LSI (Large Scale Integration) and memory LSI are three-dimensionally stacked using TCI, and in order to wirelessly connect peripheral modules, such as sensors, using TLC. This research will also definitely gather worldwide attention. And the Professor Kuroda' s unique TCI and TLC technologies will be utilized to realize small, high performance and highly reliable 3D chips, applied to systems requiring high speed and high reliability, and, as a core technology for semiconductor-applied products, applied to artificial intelligence, such as for data center, robot, machine learning and deep learning, and will contribute to the evolution of the information and communication technologies, such as for intelligent terminal, high performance small computer and next generation super computer that are made to process information at even higher speed.

Vision the Team Kuroda aims for

Data-centric computer
(Super low power consumption mobile computer for the IoT age)



ThruChip Interface (TCI)
Chips (processor and memory) are three-dimensionally integrated for higher performance

Transmission Line Coupler (TLC)
Modules (storage and sensor) are packaged like LEGO bricks for high functionality

Near-field coupling integration technology (Solution for connection problem in large-scale systems)

Super Hi-Vision camera as a surveillance camera and night vision camera

Ultra-high-performance camera with a new image sensor

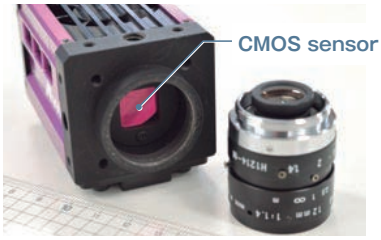
Brookman Technology, Inc.
(left: Satoshi Aoyama, President, CEO, right: Shoji Kawahito, Chairman, CTO)

A-STEP, Full-scale R&D stage
Practical Development (by SME Start-up)
"Ultra High Sensitivity and High-speed Image Sensor" Developing and implementing company (2009-2012)

Developing the image sensor for the next-generation "Ultra-Compact 8K Super Vision Camera"

The development and wide-spread use of "8K Super Hi-Vision" has been promoted with an eye on the 2020 Tokyo Olympics. This system can produce an ultra-high-definition image that offers 33 million pixels, which is 16 times that of the type of high definition currently used for broadcasting. The 8K Super Hi-Vision is expected to provide an image, even though being two-dimensional, that will make you feel as if you are really there, like what a 3D television can do. An ultra-compact 8K Super Hi-Vision camera has already been developed, and images shot with this camera were presented during the 2014 Soccer World Cup in Brazil. A lot of people were surprised with the technology that reproduced the agile movements of players and vivid colors. It was Brookman Technology, Inc. along with NHK Science & Technology Research Laboratories who developed the CMOS image sensor, which is installed in an ultrahigh- performance camera. **The ultra-high-performance camera is expected to play a crucial role in the next-generation image media.** Brookman Technology, Inc. is a university-launched venture company established by Professor Shoji Kawahito at the Laboratory for Electronics of Shizuoka University.

CMOS sensor
A high-sensitivity type CMOS sensor attached with a small video camera.
When the lens is removed, you can see the light receiving section just inside.

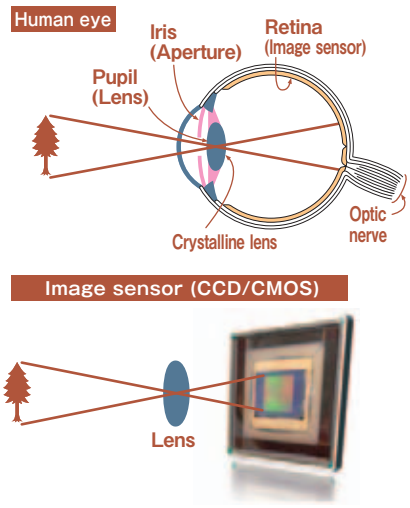


The "Electronic shutter" and "A/D conversion" technique that corresponds to the retina of a human eye determines the performance of an image sensor.

If the camera is compared to the human eye, the image sensor corresponds to the retina, which changes the light that enters into electric signals. There are two types of image sensors; the CCD and the CMOS.

The CCD carries electric signals one after another in a bucket brigade manner; on the other hand, the CMOS can process electrical signals in a batch, thus having the advantage of processing signals quickly and optimally.

The performance of an image sensor is measured by how it can capture an object with "ultra-high sensitivity" and at "ultra-high speed." Professor Kawahito worked on the development of an "electronic shutter," which plays **the role of a shutter in a film camera, and an "A/D conversion," technique that transforms analogue light information into digital light information, with the purpose of enhancing its performance**. In order to put that technique into practical use, he established Brookman Technology, Inc. as a university- launched venture company. Their research and development was accelerated after being adopted as part of A-STEP in 2009, and finally they succeeded in the development of the innovative technique and its application.



An image sensor corresponds to the retina of a human eye. It forms the image of an object on the light receiving surface of the sensor and converts the contrast of the light into electrical signals so as to produce a picture image.

Capturing the colors and movement of an object, with a high level of visibility with only the brightness of moonlight

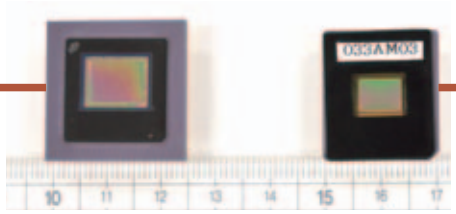
One of the produced is a "CMOS global electronic shutter" . Conventionally, a "rolling shutter," whose exposure timing is different for each pixel, was used as an electronic shutter for the CMOS image sensor; therefore when moving images were taken, distortion was found on the screen when they were reproduced. On the other hand, since the global electronic shutter used in a CCD image sensor can perform photographic exposure at one time, it can produce images without distortion; however, when the same shutter is used in the CMOS image sensor, due to the generated noise called "reset noise," the removal of which is impossible in principle, clear images cannot be obtained. However, the removal of the reset noise was successfully performed by employing their original technology. Thus, **the optimum use of a global shutter in the CMOS was made possible**.

In addition, they developed an "ultra-high sensitivity and wide dynamic range CMOS image sensor" that incorporates an A/D conversion technique, by which two problems that the conventional CMOS image sensor had were solved at one time: It could not create a clear image at the illuminance of about 1 lux (brightness of a single candle), and its dynamic range (width of the contrast that can be handled) was narrow. **They succeeded in capturing the colors and movement of an object clearly, realizing a high level of visibility and creating sharp images even at the illuminance of 0.1 lux (about the brightness of moonlight)**. For this technique, Brookman Technology, Inc. received the Prize of Smaller Enterprise Agency' s Director, the highest award presented by the Resona Foundation for Small and Medium Enterprise Promotion, in 2012.

Dim object clearly captured

The image was taken in a place with about the brightness of moonlight (illuminance of 0.1 lux). It can clearly reproduce objects such as letters even in dimness that makes color identification by the human eye impossible, so it is used in surveillance cameras. The bottom was taken with a camera with the CCD sensor.

Ultra-high sensitivity type　High-high speed type



CMOS sensors by Brookman Technology, Inc.

Capturing the fluidity of the moment

You can enjoy ultra-high-speed filming at home.
If you watch the video on the website of Brookman Technology, Inc.
(http://brookmantech.com/sample.html), you can experience the beautiful phenomenon of a milk crown.

Awarded the Japan Science and Technology Agency President Award at the first "Award for Academic Startups"

Technologies developed by Brookman Technology, Inc. are already being put to practical use in various ways. They are working on the development of an ultra-compact 8K Super Hi-Vision camera, which was introduced at the beginning of the article, with NHK Science & Technology Research Laboratories and Shizuoka University. Additionally, **the ultra-high sensitivity and wide dynamic range CMOS image sensor is used in a surveillance camera or night vision camera for filming TV programs. In recognition of the aforementioned achievements, in 2014, Brookman Technology**, Inc. was awarded the Japan Science and Technology Agency President Award of the newly established Award for Academic Startups.

In Hamamatsu, where the company was established, Assistant Professor Kenjiro Takayanagi (at that time) at Hamamatsu Industrial High School, the predecessor of Shizuoka University, succeeded in displaying a clear image of the character "イ" on a Braun tube for the first time in the world. Now, after almost 90 years after that great success, the innovation that evolved from highly original technology is being created in the birthplace of Japan' s imaging technology development.

Developing a groundbreaking artificial synthesis method for the influenza virus

Preventing a new-strain flu pandemic with revolutionary technological capabilities!

Yoshihiro Kawaoka
(Professor, Division of Virology, Institute of Medical Science, The University of Tokyo)
CREST
Translational Research for Intractable Immune Disorders and Infectious Disease
"Understanding the Replication Cycle of Influenza Virus and its Application" Research Director (2001-2007)
ERATO
"Kawaoka Infection-induced Host Responses Network Project" Research Director (2008-2014)*
*Research expanded from 2009

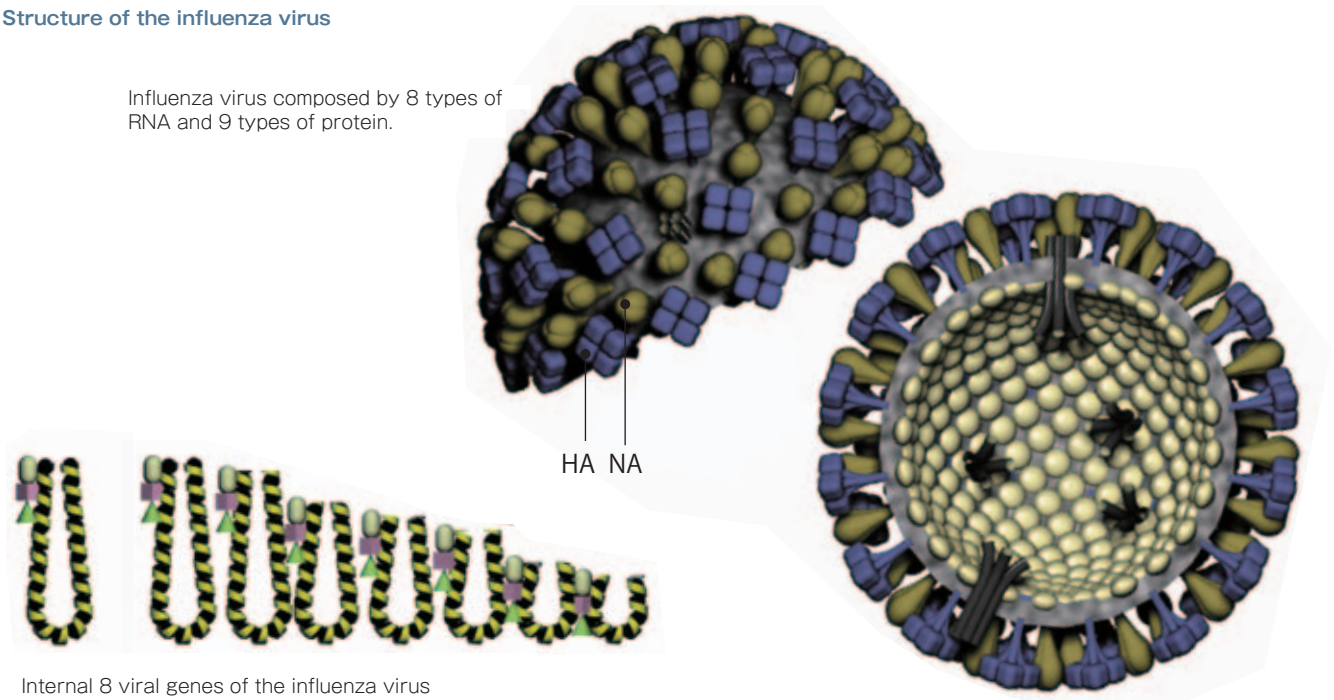
Putting an end to the fight against the influenza virus

In 2009, a new strain of influenza broke out worldwide and was declared at a Phase 6 state by the World Health Organization (WHO), indicating a pandemic level. This incident is still fresh in our memory. **According to data announced by the WHO on February 12, 2012, it caused at least 15,292 confirmed deaths in more than 212 countries and regions worldwide**. This incident helped shed some light on why modern medicine, which has come so far in the present day, was helpless against this new-strain influenza.

It is extremely difficult to gain a clear understanding of the characteristics of the influenza virus. Since new viral strains, in particular, can never be fully understood before they actually occur, vaccine development and other efforts always seem to be one step behind. Consequently, many scientists believe that if we were able to artificially synthesize such a virus, vaccines could be deployed immediately after the new strain of influenza emerges, enabling us to prevent pandemics. Research on this subject had been conducted all across the world, but it was Professor Yoshihiro Kawaoka who in 1999 **successfully developed the groundbreaking "reverser genetics method" and artificially synthesized an influenza virus**. Professor Kawaoka was recognized for this outstanding work **in 2006 when he received the most prestigious international medical science award in Germany, the Robert-Koch-Preis, which is awarded each year for outstanding work in fundamental medical research**.

Structure of the influenza virus

Influenza virus composed by 8 types of RNA and 9 types of protein.

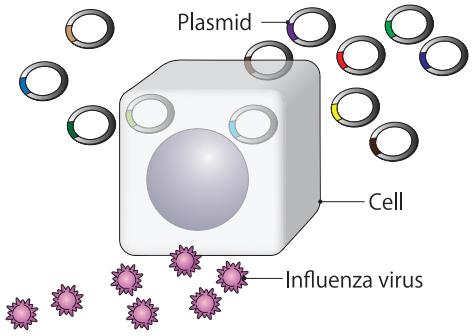


Internal 8 viral genes of the influenza virus

What does the reverse genetics method?

The research required to protect humanity against new strains of the influenza virus can be divided broadly into three fields. The first is rapid development of new-strain vaccines. The second is research into the mechanisms of infection. The third is research into the causes of death due to the virus. **The development of the reverse genetics method for artificially synthesizing the virus has spurred a great leap forward in all these areas of essential research, and has given scientists a head start in researching many virus sub-types**. Influenza research, which was previously always one step behind the vi-rus, has undergone major changes as a result of this new technology.

Artificial synthesis of influenza (conceptual diagram)



Are people aged 90+ more resistant to new flu?

The new strain of influenza that broke out at worldwide pandemic levels in 2009 had a curious characteristic. While normal seasonal influenza tends to cause more widespread harm to those with less physical resilience such as elderly persons and small children, this new influenza strain spread more among the younger generation, who tend to be healthier and have more physical resilience. Perplexed by this, Professor Kawaoka studied the blood serum of subjects with a diverse range of ages. As a result, he ascertained that many persons aged 90 years or more possessed antibodies for this virus. Why should older people possess antibodies for a supposedly new strain of flu? The question was quickly answered. **This "new" strain of influenza was actually antigenically similar as the strain known as the "Spanish flu," which had caused a worldwide flu pandemic over 90 years before**, in 1918. Antigenically, many strains of influenza exist; if exposed to a different flu antigen, a person will become infected, even if antibodies are present in their body. Conversely, if a person is infected with influenza once, antibodies will be present in their system and they will have less chance of infection.

In the current case, it is believed that antibodies that had developed 90 years previously in response to the Spanish flu were still functioning effectively in response to the new-strain flu of the same type, even after the passing of 90 years. In short, this was not a flu that was more difficult for elderly people to catch; it was rather that many elderly people already possessed antibodies to this strain of influenza.

This understanding of the mechanisms that govern the emergence of strains of influenza in the past and our establishment of treatment and prevention methods for modern new-strain influenza have been enabled by artificial synthesis of the virus, thanks to the reverse genetics method.

Establishing technology to prevent the emergence of new strains of influenza!

In light of the emergence and worldwide spread of infection of new-strain influenza in 2009, JST expanded its support for Professor Kawaoka' s ERATO project. **The urgent need was recognized for establishing a solid foundation to provide basic understanding of and prevention/treatment for potential new strains of influenza virus that are likely to emerge in future**, using the reverse genetics method: the world's first method of artificial virus synthesis.

The influenza virus keeps changing and evolving inside the human body after infection. The strains of influenza that have greatly troubled the human race in the past—Spanish flu, Asian flu, Hong Kong flu—are likewise caused by its evolution into strongly pathogenic viruses due to changes taking place inside the human body and many iterations of infection. In future, we will seek to understand the pathogenic acquisition mechanisms of the influenza virus, to shed further light upon the infection process, and to ultimately establish technology to prevent the emergence of new-strain influenza virus pandemics.

For achieving zero victims in a natural disaster

Dynamic hazard map and disaster prevention education

Toshitaka Katada (Director of the Institute of Social Technology, I.D.A Co. Ltd./Professor at the Graduate School of Engineering, Gunma University)

RISTEX Implementation-Support Program

"Establishing a Foothold for Nationwide Expansion of Tsunami Education Using a Comprehensive Tsunami Disaster Scenario Simulator" Person responsible for implementation (2007-2010)

Educational activities for disaster prevention backed by scientific evidence behind a 'miracle'

A 'miracle in Kamaishi' --. In the Great East Japan Earthquake on March11 in 2011, a great number of lives were spared, which attracted the public' s attention as a 'miraculous' event. In Kamaishi City in Iwate Prefecture, which was hit by a tsunami, 99.8% of about 3,000 elementary and junior high school students of 14 schools in the city survived. In particular, the students of Kamaishi-Higashi Junior High School were praised for their actions.

Immediately after the earthquake occurred, they led students of the nearby Unosumai Elementary School in fleeing to a facility, which was their evacuation site on a hill, and then, when they saw the cliff behind the facility collapsing and the cloud of dust caused by the tsunami rising high in the sky, they realized that they were still facing a life-threatening situation and they left the facility on the hill and fled again to higher ground at their own discretion. Only 30 seconds after that, the facility on the hill was washed away by tsunami waves.

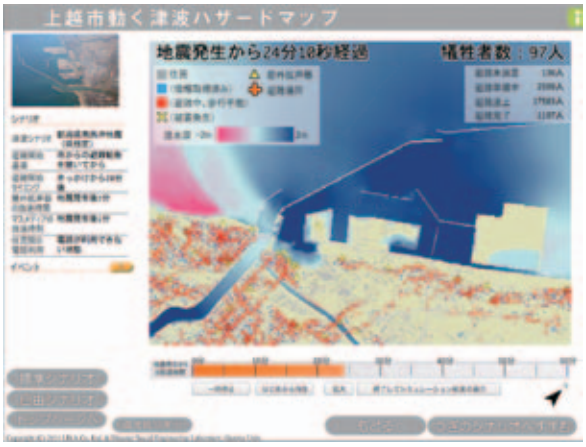
Quick action based on sound judgment; something that you wouldn' t think could be done by junior high school students saved their lives. That fact actually seems worthy enough to be called a miracle, though it is not just a miracle.

It should be known that behind that were educational activities for disaster prevention backed by scientific evidence promoted by Professor Toshitaka Katada

Elementary and junior high school students, fleeing for refuge (Photo credit: Professor Katada)

Developing an 'dynamic hazard map' by which you can see the expected tsunami disaster through dynamic images

Professor Katada specializes in disaster social engineering. **This research field aims to contribute to achieving a society with zero victims of a natural disaster through research activities including the development of a disaster prevention technique**. It is an 'dynamic hazard map' for tsunami disaster that was developed as part of such efforts. This hazard map, unlike a paper one, enables the predicted state of tsunami waves and the extent of the damage to be confirmed on the map via dynamic images according to the lapse of time from the occurrence of a tsunami, thus making it possible to realistically simulate a disaster.



One example of ' dynamic hazard maps'

Research activities conducted in university laboratories go as far as to develop 'sociotechniques' such as a disaster prevention technique that contributes to society, but after that, their implementation, that is, how to utilize such techniques in the real world, is generally entrusted into the hands of a local government.

However, **Professor Katada, who views their implementation as part of research activities, had been crisscrossing the country and devoting himself to disaster prevention education**. He also established a universitylaunched venture company where he serves as a director. The dynamic hazard map was used in the educational activities for disaster prevention that he worked on with local governments throughout the country in the Implementation Support Program, 'Establishing a Foothold for Nationwide Expansion of Tsunami Education Using a Comprehensive Tsunami Disaster Scenario Simulator' promoted by RISTEX. Kamaishi City was one of those local governments.

'Don' t trust a hazard map.' Develop the ability to protect your life yourself

Many people may associate disaster prevention education with something that specifically teaches how to act at the time of a disaster. However, Professor Katada' s disaster prevention theory, being completely different from that type of education, aims at developing the '**ability to protect your life yourself.**'

Kamaishi City had also worked on disaster prevention education based on this theory. Their approach to disaster prevention is clearly shown by the principle, '**Don' t trust a hazard map.**' Nature sometimes attacks us with forces far beyond human prediction. Professor Katada learned that fact from the damage caused by natural disasters in the past. Therefore, after showing a hazard map to children to have them visualize what a disaster would look like, Professor Katada always asked them: 'In an actual disaster, something more than this may happen. What could you do then?' Through making such efforts, Professor Katada had developed the 'ability to protect your life yourself.' That is why children could, in addition to promptly fleeing to their designated shelter when the tsunami actually struck, flee to a safer place immediately after judging that 'this shelter might not be safe' when they saw the surrounding condition.

Efforts to integrate a sociotechnique with its implementation to become increasingly important in the future

Despite the fact that quite a number of lives were saved in this way, Professor Katada can' t get rid of the feeling that the approach for disaster prevention in Kamaishi City fail. Whereas a lot of children' s lives were protected, a lot of lives of general citizens were lost. It was after Professor Katada started to provide the disaster prevention education for 'protecting your life yourself' for general citizens and when he was still in the middle of his efforts that the Great East Japan Earthquake occurred.

Since disasters such as a tsunami rarely occur, private companies are less likely to work on the prevention of such disasters. Hence, it is necessary for public institutions to make efforts toward solving issues that arise with disasters.

Presently, educational and research institutions such as universities are responsible for the development of a Science and Technology for Society and the government and local governments are responsible for its implementation; thus their roles are likely to be separated. However, it is necessary to make efforts like what was done behind the 'miracle in Kamaishi' to integrate both of them. Further development is expected to be made in the future.

'Tsunami Disaster Prevention Seminar' held in Joetsu City, Niigata Prefecture

Using the victim database

Implementation of a life recovery support system

Keiko Tamura
(Professor, Risk Management Office, Headquarters for Risk Management, Niigata University)
RISTEX Information Technology and Society
"R&D Program Governance of Ubiquitous Society" Researcher (2007-2009)
RISTEX Implementation-Support Program R&D results integrated Type
"Development of Life Recovery Support System for a Possible Tokyo Metropolitan Eathquake" Representative Researcher (2011-2013)

Developing a method to certify building damage made by anyone who have to become an investigator

When the Great Hanshin-Awaji Earthquake occurred in 1995, one of the challenges for governments became obvious. It was the problem related to "victims certification." Victims certifications are issued for disaster victims from municipal governments when disasters occur. It is an important document which describes the damage situation of houses etc., and which becomes the judgmental standard for the amount of assistance, tax allowance, allocation of monetary donation, etc. However, the standard for creating the document and the division in charge of dealing with the documents were different depending on each municipal government before 1995.

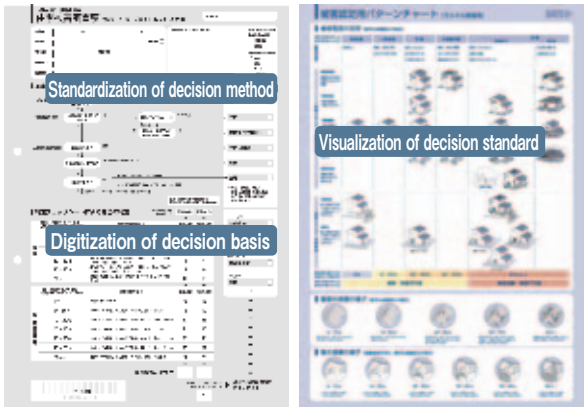
As a result, contents described in the documents lacked accuracy, and approximately 30% of disaster victims were not satisfied with the decision from municipal governments.

Ever since Professor Keiko Tamura was a researcher at Disaster Prevention Research Institute, the Kyoto University, she and Professor Haruo Hayashi who both belonged to the same institute, worked on **creating a system that can issue victims certification impartially**.

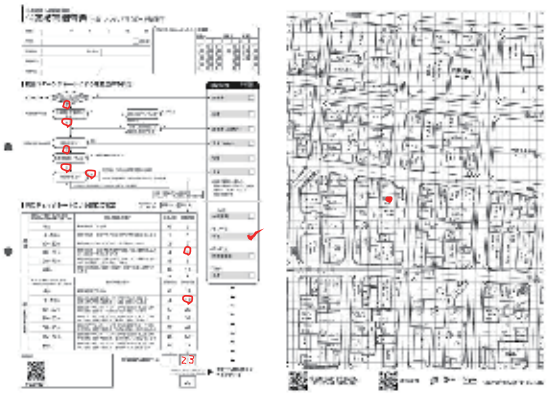
To learn from the actual case of the Great Hanshin-Awaji Earthquake, more than 12,000 photos of houses that showed their damage situation in Nishinomiya city, Hyogo prefecture, were compiled as a database, based on GIS (geographic information system) that can highly and rapidly analyze data possessing geographical information. Also, **a training system was created so that a person who is not a specialist becomes the investigator to certify building damage impartially**.

In October 2004, the Niigata Chuetsu earthquake occurred and it provided the opportunity to implement the developed system. Staffs and others from Ojiya city who had no expert knowledge made use of the system to create a database for house damage. Furthermore, more than 3,000 sheets of victims certification were issued in four days by organizing an issuing system.

Developing a method to certify building damage made by anyone who wants to do so



Digitalizing questionnaire data using QR code



Aiming for trouble-free production of victims database by digitalizing questionnaire data

In the case of the Niigata Chuetsu earthquake, there were some achievements as mentioned above, while some new challenges became obvious. The victims certification only functioned temporarily; therefore, **in order to support the life of disaster victims continuously, it was necessary to create a "victim database" to organize and preserve such information**. An attempt to create a database based on the victims certification

was made. However, since the victims certifications were created on paper media, it required a great effort to make the database. To work on this new challenge with sincere effort, in 2006, Professor Keiko Tamura took on a new assignment at Research Center for Natural Hazards and Disaster Recover, the Niigata University, which is located close to Ojiya city.

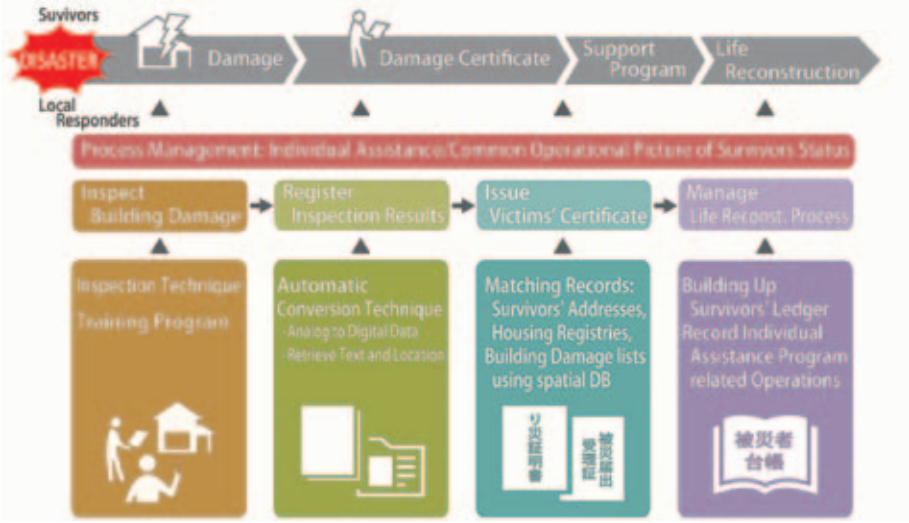
She was selected to the R&D program of RISTEX "Information and Society" R&D Area, and with the representative of the research, Professor Hayashi, she worked on digitalizing questionnaire data using QR code. When the Noto Peninsula Earthquake occurred in March 2007, she created a victim database using the developing system in Wajima city, Ishikawa prefecture.

Proactive support for people without leaving anyone untreated

When the Niigataken Chuetsu-oki Earthquake occurred in 2007, she not only created a victim database but also **worked on supporting life recovery based on the database**. However, at the place, she faced a situation where more than one-third of disaster victim households did not apply for life recovery support. There were many people who did not know the existence of the support and ones who could not come and apply for it due to family circumstances. Therefore, support for people without being left untreated was realized by reaching disaster victims from city side with a proactive approach using the victim database.

In this way, **the "life recovery support system" was prepared so as to lead to rapid and continuous support for disaster victims, based on the database that links building damage investigation, victims certification issuance, and creation of victim database altogether**. When the Great East Japan Earthquake occurred in March 2011, through cooperation with Iwate prefecture, she and the prefecture made an effort to create a victim database making use of this system and previous experiences. Based on the victim database, the prefecture proactively approached disaster victims to connect them to the life recovery support system.

Total System Design for handle transactions in all the process from the beginning to successful conclusion of survivors' life reconstruction



Acting before a disaster takes place, not after. Accelerating support

Having these approaches in mind, an attempt by the governmental administration has started from 2011 to accelerate the speed from earthquake occurrence to life recovery support system by carefully preparing for an earthquake disaster before it takes place.

With the cooperation of Tokyo, a **test was conducted in the way that the staffs actually issue damage certificates and victims certifications through trainings**. Professor Tamura has taken over the role as representative of researchers from Professor Hayashi, and she is working on the implementation of the system. Currently, implementation is completed in Kyoto and Iwate prefectures and Kobe and Chigasaki cities. In addition, it is in progress in Tokyo and Niigata prefectures.

Since Professor Tamura and others physically went to places where disasters occurred and worked on implementing the system with the persons in charge of governmental administration, the problems of life recovery support system for disaster victims were found and the system has been improved to one that is more beneficial. Continuing with this spirit of improvement, it is hoped that this system will be advanced even further with more improvement.

The "victims certification issuing experience" training was conducted as a part of emergency drill on the Disaster Prevention Day in Tokyo.

Use of Science and Technology Innovation

Aiming to reconstruct from the Great East Japan Earthquake disaster

Reduce the risk for metabolic syndrome by drinking it every day! Tasty brown rice Amazake

Project name : Research and development of fermented food for anti-metabolic syndrome utilizing functional components in brown rice
Company : Aizu Tenpo Jozo Co.,Ltd (Aizuwakamatsu-city , Fukushima)
Principal investigator : Kenji Suzuki (Fukushima Technology Center)
Research institute : University of the Ryukyus Okinawa, Fukushima Technology Center

Research summary

The Amazake, non- alcoholic sweet fermented rice drink, is highly nutritious and it is useful for the sick and those who have trouble in swallowing. Tenpo Jozo Co.,Ltd. and Fukushima Technology Center are currently working together to produce tasty and mass-producible brown rice Amazake. Also, the Study on Brown Rice from the University of the Ryukyus, which showed γ -oryzanol in brown rice is effective for preventing metabolic syndrome, made Aizu Tenpo Jozo Co.,Ltd . think brown rice Amazake also has the same effect, which led them to verify the required intake under the cooperation of the university. As a result, they confirmed the efficacy in a clinical trial at Second Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus. They have established a standard of the taste of brown rice Amazake, registered the trademark of the beverage product name, and started selling it in the health foods market in August 2015.

Expected benefits

This project draws attention in the food and health perspective since it uses the clinical study results from University of the Ryukyus and develops and proposes a functional food effective for a national concern, metabolic syndrome. A company in Fukushima works with a local research institute and has developed tasty and easy-to-drink brown rice Amazake using Aizu Hitomebore and tries to expand their product' s distribution, while ensuring the safety of the food in Fukushima. It is also expected that it will largely contribute to reducing the harmful rumors concerning the Nuclear Power Plant.

Developing Hot Pressing Technology for Molding Powdered Amber from Kuji, Iwate

Project name : Application of new high quality, efficient technology for molding Kuji amber powder
Company : Kuji Kohaku Co., Ltd. (Kuji-city, Iwate)/ Porite Corporation (Saitama)
Principal investigator : Tomoharu Shimizu (Iwate University)
Research institute : Iwate University

Research summary

Amber from Kuji City is created from fossilized tree resin from about 80 million years ago (Mesozoic Cretaceous era) which is significantly older than amber from Baltic region. Due to age, the amber is hard and brittle, with much of it excavated in fragments, creating many limitations for processing.

Our research aims to draw on the potential of Kuji amber, and establish production methods that will allow new product developments.

Research has led to establishment of high quality, prestigious amber product forming methods and hot pressing technology that solves quality inconsistencies, exceeding initial expectations. This technology has made it possible to use amber fragments that were previously discarded, enabling effective utilization of amber resources.

Expected benefits

One of the main products made using amber is amber ballpoint pens. With quantity limited by current hand production methods, market demand could not be met. Technology established through our research will make meeting this demand possible. As a result, a large increase in sales can be expected.

Furthermore, pressing technology can also be used for creating complicated shapes, enabling the development of a wide variety of new products containing amber. This will provide a foothold for new business development in a new market.

▲Rock containing Kuji amber

▲Small fragment of Kuji amber (after refined)

▲Products using pressed Kuji amber

Development of terminal stage patient-, family- and healthcare provider- friendly monitoring system

Project name : Development of a small and lightweight, electric power saving wireless ECG monitoring system for terminal stage patients under home medical care
Company : Real Design Corporation (Sendai-city, Miyagi), ImageONE Co., Ltd. (Tokyo)
Principal investigator : Makoto Yoshizawa (Tohoku University)
Research institute : Tohoku University

Research summary

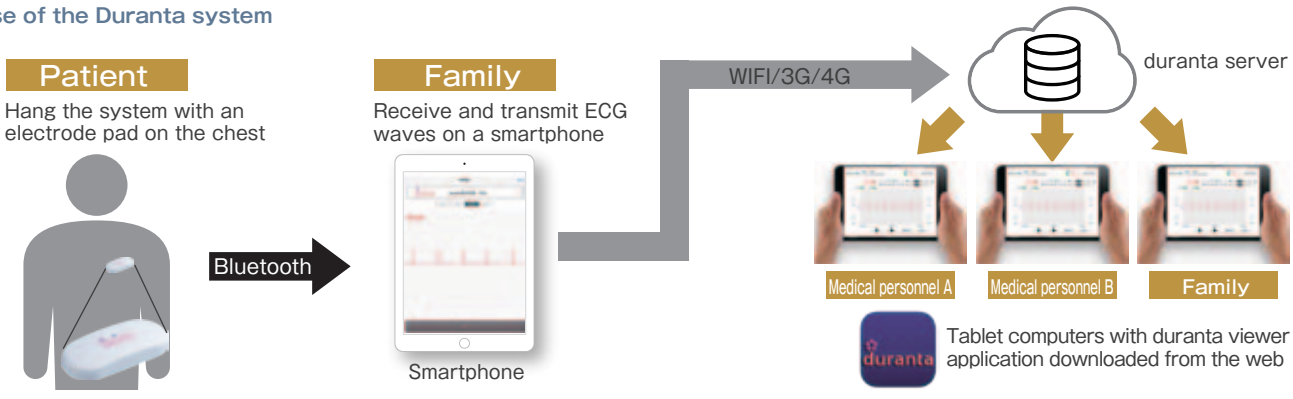
Enhancing home medical and nursing care services without relying on medical institutes is one of the most effective options for the future trend of medical care. This study has developed a monitoring system that allows doctors or family members to monitor electrocardiograms (ECGs) sent from a wireless ECG sensor. The system is available for seven consecutive days without requiring battery changes, and the waveform of ECGs can be checked online by mobile phones anytime, anywhere on real time. The system can display an alarm on the window or send a warning email to doctors in the case of abnormal heart rate. Sample products were distributed to medical institutes across Japan for verification tests and the feedback was reflected to the final product.

Based on the gathered data, the product obtained approval for medical devices in October 2014 and was put on the market under a product name duranta® in December the same year. In addition, in November the same year ImageONE Co., LTD. has concluded a business partner contract with a medical device distributor in Finland, which is aging fast as with Japan, and started expanding their business to European countries via the partner.

Expected benefits

The demand on home medical care is increasing in areas that are short of medical institutes and doctors. To satisfy this demand, duranta® becomes a new communication tool among a patient, family and healthcare provider to check the patient' s ECG, and enhances medical infrastructure in medical institutes and nursing homes. Moreover, duranta® can also monitor workers' hearts on duty, which is expected to become a comprehensive preventive medical tool by integrating with waveform analysis software.

Use of the Duranta system



Eco-friendly restoration of agricultural lands damaged with salt in the tsunami

Rape flower project

Yutaka Nakai
(professor of Graduate School of Agricultural Science, Faculty of Agriculture, Tohoku University)

RISTEX The Great East Japan Earthquake response and emergency, support for the practical application of the outcomes of research and development "restoration of agricultural land and agriculture in disaster-hit areas in Tohoku" Chief of practical application (2011)

Contribution to the recovery from the damages of the Great East Japan Earthquake with science

RISTEX (Research Institute of Science and Technology for Society) is supporting the use of research outcomes to solve various social problems with the philosophy that ***science in society and for society***. It implemented six projects for **the restoration and rehabilitation from the damages of the Great East Japan Earthquake.** One of them was **the rape flower project for the restoration of agricultural lands suffering from salt damages of the tsunami.**

Restoration with salt-tolerant crops in the family Cruciferae

Tsunamis in the Great East Japan Earthquake damaged 10,000 hectares of paddy fields in Miyagi Prefecture alone. Restoration of agricultural land damaged by the tsunami usually requires civil engineering work by spending enormous amounts of money and time. Yet, professor Yutaka Nakai and his team found the necessity to **find measures to restore the agricultural fields while farmers are farming**. As a result of preliminary investigations, they found the necessity of removing sediments in areas where sand and mud accumulated on agricultural fields. Meanwhile, planting could not be conducted immediately in areas that were only flooded with seawater without the accumulation of sediment unless the salt was removed by irrigation in which the soil would be submerged in freshwater. Still, the team found some agricultural lands from which salt had been removed thanks to rain for one year and could be restored quickly. They also found that the conditions of damage differed among agricultural lands depending on the distances from the coastline and the terrain. Professor Nakai and his team proposed **to the prefecture of Miyagi a project to improve soil and restore agriculture to suit conditions of individual agricultural lands using salt-tolerant crops in the family Cruciferae**.

Continuation as a rape flower project

Graduate School of Agricultural Science, Faculty of Agriculture, Tohoku University, where professor Nakai belongs has a gene bank,* which is the only facility in the world where crops in the family Cruciferae are registered and preserved. Research outcomes in Tohoku University were **effectively used to select crops in the family Cruciferae, which were suitable for soil improvement depending on the conditions of damage**. The final goal of the project is to establish stable production methods of crops in the family Cruciferae, methods of selling rape seed oil, and systems to produce and consume biodiesel fuel from rape seed oil.

The project quickly **attracted attention in society from the start. Volunteers from around the country** and students of Tohoku University cooperated and smoothly removed mud accumulated on agricultural lands, built ridges, and planted seeds. The project was written in the restoration plan of the city of Sendai, and **more than the expected number of companies emerged to support and sponsor the project**. With advice from fruit and vegetable wholesalers, **the project created the value of the crop as an edible rape plant**, which was not included in the initial goal. **The produce was actually sold in supermarkets and stores in the city of Sendai. Supporting companies are also building systems for selling rapeseed oil and producing and selling biodiesel fuel**.

The rape flower blossomed in May, and **the beautiful landscape became a ray of hope for farmers and disaster victims alike**. The rape flower sketching and photographing events were popular. The project launched from RISTEX **won the Japan Prize of Agricultural Science and the 52nd Yomiuri Prize of Agricultural Science** in FY 2015. The rape flower project is still actively continuing today.

*A facility that preserves and manages seeds to conserve genetic resources.

A scenario for promoting recovery and reconstruction from the Great East Japan Earthquake, based on low carbonization.

Contributing to advancement of thin-film solar cell manufacturer into Miyagi Prefecture

Center for Low Carbon Society Strategy (LCS)

Social Scenario Development for the Establishment of Low Carbon Society

Towards bright and comfortable low carbon society

LCS is proposing social scenarios **to contribute to the realization of a sustainable, "affluent low carbon society"** that is conducive to the economic and social development of the new Japan.

Specifically, LCS has set the several objectives of realizing a low carbon society. To achieve these objectives, we propose quantitative scenarios and strategies showing images of society expected in 2020-2030, which leads to society in 2030-2050, while responding to social changes.

Proposing scenarios using the renewable energy for promoting recovery and reconstruction from the earthquake

Following the Great East Japan Earthquake on March 11, 2011, LCS has established "Study Team for the special Measure-Scenarios for recovery and reconstruction from the Great East Japan Earthquake" , and has worked on the formulation of a feasible scenario for recovery and reconstruction of regions devastated by the earthquake.

LCS's scenario is promoting the recovery and reconstruction from the earthquake based on low carbonization. It enables regional characteristics to be applied and is based on the plans for the recovery plan that the Tohoku region hopes to employ.

In addition, this scenario includes various factors such as introduction of technologies and systems in order to take full advantage of the renewable energy, the construction of systems for the realization of advanced agriculture and forestry with high productivity and profitability, and the revitalization of the local communities corresponding to the aging society.

LCS proposed a low carbonization scenario for promoting recovery and reconstruction from the earthquake to Miyagi Prefecture, which was devastated by the earthquake. It focuses on a technology scenario for the development of solar cells, and also the Prefecture investigated it as the "utilization of renewable energy" in the recovery plan.

In particular, to Miyagi Prefecture, **LCS proposed inviting Solar Frontier K.K., a solar cell manufacturer which has excellent abilities and technologies for developing and manufacturing CIS thin film solar cells, and their setting up a new plant in the Prefecture**.

According to our research, CIS thin film solar cell technologies are evaluated to be far superior to the others in terms of both a low plant construction cost and the possibility of reducing costs by future technology development.

Additionally, LCS explained to Solar Frontier about the superiority of their modules and power-generating systems, using the cost scenario based on the calculation performed by LCS. And also LCS indicated the prospects of their receiving various merits from Miyagi Prefecture including the acquisition of a plant site, environmental arrangement and so on.

Towards the realization of a low carbon society in Miyagi Prefecture by integrated efforts of the Prefecture, the company and the nation

Solar Frontier constructed a plant in Ohira village, Miyagi Prefecture and it has started operation of it on April, 2015.

Solar Frontier showed appreciation for **LCS's technological scenarios and its efforts to explore the possibility of future use of CIS thin film solar cells, and effective roles to proceed with their plant construction in Miyagi Prefecture**.

This is the case of advancement of thin-film solar cell manufacturer into the Prefecture towards the realization of a low carbon society by integrated efforts of the Prefecture, the company and the nation. Especially the company has strong willingness to contribute to recovery and reconstruction of the Prefecture and Tohoku region, and to face the challenge of producing cost-competitive solar cells through the introduction of new technologies.

Koichi Yamada, Deputy Director-General of Center for Low Carbon Society Strategy (second from the right), attending the ceremony to celebrate the completion of Solar Frontier "Tohoku Plant"

Promotion and Support of international Research Cooperation in Science and Technology

Solution to Global Problems

These days, we have various problems in the fields of climate, energy, food, and more associated with global warming. These problems cannot be solved by one country, and collaboration with international society is absolutely essential. JST contributes not only to solving global problems, but also to further developing science, technology, and innovational strength in Japan including information and communication and to enhancing scientific and technological diplomacy.

Strategic International Collaborative Research Program (SICORP)

SICORP is implementing collaborative researches based on the equal and friendly partnerships among cooperative countries, regions, and research fields established under the agreement among ministries and agencies in order to further improve science, technology, and innovational strength.
(11 tasks finished, 64 tasks among 32 countries and 1 region collaboratively ongoing as of December 2015)

* SICP (Strategic International Research Cooperative Program/ started in 2003) finished new adoption in 2013 and was shifted to SICORP. (SICP: 354 tasks finished, 24 tasks among 7 countries and 1 region collaboratively ongoing as of November 2015)

Science and Technology Research Partnership for Sustainable Development (SATREPS)

SATREPS is a flagship program of scientific and technological diplomacy created in collaboration between Japanese R & D capabilities and ODA (Official Development Assistance). JST in collaboration with JICA aims to address global issues in cooperation with developing countries. (99 projects adopted among 43 countries in the world after April 2008)

* Research projects in the field of Infectious Diseases Control' and with the purpose of medical care were transferred to Japan Agency for Medical Research and Development (AMED) in 2015.

Japan-Asia Youth Exchange Program in Science (SAKURA Exchange Program in Science)

The Japan-Asia Youth Exchange Program in Science (SAKURA Exchange Program in Science: SSP) is a short-term invitational program to contribute to the advancement of science and technology and the development of Asian economy. The program aims to strengthen exchanges and friendly relations by inviting to Japan outstanding young people from Asian countries and regions, and giving those young people chances to experience cutting-edge science and technologies.

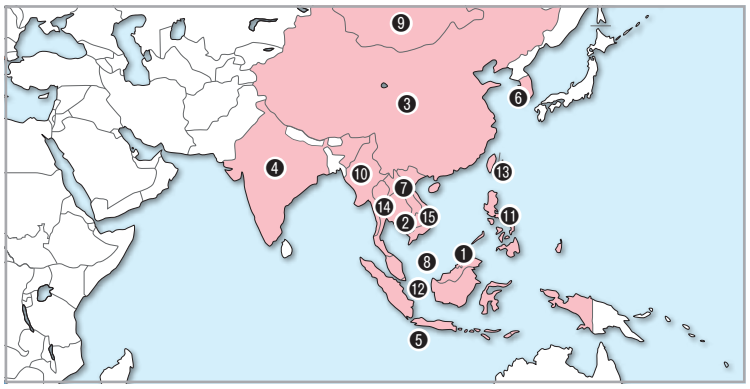
The program invited excellent young people from 488 sending organizations in all target countries and regions and provided opportunities for them to be exposed to Japanese S&T. The program achieved almost 100 percent of satisfaction rating among the participants.

Their impressions in Japan include "cutting-edge research environment is in place", "hope to come back to Japan again to study further", "enhanced interest in working for a Japanese company". These favorable responses indicated that the invitational program has achieved its objectives. (3,800 youth to be invited on a budget basis in 2015)

Countries and regions eligible to apply for "SAKURA Exchange Program in Science"

① Brunei Darussalam
② Cambodia
③ China
④ India (2015～)
⑤ Indonesia
⑥ Korea
⑦ Lao People's Democratic Republic
⑧ Malaysia
⑨ Mongolia
⑩ Myanmar
⑪ Philippines
⑫ Singapore
⑬ Taiwan
⑭ Thailand
⑮ Viet Nam

(in alphabetical order)



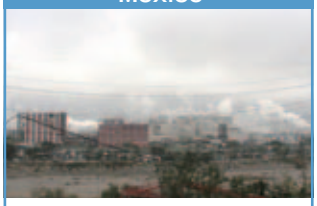
Research Exchanges and Collaborative Researches Promoted by JST

Panama

Bioresources: Comparative Studies of the Reproductive Biology and Early Life History of Two Tuna Species Yellowfin Tuna and Pacific Bluefin Tuna for the Sustainable Use of These Resources

Scientists at the Kinki University succeeded in raising the eggs of yellowfin tuna to young fish for the first time in the world in the Republic of Panama. They will raise young fish that have been successfully raised this time to full-grown fish in future and aim at newly producing juvenile fish two years later at the earliest. It is expected to establish the technology of completely farming yellowfin tunas that are listed as a semi-endangered species. (Adopted the project in 2010, "Comparative Studies of the Reproductive Biology and Early Life History of Two Tuna Species Yellowfin Tuna and Pacific Bluefin Tuna for the Sustainable Use of These Resources," Fisheries Laboratory, Kinki University, Professor Yoshifumi Sawada)

Mexico



Global-scale Environmental Issues: Formation Mechanism of Ozone, VOCs, and PM2.5 and Proposal of Countermeasure Scenario

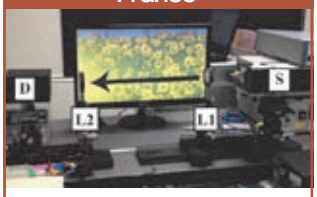
The project is working to research on air pollution regarding ozone, VOCs, and PM2.5 at three major cities in Mexico, and countermeasures against air pollution that were proposed from the project on the basis of their research results start being reflected in planning countermeasures against air pollution in each state. In Monterrey where PM pollution is significant, the proposal will be applied as next countermeasures against air polluted environment. (Adopted the project in 2010, "Joint Research Project on Formation Mechanism of Ozone, VOCs, and PM2.5 and Proposal of Countermeasure Scenario," Faculty of Agriculture, Ehime University, Professor Shinji Wakamatsu)

Israel

Conclusion of research cooperation memorandum with Israel

On January 18, 2015, the Japan-Israel Business Forum was held in Jerusalem, the capital of Israel, and the memorandum regarding research cooperation in the ICT field was concluded with the Israel Ministry of Science, Technology and Space (MOST) in the presence of Japanese Prime Minister, Abe, and Israel Prime Minister Netanyahu. A scheme to promote science and technology in both countries was discussed in the exchange of opinions with Vice-Minister of MOST, Charyl, and the promotion of cooperation research in the ICT field between two countries was confirmed.

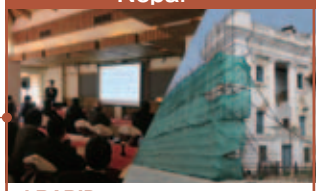
France



Next-generation wireless communication

Wireless transmission at an ultrahigh data rate was verified through cooperative research by Japan and France. It surpasses 40 Gbit/s in an unexplored frequency range up to 720GHz. This is the world's fastest uncompressed wireless transmission, which may be effectively utilized for next-generation high definition television (4K).
Adopted in FY 2009: "Wireless Communication using TeraHertz Plasmonic - Nano ICT Devices"
Taiichi Otsuji, Professor, Communication, Research Institute of Electrical, Tohoku University
Institute of Electrical, Tohoku University

Nepal



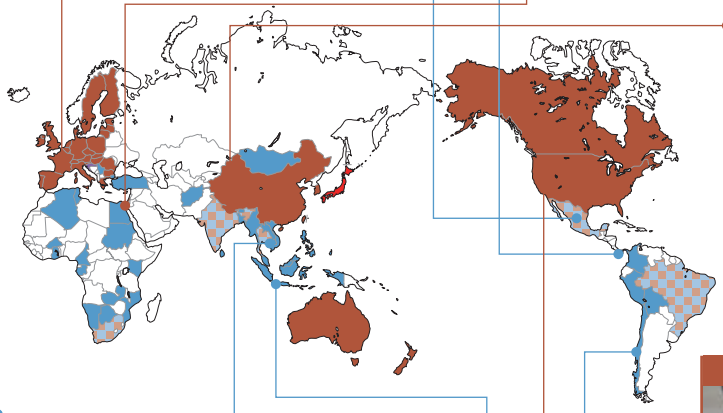
J-RAPID

In light of the Nepal earthquake occurred on April 25, 2015, an international emergency cooperative research/ investigation support program (J-RAPID) was activated. Thirteen (13) issues including damage state investigation and study for reconstruction were adopted.
Pictures
Right: Constructions in Durbar Square, World Heritage, damaged by earthquake
Left: Workshop held in Katmandu, the capital of Nepal on October 28, 2015

Chile

Disaster Prevention and Mitigation: Research Project on Enhancement of Technology to Develop Tsunami-resilient Community

Between Chile and Japan, the aim is to develop the technology of estimating tsunami damage and the technique of tsunami warning with high accuracy and propose programs to develop tsunami-resistant communities for improving tsunami prevention capability. Through these research activities, the citizens were able to evacuate quickly in the Mw 8.2 earthquake of April 1, 2014, off the coast of Iquique, Chile. (Adopted the project in 2011, "Research Project on Enhancement of Technology to Develop Tsunami-resilient Community" Port and Airport Research Institute, Asia-Pacific Center for Coastal Disaster Research, Deputy Director-General, Managing Director, Takashi Tomita)



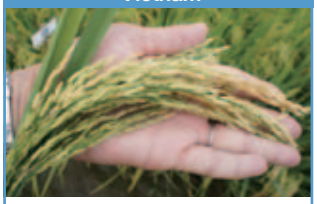
① SICP and SICORP partner countries (■) [J1]
② SATREPS partner countries (■) [J2]
③ ①and②partner countries (■) [J3]

United States

Metabolomics for a low-carbon society

In this research, open-access metabolomics databases of unicellular algae were constructed, and metabolomics data, which includes the measurement of microalgal metabolites available for industrial use, was publicized. The KNApSAcK sub database, which includes information collected from biosynthesis-related genes for metabolites from microalgals and bioactive metabolites, was also publicized.
Adopted in FY 2011: "Metabolomics: Integrating Cheminformatic Resources for Investigating Photoautotrophic and Mixotrophic Metabolism in Algae" Masanori Arita, Professor, National Institute of Genetics

Vietnam



Bioresources: Development of Crop Genotypes for the Midlands and Mountain Areas of North Vietnam

The project developed the latest rice breeding method with use of a DNA marker, and succeeded in the development of two species having useful characters of higher yield and low-temperature resistance and additionally faster growth as compared with the existing species in Vietnam. Expectations toward new species that are suitable for local weather conditions are high, and the registration of the species is now in preparation. (Adopted the project in 2010, "Development of Crop Genotypes for the Midlands and Mountain Areas of North Vietnam," Plant Breeding, Faculty of Agriculture, Kyushu University, Professor Atsushi Yoshimura)

Vietnam

Global-scale Environmental Issues: Establishment of Carbon-Cycle-System with Natural Rubber

"Lead in the natural rubber industry with new technology to suppress the global warming" The project established the refining technology for removing proteins from natural rubber, and achieved the development of application and the proposal of standardizing the evaluation technique. In addition, the development of a next-generation enzyme for converting waste rubber into fuel and a next-generation technique of treating wastewater established a system that can substantially reduce greenhouse gases. (Adopted the project in 2010,"Establishment of Carbon-Cycle-System with Natural Rubber," School of Engineering, Nagaoka University of Technology, Professor Masao Fukuda)

Indonesia

Low Carbon Society/Energy: Pilot Study for Carbon Sequestration and Monitoring

This is a CCS verification test with use of CO2 emitted from gas processing plant in Gundih, Central Java province for the first time in Southeast Asia on the basis of the partnership between both countries. They determined the press fit target stratum by a geophysical technique and performed research by an electromagnetic survey method and the like. They finished the concept design of ground facilities with support of ADB and proceed to the construction of the facilities. (Adopted the project in 2011, "Pilot Study for Carbon Sequestration and Monitoring in Gundih Area, Central Java Province, Indonesia," Graduate School of Engineering, Kyoto University, Professor Toshifumi Matsuoka)

Cameroon

Disaster Prevention and Mitigation: Comprehensive Measures and Human Resource Development for Prevention of Gas Disaster at Crater Lakes in Cameroon

The project put automatic observation buoys on Lake Nyos in North-West province to allow water temperature and electric conductivity to be observed in real time. They also put an apparatus that draws up deep water, which is driven by solar cells in Lake Monoun. They organized a team to evaluate the risk of limnetic eruption and achieved possibility evaluation by computer simulation. (Adopted the project in 2010, "Comprehensive Measures and Human Resource Development for Prevention of Gas Disaster at Crater Lakes in Cameroon," School of Science, Tokai University, Professor Takeshi Ohba)

■…SATREPS results／■…SICP・SICORP results

Giving back to society through outstanding research findings

Linking research institutions with the world of industry

Industry/academic collaboration drives market effect of around 686 billion yen!

To enable the outstanding research findings created at universi-ties and public research institutions to be incorporated into objects useful in our daily lives, cooperation with corporations is essential. Actually, no matter how remarkable some research out-comes may be, in many cases they often never reach the wider world, for a range of reasons. In order to solve this problem, JST offers support for development contracting, commissioned development, and more, as a builder of bridges between research institutions and the world of industry. JST is also involved in business promoting the establishment of venture corpora-tions. **The market effect of all this effort is around 686 billion yen, with at least 296 venture corporations established as a result of JST's business efforts**, representing a significant economic impact.

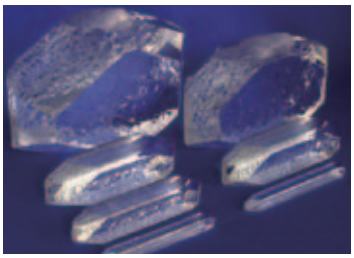
Some examples of developed outcomes of industry/academic collaborative research

*Names of research institutions, corporations and support programs are as of the time of support implementation

A.D.

Since 1958

1959 Manufacture of synthetic quartz crystals

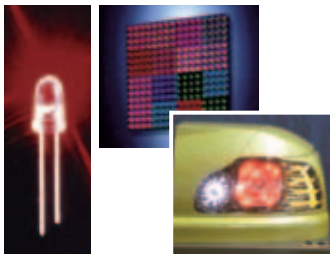


1959▶Contract development

University of Yamanashi & Epson Toyocom

Crystal oscillators (radio, televisions, clocks, computers, mobile phones) etc.

1972 High luminance red LEDs

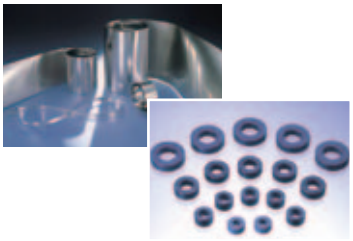


1972▶Contract development

Tohoku University & Stanley Electric

Display devices, such as large and small screen displays

1977 Manufacturing technology for magnetic material amorphous metals



1977▶Contract development

Tohoku University & Hitachi Metals (& others)

Electrical transform-ers on telephone poles, magnetic components for electronic devices

1980 Development of natural interferon-β pharmaceuticals

1980▶Contract development

Toray

Interferon drugs (medication to treat brain tumors, malignant melanomas, hepatitis B, etc.)

1981 Manufacturing technology for high-quality graphite

1981▶ERATO/Licensed

1988▶Contract development

ERATO Ogata Fine Polymer Project/ Matsushita Electri-cal Components

Developing high added-value graphite material from molecules such as polyamides. Used in heat diffusion devices for electronics etc.

1986 Manufacturing technology of gallium nitride (GaN) blue light emitting diode

1986▶Contract development

Nagoya University & Toyoda Gosei

Received the Nobel Prize in Physics (Isamu Akasaki, Hiro-shi Amano) Display devices, such as large and small screen displays

A.D.

1990

1991

1993

1998

2000

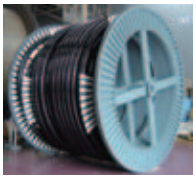
2003

2004

2006

2010

Manufacturing technology of oxide superconductor material



1990▶Contract development

The University of Tokyo (& others) & Sumitomo Electrical Industries

Superconductive ca-ble, superconduc-tive motors etc.

Manufacturing technology of polymers with phospholipid polar group

1993▶Contract development

The University of Tokyo, Tokyo Medical and Dental University, Nof

Used in contact lens-es, cosmetics, medi-cal materials, etc.

Manufacturing technology for ^{18}O-labeled water (as a PET diagnostic agent)

2000▶Contract development

Tokyo Institute of Technology & Taiyo Nippon Sanso

Contributing to early detection and treat-ment of cancer as a material for use in PET examinations

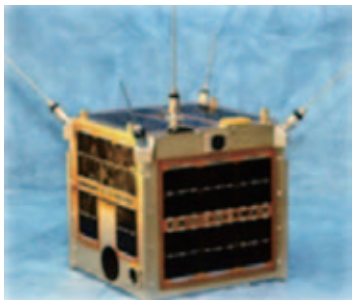
Artificial hip joint with long-term reliability

2004▶Contract development

Chubu University & Japan Medical Materials

Improving quality of life for patients with rheumatism or hip joint problems

Leading the next generation space business of ultra compact satellites with low-cost and short-term development



2006▶University-generated venture

Axelspace Corpora-tion

Leading the next generation space business of ultra com-pact satellites with low-cost and short-term development

Manufacturing optically-active alcohol vari ants

1991▶ERATO

1998▶Contracted/licensed

Kanto Kagaku & Takasago Internationals

Practical application of re-search findings that re-ceived the 2001 Nobel Prize for Chemistry (Ryoji Noyori). Can be used as raw materials for medical/agrochemical in-termediates etc.

Creating environmental technology by developing original optical materials

1998▶Regional consolidation

Kanagawa Academy of Science and Technology & others

The ability to break down photocatalysts is utilized in air clean-ing devices, construc-tion materials, etc.

Retinoic acid nanoparticles

2003▶Pre-venture

Nanoegg

Effective results antici-pated not only for cos-metic uses, but also medical uses.

High-quality and high-efficiency process technology of titanium alloy with high-brightness laser adaptive control

2010▶A-STEP Seeds Development Type

Osaka University & CHARMANT

Commercialization of high performance eyeglass frame with unprecedented precise design and an unique structure combining different materials.

Collection and use of reliable information

Creation of infrastructure for scientific and technical information

Proposals for new ways to utilize scientific and technical information

The explosion of information easily accessible via the Internet makes it more important than ever to collect and use of reliable information. JST, while maintaining and providing a wealth of easily usable content, proposes new solutions for utilizing information as "Big Data." For example, the J-GLOBAL service provides not only a one stop search service for information such as researchers, articles, patents, chemical substances and technical terms, but also "Related searches" that give serendipitous information, which leads to further breakthroughs with new perspectives and concepts.

Furthermore, these contents can be analyzed and visualized as research and development Big Data by J-GLOBAL foresight tool for both policy decisions in government and business decision making.

Websites for major services

Coordination of scientific and technical information

J-GLOBAL
科学技術総合リンクセンター
J-GLOBAL
Comprehensive Gateway Linking
Multiple Scientific and Technological Databases

J-GLOBAL foresight
J-GLOBAL foresight
Evidence-based Evaluation Methods
for Decision Making

New discoveries through different genres of scientific and technical information

- Information on researchers, articles, and patents can be searched at once by entering a single keyword. Various information databases are linked one another to allow a direct access. "Related searches" enables discovery of content similar to information of interest.
- Contains basic information on researchers (around 240,000 persons), articles (37 million items since 1975), patents (11 million items since 1993), chemical substances, genes, and technical terms (figures current at December 2015)
- Research achievements (academic papers, patents, etc.) inside and outside of Japan are analyzed, and current research trends are viewed from various angles such as by nation, organization and researcher. New analysis methods created by giving data accumulated by JST to researchers, as well as analysis methods and tools developed uniquely by JST are provided.

NBDC
National Bioscience Database Center
National Bioscience Database Center

Promotes the integrated use of life science databases by providing free services through a portal site

- [Integbio database catalog]
  Searching, viewing, and downloading of life sciences database information
  (Number of registered databases: 1,518)
- [Life sciences database cross-search]
  One-stop search combining patents and academic papers from databases in the field of life sciences
  (Number of searchable databases: 555)
- [Life sciences database archive]
  Full downloads of databases created in Japan
  (Number of public databases: 108)
- [NBDC Human Database]
  A platform to share various human-related data
  (Number of available datasets: 29)

Online access to electronic journals in Science and Technology

J-STAGE
Japan Science and Technology Information Aggregator, Electronic

Platform for electronic journal publishing in all fields of science

- Over 1,000 academic associations use to publish over 1,900 journals, most of which are openly archived.
- Expanding the genre to include Research Reports, Technical Reports, Conference Papers and Proceedings, Magazines, and Others
- Globally accessible via search services and other academic databases
- Support international data format standard of XML, earlier publication, and provide citation and cited references.

Information service to support research

JREC-IN Portal
Human resource database for researchers

Supporting researchers seeking employment and research institution seeking staff

- Contains listings not only of research positions, but also a diverse range of publicly listed industrial / academic / administrative positions connected to research work (around 17,000 per year)
- e-learning courses for researchers
- Providing information of content and events for career development

researchmap
Japan's largest comprehensive researcher database

A database containing researcher vitae information and provide SNS services for on-line academic discussion

- Access to information on 240,000 researchers

Registration of permanent identifier DOI (Digital Object Identifier)

Japan Link Center
The only DOI Registration Agency in Japan

Register DOIs and join the group for distributing academic information!

- Domestic organizations have been registering DOIs to electronic academic contents (journal articles, doctoral dissertations, books (reports), research data, and e-learning). DOIs have been registered to approx. 3.14 million of papers and articles as of the end of December 2015.
- It is jointly operated by JST, National Institute for Materials Science (NIMS), National Institute of Informatics (NII), and National Diet Library (NDL).

As of December, 2015

Voice of Users

J-GLOBAL
Comprehensive Gateway Linking Multiple Scientific and Technological Databases

- I can use it to keep track of what is happening with researchers who are acquaintances or are active in different fields. Sometimes with big projects, you have to start from nothing; in those cases, it provides an opportunity to search for researchers
- It is great that it allows you to systematically view each researchers track record. Looking at your own field of research, including tangentially related disciplines, helps you see how previously unknown or unclear research is positioned
- It is good that small- and medium-sized corporations with limited budgets can also utilize it "free-of-charge"

JREC-IN Portal
Japan Research Career Information Network Portal

- Not only me but also many researchers using this database
- There is no other large scale online employment database conducted by publicly that is very helpful
- This is very supportive database when I ahead with fair selection

Support science and technology education from various perspectives!

Fostering the Next Generation Leaders in Science and Technology

Promote the development of future global leaders in science and technology

The qualities and abilities required for human resources in science and technology have been changed in order to overcome various crisis and issues, according to the globalization. Considering the population decline and aging society in Japan, the development of world-class human resources is the key to continue achieving the highest level of research and development. To contribute to the advancement of Japanese science, JST makes continued efforts to discover the students who have excellent qualities and abilities, and to develop the talents of those students.

Support for Super Science High Schools (SSHs)!

JST offers the necessary support to further the activities of those high schools designated by the Ministry of Education, Culture, Sports, Science and Technology in Japan (MEXT) as Super Science High Schools (SSHs), as well as promoting liaisons with boards of education governing SSHs.

These SSHs are making ongoing efforts aimed at developing their curricula focusing on advanced science, technology, and mathematics, as well as undertaking advanced science/mathematics education in collaboration with universities and developing teaching methods and materials to increase creativity and uniqueness.

Currently 203 high schools nationwide have received SSH designation in 2015. Each school undertakes a range of different unique activities, with many great results evident.

Examples of SSH activities

- ○ Curriculum development
- ○ Core institution
- ○ National Consortium
- ○ International exchange
- ○ Researching issues
- ○ International Science Olympiad
- ○ Science club activities
- ○ University/school liaison

Results of Super Science High School survey

● **Survey conducted in 2014**
(targeting 201 SSHs schools)

Has your desire to learn about science and technology increased due to the SSH program?

67%

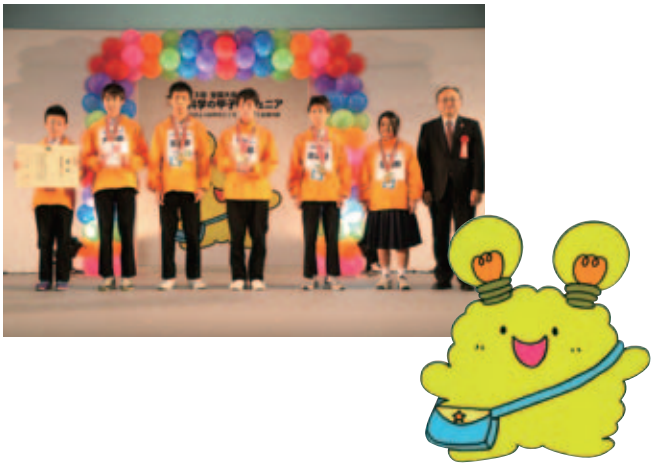
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
No. of schools supported that year	82 school	99 school	101 school	102 school	106 school	125 school	145 school	178 school	201 school	204 school
No. of SSH students	16,663 people	21,963 people	24,867 people	29,631 名	34,724 people	38,738 people	45,557 people	60,283 people	78,363 people	88,120 people

'Science Koshien' Japan High School Science Championships: a "Festival of Science" for science-loving kids

JST has conducts the 'Science Koshien' Japan High School Science Championships, in which science-loving high school students across Japan form into teams since 2011. The 'Science Koshien Junior,' for junior high school students, started in 2013, which more than 23,000 participated in a primary exam. nationwide.

The champion team of 'the nationwide Science Koshien Junior' was invited to 'the Science Koshien' , and the attendants enjoyed association that surpass generations and regions.

The 'Science Koshien' is an opportunity to encourage one another and to increase students who are fond of math and science.



Championships mascot "Appin"

Striving against the world: Support for international contests in science and technology

Many different international competitions exist in the world of science and technology. JST has implemented many programs in support of young students participating in these international contests in science and technology, and also supports various Japanese and international contests.

A great many students participate in Japanese contests; as a result, selected students competed with elite students from around the world. All 31 Japanese representatives s earned medals (eight of them won gold medals) in 2015.

Participating students replied that the experience "increased their eagerness to study," demonstrating that these events provide a place for science-loving students across the nation to actively further their education.

List of international contests in science and technology

- ○ International Mathematical Olympiad
- ○ International Chemistry Olympiad
- ○ International Biology Olympiad
- ○ International Physics Olympiad
- ○ International Olympiad in Informatics
- ○ International Earth Science Olympiad
- ○ International Geography Olympiad
- ○ Japan Students Science Awards
- ○ Japan Science & Engineering Challenge (JSEC)
- ○ RoboCup Junior
- ○ World Robot Olympiad

Total number of participants in international contests in science and technology

	2009	2010	2011	2012	2013	2014
Total participants	10,504 people	11,293 people	12,862 people	14,764 people	16,388 people	18,089 people

Performance of Japanese representatives in 2015 international contests in science and technology

	Gold	Silve	Bronze
Mathematics	0	3	3
Chemistry	2	2	0
Biology	1	2	1
Physics	1	2	2
Informatics	3	0	1
Earth Science	1	1	2
Geography	0	3	1
Total	8	13	10

Developing personnel who can take an active role on the future global stage (Global Science Campus)

In 2014, JST launched the Global Science Campus, which enables high school students with excellent motivation and abilities to participate in academic education in science field and international activities. About a thousand young students participated in seminars that were offered in the thirteen universities nationwide in fiscal year 2015, and some of them achieved fruitful results, such as presentations at the international congress and awards in the international science and engineering fair.

List of JST' s Global Science Campus (in 2015)

○ Hokkaido University ○ Tohoku University ○ University of Tsukuba ○ Utsunomiya University ○ Saitama University
○ Tokyo University of Science ○ Keio University ○ University of Fukui ○ Kyoto University ○ Osaka University
○ Okayama University ○ Hiroshima University ○ Kyushu University

Citation/Award-winning

Main Prizes and Recognition

Nobel Prize in Physics



Invention of efficient blue light-emitting diodes which has enabled bright and energy-saving white light sources(2014)

Isamu Akasaki Meijo University and Nagoya University, Japan
Hiroshi Amano Nagoya University, Japan
Shuji Nakamura University of California, Santa Barbara, USA

Nobel Prize in Physiology or Medicine

Discovery that mature cells can be reprogrammed to become pluripotent※1 (2012)

Shinya Yamanaka
Director, Center for iPS Cell Research and Application, Kyoto University
※1 Share the laureate with Sir. John Gurdon

Japan Prize

Creation of unconventional inorganic materials with novel electronic functions based on nano-structure engineering

Hideo Hosono
Professor, Materials and Structures Laboratory and Director of Materials Research Center for Element Strategy, Tokyo Institute of Technology

Canada Gairdner International Award

Discovery of regulatory T-cells, characterization of their role in immunity and application to the treatment of autoimmune diseases and cancer (2015)

Shimon Sakaguchi
Professor, WPI Immunology Frontier Research Center, Osaka University

Ground-breaking discovery of Toll like receptors and the array of microbial compounds that they recognize to provide innate resistance to infection (2011)

Shizuo Akira
Director, WPI Immunology Frontier Research Center, Osaka University

Thomson Reuter Citation Laureates

Seminal discovery concerning the nature and function of regulatory T-cells and the transcription factor Foxp3 (2015)

Shimon Sakaguchi
Professor, WPI Immunology Frontier Research Center, Osaka University

Pioneering research on new multiferroic materials

Yoshinori Tokura
Professor, School of Engineering, The University of Tokyo

Discovery of Iron-based Superconductor (September, 2013)

Hideo Hosono
Professor, Materials and Structures Laboratory and Director of Materials Research Center for Element Strategy, Tokyo Institute of Technology

Elucidating the molecular mechanisms and physiological function of autophagy※2(September, 2013)

Noboru Mizushima
Professor, Biochemistry and Molecular Biology, Graduate School and Faculty of Medicine, The University of Tokyo
※2 Share the laureate with Yoshinori Ohsumi Professor, Fr

Discovery of photocatalytic properties of titanium dioxide (the Honda-Fujishima Effect) (September, 2012)

Akira Fujishima
President, Tokyo Science University

Thomson Reuters "Top 100 Global Innovators 2015"

JST is the first public institution in Japan to receive the award (2015)

Japanese companies and organizations made up 40 of the top 100 in the list. JST is the first public institution in Japan to receive the award.

INNOVATOR OF THE YEAR

Identifying genes that cause cancer, etc.

Hiroyuki Mano
Professor, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

Selected as one of the 'Breakthrough of the year' in the US scientific journal Science


Intestinal bacteria of obese mice brew up carcinogens to trigger liver cancer.

Naoko Ohtani Senior Staff Scientist, The Cancer Institute of Japanese Foundation for Cancer Research
Eiji Hara Division Chief, The Cancer Institute of Japanese Foundation for Cancer Research

Created functional human organs made by human iPS cells such as a 'mini-liver' for the first time in the world

Hideki Taniguchi

Professor, Yokohama City University

Clarification of structure of crystals of "photochemical complexⅡ" which protein is required for producing oxygen from water and sunlight.

Jian-Ren

Shen Professor, Graduate School of Natural Science and Technology, Okayama University

To produce a fertile egg by Pluripotent stem cells of mouse (ES Cells, iPS Cells)

Mitinori Saitou

Professor, Institute for Integrated Cell-Matenal Sciences, Kyoto University

Selected as one of scientists list "Five to watch" from the British scientific journal "nature"

Using induce pluripotent stem cells (iPS) to human retinal pigment epithelium.

Masayo Takahashi

Center for Development Biology, RIKEN

Academic papers citation trend

With regards to the academic paper citation trend in Japan, JST corresponds to the second in rank behind The University of Tokyo; however, JST is first place excluding universities. The average number of citation is outclassing and it is indicate that presented paper is excerpt by many researchers.

Ranking of Japanese research institutions based on number of highly cited papers

Rank	Institution Name	Number of Highly cited papers	The ratio of the Number of Highly cited papers
1	The University of Tokyo	1,311	1.6%
equivalent to 2	**Japan Science and Technology Agency**	**827**	**2.5%**
2	Kyoto University	739	1.2%
3	Osaka University	590	1.2%
4	RIKEN	557	2.3%
5	Tohoku University	505	1.1%

Thomson Reuters: Press Release on April 16th, 2015
Created by JST based on "Thomson Reuters Identifies Japan's Top Scientific Research Institutions Based on Analysis of Number of High Impact Papers."
Database used for analysis "InCites Essential Science IndicatorsTM"
This study looked at papers published from January 1, 2004 to April 12, 2014.
*Since 2015, its funding agency JST has not been listed in the rankings; however, JST's rank corresponds to second place with 827 high cited papers and 2.5% in the ratio of the number of highly cited papers, according to the report by Thomson Reuters.

Licensing

We find out companies using networks and MEKIKI who is insight of the person in the leadership posi-tion and the other resources, Licensing of R&D based on requests from Universities, Institutions and Research result projects by JST and others.

[License] Results of 2014 No. of Companies 21 companies / No. of patents 206 patents

Example 1 of past results	Example 2 of past results
●Glutathione -A New Agricultural Fertilizer for Enhancing Plant Productivity- **Ken'ichi Ogawa** (Research Institute for Biological Sciences, Okayama (RIBS OKAYAMA) Okayama Prefectural Technology Center for Agriculture, Forestry, and Fisheries) et al.	●A packaging design for floating illusion graphic **Hitoshi Arai** (The University of Tokyo)
 Glutathione-fed millet / Glutathione-unfed millet CREST Results of CREST projects "Photo-stress in the Cryosphere and Maintenance Mechanisms of Boreal Forest" and "Innovation and Development of New CO2-Fixation-Promoting Technology for Increasing Bio-Material Production" Okayama Barley Genome Technology Co., Ltd. Kaneka Corporation	 PRESTO "Mathematical models of visual perception by means of wavelet frames" Rokkatei Seika Co.,Ltd

Outline of JST's Activities

As the core institution responsible for the implementation of Japan's S&T policies, JST is making efforts toward the maximization of R&D outcomes and solid contributor to national competiveness and the sustainability of global society.

Mission

Contributing to the Creation of S&T Innovation

Vision

1. **We actualize S&T Innovation through creative R&D.**
2. **We maximize research outcomes by managing research resources under the "Virtual-network based Research Institutes" scheme.**
3. **We establish Japan's S&T infrastructure to accelerate S&T Innovation.**

JST's Outline

The Government

Proposals

Medium Target

*Strategic Program Package

*Strategic Program Package; Comprehensive program packages of prioritized areas

Planning of R&D Strategies

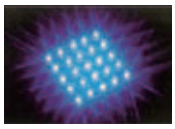
JST investigates R&D trends in S&T and the need for S&T in society and formulates strategies for more effectively promoting R&D.

Promoting the Creation of S&T Innovation

JST provides consistent funding for R&D from basic transdisciplinary research, undertakes international joint research and forms local research based to promote the creation of S&T Innovation.

Strategic basic Research

Innovation-type research by academic-industry collaboration

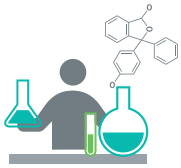


International joint research

Building Infrastructure for the Creation of Innovation

JST carries out activities to inform the public about scientific information that is available and human resources development as well as about the roles and importance of S&T.

Dissemination of scientific and technological information

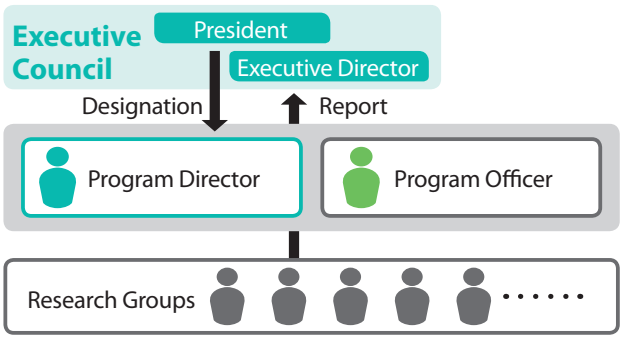


Promoting science education

Promoting communication between science and society

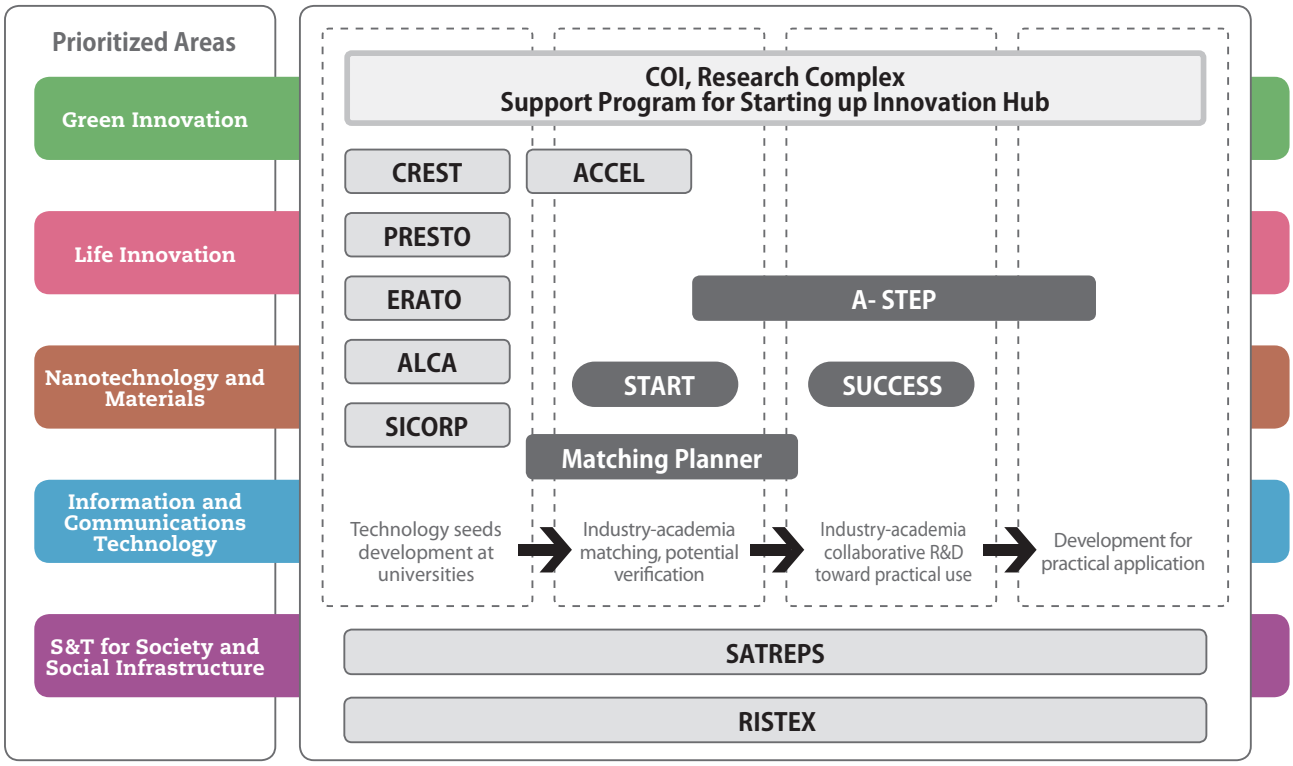
Operating Virtual-network based Research Institutes

JST constructs virtual research institutes comprising researchers from universities, enterprises and public research organs. Program Directors (PD) supervise the overall program and consider operational policies. Under management of the Program Officers (PO) such as Research Supervisors who serve as the directors of the institutes, the research groups led by principal investigators advance research by jointly working with best researchers of different institutions and with the business community toward their challenging target.



Promoting Cross-Program and Cross-Cutting Initiatives

JST has formulated a Strategic Program Package in each of the following five fields. In each priority area, JST is taking a unified approach to basic research, innovation-type research through industry-academia collaboration, international joint research and intellectual property-related activities. High-impact innovations stemming from top science are pursued by strengthening breakthrough research and seamless schemes toward industry. Also, innovation hubs are established for back-casting integrated research.



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