【ENGLISH】

# Summary of Research Project Results

## (Projects launched in JFY1997)

Japan Society for the Promotion of Science (JSPS)

# Table of Contents

# 【 Physical and Engineering Sciences】

# 1．Exploratory Research on Novel Artificial Materials and Substances for Next-Generation Industries

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Tsuyoshi MASUMOTO | (The Research Institute for Electric and Magnetic Materials) |
| | Tetsuhiko IKEGAMI | (The University of Aizu) |
| | Tatsuo IZAWA | (NTT Electronics Corporation) |
| | Takeshi KAMIYA | (National Institution for Academic Degree) |
| | Shun-ichi KOBAYASHI | (The Institute of Physical and Chemical Research) |
| | Kunio TADA | (Yokohama National University) |
| | Michihiko NAGUMO | (Waseda University) |
| | Toshio HIRAI | (Japan Fine Ceramics Center) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Research on Novel Optical Device Materials for the Wide Spectral Region | Katsumi KISHINO (Sophia University) |
| 2 | Functional Materials and Structures for Photonic Integrated Circuits | Tetsuya MIZUMOTO (Tokyo Institute of Technology) |
| 3 | Control of the Conduction Mechanism in Organic Conductors and Design of Novel Functional Material | Toshihiro TAKAHASHI (Gakushuin University) |
| 4 | Quantum Nonlinear Effects in Nanostructures and their Applications | Mitsuo KAWABE (University of Tsukuba) |

# Research on Novel Optical Device Materials for the Wide Spectral Region

**Project Leader**
Katsumi KISHINO Professor, Faculty of Science and Technology, Sophia University

**Summary of Research Project Result**

(1) Development of mid-visible wavelength (550-620nm) materials:

Novel II-VI compounds of MgZnCdSe, BeZnTe alloys, and the related superlattice materials on InP were developed. Applying these materials, the first lasing operations of yellow-green semiconductor LDs (563nm), and long life LED operations over 2500 hours at 554-644nm have been achieved. ZnCdTe/ZnTe LEDs on ZnTe substrates were developed to have the yellow emission around 587 nm.

(2) Development of novel optical communication wavelength materials:

Novel Tl-contained III-V materials, such as TlInGaAs and TlInGaP, in which temperature insensitive bandgaps are expected, have been investigated. The temperature dependency of the bandgap was suppressed to be -0.03meV/K, which is one tenth of a conventional semiconductor, for example InAs. The first lasing operation of TlInGaAs/InP LDs has been demonstrated.

The growth technology of highly strained InGaAs QW structures has been established. By use of that, the InGaAs strained QW LDs with the longest lasing wavelength of 1.2 $\mu$ m have been fabricated demonstrating the low threshold currents as small as 100 A/cm$^2$/well and the high characteristic temperature more than 200K.

Aiming to break through the limit of the conventional optical communication wavelength materials, AlN/GaN intersubband transition (ISBT) material have been demonstrated. To realize mono-layer order thickness control, the RF-MBE growth technology of nitride semiconductors has been established to grow GaN/AlN superlattices. In supelattices, the ISBTs were observed in the wavelength range of 1.07-1.6 $\mu$ m, where the value of 1.07 $\mu$ m is the shortest wavelength in all ISBT researches. The FWHM of absorption spectrum was 61meV, which is the narrowest among nitride-based ISBT experiments. The first operation of AlN/GaN resonant tunneling diodes with a high peak-to-valley ratio more than 30 has also been achieved.

(3) Development of UV wavelength region materials:

Novel B-contained nitride semiconductors such as BAlGaN on SiC substrates have been developed using MOCVD. Deep-UV emissions around 250nm were observed in the BAlGaN/AlN-MQW samples. The novel strain control technique by GaN/AlN multi-buffer layers has been developed.

# Functional Materials and Structures for Photonic Integrated Circuits

**Project Leader**
Tetsuya MIZUMOTO Associate Professor, Graduate School of Science and Engineering, Tokyo Institute of Technology

**Summary of Research Project Result**

The objective of research project is to explore materials and structures for highly functional photonic integrated circuits. We developed a new class of selective area growth in metal-organic vapor phase epitaxy as a break-through technology for realizing semiconductor monolithic photonic integrated circuits, and demonstrated photonic functional devices that have otherwise been difficult to make, such as wavelength converters, optical isolators, and all optical switches. In order to realize the nonreciprocal function, it is requested to implement magneto-optic materials. We developed a novel technology of low-temperature wafer bonding in order to integrate magneto-optic garnets on III-V semiconductor wafers, and demonstrated the performance of novel isolator that has high compatibility of integrating with semiconductor optical active devices. Electrooptic effect and nonlinear optical effect are essentially very useful in advanced optoelectronics. However, their practical applications are unfortunately limited by their poor electrooptic or nonlinear optical constants. We spotlight $LiNbO_3$ crystal families to obtain guiding principles enlarging these effects, and obtained 1.3 times higher electrooptic effect in a stoichiometric $LiNbO_3$ doped with Ce ions. As for scalability of integrated photonic circuits, it is limited by the size of devices and relatively large curvature of waveguides used for connecting photonic devices. The fourth group totally studied to investigate materials and structures for a large scale photonic integration composed of ultra-small elements. The fundamental structure is a semiconductor slab sandwiched by low refractive index media so-called *microdisk*. We developed various techniques to fabricate and design GaInAsP/InP-based microdisk lasers as well as Si-based photonic waveguides and successfully demonstrated the evidences of these devices with high performance and characteristic.

# Control of the Conduction Mechanism in Organic Conductors and Design of Novel Functional Material

**Project Leader**
Toshihiro TAKAHASHI Professor, Faculty of Science, Gakushuin University

**Summary of Research Project Result**

Conducting organic molecular complexes, i.e., organic conductors, have high possibility of useful material in near future. The purposes of this project were to investigate the mechanism of large variety of conductivity in this system and to derive the guideline to design new materials controlling their physical properties on the basis of the systematic analysis of the existing materials. We have chosen the complexes based on BEDT-TTF molecule as a model system and have analyzed the correlation between the molecular arrangement and the electronic properties in this family of material, looking for the possibility of systematic control of their electronic properties. The most prominent results are as follows.

1. Discovery of Metal-Insulator Transition accompanied by Charge Ordering<BR>

   It was confirmed that the insulating phases of non-dimerized BEDT-TTF salts of the $\alpha$- and $\theta$-type were accompanied by charge ordering and the pattern of the charge ordering with a stripe structure was first determined experimentally.

2. Characterization of New Conducting State with Constant Resistance

   The $\alpha$-type $I_3$ salt of BEDT-TTF was found to become a narrow-gap semiconductor with extremely high mobility under pressure. This state was found to be stable in a wide pressure and temperature region, and also observed in three different materials, indicating the universality of this state.

3. Control of the various ground states by applying hydrostatic and uniaxial pressure

   Pressure effects on the MI transition with charge ordering and the narrow-gap semiconducting state were examined. It was observed that the ground state can be controlled systematically among the normal metallic state, the insulating state (with charge ordering) and the narrow-gap semiconducting state by controlling the molecular arrangement with hydrostatic and uniaxial pressure.

# Quantum Nonlinear Effects in Nanostructures and their Applications

**Project Leader**
Mitsuo KAWABE Professor, Institute of Applied Physics, University of Tsukuba

**Summary of Research Project Result**

In quantum dots, resonant energies of quantum levels change their energies with the change of their sizes, the linewidths of the quantum levels are very sharp and confined electrons and holes mutually interact strongly. All of these features of the quantum dots are of benefit to sensitive optical switches operating under the weakest light. For the basic study of QDs, we have extensively studied the optical response of quantum dots by investigating the electronic states and dynamics of the excited states in quantum dots, and then have given bases to the application of the quantum dots to optical switch and optical memory. Clarifying the homogeneous optical spectra of quantum dots and its responsible physical mechanism are also extensively studied because the homogeneous width is closely connected with the optical nonlinearity. Extension of the wavelength tunability of the ultrafast optical switch of quantum dots to the infrared region and exploring the new optical functionality of quantum dots have been studied for application of QDs.

Enhancement and control of nonlinear optical effects of quantum nanostructure materials were achieved using photonic crystal structures. By doping nonlinear optical materials such as semiconductor dots in a defect layer of one-dimensional photonic crystals, drastic enhancement of the effective nonlinearity was achieved. Theoretical analysis for the optimization of the device parameters was performed and the prediction was verified by experiments. Ultrafast response of the photonic crystal nonlinear devices doped with semiconductor and metal quantum dots was observed by femtosecond pump-probe measurements.

In order to take the advantage of these properties for device application we should improve the dot size homogeneity and increase the dot density. The conventional method for dot formation is the self-assembling growth, while the fundamental growth mechanism is not clear, In this project we investigated the growth mechanism of self-assembled quantum dots for improvement of dot-size homogeneity, high density and ordering of dot array. We have successfully demonstrated 20 layer stacking of InAs QD layers without deterioration of QD size and homogeneity by using strain compensation and suppression of segregation structures.

# 2. Atomic-scale Surface and Interface Dynamics

（1）Research Promotion Committee Members

| | | |
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| | Sukekatsu USHIODA | (Tohoku University) |
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| | Kiyoshi TAKAHASHI | (Teikyo University of Science & Technology) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Dynamic Behavior of Grown Surface and Interface, and Atomic Scale Simulation | Toshiharu IRISAWA (Gakushuin University) |
| 2 | Atomic Scale Dynamics of Non-Equilibrium Surface Layer and Synthesis of New Materials | Hideo OHNO (Tohoku University) |

# Dynamic Behavior of Grown Surface and Interface, and Atomic Scale Simulation

**Project Leader**
Tosiharu IRISAWA Professor, Computer Center, Gakushuin University

**Summary of Research Project Result**

Dynamics and atomic-scale simulations of growth surfaces and interfaces were studied with collaborations between theoretical and experimental groups. To extend the range and accuracy of crystal growth theory, the theoretical groups developed a statistical crystal growth theory and made large-scale simulations. The experimental groups did experiments to discover new phenomenon and to develop new measuring devices with the aim of upgrading crystal characterization technology. To understand cooperative phenomena in crystal growth, experimental results and first-principle calculations were used to model various phenomena while retaining their important physical features. Furthermore, our advances in experimental methods are important for testing theory.

Our group used statistical mechanics and phenomenology to develop a technique that accurately obtains various physical quantities from an atomic-level model. For GaN thick-film preparation by heteroepitaxial growth on GaAs substrates, a commercialized technique was developed with help from this first-principle calculation. We also established a measurement and evaluation technology for a type of microdefect in silicon. This technique helped improve international standardization in the internationally competitive silicon industry.

We summarize results of the following five subjects (A－E) that help clarify atomic dynamics in crystal surfaces and interfaces. These were obtained through collaboration between theoretical and experimental groups. A: Establishment of a statistical mechanical theory for the formation of surface structure. B: Elucidation of step motion and growth pattern control. C: Heteroepitaxy and nucleation processes. D: Surface reactions and growth control. E: Analysis of interface reactions in a concentrated environment.

# Atomic Scale Dynamics of Non-Equilibrium Surface Layer and Synthesis of New Materials

**Project Leader**
Hideo OHNO Professor, Research Institute of Electrical Communication, Tohoku University

**Summary of Research Project Result**

(1) Integration of Magnetic Materials and Semiconductors:

Dynamics of non-equilibrium surface layers during MBE was investigated by *in-situ* techniques and modeled by Monte Carlo simulations. Using low-temperature MBE, new ferromagnetic semiconductors and materials such as GaMnSb and CrSb and their heterostructures were synthesized. Also established are 1) the origin of ferromagnetism in semiconductors, 2) electrical spin injection into semiconductors, and 3) tunnel magnetoresistance and spin-dependent scattering in semiconductor trilayers. By these, we succeeded in establishing the foundations of semiconductor spintronics.

(2)Integration of Insulators and Semiconductors:

Established that the adsorption-reaction processes of hydrogenated gas species on Si and Ge surfaces are described systematically by the Langmur type process. Atomic layer epitaxy, insulating layer formation by carbonization and nitridation, and Si epitaxy on C/P/N terminated Si surfaces are also established. Processes for ultrasmall SiGe heterojunction devices were developed and devices were made.

(3)Integration of Metals and Semiconductors:

Metal-semiconductor epitaxial heterostructures using semimetal ErAs, ferromagnetic metal MnAs and III-V compounds (GaAs, AlAs) were realized with an atomic level thickness control. Devices such as resonant tunneling diodes, spin valves, and magnetooptical devices were also made.

(4)Characterization and Control of Atomic Level Dynamics of Non-equilibrium Surface Layers:

Electronic excited states as well as vibrational states at interfaces were investigated by local spectroscopy of GaAs, ZnCdSe, and CuCl single quantum dots. Enhancement of the third order nonlinear optical susceptibility was realized in CuCl quantum dots grown on $CaF_2$ (111) by MBE.

(5)Materials Design for Non-equilibrium Growth:

Based on first-principle calculations, electronic structures and material design of magnetic semiconductors based on II-VI compounds like ZnO and III-V compounds like GaAs were established.

# 3. Advanced Processes

（1）Research Promotion Committee Members

| | | |
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| | Hideki SAKURAI | (Miyagi Organization For Industry Promotion) |
| | Hiroshi FUJITA | (Osaka University) |
| | Shun-ichi MURAHASHI | (Okayama University of Science) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Developments of Novel Carbon Nanomaterials | Hisanori SHINOHARA<br>(Nagoya University) |
| 2 | Convergent Molecular Transformation Process and Materials System | Yoshinori YAMAMOTO<br>(Tohoku University) |

# Developments of Novel Carbon Nanomaterials

**Project Leader**
Hisanori SHINOHARA Professor, Graduate School of Science, Nagoya University

**Summary of Research Project Result**

The current research project has dealt with the so-called nano-carbon materials such as fullerenes, endohedral metallofullerenes, carbon nanotubes and carbon peapods (nanotubes encapsulating various types of fullerenes). The main important results we obtained are the followings:

1. Synthesis of new types of endohedral metallofullerenes such as endohedral metallofullerenes encaging metal clusters and metal carbides. In particular, we have synthesized and purified the first metal-carbide endohedral metallofullerene, $(Sc_2C_2)@C_{84}$;
2. Synthesis and characterization of brand new types of MRI contrast agents based on water-soluble Gd-endohedral metallofullerenes. In particular, we have found that water-soluble $(Gd@C_{82})(OH)n$ metallofullerenes exhibit extremely high relaxibity (ca. 20 times higher) as compared with commercially available Gd-DTPA;
3. We developed a system to produce and separate/purify a gram quantity of endohedral metallofulllerenes;
4. Elucidation of growth mechanisms of fullerenes and single-wall carbon nanotubes (SWNT). We have successfully observed carbon clusters larger than $C_{200}$ which should play a crucial role in the early stage of the SWNT growth;
5. Real time observation by high-speed video camera of the production and growth of fullerenes and SWNTs. We have found that the growth of fullerenes should be completed in 1 ms after laser ablation of target graphite rods ;
6. Selective production of diameter-controlled SWNTs based on the studies 4 and 5 above;
7. Electronic and structural studies of carbon clusters produced by the so-called laser-furnace technique by means of photodetachment laser spectroscopy.

# Convergent Molecular Transformation Process and Materials System

**Project Leader**
Yoshinori YAMAMOTO Professor, Graduate School of Science, Tohoku University

**Summary of Research Project Result**

1. Development of convergent processes utilizing cross-benzannulation

Palladium catalyzed [4+2] cross-benzannulation of enynes with diynes was performed to give regiospecific cross-cycloaddition products in good to high yields. Phenol and aniline derivatives were also synthesized regiospecifically under the same methodology.

2. Development of convergent processes utilizing hydrocarbonation, hydroamination, and hydroalokoxylation

Palladium catalyzed hydrofurylation of alkylidenecyclopropanes was carried out to afford allylated furan derivatives effectively. Hydroamination and hydroalkoxylation were also developed. These methodologies can be used for preparation of useful compounds, such as aliphatic amines and alcohols, heterocycles, and cyclic ethers.

3. Development of convergent processes utilizing addition reactions to unsaturated compounds

Vinylation reactions of phenols, anilines, aromatic hydrocarbons, and enolates were developed using stoichiometric and, in some cases, catalytic amounts of tin or gallium reagents. Addition of phosphine or disulfide to alkynes or alkenes were conducted using palladium or rhodium catalysts.

4. Synthesis and properties of helical aromatic compounds

An optically pure helicene was prepared in multigram quantities, and various derivatives containing macrocyclic amides and alkynes were synthesized. Their properties regarding chiral recognition, asymmetric catalysis, chiral LB film formation, chiral CT complexation, and self-aggregation were examined.

# 4. Next-generation Process Technologies

（1）Research Promotion Committee Members

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| | Hiroshi KOMIYAMA | (The University of Tokyo) |
| | Hisayoshi MATSUYAMA | (Kyushu University) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Development of Process for Fabrications of Multi-functional Composites | Akira NOZUE (Sophia University) |
| 2 | Mesoscopic Process for the Development of Structural Ecomaterials | Akira AZUSHIMA (Yokohama National University) |

# Development of Process for Fabrications of Multi-functional Composites

**Project Leader**
Akira NOZUE Professor, Faculty of Science and Technology, Sophia University

**Summary of Research Project Result**

The present project is aimed at the fabrications of high loading parts (hip joints) and low loading parts (substitute materials for bones). Among the present subjects listed below, Subjects (1), (2), and (3) include the fabrication of biocompatible and high loading parts, whereas Subjects (4) and (5) include the fabrication of low loading parts:

(1) Coating on the surfaces of high strength substrate by spray hydrolysis

Precursors of the calcium phosphate films were deposited on the substrate, e.g., alumina ($Al_2O_3$) and tetragonal zirconia ($ZrO_2$), by spray-pyrolysing (i) solution (CA/P=0.50) for the adhesion for 5 h, and then (ii) solution (Ca/P=3.0) for film formation for 10 h. The substrate coated with precursors was heated at 1000℃to 1300℃ for 5h in a steam atmosphere or air to form hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$; HAp) films. The pore-size distributions were in the range of < 1 μm, 1-100 μm, and 100-200 μm. The results on the cell proliferation and differentiation using osteoblastic cell (MC3T3-E1) showed that the HAp-coated material had good biocompatibility, as compared with the control and the substrates without coating.

(2) Coating on the titanium substrates by soft solution technique

The HAp coating was conducted by immersing the Ti-6Al-4V substrate (diameter of 14 mm and thickness of 1.5mm) heated at 200℃ into (i) the simulated body fluid (5$cm^3$), (ii) the simulated body fluid and 1 mol・$dm^3$ urea (5$cm^3$), and (iii) the simulated body fluid, urea, and urease (0.03$cm^3$). The immersed substrate allowed to stand in an incubator (37℃ or 50℃) and replaced with the simulated body fluid. Larger amount of HAp was formed on the surfaces of Ti-6Al-4V substrate with increasing concentration of simulated body fluid and heat-treatment temperature. The results on the cell proliferation and differentiation using osteoblastic cell (MC3T3-E1) showed that the HAp-coated material had good biocompatibility, as compared with the control and the substrates without coating.

(3) Formation process of self-restoration function

Surfaces of the Ti-6Al-4V specimen with sizes of 35×34×4-8$mm^3$ and crack length of 17mm were modified using alkali-treatment technique, i.e., (i) the treatment of 5 mol・$m^3$ NaOH at 60℃ for 24h, (ii) drying at 37℃ for 24h, and then (iii) immersion into the simulated body fluid at 37℃ for three weeks. The HAp was precipitated not only on the surfaces but also on the introduced cracks of Ti-6Al-4V specimen. When HAp was precipitated on the Ti-6Al-4V specimen by utilizing the NaOH treatment, the fracture toughness increased from 60MPa・$m^{1/2}$ to around 72MPa・$m^{1/2}$ after 1500h of immersion.

(4) Process of bone-like composites and evaluation

The hybrid materials, i.e., HAp-poly (methylmethacrylate) (PMMA), were fabricated as follows: (i) the introduction of MMA monomer containing the azobis(isobutyronitrile) (AIBN) as a polymerization initiator into the porous HAp ceramics, and (ii) the bulk polymerization of the introduced MMA monomer by heating at 60℃ for 48h. The porous HAp ceramics with controlled porosities were fabricated using fibrous HAp with long-axis sizes of 50-100 μm. Mechanical properties of the hybrid materials were as follows: Young's modulus, ～63GPa; fracture toughness, ～2MPa・$m^{1/2}$ and; flexural strength, ～65MPa. The present hybrid materials proved to have a good biocompatibility close to the HAp ceramics.

(5) Fabrication of HAp-Collagen Composites

The porous HAp ceramics with average pore sizes of 90 μm, 200 μm, and 300 μm were immersed into the solutions with the collagen contents of 1 to 4.8 mg・$cm^{-3}$ and were freeze-dried for 24h. The heat-treated materials at 100-150℃ were immersed into the ethanol and, furthermore, were freeze-dried to obtain the composites. The amount of collagen was the largest when the average pore size and collagen content in the solution were 300 μm and 4.8mg・$cm^{-3}$, respectively. The amount of collagen increased linearly with increasing number of operation and exceeded 10% after 20 times. SEM micrographs revealed that the membrane-like collagen was present in the continuous pores and that the pores were present not only on the surfaces but also inside pores.

# Mesoscopic Process for the Development of Structural Ecomaterials

**Project Leader**
Akira AZUSHIMA Professor, Graduate School of Engineering, Yokohama National University

**Summary of Research Project Result**

Materials technology has been developed to realize better performance and higher quality. However, recent social circumstances brought about a new mission to materials science, namely harmony with our environment. In the field of structural materials, this clearly requests us to find a new process which produces materials, so called ecomaterials with high strength, in order to reduce energy loss. In this research project, materials with high strength are developed for structural ecomaterials by refining the grain size, the powder grain and so on. Groups of such materials are as follows:

(1) Metal and alloys with high strength at low temperature by side extrusion process under hydrostatic pressure.

(2) Ceramics with high strength and high reliability at high temperature by processes to control the reaction rate and microstructure in the fabrication of non-oxide ceramics.

(3) Intermetallics with high strength at high temperature by processes to control the anisotropic microstructure of TiAl intermetallic compound.

(4) The materials with low friction and low wear are produced by using surface treatment processes.

In the side extrusion process under hydrostatic pressure, the processes were repeated up to 10 passes using the carbon steels. For an example, for the ultra low carbon steel, an ultrafine grained steel with a tensile strength of over 1000MPa was developed with a grain size of 0.5 $\mu$m x 0.2 $\mu$m after 10 passes. The cold formability of the carbon steels was very good, and by the heat treatment, the uniform elongation became longer. In the process to control the reaction rate and microstructure in the fabrication of non-oxide ceramics, an unusual morphology of hollow balls of 200 to 500nm with a great deal of nano $\alpha$-sialon particles of around 10 to 30nm was discovered. By using the nano $\alpha$-sialon particles, the $\alpha$-sialon with higher strength was developed. In the processes to control the anisotropic microstructure of TiAl intermetallic compound, TiAl sheet with high oriented lamella was developed and the creep strength increased.

# 5. Intelligent Information and Advanced Information Processing

（1）Research Promotion Committee Members

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| | Masaaki SHIMASAKI | (Kyoto University) |
| | Mario TOKORO | (Sony Corporation) |
| | Makoto NAGAO | (Kyoto University) |
| | Yoshihiko FUTAMURA | (Waseda University) |
| | Takashi MATSUYAMA | (Kyoto University) |
| | Fumiko YONEZAWA | (Keio University) |

○：Committee Chairperson

（2）List of Research Project

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Researches on Advanced Multimedia Content Processing | Shojiro NISHIO<br>(Osaka University) |

# Researches on Advanced Multimedia Content Processing

**Project Leader**
Shojiro NISHIO Professor, Graduate School of Engineering, Osaka University

**Summary of Research Project Result**

In recent years, strong demand on sophisticated and integrated multimedia information processing systems has raised in many service areas including broadcasting, publishing, entertainment, and communications. The prime concern to build such systems is to establish very large multimedia database systems that will support the storing, sharing, and reuse of multimedia contents. In such database systems, besides the hardware and software infrastructures, the key issues are how to acquire multimedia data from the real world, how to store the obtained data into the databases and organize them, and how to create new and attractive multimedia contents from the stored data. The goals of this research project are to design a data model which is flexible enough to support the various user requests, to develop the system for the editing and processing of multimedia contents, and to build an architecture of very large multimedia database systems which are strong enough for the commercial use. In addition, the project emphasizes on finding new fields that can get benefits from our developed technologies.

As the results of this project, we developed the following: (1) an integrated system that involves the acquisition, editing and management of multimedia contents, (2) the content management method that supports the evolution of content's structure (i.e., handling the time aspect), (3) the content access architecture that supports the management of accesses, versioning, and broadcasting of multimedia contents, and finally,(4) the management systems for virtual and augmented reality spaces generated from the contents. We believe that the results of this project succeeded to opening and pioneering a new research field called "multimedia content processing". In fact, at the meeting where we demonstrated the final results of our project, the external referees gave high estimation to the project, mentioning that the results achieved in this project have significantly impacted on the community and industry, and will become next core technologies that will affect the developments of various infra-systems and applications.

# 6. Advanced Multimedia Information and Communication Systems

（1）Research Promotion Committee Members

| | | |
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| | Kinji ONO | (National Institute of Informatics) |
| | Shigeo TSUJII | (Chuo University) |
| | Toshiyuki TODAKA | (Doshisha University) |
| | Hitomi MURAKAMI | (KDDI Corporation) |

○：Committee Chairperson

（2）List of Research Project

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Extra High Quality Audio-Visual System for Creation of Future A-V Works and Two-Way Presence Communication | Makoto MIYAHARA (Japan Advanced Institute of Science and Technology, Hokuriku) |

# Extra High Quality Audio-Visual System for Creation of Future A-V Works and Two-Way Presence Communication

**Project Leader**
Makoto MIYAHARA Professor, School of Information Science,
Japan Advanced Institute of Science and Technology

**Summary of Research Project Result**

1. The champion performance of the high fidelity to transmit high order sensation is demonstrated. Deep emotion is evoked in the minds of observers and listeners by high quality images and creation sound of the developed Extra High Quality Visual-Audio System.
2. Fusion of Technology and Art is grown practically in the course of creation of art , and information sommeliers are educated.
3. A new inductive methodology to discover unknown factors is successfully practiced on key assessment words psychophisically.
4. A new field to feel awareness and deep sensation in a dark and silent affordance circumstance is proposed, to arise deep emotion in human minds.

# 7. Science of Synthesis

（1）Research Promotion Committee Members

| | | |
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| ○ | Naomasa NAKAJIMA | (The University of the Air) |
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| | Ichiro INASAKI | (Keio University) |
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| | Tetsuo TOMIYAMA | (The University of Tokyo) |
| | Hiromu NAKAZAWA | (Waseda University) |
| | Shuichi FUKUDA | (Tokyo Metropolitan Institute of Technology) |

○：Committee Chairperson

（2）List of Research Project

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | A Methodology of Collaborative Synthesis by Artificial Intelligence | Riichiro MIZOGUCHI<br>(Osaka University) |

# A Methodology of Collaborative Synthesis by Artificial Intelligence

**Project Leader**
Riichiro MIZOGUCHI Professor, The Institute of Scientific and Industrial Research, Osaka University

**Summary of Research Project Result**

The goal of the project is to explicate the synthetic knowledge used by designers through AI technology, to systematize it and to demonstrate the utility of such knowledge systematized. The results obtained are summarized as follows:

(1) Employing ontological engineering, seven-layer-concept/knowledge hierarchy has been developed as a framework for functional knowledge systematization which is grounded onto the physical world and successfully evaluated by deploying it into a production division of a company to share engineering know-how about their production lines among engineers.

(2) Some amount of knowledge such as functional knowledge, constraints among physical states, operations and design rationale has been described according to the framework and evaluated by implementing them in redesign, usability verification and physical constraint satisfaction modules.

(3) An interactive design support system composed of all the functional modules mentioned above has been implemented and has been successfully evaluated using two concrete examples: a handy printer for domestic use and a washing machine. This shows the interoperability and utility of the several categories of knowledge systematized.

The deployment of the knowledge systematization framework into the real-world was an unexpected success of our project. The framework has been built through four-year study on fundamental conceptual structure of functional knowledge using ontological engineering, which is almost the first serious ontological investigation on function in the world. We believe the fact that such a basic research has ended up with a successful deployment is what RFTF Program aims at.

# 8. Innovation in Energy Generation, Conversion, Materials and Systems for the Future

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Ichiro TANASAWA | (Nihon University) |
| | Yoshiaki OKA | (The University of Tokyo) |
| | Itsuro KIMURA | (Institute of Nuclear Safety System, Incorporated) |
| | Tadashi SAITOH | (Tokyo University of Agriculture and Technology) |
| | Katsuto NAKATSUKA | (Tohoku University) |
| | Satoru YANABU | (Tokyo Denki University) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Investigation on Design Methodology of Supercritical Subsurface Boiler for Next Generation Geothermal Energy Extraction | Toshiyuki HASHIDA (Tohoku University) |
| 2 | Study of New Carbon-Based Materials and Solar Cells | Masafumi YAMAGUCHI (Toyota Technological University) |
| 3 | Study on Raising Quality of Fuels by Use of the Reactions under Super Critical Conditions and on Efficient Energy Transfer System | Hiroshi TOMIYASU (Tokyo Institute of Technology) |

# Investigation on Design Methodology of Supercritical Subsurface Boiler for Next Generation Geothermal Energy Extraction

**Project Leader**
Toshiyuki HASHIDA Professor, Graduate School of Engineering, Tohoku University

**Summary of Research Project Result**

This project determined the feasibility of creating an artificial geothermal reservoir in a deep-seated rock mass, at conditions exceeding the critical point for water, with hydraulic fracturing/simulation and fluid permeability experiments delineating crack-generation processes. No macroscopic cracks are identified for low injection rates, but microfracturing does occur at 'grain-scale', with a four-order *increase* in permeability at supercritical conditions compared to the subcritical region. For high flow rates, macroscopic fracturing is characterised by planar shear- and open fractures, and a 'cloud-like' envelope of grain-scale microcracks, that provides an ideal network for thermal extraction. Laboratory tests infer equivalent permeability in the hydraulically-stimulated reservoir, with creation of a fracture-type reservoir in which to establish an energy extraction system. Stress corrosion cracking also increases rock permeability. The durability of crack generation at supercritical conditions, based on the kinetics for microcrack generation and healing, indicates microcrack lifetime of >10 years, which is acceptable for long-term energy utilisation.

The fracture network and formation mechanism of deep-seated geothermal reservoir's was resolved by geology field surveys, which identified typical petrochemical/tectonic and geofluid characteristics. Water-rock interaction studies clarified mineral dissolution and precipitation behavior in granitoids, using open and closed experimental systems.

The physical character of deep, supercritical reservoirs were investigated by: (i) measurement of acoustic velocity of granite; (ii) reflection method using AE/microseismicity; and (iii) a drill-bit reflection method. The stress state of a deep-seated rock mass was estimated by: (i) DTF (Drilling-induced Tensile Fracture); (ii) drill core analysis; and (iii) utilization of borehole temperature profile and fracture orientation.

Thermal extraction numerical modeling analysis incorporated fluid flow characteristics and thermal transfer in the surrounding rock mass, considering the effects of temperature and pressure in the supercritical fluid regime, as well as fluid density, viscosity etc. The transition from subcritical to supercritical conditions has a major effect on silica dissolution/precipitation processes. Our work shows there is an optimum injection rate to prevent possible plugging of fluid pathways (dependent on rock mass temperature), and allow long-term extraction of heat energy. Our fluid flow and thermal transfer study also predicts that silica precipitation in parts of the system can create a shell-like "sealed zone", preventing fluid loss from the artificially fractured rock mass - thus improving performance of the system.

# Study of New Carbon-Based Materials and Solar Cells

**Project Leader**
Masahumi YAMAGUCHI　Professor, Graduate School of Engineering, Toyota Technological Institute

**Summary of Research Project Result**

1. Control of physical properties of the $C_{60}$ films by the amorphization.
   ・The following physical properties of $C_{60}$ films were successfully controlled by the boron or phosphorous ion-implantation induced amorphization.
   ①Conduction type (n or p-type),②Resistivity ($10^{8}$～$10^{-1}$ Ω cm), ③Optical band gap (0.1～1.3 eV)
2. $C_{60}$/Si hetero-junction solar cells.
   ・The conversion efficiency was increased from $10^{-5}$% to 0.7% by the following cell structures.
   ①undoped $C_{60}$/Si cell: $10^{-5}$%, ②B-ion implanted $C_{60}$/Si cell: 0.02%, ③B-ion implanted $C_{60}$/i-$C_{60}$/Si cell: 0.1%, ④Excimer Laser irradiated $C_{60}$/Si cell: 0.7%
3. Thin film growth of amorphous carbon (a-C) using camphor as a precursor and homo-junction solar cells.
   ・The n- and p-type conduction of a-C was obtained by the ion beam sputtering method and thermal CVD method, respectively. The n-C/p-C/p-Si cell structure was fabricated and the conversion efficiency of 2.28% was obtained.
4. Fabrication of the $C_{60}$/a-C superlattice structures
   ・$C_{60}$/a-C superlattice structures were proposed as a new solar cell material, and successfully fabricated by the intermittent supplies of nitrogen radicals during $C_{60}$ growth. It was suggested that the effective band gap energy could be controlled by the thickness of each layer of superlattice structure.
5. Conduction type and optical band gap energy control of a-C grown by PE-CVD for the multi-junction solar cells.
   ・Amorphous carbon with low spin density ($10^{16}cm^{-3}$) was synthesized by rf plasma CVD.
   ・Band gap energy was controlled by the nitrogen, boron or sulfur doping in a-C.
   ・The n- and p-type conduction of a-C was obtained by sulfur and boron doping, respectively.

# Study on Raising Quality of Fuels by Use of the Reactions under Super Critical Conditions and on Efficient Energy Transfer System

**Project Leader**
Hiroshi TOMIYASU Emeritus Professor, Tokyo Institute of Technology

**Summary of Research Project Result**

The purpose of the present study is to establish methods for the reforming of low quality fuels and for the efficient energy conversion system through chemical reactions under supercritical conditions. In order to attain the purpose, the understanding of the physico-chemical properties of supercritical fluids is of particular importance, and the experiments have been carried out using vessels with sapphire windows to measure UV-visible, emission, and NMR spectra, and to measure Mach-Zehnder interferometer. Based on these basic studies, we have found that ruthenium(IV) dioxide acts as an enormous catalytic effect for the decomposition of any organic compounds in supercritical water. As a matter of fact, coal decomposed in supercritical water in the presence of the catalyst resulting in the formation of hydrogen gas as a major species with 20% of carbon dioxide. Although the mechanism has not been established yet, hydrogen seems to be generated from water during the decomposition of coal. Furthermore, the use of this catalyst enabled the complete decomposition of any plastics forming gas. The main species in the formed gas is methane, and about 40% of cabin dioxide and 5% of hydrogen are detected by gas-chromatographic measurements. In conclusion, the fuel reforming in the present study has been done successfully, and will be in progress for the industrial application. With respect to the efficient energy conversion system, we have established the basic data in supercritical water. The system seems to be feasible in the future.

# 9. Highly Efficient Use of Energy and Reduction of its Environmental Impact

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Yoshikazu NISHIKAWA | (Osaka Institute of Technology) |
| | Junzo KAWAKAMI | (Hitachi,Ltd) |
| | Shunsuke KONDO | (The University of Tokyo) |
| | Hideo SHINGU | (Kyoto Energy-Environmental Research Association) |
| | Taketoshi TANIGUCHI | (Central Research Institute of Electric Power Industry) |
| | Akira TOMITA | (Tohoku University) |
| | Koichi WATANABE | (Keio University) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Production- and Utilization-Technology of Hydrogen Aiming at the Hydrogen Energy Society | Masahiro SHIOJI (Kyoto University) |
| 2 | Distributed Autonomous Urban Energy Systems for Mitigating Environmental Impact | Kiichiro TSUJI (Osaka University) |
| 3 | Fundamental Research on Thermal Energy Storage to Preserve Environment | Akio SAITO (Tokyo Institute of Technology) |
| 4 | Fundamental Studies on Advanced Electric Power Systems by Application of Superconductivity | Tanzo NITTA (The University of Tokyo) |

# Production- and Utilization-Technology of Hydrogen Aiming at the Hydrogen Energy Society

**Project Leader**
Masahiro SHIOJI Professor, Graduate School of Energy Science, Kyoto University

**Summary of Research Project Result**

Based on the consideration into the most effective use of thermal energy, total energy system utilizing hydrogen as an energy carrier is proposed to establish the advanced society for protecting environment. This project is involved in four research tasks which meet the demand for a wide use of hydrogen fuel into the effective power plant and for a large-scale hydrogen-supply system materialized by water or renewable resources. Their outcomes are summarized as follows:

(1) Feasibility of a compact high-speed hydrogen engine was assessed by the experiments of performance and combustion characteristics. The optimal design and operating conditions was estimated based on exergy analysis and CFD simulation. Further development for hydrogen engine was demonstrated using a new prototype engine with rhombic link Z-crankshaft mechanism.

(2) For high-temperature steam electrolysis with a lower decomposition voltage and a faster reaction, novel technologies were investigated to develop novel solid electrolyte materials with perovskite related structure, stable and reactive materials with mixed conductive property, and synthesizing reactions of functional ceramics from aqueous solutions.

(3) Thermochemical UT-3 cycle of water decomposition was demonstrated to produce hydrogen by utilizing thermal energy at low temperatures. Also, the thermochemical recuperative hydrogen production by steam gasification was proposed to improve the overall thermal efficiency in the utilization of the carbonaceous resources. The fundamental research on the rapid steam gasification reaction of brown coal and biomass was conducted to study the reactivity of materials with steam.

(4) Effects of additives on the characteristics of $H_2$ combustion were investigated. Rate constants of the $H + O_2 + M = HO_2 + M$ reaction were determined for M = $H_2O$, $CO_2$, $N_2$, $O_2$, and Ar. Preferential diffusion effect at the hydrogen wrinkled flame was confirmed to estimate turbulent burning velocity.

# Distributed Autonomous Urban Energy Systems for Mitigating Environmental Impact

**Project Leader**
Kiichiro TSUJI Professor, Graduate School of Engineering, Osaka University

**Summary of Research Project Result**

The purpose of this investigation is to establish the concepts of "Integrated Energy Service System" and "Integrated Recycle System" in urban areas that are energy efficient and environmentally compatible.

For the Integrated Energy Service System, three planning models have been developed each of which is based on multi-objective mathematical optimization. These models can deal with the tradeoffs between primary energy consumption, CO2 emission and cost. Various energy systems for urban area that correspond to non-inferior solutions are identified. A computer supported planning system that can be used on internet has been developed. This system is based on the developed mathematical optimization models and enables energy system planners to explore variety of alternative systems including distributed generators such as PV cells and micro co-generation. See http://t-www.pwr.eng.osaka-u.ac.jp.

A concept of Integrated Recycle System that includes various recycle techniques contributing to the better environment has been proposed. On the technical side, new materials which disassembles by itself and saves energy when it is recycled, and also, a biomass conversion system which uses supercritical water for instantaneous hydrolysis and produces glucose from cellulose, have been developed. From system analysis side, methods for evaluating the effects of pollutants discharged from production activity, daily life and transportation in urban area has been established, and then the effects of introducing recycle system have been evaluated. An inventory database was constructed and it is publicly available at http://aerosol.energy.kyoto-u.ac.jp/~lca/I-Otable/public.html

For the purpose of constructing an end-use energy demand database, measurement of electricity and city gas demand in residential houses has been carried out. The first stage of the monitoring project was from Oct. 1998 until Nov. 1999. The second stage was from Dec. 1999 until May of 2001. Daily load curves for each of end-use such as space heating and cooling have been acquired successfully. The acquired data will be useful not only for comprehensive understanding of residential energy use but also for planning better energy systems in residential area.

A new electric energy distribution network that is referred to as FRIENDS (Flexible, Reliable and Intelligent Electric eNergy Delivery System) has been explored from both hardware and software points of view. The new system enables multi-menu service differentiated by the quality of electric power through Quality Control Center. Various circuit configurations have been proposed and one of which has been patented both in Japan and in USA.

With all of these developments and a number of case studies for actual cities, a concrete image of "autonomous distributed urban energy systems" has been drawn and visually demonstrated.

# Fundamental Research on Thermal Energy Storage to Preserve Environment

**Project Leader**
Akio SAITO
Professor, Graduate School of Science and Engineering,
Tokyo Institute of Technology

**Summary of Research Project Result**

The object of this project is to investigate physical phenomena and theories relating to solid-liquid phase change, which form the bases of the dynamic-type ice-making CTES.

(1) Two methods to control the initiation of freezing of supercooled water were examined. In the first method, electrical current was used as the trigger of nucleation and very small element was developed to freeze the water instantaneously. In the second method, a simple instrument was developed which utilize mechanical shock as the trigger. By the method, supercooled water, the temperature of which is higher than -0.2℃, freezes instantaneously.

(2) Two dynamic methods were developed, where ice crystals formed in ethylene glycol solution were removed automatically from the cooling surface. In the first method, the ice crystals are removed by buoyancy force acting on the ice. In the second method, the ice crystals are removed by applying horizontal vibration to a vertical cooling plate. In both methods, the cooling surface temperature can be set higher than a representative static method to produce the same amount of ice in a given space.

(3) A system to utilize LNG cold waste was proposed. The cold trap is cooled by the LNG cold waste, and water vapor is removed through a pipe line from the evaporator which is located apart from the cold waste. By supplying water shower into the evaporator, ice particles are produced continuously at the triple point. Fundamental researches were performed to evaluate and to improve the method.

(4) Methods to produce suspension of fine ice particles from oil-water emulsion were developed. High IPF (ice packing factor) was achieved in a method to produce ice particles by stirring in a vessel. As an alternative method, slurry ice is produced continuously through a pipe. In this method, the cooling surface temperature can also be set higher than a representative static method to produce the same amount of ice in a given space.

# Fundamental Studies on Advanced Electric Power Systems by Application of Superconductivity

**Project Leader**
Tanzo NITTA Professor, Graduate School of Engineering, The University of Tokyo

**Summary of Research Project Result**

The purpose of the research is to obtain advanced power systems by application of superconductivity. The research results are as follows:

Development of real time power system simulator with models of superconducting generators (SCG) and superconducting magnetic energy storage system (SMES)

Experiments on improved power system stability by use of SCG: SCG improves system stability with comparison to conventional generator. Machine parameters effective to system stability are defined.

Optimal location and parameter of SCG for improved power system stability for two typical power networks in Japan by eigenvalue control method.

Power system identification by use of SMES: By giving to small deviations of power from SMES, eigenvalues on operating condition can be obtained. Experiments were carried out by use of TNS and the models of SMES, and by use of SMES with small superconducting magnet and artificial transmission lines with rotating machines.

Development of power converter for SMES with non-forced commutation devices by application of energy transfer circuit of superconducting magnets.

Development of superconducting fault currents limiter (SCFCLs) with adjustable trigger current level: The SCFCLs have good characteristics such that the recovery time is less than 100 msec. Some experiments shows that SCFLCs can solve two problems on fault current limiting and power system stability

Surface discharge characteristics on insulation materials in Liq. N2 and Liq. He. The fundamental data obtained, by which the characteristics of any material can be obtained.

Application of bulk superconductor: Characteristics of motors or generators (Synchronous, induction, hysteresis ones with rotor of bulk superconductor) are obtained.

# １０．Computational Science and Engineering

（１）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Genki YAGAWA | (The University of Tokyo) |
| | Yasuyoshi INAGAKI | (Nagoya University) |
| | Yoshio OYANAGI | (The University of Tokyo) |
| | Shoichi KOBAYASHI | (Fukui University of Technology) |
| | Nobuyuki SATOFUKA | (Kyoto Institute of Technology) |
| | Masaki SHIRATORI | (Yokohama National University) |
| | Daiichiro SUGIMOTO | (The University of the Air) |
| | Kiyoyuki TERAKURA | (National Institute of Advanced Industrial Science and Technology) |
| | Masatake MORI | (Tokyo Denki University) |

○：Committee Chairperson

（２）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Computational Science and Engineering for Global Scale Flow Systems | Yukio KANEDA<br>(Nagoya University) |
| 2 | Development of Next-generation Massively Parallel Computers | Yoichi IWASAKI<br>(University of Tsukuba) |
| 3 | Material Science Simulation for Future Electronics | Masatoshi IMADA<br>(The University of Tokyo) |
| 4 | Development of Computational Mechanics System for Large Scale Analysis and Design | Shinobu YOSHIMURA<br>(The University of Tokyo) |

# Computational Science and Engineering for Global Scale Flow Systems

**Project Leader**
Yukio KANEDA Professor, Graduate School of Engineering, Nagoya University

**Summary of Research Project Result**

We have developed new computational-scientific methods for global scale flow systems (GSFS). In particular, we have developed (1) turbulence models free from *ad-hoc* parameter tuning techniques, (2) numerical algorithms for flows on spherical geometry, and (3) methods for large-scale numerical simulations compatible with the paradigm of Massive Parallel Processing.

(1) We have performed Direct Numerical Simulations (DNS) of turbulence based on the spectral method, which are currently the largest DNS of incompressible turbulence in the World. By using the DNS data, we have developed spectral closure theories of turbulence and Large Eddy Simulation (LES) models for GSFS. These include probabilistic LES models which provide quantitative estimates of the reliability of predictions obtained by LES.

(2) We have developed several algorithms that achieve decisive speed up in large--scale simulations of flows in spherical geometry: (a) fast spherical harmonics transform algorithm, (b) double Fourier series expansion method, and (c) combined compact finite difference scheme. A Fortran 90 package of (a) is now available on our website. The algorithms (b) and (c) were tested and their efficiency was confirmed by applying them to all seven test problems in the now standard benchmark test set proposed by Williamson *et al.*

(3) By applying the higher--order method of lines, we performed DNS with $1024^3$ grid points, and confirmed that the efficiency of parallelization is 90%. In particular, such efficiency was achieved in computations of global--scale flows in spherical geometry with 10 km horizontal mesh size, both in cubed sphere coordinates and by a grid-less method.

The LES models developed in (1) were then integrated into the codes implementing schemes (2-b), (2-c) and (3-b) and their efficiency was confirmed. A systematic study of the performance of the finite difference scheme was made by comparing DNS results obtained in (1) and (3).

# Development of Next-generation Massively Parallel Computers

**Project Leader**
Yoichi IWASAKI Vice President, University of Tsukuba

**Summary of Research Project Result**

Rapid progress of computational sciences and engineering is deeply connected with development of massively parallel computers (MPP). This project aimed to carry out R&D to enhance the speed of MPP from 1TFLOPS to 100TFLOPS. The research was carried out for MPP for continuous physical systems and for particle-based systems, whose results were integrated toward the end of the project.

For MPP for continuous physical systems, a novel processor architecture called SCIMA was developed. Using the software controllable feature of on-chip memory, this processor is shown to realize superior performance over cache-based processors for HPC applications. A high-speed flexible parallel I/O and visualization system named PAVEMENT was also developed and installed in a wide variety of platforms from MPP to PC clusters.

For MPP for particle-based simulations, a special-purpose processor GRAPE-6 for gravity/Coulomb interactions were developed. In June 2001, the GRAPE-6 system with a peak speed of 32TFLOPS achieved 11.55TFLOPS in an astrophysical simulation for galactic nuclei, for which the Gordon Bell Prize for 2001 was awarded. The GRAPE system also won the Gordon Bell Prize of 2000 for performance of the prototype GRAPE-6, and of 1999 for cost/performance of GRAPE-5.

Simulations of complex systems having both continuous and particle degrees of freedom and multiple scales of interactions are becoming more and more important in science and engineering. As a final goal of the project, a heterogeneous multi-computer system (HMCS) consisting of the CP-PACS (0.6TFLOPS) for continuous systems and GRAPE-6(8 boards and 8TFLOPS) for particle systems connected via the parallel PAVEMENT I/O system was built. With this powerful HMCS having an integrated peak speed of 8.6TFLOPS, a galaxy formation simulation treating matter, radiation and gravity rigorously was carried out for the first time.

These achievements demonstrated that HMCS provides an ideal platform for next-generation HPC in science and engineering.

# Material Science Simulation for Future Electronics

**Project Leader**
Masatoshi IMADA Professor, Institute for Solid State Physics, The University of Tokyo

**Summary of Research Project Result**

Through the materials simulation project, we have made progress in various aspects of developing efficient algorithms and applying them to long-standing challenge in many-electron problems of computational condensed matter research. In particular, algorithms for correlated electrons and complex systems have been the main subject of this project, the main achievement is summarized in the following:

(1)*Exchange Monte Carlo methods* have been proposed, and applied to treating slow relaxation processes and have clarified unusual critical phenomena of spin glasses. This method has also been applied in other fields such as folding of proteins.

(2)*Path-integral renormalization group method* has been proposed and has enabled us to treat difficult problems such as correlated electron systems with geometrical frustration. This algorithm has also been applied to nuclear physics problems.

(3)Algorithms for treating complexity such as interplay of orbital and spin degrees of freedom have been proposed and applied. Electron differentiation in momentum space and generation of hierarchy structure have been revealed by an improved quantum Monte Carlo method.

(4)*Correlator projection method* has been invented and applied with a successful reproduction of electron differentiation on the verge of metal-insulator transitions.

(5)*First principles path-integral molecular dynamics method* has been developed to consider quantum effects of light atoms and has given insights on of hydrogen phase diagram under high pressure as well as behaviors of myuonium and hydrogen in solids.

(6)*Polynomial expansion method* has been invented and developed to treat electrons coupled to classical degrees of freedom.

(7)The method, particularly the GW method, to implement correlation effects in first principles calculations have been developed and applied to total energy calculations and single particle spectra with self-energy corrections.

(8)Algorithms to implement electron correlation effects in the first principles method by taking FLEX approximations have enabled to discuss magnetic and superconducting transitions.

(9)Efficiency of *transcorrelated method* has been examined for correlated electrons.

(10)*Time dependent local density approximation* has been developed for nonequilibrium phenomena.

(11)New aspects of quantum phase transitions induced by randomness have been clarified by large-scale applications of *continuous-time loop algorithm* for quantum Monte Carlo simulations.

By using these developed algorithms, we have predicted existence of new states of matter, and revealed various novel properties.Examples are, prediction of quantum spin liquid phase near metal-insulator phase boundary. Ordering emerging from disorder effects in quantum spins, numerical evidence for the existence of chairal spin glass in 3D systems, electron differentiation in the momentum space, and localization of light atoms by quantum zero-point motion.

Those achievements have been published in 98 original papers and 40 invited talks in international conferences.

# Development of Computational Mechanics System for Large Scale Analysis and Design

**Project Leader**
Shinobu YOSHIMURA Professor, Graduate School of Frontier Sciences, The University of Tokyo

**Summary of Research Project Result**

We have developed an advanced parallel computational mechanics system for large scale analysis and design named ADVENTURE. Key technologies employed are (a) module-based architecture, (b) standardization of I/O format and libraries, (c) a parallel solver based on the hierarchical domain decomposition method (HDDM), (d) the parallel domain decomposer and (e) the parallel visualizer. Practical performances of the system are demonstrated through several static and dynamic analyses, and shape optimization calculations of 3D precise models with a half million to 100 million DOF meshes. Owing to excellent performance of the system together with open source strategy, the ADVENTURE system has already started being disseminated into a variety of industries and academia since free release of the $\beta$ version on 1st Dec. 2001. About 420 registered users in academia and industries have downloaded the programs, and about forty of them are now testing the programs. We confirm that such dissemination would be further accelerated owing to free release of all 18 modules on 1st March 2002.

During the past five years, i.e. the period of the JSPS ADVENTURE project, commodity technology including PC clusters, Linux and MPI have been improved dramatically and been popular everywhere. Furthermore, Grid-computing is about to grow. However, without good application software, these environments do not provide any practical merits to societies. We strongly expect that the ADVENTURE system and its family will become one of key application softwares in such next generation computing environments.

# 11. Photoscience

（1）Research Promotion Committee Members

○ Gin-ya ADACHI (College of Analytical Chemistry,Japan)

Chiaki HIROSE (Tokyo Institute of Technology)

Seizo MIYATA (Tokyo University of Agriculture and Technology)

Keitaro YOSHIHARA (Japan Advanced Institute of Science and Technology)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Materials for Ultrafast Opto-optical Control | Takayoshi KOBAYASHI<br>(The University of Tokyo) |
| 2 | Creation of Photo- and Electroactive Organic Materials and their Applications for Photonic Devices | Yasuhiko SHIROTA<br>(Osaka University) |

# Materials for Ultrafast Opto-optical Control

**Project Leader**
Takayoshi KOBAYASHI Professor, Graduate School of Science, The University of Tokyo

**Summary of Research Project Result**

In order to evaluate ultrafast nonlinear optical properties of materials for optolectronic devices, we develop new methods for time-resolved nonlinear spectroscopy and measure time dependence of optical nonlinearities. On the basis of these measurements we clarify mechanisms of nonlinearities, and provide guiding principles for designing new optoelectronic devices.

1.Development of ultrashort pulse laser: We have succeeded in generating 3.9 fs optical pulses, the shortest optical pulses in the world, using a newly developed noncollinear optical parametric amplifier.

2.Quasi-one-dimensional materials: Using the shortest optical pulses, we have studied vibrational dynamics in various organic materials. Especially, many new information about the nonlinear properties has been obtained for one-dimensional organic materials including conjugated polymers and J-aggregates.

3.J-aggregates: Using a scanning near-field optical microscope developed in this project, mechanism of energy transfer between two-types of J-aggregates has been studied.

4.Infrared spectroscopy: Using femtosecond infrared pulse laser system developed in this project, vibrational dynamics in organic semiconductors has been studied.

5.New polydiacetlenes: We have succeeded in composition of new plolydiacetlenes, which have large nonlinear susceptibility.

6.Cavity QED: The cavity length dependence of spontaneous Raman scattering intensity of acetonytryl in mircocavity has been studied.

7.Carrier-Envelop Phase locked laser: Using noncollinear optical parametric amplifier, we have succeeded in controlling the carrier-envelope phase of ultrashort pulses. This can be very useful for ultrashort coherent X-ray pulse generation.

# Creation of Photo- and Electroactive Organic Materials and Their Applications for Photonic Devices

**Project Leader**
Yasuhiko SHIROTA Professor, Graduate School of Engineering, Osaka University

**Summary of Research Project Result**

○ Several new concepts for the molecular design of amorphous molecular materials for use in organic light-emitting diodes (OELDs) have been presented, and novel families of hole-transporting, electron-transporting, hole-blocking, and emitting amorphous molecular materials were designed and synthesized. These materials permitted the fabrication of thermally stable, high performance OLEDs. Multi-color OLEDs using novel emitting amorphous molecular materials were also developed.

○ Photochromic amorphous molecular materials based on azobenzene and dithienyethene were created and their photochromic properties in the amorphous film were elucidated. Formation of surface relief grating with high diffraction efficiency and dual image formation at the same location were realized using these materials.

○ A photorefractive device using an amorphous molecular material as a hole-transporting host was developed. It is shown that the device exhibits a large photorefractive effect at zero electric field in the absence of the poling process.

○ Novel photochromic liquid-crystalline materials were designed and synthesized. It was found that photochemical liquid crystalline-to-isotropic phase transition can be induced by photochemical reactions of photochromic materials in nanosecond timescale and that the reorientation of liquid crystalline molecules was brought about with the molecular long axis perpendicular to the polarization direction of light. Holographic materials using these photochromic liquid-crystalline molecules were developed.

○ New techniques for the growth of high quality organic single crystals were developed. High quality nonlinear optical crystals were successfully grown by using these new techniques.

○ A series of silica-based hybrid materials containing rare-earth complexes were prepared by the sol-gel method. The luminescence characteristics were investigated. The hybrid materials containing europium (III) crown ether complexes have been found to exhibit good persistent spectral hole-burning characteristics that the holes persist even at room temperature.

# 【Life Sciences】

# 1．Higher Brain Functions

（1）Research Promotion Committee Members

○ Shigetada NAKANISHI (Kyoto University)

Hiroshi SHIBASAKI (Kyoto University)

Keiji TANAKA (The Institute of Physical and Chemical Research)

Jun TANJI (Tohoku University)

Hiroyuki NAWA (Niigata University)

Yasushi MIYASHITA (The University of Tokyo)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Integrative Studies on Higher Brain Functions and their Pathophysiology Using Neuroimaging | Hiroshi SHIBASAKI (Kyoto University) |
| 2 | Analysis of Memory and Memory Disorders by PET, MEG and Other Methods | Atsushi YAMADORI (Tohoku University) |
| 3 | Studies on Plasticity of Higher Function in Human Brain Using PET and Functional MRI | Yoshiharu YONEKURA (Fukui Medical University) |
| 4 | Neuroimaging Contributions to the Understanding of Brain Language Mechanism | Morihiro SUGISHITA (The University of Tokyo) |
| 5 | Studies on the Brain Functions by Optical Imaging and Magnetoencepharography | Mamoru TAMURA (Hokkaido University) |
| 6 | Molecular Dynamics Imaging by Use of PET | Yasuyoshi WATANABE (Osaka City University) |

# Integrative Studies on Higher Brain Functions and their Pathophysiology Using Neuroimaging

**Project Leader**
Hiroshi SHIBASAKI Professor, Graduate School of Medicine, Kyoto University

**Summary of Research Project Result**

This project was aimed at clarifying the control mechanisms of human higher brain functions and their pathophysiology by employing multidisciplinary non-invasive approaches.

(1) We demonstrated the presence of inhibitory areas in the human motor cortics which wer found abnormal in patients with dystonia. By applying SPECT, we showed an important role of the supplementary motor area (SMA) and lateral premotor area (PMA) in human gait. It was newly discovered that in Parkinson patients the SMA activity during gait was reduced, which was compensated by increased activation of the lateral PMA when special visual stimulus was presented.

(2) We showed participation of the primary and second somatosensory cortices in pain perception, and active participation of the parietal operculum and posterior insula in its emotional aspect.

(3) An important role of the inferior parietal cortex and the lateral PMA in sensorimotor integration was demonstrated.

(4) We elucidated the role of prefrontal cortex in the execution of Wisconsin card sorting test.

(5) we showed am important role of the left posterior inferior temporal lobe in Kanji processing.

(6) With the PET for animal use, we successfully obtained imaging of glucose metabolism in rat brain. Furthermore, we synthesized the radioligand specifically bound for the $\alpha 4 \beta 2$ submit of nicotinic acetylcholine receptors, and obtained its PET image in rat and human brain.

We also developed the non-invasive imaging method for dopamine D2 receptors and benzodiazepine receptors. It is hoped to extend this study further in order to elucidate the neural network involved in various higher brain functions. Noninvasive imaging of receptors and intrinsic substances in the brain is expected to be further advanced so that it can be applied to the investigation of pathological conditions of the brain.

# Analysis of Memory and Memory Disorders by PET, MEG and Other Methods

**Project Leader**
Atsushi YAMADORI Professor, Graduate school of Medicine, Tohoku University

**Summary of Research Project Result**

Our research on human memory included five tentative categories, i.e. working memory, fact (or semantic memory) memory, episodic memory, motor memory, and prospective memory.

We found working memory recruits different networks for different contents such as verbal, visual, and olfactory materials. Also networks for processing and holding materials were found to be different. For processing, strong involvement of the prefrontal lobe was demonstrated. We also found the gradual decline of the capacity of working memory in older population.We found the importance of the right fusiform gyrus in memory of human faces. On the other hand recalling of the name of acquaintances and famous people activated the left temporal pole as well as parieto-occipital area. For the memory of landscapes and streets we found the activation in the medial temporal lobe and parahippocampal gyrus. For episodic memory, we tried to separate neurological substrates for encoding, storing and decoding. Manipulation of the degree of the depth of processing at the encoding stage clearly showed the activity changes in the prefrontal, parietal, and hippocampal areas of the left hemisphere. For storing, we found strong activation of the bilateral prefrontal areas and the left hippocampus. For decoding, we found the recall of contextual information such as a place and time activated different networks that included bilateral basal forebrain, right frontal lobe, right cingulate gyrus, right temporal lobe, and the left insular area. For memory of sequential movements, we found the distributed activities in the prefrontal, premotor, and parietal association areas, in addition to the basal ganglia and cerebellum. We also demonstrated the dynamic change of activation patterns as the motor learning proceeded. For memory related with future action, i.e. prospective memory, we found the correlated activations in the bilateral frontal lobes and left hippocampus. Qualitatively different cues such as an event or a time for the remembrance and execution of a plan changed the degree of activation in these areas. These data revealed that human memory mobilizes diffusely distributed networks that are different in degree and extent depending on the modality of the content and the difference of processing.

# Studies on Plasticity of Higher Function in Human Brain Using PET and Functional MRI

**Project Leader**
Yoshiharu YONEKURA Professor, Biomedical Imaging Research Center, Fukui Medical University

**Summary of Research Project Result**

The brain is a dynamically changing structure responding to continuous alterations of the peripheral input and internal signal communication. The present project utilized noninvasive neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI), to depict functional reorganization of the brain due to deaffentation, and examined the plastic changes in relation to learning and aging proces. Functional MRI studies in the blind subjects demonstrated that the tactual information process is taken in the association visual cortex and further transferred to primary visual cortex in the subjects who lost their vision before the age of 15. Similar studies of sign languages showed that the sign activated the auditory cortex of the deaf subjects. These findings may provide biological basis for training in the handicapped, and also shed lights on how the brain organizes itself to integrate multimodal sensory input for communication. On the other hand, studies in the aged subjects revealed that parietal and temporal cortices were not utilized for the picture encoding task, and the neural activities in the hippocampus and the amygdala were also decreased during the face recognition task. These data suggested the aging-related alterations of higher brain. Furthermore, the present project extended to the imaging of a rapidly changing pattern accompanying normal human brain maturation by means of functional MRI on infants. In order to examine the molecular basis of the neuronal plasticity, a new imaging technique of positron radionuclide labeled tracers was introduced and applied to the fresh brain slices of the small animals, which successfully demonstrated the metabolic changes due to hypoxia and/or ischemia. In conclusion, noninvasive functional neuroimaging technique could be a powerful tool to investigate the functional reorganization and developmental neurophysiology.

# Neuroimaging Contributions to the Understanding of Brain Language Mechanism

**Project Leader**
Morihiro SUGISHITA Professor, Graduate School of Medicine, The University of Tokyo

**Summary of Research Project Result**

1. Verbal Tasks devised for fMRI and PET:
   (1) Using, we found that the brain regions critical to the process of writing are the anterior part of the left superior parietal lobule, the posterior part of the middle and superior frontal gyri, and the right cerebellum.
   (2) We hypothesized that early training in memorizing Chinese characters and the use of these characters in daily life shapes brain development and facilitates recall of visual forms in general. We examined what parts of the brain are commonly activated during learning characters and memorizing figures.
2. Determination of language dominant hemisphere:
   (1) Differences in brain activity in word reading in relation to visual field of presentation were found. Left hemisphere word presentations activated areas restricted to the left hemisphere, whereas right hemisphere presentations activated both hemispheres.
   (2) We devised fMRI paradigm with shiritori task useful to determine the language dominant hemisphere.
3. Improvement of the accuracy of fMRI, and its application to the evaluation of brain function:
   (1) We could established the integrated method to obtain a fine and reliable fMRI by resolving various problems as follows; (a) optimization of measurement parameters, (b) compensation of error data due to head movement, (c) establishment of routine method for data analysis of fMRI.
   (2) As for the application of this integrated method, it is possible to differenciate signal changes in visual system between mental and addition arithmetics.
4. Development of new methods for examining brain function:
   The new methods were as follows; (a) cerebral perfusion imaging using water molecule as a non-invasive tracer; (b) direct imaging of nerve cell excitation by detecting of $Ca^{2+}$ channel opening after injecting $Mn^{2+}$; (c) three dimensional imaging of nerve fiber direction by obtaining diffusion tensor imaging; (d) measurement of brain metabolism by magnetic resonance spectroscopy methods.

# Studies on the Brain Functions by Optical Imaging and Magnetoencepharography

**Project Leader**
Mamoru TAMURA Professor, Research Institute for Electronic Science, Hokkaido University

**Summary of Research Project Result**

(Hokkaido University)

We developed the new optical techniques of near-infrared computed tomography for brain function. This technique has a unique advantages, such as easy handling, low cost, qutantitative detection of brain function. Our optical CT revealed the presence of working memory when subjects performed the backword digit span. The quantitation of the performance with different subjects is now possible. Combined use of fMRI and fNIRS can give the more information concerning the brain activation.

(National Institute for Physiological Sciences)

We investigated higher brain function in humans, particularly focusing on language and face perception, using magnetoencephalography (MEG). MEG theoretically has a very high time (temporal) resolution in msec, and high spatial resolution in mm. As for language study, we focused on the hearing ability of "L" and "R", which is lacking in Japanese peaple. After training, 70 % of subjects showed a significant increase in the correct rate of differentiating "L" and R". In these people, a function was changed in the auditory cortex in the right temporal lobe, which is considered to play a major role in language study. As for face perception, we found that the inferior temporal lobe and lateral temporal lobe play an important role in the perception of static faces and eye movements, respectively. The right hemisphere is more dominant than the left for the perception of both static faces and eye movement.

# Molecular Dynamics Imaging by Use of PET

**Project Leader**
Yasuyoshi WATANABE　Professor, Graduate School of Medicine, Osaka City University

**Summary of Research Project Result**

We aimed to explore the molecular dynamics in highly functioning brain and intended to develop the molecular probes for that purpose by use of Positron Emission Tomography (PET). For the basis, we also have to unveil the brain regions or circuits responsible for such higher brain function.

(1) By PET activation studies, we unveiled the neural substrates, i. e., the brain regions responsible for higher brain functions, such as visual recognition, time perception, and learning set formation in monkeys, and laughter or smile, and metal fatigue in human volunteers. Top-down signals of smell and taste have been studied with functional MRI in human volunteers.

(2) We developed a new method for controlling local brain activities to assess the activation sites or circuits obtained by the activation study using neuroimaging techniques such as PET and fMRI. Two unique methods were developed; Photo-Dynamic Tissue Oxidation (PDTO), and a laser light irradiation into the brain tissue. Both methods were able to be applied to suppress the neuronal activity in behaving animals.

(3) We developed novel molecular probes for PET; mostly, glutamate receptor system, prostaglandin receptor, and nicotinic and muscarinic cholinergic receptor systems. PET studies were performed with these ligands, in normal volunteers and patients.

(4) We also developed the radiotracers for PET to seek for brain-specific metabolism such as lactate and acetyl-L-carnitine, and demonstrated the brain-specific role of these molecules, related to the neural function.

(5) For the imaging of gene expression, we developed the key radiotracers for labeling oligonucleotides. By using radiolabelled oligonucleotides, we showed the radiolabel when injected into rats is mostly incorporated into DNA/RNA fraction and protein binding. MicroPET was introduced for PET imaging of smaller animals for this purpose. The performance by MicroPET has been established in our group.

# 2. Cellular Signaling

（1）Research Promotion Committee Members

○ Michio UI (The Tokyo Metropolitan Institute of Medical Science)

Makoto ENDO (Saitama Medical School)

Shuh NARUMIYA (Kyoto University)

Yasutomi NISHIZUKA (Kobe University)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Adaptation Mechanism in Vision and Other Receptors | Satoru KAWAMURA<br>(Osaka University) |
| 2 | Regulation of Cytoskeletons by Intracellular Signals | Kozo KAIBUCHI<br>(Nagoya University) |
| 3 | Growth Signaling Transmitted by Cell Adhesion | Eisuke MEKADA<br>(Osaka University) |
| 4 | Downstream Effectors of PI 3-kinase in Insulin Action | Masato KASUGA<br>(Kobe University) |

# Adaptation Mechanism in Vision and Other Receptors

**Project Leader**
Satoru KAWAMURA Professor, Graduate School of Science, Osaka University

**Summary of Research Project Result**

1. S-modulin is believed to be a Ca-dependent regulator in photoreceptor adaptation. We identified seven amino acid residues as the functional sites of S-modulin.
2. S-modulin is thought to function by increasing the lifetime of light-activated visual pigment. This idea was tested and was found to be the case.
3. There are two types of photoreceptors in vertebrates, rods and cones. The light-sensitivity of a rod is high so that rods are responsible for twilight vision. The light-sensitivity of a cone is low and cones are responsible for daylight vision. We obtained purified rods and cones from carp, and asked why the light-sensitivity of a cone is low. Several reactions in the phototransduction cascade were found to be less effective in cones.
4. Bipolar cells (BCs) have antagonistic center-surround receptive field. We studied the effect of GABA on BCs using gramicidin-perforated patch clamp technique in the mouse retina, and found that GABA depolarizes ON-type BC and hyperpolarizes OFF-type BCs. Our results are consistent with the type of Cl- transporter in BCs and interpret the feed-forward connection from horizontal cell to BC.
5. We examined the spread of electrical signals in dendrites of amacrine cells and found that depolarization was boosted by persistent Na current and Ca current. The action potential conducted from the soma into the dendrite but was modulated by local GABA application. It is suggested that the non-uniform conduction of the action potentials contributes to the formation of directional selectivity.
6. Olfactory adaptation is mediated by an increase in the Ca concentration of olfactory cells. This Ca increase should be detected by Ca-binding proteins. We found a novel Ca-binding protein, p26olf, in the olfactory epithelium. This protein binds to a $\beta$-adrenergic receptor kinase-like protein in a Ca-dependent manner, suggesting that p26olf is involved in the olfactory adaptation.

# Regulation of Cytoskeletons by Intracellular Signals

**Project Leader**
Kozo KAIBUCHI Professor, Graduate School of Medicine, Nagoya University

**Summary of Research Project Result**

Research interest of our group is to understand the molecular mechanism underlying the regulation of cytoskeleton and cell adhesion through the Rho family GTPases by intracellular signals. However, how the Rho family GTPases regulate the various functions was largely unknown until recently. We previously identified Rho-kinase and MBS, as effectors of Rho, and found that Rho-kinase together with MBS regulate contractility of non-muscle cells and smooth muscle, and stress fiber and focal adhesion formation through the phosphorylation of myosin light chain. In this project, we have found the following results.

(1) Cytoskeleton:

We have identified various substrates of Rho-kinase, such as adducin, ERM family protein, intermediate filaments, and CRMP-2. We have found that the phosphorylation of adducin, ERM family protein, and CRMP-2 by Rho-kinase are important for cell migration, cytoskeletal reorganization, and growth cone collapse, respectively. We have also shown that the Rho/Rho-kinase pathway is involved in the pathogenesis of vasospasm and arteriosclerosis, and is a potent target of new therapies for these diseases. Moreover, we have shown that CRMP-2 plays critical roles in determination of axon/dendrite fate.

(2) Cell adhesion:

We have found that IQGAP1, as a effector of Rac1 and Cdc42, negatively regulates E-cadherin-mediated cell-cell adhesion by interacting with $\beta$-catenin, causing the dissociation of $\alpha$-catenin from the cadherin-catenin complex. Activated Rac1 and Cdc42 positively regulate cadherin-mediated cell-cell adhesion by inhibiting the interaction of IQGAP1 with $\beta$-catenin. Moreover, we have shown that Rac1/Cdc42/IQGAP1 system functions in cell scattering, which is thought to be a model system for dispersal of cancer cells. Our results indicate that the Rho family GTPases and their effectors regulate rearrangements of cytoskeletons and cell adhesions.

# Growth Signaling Transmitted by Cell Adhesion

**Project Leader**
Eisuke MEKADA Professor, Research Institute for Microbial Diseases, Osaka University

**Summary of Research Project Result**

Heparin-binding EGF-like growth factor (HB-EGF) is a member of the EGF family of growth factors, which interact with EGF receptor to exert mitogenic activity. This factor is synthesized as a membrane-anchored precursor protein (proHB-EGF) and then cleaved on the cell surface to yield soluble growth factor. ProHB-EGF is not only a precursor for the soluble form but also for the biologically active molecule, providing growth regulation to neighboring cells in a juxtacrine mode. ProHB-EGF forms a complex with other membrane proteins including CD9 and integrin $\alpha 3 \beta 1$. CD9, a tetra membrane-spanning protein, upregulates the juxtacrine mitogenic activity of proHB-EGF but not the mitogenic activity of the soluble form of HB-EGF. Integrin $\alpha 3 \beta 1$ is known to bind several extracellular matrix proteins including laminin 5, but the significance of the association with proHB-EGF has not been understood. ProHB-EGF-CD9-Integrin $\alpha 3 \beta 1$ complex is co-localized at cell-cell contact sites, suggesting that this protein complex may play some roles in intercellular signaling among neighboring cells.

In order to know the biological functions and physiological role of HB-EGF and its associating molecules, we have studied the following experiments: 1) in vitro assay of the growth inhibitory activity of proHB-EGF, 2) studies with mutant mice lacking HB-EGF or CD9 gene, 3) mechanism for the ectodomain shedding of proHB-EGF, 4) integrin-tetraspanin comlex formation. Results indicates that strict control of proHB-EGF ectodomain shedding is essential for the proper function of this growth factor. Deregulated proHB-EGF shedding in mice results in severe hyperplastic and developmental abnormalities. In order to know the physiological activity of CD9, mice lacking CD9 were produced. Resultshowed that CD9 is a crucial factor for mouse oocytes in fertilization.

# Downstream Effectors of PI 3-kinase in Insulin Action

**Project Leader**
Masato KASUGA Professor, Graduate School of Medicine, Kobe University

**Summary of Research Project Result**

We examined a role of PI3-kinase and its downstream effectors in insulin action *in vivo* and *in vitro*.

Although we have already shown that PI3-kinase is necessary for metabolic effects of insulin *in vitro*, physiological importance of PI3-kinase in insulin actions *in vivo* remained obscure. Therefore, we introduced a dominant negative PI3-kinase, a mutant p85 α (Δp85) lacking the binding site for the catalytic subunit, with the use of adenovirus-mediated gene transfer in mice liver. Δp85-infused mice displayed marked increase in blood glucose in response to oral glucose tolerance test. Furthermore, Δp85-infused mice showed increased plasma insulin levels in both fasted and fed states. These results indicate that PI3-kinase activity in liver plays an important role in glucose homeostasis and insulin actions *in vivo*.

We also examined roles of downstream effectors of PI3-kinase, Akt and atypical PKC (PKC λ) using adenovirus vectors encoding constitive active or dominant negative mutant of these molecules, *in vitro*. We found that Akt is necessary for insulin-dependent protein synthesis, glycogen synthase activation and phosphorylation of PDE3B. On the other hand, our data suggested that PKC λ is involved in insulin-dependent increase of mRNA of SREBP-1 in hepatocytes and insulin-stimulated glucose transport in adipocytes.

Finally, we examined a role of PKC λ in insulin action *in vivo*. Since PKC λ knockout mice were embryonic lethal, we generated liver-specific PKC λ knockout mice. These mice exhibited normal glucose levels in both fasted and fed states, however plasma insulin concentrations were lower in these mice. Furtheremore, in these mice, mRNA levels of SREBP-1 and triglyceride content in the liver were significantly decreased. These data suggest that PKC λ in the liver plays an important role in insulin action *in vivo*.

Thus, we clarified important roles of PI3-kinase, Akt and PKC λ in insulin action both *in vivo* and *in vitro*.

# 3. Organism Constructing Mechanisms (Reproduction and Development)

（1）Research Promotion Committee Members

○ Motonori HOSHI (Keio University)

Makoto ASASHIMA (The University of Tokyo)

Noriyuki SATO (Kyoto University)

Masatoshi TAKEICHI (The Institute of Physical and Chemical Research)

Ikuo TAKEUCHI (Novartis Foundation Japan for the Promotion of Science)

Yoshitaka NAGAHAMA (Okazaki National Research Institutes)

○：Committee Chairperson

（2）List of Research Project

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Mechanisms of Behavioral Pattern Development and Determination of Body Sizes and Cell Sizes | Yasumi OHSHIMA (Kyushu University) |

# Mechanisms of Behavioral Pattern Development and Determination of Body Sizes and Cell Sizes

**Project Leader**
Yasumi OHSHIMA Professor, Graduate School of Sciences, Kyushu University

**Summary of Research Project Result**

(A)Mechanisms of thermotaxis:

Distribution and movement of worms on a temperature gradient were re-examine6d in detail. The Resultshowed much wider distribution up t a 10℃ range, absence of both taxis to a growth temperature and avoidance of starving temperature, and avoidance of warm temperatures. These Resultsuggest a model involving a single thermosensony pathway in contrast to the previous model.

(B)Mechanisms of axonal elongation:

UNC-51 was expressed in cultured cells and was shown to phosphorylate tubulin and actin in vitro, suggesting that UNC-51 regulates axonal elongation through control of dynamics of microtubules and actin cytoskeletons.

(C)Identification and analysis of genes involved in learning:

A system to examine habituation learning on mechanical stimulation by a tap or a touch was developed, which allowed isolation of several mutants abnormal in the habitation such as *hab-1, 2* and *3. hab-1* gene was identified to encode a submit of mitochondoria complex 1.

(D) Functional analysis of genes involved in excitation-contraction coupling in the muscles. An embryonic lethal mutation *pat-10* was found at two positions within the troponic C gene. Troponin C molecules carrying each single mutation lacked binding activities to $Ca^{++}$ or troponin I. This is the first demonstration of a role of troponin C both in embryonic development and muscle formation.

(E) Mechanisms of determination of body and cell sizes:

About 20 mutants with a body volume increased by 50-100% were isolated. Four of them twice as big and with a longer life span were found to be *egl-4* mutants. The *egl-4* gene was cloned and shown to encode cGMP dependent protein kinases. In *egl-4* mutants, volumes of intestine, hypodermis, muscle, intestinal and muscle cells were increased but their cell numbers were not. *egl-4* gene funetions in relation to TGF $\beta$ and insulin pathways for the control of body size and life span, respectively.

# 4．Structure and Functional Control Mechanism of Biomolecules (Structural Biology and Functional Molecules)

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Kazuo MURAKAMI | (Foundation for Advancement of International Science) |
| | Keizo INOUE | (Teikyo University) |
| | Tomoya OGAWA | (The Institute of Physical and Chemical Research) |
| | Toshisuke KAWASAKI | (Kyoto University) |
| | Yoshimasa KYOGOKU | (National Institute of Advanced Industrial Science and Technology) |
| | Kenji SODA | (Kansai University) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | X-ray Crystallographic Study on Biological Molecular Interaction | Kunio MIKI<br>(Kyoto University) |
| 2 | Glycobiochemistry—Structure and Function | Shoichi KUSUMOTO<br>(Osaka University) |
| 3 | Structural Biology of RNA | Gota KAWAI<br>(Chiba Institute of Technology) |

# X-ray Crystallographic Study on Biological Molecular Interaction

**Project Leader**
Kunio MIKI Professor, Graduate School of Science, Kyoto University

**Summary of Research Project Result**

The aim of the project is to understand a variety of biological molecular interactions on the basis of the three-dimensional structures of protein molecules determined by X-ray crystallography. Biological molecular interactions include protein and protein, protein and nucleic acid and protein and small molecule (substrate, metal, cofactors etc.) interactions. We have determined the three-dimensional structures of the following proteins and protein complexes and discussed their structure-function relationship; chaperonin-60, thermosome $\alpha$ subunit complex, thermophilic photosynthetic reaction center and high potential iron-sulfur protein, and lipoprotein localization factors, LolA and LolB for protein and protein interactions, cyanobacterial DNA photolyase, and photolyase from a thermophilic bacterium and its complex with thymine, and a complex between DNA replication initiation protein RepE and DNA for protein and DNA interactions, and metapyrocatechase (a dioxygenase), human secretory phospholipase A2-IIA complex with a potent indolizine inhibitor, chitosanase, undecaprenyl diphosphate synthase, ribulose bisphosphate carboxylase/oxygenase from the hyperthermophilic archaeon (Rubisco), aldehyde reductase from a red yeast, a complex between calyculin A and the catalytic subunit of protein phosphatase 1, novel alkaline serine protease and $\alpha$-amylase, and S100 family proteins, NRP8 and MRP14 for protein and small molecule interactions. We have extensively discussed about the reaction mechanism and molecular recognition controlled by the above protein molecules. In addition, it was found that mammalian photolyase homologues are essential for maintenance of circadian rhythms and their structural studies are now in progress. Synchrotron radiation, especially that in SPring-8 has been extensively used in this project, in which several effective techniques were developed.

# Glycobiochemistry － Structure and Function

**Project Leader**
Shoichi KUSUMOTO　　Professor, Graduate School of Science, Osaka University

**Summary of Research Project Result**

Biological functions of sugar chains and glycoconjugates were studied on the basis of their chemical structures and interaction with their specific recognition proteins and/or metabolic enzymes. Improved pyridylamination was successfully applied to high sensitivity detection, isolation and structural determination of free cytosolic oligosaccharides and sugar chains of glycoproteins. The presence of brain-specific sugar chains was thus detected and tissue-specific occurrence of their receptors was observed. Study was also focused on the structure and recognition of bacterial cell surface glycoconjugates which activate the defense system of innate immunity in higher animals. Various structural analogues and isotopically labeled derivatives of lipid A, the active entity of endotoxic lipopolysaccharide, were synthesized, and their three dimensional conformation and supramolecular assembly deduced. The recognition system of lipopolysaccharide was also studied with the aid of synthetic lipid A analogues as homogeneous probes. Interaction of heparin and platelets and activation of the latter were analyzed on the molecular basis: specific key sulfated oligosaccharides were detected in heparin. A protein responsible for heparin binding was detected, isolated, and characterized. Genomic sequence of GM3 synthase (sialyltransferase-1) was determined, expressed in *Escherichia coli* and other cell lines. Genetic regulation of this enzyme, which produces the first biosynthetic member of ganglioside family, provided important information on the role of sugar chains on glycolipids. Production of an active soluble form of the enzyme initiated the study on its recognition mechanism of substrates.

# Structural Biology of RNA

**Project Leader**
Gota KAWAI
Associate Professor, Department of Industrial Chemistry,
Chiba Institute of Technology

**Summary of Research Project Result**

(1) Structure determination of RNA by NMR -- Structures of a 39-mer RNA corresponding to the dimerization initiation site of HIV-1 genomic RNA were determined in two types of conformations; kissing dimer and duplex dime. It was found that the two conformations are almost identical except for the region around the both ends of the self complement loop. Structure of a 29-mer RNA corresponding to the helix 6 of human SRP RNA was determined in the free hairpin form. The GGAG tetraloop in helix 6 adopts a similar conformation to that of GNRA tetraloop, suggesting that these tetraloops are included in an extensive new motif GNRR. Compared with the structure of helix 6 in complex with SRP19 determined previously, the GGAG tetraloop in the complex adopts a similar conformation to that of the free form, although the conformation is changed to a more open conformation upon SRP19 binding. NMR analysis of a 31-mer RNA corresponding a pseudoknot, PK1, of tmRNA revealed that the PK1 RNA is folded into a pseudoknot structure in the presence of $Mg^{2+}$. Results of NMR analyses of PK1 mutants together with their biological activities indicates that *trans*-translation requires the pseudoknot structure stabilized by $Mg^{2+}$ and specific residues G61 and G62 in loop 3. Structure of a 22-mer RNA corresponding to the P7/P9.0 region and the 3'-terminal guanosine of the *Tetrahymena* group I intron was also determined to find a new structural motif, BT-motif.

(2) Structure determination of RNA by X-ray crystallography --Single crystals for RNAs corresponding to the dimerization initiation site of HIV-1 genomic RNA and the hammerhead ribozyme in a heterodimer form are finally obtained. Structure determinations are in progress.

(3) RNA binding proteins -- RNA recognition mechanisms were revealed for the *Drosophila* Sxl protein and human U2AF protein by X-ray crystallography and NMR technique.

# 5. *Mechanisms of Plant Responses to Environment and Application to Biotechnology*

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Atsushi KOMAMINE | (The Research Institute of Evolutionary Biology) |
| | Masaki IWABUCHII | (Research Institute for Biological Sciences Okayama) |
| | Yoshimi OKADA | (The University of Tokyo) |
| | Hiroh SHIBAOKA | (Osaka University) |
| | Tatsuo SUGIYAMA | (The Institute of Physical and Chemical Research) |
| | Hiroshi HARADA | (Yamagata Agricultural Research and Study Center) |
| | Kokichi HINATA | (Iwate Biotechnology Research Center) |
| | Iwao FURUSAWA | (Kyoto University) |

○：Committee Chairperson

（2）List of Research Project

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Organ Differentiation in Plants Responding to Environmental Stimuli | Yasunori MACHIDA (Nagoya University) |

# Organ Differentiation in Plants Responding to Environmental Stimuli

**Project Leader**
Yasunori MACHIDA Professor, Graduate School of Science, Nagoya University

**Summary of Research Project Result**

Dr. Machida shows that the 6b protein encoded by oncogene 6b is associatedwith tobacco transcription factor NtSIP1 and translocated into the tobacco nucleus. In addition, recent analysis have shown that the 6b protein also interacted with histon H3, which is supposed to be involved in expression of class1 knox homeobox genes such as KNAT2 and KNAT6. Dr. Tanaka shows that the rolB protein is specifically interacted with a certain member of the 14-3-3 family. Dr. Sugiyama shows that a mutation in the SRD2 gene causes defect of shoot formation from a hypocotyl of Arabidopsis by auxin and cytokinin. He has cloned a SRD2 gene. Dr.Morikami shows that root morphology is affected by high concentrations of sucrose and that the IBA gene is responsible for such alteration in morphology. Dr. Sato demonstrates that the AtC401 gene is responsible for stimulation of Arabidopsis flowering. Dr. Tasaka have cloned the CUC1 gene and demonstrates that it belongs to the NAC family. Dr. Ishiguro shows that the HLR gene is responsible for formation of the quiescent center of roots. Dr. Toriyama generated transgenic rice plants which have derivatives of the Ac transposable element in the rice genome and mapped these elements on the rice genome. Dr. Machida has developed negative marker genes for selection of mutants generated by a homology-based gene disruption. Currently, they have obtained a candidate clone for gene disruption.

# 6. *Infectious Diseases and Bioregulation*

（1）Research Promotion Committee Members

○ Kiyoshi TAKATSUKI (Kitano Hospital, Tazuke Kofukai Medical Research Institute)

Kazuo SUGAMURA (Tohoku University)

Yoshifumi TAKEDA (Jissen Women's University)

Masaaki TERADA (National Cancer Center)

Yoshiyuki NAGAI (Toyama Institute of Health)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Functional Analysis of Cellular Immunity in Infectious Diseases | Shigeo KOYASU (Keio University) |
| 2 | Mechanisms of Epithelial Infection by Enteropathogenic Bacteria and its Application for Control | Chihiro SASAGAWA (The University of Tokyo) |
| 3 | Studies on Molecular Basis of Herpesvirus Infections | Yukihiro NISHIYAMA (Nagoya University) |
| 4 | Combined Control Strategy for Mucosal Bacterial Infections | Takeshi HONDA (Osaka University) |
| 5 | Study of Pathophysiology of HIV-1 Infection and Development of AIDS Therapy | Hiroaki MITSUYA (Kumamoto University) |
| 6 | Basic Analysis of Bacterial Infection with Respect to Escape and Virulence Mechanism of Bacteria and its Application to the Host Defense | Masao MITSUYAMA (Kyoto University) |
| 7 | Molecular Mechanism of Biological Defense against Retrovirus and Hepatitis Virus Infection | Junji YODOI (Kyoto University) |

# Functional Analysis of Cellular Immunity in Infectious Diseases

**Project Leader**
Shigeo KOYASU Professor, Faculty of Medicine, Keio University

**Summary of Research Project Result**

1) Contrary to the current model that interferon-γ (IFN-γ) is during early phase of infection produced by natural killer (NK) cells in response to IL-12 produced by antigen presenting cells (APCs) including dendritic cells (DCs) and macrophages, we revealed that interferon-γ (IFN-γ) is produced by APCs in response to IL-12 produced by themselves upon microbial infection. It is likely that APCs play a pivotal role in innate immune responses against microbial infection by producing IFN-γ in an autocrine manner.
2) Using *Leishmania* major infection, it was demonstrated that a genetic factor(s) determining Th1 vs. Th2 responses against *L. major* is carried by DCs. Phosphoinositide 3-kinase (PI3K) was shown to be involved in Th1/Th2 regulation.
3) We showed that PI3K is critical in B cell development and functions. Furthermore, we demonstrated that PI3K is essential for the development of gastrointestinal mast cells and immunity against intestinal nematode infection.
4) We identified "cryptopatches" in both small and large intestines, as anatomical sites for differentiation of intestinal intraepithelial lymphocytes in the gut. Each cryptopatch contains ~1000 c-kit$^{+}$ progenitor cells that are capable of differentiating into T cells.

# Mechanisms of Epithelial Infection by Enteropathogenic Bacteria and its Application for Control

**Project Leader**
Chihiro SASAGAWA Professor, Institute of Medical Science, The University of Tokyo

**Summary of Research Project Result**

The process of bacterial infection of mucosal barrier including the subsequent steps required for establishment of infectious diseases are quite complicated, dynamic biological events. Each infectious step is proceeded with the interaction between the pathogen and the host cells including the host cellular responses. In this research project, therefore, we have endeavored to elucidate bacterial adherence, intimate attachment, invasion and cell-cell spreading, sine they constitute of the essential early bacterial infectious step. We have studied the following bacterial infection events;(i) the mechanisms of invasion of mucosal barrier by *Shigella* including the cell-cell spreading, (ii)identification and characterization of virulence of enterohemorrhagic Escherichia coli (O157) and investigation of the intimate adherence mechanisms to the host cells, and (iii) the roles of bundle pili of enteropathogenic *Escherichia coli* (EPEC) in the initial adherence to the host cells. Accumulation of the knowledge on the bacterial infectious systems will be useful to develop new strategies required for preventing or controlling bacterial infection. The followings are the brief summary of our results gained by each study.

(i) *Shigella* direct its own internalization into macrophages by activating macrophage by delivered IpaC, while for invasion of epithelial cells, the role of VirA is important, since VirA can stimulate host Rac1 through induction of microtubule depolymerization. *Shigella* VirG, the essential protein for mediating actin-based motility can directly recruit N-WASP, thereby the bound Cdc42, profilin and Arp2/3 lead to actin polymerization at the vicinity of bacterial end.

(ii) The determination of O157 genomic sequence was undertaken by integrating our study on the virulence loci involved in bacterial attachment to epithelial cells. The attachment takes place through two-step processes mediated by the proteins encoded by LEE-genes including the other chromosomal loci and the 90-kb plasmid.

(iii) EPEC bundle-forming pili mediate not only for the initial bacterial attachment to the host cells, but also involves in determining the host specificity. EPEC possessed a 70-kb plasmid on which genes required for the biosynthesis of the pili and the regulatory elements are present.

# Studies on Molecular Basis of Herpesvirus Infections

**Project Leader**
Yukihiro NISHIYAMA　　Professor, Graduate School of Medicine, Nagoya University

**Summary of Research Project Result**

I ) Studies on the function of herpesvirus gene products. Herpesviruses are large DNA viruses whose genomes consist of a linear ds DNA molecule, 125-229 kbp. Among them, herpes simplex virus (HSV), a neurotropic human pathogen, has been most extensively studied as the prototype. Although HSV has been shown to encode at least 74 genes, the function and roles of many genes are still unkonwn. We have identified and characterized more than 20 gene products of HSV with unkown functions, and found that some of them have very interesting, unique properties; 1) US3 encodes a serine/threonine kinase which protects infected cells from apoptotic cell death; 2) UL14 protein, which can translocate the minor capsid protein and DNA cleavage/packaging proteins into the nucleus, has heat shock protein-like functions; 3) UL21 protein colocalizes and physically associates with microtubules, and promotes the long cellular processes in overexpressing cells; 4) US11 protein has intercellular trafficking activity and accumulates in the nucleolus in singly expressing cells; 5) UL56 protein is a tail-anchored type II membrane protein which localizes to both the Golgi apparatus and cyoplasmic vesicles.

II ) Studies on the immune response against HSV infection. Our studies have demonstrated the importance of memory type CD8+T cells and IL-15 in the protection against systemic HSV type 2 infection. We also investigated the effects of US2 and US3 deficiencies of HSV-2 on host immunity in a murine model of genital herpes infection, and found that a US3 deficiency dramatically alters the induction of the host immune response.

III ) Clinical studies on herpesvirus infections. We have established a rapid system to quantify herpesvirus DNAs using a real-time PCR method, and found that measuring viral loads is very useful for predicting the progression and evaluating the efficacy of treatment in a variety of human herpesvirus infections. We also found correlation between HHV-6 infection and skin rash after allogeneic BMT and that posttransplantation HHV-6 viremia occured more frequently in recipients with leukemia or lympoma than in recipients with other diseases.

# Combined Control Strategy for Mucosal Bacterial Infections

**Project Leader**
Takeshi HONDA Professor, Research Institute for Microbial Diseases, Osaka University

**Summary of Research Project Result**

< HONDA Team >

We conducted following experiments on 3 major bacterial intestinal pathogens and found: (1) Cortactin and tain, both of which are host cell molecules, are recruited beneath the EPEC-adherence sites and played an important role for EPEC-induced pedestal formation in infected cells. (2) TDH toxin produced by *Vibrio parahaemolyticus* exhibits enterotoxic activity ($Cl^-$ secretion) via activation of protein kinase, $Ca^{++}$-influx and $Ca^{++}$-activated $Cl^-$ channel. (3) We discovered a new foodborne infection attributed to *Providencia alcalifaciens*, which has invasive character.

< NAKAE Team >

To elucidate xenobiotic extrusion mechanism by the MexAB-OprM efflux pump, we carried out the following experiments. (i) We destroyed *mexA*, *mexB* and *oprM* by the gene replacement and found that all the subunits are essential for the pump function. (ii) The subunit exchange experiments between several RND-family pumps revealed that the inner membrane subunits selects the substrates. (iii) Topological localization of MexA, MexB and OprM has been analyzed and the results revealed that MexA and OprM were lipoprotein ancholing the inner and the outer membrane, respectively, and both proteins were exposed to the periplasmic space. MexB appeared to have 12 transmembrane domains and 2 large periplasmic domains. These findings provided important information in understanding of the xenobiotic efflux and self defense and for designing drugs, which combat with efflux pump.

< HAMADA Team >

(1)Antigen-specific antibodies were induced in the sera of FBP54-immunized mice, which survived significantly longer following the challenge with GAS (Group A *Streptococcus*) strain than did nonimmunized mice. (Infect. Immun. 2001) , (2) Internalization of GAS in epithelial cells is necessary and sufficient for the induction of apoptosis, which is initiated by mitochondrial dysfunction. (Cell. Microbiol. 2001)

(3) Administrations of superantigens protected mice from infection with *Listeria*, which was dependent on the enhanced *Listeria*-specific CTL activity in the presence of CD4 T cells. (Infect. Immun. 2001), (4) Fibronectin-binding protein, Fba, is an invasin of GAS, and an Fba-deficient mutant showed low mortality in mice following challenge infection, while laminin-binding protein, Lbp, functions as an adhesin. (Mol. Microbiol. 2001 & Infect. Immun. 2002)

# Study of Pathophysiology of HIV-1 Infection and Development of AIDS Therapy

**Project Leader**
Hiroaki MITSUYA Professor, School of Medicine, Kumamoto University

**Summary of Research Project Result**

In this project, we attempted to study the pathophysiology of HIV-1 infection and to identify/develop novel anti-HIV-1 agents which may serve as therapeutic agents for AIDS. We previously identified a unique set of amino acid substitutions in the polymerase region of reverse transcriptase (RT) which confer on HIV-1 a high multitude of resistance against multiple nucleoside RT inhibitors (NRTIs) in patients receiving a long-term antiviral chemotherapy including multiple NRTIs. We further clarified the virological and enzymologic profiles and mechanism of the emergence of such resistant variants (HIV-$1_{MDR}$). Moreover, we demonstrated that certain non-cleavage site amino acid substitutions in Gag protein of the virus recover the reduced replicative fitness of HIV-1 caused by mutations in protease (Gatanaga et al. *J Biol Chem* 277: 5952, 2002). We also designed, synthesized, and identified several novel NRTIs potent against wild-type HIV-1 and various HIV-$1_{MDR}$s. Such agents include (i) 2'-$\beta$-fluoro-2',3'-dideoxyadenosine, (ii) methylenecyclopropane NRTIs, and (iii) 4'-ethynyl-2',3'-dideoxynucleosides. We further designed and identified two novel protease inhibitors (PIs), JE2147/AG1776 (Yoshimura *et al. PNAS* 96: 8675, 1999) and UIC94003/TMC126 (Yoshimura *et al. J Virol* 76:1349, 2002). The former contains a flexible P2' moiety which is important for its potency toward wild type and mutant viruses, suggesting that the use of flexible components may open a new avenue for designing PIs which resist the emergence of PI-resistant HIV-1. The latter contains a unique component which has a close contact with the main chains of the protease active site amino acids, suggesting that the introduction of such a component interacting with main chains of key amino acids and seeking a unique inhibitor-enzyme contact profile should provide a framework for developing novel PIs. Through our efforts to determine the role of $NH_2$ terminus of LD78$\beta$, a variant of human MIP-1$\alpha$, we found that such a chemokine, if properly modified, may serve as effective anti-HIV-1 therapeutics while preserving chemokine-chemokine receptor interactions (Miyakawa *et al. J Biol Chem* 277: 4649, 2002). Furthermore, we identified a series of novel low molecular weight spirodiketopiperazine (SDP) derivatives which potently inhibit R5-HIV-1 infection and replication through their antagonistic effects on CCR5. (Maeda et al. *J Biol Chem* 276: 35194, 2002). One such compound E913 and its analogs are acid-resistant and orally bioavailabile in rodents. Several of such SDP derivatives have been considered for preclinical and early clinical developments.

# Basic Analysis of Bacterial Infection with Respect to Escape and Virulence Mechanism of Bacteria and its Application to the Host Defense

**Project Leader**
Masao MITSUYAMA Professor, Gradudate School of Medicine, Kyoto University

**Summary of Research Project Result**

*Mycobacterium* and *Listeria* are representative intracellular parasitic bacteria and they are capable of resist bactericidal mechanism of phagocytes. TH1-dependent protective immunity is induced in infected host and is indispensable for the host defense. The major purpose of this study was to elucidate how the virulence/escape factors of intracellular parasitic bacteria are involved in the host response in terms of cytokine response and the generation of protective immunity. In addition, experimental model of intracellular parasitic fungal infection was established and molecular mechanism of infection with virulent *Vibrios* were also examined. The major results obtained in this study are summarized as follows;

1) A novel function of listeriolysin O (LLO), the central escape/virulence factor of *Listeria monocytogenes*, was found. It was clarified that LLO is highly capable of inducing host cytokine response resulting in TH1-dependent protective immunity.
2) Cytokine inducing activity was dependent on the N-terminal domain of LLO molecule independent from the original pore-forming cytolytic activity that was dependent on C-terminal domain. A similar dual function was observed also in many other related family proteins including pnumolysin or seeligeriolysin O.
3) LLO induced first IL-12 and IL-18 in macrophages, then these cytokine induced IFN-$\gamma$ production from NK cells. Both TLR2 and 4 appeared to be involved in the initial response by macrophages. The presence of novel cytoplasmic protein was implicated in the response resulting in NF-$_K$EB activation in macrophages.
4) IL-12 and IFN-$\gamma$ responses were critical in TH1 response of the host against viable BCG and the lack of these response is related to the ineffectiveness of vaccination with killed BCG. Some proteinaceous factor is implicated in the cytokine response induced only by viable BCG.
5) TH1-dependent immune response was characterized in *S. schenkii* infection. Virulence expression was rather dependent on the inherent pathogenicity than host condition.

# Molecular Mechanism of Biological Defense against Retrovirus and Hepatitis Virus Infection

**Project Leader**
Junji YODOI Professor, Institute for Virus Research, Kyoto University

**Summary of Research Project Result**

We have demonstrated that members of the thioredoxin (TRX) system including TRX, mitochondria specific TRX2 plays important roles in the regulation of viral persistent infection and cell death by redox regulation. We showed that the TRX2 gene is essential for cell survival and regulates apoptosis using the DT-40 knock out system. We also studied extracellular functions of TRX and clarified that TRX suppresses neutrophil extravasation into inflammatory site. Influenza-induced pneumonia and Listeria infection as well as cytokine -induced interstitial pneumonia was suppressed in TRX transgenic mice, suggesting a protective role of TRX against inflammation. We also revealed the regulatory mechanism of the TRX gene through the antioxidant responsive element, suggesting the coordinated role of the TRX system and the glutathione system against oxidative stress. We newly identified TRX binding protein-2/ vitamine D3 up-regulated protein 1 (VDUP-1) as a negative regulator of TRX. TBP-2 expression was markedly abrogated in HTLV-I infected cell lines. Loss of TBP-2 expression was associated with loss of IL-2 dependency in these cell lines. TBP-2 also has a growth suppressing activity, indicating a role of TBP-2 as a tumor suppressor. Therefore, analysis of TBP-2/VDUP-1 family genes seems very important for creating a new diagnostic and therapeutic approach in HTLV-I infection.

We established an assay system for assessing natural killer (NK) cell activity by measuring the mitochondrial membrane potential ($Dy_m$). The levels of $Dy_m$, in NK cells were decreased in HCV infected patients and virus-positive patients, suggesting that NK cells in the patients who could not eliminate HCV may have impaired functions.

We analyzed the role of HCV core and non-structural protein, NS5A in the regulation of cell proliferation. We showed that core protein expressing cells were resistant to apoptotoic stimulation and this ability was correlated with the ability of core to activate NF-$_K$B. NS5A interferes the PKR function so that the NS5A expressing cells become resistant to interferon treatment. We revealed that the C-terminal region of NS5A is involved in this regulation.

Inefficient replication of HCV in a tissue culture hampers to study the pathogenic role of this virus. We established the cell line in which a part of HCV genome replicates efficiently. This system may provide a new clue for HCV research.

# 7. Genetic and Environmental Factors in Diseases Prevalent in Adults and the Elderly: Molecular and Cellular Mechanism of Vascular Complications

（1）Research Promotion Committee Members

○ Kiyoshi KUROKAWA (Tokai University)

Etsuro OGATA (Japanese Foundation for Cancer Research)

Hiroshi OKAMOTO (Tohoku University)

Toru KITA (Kyoto University)

Hisayuki MATSUO (Miyazaki Medical College)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Molecular Biology of Adipocytes: Studies on Molecular Mechanisms of Fat Accumulation and Vascular Diseases | Yuji MATSUZAWA (Osaka University) |
| 2 | A Role for Scavenger Receptor Pathway in the Pathogenesis of Vascular Disorders | Tatsuhiko KODAMA (The University of Tokyo) |
| 3 | Roles and Disorders of Receptors for Plasma Lipoproteins | Tokuo YAMAMOTO (Tohoku University) |
| 4 | Genetic Function of Molecular Network on Blood Pressure Regulation | Akiyoshi FUKAMIZU (University of Tsukuba) |
| 5 | Mechanisms for the Development of Diabetic Angiopathy and its Prevention | Hiroshi YAMAMOTO (Kanazawa University) |

# Molecular Biology of Adipocytes: Studies on Molecular Mechanisms of Fat Accumulation and Vascular Diseases

**Project Leader**
Yuji MATSUZAWA Professor, Graduate School of Medicine, Osaka University

**Summary of Research Project Result**

Atherosclerotic vascular diseases are common disorder in the industrial countries in which people are exposed by overnutrition. Accumulation of body fat may contribute to the development of atherosclerosis. This study was planned to clarify the biological characteristics of adipocytes and to identify the molecular link between adipocytes and vascular diseases.

We analyzed the expression profile of adipose tissue. Traditionally, adipose tissue has been regarded as an energy storage organ. However, adipose tissue expressed a variety of the genes for secretory proteins. Those included various complement factorsin immune system, cytokines, growth factors and vasoactive substances such as plasminogen activator inhibitor in fibrinolytic system and heparine biding EGF-like growth factor, which is a potent growth factor for vascular smooth muscle cells. We named these adipocyte-derived bioactive substances as 'adipocytokines'. Dysregulation of adipocytokines might be one of the mechanisms in the development of vascular diseases in overnutirion.

Through the analysis of human fat cDNA library, we identified a novel adipose-derived factor named adiponectin. Adiponectin was produced specifically by adipose tissue and present in circulating plasma with a range of 5-10 $\mu$ g/ml. Plasma levels of adiponectin decreased in obesity in spite of its specific expression in adipose tissue. Adiponectin had anti-atherogenic and anti-diabetic properties. Genetic lack of adiponectin in humans and rodents exhibited insulin resistance and vascular disease. The molecule may be a key factor in the disorders caused by overnutrition. We also identified glycerol channel molecule, aquaporin adipose and apotosis-inducing factor, galectin-12.

Adipocytes synthesize a variety of molecules to maintain homeostasis of the body. Disruption of this self-defense mechanism will lead to human diseases.

# A Role for Scavenger Receptor Pathway in the Pathogenesis of Vascular Disorders

**Project Leader**
Tatsuhiko KODAMA Professor, Research Center for Advanced Science and Technology, The University of Tokyo

**Summary of Research Project Result**

1. Characterization of blood vessels in various organs.

We have developed principle method for the cultivation of endothelial cell from aorta, coronary artery and brain vessel. This method enabled us to organize coculture system and transcriptome analysis.

2. Moleculat mechanism of lipid accumulation in vascular wall cells.

We have developed a co-culture system for the analysis of lipid accumulation in arterial wall cells. Hypoxia and LDL overload can induce the lipid accumulation, and during this process, the expression of leptin, adipophilin, and CL100 genes are induced.

3. Molecular mechanism of endothelial upregulation of adhesion molecule.

Upregulation of adhesion molecule plays a critical role for the accumulation of monocytes to the atherosclerotic lesion. We identified a novel GATA pathway mediating this process, which can be an important target for the therapeutic drugs.

4.Transriptome analysis of blood vessel cells.

RNA expression profile was studied during the activation of endothelial cells, hypoxia and cholesterol overload in smooth muscle cell and monocyte macrophage differentiation.The mechanism regulating these transcriptional activation has been studied.

5. Regulation of cholesterol metabolism in blood vessel cells.

Proteases involved in the proteolysis of SREBP have been studied. We developed the method for the expression of SREBP/SCAP complex on the budded type baculovirus.

6. Development of novel therapeutics for the treatment of atherosclerosis.

We developed the novel anti-atherogenic antioxidant BO653. We have also analyzed the molecular mechanism of efficacy of novel statin, NK104 and novel GATA inhibitor, K7174 and related compounds.

# Roles and Disorders of Receptors for Plasma Lipoproteins

**Project Leader**
Tokuo YAMAMOTO Professor, Gene Reseach Center, Tohoku University

**Summary of Research Project Result**

Disorder of lipoprotein metabolism is pathopysiologically linked with common diseases including atherosclerosis, diabetes and obesity. To elucidate the roles of receptors that bind apoE-contaning lipoproteins, we have been characterizing several LDL receptor related proteins (LRP), including VLDL receptor, apoE receptor 2 and LRP5. To evaluate the function of LRP5 in the development and cholesterol metabolism, we generated mice carrying a mutated LRP5 gene. Mice heterozygous and homozygous for LRP5 deficiency develop hypercholesterolemia when they fed a western-type diet containing high fat and high cholesterol. Under a normal diet, heterozygous and homozygous LRP5 deficiency caused impaired glucose tolerance in mice. In additions, we also identified a novel HDL binding protein. Molecular characterization of this newly identified protein revealed that it is a GPI-anchored protein having a distinct ligand biding specificity from that of a well-characterized HDL receptor, SR-B1.

Lectin-like oxidized LDL receptor (LOX)-1 and scavenger receptor for phosphatidylserine and oxidized lipoprotein (SR-PSOX) are type II and I membrane glycoprtoeins, respectively, both of which can act as cell-surface endocytosis receptors for atherogenic exidized LDL (Ox-LDL). LOX-1 expression can dynamically be induced by proinflammatory stimuli, and is detectable in cultured macrophages and activated vascular smooth muscle cells (VSMC), in addition to endothelial cells. LOX-1-dependent uptake of Ox-LDL induced apoptosis of cultured VSMC. In vivo, endothelial cells that cover early atherosclerotic lesions, and intimal macrophages and VSMC in advanced atherosclerotic plaques dominantly express LOX-1. LOX-1 expressed on the cell-surface can be cleaved, in part, and released as soluble molecules, suggesting a diagnostic role of plasma soluble LOX-1 levels. SR-PSOX appeared to be identical to CXCL16, a novel membrane-anchored chemokine directed to CXCR6-positive lymphocytes, suggesting another role as T-cell chemoattractant. In contrast to LOX-1 expressed by a variety of cell types, SR-PSOX expression appeared relatively confined to macrophages in atherogenesis. Taken together, LOX-1 and SR-PSOX may play important roles in atherogenesis and atherosclerotic plaque rupture.

# Genetic Function of Molecular Network on Blood Pressure Regulation

**Project Leader**
Akiyoshi FUKAMIZU Professor, Center for Tsukuba Advanced Research Alliance, University of Tsukuba

**Summary of Research Project Result**

My laboratory studies the regulated function of transcription and signal transduction and their roles in cardiovascular and brain systems. Much of the work focuses on the identification of novel genes that contribute to the homeostatic maintenance of the body, and on the creation and analyses of transgenic and knockout mice with hypertension, hypotension, or tumor transformation. A variety of molecular and cellular biological and biochemical studies underway in our laboratory concentrate upon understanding the mechanisms by which the ligand-receptor signal arrays modulate the blood-brain barrier (BBB) function and the coactivator CBP regulates the nuclear function. In this regard, we have recently revealed the impaired BBB function in angiotensinogen-deficient mice, identified a small G protein coupling with angiotensin II receptor, and succeeded in cloning a novel orphan seven-transmembrane receptor which is expressed in endothelial cells. Furthermore, we have discovered a number of leucine zipper and zinc-finger transcription factors as well as CBP-associated factors including known and novel ones, which seem to operate cardiovascular and brain cell functions. Knowledge about the regulation of ligand receptor-mediated BBB and a detailed understanding of the functional significance of the protein-protein interactions in which the zinc transcription factors or CBP-associated factors participate may ultimately provide the insights needed to develop new drugs that can be employed to either induce tumor cell death or alternatively to block cell death or to improve tissue damages in the setting of cardiovascular and neurodegenerative diseases.

# Mechanisms for the Development of Diabetic Angiopathy and its Prevention

**Project Leader**
Hiroshi YAMAMOTO Professor, Graduate School of Medical Science, Kanazawa University

**Summary of Research Project Result**

This project has revealed both environmental and genic accounts for diabetic angiopathy, which has been sufferd from by a huge Japanese population. As the environmental account, various fractions of advanced glycation endproducts were found to cause vascular derangement characteristic of diabetes, *e.g.* pericyte loss and angiogenesis, and all of them were identified as ligands of RAGE, the cell surface receptor for AGE. Transgenic mice that overexpressed this receptor in their vasculature exhibited advanced diabetic vasculopathy, and this was prevented by an inhibitor of AGE formation. The mechanism of the regulation of human RAGE gene was also clarified; tumor necrosis factor-$\alpha$, AGE ligands themselves and estradiol were identified as extracellular inducers, with an NF-$_{K}$B site and a p65-p50 complex as the *cis*-element and *trans*-factor responsive to the former two inducers and with Sp-1 sites and an Sp-1 and estrogen receptor-$\alpha$ heteromer as the *cis*-element and *trans*-factor responsive to the latter. Novel RAGE splice variants were also discovered, among which a soluble form was found to be cytoprotective and to occur in human circulation. An ELISA screen of human diabetic patients revealed that serum levels of soluble RAGE are statistically significantly higher in those without vascular complications than in those with retinopathy or nephropathy. Factors that can influence the development of diabetic glomerulosclerosis were also identified; this included a novel transcription factor A1p145, collagen-specific molecular chaperon-HSP47, and Gas6.

These molecular accounts this project has revealed are thus considered to be promising targets to overcome this life- and QOL-threatening disease.

# 8. Molecular Bioengineering of Food Animal Protein Resources

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Akira IRITANI | (Kinki University) |
| | Souichi ARAI | (Tokyo University of Agriculture) |
| | Seishiro KATO | (Fukuyama University) |
| | Ryuzo SASAKI | (The University of Shiga Prefecture) |
| | Fumio TAKASHIMA | (Tokyo University of Fisheries) |
| | Nobuhiro FUSETANI | (The University of Tokyo) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Elucidation of Life Cycle of Eel and Artificial Control of its Reproduction | Katsumi AIDA (The University of Tokyo) |
| 2 | Genetic Control of the Reproduction in Aquatic Animals of Important Aquaculture Resources | Takashi AOKI (Tokyo University of Fisheries) |
| 3 | Control of the Useful Genes by Genetic Engineering in Food Animals | Toru KOMANO (Kinki University) |
| 4 | Endocrinological and Biotechnological Control of Body Growth and Reproduction in Domestic Animals | Masugi NISHIHARA (The University of Tokyo) |
| 5 | Efficient Increase in Livestock Production by Evolutional Improvement of Developmental Engineering | Hajime MIYAMOTO (Kyoto University) |
| 6 | Development of the Highly Acceptable Food Resources for Humans | Toru FUSHIKI (Kyoto University) |

# Elucidation of Life Cycle of Eel and Artificial Control of its Reproduction

**Project Leader**
Katsumi AIDA — Professor, Graduate School of Agricultural and Life Sciences, The University of Tokyo

**Summary of Research Project Result**

1. Elucidation of Life Cycle

It was clarified that the Japanese eel spawns periodically once a month during new moon near three seamounts located Northwest of the Mariana Island. Leptocephali of *Anguilla celebesensis* and *A. borneensis* were collected in the Celebes Sea and Tomini Bay. This discovery indicated that tropical eels make shorter spawning migration compared to temperate species. Trajectories of satellite tracked Argos buoys suggested that leptocephali have been transported from the seamounts. Otolith studies revealed that Japanese eel leptocephali drift passively about 100 days and after metamorphosing from leptocephali into glass eels, they recruit to their freshwater habitats about five months after hatching. A long spawning season lasting about 8 months from May to December was also indicated. Analysis of eels collected from various areas in Japan indicated that 25-50% of eels inhabiting coast or estuarine areas had never entered freshwater. This indicates a need for studies on the reproductive contribution of this "sea resident population" from a fisheries perspective. Stable $^{18}O/^{16}O$ in the otolis of leptocephali and glass eels indicated that there was no remarkable change in water temperature between spawning and larval periods, suggesting that they spawn at 16-28C and 50-250m depth. The same swimming depth of migrating silver eels in the Pacific Ocean was also suggested by tracking artificially matured female Japanese ells using pressure-sensitive ultrasonic transmitters.

2. Artificial control of reproduction and larval rearing

Techniques for induction of ovarian and testicular maturation were developed. Weekly injection of salmon pituitary homogenate followed by a final injection of DHP was most effective for induction of ovulation. For males weekly hCG injection was effective. Hatched larvae were constantly obtained by artificial insemination. Artificial food was developed using freeze dried powder of shark eggs, oligopeptides, vitamin mixture, mineral mixture and krill extract. Hatched larvae survived more than 1 year, and developed to leptocepali of 5cm body length. It was the first success in the world. High pressure conditions of speculated spawning depth (about 200m) delayed hatching. This result suggests that hatching occurs at more developed stage of larvae under natural spawning conditions. Chloride cells were found to appear on the yolk suck membrane and body surface before the gill appears. New lectins were isolated from the skin, and primary structures were identified. In order to improve techniques for artificial maturation and egg quality, reproductive mechanisms following artificial maturation were elucidated. cDNAs encoding enzymes for the production of steroid hormones in the ovary, estrogen receptors and vitellogenin were cloned, and their expressions were analyzed. cDNAs encoding factors involved in the spermatogenesis were also cloned, and their functions were determined. Functional recombinant GTH was produced using yeast to induce gonadal maturation by homologous GTH.

# Genetic Control of the Reproduction in Aquatic Animals of Important Aquaculture Resources

**Project Leader**
Takashi AOKI Professor, Graduate School of Fisheries, Tokyo University of Fisheries

**Summary of Research Project Result**

1. We have isolated and cloned many putative biodefense and immuno response-related genes from the Japanese flounder, Rainbow trout, red seabream, and carp; these include cytokines, cytokine receptors, cell surface molecules, transcription factors, antimicrobial proteins, proteases, and protease inhibitors following EST analyses.
2. We have developed a microarray of 800 different genes of Japanese flounder. We confirmed that this microarray was useful for characterization of gene expression patterns of several cells and organs of Japanese flounder.
3. Heat shock protein (HSP) over expressed transgenic zebrafish embryos showed extensive apoptosis and abnormal morphogenesis. The enhanced HSP70 levels regulated bone morphogenetic protein 4 (BMP4) mediated apoptotic signaling in early development.
4. MAP-kinase and taurine transporter genes were cloned from fish cells and demonstrated to be as osmo-responsive genes for candidates to produce osmo-resistant fish.
5. We mapped quantitative trat loci (QTLs) for IPN resistance in a segregated population of backcross fish, derived from out-crossing the resistant strain of rainbow trout, RT-201 and the susceptible one, RT-101.
6. Foreign gene transfer method were established on red sea bream using sperm.The expression vectors using fish virus promoter were constructed and confirmed.
7. Cloned red sea bream, *Pagrus major* was produced by chromosome manipulation, clonal status of the fish was confirmed by multi-locus DNA fingerprinting. Sex differentiation and sex control of the fish were also clarified.
8. We aim to use primordial germ cells (PGCs) as an initial material of such a stem cell line in fish. As a first step in establishing a fish cell line derived from PGCs, we have developed techniques for visualization, isolation, and transplantation of viable fish PGCs.
9. DNA markers to evaluate genetic divergence were developed in order to verify their efficiency in the population genetic analysis for broodstock management in stock enhancement and aquaculture avtivities.
10. We investigated the genetic impact of stock-enhancement programs using simulation models, and constructed an effective strategy for this program. The research focuses on the conservation and the sustainable use of genetic resource in the future.

# Control of the Useful Genes by Genetic Engineering in Food Animals

**Project Leader**
Toru KOMANO Professor, Faculty of Biology-Oriented Science and Technology, Kinki University

**Summary of Research Project Result**

A transgenic pig carrying the spinach-derived Δ12-desaturase (*fad2*) gene has been constructed by a recombinant DNA technique. cDNA of the *fad2* gene was linked to the adipocyte P2 (aP2) promoter, which targets expression of linked genes specifically to adipose tissue. We observed that the Δ12-desaturase was expressed in the meat of the transgenic pigs and that the content of linoleic acid in fatty acids of the meat was increased. These Resultsuggest that the plant-oriented *fad2* gene can be functionally expressed in food animals, and that the expression can alter the composition of fatty acids of the meat of them.

In order to establish a method for the production of transgenic chicken, intra-testicular injections of foreign DNA were tested. An exogenous gene (green fluorecent protein: GFP), as a marker gene, was injected directly into the testis of matured male chicken without the laparotomy. Introduced DNA was detected by PCR analysis in embryo of next generation when the treated spermatozoa was inseminated into laying hens. Spermatozoa may act as a vector for transferring exogenous genes into the chicken.

Multidrug transporter MRP1 (multidrug resistance protein 1) expressed in the mammary glands plays a role in protecting milk against xenobiotics. We newly cloned bovine MRP1 cDNA from the mammary gland of lactating cow as one of the genes that influence the quality of daily milk. Functional analysis of bovine MRP1 revealed that the substrate specificity of bovine MRP1 differs from that of human MRP1 despite a high degree of similarity (90%) in amino acids between them.

The growth hormone (GH) gene from the pituitary gland of ostrich, the *zag1* gene from mouse zygote functioning at the zygotic gene reactivation period, and the gene for S6 kinase stimulating cell growth have been isolated and characterized. A convenient system of the targeted gene disruption in chicken at cellular level (DT40 cells) has been constructed.

# Endocrinological and Biotechnological Control of Body Growth and Reproduction in Domestic Animals

**Project Leader**
Masugi NISHIHARA Professor, Graduate School of Agricultural and Life Science, The University of Tokyo

**Summary of Research Project Result**

The purpose of this project is to establish new approaches regulating reproduction, body growth and metabolism of domestic animals. To this end, we investigated molecular mechanisms of body growth and reproduction mainly by generating several line of transgenic and knockout animal models. The main outcomes of this project are as follows.

1. Expression of 20 α-hydroxy steroid dehydrogenase (20 α-HSD) gene in the corpus luteum plays a crucial role in recurring short estrous cycle in rodents. 20 α-HSD transgenic goats may recur short estrous cycle.
2. Induction of granulin gene expression in neonatal hypothalamus by androgen is involved in sex differentiation of the brain.
3. Continuous secretion of low levels of growth hormone results in the accumulation of body fat. In addition, we found that satellite cells in skeletal muscle could differentiate into adipocytes.
4. Transgenic rats were generated by means of testis-mediated gene transfer (TMGT). Foreign gene could be also transferred by TMGT in the goat, but it was mosaic. We found that the synthetic peptide containing protamine motif could enhance the efficiency of TMGT.
5. DNA methylation pattern varies among tissues. In addition, individual cloned mice have different methylation aberrations, indicating that cloned animals are by no means perfect copies of the original animals as far as the methylation status of genomic DNA is concerned.
6. Primer pheromone is produced in the sebaceous gland of the head of male goats in a testosterone-dependent manner after its conversion to 5 α-dihydrotestosterone.
7. IL-1 signal is involved in feeding behavior, body growth and fat accumulation.
8. Facilitation of angiogenesis in follicles could increase the number of ovulated oocytes.

# Efficient Increase in Livestock Production by Evolutional Improvement of Developmental Engineering

**Project Leader**
Hajime MIYAMOTO Professor, Graduate School of Agriculture, Kyoto University

**Summary of Research Project Result**

The world population is more than 5.6 billion at the present time and is expected to exceed 10 billion by the middle of the 21st century. Foods of animal origin contain a plenty of nutrients and suit people's taste. The demand for food animal protein resources is, therefore, increasing year-by-year and animal scientists are compelled to find a solution to suffice the expanding needs and improve the quality of human life. In order to meet such an increase in demand of farm animal products such as meat and milk in the world, technological innovation based on the progress in animal sciences must be promoted. The aim of our project is to investigate the basic and practical subjects on animal reproduction as follows in order to increase efficiently livestock by the improvement of development bioengineering techniques, and the fruition of our project as follows: (1)the production of cloned animals from somatic cells in cattle, a farm animal, (2)*in vitro* maturation of oocytes, fertilization and embryo culture in the farm animals (cow and sow), (3)cryopreservation of gametes and embryos of livestock and of ovaries, and (4)other basic and practical subjects concerning animal reproduction and its relating physiology (ex. Molecular regulating mechanism of ovarian follicule selection, a critical ovarian phenomenon).

# Development of the Highly Acceptable Food Resources for Humans

**Project Leader**
Toru FUSHIKI Professor, Graduate School of Agriculture, Kyoto University

**Summary of Research Project Result**

1. Mechanisms underlying dietary fat recognition and reception in the oral cavity were investigated. We found a candidate protein for fatty acid sensing on the apical part of taste bud cells in the circumvallate papillae. The sensory signals of fatty acid chemoreception was transfered to the brain via glossopharyngeal nerve. Chemical components built the palatable taste of fresh fish were analysed and reconstituted. Mechanisms on the reception of texture in the oral cavity and taste reception of sweet protein were analyzed and obtained novel informations.
2. Voluntary intake of corn oil elicited rewarding effects in the CPP test, and we showed that effects are mediated opioidergic and dopaminergic systems. We established the Hydra biossay system which can detect and identufy trace quantity of bioactive proteins, and found that DBI increased in rat CSF after intra-oral stimulation by aversive quinine taste.
3. Formation of conditioned taste aversion was analyzed in great detail and possible routes of visceral were indicated. Taste mediated odor learning was investigated in the rat. Comparison of c-Fos-like immunoreactivity in the brainstem following taste stimulation, and possible routes of paratability formation.Considered the possibilities of manipulation of food preference in human was investigated.
4. A novel IgE response model was established with allergen-specific Tcell receptor transgenic mine, and figured out the molecular mechanisms on developing food allergy. Prepared some amino-acid-substituted analogs of an antigenic peptide and investigated the novel food stuffs which can suppress food allergy.

# 【Integrated Fields】

# 1．Information on Life Systems

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Yuichiro ANZAI | (Keio University) |
| | Koji IKUTA | (Nagoya University) |
| | Shigenobu KOBAYASHI | (Tokyo Institute of Technology) |
| | Katsunori SHIMOHARA | (Advanced Telecommunications Research Institute International) |
| | Yoshikazu NISHIKAWA | (Osaka Institute of Technology) |
| | Shigeyuki YOKOYAMA | (The University of Tokyo) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Design and Fabrication of an Interface System for a Life Information Processor and External Environment —Electrophysiological and Biochemical Approach— | Takeshi YAMAKAWA (Kyushu Institute of Technology) |
| 2 | System Theory of Bio-Informatics and its Extension towards Engineering Design Theory | Osamu KATAI (Kyoto University) |
| 3 | Construction of Intelligent System Possessing System Life | Kazuo YOSHIDA (Keio University) |

# Design and Fabrication of an Interface System for a Life Information Processor and External Environment －Electrophysiological and Biochemical Approach－

**Project Leader**
Takeshi YAMAKAWA　Professor, Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology

**Summary of Research Project Result**

＜Electrophysiological Approach＞

The adaptation function of the organs of the perception of the bodily function has been investigated by physiological experiments, and the Vision Chip which is based on the knowledge from the experiments has been established. Furthermore, the pattern recognition method and the signal separation method based on the information processing of the bodily function using some artificial neural networks techniques are established.

＜Biochemical Approach＞

G protein-coupled receptors (GPCRs) are major sensors of cells for extracellular signals and can recognize light, odorants, taste substances, hormones, neurotransmitters and others. We have screened GPCRs from the human genome sequence by taking advantage of the facts that many GPCRs do not have introns and all GPCRs have seven transmembrane segments, and estimated that there are approximately 500genes for odorant GPCRs and 400-500 genes for other GPCRs in the human genome. GPCRs, after activation by extracellular ligands, activate G protein $\alpha_{GDP}\beta\gamma$ trimer at the intracellular face, which involves exchange of GDP-GTP and dissociation of $\alpha_{GDP}\beta\gamma$ into $\alpha_{GTP}$ and $\beta\gamma$ subunits. We have prepared fusion proteins of G protein $_a$ subunits with some GPCRs including muscarinic acetylcholine receptors, $_b$ adrenergic receptors, and nociceptin receptors, and expressed them in insect cells (Sf9) using baculovirus. Membrane preparations expressing receptor-$G_a$ fusion proteins were shown to recognize ligands for the receptor and to discriminate full-, partial-, inverse-agonists and antagonists by measuring the ligand-induced change in the affinity for GDP. We have prepared fusion proteins with $Gi1_a$ or $Gs_a$ subunits of novel orphan GPCRs, which we have identified from the human genome sequence, and used them for search of endogenous or surrogate agonists. Receptor-$G_a$ fusion proteins could be used for drug screening and, potentially, as chemical sensors.

# System Theory of Bio-Informatics and its Extension towards Engineering Design Theory

**Project Leader**
Osamu KATAI Professor, Graduate School of Informatics, Kyoto University

**Summary of Research Project Result**

Based on system theoretical analyses of the roles of information on life systems, novel methodologies of synthesizing decentralized (modularized) artifact systems that have high capabilities of adaptation and coordination of interactions with humans and environments have been developed. We focused our attentions to the emergent characteristics in interactions between : (1) artifact systems and humans, (2) robots and humans, (3) robots and environments, together with, (4) the total coordination of the above interactions.

The mechanisms of order emergence have been examined through introducing an intelligent human judgmental model, an integrated simulation framework for human-machine interaction, semiotical and ecological psychological approaches to human-robot interaction, a modularlized control architecture for autonomous locomotion robot, and order emergence mechanisms in dual dynamical systems (coupled nonlinear dynamical systems).

The followings are the main results of our project: A sophisticated artificial creature in a virtual space, "virtual collaborator", mediating human operators and artifacts, human-robot shared autonomy frameworks, robot teleoperation systems using task morphologies, a highly adaptive legged locomotion robot. Through synthesizing the above architectures with physiological, psychological, semiotical and mathematical frameworks, we have found out that life-like systems are necessarily of hierarchical structures composed of redundant modules that are loosely coupled with each other where "functional complementarity" such as autonomy vs. sociality, stability vs. plasticity, differentiation vs. integration, and order formation vs. order destruction plays important roles in the vital functioning of information in these systems.

# Construction of Intelligent System Possessing System Life

**Project Leader**
Kazuo YOSHIDA Professor, Faculty of Science and Technology, Keio University

**Summary of Research Project Result**

The artifact-systems created by humans generate a deep and huge interaction with the surrounding natural world, and reflect a large-scale influence on our human lives. The most creditable concept to this critical issue of scientific and technological development seems to be "System Life" that is an innovative competence to be embodied into any artifact-systems for creating harmony in the world of the natural entities and artifacts-systems interacting each other. The system life is defined as a seamless fusion system of sensing, processing, activating and expressing mechanisms governed by system life information. This project aimed at the construction of intelligent systems possessing the system life integrating four research groups concerning the system life.

The first group established the concept of system life comparing with the conventional design methodology, developed an innovative intelligent control methodology that can cope with unpredicted failures, and manufactured various intelligent robots, a skiing robot, autonomous soccer robots, a game playing robot, an autonomous running bicycle robot and so on as new concrete artifact-systems designed by the system life concept. The second group dealt with natural systems, clarified the behavior of cellular tissues subjected to physical stimuli, and demonstrated the possibility of artificial liver organs. Third group researched about the methods of recognition and expression of information. As a result, a soft computing method using neural networks was presented for the recognition of information and various expression methods were proposed. The final group performed mainly two kinds of researches. One of them is an innovative development of a smart skin which can control the fluid by sensing the pressure and the fluid velocity. The other one is also an innovative development of the three-dimensional recognition of space using the measurement of supersonic waves. The group succeeded in these developments. To summarize the results of this project, the technology developments of the elements and the system integration methods on system life were achieved.

# 2. Tissue Engineering

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Yoshito IKADA | (Suzuka University of Medical Science) |
| | Minoru UEDA | (Nagoya University) |
| | Yasuhiko SHIMIZU | (Kyoto University) |
| | Kikuo NOMOTO | (Japan Organ Transplant Network) |
| | Masatoshi MAKUUCHI | (The University of Tokyo) |
| | Takehisa MATSUDA | (Kyushu University) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Functional Regeneration by Medical Bioengineering | Tomomitsu HOTTA<br>(Tokai University) |
| 2 | Biological Tissue Engineering | Yukichi UMAKOSHI<br>(Osaka University) |

# Functional Regeneration by Medical Bioengineering

**Project Leader**
Tomomitsu HOTTA Professor, School of Medicine, Tokai University

**Summary of Research Project Result**

The purpose of this project was to develop of next stem cell-therapies to repair the organ functions in intractable diseases such as hematological malignancies, diabetes mellitus, ischemic heart disease and chronic intestinal inflammation using stem cell system. The stem cell system may provide high-functional, less invasive and lower expensive therapies for aged patients.

We develop a novel co-culture culture system in which CD34+ cells were separated by filter membrane from mouse stromal cells as feeder cells. The fold of expansion was estimated by the NOD/SCID mouse repopulating assay. We planned a clinical research to evaluate the safety and efficacy of expanded CD34+ cells. We also developed a culture system for produce CD34+ cells from CD34 negative stem cells.

We established a fat cell line transduced with the insulin gene which responded to the concentration of surrounding sugar level. The cells enclosed in a capsule consisting of immuno-dissecting menbrane were implanted in intraperitoneal cavity of diabetic model mice. The diabetic state of the implanted mice was well controlled for months.

We isolated a cardiomyocyte cell line (CMG) from adult mouse bone marrow using 5-azathytidine which showed self-beating automatically. When the cardiomyocytes were transplanted into ischemic heart tissue, they survived and functioned in the cardiac tissue.

As to the regeneration of intestine, we develop a new drug-delivery system using microsphare to distribute cytokines specifically to small intestine. Using this DDS, we tried to regenerate the MALT tissues of intestine.

# Biological Tissue Engineering

**Project Leader**
Yukichi UMAKOSHI Professor, Graduate School of Engineering, Osaka University

**Summary of Research Project Result**

The purpose of this project is to evaluate the regenerated tissue and organ and develop the evaluation method. Main results obtained by this project are as folows.

(1) Mechanical properties of dog's tracheas, artificial tracheas and regenerated tracheas were measured. Mechanical properties of artificial tracheas, regenerated tracheas were compared changing materials and shapes. Most favorable shape and materials of artificial tracheas were designed for development of regenerated tracheas.

(2) Preferential orientations of hydroxyapatite (HAp)crystallites in various biological normal and regenerated hard tissues were analyzed by the micro-beam X-ray diffractometer. HAp texture diffres in the normal hard tissue with different shapes under various stress conditions in vivo. Predominant alignment of c-axis in HAp was observed as one orientation along the longitudinal axis in a rabbit ulna and as two-dimensional orientation in a rabbit skull along the surface. Using this method the difference between natural and regenerated hard tissues can be evaluated.

(3) Using ultrasonic wave, Young's modulus, shape and thickness of cartilage can be measured. This new method can be applied for measurement of shape and damage of cartilage and evaluation of regenerated cartilage.

(4) To clarify the multiple functionality of connective tissue growth factor, the effects of nascent CTGF within the cell by transient expression were examined. In Cos-7 cells, expression of human CTGF induced an altered cell morphology. This CTGF was operative for regeneration of various tissues and organ and it was very attractive for stimulating the regeneration process of bone, cartilage and blood vessel.

# *3. Production of Novel Useful Substances through Integration of Life Sciences and Chemistry*

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Teruhiko BEPPU | (Nihon University) |
| | Yaeta ENDO | (Ehime University) |
| | Takahisa OTA | (The University of Tokyo) |
| | Kyozo OGURA | (Tohoku University) |
| | Haruo SETO | (Tokyo University of Agriculture) |
| | Susumu NISHIMURA | (Banyu Pharmaceutical Co., Ltd) |
| | Hideaki YAMADA | (Kyoto University) |
| | Kimitsuna WATANABE | (The University of Tokyo) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Chemical Approach to Creation of Artificial Nucleic Acids Having New Functions | Mitsuo SEKINE<br>(Tokyo Institute of Technology) |
| 2 | Fine Enzymatic Syntheses of Useful Compounds | Sakayu SHIMIZU<br>(Kyoto University) |

# Chemical Approach to Creation of Artificial Nucleic Acids Having New Functions

**Project Leader**
Mitsuo SEKINE Professor, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology

**Summary of Research Project Result**

The aim of this project is to create useful artificial nucleic acid derivatives having a new function which is designed by chemical approaches. During the past five years, the following representative results from this project were obtained. To realize our purpose, we developed new efficient methods for the synthesis of DNA without protection of base residues. As the result, we created a new innovative method called "proton-block method", where the base parts are protected by a simple proton and nearly 100% selective internucleotidic bond formation was achieved at the dimer level. We also found the hitherto most selective method for the internucleotidic bond formation by use of a new activator, i.e., *N*-hydroxybenzotriazole (HOBT).

This reagent enables us to synthesize oligonucleotides without *N*-phosphorylation. The synthesis of the 5'-terminal 4mer of U1 snRNA having a unique trimethyl-G cap structure was successfully done by use of the solid phase synthesis and used for isolation of 2,2,7-trimethylguanosine-cap binding proteins.

Consequently, snurportin 1 was discovered as a TMG-cap carrier to nucleus from cytoplasm. The mechanism of nuclear transport of U1snRNA was now elucidated by this study. We succeeded in synthesize a sterically locked "bent structural motif" of UpU derivative, which was successfully incorporated into RNAs. On the other hand, it was found that oligonucleotides having a sterically fixed linear UpU derivative have considerably higher Tm values than unmodified oligonucleotides.

This Result suggest that this type of modification could provide a very useful antisense DNA molecules. Incorporation of 2-thiouridine derivatives into RNAs resulted in precise recognition of the complementary base of A without formation of mismatched base pair which has been a serious problem in gene diagnosis. Other innovative research results, the following new nucleic acids were synthesized: *N*-aminoacyl phosphoramidate derivatives as the most ideal analogs of aminoacyl adenylate, DNA oligomers having 3'-3' terminal linkage capable of bind to DNA duplexes, artificial DNA molecules capable of selective cleavage of target RNAs in specific positions.

# Fine Enzymatic Syntheses of Useful Compounds

**Project Leader**
Sakayu SHIMIZU Professor, Graduate School of Agriculture, Kyoto University

**Summary of Research Project Result**

We have developed a novel bioreduction system, in which *Escherichia coli* transformant cell co-expresing an NAD(P)H-dependent carbonyl reductase gene and that of glucose dehydrogenase as a cofactor regenerator are used as a catalyst, for asymmetric reduction of prochiral carbonyl compounds to corresponding chiral alcohols. This bioreduction system is applicable to the production of many useful chiral alcohols, by replacing the carbonyl reductase gene for appropriate reductase genes.

We have also succeeded to develop some new reactions, such as hydrolysis of nitriles, asymmetric decarboxylation of α-arylmethylmalonate, which are useful for the synthesis of chiral molecules. Based on the mechanism, we have succeeded in the inversion of enantioselectivity of the decarboxylase via site-directed mutagenesis.

The derivatives of biologically active peptides having sugar chain were chemo-enzymatically synthesized by *Mucor hiemalis* endo-β-N-acetylglucosaminidase (Endo-M). The synthesized glycopeptides were those of peptide T, Substance P, etc. They were resistant to the attack of proteases and retained their original activities. The cDNA of Endo-M was cloned and overxpressed in *Candida boidonii*. The high mannose type sugar chain of bovine serum RNaseB was remodeled to complex type sugar chain. These Resultstrongly indicate the important role of the enzyme in the development of glycotechnology in future.

The structural genes for many kinds of prenyltransferases that catalyze (*E*)-type prenyl chain elongation had been identified and characterized. However, no information has been available about the structures of (*Z*)-prenyl diphosphate synthases until our isolation of the gene for the *Micrococcus luteus* undecaprenyl diphosphate (UPP) synthase. The amino acid sequence of the (*Z*)-prenyl diphosphate synthase is totally different from those of (*E*)-prenyl chain elongating enzymes. Moreover, the crystal structure of the UPP synthase has been determined at 2.2 Å resolution as the first three dimensional structure among *cis*-prenyl chain elongating enzymes. This enzyme shows a novel protein fold, which is completely different from those for the enzymes relating to isoprenoid biosynthesis.

# 4．Biomedical Observation and Control

（1）Research Promotion Committee Members

○ Toshiyuki FURUKAWA (Osaka National Hospital)

Tadashi KAWAI (International Clinical Pathology Center)

Satoshi KAWATA (Osaka University)

Ryoji SUZUKI (Kanazawa Institute of Technology)

Kunihiro CHIHARA (Nara Institute of Science and Technology)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Systematic Research and Development of New Techniques for Monitoring and Processing Information of the Living Body | Kunihiko MABUCHI (The University of Tokyo) |
| 2 | Innovational Basic Technology for Ultrasonic Diagnosis and Treatment | Masatsugu HORI (Osaka University) |
| 3 | Application of Heuristic Solution of Inverse Problem to Medical Diagnoses and Biological Research | Hisashi KADO (Kanazawa Institute of Technology) |
| 4 | Photonic Biomedical Sensing and Control | Satoshi KAWATA (Osaka University) |

# Systematic Research and Development of New Techniques for Monitoring and Processing Information of the Living Body

**Project Leader**
Kunihiko MABUCHI Professor, Center for Collaborative Research, The University of Tokyo

**Summary of Research Project Result**

The subjects which were investigated in the "Research for the Future Program" and the results that were obtained are as follows:

**1) Measurement and control of sensations:**

1-1) We developed a) a robot arm manipulation system capable of various movements required during medical treatment, and b) various "smart tools" for medical treatment using a 1 msec visual feedback system (vision-chip) and impedance force feedback control.

1-2) We developed two novel visual systems for use in remote surgery systems. One is a telexistence visual system in which the image at the slave manipulator is projected on fixed screens at the master side, with the position of the video camera being tracked in accordance with the movements of the subject's head. The other is an "object-oriented visual display system" in which the real environment is painted with a retroreflective material and then used as a screen; the video image is then projected on it using a head-mounted projector. We also developed a force-feedback system for use in a master-slave telesurgery system in which the force-feedback system employed a force-reflection servo-type impedance controller; the master-slave manipulation system was able to perform the required tasks.

1-3) We established a method to evoke artificial sensations by electrically stimulating corresponding sensory nerve fibers; we also developed a prototype of an artificial limb system capable of sensing mechanical stimuli and transferring them to the subject so that the subject experiences the stimuli as the corresponding somatic sensations.

1-4) We developed a control system for an artificial heart (AH) system in which the AH system alters its driving condition in accordance with information received from the autonomic nervous system.

**2) Development of non-invasive methods for evaluating functions of the living body:**

2-1) We developed a non-invasive method for diagnosing stenoses of the coronary artery using a Laser doppler deviation meter to detect extremely tiny vibrations which are generated by turbulence at the stenotic position.

2-2) We developed a data processing system that yields a time series of rapidly-scanned far-infrared images which allows the display of rapidly-changing thermal phenomena of the living body and the evaluation of functions of the autonomic nervous system or the mental stress that underlie fluctuational changes in the skin temperature.

2-3) We also attempted to develop a system for measuring the concentrations of biochemical substances at the subcutaneous tissue non-invasively from outside the body. The system adopted photo-acoustic spectroscopy (PAS) for the detecting system, and was able to measure the concentration of glycohemoglobin in the subcutaneous tissue with adequate resolution.

**3) Development of an implantable probe to allow long-term observation of the microcirculation in the living body:**

We developed an implantable probe which uses a CCD element and which will allow long-term observation of the microcirculation of tissues inside the body.

**4) Analysis of the control mechanism of the biosystem - dispersal and autonomous control at the periphery, and systematic integration at the center:**

We attempted to analyze how the peripheral circulation, which is controlled autonomously and individually, is systematically integrated and regulated by the central system. We developed a very small artificial heart (AH) system, and attempted to control the blood flow to each viscera independently using the AH system. Although at present we have only been able to connect the AH system to the kidney, we believe that this will contribute to the analysis of pathophysiology in various circulatory disorders.

**5) Reconstruction of tissues and organs from cultured cells (control of the arrangement of cultured cells):**

We attempted to develop techniques for the reconstruction of tissues or organs from (various kinds of) cultured cells. We developed a method similar to stereo-lithography using photopolymerizing gelatin which is hardened by visible light (wavelength 400 - 500 nm). We also designed a technique to eliminate cells at any given position by irradiation with light of a specific wavelength in order to induce apoptosis. Both of these methods are useful during the reconstruction of tissues and organs from cultured cells.

# Innovational Basic Technology for Ultrasonic Diagnosis and Treatment

**Project Leader**
Masatsugu HORI Professor, Graduate School of Medicine, Osaka University

**Summary of Research Project Result**

We have investigated ultrasound utilization for medical filed in this research project. The key words of our research objectives were signal processing, post processing and utilization of ultrasound energy. Although current medical imaging devices using a sequential scanning method to take a cross sectional and a three dimensional image of the body, we achieved to built a non-scanning volume imaging system which enables simultaneous grabbing of multi-directional information and rendering super high-speed volume image which does not have time-spatial distortion that a sequential scanning system has.

We also developed an ideal point source of ultrasound for our imaging algorithm under a collaboration of the photonics research group in this "Research for the Future" program. Real-time post-processing of ultrasound image show moving stereo pictures of inside body of us which provide a chance for instant recognition of complicated anomaly of fetus and make a maternal-infant relationship deeper because of its quasi-real face picture of her baby provided a. surface modeling. Non-linear models of signal processing show us further potential of ultrasound diagnosis. Information of tissue character on an ultrasound propagation path could be convoluted on received ultrasound signal. We have tried to utilized analysis of fractal dimension that represented complexity of tissue fibrosis of cardiomyopathy and the Gold'burg number promised to utility of a parametric approach for function of wave distortion that indicates transient tissue elasticity changing.Transient response of biological tissue for ultrasound exposure is quite interesting phenomenon. It was considered as a part of the thermal or a part of cavitational effect for a long time.

We showed a biological response of cultured mammalian cell consistent with a mechanical stimulation of ultrasound. Those mechanical effects of ultrasound might be enhanced by pin pointed medication which ultrasonic activation of chemical holding micro capsules.

# Application of Heuristic Solution of Inverse Problem to Medical Diagnoses and Biological Research

**Project Leader**
Hisashi KADO Professor, Applied Electronics Laboratory, Kanazawa Institute of Technology

**Summary of Research Project Result**

Our activity for this project was on the study the heuristic algorithm of inverse problem, and our goal was to a establish a heuristic solution to the inverse problem which could be applied to the technology development of estimation of the magnetic source in MEG (magnetoencephalograph) measurement, and also to be applied to the cochlear implant which is an artificial internal organ.

We have developed the AMAIKE method which is the base for the study, a series of library software which operates the method, and the PC-based parallel connected system which acts as the platform for the method. We have also developed a time-series 3-dimensional information visualization software, 3DV, which helps to intuitively understand the magnetic source information obtained by the algorithm. Further, using the original filtering technology, a medical image information extracting software called Synapse was developed, which extracts only the anatomical information from the generally-used medical information and which then visualizes the extracted information three dimensionally.

The new and advanced studies on MEG such as the environmental magnetic noise reduction method CALM, active shielding technology, and SQUID sensor advancement were carried out for the project in order to support the algorithm study.

The medical image information extracting software Synapse was distributed as freeware to public through internet, and met a large response from medical and cognitive science research field both in and abroad.

In the frame of this project, we have actually applied the above results to the activities at medical or cognitive science research institutes, and gained new knowledge and information on new diagnostic methods or cognitive science field.

A new field to apply this project's result was found through a derivative technology of MEG measurement; the measurement of magnetic fields evoked from spinal and peripheral nerve is a derivative. The studies at a medical institute were performed using this new measurement system and are producing excellent results. Marketwise, the system is also a new discovery which can expect a different market from the MEG system users.

The results of this project is assessed to be quite valuable both academically and industrially, with greater progress to be expected. A new project has already begun which aims at the further advancement of the study.

# Photonic Biomedical Sensing and Control

**Project Leader**
Satoshi KAWATA Professor, Graduate school of Engineering, Osaka University

**Summary of Research Project Result**

1. A transcutaneous power transmission system has been developed which uses near-infrared light as a medium. This technique is for powering implanted devices such as cardiac pacemakers. The system was successfully applied to live rats. This technique was also applied to driving an optical transmitter for transcutaneous telemetry.
2. A real-time two-photon microscope using ultra-short laser pules has been developed. This microscope was used to image calcium ion concentration in living cells. With this microscope, in situ imaging of whole rat hearts was successfully performed, and abnormal calcium waves were discovered in injured hearts.
3. Near-infrared diffuse reflectance spectroscopy has been applied to different kinds of rat organs for their characterization. This technique was also used to differentiate diseased organs from normal ones.
4. A new ultrasound imaging technique has been proposed, which uses ultrasound caused by laser-induced breakdown of water. In order to cause the laser-induced breakdown, ultra-short laser pulses are focused in water. With this technique, real-time, high-resolution ultrasound imaging is possible.
5. Optical tomography using interactions between light and pulsed ultrasound has been developed. This technique was applied to a thick scattering sample. The spatial resolution of the measurement was less than 1 mm.
6. Ultra-short laser pulses have been used to induce calcium ion waves of in living HeLa cells. Calcium waves were imaged by fluorescence and were observed to propagate from the laser focal point inside the cell.
7. A microscope has been developed which images coherent anti-stokes Raman scattering by use of ultra-short laser pulses. This microscope can be used to observe molecular distribution in living cells without staining them.
8. A microscope has been developed which images second harmonic waves generated by ultra-short laser pulses. This microscope can image membrane potentials in living cells in real time.

# 5. Causes and Effects of Environmental Loading and its Reduction

（1）Research Promotion Committee Members

○ Motoyuki SUZUKI (The United Nations University)

Kazuhiro UETA (Kyoto University)

Toshio OJIMA (Waseda University)

Tohru KODAMA (The University of Tokyo)

Mitsuo KOBAYAKAWA (The University of Tokyo)

Takeshi SHIGA (Osaka University)

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Sociological Experimental Study of Low Environmental Impact and Resource Circulation Habitation System | Toshio OJIMA (Waseda University) |
| 2 | A New Technology to Evaluate the Risk of Environmental Toxic Agents to Human | Yasuo IGARASHI (The University of Tokyo) |
| 3 | A Systematic Study on the Environmental Assessment and Possible Mitigation Schemes for Temporal and Spatial Changes in Global Hydrologic and Biogeochemical Balances by Anthropogenic Activities | Katumi MUSIAKE (The University of Tokyo) |
| 4 | Development of Wastes Recycle Technologies Using High Temperature and High Pressure Treatments | Koichi FUJIE (Toyohashi University of Technology) |
| 5 | Establishment of New Technology for the Risk Estimation on Humans by Environmental Toxic Agents | Taisei NOMURA (Osaka University) |
| 6 | Evaluation and Restoration of the Effects of Oil Pollution on Coastal Ecosystem | Mitsumasa OKADA (Hiroshima University) |

# Sociological Experimental Study of Low Environmental Impact and Resource Circulation Habitation System

**Project Leader**
Toshio OJIMA Professor, School of Science and Engineering, Waseda University

**Summary of Research Project Result**

This research has presented the concept of the "Perfect Recycle House," described the design method and experiment system for two types of model houses and verified the result. A summary of the result of this research is as follows,

(1) The following PRH concept was presented : in order to realize the perfect recycling of houses, it is necessary to establish the "recycling of buildings facilities." "Recycling of buildings" means the use of materials which are durable and capable of being recycled and adoption of dismantling-friendly building methods and "recycling of facilities" which aim to establish a circulatory system from the level of the site to the wider area.

(2) Based on the PRH concept, two types of model houses were presented by thoroughly pursuing reuse and recycling; the reuse type of W-PRH based on the traditional wooden house method and the recycle type of S-PRH made of steel frame.

(3) To evaluate the circulation of resources in this research, a "PRH Value" was suggested as one of the evaluation methods for the Life-Cycle Mass.

(4) Comparing the W-PRH and S-PRH with conventional houses (wooden houses and light gauge steel frame houses) by PRH value, the PRH's were very good; W-PRH shows a PRH value of 170 and S-PRH value of 402. The PRH value for conventional houses were estimated as predicted value assuming maximum dismantling and separation and using LCA calculation model house data provided by the Japan Institute of Construction Engineering.

(5) From the result of an actual building performance survey, both perfect recycling houses applied materials capable of recycling methods which did not use adhesives, showed good airtight performance and extremely low air contamination; they are found to produce a very healthy environment.

(6) Both the Greenhouse in W-PRH and the Double-skin Space in S-PRH showed an increase of comfort and reduction of air-conditioning load, which confirms their validity.

(7) The actual life experiment is still under way both in W-PRH and S-PRH, however, the results are almost as expected in each system; energy, water and waste. The effect of improvement at rebuilding will be clarified in future research.

# A New Technology to Evaluate the Risk of Environmental Toxic Agents to Human

**Project Leader**
Yasuo IGARASHI Professor, Graduate School of Agricultural and Life Sciences, The University of Tokyo

**Summary of Research Project Result**

The microbial community working in the process of degradation of urban waste (house garbage) was analyzed by modern molecular ecological techniques. A unique Bacillus-like microorganism which seems to be dominant in various processes of waste treatment was isolated and characterized.

This organism has only highly limited abilities to degrade organic substrates and the reason for the dominance of this microorganism in waste-degrading processes is unclear. When oil-degrading Bacillus or E. coli are introduced in higher amount into the microbial community, those outsider microorganisms are easily expelled from the community. The waste-degrading community seems to form a special society. Development of new techniques is necessary to analyze the structure and stability of this microbial society.

# A Systematic Study on the Environmental Assessment and Possible Mitigation Schemes for Temporal and Spatial Changes in Global Hydrologic and Biogeochemical Balances by Authropogenic Activities

**Project Leader**
Katumi MUSIAKE Professor, Institute of Industrial Science, The University of Tokyo

**Summary of Research Project Result**

Due to the possible increase of population and related environmental changes, the most necessary resources for human beings -crops and water- will become scarce resources in the world in the future or probably already now. Using various kinds of global datasets including remotely sensed data from space and with the utilization and development of sophisticated global-scale hydrological models, biogeochemistry models and crop production models, the assessments of crop production and water resources over the world on fine grid resolution basis were carried out in order to assess potential human sustainability with adequate amounts of such indispensable resources. For the purposes above, global-GIS techniques and super large-scale detabase systems were developed. In addition, a very advanced user interface was developed which enables us to handle huge datasets of global environment.

The visualization technology of it with VRML provides us the first opportunity for feeling of 3D global environment. Since water resources cannot be traded basically, severe situations in the current world and in the projected future worlds may be captured easily in terms of water resources scarcity. Actually as a result of the research, the water scarcity already exists in several notorious basins such as Yellow River, Indus, the western coast of America and so on to considerably severe extent. Water scarcity areas are expected to enlarge around such current scarce areas in the near future. Such projections were carried out with the extrapolations of statistical data on waters and crops and scenarios. However, thinking that every situation - population, land use, climate, society structures, human behaviors and so on - will change in the coming few decades, more dynamic model which will be developed combining these models developed in this research project should be indispensable.

Even though the assessed results by this project is plausible as first approximation of the future world, development of such dynamic combined model and assessment of the world using it could be a promising challenge of research in the next few years. We already have started the challenge.

# Development of Wastes Recycle Technologies Using High Temperature and High Pressure Treatments

**Project Leader**
Koichi FUJIE Professor, Faculty of Engineering, Toyohashi University of Technology

**Summary of Research Project Result**

The present research aimed to develop a novel technology for wastes reclamation to establish recycle-based emission minimized society. The effect of reaction conditions such as temperature, pressure, reaction time, etc. on the production of amino acids from hydrolysis of proteinaceous wastes such as fish wastes and silk wastes in high temperature and pressure water was studied comprehensively. The type operations of reactors utilized for the present research are semi-batch, batch and continuous flow under the sub- and super critical condition. The degradation pathway of the proteinaceous materials to amino acids and then to organic acids followed by mineralization was investigated and clarified under various reaction conditions. The degradation of various amino acids and polypeptides were also studied for the kinetic analyses of reactions. These results were effectively utilized to make a model to estimate an optimal reaction condition to increase the yield of target materials.

The similar investigation was carried out for the degradation of woody wastes to produce value added materials for recycle. The reaction pathway and inventory of possible reactions occurred in the sub- and super critical water were summarized and categorized. The information can be utilized to estimate the reaction for the treatment of cellulose, hemicelluloses and lignin in sub- and super critical water. Multi-stage reaction process was developed using a screw feeder pump for the simultaneous treatment of cellulosic wastes and extraction of value added materials produced. Other applications of the sub- and super critical water reaction for wastes recycle such as plastics, carbon fiber reinforced plastics, waste cast sand and so on were developed as well. It was shown that the sub- and super critical water reaction is a promising technology for various areas from the environment conservation to the industrial production.

# Establishment of New Technology for the Risk Estimation on Humans by Environmental Toxic Agents

**Project Leader**
Taisei NOMURA Professor, Graduate School of Medicine, Osaka University

**Summary of Research Project Result**

New technologies were established for evaluation of the risk of environmental toxic agents, especially dioxins, to humans, and the following results were obtained.

1. A novel biotechnology to evaluate environmental hazards in normal human organs and tissues maintained in SCID (severe combined immunodeficient) mice.
   (1) Establishment of SCID mice defective T, B, NK and/or macrophage function, *i.e.* defective of rejection of normal human tissues.
   (2) Morphology and function of normal human organ and tissues (lung, liver, intestine, thyroid, skin, bone marrow, *etc.*) are well maintained for long period (> 2 years), including human embryo.
   (3) First success to induce mutation and cancer in normal human skin by UVB and morphological and functional damage (secretion of hormone) and changes in gene expression in human thyroid tissues by low doses of dioxin (TCDD).
2. Establishment of super-sensitive and rapid detector.
   (1) Super-sensitive and rapid detector (GC-MS) enabled to quantify the small amounts of dioxins in 5 ml of blood in human, *i.e.*, in femto-gram ($10^{-15}$g) order.
   (2) Detection of dioxins via the milk and placenta.
   (3) Production of highly mutagenic Nitro-PAHs instead of dioxins which were reduced by the waste incinerator at high temparature.
3. Economic policy for the waste control.
   (1) Large amounts of electricity were produced by a new incinerator (K-plant) for waste treatment.
   (2) High cost materials (Methanol and DME) can be produced by treating plastics wastes (M-plant).
   (3) Economic benefits were calculated for waste control by K and M-plant; essential for "Recycling ".

# Evaluation and Restoration of the Effects of Oil Pollution on Coastal Ecosystem

**Project Leader**
Mitsumasa OKADA Professor, Graduate School of Engineering, Hiroshima University

**Summary of Research Project Result**

The following results were found in this research.

1) Quantitative analysis of the impact of oil pollution on the coastal ecosystem was done using the mesocosm and microcosm experiments. Change in the cluster of bacteria and fluctuation of a vegetation network has occurred. In addition, differences in the recovery speed of the different species of seaweed, shellfish and marine plants were observed. On the other hand, there is almost no direct impact of oil pollution on eelgrass except for some effects including shading and change in the species of macro benthos by oil drifting ashore.
2) It was found that the oil penetration in the beach sand was affected by wave movement, and there is much difference between penetration of oil and that of water. The economical method was used for the evaluation of tideland environmental value aggregated among Kanto area households, and a societal benefit value was estimated as [yen per hectare].
3) It was confirmed that the dispersant treatment was one of the effective methods for oil treatment, because it increases the solubility of oils which increase biological degradation of oils. However, the dispersant also increases the solubility of high molecular PAHs, leading to the increase of toxicity. The dispersant should be used carefully.

# 6．Environmental Conservation in the Asian Region

（1）Research Promotion Committee Members

| | | |
|---|---|---|
| ○ | Hiroya KAWANABE | (Lake Biwa Museum) |
| | Yukiko KADA | (Kyoto Seika University) |
| | Takeshi KUROKAWA | (The Institute of Behavioral Sciences) |
| | Masahiro KURODA | (Keio University) |
| | Satohiko SASAKI | (Nihon University) |
| | Toshiaki TADANO | (Tokyo University of Agriculture) |
| | Masanobu HASATANI | (Nagoya University) |
| | Tsuneyuki MORITA | (National Institute for Environmental Studies) |

○：Committee Chairperson

（2）List of Research Projects

| No. | Research Project | Project Leader |
|---|---|---|
| 1 | Inter-Disciplinary Studies for Sustainable Development in Asian Countries | Kanji YOSHIOKA<br>(Keio University) |
| 2 | Developing the Standards for Global Watch through a Multi-disciplinary Catchment Study | Eitaro WADA<br>(Kyoto University) |
| 3 | Impact Analysis of Metropolitan Policies for Development Environmental Conservation in the Philippines | Tatsuo OHMACHI<br>(Tokyo Institute of Technology) |
| 4 | Development of Environmental Friendly Industrial Municipal System Based on Coal Energy in the Southern Area of China | Shigekatsu MORI<br>(Nagoya University) |

# Inter-Disciplinary Studies for Sustainable Development in Asian Countries

**Project Leader**
Kanji YOSHIOKA Professor, Institute for Economic and Industry Studies, Keio University

**Summary of Research Project Result**

The project contains five main results according to the five working groups.

First, the working group I (WG-I) established the environmental input-output tables (EI/O) for the nine Asian countries. It is a completely original work and is impossible without intense collaboration between the Japanese members and the statisticians of each country. These tables show not only how much $CO_2$ and SOx emission are induced by production in any one of the nine country, but also how such emissions are transmitting and affecting through the trade among these nine countries. This is the basic data and invaluable information for the following simulations in WG III to V.

Second, WG II investigates the 52 alternative technologies to reduce $CO_2$ with the Japan's environmental input-output table. The Japan's EI/O has been developed by the project and it contains 400 sectors with one of the most detailed classification in the world. Among the 52 technologies, the solar power satellite is the most promising technology to reduce $CO_2$ in the future. And utilization of low temperature water supply is the most cost efficient method for $CO_2$ reduction.

Third, the experimental investigation of WG III for the bio-coal briquette and alkali-soil improvement has developed an important contribution of multi-purpose international cooperation. The pair of bio-coal briquette and its ash is efficient to reduce SOx in the atmosphere and to neutralize alkali base in the desert soil close to Inner Mongolia.

Fourth, WG IV is a true interdisciplinary work between engineers, economics and politics to find the most efficient political system for the introduction of bio-coal briquette technology and to evaluate China's nation-wide effect with the economic model.

Finally, WG V gives a perspective of the complete economic model for the nine Asian countries, which incorporates every aspect of economic behaviors with technological information.

# Developing the Standards for Global Watch through a Multi-disciplinary Catchment Study

**Project Leader**
Eitaro WADA Professor, Center for Ecological Research, Kyoto University

**Summary of Research Project Result**

This project has developed a method to collect and integrate extensive environmental information in order to answer the following questions: What, where and how are the changes in water-enviroment in diverse Asian watershed? What is important information for watershed management?

The final goal is to compile a practical manual that is useful for researchers who work with researchers of different discipline, policy-makers and residents in investigating diverse Asian watershed.

Output

ⅰ )A total manual for watershed management

Part 1: The characteristics of environmental issues in Asia

Part 2: Four methods of environmental diagnosis

Part 3: An application of the method to the Lake Biwa - Yodo River watershed

ⅱ )Atlas for four selected watershed: Lake Biwa - Yodo River, Japan; Lake Baikal -Serenge River; Mekong River and Yangtze river

ⅲ) Report of multi-disciplinary case studies in the small catchment of Lake Biwa

# Impact Analysis of Metropolitan Policies for Development Environmental Conservation in the Philippines

**Project Leader**
Tatsuo OHMACHI Professor, Graduate School of Science and Engineering,
Tokyo Institute of Technology

**Summary of Research Project Result**

Simulation models to predict the future state of the urban environment were among the developments of the project. Three kinds of simulation models that includes physical/socioeconomic aspects and institution and governance, were used to study the respective systems. Since the structures and components of these systems differ so greatly, it was necessary to use three separate models, each with the versatility to adapt to other areas. Quantitative models, for example, were developed for simulation of the physical systems, which include the atmosphere, traffic patterns and natural disasters. The socioeconomic systems, which include population, land use and urban activity, were also used in quantitative models. The former models are versatile and adaptable to other areas, making it necessary to change only the input data, though the input data are not always sufficient for utilizing the models in developing countries. Likewise, the latter models can also be adapted to other areas, however, when the latter models are applied to other areas, it is necessary to carefully adjust model parameters reflecting any unique or particular cultural and citizen preferences. The models for institution and governance were descriptive models with frameworks that can also be adapted to other areas.

In conclusion, it should be stressed that collaboration and the mutual exchange of ideas between experts in the arts and sciences are important and valuable for establishing truly effective urban environmental policies in Asian metropolises.

# Development of Environmental Friendly Industrial Municipal System Based on Coal Energy in the Southern Area of China

**Project Leader**
Shigekatsu MORI Professor, Graduate School of Engineering, Nagoya University

**Summary of Research Project Result**

An environmental friendly industrial municipal system based on coal energy matching with the southern area of China is studied. The emphasis is placed on the development and examination of the elemental technologies and systems to realize the proposed new total system from the combination of them. This project was organized by Nagoya University, and was accomplished by the joint research group of Japanese and Chinese academic researchers.

The following main results were obtained:

1. An efficient power generation system by pure oxygen combustion of coal is proposed, and the stable combustion was studied by the examination in the drop tube furnace.
2. A city gas production process from Refuse Derived Fuels (RDF) in the circulating fluidized bed is developed, and gas with higher heating value than 20MJ/$m^3$ was produced by the system.
3. The lifecycle evaluation of the civil engineering structures, especially transport infrastructures, was performed to reduce the total environmental load such as the $CO^2$ emission and energy consumption.
4. The estimation of the amount of pollutants discharge in the atmosphere and its adverse impact on environment is carried out, and an advanced future transport system using clean energy in Guangzhou metropolitan area, China was proposed.
5. The evaluation of the energy saving potential by the introduction of decentralized energy plant was performed, and the total operation technology of the central energy system and various decentralize energy plants are developed.
6. Hybrid separation techniques for complete recycling of metallic compounds composed of harmful elements, such as Ga-As scrap and Se-As scrap, were developed.
7. The process to treat the surface water containing the humic substances by adding both the polyaluminum chloride and the powdered activated carbon and filtering with the ultrafiltration membranes was developed.
8. The analytical methods for environmental monitoring and multielement determination of about 40 elements and chemical speciation of trace metals by using ICP-MS (inductively coupled plasma mass spectrometry) have been developed to evaluate the pollutants in the environment.
9. A system of Clean Development Mechanism and its influence to China is surveyed, and environmental law system and policy at Local Levels (Canton Province and Guangzhou ) are inquired.

# ***Projects Proposed by Advisory Committee to University-Industry Cooperative Research Committees***

# 1．Creation of Functionalized $C_{60}$ andDevelopment of their Novel Functions

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Creation of Functionalized $C_{60}$ and Development of their Novel Functions | Kazuhiko SAIGO<br>(The University of Tokyo) |

（2）University-Industry Cooperative Research Committee

Name of Committee：

116th Committee on Chemistry Creating Organic Compounds with Novel Functions

Committee Chairperson：

Zen-ichi YOSHIDA (Kyoto University)

# 2．Harmonized Nano-Macro-Information Study on Advanced Materials with High Mechanical Properties and Reliability

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Harmonized Nano-Macro-Information Study on Advanced Materials with High Mechanical Properties and Reliability | Hiroaki MASUI<br>(Teikyo University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：

129th Committee on Strength and Fracture of Advanced Materials

Committee Chairperson：

Takeo YOKOBORI (Teikyo University)

# 3．Ultimate Information Proceeding Devicesand Systems Using High-Functional Spatial Light Modulation Method

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Ultimate Information Proceeding Devices and Systems Using High-Functional Spatial Light Modulation Method | Kenya GOTO<br>(Tokai University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：

130th Committee on Optoelectronics

Committee Chairperson：

Humio INABA (Tohoku University)

# 4．Advanced Research and Developmenton High Density Magnetic Recording Deviceby Means of Atomic Interface Design

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Advanced Research and Development on High Density Magnetic Recording Device by Means of Atomic Interface Design | Tetsuya OSAKA<br>(Waseda University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：

144th Committee on Magnetic Recording

Committee Chairperson：

Shunichi IWASAKI (Tohoku Institute of Technology)

# 5. Fabrication and Device Technology of Extremely Small Magnetically Hard Materials

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Fabrication and Device Technology of Extremely Small Magnetically Hard Materials | Yutaka SHIMADA<br>(Tohoku University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：
147th Committee on Amorphous and Nano-Crystalline Materials
Committee Chairperson：
Tsuyoshi MASUMOTO (The Research Institute for Electric and Magnetic Materials)

# 6. Investigation of New High Performance Piezoelectric Single Crystals and Thin Films, and Applications for Next Generation Electronics and Communication Systems

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Investigation of New High Performance Piezoelectric Single Crystals and Thin Films, and Applications for Next Generation Electronics and Communication Systems | Ken YAMADA<br>(Tohoku University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：
150th Committee on Acoustic Wave Device Technology
Committee Chairperson：
Kazuhiko YAMANOUCHI (Tohoku Institute of Technology)

# 7．Development of Ultra-high Rate Thermal Plasma Cluster Deposition Method for Well-controlled Nano-scopic Electronic Materials

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Development of Ultra-high Rate Thermal Plasma Cluster Deposition Method for Well-controlled Nano-scopic Electronic Materials | Toyonobu YOSHIDA<br>(The University of Tokyo) |

（2）University-Industry Cooperative Research Committee

Name of Committee：

153th Committee on Plasma Materials Science

Committee Chairperson：

Yasuhiro HORIIKE (The University of Tokyo)

# 8．Multiple Molecular Improvement of hotosynthesisand Plant Performances for Crop Productivity

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Multiple Molecular Improvement of Photosynthesis and Plant Performances for Crop Productivity | Akiho YOKOTA<br>(Nara Institute of Science and Technology) |

（2）University-Industry Cooperative Research Committee

Name of Committee：

160th Committee on Plant Biotechnology for the Environment, Food, and Resources

Committee Chairperson：

Akira ISOGAI (Nara Institute of Science and Technology)

# 9. Growth and Characterization of Single Crystals for Active Elements

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Growth and Characterization of Single Crystals for Active Elements | Tsuguo FUKUDA<br>(Tohoku University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：
161th Committee on Science and Technology of Crystal Growth
Committee Chairperson：
Tsuguo FUKUDA (Tohoku University)

# 10. Integrated Network Architecture for Advanced Multimedia Application Systems

（1）List of Research Project

| Research Project | Project Leader |
|---|---|
| Integrated Network Architecture for Advanced Multimedia Application Systems | Hideo MIYAHARA<br>(Osaka University) |

（2）University-Industry Cooperative Research Committee

Name of Committee：
163th Committee on Internet Technology
Committee Chairperson：
Hideo MIYAHARA (Osaka University)

# Creation of Functionalized $C_{60}$ and Development of their Novel Functions

**Project Leader**
Kazuhiko SAIGO Professor, Graduate School of Frontier Sciences, The University of Tokyo

**Summary of Research Project Result**

We carried out intensively the present research on the creation, reactions, properties, and functions of new compounds and materials derived from $C_{60}$. The research results, categorized roughly into six, are as follows.

(1) Creation of $C_{60}$ Supramolecular Complexes and Their Reactions

◎ Creation of a Monocapped γ-Cyclodextrin/$C_{60}$ Supramolecular Complex

◎ Creation of a Bicapped γ-Cyclodextrin/$C_{60}$ Supramolecular Complex

(2) Creation of $C_{60}$ Derivatives Having New-Type Bond(s) and Their Reactions

◎ Development of a General Method for the Preparation of Methano[$C_{60}$]s by the Fluoride Ion-Mediated Reaction with Silylated Nucleophiles

◎ Development of a New Method for the Preparation of Formylmethano[$C_{60}$]

◎ Development of a New Method for the Preparation of (Chlorocarbonyl)methano[$C_{60}$]

(3) Creation of $C_{60}$ Polymers and Their Structures

◎ Creation of *equatorial*-Biscyclopropanated $C_{60}$ Pearl-Necklace Polyamides

◎ Creation of *trans*-2-Biscyclopropanated $C_{60}$ Pearl-Necklace Polyamides

◎ Creation of *trans*-4-Biscyclopropanated $C_{60}$ Pearl-Necklace Polyamides

(4) Properties and Functions of New Materials thus Created

◎ Elucidation of the Dinitrogen Reductability of the Bicapped γ-Cyclodextrin/$C_{60}$ Supramolecular Complex Anion

◎ Elucidation of the Catalytic Reductability of the Bicapped γ-Cyclodextrin/$C_{60}$ Supramolecular Complex Anion

◎ Elucidation of the Catalytic Asymmetric Reductability of the Bicapped γ-Cyclodextrin/$C_{60}$ Supramolecular Complex Anion

(5) Prediction of the Reactivity of $C_{60}$ and Its Derivatives

◎ Explanation of the Product Distribution for the Cyclopropanation of $C_{120}$

◎ Explanation of the Regioselectivity for the $C_{60}$ Bisadduct Formation

◎ Explanation of the Effect of the Leaving Groups in Tehter-Directed Biscyclopropanations of $C_{60}$

(6) Large-Scale Production of $C_{60}$

◎ Proposal for the Large-Scale Production of $C_{60}$ by the Shock Heating

◎ Development of a Method for the Large-Scale Production of $C_{60}$ from Carbon Black by the High-Pressure Burning

# Harmonized Nano-Macro-Information Study on Advanced Materials with High Mechanical Properties and Reliability

**Project Leader**
Hiroaki MASUI Professor, School of Science and Engineering, Teikyo University

**Summary of Research Project Result**

(1)Derivation of simple and feasible formula for strength and fracture based on nano-macro nonlinearily combined mechanics.

(2)Derivation of the prediction law for fracture life and remaining life under high temperature creep, based on nano-macro nonlinearily combined concepts.

(3)Establishment of standardization of the basis of the high temperature creep crack growth testing method.

(4)The clue has been obtained for solving the strength and fracture problems as complexity system science.

(5)Establishment of the basis or the computationaly aided prediction of plastic forming.

(6)Developing the various advanced composites, such as CMC, MMC etc.

(7)Invention of non-invasive diagnostic device for degradation of artery

# Ultimate Information Proceeding Devices and Systems Using High-Functional Spatial Light Modulation Method

**Project Leader**
Kenya GOTO Professor, School of High Technology for Human Welfare, Tokai University

**Summary of Research Project Result**

Near-field semiconductor probe arrays with very high throughput efficiency had been developed in this project. This was done by developing nano-fabrication processes with self-alignment technology between the focal points of the micro-lens array fabricated on the probe substrate and the nano apertures of the near-field optical probe array on the same substrates, which had been developed in this project using special photo-resist layers that consist of an UV sensitive photo-resist and a special IR sensitive emulsion. One of the reasons why the throughput efficiency of this array on the semiconductor substrate is more than thousand times as high as compared to the conventional probes is the success of fabrication processing for the micro-lens array on a single crystal semiconductor thin wafer. The self-alignment technology in this project can cause the laser beam to focus within just inside of the near-field semiconductor probe with the accuracy of 10 nano meter between optical axe and center of the aperture. As there is no loss from the output windows to the flat top aperture tip of the near-field optical probes, the conversion efficiency between the far-field light to the near-field light which can be observed just outside of the aperture of the probes is depended on the far-field beam waist size vs. evanescent wave aperture size.

Finally we could get more than 10 % throughput efficiency for the case of 100 nm aperture sizes. In the case of the near-field arrayed apertures located periodically on the surface of the metal film or dielectric material mutual interaction between the evanescent lights emitted from each aperture emphasis each other the evanescent light intensity. This may be occurred by owing to the surface plasmon polariton effect. More appropriate aperture distance and location distribution will make the enhancement stronger with the improvement of the fabrication process for the aperture array. Beside the great improvement of the probe array for the writing bits on the surface of the disk a novel signal detection method from the super high density optical written disk surface was also improved by using the same VCSEL array optical head which has both the micro-lenses and periodically positioned optical apertures.

The VCSEL impedance between the two electrodes of the each VCSEL element changes with the reflected feed back light from the disk. This can be a very good new signal detection method in a higher density optical phase change disk. The simulation of in both the probe array and the signal detection analysis were performed using improved time domain finite differentiation (FDTD) method which had been published by us. Two dimensional optical head will lead very high data transfer rate in the optical disk in near future.

# Advanced Research and Development on High Density Magnetic Recording Device by Means of Atomic Interface Design

**Project Leader**
Tetsuya OSAKA Professor, School of Science and Engineering, Waseda University

**Summary of Research Project Result**

This project is divided into three subjects which are relevant to a perpendicular magnetic recording system: (1) Development of ultra-high density perpendicular magnetic recording media, (2) Development of writing head materials for ultra-high density magnetic recording, (3) Study on read/write system for ultra-high density perpendicular magnetic recording. Main research results are as follows.

(1) A CoNiFe soft magnetic thin film with a high saturation magnetic flux density ($B_6$)of 2.1*T*, which was much higher than that of permalloy, was developed using electroplating. That film was practically adopted by several industries as a writing head core material for high density magnetic recording. Furthermore, CoNiFeB soft magnetic thin films with a high $B_6$, a high electrical resistivity, and a low magnetostriction were developed with electroless plating.

(2) Co/Pd multilayered perpendicular magnetization films with amorphous C or Si underlayer were developed using magnetron sputtering. This media exhibited both excellent magnetic properties and read/write characteristics, namely, a high coercivity, a strong thermal stability, and a low signal to noise ratio. Furthermore, the double-layered perpendicular magnetic recording medium, which consisted of the multilayered perpendicular magnetization film with high magnetic anisotropy and the high $B_6$ CoNiFeB soft magnetic thin films, was proposed as a promising candidate for ultra-high density perpendicular magnetic recording media in the next generation.

(3) A novel read/write system with a ring typed head was proposed for ultra-high density perpendicular magnetic recording.

# Fabrication and Device Technology of Extremely Small Magnetically Hard Materials

**Project Leader**
Yutaka SHIMADA Professor, Institute of Multidisciplinary Research for Advanced Materials
Tohoku University

**Summary of Research Project Result**

The superparamagnetism for ferromagnetic materials downsized to the nanometer scale is an unavoidable obstacle to development of the spin-electronics technology. The commercial magnetic recording media that consist of Co-Cr fine particles are now seeing the limitation of the recording density because for further increase of the recording density the particles are required downsizing into the few nm scale region where the superparamagnetism makes the magnetic memory unstable. Confronting this limitation our research project worked on four subjects. The subjects and the achieved results are as following.

1) The surface anisotropy, that is, concentration of the magnetic energy density on the surface of ferromagnetic material is expected to play a dominant role as the size of the material becomes smaller. We made a search for a giant surface anisotropy for a variety of surfaces and interfaces. The result is that for transition metal particles the surface anisotropy is enhanced by forming the interfaces where a stress by hydrogen absorption, increase of orbital moment by rare earth addition, or a hard layer formation by oxide are introduced. In the final stage of the research we found a giant surface anisotropy in the trilayer of MgO/FePt($L1_0$)/Pt, that is several ten times larger than the usually observed surface anisotropy. The ordered L10 phase has also a very high crystalline anisotropy and is expected to be a good candidate as ultra-high density recording recording media
2) The ordered $L1_0$ FePt alloy in 1) has, however, been available only when annealed at high temperatures in the range 500～700℃. This high temperature annealing destroys the nano-size particle structure. We investigated how to lower this ordering temperature and found that by addition of insoluble metals with low melting points, by addition of interstitially stable boron, by accelerating coalescence of the particles or by making use of the intensive atomic diffusion at the interfaces of Fe and Pt multilayers, the ordering temperature was successfully reduced down to 300℃. Based on these results a process of two-dimensional assembly of ordered FePt particles was developed. This assembly exhibits a powerful feature as a new magnetic recording media.
3) Another means to overcome the superparamangetism in the recording technology is the patterned media. In the media one memory bit is recorded in a small ferromagnetic dot and, if the dot size, the material and the dimension are designed as to overcome thermal agitation, the dot pattern may have a high potential as ultra-high density recording media. In the initial stage of the project Read/Write experiments were performed and a possibility of 29Gbit/inch$^2$ was demonstrated. In the final stage, patterning of 130Gbit/inch$^2$ and a very high potential of FePt were confirmed.

# Investigation of New High Performance Piezoelectric Single Crystals and Thin Films, and Applications for Next Generation Electronics and Communication Systems

**Project Leader**
Ken YAMADA Associate Professor, Graduate School of Engineering, Tohoku University

**Summary of Research Project Result**

The purpose of this research is to investigate on new high performance piezoelectric single crystals and thin films and their application for next generation electronics and communication systems. The main results of this research are summarized below.

1. The BGS surface wave of ultra high coupling ($k^2$=0.54) was found to exist on *Z*-axis cylinder cuts of $KNbO_3$. Large size $KNbO_3$ single crystals were grown using a TSSG method. The efficiency of the convolver using 45° *Y*-*X*$KNbO_3$ was found to be 25dB higher than that of the *Y*-*Z*$LiNbO_3$ convolver. The collinear interaction of the BGS wave with optical waves was theoretically analyzed. It offers very efficient TE-to-TM optical mode conversion, thereby yielding an efficient tunable optical filter.
2. The orientation dependence of coupling factors for various modes of vibrations in $KNbO_3$ was calculated. Especially, the coupling factor $k_t$ for the thickness-extensional mode was found to be 70% for the 49.5° -rotated *X*-cut, which is the highest among known piezoelectrics.
3. ZnO films with the c axis lying in the film plane were found to be epitaxially grown rotated *Y*-cuts of $LiTaO_3$ by ECR-MBE. The SH-SAW in the (110)ZnO/42° *Y*-*X* $LiTaO_3$ showed a high coupling factor due to the piezoelectric contribution of $LiTaO_3$ and ZnO. Ferroelastic and ferroelectric $Ta_2O_5$ thin films useful for SAW devices were also obtained by a new linear rapid thermal annealing technique. The maximum value of the electromechanical coupling factor for the SAW was 4.56%.
4. A 2.4GHz $AlN/Al_2O_3$ surface-acoustic-wave matched filter was developed. Using it, we have designed and implemented a spread-spectrum (SS) wireless switch system and a packet spread-spectrum code-division multiple-access (SS-CDMA) system.
5. The leaky SAW on $SiO_2/LiNbO_3$ was found to have a large $k^2$ of leaky SAW over 0.2 and zero propagation attenuation for the metallized surface at $H/\lambda \fallingdotseq 0.15$~0.2 (*H*:$SiO_2$ film thickness). This substrate makes it possible to obtain wide band SAW filters and VCOs.
6. A new type of piezoelectric film resonator using $\lambda/4$ acoustic multilayers was investigated theoretically and experimentally. As a result this new type of resonator was demonstrated to be promising as a communication device in a super high frequency range from 1 to 20GHz.
7. The propagation characteristics of Rayleigh waves and leaky surface acoustic waves in $La_3Ga_5SiO_{14}$ were theoretically investigated for all cuts and propagation directions. The maximum value of $k^2$ with a zero TCD was 0.5% for Rayleigh wave on (0° , 149.16° , 24° )-cut.
8. Fast and precise simulation techniques were established for the design of SAW single-phase unidirectional transducers and RF devices employing shear-horizontal-type SAWs.

# Development of Ultra-high Rate Thermal Plasma Cluster Deposition Method for Well-controlled Nano-scopic Electronic Materials

**Project Leader**
Toyonobu YOSHIDA Professor, Graduate School of Engineering, The University of Tokyo

**Summary of Research Project Result**

The principal findings by the members of the team can be summarized as follows:

1. A ultra-clean thermal plasma deposition system was developed and was applied for the ultrafast deposition of Si films by injecting $SiH_4$. The improvement of stability, controllability, and cleanliness of the process enabled the deposition of microcrystalline Si films at the ultrafast rate of over 1000 nm/s. Moreover, a minimum defect density of $7.2\times10^{16}cm^{-3}$ was achieved. Simulation and step coverage analysis suggested that the precursor is an approximately 1 nm cluster with a sticking probability of about 0.6.
2. A thermal plasma liquid-spray deposition system was developed. Using the system, epitaxial $Li(Nb_xTa_{1-x})O_3$ films were successfully prepared on $Al_2O_3(001)$ substrate with injecting the mixture of litium-niobium-tantalum alkoxide solutions. Deposition rates up to 0.5 $\mu$ m/min could be achieved. The film quality was found to be comparable with those deposited by other techniques.
3. We have developed a spatially high resolution chemical-structural analysis technique and high contrast imaging technique. The spatial resolution in chemical analysis was much improved for Energy Dispersive X-ray Spectroscopy, namely, probe current larger than 2nA could be obtained even in a probe diameter of 0.5nm. Moreover, the high resolution was clearly confirmed by direct observation of B and N atoms in a c-BN test specimen.
4. A joint system of external quadrupole static attraction ion trap (EQSIT) and quadrupole mass spectrometer or deposition stage has been constructed. When silane and decaborane gases were introduced, $Si_xH_y^+$ (x=1-4) and $B_xH_y^+$(x=1-20) ion clusters were observed. When number of boron atoms, x, is larger than 15, the nido-structure seems to be realized. On the other hand, the clusters with smaller x than 9 prefer fewer hydrogen atoms and may have more metallic bonding. Mixed ion cluster, $B_{10}SiH_y^+$, was also produced by introducing the gas mixture.

# Multiple Molecular Improvement of Photosynthesis and Plant Performances for Crop Productivity

**Project Leader**
Akiho YOKOTA Professor, Graduate School of Biological Science,
Nara Institute of Science and Technology

**Summary of Research Project Result**

This project aimed at clarifying the molecular basis for improving the productivity of plants.The following findings were obtained in the project for 5 years.

We analyzed the functions of the gene and the proteins functioning in acclimation of the plants to high light intensity and found several new genes and proteins involved in the regulation of energy production in photosynthesis. Two genes for CO2 pump and two genes for HCO3- pump were identified with *Synechocystis* PCC6803.With the green alga *Chlamydomonas reihardii*, the signal transduction pathway for signaling the low CO2 concentration to the downstream genes.

We devised the method to synthesize up to 200 mg/ml of a foreign protein in chloroplasts by tobacco chloroplast transformation. This will open a window for the industrial production of medical or pharmaceutical proteins in plants. The expression of the gene for cyanobacterial FBP/SBPase in tobacco chloroplasts caused the productivity of the transformant to increase 50% compared with the wild plants. This finding gave us a chance to get an international patent, that have attracted foreign companies. We cloned five genes essential for differentiation of flower of rice plants.

We devised a molecular method to increase the content of lipids in tobacco seeds with aid of chloroplast transformation. The genetic manipulation of the lipid metabolism also caused the increase in the lipid content in leaves and thereby retarded senescence of leaves. It was also found that the increment in the assimilation power for sulfur rendered plants to be resistant to heavy metals.

We also examined the methods to increase the frequency and expression of the genes transferred into the nucleolus and chloroplast genomes. These findings will be important for designing high-productivity plants in the future.

# Growth and Characterization of Single Crystals for Active Elements

**Project Leader**
Tsuguo FUKUDA Professor, Institute for Materials Research, Tohoku University

**Summary of Research Project Result**

1. Crystal growth for ultraviolet coherent light source
   a) 3-4 inch Ce:$LiCaAlF_6$ (LiCAF) and Ce:$LiLuF_4$ (LLF) single crystals could be grown in this year and could get 98mJ laser output at 290nm.
   b) 2 inch $Gd_xY_{1-x}Ca_4O(BO_3)_3$, which is the promising crystals for UV light source using their highest nonlinear constant, could be grown using solution mixing method.Consequently, the laser thresholdimproved up to 25.4GW/$cm^2$, which is twice higher than that of previous one.
   c) Oriented $LaF_3$ thin films were successfully grown by laser abrasion method.
2. Piezoelectric crystals for digital mobile communication
   a) $Sr_3NbGa_3Si_2O_{14}$ (SNGS), $Ca_3NbGa_3Si_2O_{14}$ (CNGS) crystals, which have smaller dependence of piezo-electric constant($d_{12}$)v.s. temperature were successfully grown by $\mu$-PD and Cz method. They can be candidate materials for SAW filter device of digital mobile communication.
   b) Stability at high temperature of SNGS and CNGS were improved by substituting Ga site with Al, so that they can also be used as torque sensor at high temperature
3. Shaped crystal growth technology and segregation control using micro-pulling-down ($\mu$-PD) method
   Modified $\mu$-PD method was developed by precise design of the crucible shape. With modified $\mu$-PD method, diameter and shape of crystals could be controlled.
4. Machining and crystallinity characterization of developed new functional crystals and their device application
   a) We found out XPS signal of O(1s) from mixed perovskitestemmed from O ion polarization.
   b) Light Scattering Tomography (LST) method allows to investigate dislocation density easily with high accuracy.
5. Design and development of new functional synthetic crystal for crystal growth engineering
   a) $Tb_3Al_5O_{12}$ (TAG) has highverdet constant and promising material for faraday rotator, but because of it's incongruency,bulk crystal growthwas regarded to be impossible. Butusing our design concept, 1-inch size TAG crystals were successfully grownby substituting Al site by Sc.
   b) Tm,Ho:$LiLuF_4$, Tm,Ho:$LiYF_4$, Tm,Ho:$Lu_3Al_5O_{12}$ single crystals for eye-safe laser could be grown and succeeded to obtain 2mm cw at room temperature.
   c) (Nd, Sr)(Al, Nb)O3(NSAN), (La, Sr)(Ga, Nb)$O_3$ (LSGN) single crystals for GaN epitaxial wafer were developed. NSAN and LSGN have much smaller lattice mismatch with GaN of 1.04%(NSAN) and 0.62%(LSGN). We succeeded to grow GaN thick film using these crystals.
   d) $Ca_8La_{1-x}Yb_x(PO_4)_6O_2$, which has higher crystal field than other oxide were successfully grown and emission cross-section about $s=2.8\times10^{-20}cm^2$ was obtained. This is the best result among the oxide laser crystals.
   e) Ti:b-$Ga_2O_3$ single crystal for solar cell and liquid crystal display application was developed and carrier concentration and mobility of this crystal was characterized quantitatively.
   f) 1-inch size ZnO single crystals, which are candidate material for blue light emitter and GaN epitaxial wafer, were grown by the hydrothermal method.
   g) Succeeded to grow SiGe bulk crystal with uniform composition and multicrystalline SiGe with large compositional distribution for new solar cell applications by directly controlling the growth temperature at the crystal-melt interface using in-situ monitoring system.
6. Control of thermal convection, spiral growth problem andheat transportation
   a) Relation between rotation rate and behavior of melt was investigated when during the growth of LiCAF crystal with Cz Method.
   b) Band calculation of $ABF_3$-type fluoride perovskite materials was carried out and it revealed imaginary materials $LiBeF_3$, $NaBeF_3$, $KBeF_3$, $RbMgF_3$ and $SrLiF_3$ must have wide band gap.

# Integrated Network Architecture for Advanced Multimedia Application Systems

**Project Leader**
Hideo MIYAHARA Professor, Graduate School of Engineering Science, Osaka University

**Summary of Research Project Result**

The main objective of the project is to build an integrated network architecture for realizing advanced multimedia application systems. Several networking technologies - Internet, ATM (Asynchronous Transfer Mode), and xDSL (Digital Subscriber Line) - are integrated to support various multimedia applications requiring different types of QoS(Quality of Services).

○1997 BULDING TEST-BED

A test-bed for experimentation of existing networking technologies has been developed at Osaka University, Japan. This test-bed combines various networking technologies including Internet, ATM, xDSL, and CATV.

○1998 APPLICATION PROTOTYES

Several Prototypes of advanced multimedia applications have been developed on the test-bed. Requirements of those application prototypes on future networking technologies have been clarified.

○1999 NETWORK ARCHITECTURE

An integrated network architecture has been designed and proposed. Protocols in three layers (i.e., link, network, and transport layers) have also been designed.

○2000 IMPLEMENTATION AND EVALUATION

We are currently working on implementing proposed protocols. After finishing implementation, performance evaluation of the proposed protocols will be performed. We also plan to participate in standardization activities.

○2001 FINAL INTEGRATION

The proposed protocols in three layers will be integrated. Effectiveness of our network architecture will be demonstrated using several advanced multimedia applications.

# Index to the Project Leaders