Science Transcending Boundaries
- Answer from WPI -

World Premier International Research Center Initiative (WPI)

1. Top-quality science
2. Interdisciplinarity
3. Globalization
4. Reform of research system
Transcending Borders and Barriers

Four Missions of WPI Program

1 Science (Implementing the world’s highest level of research)

- Nearly 50% of published papers stem from international joint research, evidencing the position of WPI centers within international research networks.
- Two principal investigators at WPI centers have won Nobel Prizes. WPI researchers have also received prestigious international awards such as the “Canada Gairdner International Award” and top domestic awards such as Japan’s “Order of Culture.”
- WPI centers receive large donations and investments from foundations, corporations, and other private entities made in recognition of their excellent research capability despite being focused on basic research.

2 Interdisciplinary (Generating fused research domains)

- A “flat” organization with no partitioning between research fields and an open building architecture with no walls between labs spawn intellectual inspiration and a collaborative atmosphere of friendly rivalry among researchers.
- A cascade of fused research achievements is being generated. Examples include an elucidation of the structure of glass by fusing mathematics and materials science and the discovery of a method for combating the parasitic plant fungus made by fusing animal/plant biology and synthetic chemistry.

3 Globalization (Creating international research environments)

- English is the working language in WPI centers. Overseas researchers make up approximately 40% of the centers’ researcher staff.
- In addition to their top-world research levels, international recruitment and enhanced support attract overseas postdoctoral researchers to WPI centers. An increasing number of overseas postdocs are applying for posts at the centers.
- Many of the postdocs at WPI centers have gone on to acquire their next positions in Japanese and overseas organizations. WPI contributes to advancing global researcher mobility.

4 Reform (Innovating research organizations)

- WPI centers act as the nucleus for system innovation within their host universities and research institutions. The reforms they achieve are shared and applied to their host institutions, elevating system-wide internationalization and strengthening research capabilities. Some spinoffs of center reforms include:
  - Top-down management
  - A cross-appointment system
  - Providing an environment in which researchers can work comfortably
Transcending Disciplines through WPI Program

Fostering “globally visible research centers” that function as hubs for the international circulation of gifted researchers, the WPI Program creates new scientific domains by synergistically fusing diverse fields of research. Each of the thirteen WPI research centers employs a top-down strategy for creatively advancing interdisciplinary research while spawning bottom-up initiatives for cultivating revolutionary ideas. The substantial results achieved by their programs are described on the following pages.

AIMR:
- Creating new material sciences using mathematics ................................................. 6

Kavli IPMU:
- Cross-disciplinary research exploring the origin and evolution of the universe .......... 7

iCeMS:
- Creating a new field of “integrated cell-material science” ........................................ 8

IFReC:
- Advancing immunology and medical sciences by synergizing immunology,
  bio-imaging and bioinformatics .................................................................................. 9

MANA:
- Creating the new field of “Nanoarchitectonics,” innovative paradigms
  pioneered in materials development ........................................................................... 10

iCNER:
- Linking scientific disciplines, policy-making and educational outreach
  in a leap toward carbon-neutral society ..................................................................... 11

IIS:
- Probing the mechanisms of sleep and solving its mysteries ...................................... 12

ELSI:
- Globally-advanced interdisciplinary research elucidating the origins
  of the Earth and life ........................................................................................................ 13

ITbM:
- Changing the world with “transformative bio-molecules”
  —converging chemistry, biology and theory ................................................................ 14

IRCN:
- Tackling the ultimate question: “How did human intelligence emerge?” ................. 15

NanoELSI:
- “Nanoprobe life science”—applying nanoimaging to expanding
  life science frontiers ....................................................................................................... 16

ICReDD:
- Pursuing an in-depth understanding and innovative development
  of chemical reactions ................................................................................................. 17

ASHBi:
- Discovering how key biological traits that make us “human” can lead
to cures for diseases ...................................................................................................... 18
Mathematical analysis predicts morphology of diblock copolymers

Keywords: diblock copolymer, micro-phase, morphologic prediction, Cahn-Hilliard equations

Now, we have used a set of coupled equations to numerically explore the morphologies and phases of diblock copolymers confined within spheres. This model, which shows the relationship between the free energies and morphologies of diblock copolymers confined in small particles, has great predictive power and consistency with experimental results (see figure). This ability to modify the shapes, and hence the properties, of diblock polymers is generating much interest because it holds promise for making tiny chemical reactors and nanoparticles for drug delivery, among other possible applications.

(Yabu et al. Soft Matter, 2016)

Topological data analysis uncovers hierarchical order in amorphous materials

Keywords: glass, topological data analysis, persistent homology, hierarchical structure

We proposed an new framework based on topological data analysis that extracts hierarchical structures of various amorphous solids. The key methods are **persistent homology** and **persistence diagram**, which extract topological features of rings and cavities embedded in atomic configurations. The methods are universal enough to be applied into various disordered systems such as silica glass, the Lennard-Jones system and Cu-Zr metallic glass. The methods highlight hierarchical structures that conventional techniques could not have detected appropriately.

(Hiraoka et al. Proceedings of the National Academy of Sciences, 2016)
Kyoto University iCeMS (eye-semz) seeks to illuminate the chemical basis of cells; to create chemical compounds controlling cellular processes and functional materials inspired by cellular processes; and to ultimately contribute to the fields of industry, medicine, and drug discovery.

Biochemical approach opens a new era for patient-centered cancer treatment

**Keywords:** chemicalbiology #ovariantumor #nanoparticle #cancertherapy

**The chicken egg cancer model**

Fuyu Tamanoi of iCeMS succeeded in establishing a versatile, powerful and convenient model to analyze human cancer. They transplanted ovarian cancer cells on top of the membrane that surrounds a 10-day-old chicken embryo, and an ovarian tumor formed within three days of transplantation, maintaining the characteristics of the patient's tumor.

**New nanoparticles to carry anti-cancer**

The team also developed a new type of biodegradable silica nanoparticle called "B-PO." B-PO carrying anti-cancer "doxorubicin" quickly eliminated the human ovarian tumors without affecting other organs in the chicken embryo. This outcome makes a major step toward individualized medicine for cancer patients.

Cutting-edge MRI analysis identified a new type of macrophage

**Keywords:** fibrosis, macrophage, MRI

"Pulmonary fibrosis is one of a family of related diseases called interstitial lung diseases. Most cases of pulmonary fibrosis have no known cause."

(American Lung Association)

Shizuo Akira group identified a new type of macrophage, Segregated nucleus Atypical Monocytes (SatM). SatM have a bi-lobed segmented nuclear shape, and are 'disorder-specific monocyte/macrophage subtypes' corresponding to fibrosis. It may also now be possible to develop novel, more specific therapeutic targets for this intractable disease in the future.

(Satoh et al. Nature 2017)

High-throughput structural modeling and analysis for immune cell sequences

**Keywords:** antibody, structure, prediction

Kazuo Yamashita and his colleagues won the first prize at the "World Completion of Structure Prediction for Antibody". They established KOTAI Biotechnologies, Inc.® in 2017. Their platform technology, which uses artificial intelligence is expected to reveal the structure and function of immune cell receptors with unprecedented resolution from a routine blood sample.

(NUCL: https://www.kotai-bio.com/")

Interdisciplinary Research at IFReC

IFReC aims to determine the dynamism of individual immune cells while furthering our understanding of immunity as a live response occurring in the body as a whole. For the purpose, IFReC has been advancing interdisciplinary research with a team of excellent researchers combining immunology, bioimaging and bioinformatics.

Immunology Frontier Research Center (WPI-IFReC)

Osaka University

**Immunology**

**Bioinformatics**

**Imaging**

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Pioneering a New Paradigm in Materials Development on the Basis of Nanoarchitectonics

Nanotechnology has made astonishing progress and become a modern pillar of materials discovery and development. WPI-MANA is pursuing innovation on the basis of our concept of "nanoarchitectonics," where new materials and functions are created by rationally integrating and joining nanoscale parts.

Ionic Device for Reward Maximization by Materials Scientists and Theorists

Keywords: Ionic Decision-Maker, Multi-armed Bandit Problems, Solid State Ionics

A lot of attention is being paid to Multi-armed Bandit Problems (MBPs); mathematical problems in which a gambler given a choice of slot machines must select the appropriate machine to play so as to maximize the total reward. Such attention is due to the fact that efficient solutions of MBPs can be applied to many decision-making scenarios; deciding the best advertisements to send to customers, finding the most efficient network routing path, and so on.

At WPI-MANA, material scientists and theorists have worked together to create a device to solve MBPs. Inside the device, ionic/molecular concentrations are sequentially modulated by the results of previous trials, which direct the device to the most efficient choice for reward maximization with minimum investment, even in a dynamically changing environment.

The ionic decision-maker forms the basis of a new “material-based intelligence” research field. (T. Tsuchiya et al., Science Advances, 4, 2018)

Material Science & Computer Science Collaboration Work Opens The Way to Mobile Olfaction with Nanomechanical Sensors

Keywords: Membrane-type Surface stress Sensor (MSS), Big Data Analysis, Mobile Olfaction

The MSS is a versatile, small and sensitive sensor element capable of measuring diverse molecules in the atmosphere and in liquids. The MSS can achieve high sensitivity with a compact system thanks to the comprehensive structural optimization with electric read-out based on piezoresistors. Its sensitivity is more than 100 times higher than that of conventional piezoresistive nanomechanical sensors, even surpassing that of optical read-out.

Big data analysis allowed researchers handle the detected data in detail and it was the last piece to realize “mobile olfaction” device. The MSS will be utilized in various fields such as foods, cosmetics, medicine, the environment and safety, anytime, anywhere and for anybody. (G. Yoshikawa et al., Nano Lett. 11[3] 2011)

Membrane Thinning for Efficient CO2 Capture

Keywords: Carbon-Neutral, Gas Separation, Nanomaterials

Carbon dioxide separation by membranes is considered as a promising option for carbon capture. Membrane thinning is one of the most promising approaches to achieve high fluxes. In this review, Prof. Fujikawa and his team summarize the state of the art membrane thinning for CO2 (gas) separation membranes, especially from the viewpoint of thinning the selective layers and the membrane itself.

. (Roman et al. Science and technologies of advanced materials, 2017)

Effect of Surface Coverage and Composition on the Stability and Interfacial Dipole of Functionalized Silicon

Keywords: Energy/Fuel (non-petroleum), Materials, Theoretical Chemistry

Photoelectrochemical (PEC) cells are used to convert the solar power incident on Earth into electricity and/or chemical fuels. In this work, Dr. Kara Kearney and her team describe a method for using density functional theory calculations to predict the stability and band-edge positions of an arbitrary molecule. The outcome of this work is to increase power conversion efficiencies so that PEC cells are a viable technology for the production of carbon neutral energy.

**“Sleep Science” integrating three fields**
Sleep is one of the biggest black boxes of today’s neuroscience. IIIS aims to uncover the mysteries of sleep and to solve sleep-related social problems.
To accomplish our mission, IIIS has established the highly ambitious and novel research field “sleep science” by integrating neuroscience, experimental medicine, and pharmaceutical science.

**A new therapeutic avenue for treating insomnia**
*Keywords: drug discovery, adenosine, insomnia*

Lazarus and Nagase groups at IIIS identified the first allosteric modulator of adenosine A₂₅ receptors, denoted as A₂₅R PAM-1, and demonstrated that it induces slow-wave sleep in mice. Unlike adenosine A₂₅ receptor agonists, there was no side-effect on cardiovascular functions. This type of compounds may be an alternative strategy for treating insomnia, overcoming problems of existing sleeping pills such as drug tolerance and dependence.

*(Korkutata et al. Neuropharmacology. 2018)*

**Join in our interdisciplinary research! -The Ph.D. Program in Humanics**

This program cultivates leaders with doctoral-level knowledge and skills in the fields of biomedical sciences and physical sciences/engineering/informatics. Candidates are expected to integrate different research fields and apply new scientific discoveries on key aspects of human society. IIIS welcomes students who are willing to explore new frontiers of sleep science in this program!

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**Earth-Life Science Institute (ELSI)**
Tokyo Institute of Technology

**Interdisciplinary approach of ELSI**
ELSI’s aim is to answer the fundamental question that has long captured humanity’s imagination: when and where did life originate, and how did it evolve? Until recently, discussions about the origin and evolution of life have mainly been limited to the biochemistry of proto-life forms. We at ELSI will focus the discussion primarily on the relationship between Earth and Life. Life is a phenomenon that is sustained through the exchange of energies and matters with the surrounding environment, thus the origin of life question cannot be separated from the study of the origin and evolution of the Earth.

…and Life in the Universe

By elucidating the origins of life in the context of the Earth, we will learn about both the unique and universal aspects of our planet that allowed life to emerge and evolve. Our research will therefore shed light upon the possibility and characteristics of life elsewhere.

**Recent Research: Chemical Diversity of Metal Sulfide Minerals and its Implications for the Origin of Life**

The origin of life on Earth is generally envisioned as having started from abiotic syntheses of basic building blocks requisite for metabolism and replication. Metal sulfides have been proposed as key players in these prebiotic processes.

ELSI researchers studied the chemical diversity of mineral catalysts by the technique of data-mining, and discussed the approaches to rationally predict the catalytic functions of metal sulfides. They propose a model of geoelectrochemistry-driven prebiotic synthesis for chemical evolution based on this study. Their technique developed here will aid in the rational screening of mineral catalysts involved in the origin of life.

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The model of chemical evolution for the origin of life in deep sea hydrothermal vent environment, using metal sulfide minerals as the catalysts. For catalyzing carbon and nitrogen conversion reactions efficiently and selectively, the metal sulfide catalysts should be comprehensively screened.

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**Follow ELSI on Twitter: @ELSI_origins**

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Molecules to combat parasitic plant Striga spreading over Africa

*Keywords: synthetic chemistry, plant biology, Striga*

Striga is a parasitic plant that causes drastic damage to agriculture in Africa. ITbM’s chemists and plants biologists have worked together, and have rapidly developed a molecule "Yoshimulactone green (YLG)", which exhibits green fluorescence upon binding to the receptor associated to the germination process of Striga. This achievement resulted in the identification of the unrevealed SL receptor of Striga, and led to the development of the exceptionally active biomolecule sphynolactone-7 (SPL7). The SPL7 acts as an agonist for the SL receptor of Striga to induce germination and led it to suicide in a femtomolar \((10^{-15})\) range. ITbM’s research team is planning to extend the discovery to the field trial of SPL7 in Kenya (Tsuchiya et al. Science, 2018)

At Last: Beautiful, consistent carbon belts

*Keywords: carbon nanobelt, synthetic chemistry*

Chemists have tried to synthesize carbon nanobelts for more than 60 years, but none have succeeded. Our team reported the first organic synthesis of a carbon nanobelt. Carbon nanobelts are expected to serve as a useful template for building carbon nanotubes and open a new field of carbon nanotubes (Itami et al. Science, 2017)

**Institute of Transformative Bio-Molecules (WPI-ITbM)**
Nagoya University

“**Ambitious, full-scale collaboration of Chemistry and Biology**”

ITbM aims to develop molecules that change the way we live, i.e. “transformative biomolecules”. To achieve this goal, ITbM has been promoting a full-scale collaboration of chemists and plant/animal biologists via set-up of “Mix Labs”, where chemists and biologists are working side by side. The Mix Labs have largely promoted their interactive discussion on a daily basis, and various unique research outcomes have been achieved.

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**International Research Center for Neurointelligence (WPI-IRCN), The University of Tokyo**

Tackling the ultimate question

"**How does human intelligence arise?** — We transcend boundaries"

**Our Global Network**

**Our Interdisciplinary Research**

Establishing a new discipline

CUBIC-X: a new method to implement single-cell based whole-brain imaging

*Keywords: 3D mouse brain atlas, tissue clearing, single-cell mapping*

The brain is a complex object like the universe comprising intricate networks with a tremendous amount of neuronal cells. To understand this structural complexity and its functions, brain atlases that can show fine-scale structures and connections of cellular circuits are a requisite tool for neuroscientists. Recently, Ueda and his team developed a fluorescent-protein-compatible, intensive tissue-clearing method combined with a tissue expansion protocol, CUBIC-X, which enables seamless imaging of the whole mouse brain. They succeeded in improving the transparency of brain tissue and constructed a point-based mouse brain atlas with single cell annotation (CUBIC-Atlas). Using this 3-D whole-brain atlas, future studies can add activity/gene expression mapping and explore undefined anatomical areas. The editable CUBIC-Atlas is available to the research community and public (http://cubicatlas.rikens.jp) as a single-cell-resolution platform for unbiased systems-level analysis of mammalian brain.


Whole-brain imaging of a CUBIC-X expanded Thy1-YFP-H mouse brain with customized light-sheet fluorescence microscopy

A reconstructed whole brain image based on the acquisition of image data comprising more than 1 million sheets (Whole brain field), Partly-reconstructed brain image data (Magnified View1), Reconstructed image data focusing on neurons (Magnified View2), Reconstructed image data focusing synaptic structure (Magnified View3)

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NanolSI promotes transdisciplinary research by applying *nano imaging to life science*. We will establish a new field of study called Nanoprobe Life Science, which integrates the studies of nanometry, life science, supramolecular chemistry, and computational science.

**Visualization ‘molecular scissors’ of the CRISPR-Cas9 genetic-engineering technique**  
*Keywords: genetic engineering, atomic force microscopy, CRISPR-Cas9*

In genetic engineering the CRISPR-Cas9 nuclease system is used to cut DNA at the desired site to enable addition or deletion of genes. Now, in groundbreaking research, a team led by Mikihiro Shibata from NanolSI has visualized the dynamics of the CRISPR-Cas9 complex, in particular how it cuts DNA, providing valuable insights into the CRISPR-Cas9-mediated DNA cleavage mechanism. The high-speed movies from this research “provides unprecedented details about the functional dynamics of CRISPR-Cas9,” says Shibata. (M. Shibata et al., *Nature Comm.* November 2017)

**Picture from 2nd NanolSI symposium.**  
53 people including general participants (23 from overseas and 5 from Japan) attended in the symposium.

The 2nd NanolSI symposium was held on Nov. 19, 2018, in London where our satellite center is located. Researchers from NanolSI introduced their current research. Invited researchers from around the UK gave lectures on nanometry and other related fields. These lectures and a poster exhibition helped to establish connections for future collaborative research crossing disciplines and regions.  

The 3rd NanolSI symposium will be held on Aug. 8, 2019, at the University of British Columbia in Vancouver, Canada.

**Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University**

**Promoting Transdisciplinary Research**

In-depth understanding and efficient development of chemical reactions through the interdisciplinary research of computational science, information science, and Chemistry.

**Keywords: Computational Science, Information Science, Chemistry**

**To realize high-level design and rapid development of chemical reactions**

The current trial-and-error approach to the development of new chemical reactions is time-consuming and inefficient. The ICReDD uses state-of-the-art reaction path search methods based on quantum chemical calculations* and applies concepts of information science in order to extract meaningful information for experiments, thus narrowing down optimal experimental conditions. This approach enables “pinpointing” promising experiments.

In addition, data obtained by the experimental scientists is circulated back to the computational scientists to realize high-level design and rapid development of chemical reactions. We hope to establish the new academic field “CreDD” which will allow efficiently developing advanced chemical reactions and materials. The integrated research on CreDD should lead to the development of highly efficient chemical reactions that should afford high-value-added chemicals with applications in agro- and environmental chemistry, pharmaceutical and materials science, medical technology, as well as energy and resource management. The target reactions and molecules are carefully selected based on the impact to the society through discussion among broad research communities and with many companies.


**The establishment of the CreDD, and the collaborations at MANABIYA**

To establish the new academic field “CreDD” that integrates computational, information and experimental sciences in order to accelerate the efficiency of the development of new chemical reactions which is indispensable for a prosperous and sustainable future of humanity.

**MANABIYA system:** Young researchers and students from domestic and overseas collaboration institutes stay at the ICReDD for about three months, master the new reaction development method through collaborative research, and each researcher will utilize it in the future. After 10 years, the MANABIYA network will comprise several hundreds researchers, which will support the further development of this new field.
The Institute’s objective is to address what it is to be human as a biological entity. To this end, we will proactively promote interdisciplinary studies between biology, mathematics and bioethics, and adopt the latest technique based on genome editing in nonhuman primate.

Biology & Mathematics
Keywords: Topological Data Analysis, Dynamical System, Machine Learning

We will promote interdisciplinary research between biology and mathematics, such as topological data analysis, dynamical system and machine learning. By applying these advanced mathematics to multi-species/multi-cell type/multi-hierarchical omics information, the Institute will define the principles of the emergence of species differences in phenotypes of homologous cells among humans, non-human primates, and rodents, allowing better extrapolation of the knowledge from model organisms to humans as well as providing insights into the principles for the creation of organismal diversity through evolution.

Biology & Bioethics
Keywords: Philosophy, Survey, Outreach, Policy

Appropriate use of experimental subjects (human and non-human primate materials) and research outcomes (e.g., artificial gametes, artificial cerebral cortices, and genome-edited monkeys) will be key issues. Dealing with these issues, we try to create a world-standard bioethics through the following efforts: 1) theory-driven study (discussing key philosophy issues including the creation of artificial human embryos, human embryo cultures beyond 14 days, etc.), 2) empirical study (conducting surveys to investigate the perceptions of scientists and the general public regarding such key issues), 3) outreach activities (holding public symposia to create opportunities for more open and public discussions), and 4) policy proposals (publishing papers asserting the Institute’s position on these issues in order to spur the generation of new regulations).

Genome Editing in Nonhuman Primate
Keywords: Frontal Lobe functions, Hand Dexterity, Basal Ganglia Disorder, Macaque Model, Genome Editing

We will study the genetic and neural mechanisms underlying higher cognitive function and highly skilled motor control which have specifically developed in primates: (1) frontal lobe functions such as working memory and self-monitoring, (2) those underlying the basal ganglia disorders, and (3) motor systems controlling dexterous hand functions. For this purpose, we will generate the genome-edited macaque monkeys of the key genes in collaboration with the Primate Genome Engineering Core in Shiga University of Medical Science.