

## FEATURE

Associate Professor

**Izumi Iwakura**

Laser Chemistry and  
Physical Organic Chemistry

Professor

**Tadashi Sugawara**

Physical Organic Chemistry

Professor

**Kinya Hibino**

High-energy cosmic ray  
research on the Tibetan  
Plateau

Distinguished Professor

**Daisuke Uemura**

Compound Hunter

Assistant Professor

**Sachi Yamaguchi**

Mathematical Biology

Professor

**Nobuhiro Kihara**

Organic Chemistry,  
Bioorganic Chemistry

Professor

**Susumu Izumi**

Molecular biology,  
Insect physiology and  
biochemistry

## ESSAY : SCIENCE INSIGHTS

Professor Emeritus

**Wasuke Mori**

Magnetic chemistry,  
Functional materials  
chemistry,  
Complex chemistry

KANAGAWA UNIVERSITY

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Professor Emeritus

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Magnetic chemistry,  
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## PROUD BLUE ISSUE:

Kanagawa University published “PROUD BLUE” in Japanese as a public relations magazine focused on our research and researchers. The title is associated with the school color, and the first issue was published in February, 2015 and the third issue in February, 2016. This English version was based on the above Japanese versions of the first and third issues.

## FEATURE

# Unobservable bond *breaking* and bond *reforming* steps during chemical reactions

$2\text{H}_2 + \text{O}_2 \rightarrow 2\text{H}_2\text{O}$ : This is one of the most well-known chemical reactions in science textbooks. Indeed, even if you are not a scientist, you have most likely seen this chemical reaction at some point. It describes the oxidation of hydrogen, where hydrogen reacts in the presence of oxygen to produce water.

The arrow symbol in this familiar chemical reaction indicates an unknown reaction mechanism, as it has so far been impossible to determine when and how the bond *breaking* between the hydrogen atoms and oxygen atoms, and the bond *formation* between the hydrogen and oxygen atoms occur during the reaction. Dr. Izumi Iwakura is a chemist who explores such unobserved reaction mechanisms using ultrashort pulse lasers.

## A five-femtosecond strobe that reveals the reaction process

In the last 100 years, many hypotheses have attempted to explain the unobserved reaction mechanism of the Claisen Rearrangement, a reaction originally reported by the German scientist, Rainer Ludwig Claisen in 1912. During the Claisen rearrangement of allyl vinyl ether ( $\text{CH}_2\text{CHCH}_2\text{OCHCH}_2$ ), the carbon-oxygen bond is broken upon heating, and a new carbon-carbon bond is formed. Three hypotheses exist to explain the unobserved reaction mechanism, and the transition state of the reaction: i) The C-O bond is broken first and then the C-C bond is formed; ii) C-C bond formation occurs first; and iii) Bond breaking and bond formation occur simultaneously. Although one can speculate, it was considered impossible to actually observe the transition state and the structural changes taking place in this transformation. Indeed, these steps are exactly what Iwakura is attempting to visualize, which leads to the question, how exactly can she visualize this? The actual visualization of chemical reaction processes began with the pump-probe measurement study in 1949. The time resolution of this study was limited by a flash pulse duration of microseconds ( $10^{-6}\text{s}$ ), while in the last 50 years, the visualization of chemical reaction processes has now approached the femtosecond ( $10^{-15}\text{s}$ ) scale.

Using a high-speed imaging camera, workers have visualized the "milk crown," i.e., the crown-shaped structure formed when a drop of milk impacts on a thin layer of milk or any other liquid. They wondered if a chemical reaction process could be visualized using a strobe, just as a high-speed imaging camera can capture an instant snapshot that cannot be observed by

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the naked eye. Thus, a strobe with a short flash time is required to visualize the bond breaking and bond reforming steps during a chemical reaction. More specifically, the required flash time of the strobe would be shorter than the duration of molecular vibrations. This led to Iwakura developing the five-femtosecond pulse laser for such a purpose.

### **The third type of chemical reaction that creates an observable condition**

In 2002, Takayoshi Kobayashi (a specially appointed professor by The University of Electro-Communications), with whom Iwakura had a fateful encounter later on, developed a visible-five-femtosecond pulse laser that allowed for the real-time spectroscopy of molecular vibrations. Kobayashi conducted a study to visualize the bond breaking and bond reforming steps during a photoreaction. This was followed by Iwakura's attempt to apply it to visualize

these steps during a thermal reaction. Chemical reactions can be generally divided into two main groups, namely thermal reactions and photoreactions. A thermal reaction is triggered when the molecular vibrations are excited by heat, while a photoreaction is triggered when the electrons are excited by light. Indeed, thermal reactions will likely be familiar to many. In terms of photoreactions, perhaps one of the most well-known of these is damage to DNA caused by ultraviolet irradiation, which can result in the formation of skin cancers. One of the main reasons for difficulties in visualizing the movement of atoms in molecules is disorganized molecular vibration. The movement of atoms in a disorganized manner is like a large party where everyone is talking at once, and it is difficult to hear anyone in particular. Eventually, the noise takes over and the situation cannot be understood. Thus, to control the situation, Iwakura successfully developed a novel type of reaction, called

### **Izumi Iwakura**

Izumi Iwakura graduated from the Department of Chemistry, Faculty of Science and Technology, Keio University in March 2001 and completed her doctoral studies (science) in the same institution in September 2005. Following positions such as the Japan Society for the Promotion of Science Research Fellowship and PRESTO, and the Japan Science and Technology Agency full-time researcher, she joined the Department of Material & Life Chemistry, Faculty of Engineering, Kanagawa University in 2012. She later became an associate professor in the Department of Chemistry at the same faculty in 2014.



as reactions induced by coherent molecular vibration (RCMV). This third type of chemical reaction excites the molecular vibration instantly using a five-femtosecond pulse laser.

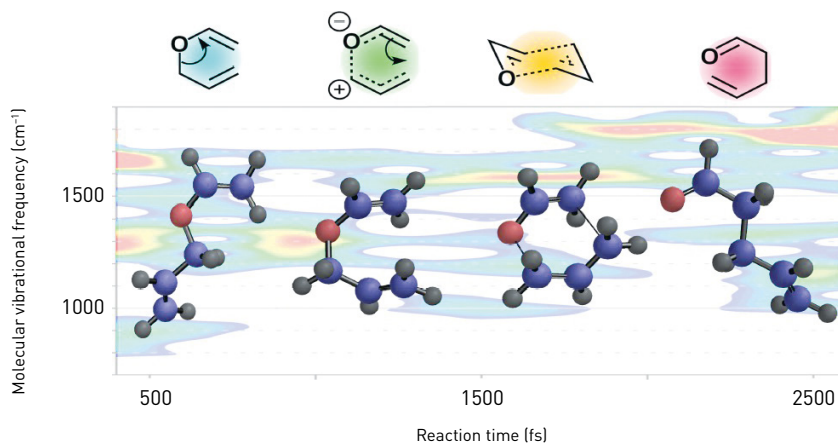
In a typical thermal reaction, molecules move in a disorganized manner. However, in the RCMV triggered by irradiation using a five-femtosecond pulse laser, all molecules vibrate in unison to trigger the thermal reaction. Upon irradiating with a flash time of five femtoseconds, which is shorter than the molecular vibrational period, the atomic positions are measured as if in strobe light photographs, and the changes in molecular structure (i.e. when and how bond breaking and bond reforming occur) during a reaction can be visualized as instantaneous molecular vibrational frequencies.

This was the moment when Iwakura finally visualized this key transformation that had been shrouded in mystery for over 100 years.

## From observing molecules to creating molecules

Iwakura's obsession with chemical reaction mechanisms began in the synthetic organic chemistry laboratory where she spent her undergraduate to graduate school years. Iwakura notes that while shaking flasks, she was always thinking about chemical reaction mechanisms, "I preferred thinking about the reaction mechanisms in a simulation using theoretical calculations more than synthesis. I am really not good at organic synthesis. I thought if I understood the reaction mechanisms and the best conditions about catalysts or solvents through theoretical calculations, even I could synthesize. That's what I was thinking back then." Indeed, a large portion of Iwakura's doctoral program focused on this idea. Traditionally, theoretical calculations were employed after questioning what was taking place during the reaction. In contrast, she employed theoretical

## Transition state spectroscopy of the Claisen Rearrangement



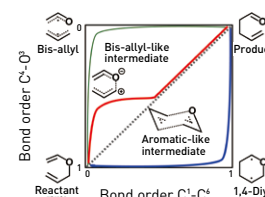
Changes in molecular vibration accompanying the thermal Claisen Rearrangement were visualized using a five-femtosecond pulse laser. The resulting spectrum indicated when and how bond breaking and bond reforming occurred.

calculations to simulate reaction mechanisms, and based on the results, she developed the novel reaction. This led to Iwakura's desire to observe actual chemical reaction processes. During her studies, she met Takayoshi Kobayashi, who was teaching at the University of Tokyo, and learned that she could indeed visualize actual chemical reaction processes. As such, she began to study the real-time spectroscopy of molecular vibrations, including the transition states of photoreactions. Indeed, the real-time spectroscopy developed by Kobayashi is now being applied to the RCMV that Iwakura developed later on. While Kobayashi developed spectroscopy for photoreactions, Iwakura developed spectroscopy for thermal reactions using the RCMV.

Regarding the RCMV, she said, "the RCMV takes place when all molecules are in synch. I am wondering if I could develop a new synthetic reaction utilizing that."

After observing the previously unseen reaction mechanism, she now wishes to create something that no one else has ever succeeded in doing. Of course, her challenges are always novel.

## Step-wise reaction mechanism of the thermal Claisen Rearrangement



The C-O bond begins to break, and after going through a stable aromatic-like six-membered intermediate, the C-C bond is formed. This three-step reaction mechanism was found to be different from traditional hypotheses.

## SIDE STORIES

### Interest motivates researchers

"If you succeed, you are a genius. If you fail, you are an idiot." That is a common predicament for researchers who aim to take on new challenges. According to Iwakura, the driving forces that carry researchers forward are curiosity and interest. Indeed, these have been the driving forces of her research since her school days, and explains why Iwakura encourages students to "enjoy research."

### The interaction of electrons is similar to soccer



Iwakura loves to watch soccer games. But she does not care about winning or losing. She says, "it is fun to watch how they pass a ball and score a goal," which is similar to electron transfer. In a chemical reaction, where and how to pass the electron (ball) determines the direction of the reaction (i.e., whether a goal is scored or not).



## FEATURE

# One more theory bringing us closer to the mystery of the origin of life

## The rich behavior of the “membrane”, clarified through “artificial cells”

The origin of life is still surrounded by mystery. It is still conjecture, but the currently accepted theory is that primitive life originated around 3.7 to 4 billion years ago.

Biologists are debating whether life “started with RNA” (RNA hypothesis), or “started with protein” (protein hypothesis). The chemist Tadashi Sugawara is responding to the challenge of the mystery of life. The clue he is looking at is the thin “membrane” that separates an individual life from the outside world.

### Human attempts to create artificial cells

The origin of life is still surrounded by mystery. The mainstream view is currently that the reductive approach used since Descartes is no longer adequate to solve the mystery of life; instead, a constructive approach is effective to understand how to fabricate systems while focusing on interactions between elements. In this context, in 2001, two celebrated American professors of genetics, Szostak, Bartell, and Luigi in Switzerland, a pioneer in chemical evolution, proposed an idea of a minimum cell endowed with three indispensable elements for life.

Sugawara explains that at this time, professors Szostak, Bartell, and Luigi listed three elements fundamental to cells. “The first is a ‘boundary’ to separate the inside from the outside, which is essentially the cell membrane. The second is ‘information’, which characterizes the individuality of the cell, namely the genes. The third is a ‘catalyst’ required for cellular biological activity and reproduction. If a substance prepared with these elements was created artificially and if replication of the ‘information’ and production of the ‘boundary’ (the dynamics of cell division) were generated, then could that not be called life? This was the assertion made by Szostak, Bartell, and Luigi. Around the same time I also started research on artificial cells based on almost the same idea, so I felt exactly the same way.”

### The “membrane” was the start

Professor Luigi was already interested in the self-production mechanism of the cell membrane, which is the ‘boundary’ separating the inside and the outside of the cell, and had pioneered research in this field.

The cell membrane structure is made up of two layers of phospholipids (see figure on the following page). A phospholipid is an ‘amphiphilic’ substance that dissolves in both water and oil. If phospholipids are dispersed in water, hydrophobic parts move away from water, while hydrophilic parts face to water when they get together.

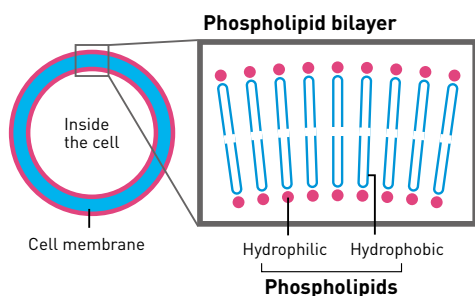
Hydrophobic parts subsequently assemble together with other hydrophobic parts, while hydrophilic parts assemble together with other hydrophilic parts, forming a spherical membrane. At this point the membrane has become a ‘boundary’ that separates the inside, filled with water, from the outside. The pouch formed by the membrane is known as a ‘vesicle’ in scientific terms.

“Professor Luigi reported that he observed a

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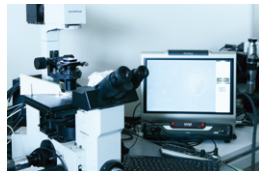
Physical Organic Chemistry



The phospholipid bilayer that forms the cell membrane. Hydrophilic parts that can dissolve in water face the outside of the membrane, while hydrophobic parts, which cannot dissolve in water, are lined up on the inside of the membrane.



The laboratories that are producing artificial cells are not biological laboratories, but organic chemistry laboratories. Several types of laboratory equipment in organic chemistry laboratories are not often seen in biology laboratories.



Optical microscope, which captures the appearance of dividing artificial cells. It is possible to check the appearance of vesicles on the monitor while filming a video of the process. Quite a number of videos have been taken as an evidence for the creation of artificial cells.

division phenomenon similar to that of cells with vesicles made from oleic acid. My colleagues and I created artificial membrane molecules and attempted an experiment to create a vesicle reproduction system. We inserted hydrophobic materials for membrane molecules inside the vesicle and added hydrophilic materials from the outside. Hydrophobic and hydrophilic parts inside the vesicle bound together to form membrane molecules, and we successfully created a system where the vesicle could reproduce itself. Under a microscope we also observed pouches emerging from the original ones, like in cell division."

However, there was an issue with the method used at that time. Once the vesicle had reproduced a number of times, and the material inside the vesicle ran out, division stopped. However, Sugawara made fine improvements and developed a method that enabled repeated divisions. That was in 2004.

### Creation of the "artificial cell" – wowing the world

Sugawara was excited by this outcome, thinking that he could be dealing with a primitive form of living organism. However, biologists who saw the video made comments like "yes, that's very interesting, but it would be much more cell-like if it contained informational molecules".

Sugawara heard these opinions, consulted his fellow researchers and designed a subsequent

research strategy.

Five years later, Sugawara and his colleagues established a method that enabled DNA replication and amplification inside the vesicle. It was a method in which heat is added and the 'PCR method' is applied to obtain DNA replication and amplification. The 'PCR method' itself had been established as a biological experimental method, but this was the first example in which DNA was synthesized inside a vesicle large enough to be seen with an optical microscope.

As they adjusted conditions repeatedly, refining the method, they discovered a compelling fact. "How was DNA amplification linked with vesicle division? This was a major issue, but we discovered that amplified DNA moves into the inner side of the vesicle membrane and serves a role similar to an enzyme to promote division."

Inside the cells of living organisms, proteins, synthesized from DNA-derived information, play a variety of roles, and DNA amplification is synchronized with cell division. However, Sugawara claims, "it is difficult to imagine that primitive life had such complex reaction systems." "Even without the complex system mediated by proteins, DNA replication occurs in concert with membrane molecule reproduction reactions and morphological changes, and vesicles divide with even DNA distribution. These findings represent a clue to discover the shape of primitive life."

The results of Sugawara's research were published in September 2011 in *"Nature Chemistry"* and garnered significant attention from around the globe.

### Passed down from mother to daughter, and from daughter to granddaughter

The "artificial cell" at this time still had issues. The DNA material in the vesicle after division was depleted and the second division did not

## SIDE STORIES

### We will become the world's molecular novelists



Sugawara was taken by his grandparents to see Kabuki when he was about four years old. He always wanted to create a link between his research and Kabuki, and recently achieved this goal. He created a scenario casting roles for molecules and prepared a stage. Then, unexpectedly, supporting characters began to play an important role. Will "artificial life" make an appearance some day in the fiction created by Sugawara?

### Results of artificial cell research



(Publication on the Right) The results of the research on membrane (vesicle) self-reproduction were published with the title "How do we understand Life Systems?" (Kyoritsu Shuppan, Makoto Asashima Editor, May 2007 issue).

(Publication on the Left) "Synthetic Biology (Introduction to current biological science Vol. 9)" (Iwanami Shoten, May 2010 issue) provides an overview of the constructive understanding of the function of organisms at a molecular level. Makoto Asashima, who worked as the aforementioned editor, is a biologist roughly the same age as Sugawara. His research into animal development is highly regarded.



occur.

Sugawara and his team introduced a mechanism to supply DNA from the outside to the inside of vesicles using hints provided by substance transport mechanisms inside cells. Then, they successfully reconstituted division of the granddaughter artificial cell from the daughter artificial cell divided from the parent artificial cell. Furthermore, they observed cycles made of four stages during division of the primitive artificial cell. These stages looked similar to cell cycles seen during division of biological cells (see figure on the right). In September 2015, these results were published in *"Nature Communications"*, again creating massive reverberations. However, there was still one remaining question.

DNA provides the "information" that makes proteins inside living bodies. However, was the DNA added as genes in the artificial cells created by Sugawara and his team working as an information molecule?

Sugawara responded to this question as follows: "In subsequent detailed experiments we ascertained that DNA was functioning as a type of "information" in the artificial cells. The "information" was the length of the DNA, and it was influencing morphology and behavior during divisions of the vesicles."

Sugawara and his team are also looking at experiments that will bring "information" into artificial cells, using a substance far simpler than DNA. They are aiming to create an artificial cell using only simple substances that would have existed on ancient Earth. In other words, Sugawara is aiming to artificially reproduce the birth of life.

## Neither RNA nor protein

There are two main hypotheses on the origin of life in biology: the "RNA hypothesis" and the "protein hypothesis".

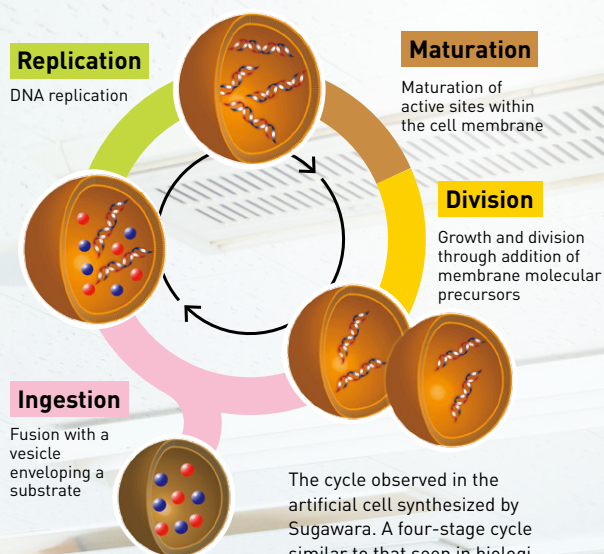
RNA is a substance that forms a bridge between DNA and proteins, when proteins are synthesized based on DNA information. The basis of the "RNA hypothesis" is that RNA can self-replicate and also play the role of an enzyme.

However, the "protein hypothesis" claims that RNA and DNA appeared as specialized signal transducers, while proteins, with their various functions, underwent repeated pseudo-replications.

There is also a third hypothesis, the "lipid hypothesis". Sugawara strongly supports it as a chemist who took up the challenge of synthesizing an artificial cell.

"RNA and proteins are both too complex as molecules, so it is difficult to believe that primitive life began from them. From a chemist's perspective, it is natural to consider that simple substances such as lipids, which constitute biological 'membranes', incorporated enzymes and information substances that promote division into the membrane pouch while drifting in the ancient seas." Sugawara also adds the following: "The existence of bacteria that progress with cell division using enzymes that produce the cell membrane without relying on the functions of proteins, has recently been discovered. It is debated whether this is the oldest form of cell division, given that the shape of these bacteria is extremely similar to the vesicles we reconstituted."

Research on artificial cells started from the "membrane". Life itself may have in fact started from the "membrane" that separates its content from the outside world.



The cycle observed in the artificial cell synthesized by Sugawara. A four-stage cycle similar to that seen in biological cells was observed, which illustrates the "biological likeness" of the artificial cell.

## Tadashi Sugawara

Sugawara was born in Tokyo in 1946. He completed his postgraduate studies at the School of Science, University of Tokyo (Doctor of Science). He then worked as a postdoctoral researcher at the University of Minnesota and at the University of Maryland; he later became Assistant Professor at the Institute for Molecular Science, Okazaki National Research Institutes, Professor at the Department of Basic Science, College of Arts and Sciences, University of Tokyo, Professor of Basic Science, Department of Multi-Disciplinary Sciences, University of Tokyo Graduate School of Arts and Sciences, and is currently Professor at the Faculty of Science, Kanagawa University. Sugawara is also an honorary professor at the University of Tokyo.



## FEATURE

# We are looking into space from here

We are able to see the spectacle of space extending far into the distance through telescopes like the Hubble Space Telescope. However, if we slightly change the visible light wavelength, space shows us a completely different face.

Kinya Hibino is a 'cosmic ray astronomer' who is closing in on a new appearance of space by observing ultra-high-energy 'cosmic rays'.

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**Kinya Hibino**

Department of Physics,  
Faculty of Engineering

High-energy cosmic ray  
research on the Tibetan  
Plateau

## The language of space as spoken by lightning

Prof. Hibino is standing on the roof of Building 6 in the Yokohama Campus of Kanagawa University with a line of "scintillation detectors" used for the observation of cosmic rays. A number of these scintillation detectors can also observe gamma rays released from lightning. Prof. Hibino says, "They have no effect on humans, but extremely powerful gamma rays are emitted by lightning. We can even close in on the mysteries of space with this kind of phenomena close to home."

The true character of cosmic rays is demonstrated by high-energy particles such as atomic nuclei and elementary

particles flying in outer space. Masatoshi Koshiba (Honorary Doctorate from Kanagawa University, Special Honorary Professor at the University of Tokyo) is an award-winning physicist who was awarded the Nobel Prize in Physics in 2002 for building the world's largest Water Cherenkov detector in 1983, the Kamiokande-II, to detect neutrinos that reached the Earth from the Large Magellanic Cloud (LMC), which is a satellite galaxy of the Milky Way.

Cosmic rays are believed to reach Earth when particles accelerate in the nucleus of the Milky Way and in supernova explosions, but the actual mechanism remains one of the mysteries of space.

"There are various mechanisms that can accelerate particles, but, for example,

## Kinya Hibino

In 1991, he completed the Graduate School Doctoral Program in Physics at Konan University (PhD Physics); in 1991-1993, he worked at the Institute for Cosmic Ray Research, University of Tokyo; in 1992, he became a fulltime lecturer at Kanagawa University; in 2003, he became an Assistant Professor in the Department of Engineering, Kanagawa University; and since 2008, he has been working as a Professor in the Department of Engineering, Kanagawa University.

owing to the phenomenon known as a pulsar, particles are thought to be accelerated by powerful electric and magnetic fields. However, it is difficult to directly observe pulsars; therefore, we are studying how particles are accelerated and how gamma rays are emitted by lightning, a familiar strong electric field, to elucidate the mechanism of acceleration of particles that originate as cosmic rays." Hibino's research team is composed of "cosmic ray astronomers": they observe space through cosmic rays rather than through light and radio waves. Furthermore, Hibino indicates the possibility that lightning itself may be caused by cosmic rays. Lightning is a discharge phenomenon generated by a strong electric field born in a cloud. Specifically, a dielectric breakdown generates lightning in the cloud, but it is believed that a strong electric field does not exist. What are then the "seeds of lightning"? One theory is that cosmic rays originating in space may act as triggers for lightning.

## The Sun as seen with cosmic rays

The location has moved to the Yangbajing Plateau in Tibet, located approximately 4300 m above sea level; from here, Hibino looks up at the sky. This is where the cosmic ray telescope Tibet Air Shower Observation Array is located for astronomical observation of high-energy gamma rays as a Japan-China international joint research project.

"Air shower" is a phenomenon in which particles formed from cosmic rays rain down on Earth, resembling a shower. When cosmic rays enter the Earth atmosphere, they react with oxygen and nitrogen molecules in the air, destroying atomic nuclei and generating a large number of secondary cosmic rays. These rays subsequently collide with the surrounding atomic nuclei, increasing the number of

secondary cosmic rays, and repeating the cycle in a geometric progression. Thus, a vast quantity of particles rain down on Earth. The Tibet Air Shower Observation Array takes detailed measurements of these air showers, thus enabling astronomers to ascertain the energy and the direction of arrival of cosmic rays; measuring these cosmic rays will enable us to investigate the activity of the sun. "The sun and the moon create interference in the measurement of cosmic rays that come to Earth from the center of the Milky Way, and they are detected as "shadows" in the data acquired. Recently, we have started investigating the structure of the magnetic field in the heliosphere."

During the "solar minimum period", when the sun is not very active, cosmic rays are intercepted by the sun, and the sun's shadow is clearly projected. Conversely, during the "solar maximum period", when the sun is very active and when there is reversal of the sun magnetic poles, cosmic rays are distorted by the magnetic field, blurring this shadow. We can observe the sun's activity through changes in these shadows.

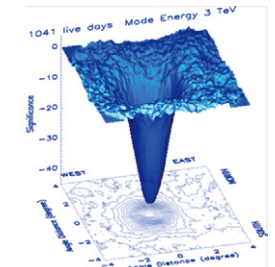
Furthermore, Hibino and his team created a simulation of "antiparticles" that are fired back from Earth towards the sun and created a detailed image of the magnetic field between the Earth and the sun.

"When we humans will progress further into space, particularly when we will progress beyond our own solar system, knowledge about the phenomenon of cosmic rays will be extremely useful."

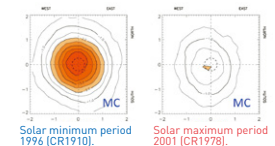
Hibino's "eyes" are looking from lightning gamma rays, through cosmic rays, into the sun magnetic field, and ultimately outside of the Milky Way. He is also casting his gaze into the future.



Tibet Air Shower Observation Array. Scintillation detectors are composed of approximately 800 units arranged over approximately 3.7 ha.

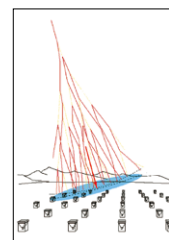


The moon shadow's captured with cosmic rays. The moon has no magnetic field and thus it appears as a clean "shadow" in the data.



The sun's shadow captured with cosmic rays. The shadow is clear during solar minimum periods and not visible during solar maximum periods owing to the influence of the magnetic field.

## Cosmic ray "air shower"



The cosmic rays that enter the Earth atmosphere react with oxygen and other particles in the air and rain down on Earth as a shower formed by approximately 100 trillion low-energy muons, neutrinos, neutrons, gamma rays, electrons and positrons.

## SIDE STORIES

### Kubrick's space odyssey opened the door of interest

STANLEY KUBRICK COLLECTION



Hibino developed an interest in space based on the feeling that he "liked things he could not understand by himself". The mysterious nature of the movie "2001: A Space Odyssey" drew Hibino to space.

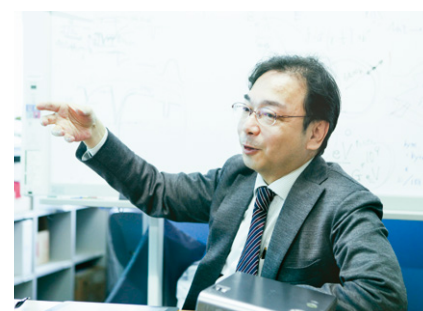
### The actual situation in Tibet where the observation takes place

The Tibet Air Shower Observation Array is located in the Tibetan autonomous region, approximately 80 km northwest of the central city of Lhasa. Barkhor Street in the Tibetan holy place in Lhasa is set up so that the public cannot gain access to the area without passing through security. In addition, once tourists leave Lhasa, they are unable to freely move around. Hibino and his team have special permits to enter the area, but they are often denied access.

### Gazing intently at space with music



Hibino always listens to music while conducting his analysis. He often listens to jazz. Since he started listening to club jazz, he has taken a liking to "FreeTEMPO", the solo project of the DJ/song writer Takeshi Hanzawa.



## FEATURE

# Chemical approach to the strategies of life

The many living things that currently thrive on Earth are based on strategies that were acquired by trial and error over a span of 3,500 million years. The natural organic compounds in organisms are the “book” in which these strategies are written. Daisuke Uemura has sought to decipher the chemical structures of these natural products, and to connect these structures with innovative drug discovery.

## Ideas for solving the obesity problem inspired by marine life

Obesity has become a major public health problem in developed nations. Some patients have become so obese they can barely move and take part in social activities. All over the world, many people are waging a war against fat, with some undergoing surgery to have gastric bands fitted. Urgent measures are needed to keep people healthy, prolong their lives, and reduce burgeoning medical costs. Currently, we are attempting to develop a new tool to battle this problem. In particular, we hope to identify an anti-obesity drug that reduces the fat that has accumulated in the cells of the body.

Distinguished  
Professor  
**Daisuke  
Uemura**  
Compound  
Hunter

### Daisuke Uemura

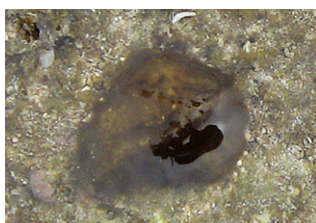
Daisuke Uemura received his Ph.D. from Nagoya University in 1975. In 1982, he began research as a visiting scholar at Harvard University. In 1997, he started working as a Professor at the Nagoya University Graduate School of Science, and in 2009, he was awarded the Medal with Purple Ribbon by the Government of Japan. In 2011, he began work as a Professor in the Department of Chemistry, Faculty of Science, Kanagawa University, and became Director of the Research Institute of Natural Drug-Leads. He was designated Professor Emeritus at Nagoya University in 2008 and a Distinguished Invited Professor at Kanagawa University in 2016.

Uemura and co-workers found that the administration of a compound they identified, 'yoshinone A', to mice fed a high-fat diet inhibited the accumulation of fat. Yoshinone A elevates lactic acid levels in the body, which results in "a state similar to running". When humans exercise, lactic acid levels in the body increase. This lactic acid is metabolized and reverted to sugar, and energy is consumed in the form of ATP (adenosine triphosphate) molecules. When ATP is consumed, fat is steadily metabolized and depleted. Yoshinone A creates conditions in the body similar to those induced by exercise, and thus reduces fat in fat cells of the body. Uemura stated that "yoshinone A has no adverse reactions in gastrointestinal organs such as the stomach and also does not cause fatty liver. It may truly become the ideal anti-obesity drug. It first should be made available to people struggling with extreme obesity." Current anti-obesity drugs include drugs that suppress the action of the satiety center, drugs that inhibit the action of fat-degrading enzymes, lipases, and glucose transporters, etc., but all of these drugs can elicit adverse reactions. Yoshinone A, which may represent a breakthrough in anti-obesity drugs, was discovered in the blue-green algae "Cyanobacteria", which live in the seas around Ishigaki Island of Okinawa.

### The challenge posed by "toxins" in cancer: the modern enemy

Living organisms use various strategies to protect their own bodies from external attack, and to harmonize with their environment, to maintain their lives. Small molecules have important functions, including promoting changes in protein function and influencing the permeability of ions. This is the world of natural organic compounds. Uemura searches for "life ideas" from nature, identifies their chemical structure, and uses them to develop drugs for humans.

For example, Uemura used a 'toxin' in the black sea sponge *Halichondria okadai* to develop an anti-cancer drug. Although sponges are sessile, they have survived for 500 million years without being attacked by other creatures. Uemura



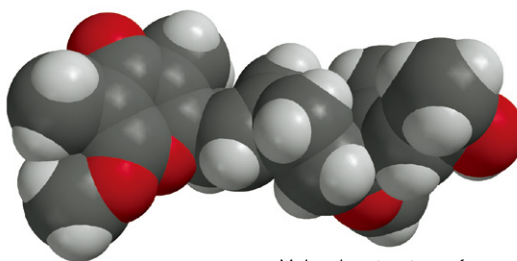
Leptolyngbya, the Cyanobacterium in which yoshinone A was discovered. It has a diameter of approximately 4 cm. The name yoshinone comes from the Yoshihara beach on Ishigaki Island where Cyanobacteria were collected.

conducted a great deal of research on the presumption that "sponges must have original ideas to protect themselves". This research led to the discovery of the large molecule halichondrin B, which is a potent toxin. A large number of microorganisms coexist within *H. okadai*, and these microorganisms are thought to defend their host. To enable these microorganisms to coexist within their bodies, *H. okadai* must temporarily reduce its own vital functions. The substance that mediates this process is thought to be halichondrin B, which inhibits mitosis.

Uemura focused his attention on the function of halichondrin B, and the pharmaceutical company Eisai continued this research and successfully developed the anticancer agent Eribulin (brand name Halaven), which is used to treat breast cancer. This substance has an extremely large molecular weight and a complex chemical structure. Chemosynthesis of this substance alone led to drug development, which represents a brilliant achievement in synthetic chemistry. It is now approved in 64 countries worldwide and is supporting the lives of many breast cancer patients.

Uemura tells us, "Molecules derived from organisms have structures that have been polished within the history of the organism, and show a variety of biological activities and involvements in life phenomena we would never expect. Elucidating these mechanisms and tying them in with opportunities for drug development is extremely compelling".

Uemura is now approaching the characterization of a substance from the same black sea sponge that suppresses prostate cancer; his quest to transform ideas from nature into valuable drugs seems to be on track to continue for a long time yet.



Molecular structure of "yoshinone A". Potent inhibition of the differentiation of cells to fat cells in the 3T3-L1 mouse model, which makes it a promising candidate as an anti-obesity drug.

## SIDE STORIES

### "Souvenirs entomologiques" – Touching upon the wonders of living things



Jean-Henri Fabre wrote that spider wasps are "master surgeons". Spider wasps pierce the exoskeletons of target spiders, paralyze them and then lay their eggs in the spider abdomens. The spiders remain paralyzed but do not die until the eggs hatch, at which time the spiders are eaten by the larvae. In other words, spider wasps paralyze spiders to make them a food source for their larvae. Uemura investigated spider wasps and discovered that they produced a narcotic protein.

### Future drugs will be discovered through inspiration and innovative experiments



Uemura embarks on a new experiment when he has a flash of inspiration. For example, he wondered how cicada larvae acquire their antibacterial properties while underground, and conducted an experiment to discover that cicada larvae have sugars in their bodies with antibacterial properties. This is how his process of discovery unfolds. The photograph shows a platypus, which is a poison-producing mammal. When Uemura investigated the poison in the spurs of male platypus, he found that it could be used to anesthetize joints. He is now verifying the chemical structure of the poison and searching for a therapeutic agent that could be beneficial in patients with rheumatoid arthritis.

## The mystery of the sexuality of the barnacle

It could be said that the 'aim' of the existence of organisms is to leave behind their own descendants. Unicellular organisms undergo cell division to increase the number of individuals, while organisms with 'genders' reproduce through male and female copulation and fertilization. The human 'gender' is separated, with each individual being male or female, but Yamaguchi tells us that, if we look around the world of organisms, there is a wide spectrum in genders or sexuality. "In plants, the 'hermaphrodite' is widely known: both the male (stamen) and the female (pistil) are located in a single individual. Even some animals, in addition to the 'sequential hermaphrodite' animals, can change from male to female or from female to male during their lifetime."

The target of Yamaguchi's research is the

marine organism 'barnacle'. It is classified as a crustacean and is related to shrimps, lobsters, and crabs. It is an animal, however once it grows past its larval stage; it drifts in the ocean, it attaches itself to a surface such as a rock or a crab shell, and does not move once it has decided its habitat. It has legs like the shrimp or the crab, but these legs are not designed for walking. Its legs have segments that can filter plankton, which it feeds on, from the ocean. There are several different types of barnacles. The barnacles that look like Mt. Fuji are well known, but the barnacle that Yamaguchi is examining is the goose barnacle, which looks like an ice-cream cone. This barnacle has a mysterious sexuality, which attracted Darwin's attention. "The goose barnacle has a number of sexual systems First, during the larval stage, its sexuality is undifferentiated; the goose barnacle is thought to select its sexuality when it has grown, and has attached to a surface. The most

## Sachi Yamaguchi

Yamaguchi was born in Nara prefecture in 1982. She graduated from the Department of Physics, Faculty of Science, Nara Women's University in 2005. She gained her PhD (Science) from the Graduate School of Humanities and Sciences, Nara Women's University in 2009. She worked as a postdoctoral fellow at the Japan Agency for Marine-Earth Science and Technology and at Kyushu University. She is currently working as a Special Assistant Professor, Department of Engineering, Kanagawa University. In July 2014, she was awarded the Research Encouragement Award by the Japanese Society for Mathematical Biology.

Assistant Professor

**Sachi  
Yamaguchi**

Department of Information  
Systems Creation  
Faculty of Engineering

Mathematical Biology

FEATURE

The mysterious sexuality of the marine organism that confounded Darwin. We are challenging this mystery with a mathematical model.

Charles Darwin (1809-1882), who proposed the concept of evolution with his work "The Origin of the Species," was interested in the sexuality of this marine organism. This mystery remained unsolved for more than 150 years until the young researcher Sachi Yamaguchi attempted to solve it. Her weapon was a mathematical model.

common sexuality is the hermaphrodite, which lives in the shallows of the ocean. The second most common type is a hermaphrodite with a small (dwarf) male attached, and it can also be found in relatively shallow parts of the ocean. The third type is found in the ocean depths, and is characterized by a female with a dwarf male attached. Hermaphrodites and females are a few centimeters long, while the body length of dwarf males is less than 0.1 mm, making them difficult to see with naked eye."

Hermaphrodites do not fertilize their own eggs with their own sperm. The male reproductive organ (penis) extends to several times the length of the animal's body to deliver sperm in the eggs of another individual, and the eggs accept the sperm of other individuals. If hermaphrodites are densely packed together, then they are very likely to be able to leave behind their descendants. However, occasionally dwarf males affix themselves to hermaphrodites or to females. The dwarf male always attaches immediately next to the egg, and although it is short-lived, it also extends its penis and reproduces. Darwin, who advocated the concept of 'evolution', also discovered the barnacle dwarf male. Why does such a small male exist? This mystery attracted Darwin's attention, but it remained unsolved for over 150 years.

## The big mystery of the small male

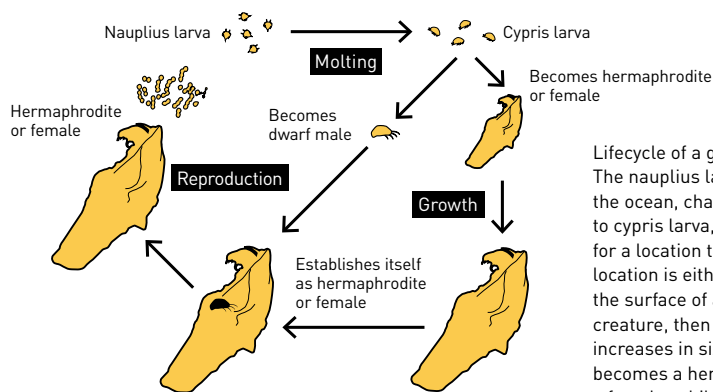
Yamaguchi attempted to solve this mystery using a mathematical model. "Barnacles select the optimal sexuality within their own environment to maximize the offspring they can produce in their own lifetime. Based on this hypothesis, I came up with a mathematical model. Of course, individuals do not consciously behave like this, so I believed that the life history we observe now had been acquired through the process of evolution." Animals need to eat to survive. If food is plentiful, they can grow large and this is beneficial for survival and reproduction. "In the shallow parts of the ocean, where plankton are abundant, the most effective strategy for increasing the offspring is to become a large

hermaphrodite. The larger the animal body, the further away it can reach to procreate with other individuals. The deeper the ocean, the less abundant the food sources, so fewer individuals can grow to a large size. It is believed that to survive and produce offspring in these environments, some individuals become dwarf males. In even deeper parts of the ocean, the number of individuals that can survive within a certain range becomes even more limited. It is surmised that if an individual has both female and male functions, but there are no other individuals to reproduce with, the reproductive allocation is wasted, so that is why we see the exclusive combination of female barnacles with dwarf males."

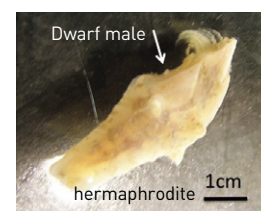
In the background of the various sexualities of the barnacle is the problem of the trade-off of how to distribute food sources from the environment for survival, growth and reproduction. If there are large numbers of individuals in the environment, then there is also competition for food and reproduction.

Ten years have passed since Yamaguchi started researching the sexualities of barnacles in an earnest manner. Why does the dwarf male need to be this small? The answer to this puzzle has still not been found, but Yamaguchi embraces a certain concept.

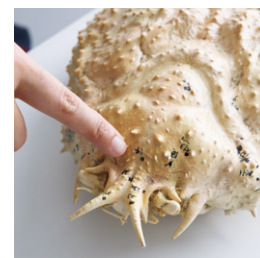
"The dwarf male is a phenomenon seen in a variety of marine organisms, not just barnacles. In the near future I will solve the mystery of the dwarf male using a mathematical model, and I want to build the field of 'dwarf male science'". This young researcher has huge ambitions beyond the mystery that originally baffled Darwin.



Lifecycle of a goose barnacle. The nauplius larva drifts in the ocean, changes its form to cypris larva, and then looks for a location to attach. If that location is either a rock or the surface of another living creature, then the barnacle increases in size and it either becomes a hermaphrodite or a female, while if the larva attaches to a large barnacle it is thought to become a dwarf male.



Goose barnacle individual where a dwarf male (small male) is attached to a hermaphrodite. The dwarf male is indicated by the tip of the arrow. The photo is of a specimen from the Osaka Museum of Natural History.



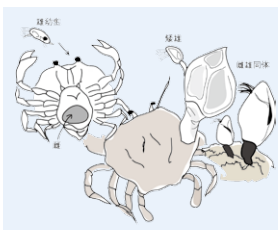
Barnacles also live on crab shells. The black spots are locations where hermaphrodite barnacles have taken up residence. Their body length is only a few centimeters, but the male reproductive organ (penis) can extend several times their own body length, so the penis supplies sperm to nearby hermaphrodite eggs and fertilizes them.

## SIDE STORIES

### Her heart is always in marine life

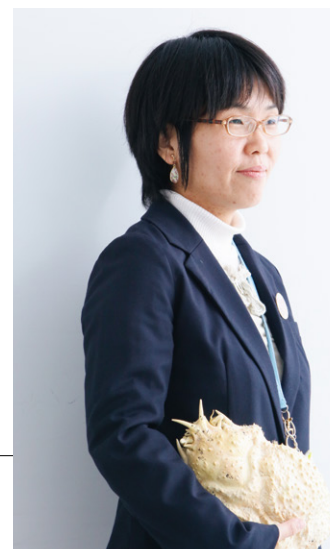


For Yamaguchi, marine life is much more than simply a field of research. On her days off, she enjoys going to aquariums and buying soft toys from the museum shop.



### Drawing sea life

Since she started her research, Yamaguchi also started drawing pictures. The theme of her drawings is of course marine life. During the interview, she deftly drew pictures to illustrate the ecology of barnacles.



## FEATURE

# Chemical reconstruction of the underlying molecular concept in organisms

When we were born and every day when we eat, the interaction of diverse molecules in the body plays a crucial role in the process of being “alive.” As an orchestra creates a single piece of music through the assembly of the sounds coming from various musical instruments, so do these molecules work together to create a single body through their individual small actions. Chemically replicating the behavior of these assemblies is the challenge taken up by Nobuhiro Kihara.

Professor  
**Nobuhiro  
Kihara**

Department of Chemistry,  
Faculty of Science

Organic Chemistry,  
Bioorganic Chemistry

Nobuhiro Kihara

Born in Miyagi Prefecture in 1963, Kihara dropped out of a PhD course in the Graduate School of Engineering, the University of Tokyo. He then became a Research Associate in the Research Laboratory of Resources Utilization, Tokyo Institute of Technology for 4 years, and worked as a Research Associate in the Department of Polymer Chemistry in the same University for 4 years. Thereafter, he worked as a Lecturer for a year, and held the position of Associate Professor in the Department of Applied Chemistry, Osaka Prefecture University for 6 years. He is now a Professor in the Department of Chemistry, Kanagawa University.

## The wondrous ‘chemical systems’ of organisms

If an amateur were to pull apart a watch finely assembled by a watchmaker, he would then be unable to put it back together. If those parts were put into a flask, shaken, and then observed to return to their original form, no doubt everyone would gasp with surprise and think that it was magic.

However, if we look at the ‘chemical system’ of our bodies, it comprises miraculous phenomena where separate parts come together to form products as if they have a will of their own.

“The construction of human body starts with the ‘development’ of an embryo. When the body is taking shape within the uterus, a series of proteins is being made in the cells based on the information present on the DNA. When proteins are released from a protein factory known as the ribosome, they reach their functional location and begin to function without requiring any commands or impetus. Proteins constitute the human body as the parts that move to their specific locations without having brains and eyes.” Indeed, we are born as if we were watches that have been automatically assembled inside a flask. From a chemistry-based viewpoint, embryo is a ‘reaction field’ where molecules correctly arrange themselves and then progress autonomously with the reactions required for birth.

## From digestion to cell division, the story told by molecules

“This behavior occurs commonly within living creatures, so it must be able to be replicated with artificial molecules.” Professor Nobuhiro Kihara’s research efforts are focused on artificially facilitating ‘recognition’ and ‘response’, which are the key functions of molecules that organisms use for ‘reaction control.’

For example, let us have a look at our meals from Kihara’s perspective. When we eat food, our digestive system degrades it and absorbs the required nutritional elements. During this process, food is degraded under gentle conditions inside the body, without the need for heat or light.

“A variety of enzymes are at work during the digestion process. For example, to digest proteins, particular enzymes recognize a specific linkage between amino acids through ‘intermolecular interactions’ and disassemble it. The protein molecule is recognized and the



digestion reaction occurs as the response. Because each reaction is very specific and functions correctly, only the ingestible molecules, or 'nutrients', are digested." Furthermore, the behavior of molecules during cell division is another example of a marvelous 'reaction control'. During cell division, a set of genes in the cell duplicates, and each set is delivered to each side of the cell, before the cell divides into two. During this process, a special reaction occurs whereby a molecule, named as a 'molecular motor', works to pull each set of genes to the opposite directions. Kihara has successfully reproduced this chemistry by using artificial molecules for the first time. "When our first ancestor was born at the bottom of the sea, 4.5 billion years ago, life came into being with trial and error, with very few chemical 'tools.' However, now, we humans can use our brains and sciences as powerful and goal-directing tools. If we select specific functions of a biological system, we can design artificial compounds to replicate them, even though the flexible improvement of biological system with unnatural compound is impossible in organisms. This is my research."

## Create chemistry that changes the worldview

Dexterity in the technique of organic synthesis is necessary for artificially reproducing the functions of organisms. By using sophisticated techniques of organic chemistry, Kihara has successively created highly scarce substances such as microscopic chain-like molecule named "polycatenane."

One day, by chance, Kihara encountered a unique substance, the oxidatively degradable polymer. The oxidatively degradable polymer is a new class of material that rapidly decomposes and disappears, when exposed to a commercial chlorine-based bleach. Kihara states, "we anticipate the application of this polymer as a material that immediately degrades at any desired time-point." This enables its use as an adhesive that can be removed when desired

and as a paint that can be peeled from the surface without damaging it. This new material with this unique property was created accidentally from an unsuccessful attempt to prepare a polymer of carbon dioxide. "I thought it would have been interesting if we were able to prepare a polymer of carbon dioxide. It can also be used as an explosive." An explosion occurs when a volume expands faster than the speed of sound. When the decomposition of a solid polymer into gaseous carbon dioxide happens, the volume changes rapidly, potentially causing an explosion. Such a material can be used as a high-energy compound.

"However, when we actually attempted to prepare the polymer, it decomposed and disappeared as soon as it was synthesized. We then attempted to prepare a similar polymer using an inorganic compound, hydrazine. Instead of an explosive, we discovered an oxidatively degradable polymer, with a completely different potential application." Currently, his interest is on developing a novel polymer that degrades by blowing a special gas onto it instead of using chlorine-based bleach. Kihara started his research on molecular 'recognition and response,' when he was a graduate school student working on molecular 'recognition.' Kihara recalled, "In the biological systems, molecular recognition triggers the response for the next recognition; therefore I believed that the response should be the research target next to the recognition." He was also interested with that no one had tried researching on the chemical response, which is technically more difficult than the physical response.

"We are undertaking the research on the concept 'molecules that react in response to the recognition', because it will open new important possibilities in chemistry. New concept can change the ways of thinking and understanding the world."

Molecular systems have the potential to change the world through chemistry.



Oxidatively degradable polymer, when used as the paint, a coat can be applied and removed, when desired. A large number of biodegradable macromolecules have been created as the so-called environmentally friendly material, but we cannot control their degradation. In the case of the oxidatively degradable polymer, the timing of degradation can be freely manipulated, and the product of degradation is clear and clean. This useful new material is also environmentally friendly.



Inside the laboratory, there are several types of equipment and reagents for the synthesis of newly designed organic compounds. Among the glassware, some were manufactured by Kihara himself; he said, "If the appropriate glassware is not available, you may make it."

## SIDE STORIES



### The orchestra is the reaction field of music

Kihara started playing contrabass as an orchestra member when he was a student. In the 'spring concert' held at the Annual Meeting of the Chemical Society of Japan, he and many chemists gathered from all over Japan to play music. His favorite composers are Shostakovich, Wagner, and Mahler.



### Reproducing the light of the jewel beetle with liquid crystals

On the surface of the jewel beetle, there are extremely fine grooves at regular intervals. Only light with wavelengths that correspond to the width of these grooves is reflected, releasing particular colors. These principles were reproduced with molecular recognition in liquid crystal, with which own key holders are prepared.

Professor

# Susumu Izumi

Department of Biological Science,  
Faculty of Science

Molecular biology,  
Insect physiology and  
biochemistry

## Susumu Izumi

Susumu Izumi was born in Toyama Prefecture in 1952. He completed a PhD in biology in the Postgraduate School of Science, Tokyo Metropolitan University in 1989. In the same year, he became an assistant in the Faculty of Science, Tokyo Metropolitan University. In 1993, he became an Assistant Professor in the Faculty of Science, Tokyo Metropolitan University. In 2005, he became an Assistant Professor in the Graduate School of Science and Engineering, Tokyo Metropolitan University, and he is currently a Professor in the Faculty of Science, Kanagawa University.

## An insect with plant-like wisdom

The silkworm is an insect that weaves its own 'cradle', a cocoon made of silk thread. The growth process of this insect, during which it changes into various forms, is truly dramatic. A larva that has just hatched from the egg is called a 'first instar larva'. It repeatedly molts, becoming a second, third and fourth instar larva, before finally becoming a fifth instar larva with a body length of approximately 10 to 20 cm. At this stage, it begins to eat even more mulberry leaves, and secretes silk thread to create a cocoon. Inside the cocoon it molts once again, becoming a hard pupa, and waits for its emergence from the cocoon.

The aim of Izumi's research is to elucidate insect 'metamorphosis' from the perspective of molecular biology, using the silkworm as a model organism.

"Nature is truly interesting. For example, when a silkworm becomes a pupa inside the cocoon, its outer skin hardens and protects the body from outside physical stimuli. In fact, the enzyme at work during this process is 'laccase', which performs the same activity as the enzymes at work when lacquer, the natural paint used for lacquer-ware, hardens. So why does this insect have plant-like wisdom even though it is an animal?"

Izumi has spent a significant portion of his research career investigating the outer skin of the silkworm. During metamorphosis of the silkworm, the outer skin also undergoes dramatic changes. While the silkworm is a larva, its skin has elasticity, but once it becomes a pupa, it hardens to protect the silkworm body from external stimuli. Then it once again acquires elasticity when the silkworm becomes a mature insect. It is as if the silkworm is changing its clothes seasonally, covering its body with an outer skin that is suitable for particular circumstances. However, these outer skins are all produced by skillfully changing the same 'cuticular protein'.

"Regulation of gene expression, the blueprint of life, governs all these changes."

## The silkworm 'plan' seen from gene expression

The 'expression' of genes refers to the synthesis of proteins based on the genetic information in the body. Izumi conducted research on how proteins in the hemolymph of silkworms correlated with their circumstances at a certain time. What he discovered was a skillful planning of genetic expression that shaped the life of silkworms. "For example, after day 3 of the fifth instar larval stage, '30K protein' appears in the

## FEATURE

# A life mechanism hidden within the silkworm, glimpsed through molecular biology

From larva to adult, a mysterious life process unfolds inside the silkworm cocoon. The mystery of this small life form is explained through molecular biology. Here we discovered various mechanisms that form life, including gene expression that skillfully plans the workings of life, and the existence of neurotransmitters that are similar to those in humans.

hemolymph, which was never made prior to that stage. Once that protein starts to appear, the silkworm begins to produce silk thread, and it can then pupate."

A number of these proteins that appear in sync with the metamorphosis have been observed in the body of the silkworm. The growth plan moves to execution mode with planned gene expression. Several factors fulfill the role of switching on gene expression, and insect hormones in the body are said to participate in the synthesis of 30K protein. In the body of the silkworm larva, the 'juvenile hormone' is secreted to maintain the silkworm in its larval state until it becomes a fifth instar larva. However, once it becomes a fifth instar larva, the secretion of that hormone is inhibited. Then the protein 30K is synthesized, the cocoon is made, and the silkworm becomes a mature insect.

"I wanted to research and clarify insect metamorphosis, which is replete with mystery, at the gene expression level. I have had this wish for a long time."

The cuticle that forms the exoskeleton of the insect binds to various cuticular proteins expressed during the process of molting and metamorphosis to 'chitin nanofibers', enabling the cuticle to become either softer or harder. The life cycle of the silkworm is skillfully controlled by regulation of gene expression.

### The common language of neurotransmission spoken by the silkworm

Furthermore, Izumi conducted research to investigate the central nervous system of insects using the silkworm as a model. This research is on the key neurotransmitter 'acetylcholine', which is related to the cholinergic nerve of the silkworm. Acetylcholine performs a variety of actions, but it is present in vertebrates, including humans, and is mainly involved in the contraction of muscles mediated by the motor neuron.

"Research on insect neurotransmitters was preceded by research on the fruit fly (*Drosophila*), and it was found that the insect central nervous system was cholinergic, as acetylcholine was used as a neurotransmitter. We attempted to verify if the silkworm, a Lepidoptera insect, also had a cholinergic central nervous system."

The results clearly show that acetylcholine is used as a neurotransmitter in the central nervous system of silkworm larvae.

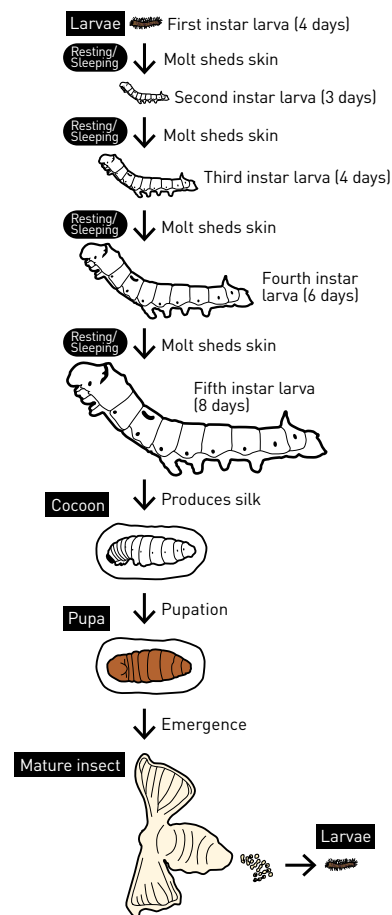
"The expression level of acetylcholine increases even further in the mature insect. I want to continue with more research, to look into how the nervous system is reorganized during the process of metamorphosis, and how the use of neurotransmitters changes at a molecular level."

Humans also use acetylcholine for neurotransmission. Human muscles contract upon secretion of acetylcholine. The acetylcholine degrading enzyme acetylcholinesterase acts upon contracted muscles to relax them, which is how we normally control our skeletal muscles. If acetylcholinesterase is inhibited, muscles remain contracted and this produces symptoms such as breathing difficulty and seizures. Incidentally, the nerve gas 'sarin' that was used by the Japanese religious group Aum Shinrikyo in terrorist attacks, was a potent inhibitor of acetylcholinesterase.

Neurotransmitters are a 'common language', and there is no significant difference between molecules that act as neurotransmitters in humans or insects. These discoveries in silkworms may be deployed to other areas of research.

"Observation is everything to natural scientists. If they have any doubts about something, they will discover many interesting things if they look closer. My life as a researcher has been like that from the beginning until today." Izumi is starting his next journey to seek out the mysteries of the silkworm.

### Silkworm lifecycle



## SIDE STORIES

### Creating a high-class gentle breeze The laboratory specialty product, the silk fan



Making use of the silkworm behavior, we created a silk fan that bestows a high-class cooling sensation when fanning one's face. For the silk over the 'bones' of the fan, we used a number of fifth instar larvae that had started producing silk. If the silkworms are kept horizontal, they do not make cocoons, instead they created enough silk to cover the entire fan.

### Observant eye for nature - High-performance Olympus Pen



The film camera Izumi received as a present when he was in middle school - Olympus Pen D3 (camera on the left). At that time, Izumi used a closet as a dark room and developed photographs himself. Influenced by his father, who loved cameras, photography remains a favorite hobby of Izumi's to this day. The nature surrounding the Shonan Hiratsuka campus is the main subject of his photographs. The camera on the right is an Olympus Pen F.



The silkworm is a domesticated insect, and since it is easy to rear, it makes a superior subject for experiments. It lies quietly on the palm of the hand and does not run away.

# Measuring novelty

We herein present a mysterious metal complex that stores a large amount of gas, and discuss its potential for practical use in gas storage, moving toward a hydrogen society. After its discovery by Wasuke Mori, this material and concept was further developed by many brilliant researchers and has grown to be a field that attracts international attention. Its beginning was not particularly inspirational, nor was it discovered in an ideal experimental environment, but rather, a small accident was responsible. We therefore ask, what is required for science to create novelty? We herein present you with a series about a great scientific drama surrounding a mysterious metal complex.



## Professor Emeritus Wasuke Mori

Department of Chemistry,  
Faculty of Science

Magnetic chemistry,  
Functional materials  
chemistry,  
Complex chemistry

### Wasuke Mori

Born in Aichi Prefecture in 1941, Wasuke Mori left the Chemistry Program of the Graduate School of Science, Nagoya University in 1968, and took up positions as assistant, lecturer, and associate professor at the Liberal Arts Department, later moving to the Faculty of Science at Osaka University. In 1996, he became a professor in the Faculty of Science, Kanagawa University. After serving in the positions of vice president and executive director at Kanagawa University, he became an honorary professor, a title which he currently holds.

### Creating novelty

Creating novelty is an important role of science, but the key question is, what is required for novelty to be born? Could it be good conditions for experiments and measurements? We're not so sure. Although modern experimental facilities are breathtaking, conditions may actually be too good, and could actually hinder creating novelty at times.

Firstly, to recognize novelty, something must be measured. Previously, it was necessary to build our own devices to perform measurements. For example, my expertise is in magnetic chemistry, a science that approaches subjects through magnetism. I previously used a magnetic balance that I built myself to examine magnetic interactions between various atoms and molecules on a daily basis. But one day, an accident occurred, due to a metal complex known as copper(II) terephthalate.

As the name implies, the magnetic balance was composed of a balance and a magnet, and the samples to be measured were placed in a container called a cell. A glass tube was used to cover the cell from above, and the inside of the container was sealed to create a vacuum. To improve heat

conduction, a small amount nitrogen gas that is about 1/50 of atmospheric pressure was added. In addition, since weaker interactions can be measured more clearly at lower temperatures, the sample was cooled externally using liquid nitrogen at 77 K (Figure 1).

When the measurement was performed under standard conditions, mysteriously, the balance tipped immediately and stopped moving, suggesting that the sample became too heavy for the balance to measure. As the apparatus set-up did not allow us to observe what was occurring inside, we had no choice but to remove the liquid nitrogen Dewar from the outside. At that point, the sample spurted out of the cell and covered the interior of the magnetic balance. I panicked. As the magnetic balance is an extremely sensitive instrument, my concern was that if it was contaminated inside, it may never be usable again. I quickly disassembled the magnetic balance and carefully cleaned the inside. Thankfully, I was able to rebuild it and it worked fine; it must have been a rather well-built balance!

However, the problem was that I didn't learn my lesson the first time. To try to determine what had happened, I repeated

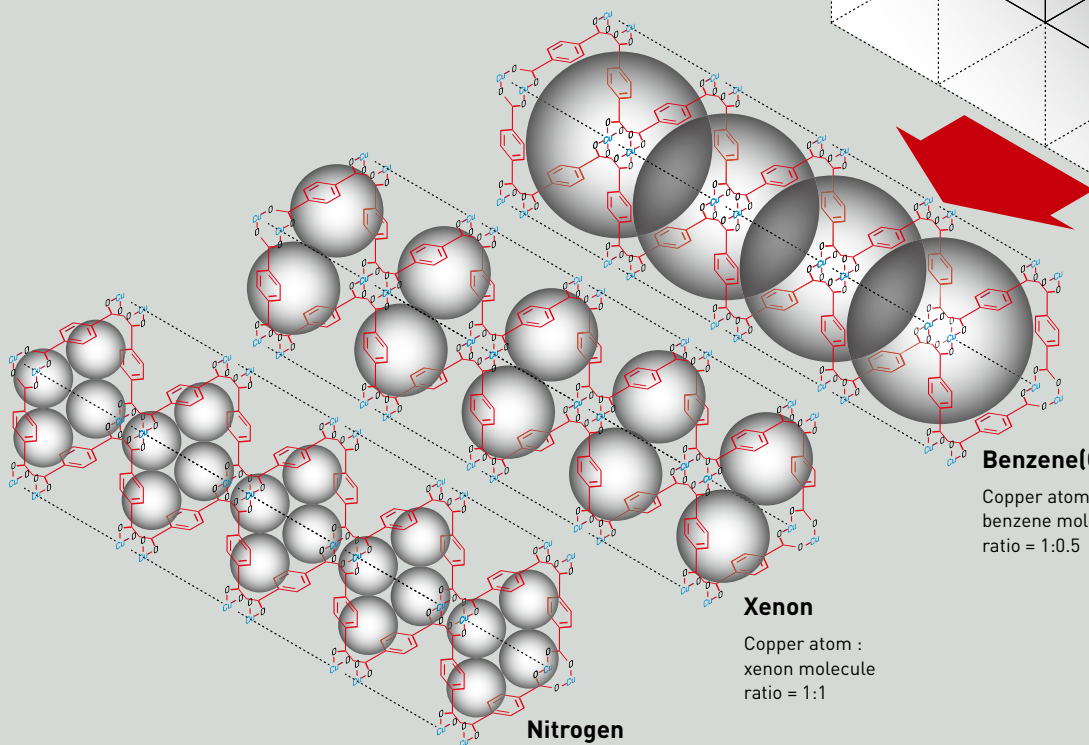


Figure 2

**Copper(II) terephthalate 100g**

This compound has a nanopore structure exhibiting a large number of holes

**Benzene (C<sub>6</sub>H<sub>6</sub>)**

Copper atom :  
benzene molecule  
ratio = 1:0.5

This structure  
can store  
**30e**  
of either nitrogen  
or oxygen

**Xenon**

Copper atom :  
xenon molecule  
ratio = 1:1

**Nitrogen**

Copper atom :  
nitrogen molecule  
ratio = 1:2

**The “nanopore” structure containing fine holes stores the gas**

The figure shows models presenting how much gas (e.g., benzene [C<sub>6</sub>H<sub>6</sub>] vapor, xenon, or nitrogen) can be stored in the copper(II) terephthalate nanopore structure. Due to its excellent storage abilities, this structure may be suitable for application in hydrogen storage technologies.

this “accident” three times, each time with the same consequences, and I still was no wiser as to what caused it.

Other professors and researchers joined me in contemplating this issue, and we came up with the idea that the small amount of nitrogen gas present in the magnetic balance used to improve heat conduction may have been adsorbed by the sample. This would result in the mass of the sample increasing and the magnetic balance being overwhelmed. It was a simple hypothesis.

To confirm this idea, we carried out the same measurement using a vacuum inside the magnetic balance. In this case, the balance moved normally, and the measurement was performed without any problems. We therefore concluded that the excessive weight of the sample was caused by the adsorption of nitrogen gas by copper(II) terephthalate at very low temperatures.

**A large number of holes store the gas**

At that point, there was nothing to stop my curiosity. We discovered that 100 g of copper(II) terephthalate could occlude almost 30 L of either oxygen or nitrogen. When considering the mechanism of occlusion, it

became clear that the copper(II) terephthalate structure contained a large number of pores, and that oxygen and / or nitrogen could be stored in these holes (Figure 2).

This accounted for sample sputtering during the measurement, as removal of the Dewar increased the temperature of the cell, and the nitrogen gas stored inside the sample at low temperatures exited the structure rapidly.

I presented this mysterious phenomenon in 1972 at the Chemical Society of Japan, but it was not well received. It took 20 years before it was accepted when I presented the same idea overseas. After many years, that mysterious metallic complex that I had discovered finally became a novelty.

Current research environments are extremely suitable for young researchers. However, if the conditions are too good, the results of experiments are obtained quickly, and as young researchers do not have much time to consider what they are discovering, a new opportunity may be overlooked. As novelty comes from unexpected potentials and probabilities, scientists should try to value the concept of novelty.

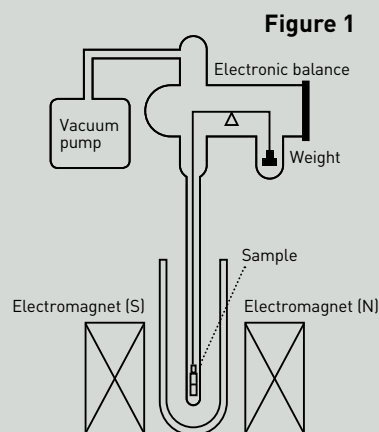


Figure 1

**The high performance creation: A magnetic balance that measures novelty**

This device consists of a balance and a magnet, and measures small magnetic interactions between atoms and molecules. A cell containing the sample (cooled using liquid nitrogen) is hung between electromagnets that create a strong magnetic field for measurement. Due to the preciseness of this balance, many students have visited Mori’s laboratory to use it for their measurements.



## Chemistry that mesmerizes the world

In the spring of 1968, when I took up a position in the Liberal Arts Department at Osaka University, I was measuring the magnetic interactions between atoms and molecules for various metallic complexes under the supervision of Professor Michihiko Kishita, using the magnetic balance that I designed. However, one of the compounds I was studying displayed an interesting phenomenon during its measurement. The balance swung all the way over, indicating that the sample was heavier than what the balance could measure. This led to the discovery of the unique characteristic exhibited by copper(II) terephthalate, namely, its ability to store gases.

Following much research worldwide, it appears that this compound is likely to play an important role in achieving a "hydrogen society." In particular, it is receiving increasing attention for its ability to store gases, to store and separate a large amount of hydrogen gas, and to contribute to the basic technology of hydrogen production in its role as a catalyst. Indeed, this metal complex appears to have immeasurable potential.

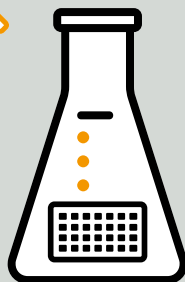
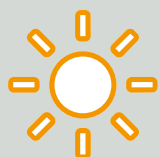
### Attracting researchers worldwide

Since 1993, I have been conducting research into the application of copper(II) terephthalate in the storage of natural gas, in cooperation with Osaka Gas. Our objective was the practical use of this complex in natural gas storage through increasing its storage capacity.

In this case, natural gas is stored under pressure with copper(II) terephthalate in a storage container (gas cylinder). This is possible due to the lattice structure of copper(II) terephthalate, which contains numerous pores (nanopores) that can store gas molecules. Thus, we studied a number of ways to increase the size of these pores to increase the storage capacity. Indeed, we confirmed methods of increasing the pore size while maintaining the strength of the material through the use of a carboxylic acid longer than terephthalic acid, along with pyrazine as a bridging ligand.

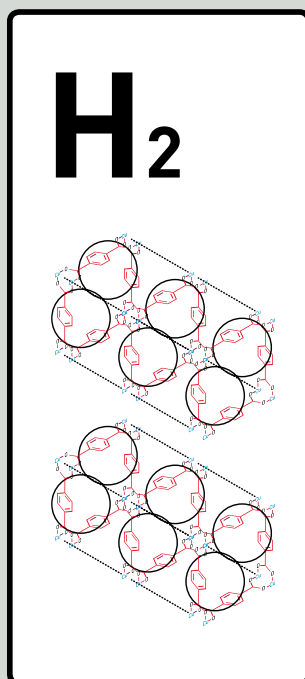
In 2000, it was selected as a NEDO (New Energy and Industrial Technology Development Organization) project, and we conducted research and development in cooperation with a number of

## A hydrogen society achieved using a metal complex



### Hydrogen generation

A metal complex is used as a photocatalyst in order to synthesize hydrogen from water using sunlight



Using a metal complex, hydrogen is stored



Fuel cell



Gas turbine power generation

Providing electric power to society including each household



Hydrogen cars

Energy source to support transportation infrastructure

companies and universities, including Kyoto University and Osaka Gas. We successfully achieved the low pressure storage (20–30 times atmospheric pressure) of natural gas. At low pressures, the force on the container was lower, increasing the choice of containers available for the system. Ultimately, we employed a thin and flat rectangular container instead of a conventional sturdy cylindrical high pressure container (200 atm). Thus, we increased the storage capacity while using a more compact container.

With this technology, we were able to efficiently install a fuel tank on either the roof or the undercarriage of natural gas cars as desired, which saved space. As the storage capacity increased, the driving distance was increased to 500 or 600 km, which is equivalent to that of a conventional gasoline-powered car.

Hydrogen storage studies were also conducted by major automobile companies. However, although copper(III) terephthalate can theoretically store a large amount of hydrogen, storage temperature is an issue. Hydrogen is extremely light, and has a low boiling point. As such, unless the temperature is extremely low (90 K, approx.  $-183^{\circ}\text{C}$ ), it would not be stable.

What is certain is that although hydrogen is generally stored under high pressure (e.g., 900 atm), if metal complexes such as copper(II) terephthalate are employed, hydrogen storage can be achieved at significantly lower pressures. As such, this technology has the potential to greatly improve the storage method for a future hydrogen society.

Currently, research is ongoing worldwide to establish hydrogen storage technologies that function at normal or ambient temperatures.

### Hydrogen synthesis using a metal complex

In addition to its hydrogen storage properties, the use of copper(II) terephthalate as a photocatalyst could lead to hydrogen production.

At present, the results of experiments employing metal complexes of rare metals such as ruthenium and rhodium as photocatalysts are quite favorable. We hope to obtain similar good results with more typical metals such as iron, and to challenge reactions such as photosynthesis, which involve the use of  $\text{CO}_2$  gas.

These wonderful results remind me of my childhood when I admired photosynthesis.

By the simple action of exposing plants to sunlight, starch can be synthesized from water and  $\text{CO}_2$ . Of course, I was awestruck by this amazing ability exhibited by plants. Previously, it was considered impossible to decompose water into hydrogen and oxygen using sunlight alone, but we are actually relatively close to achieving this. Indeed, I believe that the society in which hydrogen can be manufactured, separated, and stored in a controlled manner without putting a burden on the environment is just around the corner. In addition, the establishment of this technology could lead the way to solving a range of global issues, such as food shortages and the energy crisis.

However, to achieve this, we need young researchers. In science, fresh ideas are abundant until a researcher reaches their 30s. I therefore hope that young researchers will not only focus on achieving results, but will also look at their infinite potential and future.



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