Health and Science Technology

Predictive Diagnosis and Risk Reduction of Diseases

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Engineering for Human Health

Hiroshi Kuriyama
Research Coordinator for Life Science & Technology

Everyone hopes to remain healthy

Everyone hopes to remain healthy, and upon experiencing illness, to return to good health rapidly. The maintenance of good health allows one to fully address one's work and hobbies, and to enjoy everyday life. Some individuals lead a very cheerful life in spite of disease. In particular, perfect health is generally very rare for senior citizens. However, such individuals also hope to live a happy life without serious diseases, such as cancers, cardiac diseases, cerebrovascular disorders, and diabetes.

If the population requiring hospitalization expands, the social vitality will decline and the national finance will become tighter, due to the swelling cost of medical insurance. It is therefore necessary to minimize the health risks present in the social environment, to maintain and enhance the health of individual residents, and to establish systems for medical examination and treatment in order to discover and cure diseases before they become serious.

Challenges in health engineering

In order to facilitate the early identification of disease symptoms, methods must be developed for precise physiological testing, to check for organ disorders. More precision is also required in existing tests (e.g., a check of blood protein changes, measuring cellular activity in organs, and visual tests with contrast media). Furthermore, additional improvements are required in the treatment of symptoms associated with serious diseases identified via the above tests. On the other hand, an improvement in lifestyle is also necessary, to reduce the incidence of lifestyle-related diseases. The guidelines for necessary lifestyle improvements should be established based on scientific studies. Beyond physical health, simultaneous efforts must also be made to pursue appropriate methods for maintaining a balanced state of mind, which fosters a mentally and physically healthy life. Numerous factors in the living environment pose threats to the public health. It is also important to develop technologies to measure and remove these factors.

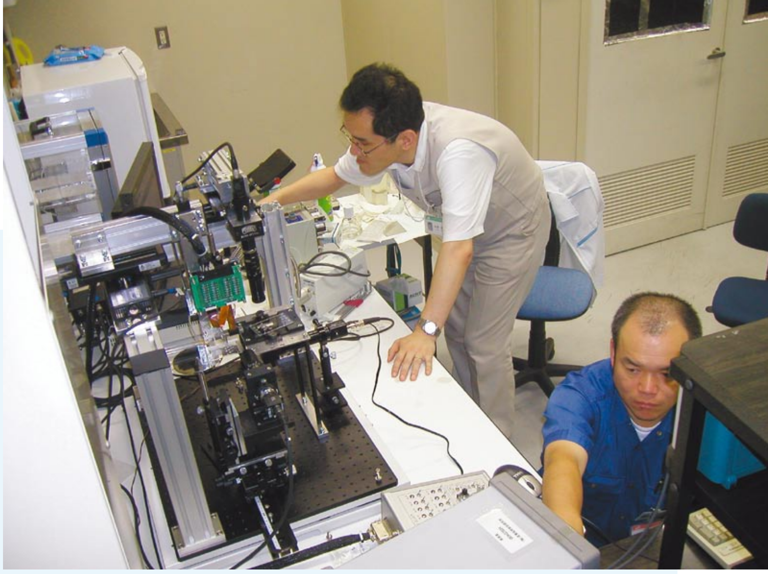
Strategic targets in life science at AIST

To meet the aforementioned requirements, AIST established the following five strategic targets in life science in April of 2005, when AIST initiated its second stage:

- Promoting preventive medicine through

Engineering at AIST for Better Human Health

Hisao Ichijo
Director, AIST Shikoku



Health engineering is a developing field for which a comprehensive system of engineering has not yet been established. Also, its relevant concepts and technological subjects have not yet been defined. However, it is expected to emerge as a new field of industrial technology, to be promoted by AIST towards the establishment of a safe, secure, and sustainable society based on technologies to maintain and enhance health, rather than simply dealing with diseases and patients.

In the Shikoku region, where the decline and aging of the population continue, there are great expectations for the health-related industry. This sector therefore forms an important part of the plans of Shikoku's industrial cluster. Many leading companies in the Shikoku region are engaged in the development of welfare and nursing equipment, health and functional foods, diagnostic and testing devices, and medical apparatuses.

At AIST Shikoku, departments in charge of collaboration between industry, academia, and the administration will cooperate with the Health Technology Research Center, which was opened in April of 2005, to promote activities as a center for research and partnership in the development of the health industry in Shikoku. In addition, the Next-generation Bio-nano Industrial Technology Workshop was established in 2004, and has initiated examinations to make project proposals linking the nano- and bio-technological fields, in cooperation with industrial, academic, and administrative representatives.

We at AIST Shikoku plan to establish a forum for the participation of researchers from businesses/corporations, universities, and public institutions who have been engaged in research and development in close collaboration with us, via joint research projects and technical consultations. Also planned are activities to further the formation of health industry mini-clusters, with the Health Technology Research Center as their hub.

the development of technologies for early diagnosis, and realizing tailor-made medicine based on genomic information;

- Realizing safe and effective medicine with detailed diagnosis and regenerative medicine;
- Extending the healthy lifespan by evaluating and rejuvenating human functions;
- Producing bio-products with an efficient production process, using biological functions; and,
- Establishing an infrastructure to promote the development and application of medical equipment and to support a more competitive bio-industry.

We thus place an emphasis on health engineering, featuring diagnostic and other related technologies.

Health engineering at AIST and the Health Technology Research Center

AIST research fields extend to nano-technological materials and information science, to conduct health-related studies in diverse areas. Research subjects cover, for instance: anthropometry, drug delivery systems, new diagnostic technologies, artificial organs, and risk reduction in human environments. The strong points of AIST lie in its capability to challenge new tasks linking the life sciences to other areas.

We have 14 research units in the life science area, which respectively address different projects concerning the predictive diagnosis and prevention of diseases. In addition to genomic studies, we also conduct, for example, physiological research on the influence of physical exercise on circulatory organs at the Institute for Human Science and Biomedical Engineering.

The Health Technology Research Center was recently opened at AIST Shikoku, and is expected to serve in the integration of health engineering-related studies at AIST. We hope that applicable studies underway at many AIST research units will be linked to each other, and generate excellent achievements in collaboration with external businesses and institutions, thereby furthering their contributions to the development of the health industry.

Promoting Health through Technological Approaches

Tomokuni Kokubu
Director, Health Technology Research Center

Health maintenance as a social task

In the 21st century, Japan is experiencing a typical sociological aging. The percentage of senior citizens in the total population continues to rise, with the country's population expected to take a downward turn in 2007, due to the declining birth rate.

This will lead to serious social phenomena, including a diminishing labor force and a swelling in national medical expenses. The latter is expected to grow to ¥41 trillion in 2010, from ¥30 trillion in 2001 (estimation by the Ministry of Health, Labour and Welfare). To help to provide a sustainable, secure, and fulfilling life for national citizens under these circumstances, the Japanese government is examining policies to deregulate working age restrictions for older people, and to reduce medical expenses via disease prevention and health maintenance/enhancement.

The social importance of health maintenance and enhancement is drawing increasing attention in the U.S. and Europe, as well.

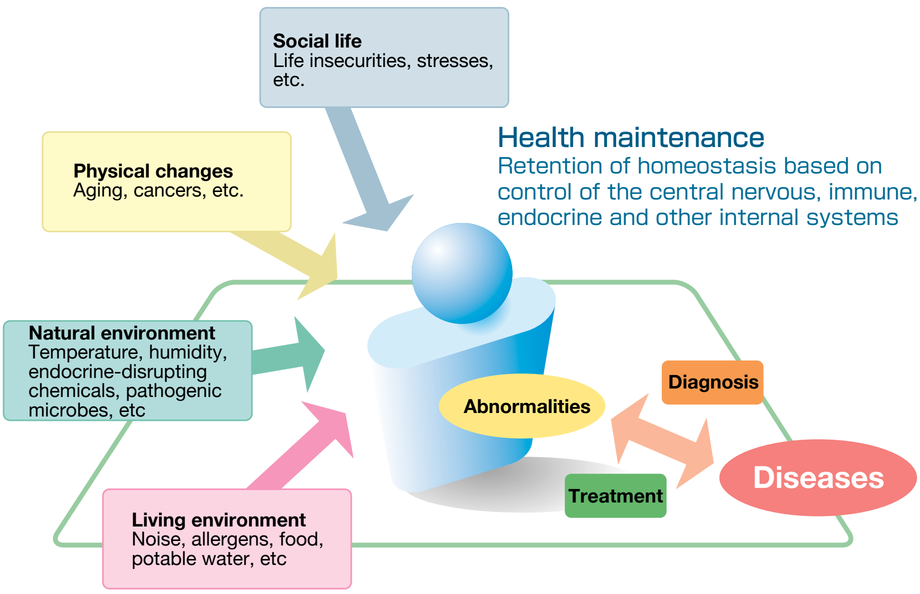


Figure 1 : Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO Charter, 1948).

Technological approaches to health

The Health Technology Research Center was established in the Shikoku region in April of 2005 for solving the above-mentioned social problems, and it has 22 regular members. This center is designed to contribute to society, and promote health-related industries, through engineering studies on the analysis of physical health as physiological phenomena, thereby maintaining and enhancing the healthy state.

Humans receive diverse stimuli from both inside and outside of the body, via signs from perception and movement. Human health is maintained by the homeostatic mechanism that arranges the central nervous, immune, endocrine, and other internal systems, in response to such stimuli (Figure 1). Therefore, a very wide range of research fields must be covered in health studies, including the interaction between humans and the natural or living environment, the retention of physiological homeostasis, the physiological and psychological impacts of various stresses in social life, and the recovery from physical or physiological dysfunctions.

Based on such studies, we must ultimately determine methods to maintain and enhance the healthy state of human individuals, both mentally and physically. Therefore, the major goals of health engineering lie in: (i) identifying the physiological state of individuals by integrating information from genetic, cellular, individual, and other perspectives; (ii) establishing technologies to treat problems identified in (i); (iii) discovering, analyzing, and evaluating risk factors (existing or unknown) that threaten health; and (iv) establishing technologies to effectively protect individuals from the risks identified in (iii).

Health engineering thus has many problems to solve in its pursuit of health maintenance and enhancement, which was initiated only recently. In practical research activities, we must accumulate knowledge from diverse related areas including biotechnology, human engineering, environmental engineering, information technology, materials engineering, and social engineering, and integrate these technologies with new technologies specifically developed in the pursuit of health engineering.

AIST Shikoku has been engaged in advanced research at the global level, on such subjects as the technologies and devices for predictive diagnosis, based on the performance analysis of biological materials involved in cancers and lifestyle-related diseases. We have also developed technologies to remove and detoxify trace toxic substances, in order to ensure potable water and medical solutions in living areas. The Health Technology Research Center

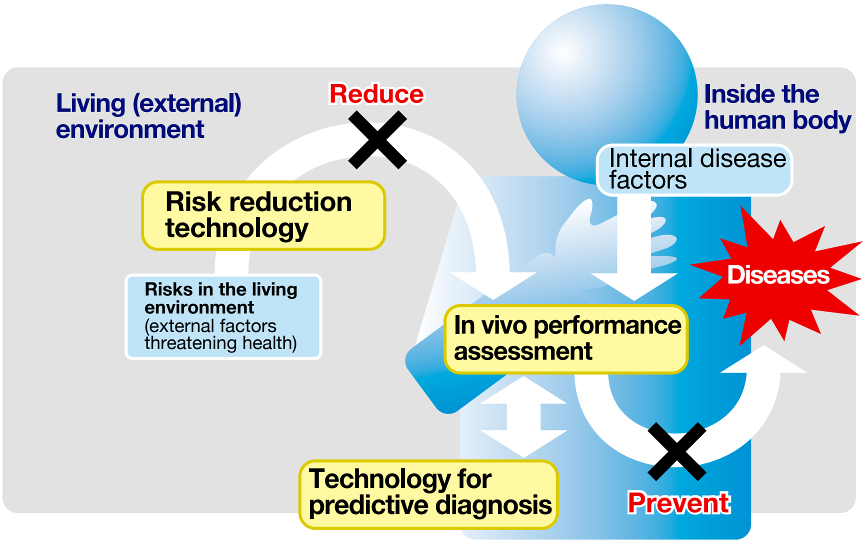


Figure 2 : Comprehensive disease prevention via risk reduction and predictive diagnosis

is designed for the further promotion of these studies, and also aims to establish advanced diagnostic technologies capable of identifying the physiological status of humans in the pre-clinical ("mibyo") stage, thus assisting disease prevention. For this purpose, the center plans to incorporate a research team for the analysis and assessment of functional materials in the human body, such as saccharides and glycolipids possessing many unknown properties in vivo. The center also seeks to promote the development of technologies to eliminate diverse risk factors present in the living environment, and to feed back these achievements to society to provide individuals with a safer life (Figure 2).

As a center of health engineering research

As described above, health-related studies require the assistance of a very wide range of scientific fields. We at the Health Technology Research Center therefore plan to promote its studies effectively, through close collaboration with AIST research units in charge of health engineering-related studies, the Ministry of Health, Labour and Welfare, and related businesses and universities. The center is thus expected to promote health-related industries, as well. Shikoku is a typical region in Japan, which is characterized by a declining birth rate and an aging population. The Shikoku regional governments expect lifestyle-related and other diseases to expand rapidly. We hope to contribute to the society of Shikoku and other parts of Japan, through research and development at the Health Technology Research Center, as a hub of promotion for health-related industries (Figure 3).

Health-related research will continue to expand throughout the world. We believe that this center will contribute to the development of health engineering as a young scientific sector, and to the promotion of health-related industries, through the development of technologies for predictive diagnosis, and for the reduction of risk factors threatening the public health.

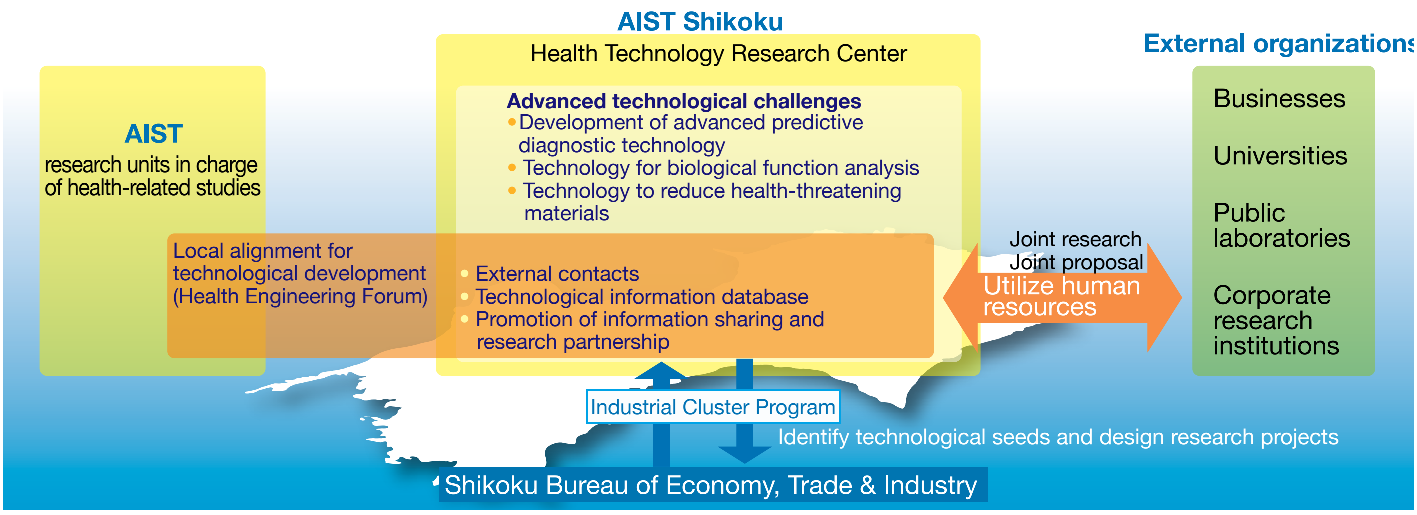


Figure 3 : Research collaborations at the Health Technology Research Center

Aiming at the Reduction of Health Risks

Takahiro Hirotsu
Principal Research Scientist and Leader of Health Hazards Reduction Team, Health Technology Research Center

Presence of various health risks

The increasing sophistication and globalization of industries will provide great convenience and possibilities for our society. Concomitantly, the potential for health risk caused by a wide variety of chemical substances or previously unknown pathogenic bacteria and viruses are expected to increase in the surrounding environment (i.e., the living environment). Arrival of various substances may enhance the risk of health damage, because such substances can be hazardous even in trace amounts, or accumulate without notice due to a long latency period. In addition, recent worldwide viral infections suggest that the globalization of our society may produce harmful health effects on people all over the world. In order to sustain social development, the maintenance of human health by reducing these risks is therefore critical. Health risk factors (Figure 1) interact with the human body and result in symptoms, particularly when entering into the body. Technological inventions for preventing risk factor invasion via removal or external detoxification are important challenges required for health risk reduction.

Basic technologies to resolve health-related issues

First of all, materials that recognize and capture objects harmful to health (e.g., ions, molecules, and microorganisms) in a highly selective manner are essential to the development of technologies to deal with health hazards. For health risk reduction in a variety of surroundings, it is very important to specifically recognize the minimal concentration of noxious objects, even when embedded in a multi-component system.

We have studied the recovery of uranium and lithium from seawater, and have created original technologies to design materials that are capable of recognizing and isolating specific target ions in a multi-component system, such as seawater. We have proposed an ion-templating technique for designing cation exchangers. Ion exchangers with sieving effects on target cations are produced by mixing target cations (template ions) with inorganic oxides to form composite-oxide precursors under specific conditions. The precursors are then treated with acids to elute only the template ions, without altering the crystal structures of the matrices. Using this technology, we have succeeded in developing the first practical lithium-ion exchanger to selectively adsorb lithium ions from seawater. To date, ion exchangers specific for sodium or potassium ions have been developed. We have successfully conducted joint research with industry on the production of ultra-high purity potassium chloride and sodium chloride, by utilizing the respective exchangers.

We have challenged to extend the concept of ion sieving to the separation of anions, and recently have demonstrated that inorganic layered compounds specifically adsorb oxo-anions, when interlayer distances are appropriately adjusted. Our final goal is to develop materials that can selectively recognize different substances in the size range from < 1 nm to 100 nm, including organic compounds and viruses (Figure 2). To achieve this goal, we design appropriate capturing sites based on the chemical properties and sizes of the target

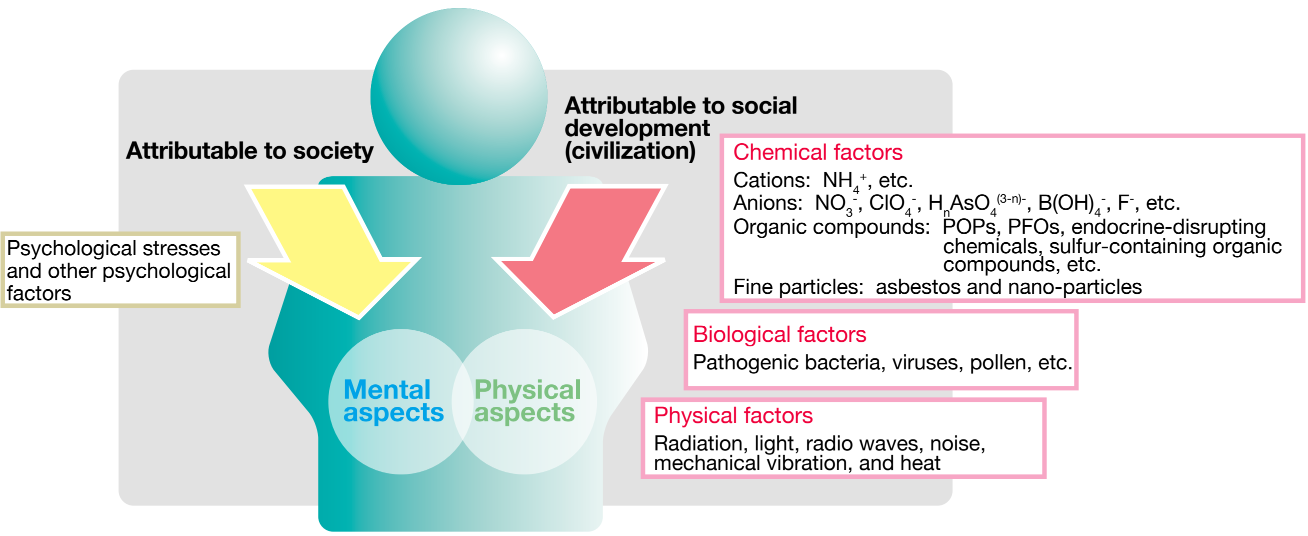


Figure 1 : Multiple risk factors in the living environment

substances. These systematic approaches are expected to be a significant methodology to reduce health risks.

Technologies to reduce health risks

I would like to introduce several unique approaches relating to health risk reduction (Figure 3). Nitrate ions (NO_3^-) are known to cause developmental disorders in infants (methemoglobinemia) and to have carcinogenic potential. Water quality standards for drinking water provide that the concentration of NO_3^- should be 10 ppm or lower. We have recently developed an inorganic layered compound that sieves out NO_3^-. Adjustment of interlayer distances by controlling the types and composition of constituent metal ions generates the sieving effects. This ion exchanger has been demonstrated to adsorb trace quantities of NO_3^- in seawater. Owing to its very high specificity, the NO_3^- ion exchanger can selectively adsorb NO_3^- ions and effectively remove them in an aqueous system containing anions other than NO_3^-. According to data obtained from the measurement of groundwater quality in 2003, approximately 7% of the groundwater in Japan exhibits NO_3^- levels exceeding that defined by the water quality standards. The NO_3^- ion exchanger can provide safe water, for example, in emergency situations caused by disasters, in which utilization of groundwater may become necessary.

A similar idea has been adopted for continuous antibacterial activity in aqueous systems, which is a completely different attempt. Silver-based antibacterial agents are safe and well-known, but function poorly in systems containing chloride ions. We have inserted silver ions or silver complex ions between layers of inorganic layered compounds to ensure sustained ionic release, and thus continuous antibacterial effects regardless of the presence or absence of chloride ions. Antibacterial effects in seawater have already been observed with some complex ions. The development of methods for maintaining these effects will be an important issue hereafter.

Unlike materials previously used for resource collection, recognition materials for health risk reduction must be composed of safe substances. To maximize effects, nano-sized recognition materials need to be dispersed and embedded in porous polymer matrices, prior to being shaped. Therefore, the development of a nano-particle fixation method is also required as a basic technology to overcome nano-risks. We hope to realize health risk reduction in the living environment, through the development and integration of these advanced technologies.

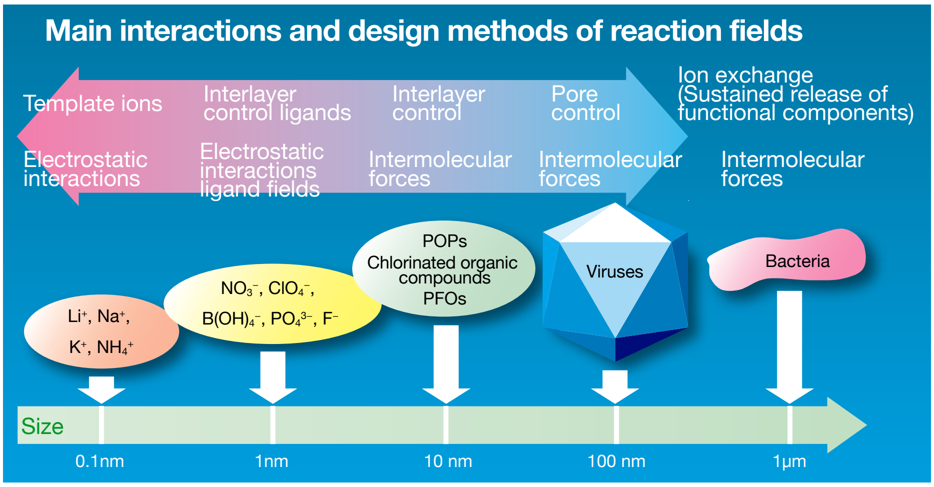


Figure 2 : Design of reaction fields corresponding to objects

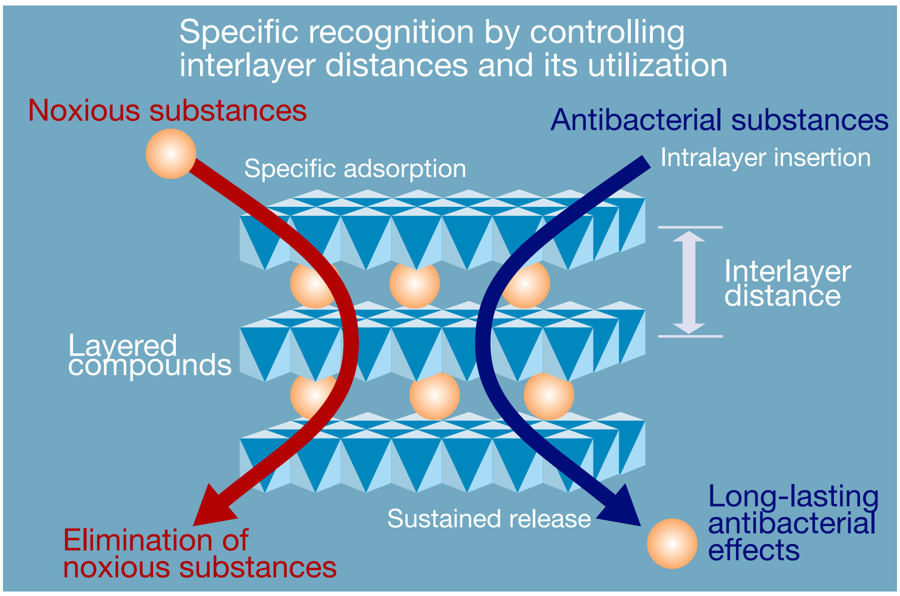


Figure 3 : An approach to reduce health risks

Fusion of Biotechnology and Nanotechnology: What It Brings

Yoshinobu Baba
Deputy Director (Nano-bio Research Supervisor), Health Technology Research Center
Professor, Graduate School of Engineering, Nagoya University

Nanotechnology breaking fresh ground in medicine

To advance the creation of new technologies through a combination of nanotechnology and biotechnology, we have undertaken research on the basic technologies shown in Figure 1 (single-molecule DNA analysis, diagnostic nano-bio devices, and single-cell diagnosis), and the combination of them. This research provides a foundation for the practical application of new systems that enable us to comprehend physical conditions, and diagnose diseases based on individual genetic information. Mobile or wearable devices for evaluating an individual' s condition at home are the fruition of these research efforts. In addition, our recent invention to fuse semiconductor nanoparticles and biomolecules has attracted attention. This innovation has produced encouraging results and provided a new perspective on nanotechnology. It may lead to “super” early diagnosis, as well as new cancer treatments. In the future, these research efforts will contribute to the development of the predictive diagnostic technology, facilitate the transformation of treatment-oriented health care into a prevention-oriented one, and realize an active aging society.

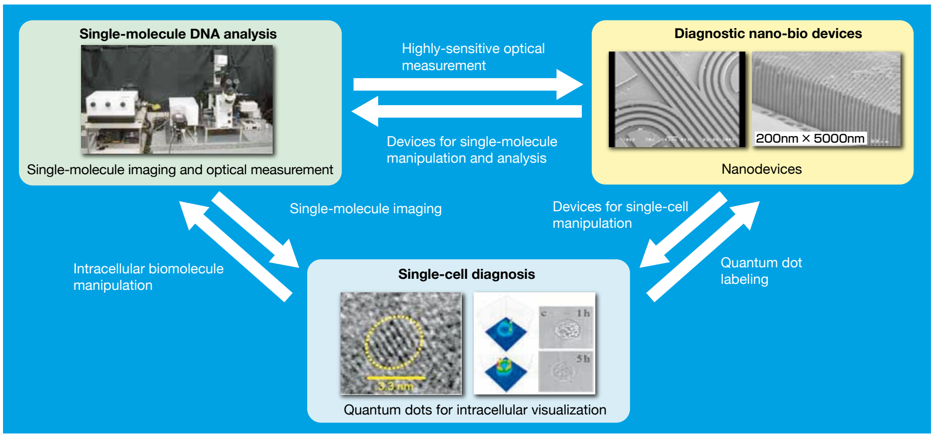


Figure 1 : Research objectives to develop the predictive diagnostic technology
New technologies for predictive health diagnosis will be developed by combining three basic technologies cultivated at the Health Technology Research Center.

Development of a genetic diagnostic device requiring only a fraction of the blood

Using our semiconductor technology, and in collaboration with Kyoto University and Starlite Co. Ltd., we have developed a technology for producing plastic chips for genetic diagnosis at a lower cost. An electromicrograph of the chip is shown in Figure 2. This extremely small chip possesses 10 microchannels, with a width and depth of 50 µm, which allows the simultaneous analyses of blood samples from 10 individuals. We have succeeded in placing 10 channels within a 1-mm width. By expanding this technology, one chip with a size of several centimeters will be sufficient to analyze the genes of more than 1,000 individuals. Moreover, a highly sensitive device that can rapidly analyze genetic information on chips and make diagnosis has been contrived.

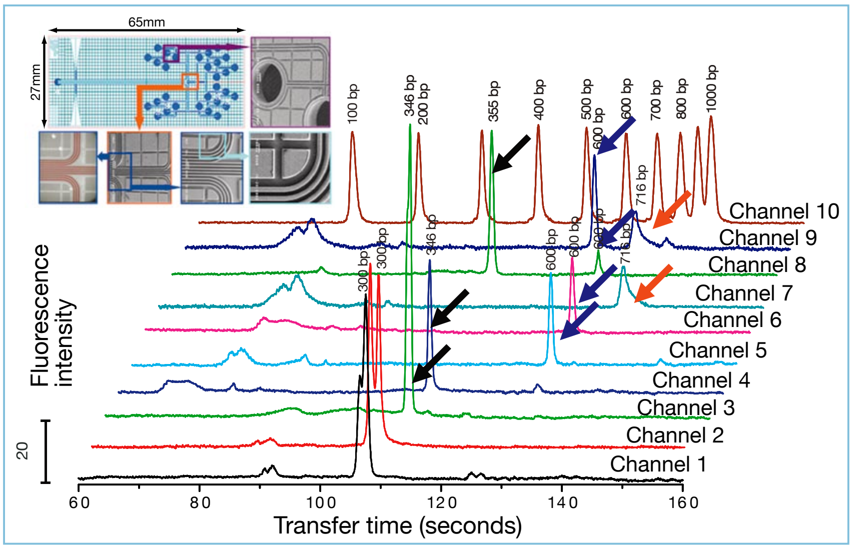


Figure 2 : Development of a genetic diagnostic device and its application to lung cancer
We have collaborated with a university and a private company to develop a technology for producing diagnostic biodevices at low cost, and with a university hospital to apply the resulting device to lung cancer. Blue arrows indicate normal genes, while red and black arrows indicate potentially pathogenic genes of altered size.

Figure 2 illustrates the genetic diagnosis of lung cancer. Conventional genetic tests require 1-2 days to obtain the results. Our device has successfully shortened the diagnostic time, requiring approximately 10-20 minutes. In addition, the amount of blood necessary for testing has been reduced to 1/100 or less. Our technologies will also lower the cost of genetic testing to 1/10-1/100 or less, relative to previous tools. These improvements are believed to reduce the burden on patients. The system is roughly the size of a desktop computer at present, but will be downsized to the size of a laptop computer, or even to a mobile or wearable size.

Development of single-cell diagnostic technology that realizes "super" early diagnosis

A single-cell diagnostic device using nanotechnology and its application to cancer diagnosis are illustrated in Figure 3. This device enables us to manipulate single cells freely, and perform highly sensitive analyses for trace quantities of intracellular genes and proteins. Additionally, a new reagent named as quantum dots can be used for cell imaging instead of conventional organic fluorescent dyes or fluorescent proteins. Quantum dots are an inorganic semiconductor material with a diameter of 2-5 nm. When irradiated with ultraviolet rays, they emit fluorescent light ranging from violet to red, according to diameters. Although quantum dot performance is excellent, their application to biotechnology had been limited because they are not compatible with proteins and other biomolecules. To overcome this problem, we have developed a new technology to fuse quantum dots with proteins. Using this technology, quantum dots can be fused to lectin molecules that specifically recognize cancer cells, or to antibodies that recognize specific proteins. These fusion quantum dots, together with single-cell diagnostic chips, are employed in the cytopathological diagnosis of cancer. As shown in Figure 3, the addition of quantum dots to cancer cells followed by irradiation with ultraviolet rays produces a bright green fluorescence resulting from the binding of quantum dots to the surface of cancer cells. In contrast, no fluorescence was observed in normal cells, due to the absence of an interaction between the quantum dots and normal cells. The presence of disease is revealed using this technology, which may detect cell populations as small as a few to several dozens of cancer cells. Cutting-edge diagnostic imaging systems, including magnetic resonance imaging and positron emission tomography are costly and do not detect cancer tissues smaller than 1 millimeter in size. Considering the above, the improvement of the sensitivity and accuracy of quantum-dot technology will lead to "super" early diagnosis and more effective cancer treatment.

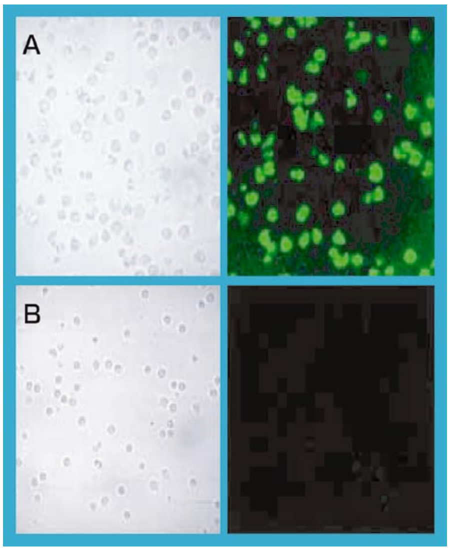


Figure 3 : Development of single-cell imaging and its application to cancer cell detection
Cancer cells were selectively detected by integrating a nanodevice technology and single-cell imaging. Cancer cells, but not normal cells, emitted fluorescence.
(A) A mixture of cancer cells and normal cells. Dozens of cancer cells were detected in groups. (B) Normal cells. No signal was detected.

Novel applications of nanotechnology to medicine

The devices and quantum dots mentioned above, as well as other technologies utilizing nanostructures can introduce new physical phenomena into the field of biotechnology, and allow us to invent unimaginable revolutionary technologies. For example, very small amounts of disease-related proteins present in cells will be detected using different types of quantum dots. Though fluorescence diminishes when conventional fluorescent reagents are used in combination, such an effect is not observed in quantum dots, which facilitate the highly sensitive detection of target proteins.

Furthermore, it has been elucidated that approximately 60 minutes of ultraviolet irradiation induces apoptosis in cancer cells, but not in normal cells, following the diagnostic test described above. Quantum dots absorb ultraviolet energy, a portion of which reacts with oxygen to generate noxious oxygen species, including the radical oxygen that causes apoptosis in cancer cells. Such an event may occur only when nanomaterials are used. Combining these technologies with an endoscopic approach, not only "super" early diagnosis, but also the treatment of detected cancer cells by inducing apoptosis will become practical. The development of technologies that integrate diagnosis with treatment is not fantasy (Figure 4).

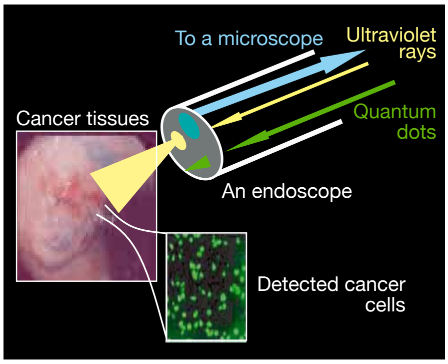


Figure 4 : Invention of a quantum dot-based technology in the biomedical field
Our aim is to develop modalities for the simultaneous diagnosis and treatment of cancer.

Future perspectives

The application of nanodevices and quantum dots to the biomedical field has just begun. Further research will lead to the development of technologies that make the early diagnosis of diverse diseases possible. The fusion of nanotechnology and biotechnology will realize health care that has been considered impossible with conventional diagnostic tools and treatment measures.

NEWS

AIST Concludes Comprehensive Partnership Agreement with Five National Universities in Shikoku

AIST integrates with universities to advance a “Health Island Shikoku” initiative

On August 10th, 2005, AIST and five national universities in Shikoku signed a comprehensive partnership agreement. This agreement is intended to create a more efficient and effective cooperative research partnership, harnessing shared research capabilities and human resources to contribute to society through research and development. The five national universities are the University of Tokushima, Naruto University of Education, Kagawa University, Ehime University, and Kochi University. This marks the first time in Japanese history that a public research organization forms a comprehensive partnership with every national university in a specific region.

The partnership matches AIST with all of Shikoku’s national universities, known for their distinctive research and education activities, with their strengths complementing one another. In addition to producing world-class researches through wide-ranging human resource sharing and research cooperation, from science, engineering, agricultural science, medicine, and economics to education, the partnership also aims to speedily give back the fruits of these researches to industry and society, especially in Shikoku itself. AIST Shikoku will form the contact point, functioning as the research base and partnership base.

The agreement is expected to promote research cooperation and interaction inside and outside of Shikoku, realizing an economically and socially dynamic “Health Island Shikoku” through education and research.

From left: Yusuke Sagara, president of Kochi University; Yoshitsugu Kimura, president of Kagawa University; Toshihiro Aono, president of the University of Tokushima; Hiroyuki Yoshikawa, president of AIST; Hajime Takahashi, president of Naruto University of Education; and Masayuki Komatsu, president of Ehime University.

The agreement will generate synergy in the following areas:

1. The fusion of nano-technology and life sciences

Related to research in health engineering, this is the prevailing theme in Shikoku's "Industrial Cluster Program" and is closely tied with the "Intellectual Cluster" system being advanced by Shikoku's national universities. In the development of measuring and other devices for predictive diagnosis of health conditions, individual themes like precision optical measurement, nanoprocessing, and functional analysis of biological material are already explored collaboratively by AIST Shikoku and the national universities. These themes are also expected to be integrated and expand to include all of the AIST research units.

2. Creation of aquatic environments for health maintenance and enhancement

Shikoku has recently suffered from droughts. The extreme importance is thus given to development of technologies for creating healthy living areas such as a provision of healthy aquatic environments for safe and secure living, as well as rapid preservation of clean water in emergencies situations. Although the focus has been on engineering research up to this point, we are now looking toward broader and more integrated results, making use of medical and other findings coming out of the national universities

3. Manufacturing Technology

This is one of the Shikoku Bureau of Economy, Trade and Industry's priority sectors. AIST Shikoku is cooperating on research with companies in the Toyo area and universities, based on AIST's experience in nanoprocessing and metal and ceramic joining, cutting, and surface treatment. While continuing to work with Shikoku businesses, we will integrate with the manufacturing-related research arms of the Shikoku national universities and all AIST units, building up internship and research fellow programs, effecting a revitalization of Shikoku's manufacturing industry.

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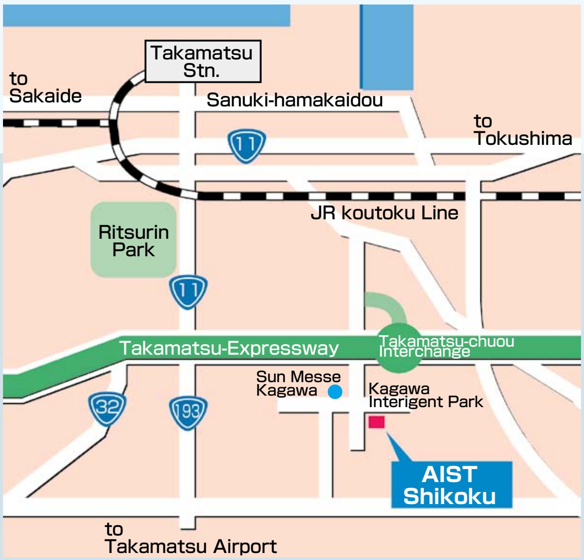
Access

Air Route
Haneda Airport to Takamatsu Airport

By Taxi from Airport
15 km from Takamatsu Airport to AIST

JR Marine Liner (from Okayama Station
Get off at Takamatsu Station (9 km from Takamatsu Station)

By Bus (from bus stop in front of Takamatsu Station)
Kotoden Bus
Go to the Sunport Takamatsu #8 bus stop and get on the Sunmesse-Kawashima Line or Sunmesse-Nishiueda Kawashima Line.
AIST is three minutes walk from the Sunmesse Kagawa stop, or 15 minutes walk from the Hayashi Shisho stop.



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