Chapter 1 Progress in Science and Technology and Socioeconomic Changes

Society and lifestyle have constantly changed with fast-evolving science and technology. We are so accustomed to enjoying affluent and convenient lives on a daily basis by utilizing new technologies and products that we rarely think about the progress in science and technology or the basic scientific and technological study that underpins it.

This chapter presents practical examples of lifestyle changes in the last decade, as science and technology have progressed in Japan, and outlines how science and technology have helped solve various socioeconomic problems while estimating long-term socioeconomic changes. Finally, it introduces a range of recent scientific and technological events in order.

Section 1 Progress in Science and Technology and Lifestyle Changes

In recent years, scientific and technological achievements have swiftly made their presence felt in our lives, in the form of cutting-edge gadgets like LED lights and smartphones. How have science and technology been developed and utilized in Japan? This section introduces some scientific and technological achievements that changed our lives, covering the entire process from the emergence of a seed to commercialization, efforts made by researchers and supportive measures provided by government.

1 Photocatalysts

When looking at new walls of a new house, or cleaned window glass, many of us long to keep them that way forever. This section explains about stain-resistant, antibacterial and deodorant photocatalysts used to coat exterior walls and window glass of the house.

○ Background and progress of R&D

A photocatalyst is a material that accelerates a chemical reaction without changing its structure when light is irradiated. There are several photocatalytic materials, but titanium oxide is used for most photocatalytic products, due to its high photocatalytic activity, chemical stability and affordable price.

Titanium oxide has two distinct features, "oxidative decomposition" and "superhydrophilia[1]." It is currently used in various fields, including purification of air and water and antibacterial-, antifouling- and defogging materials (Figures 1-1-1 and 1-1-2) and typical examples include external building materials. Photocatalyst-coated external wall materials decompose stains and molds with oxidative decomposition properties of photocatalysts, or exert "self-cleaning" capability which allows rainwater to permeate under the stains and to wash them away by superhydrophilic property when rain hits external walls. These two properties keep the wall surface free of molds or stains for an extended period, which makes its maintenance cost cheaper. For instance, the white tents installed at the Yaesu exit of Tokyo Station are

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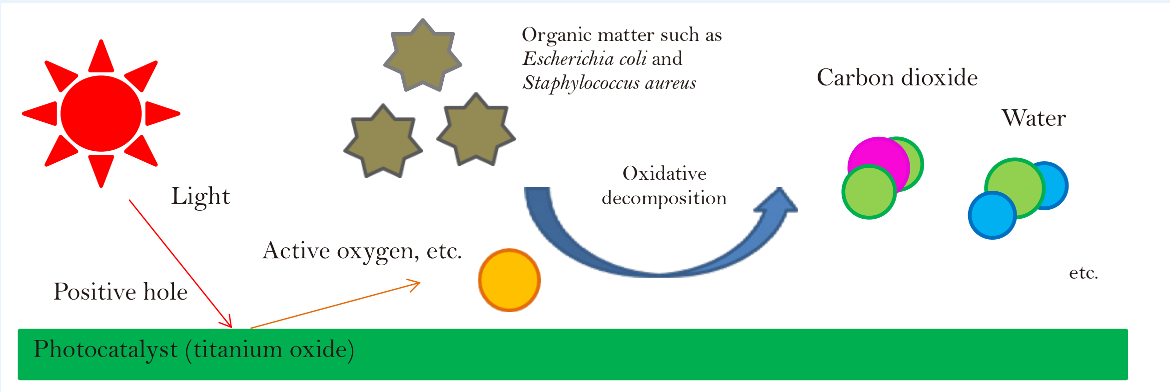
1 The arc of contact between a droplet and material surface indicates the hydrophilic level of the material surface. The arc of contact is an angle made by the tangent lines of the material surface and a droplet on the edge of the droplet that falls onto the material surface. Materials with large and small arcs of contact are respectively described as water-shedding and hydrophilic, while a material having near-zero arc of contact is superhydrophilic. Droplets on superhydrophilic materials are flattened and do not retain their spherical shape due to the very small arc of contact.

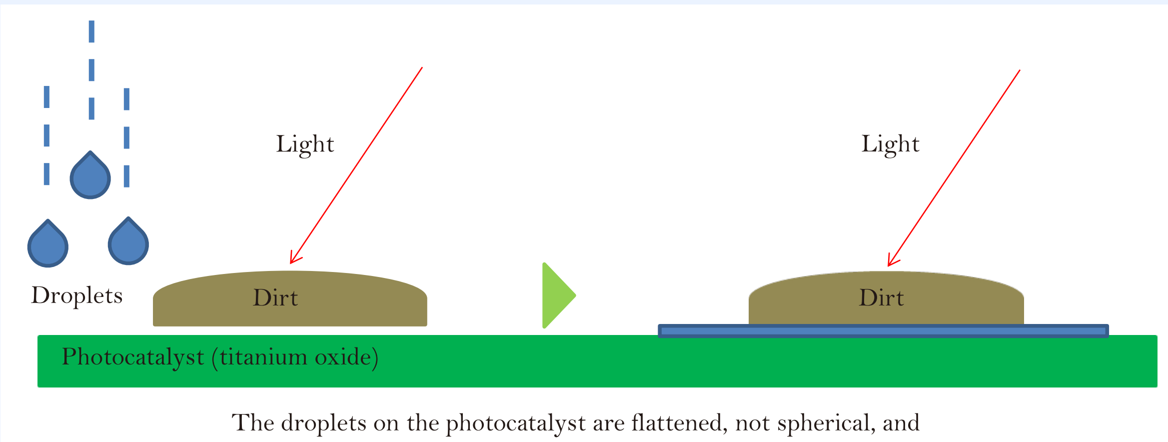
photocatalytic tents which hardly get dirty because of their excellent photocatalytic properties. In addition, the white tent sheet lets light through in daytime to help brighten the space underneath without artificial lighting and also save energy, since white reflects light well and thus helps keep the internal temperature low. The market of photocatalyst applied in a wide range of industries is said to be worth 100 billion yen.

■ Figure 1-1-1/Mechanism of Oxidative Decomposition by Photocatalyst



Source: MEXT

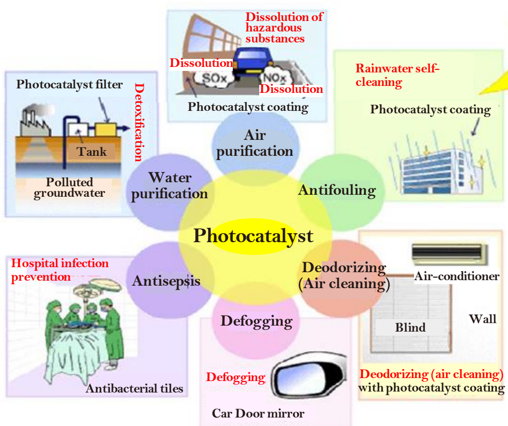
■ Figure 1-1-2/Self-cleaning of superhydrophilic property



Source: MEXT

The study of photocatalysts began with an experiment by Akira Fujishima, then postgraduate student and current President of the Tokyo University of Science, under the tuition of then Prof. Kenichi Honda of the Institute of Industrial Science at the University of Tokyo (later becoming Professor Emeritus of the University of Tokyo). He discovered the photocatalytic property of titanium oxide, when water containing titanium oxide and platinum electrode decomposed and oxygen and hydrogen bubbles were generated by irradiating ultraviolet rays. This "Honda-Fujishima Effect" was presented at an academic conference in Japan, but the finding was initially rejected because the idea that light energy was strong enough to cause the electrolysis of water defied common sense at the time. Later, in 1972, a paper of this finding was published in Nature magazine and attracted considerable attention from researchers of all over the world. When the first oil crisis happened in 1973 and hydrogen energy began to be discussed as an alternative to petroleum, the experiment using the light to produce hydrogen drew increasing attention, both domestically and overseas.

However, the study of photocatalysts had not been put into practical use in the next 20 years. Although ultraviolet rays did decompose water, in reality, the resulting hydrogen and oxygen reverted to water during a back reaction. Nevertheless, a breakthrough was made by Tadayoshi Sakata of the Institute for Molecular Science in Okazaki, Aichi Prefecture (now Professor Emeritus at the Tokyo Institute of Technology) and Tomoji Kawai (now Designated Professor at the Institute of Scientific and Industrial Research, Osaka University.) They succeeded in eliminating the back reaction and generating vigorous hydrogen bubbles by mixing alcohol in water. In 1989, Kazuhito Hashimoto (now Professor of the Graduate School of Engineering, the University of Tokyo), then co-researcher of Sakata and Kawai for the applied study of the Honda-Fujishima Effect, became a lecturer of the Department of Applied Chemistry, Faculty of Engineering at the University of Tokyo where Fujishima worked. Based on the idea suggested by Hashimoto, namely to use a photocatalyst to dissolve hazardous substances which are problematic, even in minute traces, Fujishima commenced joint research with TOTO Co., Ltd. (then TOTO Kiki Ltd.) in 1990 to accelerate the commercial application of titanium oxide. When the tiles used for a lavatory were coated with titanium oxide and irradiated with light, microorganisms on them, such as Bacillus coli and Staphylococcus aureus, were inactivated. In 1993, TOTO placed titanium oxide-coated tiles on the market as "photocatalytic antibacterial, antifouling, deodorizing tiles." In the course of the applied study, the research group discovered superhydrophilia, a phenomenon whereby water on the surface of the titanium oxide-coated glass spread over the entire surface when light was irradiated.



Application Areas of Photocatalyst
Source: METI

○ Government roles

The major roles of the government in developing and disseminating photocatalysts are the support of the basic research phase with the Grants-in-Aid for Scientific Research ("KAKENHI") and the international standardization of R&D outcomes. Commercialization of photocatalysts began in 1993. However, there was no way to objective evaluation of performance and the photocatalytic property of some products on the market remained questionable, which made it difficult for consumers to select the right products.

METI launched a commissioned project to standardize photocatalyst test procedures during the period FY 2003 to 2006 to integrate test methods for evaluating photocatalyst performance and drafted detailed international standards to measure hydrophilic and oxidative decomposition properties based on test data. International standards for the method of evaluating self-cleaning performance were established later. As international standards for measuring and evaluating various self-cleaning features of photocatalysts have been successively established, this has allowed products on the market to be properly evaluated and has helped facilitate the marketing of new products.

Up to that time, titanium oxide reacted only with ultraviolet rays having high photon energy and accounting only for 3 to 4% of sunlight. Because visible lights with low energy and comprising about 43 percent of sunlight could not be used, photocatalytic reactivity was only expected in limited locations such as outdoors, where strong ultraviolet rays are irradiated, which significantly hindered extensive commercialization. The research group led by Hashimoto developed a new photocatalyst in the "HASHIMOTO Polymer Phasing Project" as part of the then Exploratory Research for Advanced Technology (ERATO)[1] of the Japan Science and Technology Agency (JST) from FY 2006 to 2011 and found that it showed a high response to visible light in the photolytic reaction of organic matter. Building on this finding, the "Project for Creating Photocatalyst Industry to Realize Recycling-Oriented Society" of the New Energy and Industrial Technology Development Organization (NEDO), implemented during the period FY 2007 to 2012 focused on developing highly practical photocatalysts and made significant progress. This project, intended for marketing from the beginning, set an ambitious goal of increasing photocatalytic reactivity with visible lights ten times higher than usual and achieved this goal. Further, the feasibility test for products using this photocatalyst at hospitals and airports proved its effect in practical environments, establishing a foothold for commercialization.

○ Future prospects

The potential applications of photocatalysts in the medical sector, including the study of cancer treatment, are planned. For instance, one experiment aimed to suppress cancer cell growth by injecting titanium oxide particles into cancer cells and irradiating ultraviolet rays is performed. This application involves many issues to address -- how to expand titanium oxide particles in the cancer-affected area, or how to irradiate ultraviolet rays, but medical treatment using photocatalysts has advantages in that a reaction can only be evoked when ultraviolet rays are irradiated, which makes it easy to control.

1 The Exploratory Research for Advanced Technology in Strategic Basic Research Programs by the present JST. Based on the policies in the Science and Technology Basic Plan, "strategic goals" are determined as prioritized R&D subjects and "research areas" are set. This is intended to help create new technology seeds that may spawn science, technology and innovation and, through subsequent joint research with R&D institutions and companies, contribute to resolving critical issues in Japan.

In addition, the purification of polluted soil has also been actively studied. For instance, the decomposition of growth retardant in the nutriculture was attempted[1] at a plant factory. This application requires the development of a system with an agricultural mindset to use sunlight with low energy density effectively, such as acquiring sufficient energy by spreading a sheet-type photocatalyst on the ground to collect sunlight widely on a plane. In fact, photocatalytic sheets were developed to purify and circulate waste fluid from nutriculture, purify used pesticides and cleanse areas of land polluted by volatile organic compounds and field tests were conducted.

Using newly developed photocatalysts that absorb visible light, acquiring energy by decomposition water into oxygen and hydrogen, namely the original goal of the Honda-Fujimoto Effect, has made the progress. The Artificial Photosynthesis Project, launched by METI in FY 2012 as a Future Pioneering Project, promotes R&D into a means of producing hydrogen from water efficiently by boosting the efficiency of direct use of solar energy for decomposing water using a photocatalyst (solar energy conversion efficiency) up to 10 percent.

A new phase of photocatalytic study has been introduced every decade to date and now, in the 21st century, a significant step has been taken in the basic research of material search, as well as a large progress in the study of application to the environment and energy fields. Technologies using photocatalysts are expected to be developed in various fields and bring positive changes to our lives in future.

2 Smartphones and IGZO

○ Rapid diffusion of smartphones

The ownership rate of smartphones by households in Japan was 9.7% at the end of 2010 and had increased to 62.6% at the end of 2013.[2] The videos in Shinjuku Station taken immediately after the Great East Japan Earthquake in March 2011 showed that the majority of people trying to contact their family and acquaintances with mobile phones in hand, but now, many passengers in a commuter train hold smartphones. The speed with which new ICTs penetrate our lives is amazing.

Smartphones have transformed our lives and supply all the functions formerly provided by individual devices, such as phone calls, Internet access, information management, media player, camera, games, electronic books, navigation, television and radio, in a portable and light gadget that fits into the palm of a hand and serves us anytime, anywhere. It is becoming a must-have item in our lives with irreplaceable convenience.

While wide-ranging science and technology is used in smartphones, Japanese science and technology stands out in core electronic components such as lithium-ion batteries, liquid crystal displays, memories, electronic and camera sensors, which make smartphones lighter, power-saving, highly accurate and slimmer.

For instance, the lithium-ion battery was the product of key findings by Japanese researchers during the R&D phase and a Japanese manufacturer succeeded in commercializing their achievements as a world first (see Column 1-6). By virtue of the high energy density, the lithium-ion battery can be downsized with

1 A method for growing plants in cultured fluid, instead of soil
2 “2010, 2013 Communications Usage Trend Survey” by MIC

higher capacity and this technology has been used to downsize and lighten various mobile devices. As mentioned in Feature 1, LED lights are used to back-light liquid crystal displays (LCDs). The IGZO thin film transistor (TFT), which is increasingly used for liquid crystal displays of some smartphones, tablet PCs and large screen, organic EL[1] televisions, is also science and technology developed in Japan.

○ Features of IGZO LCDs

IGZO is an oxide semiconductor comprising indium, gallium, zinc and oxygen and LCDs using IGZO as the TFT are called IGZO LCDs. It was first commercialized by a Japanese company. The TFT is an essential component of the LCD, which is used to amplify electric signals and switch circuits. Image information on the LCD can only be recognized when the TFT controls the light for each pixel[2] emitted from the light source on the back of the LCD.

The resolution of LCD images is proportional to the mobility of electrons in the semiconductor (electron mobility). IGZO has around 20 times the electron mobility of the amorphous silicon semiconductor[3] generally used in LCDs, allowing TFTs to be downsized, with finer resolution and larger images.

Another significant IGZO feature is the minimal current leakage to the insulated area when the TFT is active. Leakage of current may cause malfunctions as well as excess heat and power consumption. In TFTs made of amorphous silicon semiconductors (amorphous silicon-TFT), current remains in circuits, even when still images are displayed or pixels are inactive (the inactive time is about 1,000 times the active time), which increases power consumption. In contrast, IGZO-TFT features a leak current smaller than amorphous silicon-TFT by several digits and retains images for a certain period after the current supply stops. Accordingly, intermittent ON/OFF control of current is possible for LCDs with IGZO-TFT, helping reduce power consumption and the recharging frequency of smartphones.

Good electrical properties and ease of production will accelerate the use of IGZO-TFT in future. Its application will extend beyond small- and medium-sized LCDs to 4K or 8K high-resolution and large LCDs, which are difficult to control with amorphous silicon-TFT and to computer monitors. IGZO-TFT was also used in a large-screen organic EL television set (photo) placed on the market in 2014, suggesting the feasibility of using it for large-screen organic EL displays which is in the spotlight as a post-LCD display.

55", 4K organic EL TV set driven by IGZO-TFT
Source: Hosono Laboratory

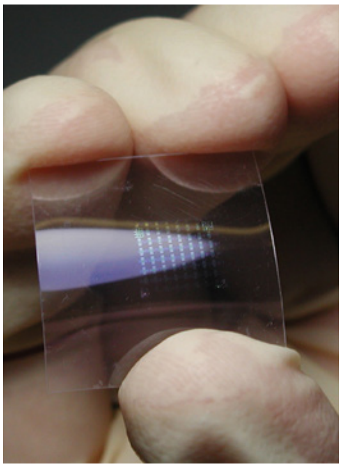
○ Progress for commercialization of IGZO LCD

The crystal structure of IGZO was identified by Noboru Kimizuka et al. of the National Institute in Inorganic Materials (now National Institute for Materials Science) in the mid-1980s, but Hideo Hosono, then assistant professor of the Industrial

1 In organic EL (Electro-Luminescence), certain organic substances emit light when voltage is applied. Unlike the LCD display, which does not emit light itself, the organic EL display does not need backlighting to illuminate the screen.
2 Pixels are the smallest unit of color information on the display screen.
3 A semiconductor made of hydrogen-containing silicon. Amorphous is the antonym of crystal, indicating no regularity in the row of atoms, nor any sharp peaks in the X-ray analysis.

Material Laboratory at the Tokyo Institute of Technology (now professor of the Material & Structures Laboratory at the Tokyo Institute of Technology) and his research group conducted research focusing on TFT for use in semiconductors. The initial research around 1990 was supported by KAKENHI and private financial groups. According to conventional wisdom at the time, "Transparent amorphous materials such as glass do not conduct electricity." However, Hosono continued researching nonetheless and in 1994, found a material that retained high conductivity and electron mobility in a transparent amorphous state. The following year, he proposed a guideline for material design based on his speculation about the trajectory that forms a conducting path of electrons and presented a range of potential materials to produce transparent amorphous oxide semiconductors (TAOS) with high electron mobility based on the periodic table of the elements at the 16th International Conference on Amorphous Semiconductors held in Kobe. However, his presentation received a lukewarm response from academic society and researchers. At the time of this presentation, in 1995, Braun tube television sets were the mainstream and LCD was mainly applied to mobile phones and laptop computers. The history and achievements of amorphous silicon semiconductors were highly evaluated, which said it all.

Later, Hosono was appointed project leader of the Exploratory Research for Advanced Technology (ERATO) Program of JST from October 1999 to September 2004 and led an experimental study to prove the validity of the TAOS design guideline proposed at the previous international conference. As part of this study, he presented the crystalline IGZO-TFT in the Science magazine in 2003 to show the potential of IGZO as the new technology seed. He was also engaged in basic research and an application study at the same time from October 2004 to March 2010 in the research program, Solution-Oriented Research for Science and Technology [1](SORST), targeting to apply the ERATO study for practical use and commercialization in the future. During this period, he successfully proved the validity of the TAOS design guideline by electronic state analysis[2] using Super Photon ring-8 Gev (SPring-8)[3], and established the TAOS material design basis.



IGZO thin-film transistor
The thin film produced on a plastic substrate can be easily bent.
Source: Hosono Laboratory

In 2004, Hosono, who had convinced that "A material in use is a material indeed," also produced a prototype IGZO-TFT, a type of TAOS. Conventional TFTs using amorphous silicon semiconductors need high temperatures to produce thin films and a hard substrate like glass plate to mount TFTs, while IGZO-TFTs can be easily fabricated to thin films at room temperatures. This means a lot. A thin and bendable plastic plate substrate reduces the size and weight of small electronic devices such as mobile phones. Further it could produce more exotic products beyond the bounds of common sense, so-called flexible electronics such as displays that can be rolled up like a projector screen or wrapped around a column, or sun blinds that project TV screens.

1 A research program such as ERATO targets significant results, which may be key for future science and technology, or contribute to future commercialization by continuing research, potentially obtaining good results and sparking future development beyond the initial research period.

2 Analysis of the internal conditions (electron state) of materials using light. The physical properties of materials depend on differences in the electron state in materials and analytical results can be used to increase the performance of devices using these materials, such as displays.

3 A facility open to researchers in Japan and abroad and within industry, academy and government. Built by RIKEN, this facility can generate globally unrivaled radiation beams, which are thin and powerful electromagnetic waves produced by accelerating electrons nearly to the speed of light and bending their direction by a magnet.

Moreover, IGZO's electron mobility is about 20 times that of amorphous silicon semiconductors, satisfying the requirements for 3D televisions and high-performance, large-screen displays. The results of these studies were presented in Nature magazine in 2014 and made a great impact worldwide. The IGZO-TFT appeared on the market just in time when it was starting to seek flexible electronics and high-performance, large-screen displays.

Since then, many research institutions and companies in Japan and abroad started R&D to commercialize high-resolution displays using IGZO and competition is intensifying. In the closing section of the SORST study completion report, Hosono recalled what was often said: commercialization of material research needs at least 10 years and "10 years after ERATO got underway to the end of SORST, a favorable situation paving the way for large-scale applications, such as TAOS-TFT, finally emerged. If the research did not go beyond ERATO, I might have changed my themes," and emphasized the importance of long-term and continuous financial support from basic research to commercialization according to research phases such as "from the initial phase in the 1990s, which was a low-key period supported by KAKENHI and research funds from financial groups, to the growth phase in ERATO and to the device prototyping phase targeting application in SORST."

In 2012, more than 20 years since the start of basic studies, IGZO-TFT driven high-definition displays were mounted on new tablet computers and smartphones and finally delivered to consumers as thin, light, energy-saving products with high-quality image displays. The commercialization of flexible electronics equipped with large and high-performance displays is expected to emerge in future.

JST licenses the patents on IGZO owned by JST and related patents, including production technologies required for commercialization, jointly applied by the Tokyo Institute of Technology and partner companies, as a patent group to many material and display manufacturers on a non-exclusive basis.[1] Packaging related patents into a patent group will facilitate business deployment because the individual use of patents owned by universities and research institutions hinders commercialization efforts.

3 Medical and Welfare Robot Suits

○ Background and progress of R&D

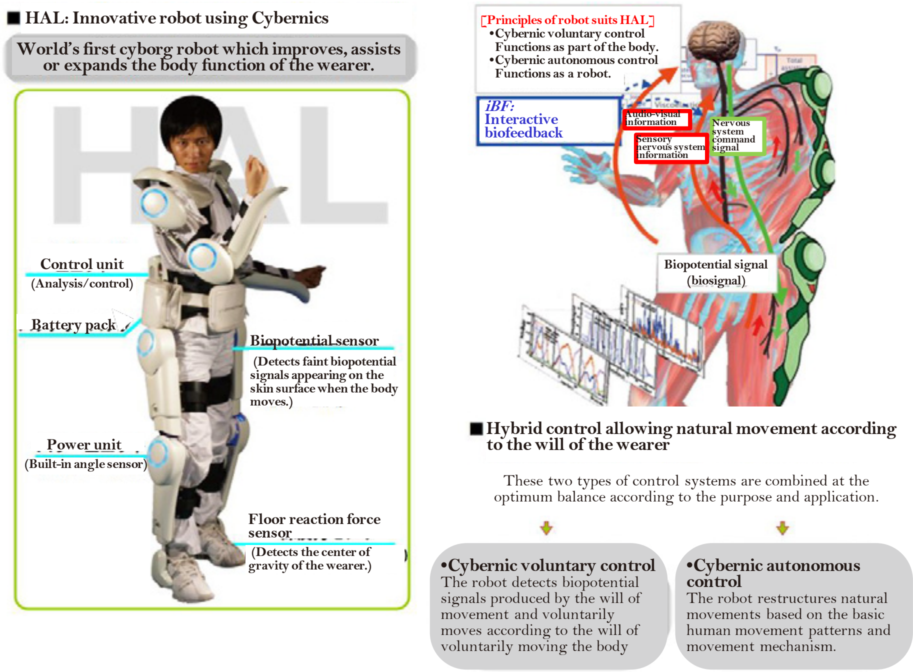
In Japan's rapid population aging, one in three people will be classed as elderly by 2035.[2] Under these circumstances, the development of robots for nursing care and assisting with domestic work has recently become increasingly prominent.

As the baby boomer generation advances to the old age bracket immediately and the aged population increases, the demand for caregivers follows suit. The estimated number of caregivers required in FY 2025 will be 2.37 to 2.49 million.[3] In this forecast society, overburdening of caregivers must be prevented. If wearable power-assisting equipment is available for caregivers, the burden of assisting movement, e.g. from bed to wheelchair and vice versa, may be largely reduced.

Prof. Yoshiyuki Sankai of the Graduate School of Systems and Information Engineering at the University of Tsukuba, who firmly believes that science and technology, including medical and

1 Permission of the rights holder to use intellectual property
2 "Population Projection for Japan (January 2012)" National Institute of Population and Social Security Research
3 "Long-term Medical and Nursing Care Projection" MHLW

engineering, are only meaningful when useful for humanity and society, started basic research in around 1991 and proceeded to R&D to produce a world-first cyborg-type robot called "Robot Suit HAL" (Hybrid Assistive Limb) to improve, support and boost body function. The robot suits were designed for particular purposes, such as a welfare model worn on the lower part of the body, for example, for people who have lost their lower-limb motor function, to assist the motor function of the wearer with the robot function and a lumbar model, to reduce the burden on the lower back of a caregiver when assisting a patient to move. Prof. Sankai has proposed and developed new treatment control methods to improve body function from the initial R&D phase, including the HAL principles.



Cyborg-type HAL Robot Suit

Source: CYBERDYNE Inc. / Prof. Sankai, University of Tsukuba

HAL has been developed for a broad range of applications, including a medical model for improving neural, nerve and muscular systems, a welfare model for supporting independence, a caregiver model for supporting the lower back of caregivers, a worker model for supporting the lower back of workers who carry heavy materials at construction sites and factories and an emergency model for responding to disasters, and these models begin to be increasingly used for solving various social issues. The CE marking for medical equipment was granted to the medical-type HAL as a world-first robot therapeutic instrument and the model has now been distributed within Europe without restrictions. In Germany, all medical expenses for spinal cord injury and cerebral apoplexy are currently covered by public industrial injury insurance, including functional improving treatment.

HAL for medical use, lower lumb type

Source: CYBERDYNE Inc. / Prof. Sankai, University of Tsukuba

○ Government role

The HAL robot suits developed by Prof. Sankai are the result of commercialization supported by KAKENHI based R&D over 20 years, including "Research of Medical Interface containing Virtual Human Body" (KAKENHI to Encourage Young Scientists (A) in FY 1991) and "Development of the Autonomous Control and Power Assist Compound Type Exoskeleton System HAL for Walking Aids" (KAKENHI for Scientific Research (B) from FY 2000), as well as the "Development of fundamental technologies for practical use of human-assisting robots" of NEDO.

In 2009, the research led by Prof. Sankai was selected for the "Funding Program for World-Leading Innovative R&D (FIRST)" sponsored by the Cabinet Office to promote advanced researches from the basic study for creating new knowledge to the application stage stepping forward to the final stage, targeting world leaders in various fields and at various stages. In this program, an advanced, world-leading R&D base for Cybernics[1], a new academic field and a system blending people, machine and information, was jointly established by the University of Tsukuba, site of a core research center, in partnership with the Graduate School of Medical and Mechanical Engineering Departments at Osaka University and venture company CYBERDYNE Inc. By FY 2013, clinical tests were conducted at the University of Tsukuba by patients and data on 71 cases using the welfare robot suits was collected. Analyzing this data revealed that walking ability had improved with robot suits for about 90 percent of patients. Based on such knowledge compiled, verification of the clinical tests at the Karolinska Institute in Sweden, Bergmannsheil University Hospital in Germany and a doctor-centered clinical trial at Niigata National Hospital in Japan are underway as the first step toward a global launch.

In addition, using analytical data on the safety of life support robots like HAL, obtained in the "Project for Practical Applications of Service Robot" of NEDO, the welfare model of HAL robot suit won the international safety standard, ISO/DIS 13482 Certification in February 2013 as a world first for a personal care robot. For the full-scale introduction of life support robots designed to come into frequent contact with the human body, technologies, standards and rules for ensuring contact safety are required. Winning the international safety certificate is a benchmark to ensure the safety of HAL robot suits worldwide and a stepping stone toward their global launch.

○ Future prospects

The present Pharmaceutical Affairs Law (Act No. 145 of 1960) in Japan does not approve HAL as medical equipment, but there is demand for HAL to be used as medical equipment for treating and preventing diseases in the medical field. A doctor-centered clinical trial has already been conducted from March 2013 to study the effect of wearing the medical HAL robot suit on improving gait in patients suffering from scarce and incurable neurological and muscular diseases. The clinical trial completed in August 2014. The coordinating investigator created a clinical study report, based on which an application for the approval of medical devices for the HAL robot suits was submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in March 2015. Earlier, in December 2014, the medical lower-limb model of HAL was designated as medical equipment for rare diseases by MHLW and subject to an approval

1 Cybernics is a novel, interdisciplinary academic field that combines neuroscience, physiology, robotics, IT technologies, and regenerative medicine, among others.

examination in preference to other medical equipment (preferential examination). The approval for medical equipment is expected to be granted during FY 2015.

CYBERDYNE Inc., which manufactured the robot suits in September 2014, started a rental business for HAL work support models to reduce the burden on the lower back of workers during work with motor assistance. The R&D of HAL originally targeted its application in medical fields, but this was the first deployment of HAL for supporting work. Obayashi Corporation employed work supporting HAL for verification from November 2014 in construction sites where workers often carried heavy materials and adopted semi-crouching positions.

A worker wearing a robot suit is picking up materials.

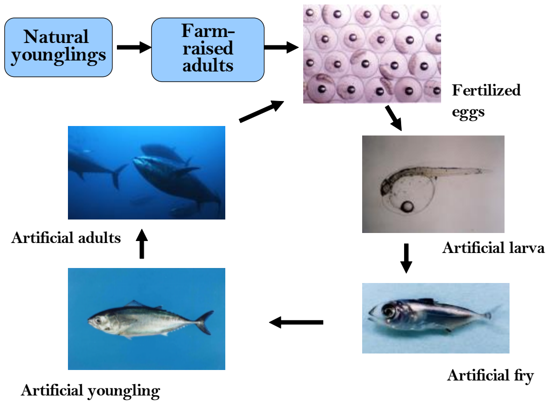
Source: Obayashi Corporation

HAL robot suits are expected to be applied in various areas in future. In particular, innovative new field development is expected to be accelerated by combining innovative robot technology with science and technology elsewhere, such as complex medical treatment using regenerative medicine and HAL, or complex therapy using drugs and HAL.

4 The World-first Complete Farm-raising of Bluefin

○ Completely farm-raised Bluefin for ordinary food supply and international situation of Bluefin

In February 2015, plates of bluefin produced by complete farming technology[1] were turning on the conveyors of major kaiten (conveyor-belt) sushi chain stores. Kinki University was involved in producing this bluefin[2]. The bluefin, produced by Kinki University and purchased by a major restaurant chain made headlines as potential ordinary food for consumers in future.



Complete farming cycle

Source: Kinki University

Kinki University succeeded in complete farm-raising of bluefin in 2002 as a world first. The university-raised bluefin was first shipped to shops, including department stores, in 2004 as “Kindai Maguro” (Kinki University Tuna), all of which were raised in captivity from eggs to adults by Kinki University and a venture company founded by the university.

Kinki University started selling artificially produced fry to fishing companies and aquaculture operators from 2007 to promote the mass production of artificial seedlings by complete farm-raising and the stable supply of bluefin to the market. The bluefin, grown to adult fish in the tanks of these companies, is supplied to the market under the unique brand name of each company.

A private trade company, which raised bluefin tuna fry under the technical guidance of Kinki University

1 A technique to raise artificially hatched fingerlings to adult fish, which involved collecting and artificially hatching eggs to produce the next generation.

2 The Bluefin was raised by an aquaculture operators, who purchased artificial seedlings produced and shipped by Kinki University.

in partnership with the university since 2010, was permitted to ship bluefin as "Kindai Maguro" for the first time in November 2014. Since then, the annual supply of "Kindai Maguro" increased from 2,000 to 3,000 fish. The university plans to increase the annual supply to 6,000 fish (240 tons[1] as the amount of adult fish shipped), doubling the present shipment, by 2020.

Tuna has been eaten and counted in fish catches throughout the ages in Japan, but demand for tuna has recently soared due partly to the present worldwide boom in the Japanese food. Catches of tuna species[2] have increased worldwide and tuna fisheries have had restrictions imposed, with resource conservation in mind. The bluefin was designated an endangered species by the International Union for Conservation of Nature and Natural Resources in November 2014.

About 1/4 of the global catch of tuna species was supplied to Japan as of 2008[3]. As for bluefin, around 80% of global catches and farm production is supplied to Japan[4].

Under these circumstances, the complete farm-raising technology of Kinki University is expected to help protect bluefin. At present, the university plays a key role in increasing the production of completely farm-raised bluefin. Remaining issues, such as stable egg harvest and production costs, must be addressed to achieve full-scale commercialization in future. The government set a goal to completely commercialize farm-raised fish, including bluefin, by 2020 by developing large-scale complete farm-raising systems in the "Comprehensive Strategy on Science, Technology and Innovation 2014."[5]

○ Progress of R&D

R&D of the complete farm-raising of bluefin began with the "Development of tuna culture techniques" (1970 to 1972) in the "Large scale aquaculture experiment of commercial fish" by Ministry of Agriculture, Forestry and Fisheries (MAFF) to establish the technologies of raising younglings and those of producing and raising hatchlings and fry through artificial maturation and hatching. The purpose of this project was to raise captured natural younglings into adults, capable of spontaneous spawning. Five research institutions, including Kinki University, participated in the project, but all failed to achieve the goal at the time due to the extreme difficulty in farm-raising bluefin

After the termination of the project, a group of scientists in Kinki University started studying bluefin farming at the Shirahama Fisheries Laboratory (now Fisheries Laboratory) under the leadership of then director Teruo Harada and succeeded in raising younglings into adults by seeking optimal approaches to catch natural younglings, expanding the preserve to increase the survival rate of natural younglings with delicate skin, which were difficult to handle and changing the preserve materials to reduce damage from typhoons.

Later in 1979, the study group succeeded in spontaneous spawning of farm-raised adult fish. However, all fingerlings died by the 47th day after hatching, because there were many unclear points about the bluefin behavior and it was difficult to handle it.

Breeding techniques could not be studied for 11 years after 1983, during which the adult fish stopped spawning. In 1994, spawning was finally observed.

1 Calculated based on one adult fish weighing 40 kg
2 Bluefin, southern bluefin tuna, big-eyed tuna, yellowfin tuna, and albacore
3 Fisheries of Japan - FY2010
4 Fisheries of Japan - FY2009
5 Cabinet Approval on June 24, 2014

There were three significant hurdles for newborn fingerlings to grow into adult fish. The first hurdle was "surfacing death" due to the surface tension of the water, which pushed fingerlings up to the surface and caused death due to breathing difficulty and "bottoming death", in which the fingerlings touch the bottom of the tank and microorganisms there adhere to their body and attack them to death. This problem peaked during the period 4 to 7 days after hatching, but countermeasures such as circulating the water with an aerator and dropping oil on the surface of the water were effective. The second hurdle is the significant decline in population for 10 to 20 days after hatching due to eating each other. This problem was solved by feeding freshly-hatched larval fish of parrot bass, etc. to keep the fry from fasting.

After these measures, the fry successfully grew up to be moved from the tank to the sea preserve, but again, all fry died by the 246th day after hatching. The third hurdle was "collision death."

To overcome the third hurdle, the preserve was expanded and the light kept on all night according to the findings of surveys on the development of bluefin organs about the lack of swimming control capability (turning and stopping) for a certain time from fry to youngling stages and about the panic of fry in response to flashing light from vehicles and fishing boats at night.

The survival rate of fry and younglings improved after these measures had been taken. In 2001, 52 fry born in 1995 and 1996 grew up into virtually adult fish, as well as about 400 individuals who grew into adult fish. That year, Typhoon No. 11 directly attacked the Japanese Archipelago and killed almost all individuals, mainly through suffocation due to the muddy water, although a group of 20 individuals who survived the storm grew up into adult fish. In 2002, spawning was finally observed and larvae smoothly hatched. At last, Kinki University had succeeded in complete farm-raising of bluefin 32 years after the study had been started.

The complete farming was achieved by addressing issues at each development stage with countermeasures led by the thorough observation of bluefin behavior. The university has further promoted R&D, including improving measures against surfacing death and developing artificially assorted feeding for quantity and stable production of bluefin.

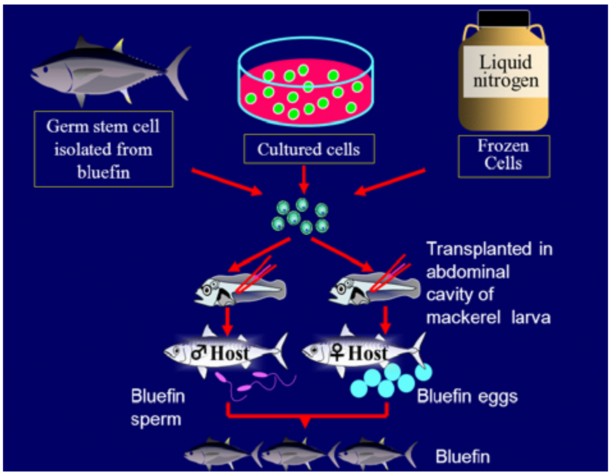
Bluefin consume a lot of feed and are more prone than other fish to accumulate mercury. Kinki University has also addressed the reduction of mercury contained in bluefin and the need to enhance safety by avoiding large live bait such as bonito, which accelerate mercury content.

MAFF started a project called the "Technology Development for Selecting and Storing Bluefin Parent Fish Most Suitable for Farming" from FY 2011 to acquire parent fish to collect good eggs constantly and efficiently. In this project, the Fisheries Research Agency, Kinki University and other institutions jointly conduct R&D into technologies for selecting individual bluefin with positive characteristics, including premature maturation, high growth and disease resistance, etc. to form a group of parent fish.

MAFF has also promoted the "Development of Sustainable Aquaculture Technology Independent of Wild Fishery Resources" from FY 2012 to develop technologies for producing and supplying artificial bluefin fry in bulk for farming at low cost, targeting efforts to improve the current state of bluefin farming in Japan, whereby natural fish are caught and raised to adult fish in most cases. This targets stable spawning using a large land-based tank that can be easily conditioned, rather than a sea preserve, which is prone to changes in water temperatures and other factors. Spawning of bluefin was observed in May 2014 in a large land-based tank installed for egg collection and eggs could be acquired as a world first.

Because the adult fish of tuna species is large, significant labor, cost and space are required for farming management and artificial seedling production. MEXT develops technologies to produce fertilized eggs of tuna using smaller relative species such as mackerel as the surrogate parent at the Tokyo University of Marine Science and Technology in its "Technology Upgrading for Securing Living Marine Resources". When this technology is put to practical use, a stable supply of fertilized tuna eggs will be possible with small land-based tanks and reduced labor and cost.

R&D is expected to resolve problems affecting the complete farm-raising of bluefin, improve productivity and ensure the stable and safe supply of bluefin. Marketing completely farm-raised bluefin in captivity will protect natural bluefin, which are increasingly scarce. The promotion of R&D is therefore crucial.



Development of new bluefin egg supply method (Technology Upgrading for Securing Living Marine Resources)

Source: Tokyo University of Marin Science and Technology

5 Regenerative Medicine and Drug Discovery using Human iPS Cells

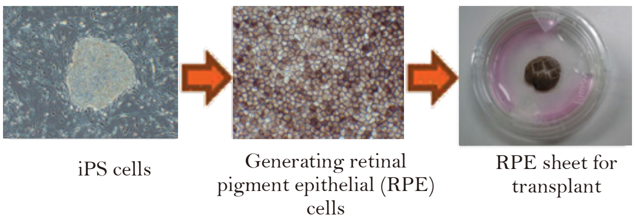
○ First step of regenerative medicine using iPS cells

On September 12, 2014, the first step toward regenerative medicine using iPS cells (induced pluripotent stem cells) was taken.

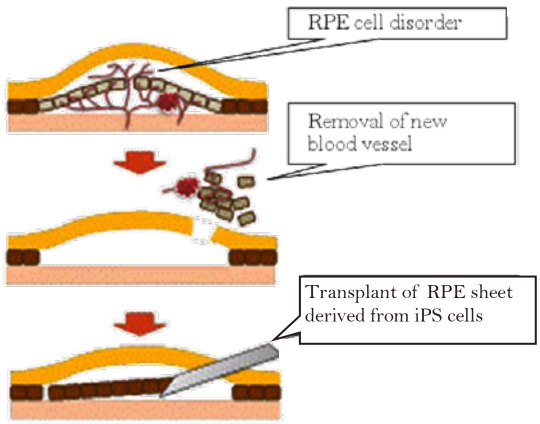
> iPS cells are stem cells which have an artificially induced ability to differentiate into almost any type of cells of tissue or organ within the body. Prof. Shinya Yamanaka, et al. at Kyoto University invented a method of generating these cells. Prof. Yamanaka won the Nobel Prize in Physiology or Medicine on October 8, 2014 for the "discovery that matured cells can be reprogrammed to have pluripotency."
>
> Prof. Yamanaka, et al. successfully produced iPS cells by introducing four genes into the skin fibroblast cell and reported the creation of mouse iPS cells in 2006 and human iPS cells in 2007.

The retina cells (retinal pigment epithelial sheet) differentiated from iPS cells produced from skin cells of a patient suffering from exudative age-related macular degeneration (an intractable eye disease which prevents the eye from focusing due to the aging-related failure of macula retinae at the center of the retina and which may result in blindness as the manifestations progress) were transplanted to this patient at Institute of Biomedical Research and Innovation Hospital in Kobe. The research was part of clinical research conducted by a project led by Masayo Takahashi, et al. of the RIKEN Center for Developmental Biology in collaboration with the foundation research staff based on the result of "Research Center Network for Realization of Regenerative Medicine" program[1] by JST. The main objective of this clinical research was to confirm the safety of the cells derived from iPS cells, rather than significant eyesight recovery, but the research was noted as the world-first transplant of cells derived from iPS cells to the body of a patient.

○ Expectation to iPS cells



Creation of retinal pigment epithelial (RPE) sheet derived from iPS cells
Source: RIKEN



Transplant operation procedure
Source: RIKEN

Two main achievements are expected for practical application technology using iPS cells.

One is the application to regenerative medicine, which aims to partially compensate for the lost functions of organs or tissues lost or damaged by diseases or injuries by transplanting cells cultured in vitro. In addition to the above-mentioned transplant of RPE sheets, many researches targeting practical application are also underway at present.

For instance, a group led by Prof. Yoshiki Sawa et al. of the Graduate School of Medicine at Osaka University succeeded in recovering the cardiac function of a rat with cardiac infarct by transplanting

1 An "All-Japan" project, targeting R&D of regenerative medicine to apply the iPS cell technology developed by Japan to practical regenerative medicine as a world first

sheet-type cardiac tissue derived from human iPS cells in May 2012. In January 2015, Prof. Sawa et al. transplanted the myocardial cells derived from iPS cells to the rat heart, observed them using a large-scale synchrotron radiation facility (SPring-8) and confirmed that they moved in harmony with the own myocardial cells of the heart as the world first. Prof. Jun Yamashita et al. of the Center for iPS Cell Research and Application at Kyoto University generated a cardiac tissue-like sheet composed of both myocardial cells and vascular cells derived from human iPS cells, and transplanted them to a rat with cardiac infarct. Then they confirmed the recovering the cardiac function and highly efficient survival of transplanted cells. These studies are expected to be used to treat heart failure.

Other studies of iPS cell applications to regenerative medicine are also underway for diseases and disorders affecting many patients, including cancer, cerebral infarction, diabetes, knee osteoarthritis and spinal cord injury and incurable conditions such as Parkinson disease, muscular dystrophy, and inflammatory bowel diseases (ulcerative colitis, Crohn's disease).

The other expectation to iPS cells is the acceleration of studies to understand the pathological mechanism and new drug discovery using iPS cells. It is difficult to harvest patient's tissues even for studying the disease. It is possible to clarify the pathological conditions and confirm the effect or safety of new drug seeds by using the cells or tissues, which have characteristics of diseases, differentiated from iPS cells derived from cells sampled from the skin or blood of patients.

These cells and tissues are useful for determining which drug is effective for a targeting disease among drugs assuring safety and put on the market for other diseases. For instance, Prof. Noriyuki Tsumaki et al. of the Center for iPS Cell Research and Application at Kyoto University discovered that the hypercholesterolemia treatment drugs may also be effective for achondroplasia, which is an intractable disease accompanying short stature, using iPS cells derived from cells of a patient with the disease.

Prof. Yamashita et al. at Kyoto University are developing a mass culture technique to produce myocardial cells for evaluating the safety of candidate substances for new drugs such as the risk of irregular heartbeat jointly with a private corporation and supported by NEDO. This safety evaluation technique, using myocardial cells differentiated from human iPS cells, is expected to accelerate new drug discovery and reduce costs.

○ Government support for the iPS cell study

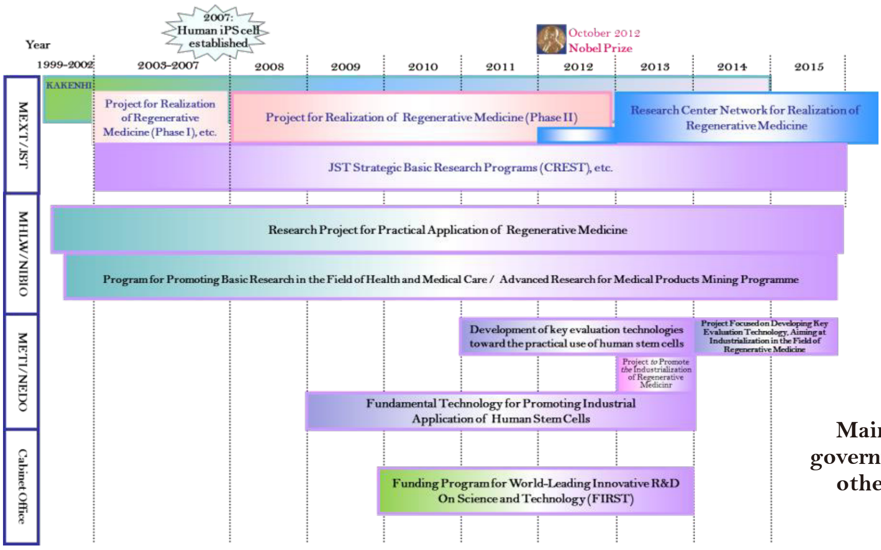
Shinya Yamanaka, Director of the Center for iPS Cell Research and Application at Kyoto University, presided over a laboratory as Assistant Professor at the Nara Institute of Science and Technology in 1999. The previous year, in 1998, a human ES cell[1] was established in the U.S., but they raise an ethical issue that they must destroy embryos, which may grow into human. Prof. Yamanaka set a theme for the laboratory to generate pluripotent stem cells, acting like ES cells, from somatic cells and devoted himself to research. The results of the study in his assistant professor days, supported by KAKENHI, are the basis for generating iPS cells. Prof. Yamanaka spoke at the press conference after receiving the Nobel Prize that researchers must select themes of unknown value and the system of supporting studies in a nebulous condition, such as KAKENHI is very important to retaining national strength in technology.

Later, Prof. Yamanaka et al. successfully established human iPS cells in November 2007, as an

1 Embryonic stem cell: Artificial stem cells produced by culturing cells extracted from the embryo and capable of differentiating into any cells.

achievement of supports by the CREST[1] project of JST Strategic Basic Research Programs launched in 2003, Project for Realization of Regenerative Medicine (Phase I) by the MEXT and the Basic Research Promotion Program of the National Institute of Biomedical Innovation (NIBIO). Prof. Yamanaka recalled "iPS cells were selected as the CREST theme, despite the low feasibility at the time. CREST was extremely effective as a bridge between basic research supported by KAKENHI and large-scale national projects. The seeds acquired by KAKENHI will be lost unless used in national projects."

After iPS cells were established, the government launched a series of "All-Japan" national projects, one after the other, from basic research to clinical applications for long-term support.



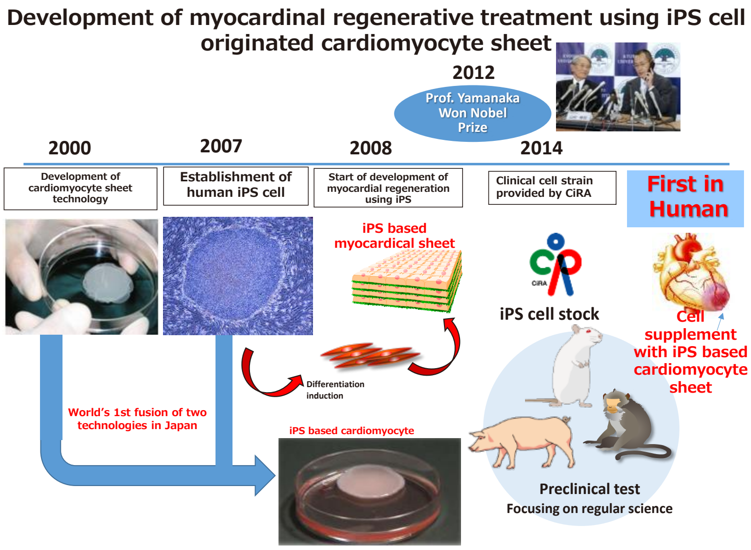
Main support from the government for iPS cell and other stem cell studies

Source: MEXT

The above-mentioned transplant of RPE sheet was conducted only seven years since the establishment of human iPS cells. It should be noted that the clinical application in such a short period was possible since techniques to isolate, purify and culture cells and differentiate those cells to specific cells which had been acquired by long-term R&D of embryonic and other stem cells could also be applied to iPS cells. For instance, Prof. Sawa et al. at Osaka University started researching the differentiation and the induction of somatic stem cells (see Column 1-1) to cardiac muscle cells in 2000. This research was followed by research into the generation of cell sheets from the myoblast[2] cells of skeletal muscle and clinical application of transplanting these sheets to the hearts. The above-mentioned myocardial sheets generated from iPS cells are an application of these techniques. It will be passed about 20 years since the start of research using skeletal muscle cells to the clinical application of myocardial sheets generating from iPS cells.

1 Stands for Core Research for Evolutionary Science and Technology, namely team research for promoting innovational, strategic-based research to achieve strategic goals set by government and create the seeds of innovational technologies.

2 Cells in the process of differentiation, from skeletal muscle stem cells, which are one of somatic stem cells, to muscle fibers of skeletal muscle



Development of myocardial regenerative treatment using iPS cell originated cardiomyocyte sheet
Source: Prof. Yoshiki Sawa, Osaka University

○ Present approaches and issues of propagation

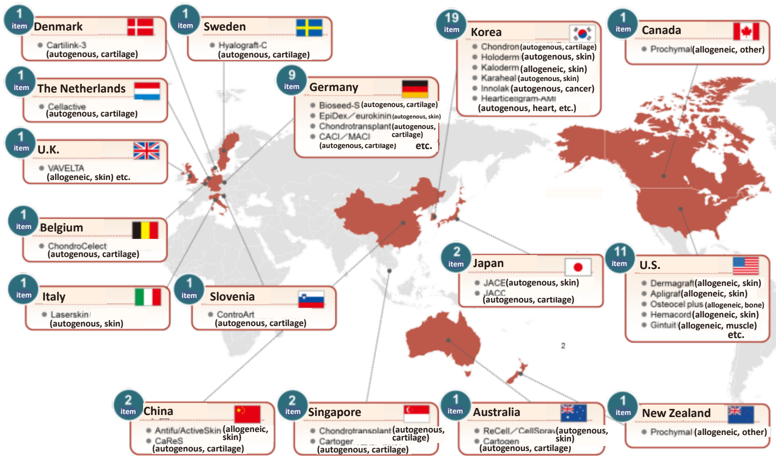
Treatment using iPS cells derived from the patient's own cells in regenerative medicine is advantageous in that it eliminates rejection in the patient, despite the cost for establishing iPS cells and differentiation into target cells is expensive. It is a so-called "order-made deluxe car". Another issue is that the transplant of iPS cells cannot be carried out in time. In some cases, for example, of emergency medicine or cord injury (some reports suggest that transplant within nine days after the damage is appropriate). Because it takes too long time to generate cells for transplant after sampling the patient's own cells where the need for transplant of iPS cells has been determined, MEXT, MHLW and METI have collaborated to build an "iPS cell stock for regenerative medicine" to store wide-ranging (immunological) types of human iPS cells to provide prompt and semi-custom treatments for a number of patients.

Japan is regarded as a world leader in the research of regenerative medicine, but commercialized products remain scarce compared to the U.S. and European countries. MHLW examined a system for promoting the commercialization of regenerative medicine based on a policy to "improve the environment to promote commercialization of regenerative medicine" in the "Japan Revitalization Strategy."[1] The institutional framework[2] was built in November 2013, which was then enforced in November 2014. This framework provides screening procedures for regenerative medicine, etc. based on the level of risks and allows outsourcing of cell cultivation and modification to external organizations not only medical organizations. In light of the characteristics of regenerative medicine, whereby cell quality is uneven because human cells vary among individuals, MHLW also implemented a system to give early approval under specific conditions and on a temporary basis if effectiveness were foreseeable and safety had been confirmed in a certain number of specific cases and final approval following continuous verification of effectiveness and safety after commercialization.

Issues remain to be tackled for the progress of industrialization of iPS cells in future. For this purpose, a method of producing high-quality and safe iPS cells is required, as well as a safety evaluation standard for risks such as tumorigenic transformation through deep insight into the mechanism of iPS cells to acquire

1 Cabinet Decision on June 14, 2013
2 Act to Ensure the Safety of Regenerative Medicine, etc. (Act No. 85 of November 27, 2013) and Act for the partial amendment of Pharmaceutical Affairs Act (Act No. 84 of November 27, 2013)

the ability to differentiate themselves into other cells. Genes transform by aging, but rarely affect normal cell multiplication. A standard for allowable differentiation levels of iPS cells should be provided.



Japan 6 items under clinical trial

- U.S. Clinical development, “skeletal myoblast” and 88 items
- Europe Clinical development, “hematopoietic stem cell” and 42 items
- Korea Clinical development, “cartilage cell” and 31 items
- Other Clinical development, “autogenously cultured cartilage” and 23 items

Developing company	Autogenous/ allogeneic	Origin	Application
JCR Pharma.	Allogeneic	Mesenchymal progenitor cell	Graft versus host disease (GVHD)
TELMO	Autogenous	Skeletal myoblast	Cardiac arrest
J-TEC	Autogenous	Cultured epidermides	Epidermolysis bullosa
Foundation for Biomedical Research and Innovation	Autogenous	Cartilage cell	Knee cartilage damage
Sapporo Medical University Hospital	Autogenous	Bone marrow mesenchymal stem cell	Brain infarction
Sapporo Medical University Hospital	Autogenous	Bone marrow mesenchymal stem cell	Bone-marrow damage

Note: JCR Pharmaceuticals and TELMO completed testing, and now apply for approval. J-TEC completed testing of cultured epidermal cell product for epidermolysis bullous.
Source: Created by Mitsubishi Research Institute based on the data of SKIP (https://www.skip.med.keio.ac.jp/frontline/worldprod/), March 11, 2015

Regenerative medical products in the world markets
Source: “The Survey Report on Topics Such as the Acquisition of Raw Material Cells For the Sake of Industrializing Regenerative Medicine” METI

Regenerative medical products distributed to international markets

Source: “The Survey Report on Topics Such as the Acquisition of Raw Material Cells For the Sake of Industrializing Regenerative Medicine” METI

In addition to R&D, efforts to raise public awareness of the effects and risks of regenerative medicine, including iPS cells, protect the personal information of those offering their cells (genetic information) and provide guidelines for ethical issues are also needed.

Column 1-1 What are Stem Cells?

The key feature of stem cells is their ability to differentiate into other types of cells. Fertilized eggs produce all cells of a body. They differentiate themselves into various cells in the process of cell division and almost complete differentiation at the time of birth at which differentiated cells work with specific function (Figure 1).

However, some cells in the body remain as stem cells, known as "somatic stem cells" and differentiate into limited type of cells at designated locations in the body. For instance, hematopoietic stem cells in bone marrow and peripheral blood differentiate into about ten types of blood cells, including red and white. There are liver stem cells that differentiate into liver cells and neural stem cells that differentiate into neuron (Figure 2).

These stem cells are originally present in the body, but artificially produced stem cells also exist. ES cells (Embryonic Stem cells) and iPS cells (induced pluripotent stem cells) are typical examples. These cells are called "pluripotent stem cells" because of their ability to differentiate into any cell in the body. ES cells are made from the embryo and iPS cells from somatic cells (Figure 3). These two types of cells have similar properties except for differences in precursor cells and study data on ES cells may be used for iPS cells.

Figure 1

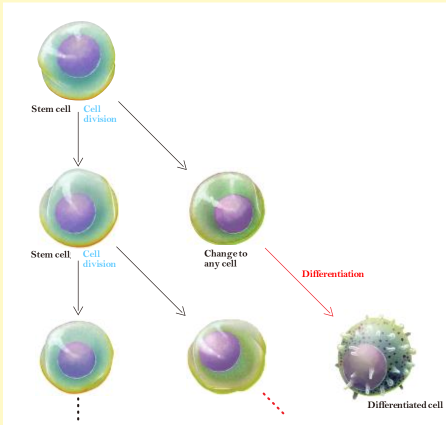


Figure 2

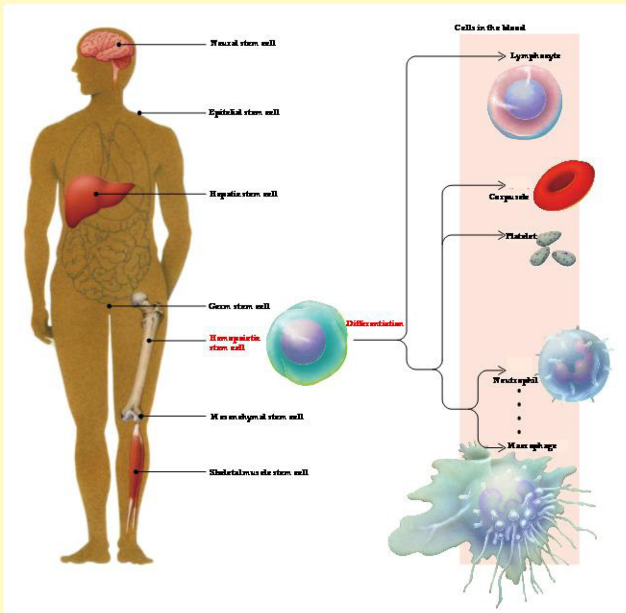
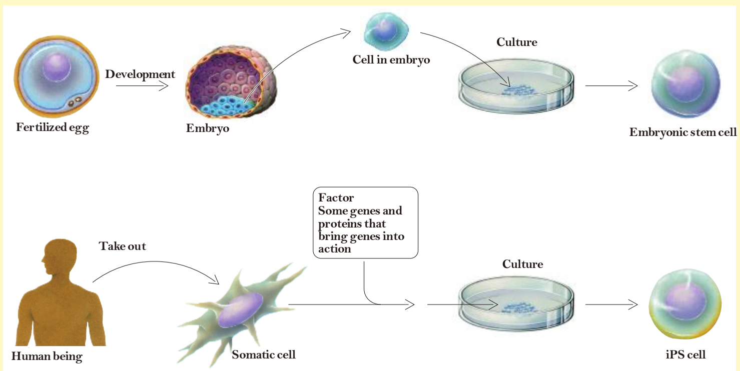


Figure 3



Source: Center for iPS Cell Research and Application, Kyoto University
Illustration: Tomoyuki Narashima

6 Earthquake Early Warning (EEW) System

"I ran to a place that seems to be safe. Later on, I found an old chimney laid down where I had been before the EEW."

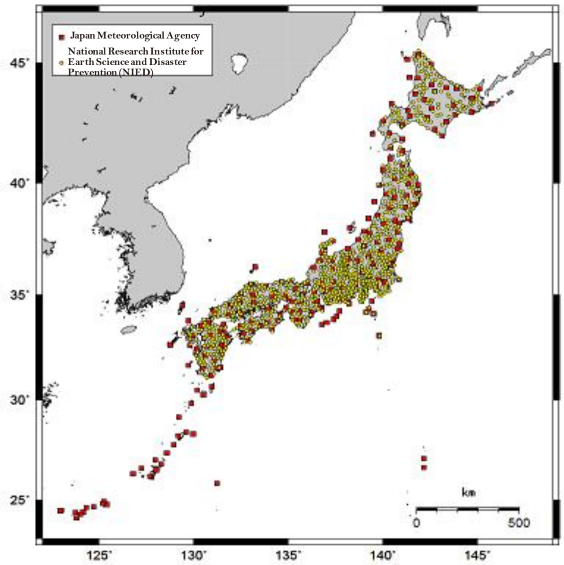
"I passed the elevator."

"I managed to turn off the cooker."

"I could collect necessary medicines."

"I woke up at night and managed to hold my child with a flashlight in hand before the power outage."

"I could open the automatically locked door in the company to secure the escape route."



Seismic stations used for EEW
(As of April 4, 2013)
Source: JMA

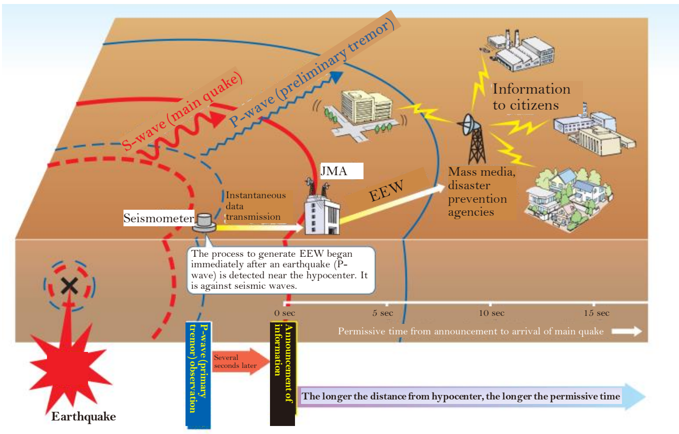
These are typical actions of people who received an EEW via TV and mobile phone.[1]

Japan is a country where earthquakes often occur and is exposed to about 20 percent of the total major earthquakes worldwide.[2] Various researches have been promoted nationally to counter earthquakes and the Earthquake Early Warning (EEW) system was launched by the Japan Meteorological Agency (JMA) in October 2007.

As of April 1, 2013, the EEW system is operated based on about 1020 seismic stations[3] nationwide.

○ EEW scheme

The arrival time of strong quakes and seismic intensity are estimated immediately after the occurrence of an earthquake and when a quake measured 5-lower or more on the Japan seismic intensity is expected, an EEW is issued via TV, radio and mobile phone, etc. as quickly as possible.



EEW scheme
JMA Leaflet (October 2006)

The EEW system uses seismic waves propagating underground from the earthquake's hypocenter. Seismic waves comprise P-[4] and S-waves[5]. P-waves are faster than S-waves, while S-waves tend to cause greater damage due to strong quakes. Using these characteristics of seismic waves, warnings are issued moment after the detection of preceding P-waves or before the arrival of S-waves. The seismic

1 Surveys on utilization of Emergency Earthquake Early Warning System (JMA: Published on December 14, 2012)
2 No. of earthquakes of magnitude 6.0 or greater worldwide during 2003 to 2013 (Cabinet Office: 2014 White Paper on Disaster Management)
3 Installed by JMA at about 220 locations and by the National Research Institute for Disaster Prevention at about 800 locations
4 Seismic waves propagating at about 7 km/sec and mostly causing vertical shaking of the ground.
5 Seismic waves propagating at about 4 km/sec and mostly causing horizontal shaking of the ground.

stations, which detect the P-waves of an earthquake, instantaneously transmit data on the arrival time and amplitude of P-waves to JMA, which, in turn, immediately analyzes the data and estimates the hypocenter and magnitude. Based on this result, JMA forecasts the Japan seismic intensities for the relevant regions and announces an EEW.

An EEW is issued instantly as P-waves observed near the hypocenter of an earthquake are analyzed and information is transmitted in completion with the speed of the seismic waves. So an EEW has theoretical limitations that the estimated seismic intensities may result in an error, the strong quakes may arrive within a period of less than several tens of seconds from the EEW, the EEW will be too late for the areas near the hypocenter, or strong quakes may come just after the EEW is announced. JMA has actively raised public awareness of these limitations of EEW through leaflets and PR and recommended the effective use of EEW, such as protecting oneself when detecting quakes, regardless of EEW, or imaging actions when an EEW is announced during normal time.

○ Development of the EEW system

After the 1970s, JMA, universities and research institutions expanded and upgraded earthquake observation networks. The Railway Technical Research Institute (former Railroad Technology Laboratory of Japanese National Railways) started pioneering R&D on techniques to forecast quakes immediately after the occurrence of an earthquake in the early 1980s to ensure the safety of Shinkansen running at high speeds. JMA, Railway Technical Research Institute and National Research Institute for Disaster Prevention expanded their scope of knowledge for quake forecasts through R&D.

Although immediately announcing accurate information is one of the crucial issues when starting the EEW system operation, accuracy and speed are conflicting factors. To prioritize speed, data analysis should be started when P-waves arrive at only a few observation points. In contrast, data transmitted from observation points may contain artificial fluctuation (noise), or data on two simultaneous earthquakes.[1] Analysis using data from only a few observation points would, therefore, risk a false conclusion about the occurrence of an earthquake or location of the hypocenter.

In "Research project for the practical use of Real-time Earthquake Information Network" launched by MEXT during the period FY 2003 to 2007, the National Research Institute for Disaster Prevention developed an automatic hypocenter location system[2], a technique to remove erroneous data. In the same project, JMA developed a technique to integrate the results from the single-observation-point processing method[3] jointly developed by the Railway Technical Research Institute and JMA, the multiple-observation-point processing method[4] developed by JMA and automatic hypocenter location system. The National Research Institute for Disaster Prevention and JMA verified the accuracy of automatic operations for processing actual observation data by comparing data with manually processed results over four years and when an operational inaccuracy was found, examining the cause of inaccuracy and improved software.

At the same time, JMA started a model experiment involving residents of specific regions from

1 The hypocenter of about 300 earthquakes, including micro earthquakes, is identified daily in Japan.
2 A technique to remove erroneous data such as noise by noting the points at which seismic waves have arrived and not arrived respectively
3 A technique to estimate the distance and direction of seismic wave propagation and the magnitude of an earthquake using seismometer data at one point
4 A technique to estimate the hypocenter area using seismometer data at three to five points and a technique to determine whether seismometer data is derived from an earthquake or noise.

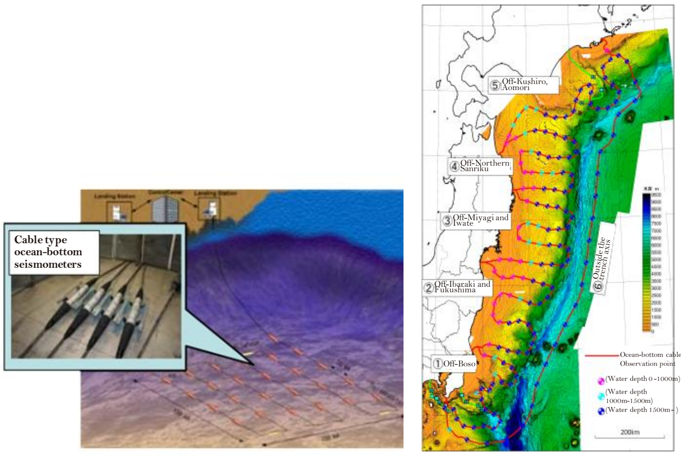
November 2006 and the "Liaison Conference of Ministries and Agencies Concerned with Early Earthquake Warning System" (Cabinet Office) was launched to extensively raise public awareness of the advantages and restrictions of EEW from March 2007.

As a result of these efforts, the EEW for the general public was started from October 1, 2007.

The EEW system was realized by developing highly reliable observation networks and consistent studies, combined with progress in infocommunication technology, smaller computers, lower communication costs and acceptance by society.

○ Future prospects

JMA, National Research Institute for Disaster Prevention and Japan Agency for Marine-Earth Science and Technology installed seismometers around the Nankai Trough region, which is at high risk of giant earthquakes and deep underground, as close to potential hypocenters as possible, targeting the earlier announcement of EEW. After the Great East Japan Earthquake, the National Research Institute for Disaster Prevention started installing ocean-bottom seismometers around the Japan Trench in the Pacific Ocean to commence observation in FY 2015.



Japan Trench Submarine Earthquake and Tsunami Observation Networks
Source: MEXT

At the end of March 2015, JMA started applying part of the observation data from seismometers around the Nankai Trough region and deep underground in metropolitan areas to EEW. Applying more observation data from these seismometers to EEW in future will accelerate and improve EEWs in areas most prone to large earthquakes.

Column 1-2 EEW Chime Sound

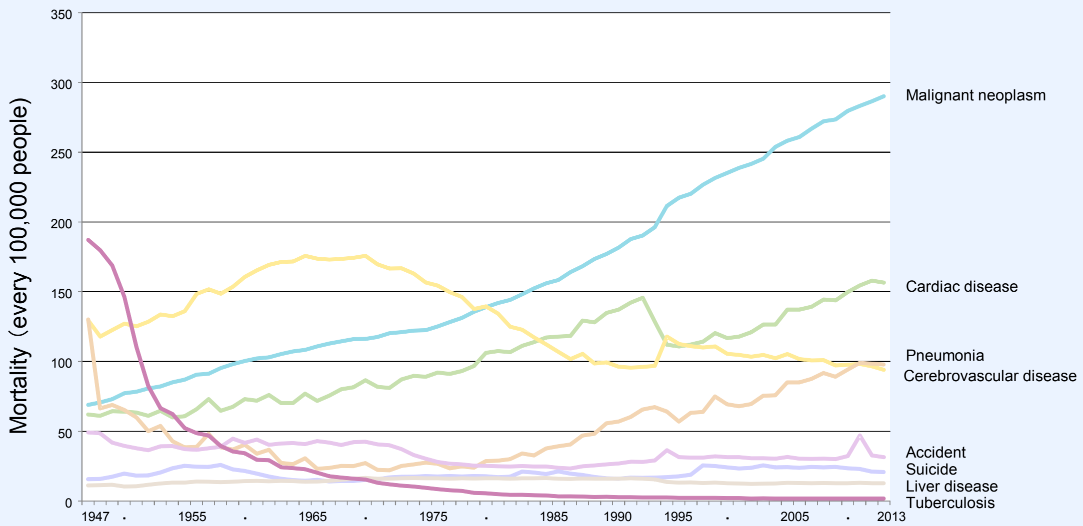
The EEW chime for TV, etc. was created under the supervision of Toru Ifukube, professor emeritus at the University of Tokyo specializing in welfare engineering. It is designed to be immediately distinguishable from existing popular sound effects and chimes to alert people and be both highly alarming and triggering people into immediate action, while not being excessively scary to freeze listeners with fear and reflecting special consideration to alert as many hearing-impaired persons as possible. These considerations are unique to the welfare engineering expert, who is accustomed to designing equipment supporting visually and hearing-impaired persons.

7 The Drug to Treat Hypercholesterolemia

○ Progress of R&D

Cardiac diseases, including coronary artery diseases such as myocardial infarction, are the second most common cause of death following malignant neoplasm (cancer) in Japan (Figure 1-1-3). Acquiring coronary artery diseases is highly likely when blood cholesterol levels are high. This was emphasized in epidemiological studies in the U.S. as early as around 1961. In subsequent years, several drugs to reduce blood cholesterol levels were developed, but low beneficial effects and strong side effects were problems at the time.

■ **Figure 1-1-3 / Annual changes in mortality by main causes of death**



Source: "2013 Fact Sheet for Annual Total of Monthly Vital Statistics (Approx. Figure)" MHLW

In 1971, a research team at the Ferment Laboratory of Sankyo Co., Ltd. (now Daiichi Sankyo Co., Ltd.) started a research project to find out a cholesterol synthesis inhibitor from microbial broth, with two hypotheses: "Blood cholesterol can be reduced far more efficiently by preventing cholesterol synthesis in the liver than restricting the absorption of cholesterol taken from food" and "the cholesterol synthesis inhibitor is present in microbial product." Akira Endo (now Honorary Professor Emeritus at the Tokyo University of Agriculture and Technology) was the researcher in charge and proposed the project. In summer 1973, he found the first desired cholesterol inhibitor, ML-256B ("compactin") from a strain of blue mold after completing a study of 6,000 strains of microorganisms. After this material was isolated, it was revealed that the target of compactin is HMG-CoA reductase, which is the rate-controlling enzyme of cholesterol synthesis[1].

The subsequent development progress was of great global interest. Materials resembling compactin and containing totally synthesized materials were researched worldwide and in 1987, Merck and Company in

1 An enzyme at a stage to determine the reaction speed of a series of reaction pathways for producing a material

the U.S., which had taken a deep interest in the development of statin[1] by Sankyo from the beginning, successfully commercialized statin in the U.S. as a world first. Two years later, in 1989, a commercial product "Pravastatin" was produced by adding hydroxyl to the chemical constitution of compactin in Japan.

At present, statins are said to be administered to nearly 40 million patients daily worldwide as a first-line drug for hypercholesterolemia and because of its significant contribution to preventing coronary artery diseases and cerebral stroke, it is referred to as a miracle drug equivalent to penicillin produced from the same penicillium It has saved millions of familial hypercholesterolemia patients with high LDL-cholesterol levels by nature and who have developed coronary artery disease from a young age

○ Government roles

One of the major roles played by government in developing and disseminating hypercholesterolemia treatment drugs is the launch of a large clinical trial, the MEGA[2] Study in 1993, to ensure safe and effective treatment. This was a research project contracted by MHLW (then Ministry of Health and Welfare) to determine the suitability of lipid-lowering therapy for Japanese hypercholesterolemia patients. Despite the fact proven in clinical trials in the U.S. and Europe for the ability of lipid-lowering therapy to reduce the risk of cardiac episodes, the suitability of this method for Japanese remained unproven, because the mortality of coronary artery diseases, hemorrhagic stroke, blood cholesterol levels, dietary habits and build of Japanese differ from those of Westerners. This clinical study was the first of its kind for hypercholesterolemia patients in Japan. 8,214 light- to moderate hyperlipidemia patients with no record of coronary artery disease and 220 to 270 mg/dL total cholesterol levels were selected[3] and divided into two groups for comparison, the diet-only group and the group of diet combined with hyperlipidemia treatment drug pravastatin. As a result, coronary artery disease and cerebral infarction were significantly limited in the pravastatin combined group while no significant difference emerged between the two groups in terms of safety, or the occurrence of adverse events such as cancerogenesis.

Although large clinical trials are often conducted in the U.S. and Europe with ample funds, the MEGA Study was the first large clinical trial using statin therapy in Japan and Asia. The constitutional features of Japanese people, such as their low LDL-cholesterol levels and the low incidence of coronary artery disease compared to Caucasians, means collecting data unique to Japanese through a large clinical trial like the MEGA Study may pave the way for safe medication for various patients in Japan. In this sense, the MEGA Study is a successful example of a private-public initiative.

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1 A generic name for medicines reducing blood cholesterol by blocking HMG-CoA reductase
2 Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
3 7,832 patients were subject to analysis.

Column 1-3 Heavy Particle Cancer Radiotherapy

In 1983, "Research on Development and Application of Advanced Radiotherapy Treatment Technology" was included in "10-year Cancer Strategy" established by the former Nakasone cabinet as one of the top priority issues. In response, the National Institute of Radiological Sciences (NIRS) started developing HIMAC (Heavy Ion Medical Accelerator in Chiba) in 1987 and conducted a clinical trial into heavy particle cancer radiotherapy[1] in June 1994 as a world first. Since then, more than 9,000 cases have been handled over 20 years.

After the launch of the clinical trial, NIRS has been engaged in various technological improvements, including the development of small popular models and a heavy particle rotary gantry[2]. Following such R&D, heavy particle cancer radiotherapy facilities were constructed in Hyogo, Gunma and Saga prefectures and clinical data has been accumulated. From now on, efforts including demonstrating the effectiveness and safety of these facilities and human resource development for future leadership is to be preceded so that heavy particle cancer radiotherapy is more open to many patients.

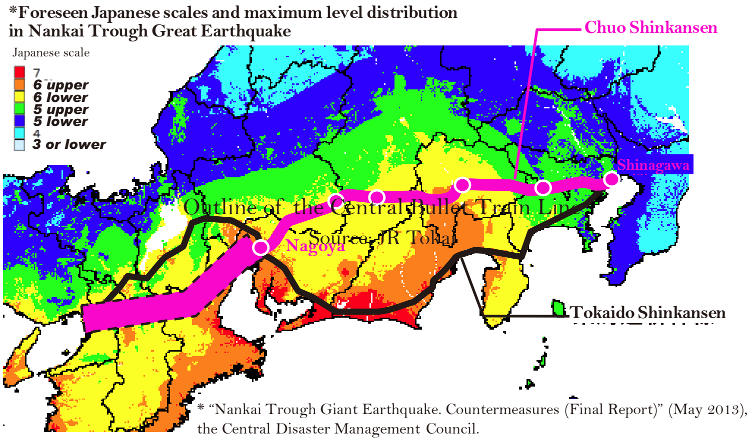
Heavy particle radiotherapy HIMAC
Source: National Institute of Radiological Sciences

Heavy particle radiotherapy (image)
Source: National Institute of Radiological Sciences

8 Development of Maglev Trains

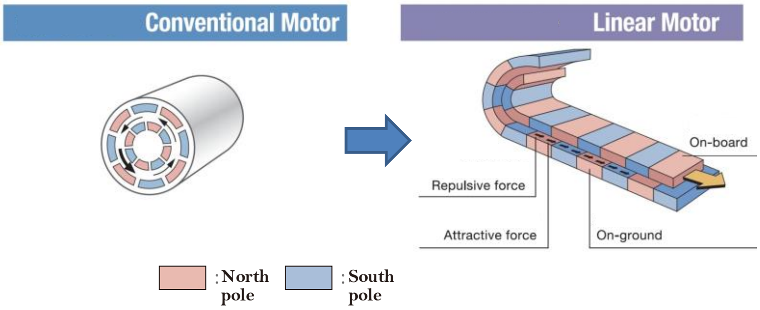
○ Toward opening the Maglev Chuo Shinkansen

Maglev running tests started in April 1997 at the Yamanashi Maglev Test Track.[3] The test is open to the public at the Yamanashi Prefectural Maglev Exhibition Center. Public interest in maglev trains was so great that around 118,000 applications were submitted for 8 days of trial riding in November and December 2014 and the average winning rate reached about one in 125.



Planned Route of Chuo Shinkansen
Source: JR Tokai

1 A type of radiotherapy to irradiate carbon ions accelerated in an accelerator to the cancer accurately and strongly. The equipment is adjustable to pinpoint the cancer deep inside the body.
2 A treatment apparatus capable of irradiating beams without changing the location and direction of the patient's body.
3 As mentioned later, the maglev on the Yamanashi Test Track is a superconducting maglev.



Linear motor mechanism

Source: JR Tokai

Maglev trains have been widely known in Japan as the dream bullet train of the 21st century, since a model was exhibited in the Japan World Exposition in 1970. Maglev trains glide above a track using a linear motor, which is a rotary motor expanded on a straight line. There are three main types of maglev system depending on the structure: Superconducting magnetic levitation systems, normal conducting magnetic levitation systems[1] and railway systems[2]. The superconducting magnetic levitation system or superconducting linear technology was planned to be used for the Chuo Shinkansen (Central New Truck Train) by the Central Japan Railway Company ("JR Tokai"). This line is intended to transform Japan's main transport artery into a dual trunk-line system, with both Tokaido and Chuo Linear Shinkansens interconnecting the metropolitan area, Chukyo and Kinki regions and providing a radical safeguard for future aging degradation of Tokaido Shinkansen trains, which recently celebrated their 50th anniversary, as well as for large-scale disasters. More than 40 years after superconducting maglev was exhibited at the Japan World Exposition in 1970, phase 1 construction of the Chuo Shinkansen between Shinagawa and Nagoya started in December 2014 and the line is scheduled to be opened in 2027.

When the line between Shinagawa and Nagoya starts commercial service, the travel time between Shinagawa and Nagoya will be cut to 40 minutes at maximum speed, less than half the time taken by Nozomi bullet trains. The travel time between these major cities will be drastically cut and the distance between the two cities, which is now considered a day trip area, may be turned to a commutable area. The whole line is scheduled to start commercial service in 2045, which will cut the travel time between Tokyo and Osaka to 67 minutes at maximum speed. This substantial reduction in travel time will form a mega urban area containing half the national population and revitalize socioeconomic activities.

According to an analysis by the Transport Policy Council of MLIT, the benefit of opening the whole line between Tokyo and Osaka will reach 710 billion yen annually and the annual production value will increase by 870 billion yen.

○ Progress of maglev development

The "superconductivity" used for the Chuo Shinkansen is a phenomenon whereby the electrical resistance of certain metals, alloys and oxides falls to zero when temperatures drop to a certain level. When an electric current is applied to superconducting coils, a strong magnetic field is generated. This

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1 Trains are levitated using the suction power of a normal electromagnet. The system was developed by Japan Airlines and Nagoya Railway in the 1970s in Japan. Later, HSST (magnetic levitation type high-speed surface transport rail) was developed by the Chubu HSST Development Company and TRANSRAPID (magnetic levitation type high-speed rail) developed in the 1960s in Germany. HSST was put in service in the Tobu Kyuryo line of Aichi Kosoku Kotsu of Aichi Rapid Transit Co., Ltd., used for transportation between downtown and the EXPO 2005 site and still used in the suburbs of Nagoya. TRANSRAPID is operated by Shanghai Transbit and connects Shanghai Airport and downtown Shanghai.

2 Trains run with regular rail wheels on regular rails using a linear motor. Except for the motor, the system is the same as regular railways and is used for subways in various parts of the world. In Japan, it was put in service in the Horikoshi Tsurumi Ryokuchi line of the Osaka Municipal Subway in 1990 and used in the Oedo line of the Metropolitan Subway, the Nanakuma line of Fukuoka City Subway and various other subways nationwide.

electromagnet is called the "superconducting electromagnet", which raises and runs maglev trains at ultra-high speeds.

The maglev development was started by the Railway Technology Research Center of the former Japanese National Railways (JNR) in 1962 and after the JNR was divided and privatized, JR Tokai and the Railway Technical Research Institute (RTRI) took over the R&D. MLIT supported the R&D with technical assessments and financing. In July 2009, the Superconducting Magnetic Levitation Technological Practicality Evaluation Committee of MLIT confirmed that the technical level was suitable for commercial operation and in December 2011 and August 2012, the Minister of Land, Infrastructure, Transportation and Tourism implemented the technical standards for maglev trains. In April 2015, a maglev train reached 603 km/h, a record high speed for a manned train. In addition, various cutting-edge technologies were introduced and selected after repeated trial and error.

For instance, when the train passes through a tunnel at high speed, the air in the tunnel is pushed out by the train, causing pressure (microbarometric) waves at the outlet of the tunnel, which, in turn, generates an impact sound and vibration. To improve this aerodynamic phenomenon, Simulation of Blast Wave Propagation, developed by the Japan Aerospace Exploration Agency (JAXA), was used when designing the lead vehicle (R&D was conducted in 1999 and 2000 by this simulation program).

Maglev on the Yamanashi Test Track
Source: JR Tokai

This technology provides insurance against accidents and is used to estimate the secure distance in case accidents occur during rocket launches by simulating the attenuation of blast wave strength with distance, including topographical influence. The simulation was also used to develop the "500 series bullet train" by the West Japan Railway Company. The lead vehicle of the present maglev was designed according to the simulation result. The microbarometric wave is reduced by reducing pneumatic resistance and minimizing the air pushed out from the outlet.

While the cumulative running distance of the Yamanashi Maglev Test Track exceeded 1,230,000 Km in April 2015, improvements to maglev in the form of practical technology remain ongoing. The MLIT provides financial support to maintain test lines and runs and evaluates the technology.

○ Development of high-temperature superconducting electromagnet technology

Very cold (-269°C) niobium-titanium alloy is used as the superconducting material for trains on test lines at present and R&D to find a superconducting electromagnet using superconducting materials which turn to superconducting state at higher temperatures is underway. Using these so-called high-temperature superconducting materials, the superconducting electromagnet can be cooled directly by a refrigerating machine without the need to use liquid helium, which could simplify the superconducting electromagnet and cooling structure and reduce costs. Many superconducting materials were found in Japan by the National Institute for Materials Science (NIMS), including a bismuth series material found in 1988 which reverts to a superconducting state at a temperature 100°C higher than for niobium-titanium alloy.

JR Tokai has conducted R&D into superconducting electromagnet using bismuth system material and successfully run prototype vehicles using this magnet in 2005. The Railway Technical Research Institute has also promoted R&D into superconducting magnets using an yttrium series material with the support of MLIT.

As seen above, the maglev is expected to connect large cities and contribute to the prosperity of Japan through further technological improvement.

Column 1-4 Application of Superconducting Technology to Medical Practice

The superconducting technology used for maglev is also used for MRIs[1] in hospitals for detailed examinations, etc. and is applied to improve MRI performance by increasing the magnetic field.

Around 6,150 MRI systems were in service in Japan in 2009. A superconducting magnet was used in around 4,100 of these units, providing clearer images of the inside of the body compared to conventional MRI systems.

In addition, superconducting cables, power storage systems using superconducting technology (e.g. superconducting flywheels and SMES[2]) and various other products have been developed using high-temperature superconducting technology. The practical use of such products to enhance our social lives is expected.

1.5 tesla superconducting MRI system

Source: Japan Community Health Care Organization

1 Magnetic Resonance Imaging
2 Superconducting Magneto Electric System

Column 1-5 Car Collision Preventing Millimeter-Wave Radar

Recently, many cars have been equipped with an automatic braking system, which recognizes objects around the car with a sensor installed in front of the car and if identifying a dangerous situation, automatically applying the brake to decelerate or stop the car. The automatic braking system is not only useful but to be expected to provide significant socioeconomic benefits by reducing car crash accidents and traffic congestion and by improving fuel consumption.

The millimeter-wave radar[1] using 76 GHz band frequencies is used for sensors which play the roles of our eyes. Unlike other sensors, such as those used in cameras and infrared laser radars, the millimeter-wave radar uses radio waves for detection and is hardly affected by darkness at night or heavy fog, making it suitable for monitoring at distances of over 100 meters.

When a manufacturer commercializes the millimeter-wave radar for automatic braking systems for cars, technological elements such as semiconductors operating at high frequencies and electronically controlled antennas[2] obtained in the course of developing high-performance radars for fighters by the Ministry of Defense, take major roles. This owes much to the companies participating in long-term R&D of high-performance radars by the Ministry of Defense and accumulating basic technologies to design and manufacture such radars in the process of R&D.

MIC, responsible for institutional development concerning radio waves, carried out institutional reform[3] in 1999 to allow the use of millimeter-wave radars in the 76 GHz band in Japan and provided technical standards for 79 GHz band, high-resolution radars[4] in 2012.[5]

Radars have evolved remarkably since they were first practically deployed for military purposes in the U.S. and Europe during WWII to date, alongside the development of science and technology. The Ministry of Defense in Japan also continues R&D as one of the major defense technologies and they are installed in satellites for use in space. MIC is also engaged in R&D of 79 GHz band high-resolution radars for installation on the roadside[6] to detect pedestrians in intersections and R&D of 140 GHz high-resolution radars for the 3D detection of small objects to automate construction machines currently used in dusty surroundings.

The millimeter-wave radar and other radio wave sensor technologies will be improved, mainly in defense and space applications in future, while they are also expected to contribute to safe and secure transportation such as automatic driving systems as private sector applications are promoted.

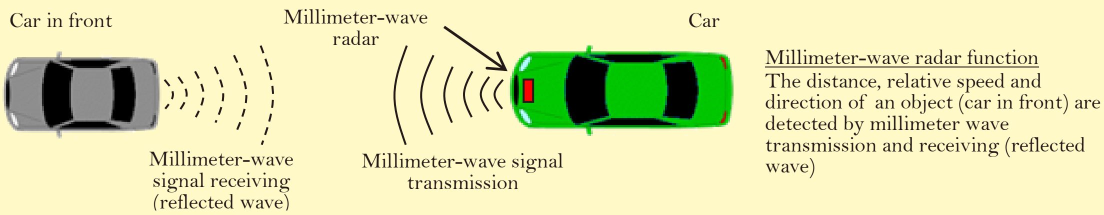

Figure: Millimeter-wave radar function

1 Frequencies at 76 GHz band used for millimeter-wave radars are 50 to 100 times higher than those used for cell phones.
2 A radar that receives radio waves from a desired direction without adjusting the antenna. Unlike mechanical antennas, it does not require a turning mechanism, allowing more compact and lighter structures.
3 Amendment of institutions (e.g. Radio Installation Rules) relating to the Radio Act.
4 76 GHz band radars detect objects of automobile size, while 79 GHz band high-resolution radars detect smaller objects (independent pedestrians). Their use in the field is awaited.
5 Amendment of institutions (e.g. Radio Installation Rule) relating to the Radio Act.
6 A 79 GHz band high-resolution radar is installed on the road side, such as on power poles at intersections to detect pedestrians. For instance, the detection information may be sent to the cars by radio to let the drivers avoid pedestrians.