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Remaking natural complexity

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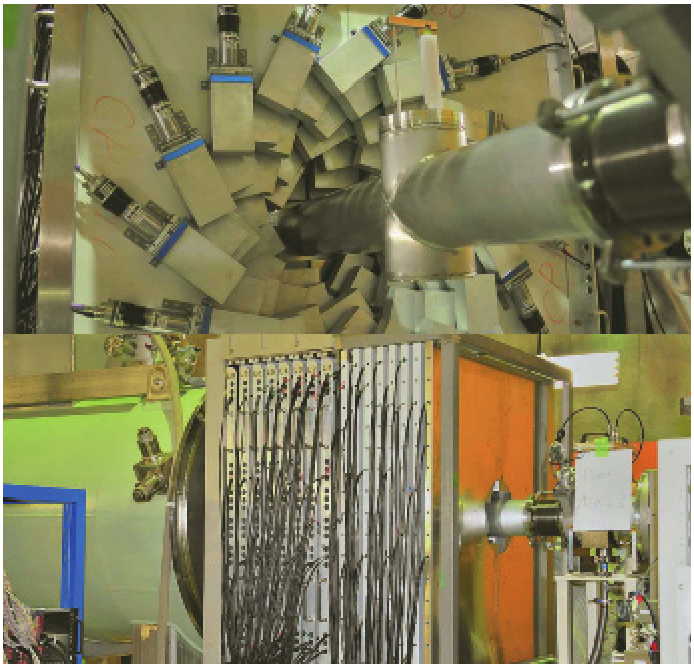
Too many neutrons break the rules

Unusual behavior in an exotic isotope of neon challenges the traditional foundations of nuclear physics



Li Kuoang

Figure 1: The detector array, DALI2, used to measure the gamma-rays emitted after excitation of ^{32}Ne nuclei, during construction (top) and completed (bottom). About 180 detectors are arranged around the beam pipe, in which ^{32}Ne nuclei collide with a carbon target.

Nuclear physicists are fascinated by so-called 'exotic' nuclei, which are always on the edge of breaking apart because they contain too many, or too few, neutrons. Studying them, however, is problematic because exotic nuclei are very difficult to produce, and have a very short lifetime.

Now, physicists can work with a strong beam of exotic nuclei produced in the Radioactive Ion Beam Factory (RIBF) at the RIKEN Nishina Center for Accelerator-Based Science in Wako. The RIBF contains the world's most powerful cyclotron, which can accelerate ions close to the speed of light and produce unstable isotopes that have never been studied before.

RIKEN's Pieter Doornenbal and Heiko Scheit, and their co-workers from Japan, China, France and Germany have used the RIBF to produce and study an exotic isotope of neon (Ne), called ^{32}Ne. They report that ^{32}Ne belongs to a rare group of isotopes that are strongly deformed, and challenge the traditional foundations of nuclear physics[1].

Magic numbers get tricky

Protons and neutrons at the center of an atom are generally modeled as individual particles moving in particular orbits, or shells, similar to the electron shells orbiting around a nucleus. 'Magic numbers', which represent some particularly stable configurations of protons and neutrons, are an important concept in the nuclear shell model. The magic numbers are: 2, 8, 20, 28, 50, 82 and 126.

Atomic nuclei containing a magic number of protons or neutrons tend to be more tightly bound together, and are less likely to undergo nuclear decay, because there are large gaps in the energy spectra of orbits that these particles can occupy.

However, exotic nuclei disobey these rules, especially when they have many more neutrons than protons. For example, isotopes of neon, sodium and magnesium that contain 20 neutrons show no large energy gaps, even though 20 was traditionally a magic number.

"It was shown … that 20 is not a magic number anymore for these nuclei, which was a great surprise," says Scheit. Nuclear physicists now refer to this group of misbehaving isotopes as the 'island of inversion'.

"The island of inversion is a region in the nuclear chart where the standard ordering of single particle energies is inverted, meaning that the isotopes have a completely different structure from their counterparts nearer to stability."

Targeting the island of inversion

The island of inversion for neon begins at ^{30}Ne, which has 20 neutrons, but no heavier neon nuclei have been studied until now. Scheit and co-workers were able to perform the first spectroscopic study of ^{32}Ne (22 neutrons) thanks to the technology in place at the RIBF.

"The RIBF is a new-generation radioactive ion beam facility," explains Scheit. "We wanted to study ^{32}Ne for a long time, but we were not able to do so until the RIBF was completed [in 2007]."

The RIBF produces over a hundred times more ^{32}Ne than any other facility in the world, mainly because its ion beams are far more intense and energetic.

In 1990 at the French facility GANIL, the rate of production of ^{32}Ne was only four nuclei in two days, and in 1997 at RIKEN only 90 nuclei per day could be produced, according to Scheit. "Now, at the new facility, we have five nuclei per second!"

Finding neon

To produce ^{32}Ne, the researchers direct a powerful beam of calcium-48 ions onto a

Heiko Scheit

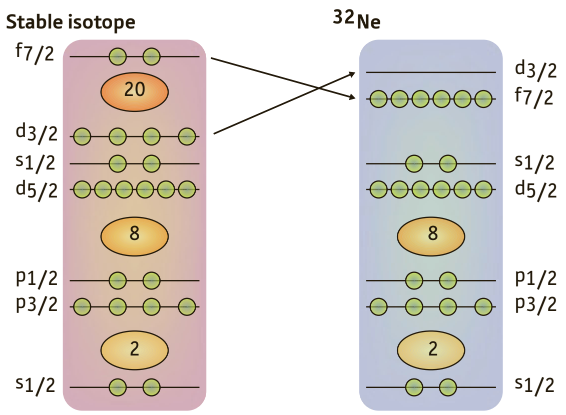


Figure 2: Schematic showing the neutron shells for a stable nucleus (left) and ^{32}Ne (right) (orbitals labeled f, d, s or p; total angular momentum labeled $_{7/2,\,3/2,\,1/2,}$ or $_{5/2}$). The small circles represent the 22 neutrons in each nucleus and the numbers in ellipses represent magic numbers. The large energy gap in ^{32}Ne, where the magic number is 20, no longer exists. The $f_{7/2}$ orbital is now below the $d_{3/2}$ orbital so has 'intruded' into the sd-shell giving rise to intruder configurations—a major characteristic of nuclei belonging to the island of inversion.

rotating target made of beryllium. During this collision, if exactly ten protons and six neutrons are 'knocked off' a calcium ion then ^{32}Ne is the remainder and continues down the beamline. "The probability of this happening is so low it takes 10^{11} (100,000,000,000) calcium-48 ions to produce one ^{32}Ne nucleus!" says Scheit.

All the collision products are detected by the BigRIPS fragment separator—a cutting-edge machine and another key to the RIBF's success. BigRIPS contains huge superconducting magnets that sort the different types of particle based on their charge and mass. Most are discarded, leaving a beam of separated ^{32}Ne.

"The ^{32}Ne in the beam is in its ground state," explains Scheit. "To excite it we focus it onto a thick carbon target. After excitation, a gamma ray is emitted and the nucleus is again in the ground state. By measuring the energy of this gamma ray, we know the energy of the first excited state."

After just eight hours of running their experiment (Fig. 1), the researchers detected enough gamma rays to prove that the energy of the first excited state of ^{32}Ne is very low. There is no shell energy gap, meaning that ^{32}Ne, like ^{30}Ne, belongs in the island of inversion.

The results imply that ^{32}Ne nuclei are very deformed, despite being close to the magic number of 20 neutrons. The energy levels of individual protons and neutrons interfere with one another forming so-called 'intruder configurations'.

"Normally the single particle energy levels are ordered in a certain way," explains Scheit. "If that order is inverted, we speak of intruder configurations, because the normally upper levels now 'intrude' into the lower levels (Fig. 2)."

The researchers who collaborated to produce unstable ^{32}Ne-nuclei using the Radioactive Ion Beam Factory (RIBF) at RIKEN, including Heiko Scheit (front row, third from left), Pieter Doornenbal (back row, fifth from left) and head of laboratory Hiroyoshi Sakurai (front row, seventh from left).

New candidates already in their sites

These findings come almost exactly 30 years after French researchers[2] first noticed a much lower than expected energy of the first excited state in the magnesium isotope ^{32}Mg. Scheit hopes that the world-leading facilities at the RIBF will help scientists unravel more mysteries about exotic nuclei.

"Soon we would like to extend our studies to ^{38}Mg and also study other properties of ^{30}Ne, ^{32}Ne and ^{36}Mg," he says. "All these studies are currently only possible here at the RIBF." ■

1. Doornenbal, P., Scheit, H., Aoi, N., Takeuchi, S., Li, K., Takeshita, E.,Wang, H., Baba, H., Deguchi, S., Fukuda, N. *et al.* Spectroscopy of ^{32}Ne and the "island of inversion". *Physical Review Letters* **103,** 032501 (2009).
2. Détraz, C., Guillemaud, D., Huber, G., Klapisch, R., Langevin, M., Naulin, F., Thibault, C., Carraz, L.C. & Touchard, F. Beta decay of $^{27-32}$Na and their descendants. *Physical Review* **C 19**, 164–176 (1979).

About the researcher

Heiko Scheit was born in Germany in 1971. After completing basic physics training at the Friedrich-Schiller-University in Jena, Germany, he went to Michigan-State-University (MSU) in Michigan, USA, where he specialized in nuclear physics and obtained his MS (1997) and PhD degrees (1998) carrying out research projects at the National Superconducting Cyclotron Laboratory (NSCL) located on the MSU campus. Next he went to Max-Planck-Institute for Nuclear Physics in Heidelberg, Germany, where, after two years of postdoctoral experience, he became the nuclear physics group leader in the division of Dirk Schwalm. After a short visit to the NSCL, he took up a permanent staff position at the RIKEN Nishina Center in the Radioactive Isotope Physics Laboratory. His research focuses on the experimental study of the structure of light exotic nuclei far from stability, which are produced at the newly commissioned Radioactive Ion Beam Factory of the RIKEN Nishina Center.

Chemistry gets a new set of eyes

Imaging electron movements that cause chemical reactions is now possible by using high-speed lasers

Electrons can initiate chemical reactions at such breakneck speeds—often within a trillionth of a second—that the details of their movements remain largely inscrutable. But now, RIKEN researchers have developed a laser spectroscopy technique with unprecedented time resolution that can trace the paths of electrons during a photochemical reaction[1].

According to Toshinori Suzuki from the RIKEN Advanced Science Institute in Wako, the principal author of the study, this new method promises chemists a clearer view of chemistry and molecular functionality than ever before.

"Chemical reactions are after all just the motion of nuclei pushed by electrons," says Suzuki. "Therefore, the key is to know why and how electrons push them."

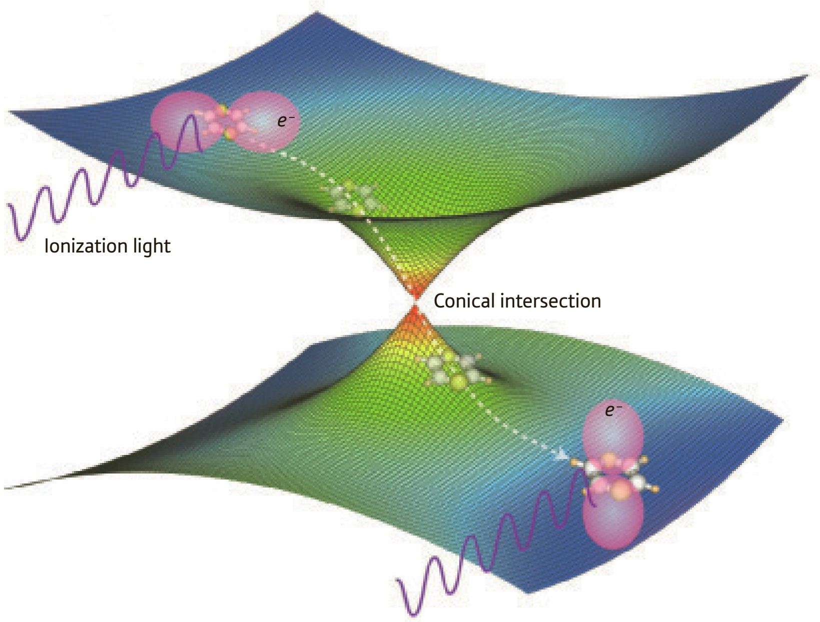


Figure 1: Schematic of internal conversion via conical intersection of potential energy surfaces. Ionization from the upper electronic state creates photoelectrons ejected perpendicular to the laser polarization, while the lower state provides parallel ejection.

A need for speed

In their latest work, Suzuki and his team tackled a fundamental chemical problem: how do electrons move in a molecule after coming into contact with light? Answering this question can provide insight into many molecular reactions, including the stability of DNA exposed to ultraviolet light.

When DNA absorbs ultraviolet radiation, it must quickly disperse this excess energy through internal conversion, a process where electrons jump from higher to lower energy states, to prevent formation of free radicals that can split this vital polymer apart.

After undergoing internal conversion, electrons in DNA stimulate the nuclei to move, which releases the excess energy. These nuclear movements take place through what is known as a conical intersection (Fig. 1)—a quantum mechanical version of a funnel—that ensures DNA rapidly returns to its original state without free radicals.

For the past ten years, Suzuki has wanted to study internal conversion through conical intersections, but was hampered by technical limitations. "This is one of the fastest electronic deactivation processes," states Suzuki. "To observe it in real-time, we needed lasers with as short a pulse duration as possible."

The right tools for the job

To visualize electron movements, Suzuki and colleagues pioneered the development of time-resolved photoelectron imaging[2]. This technique uses two lasers that emit light in quadrillionth of a second, or femtosecond, bursts—faster than atoms can move—to track the distribution of electrons in a molecule during a photo-reaction.

The first laser burst, called the pump, excites an electron in a molecule from a lower to a higher energy state. This photo-excitation initiates internal conversion in the molecule. Then, the second laser burst, called the probe, ejects an excited electron from the molecule, creating an easily detectable photoelectron.

The signal of photoelectrons is strongest immediately after the pump burst: this is when the most electrons are moving in the molecule. Capturing this short-lived signal requires an exceptionally brief time delay—on the order of 20 femtoseconds—between the probe and pump lasers.

Depending on the pump–probe time delay, photoelectrons are generated from different molecular orbitals—finite regions of space with distinct energies and symmetries. Suzuki developed a two-dimensional detector that records the photoelectron angular distributions (PADs)—the ejection angles from

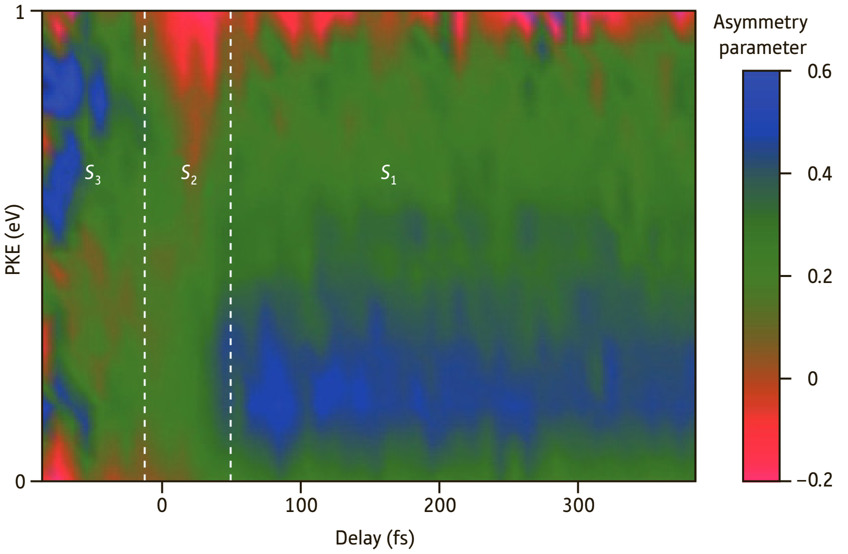


Figure 2: Two-dimensional map of photoelectron asymmetry for different times in femtoseconds (fs) and photoelectron kinetic energy (PKE). Three different electron transitions (S_1–S_3) were observed in the experiment. Red colors indicate photoelectrons ejected perpendicular to the laser probe, while blue colors indicate parallel ejection.

molecular orbitals—and kinetic energies to disentangle the measured signal into separate orbital pathways.

"The PADs carry information about the three-dimensional distribution of electrons in a molecule," says Suzuki. "They give us direct knowledge about how electrons are moving around."

Seeing pyrazine in a new light

Using these high-speed tools, the researchers mapped out how electrons in a molecule called pyrazine, a hexagonal ring containing four carbon and two nitrogen atoms, initiate movement through a conical intersection when excited by ultraviolet light.

According to Suzuki, there were two main types of molecular orbitals in pyrazine involved in the photochemical reaction. One, called the pi orbital, was delocalized around the 6-membered pyrazine ring. The other, called a non-bonding orbital, was localized on the nitrogen atoms.

The researchers used the pump laser to excite one of the pi orbital electrons into a higher energy state. This created a vacancy in the pi orbital, which, within 24 femtoseconds, was filled by an electron from the nitrogen non-bonding orbital.

Because the non-bonding electron is energetically higher than the pi electron, it carries an excess of energy when filling the vacancy. The excess energy dissipates through molecular vibrations that funnel the nuclei through the conical intersection.

Picture-perfect detection

Suzuki says that because the kinetic energy distribution of photoelectrons did not change greatly during the experiment, only the PADs could provide unique evidence of internal conversion and fingerprint the participating electronic states.

A two-dimensional map of electron movements was created by plotting how the photoelectron asymmetry parameter—the ratio of signal intensity at any two ejection angles—changed with pump–probe time delay and kinetic energy (Fig. 2).

The initial fast movement of an electron from non-bonding to pi orbital in pyrazine was identified on the map as a change in photoelectron asymmetry parallel to the laser light polarization—indicating an excited electron created by internal conversion from a higher to a lower energy state.

Processes where excited electrons were ejected from a higher energy, without internal conversion, produced asymmetry regions on the map oriented perpendicular to the probe laser. These graphic illustrations of polarization gave the scientists a real-time view of electron distributions.

Eyeing success

Now that chemists have a new set of eyes to observe fast electron movements, Suzuki expects a more complete picture of complicated chemical reactions to emerge.

"It is not rare that electronic states change several times during single chemical reactions," states Suzuki. "Our method allows us to see such changes more clearly than ever."

"And," he says, "such important concepts come along not only with sweat and tears, but with beautiful images as well." ■

1. Horio, T., Fuji, T., Suzuki, Y.-I. & Suzuki, T. Probing ultrafast internal conversion through conical intersection via time-energy map of photoelectron angular anisotropy. *Journal of the American Chemical Society* **131**, 10392–10393 (2009).
2. Suzuki, T. Femtosecond time-resolved photoelectron imaging. *Annual Review of Physical Chemistry* **57**, 555–592 (2006).

About the researcher

Toshinori Suzuki was born in Yamagata, Japan, in 1961. He graduated from the Department of Chemistry, Faculty of Science, Tohoku University, in 1984, and obtained his PhD degree in 1988 from the same university. He then became a research associate at the Institute for Molecular Science (IMS) in Okazaki, between 1988 and 1990, and a JSPS fellow for research abroad to carry out research on molecular beam scattering at Cornell University and the University of California, Berkeley, between 1990 and 1992. He returned to Japan as an associate professor at IMS, where he started his independent research group on chemical reaction dynamics in 1992. He moved to RIKEN to become a chief scientist and the director of the chemical dynamics laboratory in 2002. He has received the Broida Award from the international symposium on free radicals, the JSPS Award, and the IBM Science Award, the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology for his achievements in chemical reaction dynamics.

Capturing electrons in action

A technique for characterizing ultrafast light pulses will lead to better optical probes for studying electron dynamics

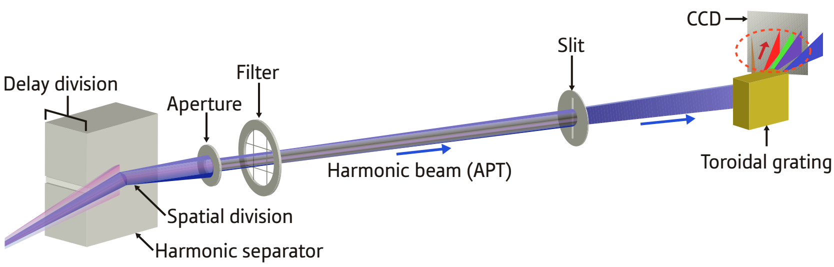


Figure 1: The experimental set-up for measuring the coherence between pulses in an attosecond laser pulse sequence. The higher harmonics of a light pulse (blue) are spatially separated from one another in the harmonic separator. Each harmonic is then split in two parts, which travel down the arm of the instrument, before being recombined and focused onto a CCD camera.

Scientists at RIKEN have developed a way to measure the wavelike properties of ultrafast (attosecond) light pulses—an important step toward being able to probe the dynamics of electrons, atoms and molecules.

Quantum mechanics theory can completely describe the structure of atoms and molecules. But directly observing electronic motion in an atom requires a technique that can take snapshots of the electron on time scales of less than a femtosecond (10^{-15} s). To this end, scientists are working to generate ultraviolet light pulses that are only 10–100 attoseconds (10^{-18} s) long.

Electrons, like light, have wavelike properties. Thus, when a fast optical pulse—or sequence of pulses—interacts with the electrons in an atom, it creates an interference pattern that can effectively image the electron over time.

The challenge is to create a sequence, or 'train', of pulses, each with the same, well-defined wavelike properties. For this reason, the technique developed by Yasuo Nabekawa and colleagues at the RIKEN Advanced Science Institute in Wako allows them to compare consecutive pulses in an attosecond light pulse series[1].

"Ultimately, the goal of our research is to control atoms and molecules with the attosecond pulse train," says Nabekawa.

To produce the attosecond pulses, the team started with a series of intense laser-generated ultraviolet light pulses, each approximately 40 femtoseconds in duration. When the laser pulses interacted with a gas of xenon atoms, they generated pulses of light with odd integer (1, 3, 5, etc…) multiples of the frequency of the original laser pulse. These higher frequency pulses—or, 'harmonics'—reached into the attosecond range.

Detecting ultrafast motion in atoms and molecules requires that the pulses in the train are 'coherent' with each other, meaning they are in phase, similar to soldiers marching in lock-step. The team therefore designed its experiment specifically to determine the coherence between the pulses in each of the higher harmonics.

Spatially separating the harmonics allowed the team to measure the coherence between pulses of each harmonic individually. Each harmonic was then split into two beams that traveled down a long arm, before being recombined (Fig. 1). A CCD camera measured the interference pattern between the recombined beams, which provides a measure of the coherence between pulses.

While the current measurements relate to characterizing the optical pulse itself, the RIKEN team plans to build upon these experiments to study ionization and dissociation of electrons from atoms and molecules. ■

1. Nabekawa, Y., Shimizu, T., Furukawa,Y., Takahashi, E.J. & Midorikawa, K. Interferometry of attosecond pulse trains in the extreme ultraviolet wavelength region. *Physical Review Letters* **102,** 213904 (2009).

Rolling out the nanotubes

Synthesis of graphitic nanotubes containing platinum metals achieved through self-assembly techniques

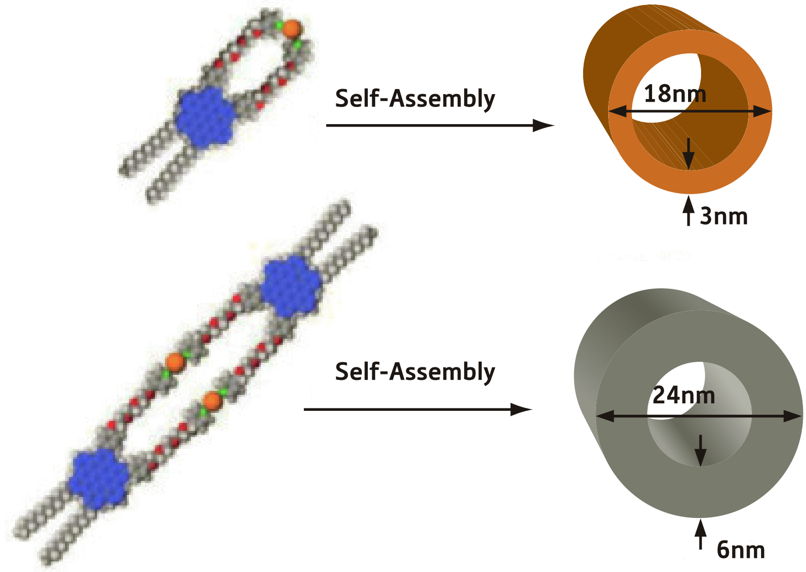


Figure 1: Two examples of nanotubular assemblies fabricated from single hexabenzocoronene amphiphile building blocks (blue/grey/red spheres) and platinum (Pt) metal ions (orange spheres).

Nanoscale materials with well-defined shapes, such as one-dimensional hollow tubes, have attracted the interest of scientists seeking to utilize their unique properties. Nanotubes have large inner and outer surface areas that are accessible to many smaller molecules, meaning they have the potential to be developed into new types of sensors and catalysts.

Efficient techniques to synthesize nanotubes, however, are uncommon. Now, Takuzo Aida and Takanori Fukushima of the RIKEN Advanced Science Institute in Wako and colleagues from the Japan Science and Technology Agency have developed a way to controllably self-assemble graphitic molecules and platinum metals into nanotubes with specific dimensions and structural features[1].

Aida and his team used a molecule called hexabenzocoronene (HBC) as the base for their new nanotubes. Consisting of thirteen aromatic benzene rings interlocked into a large, flat cyclic structure that resembles graphite, HBC is normally used as a building block for liquid crystalline semiconductors.

In 2004, Aida, Fukushima, and colleagues discovered that by adding long hydrocarbon groups and polar chains called triethylene glycol to HBC, they could make the graphitic molecule into an amphiphile[2]—a surfactant that can be dissolved in organic solvents. Recrystallizing a solution of the HBC amphiphiles spontaneously produced new graphitic nanotubes.

In their latest work, the researchers incorporated platinum metals into their nanotubes structures. According to Fukushima, transition metals such as platinum can add useful catalytic, electronic, luminescent, and magnetic functionalities to the nanotubes.

In order to attach platinum metals to the nanotubes, the scientists added a molecule known as pyridine, a nitrogen-containing benzene ring, to the ends of the triethylene glycol chains on the HBC amphiphile.

"Pyridine is one of the simplest and most common molecules for binding transition metals," explains Fukushima. "We thought it fit to use such a general binding molecule in our first attempt to functionalize the HBC nanotubes with transition metals."

By heating a solution of the HBC amphiphiles with platinum metal ions, then allowing the mixture to cool to room temperature, the scientists observed spontaneous formation of new metal-ion-coated graphitic nanotubes (Fig. 1). Altering the assembly conditions produced tubular assemblies with different diameters, lengths, and wall widths.

"Our nanotube can serve as a unique one-dimensional nano-scaffold with not only high structural integrity, but also with beneficial electronic properties such as energy and charge transport capabilities," says Fukushima. "We expect that the combination of these two components might lead to unprecedented phenomenon and functions.". ■

1. Zhang, W., Jin, W., Fukushima, T., Ishii, N. & Aida, T. Metal-ion-coated graphitic nanotubes: controlled self-assembly of a pyridyl-appended gemini-shaped hexabenzocoronene amphiphile. *Angewandte Chemie International Edition* **121,** 4841–4844 (2009).
2. Hill, J. P., Jin, W., Kosaka, A., Fukushima, T., Ichihara, H., Shimomura, T., Ito, K., Hashizume, T., Ishii, N. & Aida, T. Self-assembled hexa-peri-hexabenzocoronene graphitic nanotube. *Science* **304,** 1481–1483 (2004).

Natural products: Cage closed

Synthesis of a complex substructure of a biologically active plant-derived organic compound will allow investigation of its mechanism of action

A team of RIKEN researchers has synthesized a key fragment of the natural product called physalin B, which shows both antitumor and anti-inflammatory activity. The work will make an important contribution towards the goal of synthesizing the whole compound, which has eluded chemists since its discovery in 1969. Mikiko Sodeoka from the Advanced Science Institute and co-workers report their achievement in the journal *Angewandte Chemie International Edition*[1].

Physalin B is a secondary metabolite of plants of the genus *Physalis*—commonly known as ground cherries. This group of plants is native to tropical and warm temperate regions and is related to the tomato. The round fruit are encased in a papery husk and have a red/orange skin. Some members of the group are decorated as lanterns in honor of ancestors during Japan's *Obon* season (Fig. 1). Some are also a popular food in France, and are a well-known ingredient of traditional Chinese medicine.

"Physalin B contains 8 rings and 11 stereocenters in a very compact structure," explains Sodeoka. "We were interested by the biological activity of the compound, but as synthetic chemists, we also found the complex structure of the compound intriguing."

On close examination, the octacyclic structure of physalin B contains a bicyclic structure common in a number of natural products, and a far less common tetracyclic cage-like structure (Fig. 2). Sodeoka and colleagues anticipate that the interesting biological activity of physalin B arises from this unusual structure. They also expected that synthesis of this fragment of the structure would be

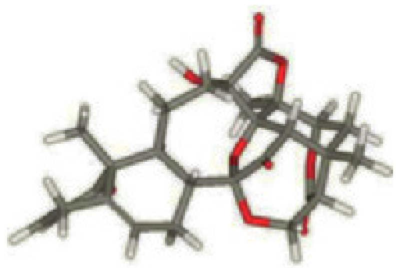


Figure 2: The structure of the natural product physalin B. (Carbon atoms, grey; oxygen, red; and hydrogen, white).

challenging, as it contains a large number of stereocenters—in this case, carbon atoms with four different substituents that have non-identical mirror images—each of which must be constructed in a selective fashion.

"The key to our process is a four-step sequence of chemical reactions that occur in a single pot under very mild conditions," says Sodeoka. "The occurrence of [so-called] domino reaction sequences under such mild conditions points towards how these molecules arise in nature," she continues.

Ultimately, Sodeoka and co-workers plan to complete a total synthesis of physalin B. Alongside this, the team hopes to construct synthetic analogues of physalin B to identify which parts of the complex structure are important for the biological activity. They hope that this will allow them to identify which proteins the physalin B binds to and help to determine the mechanism of action of this interesting molecule. ■

Figure 1: A fruit from a plant of the *Physalis* genus, the source of the biologically interesting natural product physalin B.

1. Ohkubo, M., Hirai, G. & Sodeoka, M. Synthesis of the DFGH ring system of type B physalins: highly oxygenated, cage-shaped molecules. *Angewandte Chemie International Edition* **48**, 3862–3866 (2009).

Of fibers and filaments

A chance observation leads to potential insights into the basis for cell damage associated with disorders like Alzheimer's disease

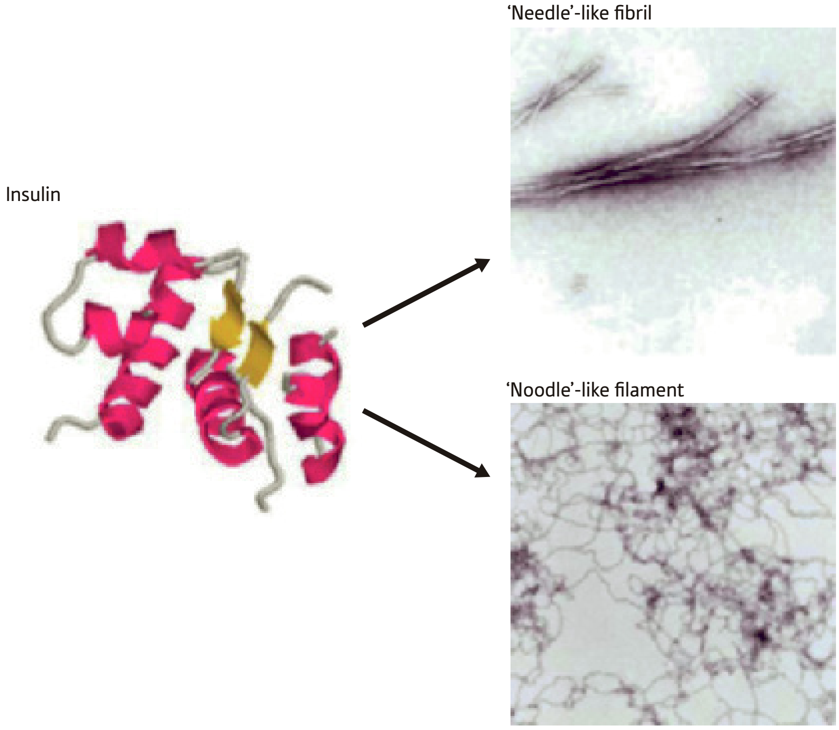


Figure 1: Structural differences of the insulin protein. Under different chemical conditions, the normally helical insulin protein rearranges into amyloid plaques composed of stiff 'needle-like' fibers or floppy 'noodle-like' filaments, with different physiological effects.

Decades of research have failed to conclusively crack the mystery of how amyloid-associated diseases like Alzheimer's do so much damage, but new findings by researchers at RIKEN suggest that part of the answer may lie in the structural rearrangements observed in plaque-forming proteins.

Although there is a 'preferred' structure for any particular protein, certain conditions can cause proteins to rearrange into new conformations that may dramatically alter their activity. For instance, the pathology of many serious diseases—including Parkinson's and Alzheimer's diseases—has been linked with formation of specific proteins into dense, clumps of fibrils known as amyloid plaques.

The hormone insulin, normally composed of two helical subunits, undergoes dramatic rearrangements under acidic conditions that cause it to form toxic amyloid fibrils. Although this transition is well known, Tamotsu Zako and his colleagues at the RIKEN Advanced Science Institute in Wako were recently taken aback to find that bovine insulin undergoes a different type of rearrangement when prepared in the presence of the reducing agent tris(2-carboxyethyl)phosphine, forming spidery filaments rather than stiff fibrils[1] (Fig. 1).

In its fibrillar state, insulin loses its helical characteristics and assumes a structure known as a β-sheet, a two-dimensional strip composed of multiple linear protein strands. On closer analysis, Zako's team noted that insulin subunits within filaments also assume a β-sheet conformation. However, they noted a subtle difference: in filaments, these sheets are antiparallel rather than parallel, consisting of aligned polypeptide chains that zigzag back and forth rather than running in the same direction.

There was a more important difference, however. When cultured cells were treated with increasing doses of fibrillar insulin, they died in greater numbers, but no such toxicity was observed from filamentous insulin. "It was very unexpected and surprising that the cell toxicity of 'noodle-like' insulin was much different from 'needle-like' fibrils," Zako says.

This suggests that the secret of amyloid toxicity may lie in the structure of the protein aggregates, perhaps resulting from direct physical damage to cell membranes by fibrils. Zako's team is now attempting to resolve the basis for these differences in toxicity through structural analysis, but is also examining characteristics of another protein with similar behavior to see whether their findings may have broader implications for other amyloid-forming proteins linked with human pathologies, such as Alzheimer's-associated amyloid-β protein. "We want to know whether other filamentous amyloids are also non-toxic," he says. "If so, it will become possible to generalize our findings." ■

1. Zako, T., Sakono, M., Hashimoto, N., Ihara, M. & Maeda, M. Bovine insulin filaments induced by reducing disulfide bonds show a different morphology, secondary structure, and cell toxicity from intact insulin amyloid fibrils. *Biophysical Journal* **96**, 3331–3340 (2009).

One gene shy of confidence

A timid knockout mouse separates conflicting emotional behavior for the first time

Figure 1: Mice lacking active *X11L* genes show abnormal 'approach' behavior to food in the presence of other mice.

A RIKEN-led group has developed a novel mouse strain that opens a door to future research into emotion.

Animal behavior is typically the outcome of conflicting emotions. The novel mouse shows abnormal approach, but not avoidance, behavior. So researchers can use it to dissect how emotions make us decide to approach or avoid, which may provide a key to understanding shyness.

Group leader Shigeyoshi Itohara and colleagues at the RIKEN Brain Science Institute in Wako and at Hokkaido University genetically engineered a mouse strain in which the *X11L* gene was purposefully deleted or 'knocked out'. The researchers recently published a detailed analysis of the mutant mice in *The Journal of Neuroscience*[1].

X11L is a protein known to modulate neural activity in the brain. It also suppresses synthesis of the fibrous protein amyloid β, thought to cause Alzheimer's disease. The X11L knockout (X11L-KO) mouse was originally developed in the hope of producing a model for Alzheimer's disease, but it exhibited normal memory functions and learning capabilities.

The researchers did notice something unusual, however. The X11L-KO mice were subordinate to normal mice under conditions when the two needed to compete for food (Fig. 1). Mutant mice always lost weight compared to normal mice, yet displayed no loss of appetite or physical weakness.

The researchers then ran a series of experiments to identify the origin of this subordinate behavior. When placed in situations used to examine anxiety—in open fields or on elevated mazes, for instance—the X11L-KO mice responded normally. Itohara and colleagues found that resident X11L-KO mice were less likely to approach intruders, and demonstrated a decreased tendency to dig and burrow, and to bury marbles. These tests indicated the subordinate behavior of X11L-KO mice was due to a deficit in motivated approach behavior, not heightened anxiety or depressive characteristics—both of which are thought to be associated with avoidance behavior.

Chemically, X11L-KO mice displayed an imbalance of monoamine nerve modulation compounds in the forebrain. The abnormal responses could be reversed by the addition of active *X11L* genes to X11L-KO mice during development.

"These findings suggest that X11L is involved in the development of the neural circuits that contribute to conflict resolution," says Itohara. "This mouse will provide us with opportunities to understand the mechanisms underlying approach behavior, and how to moderate it. With sufficient knowledge, we may be able to selectively modulate behavior, and possibly help overcome shyness in people." ■

1. Sano, Y., Ornthanalai, V.G., Yamada, K., Homma, C., Suzuki, H., Suzuki, T., Murphy, N.P. & Itohara, S. X11-like protein deficiency is associated with impaired conflict resolution in mice. *The Journal of Neuroscience* **29,** 5884–5896 (2009).

Sense of attraction

Researchers identify a population of olfactory sensory neurons that is responsible for zebrafish attraction towards amino acids

Figure 1: A zebrafish searching for food.

Many olfactory cues pervade the aquatic environment of fish. These cues stimulate various important behaviors, such as escape from predators, or attraction towards food sources or potential mates.

Amino acids are the building blocks of proteins, and are therefore key nutrients in the diet of various animal species, including the zebrafish (Fig. 1). Now, a group of scientists led by Yoshihiro Yoshihara and Tetsuya Koide at the RIKEN Brain Science Institute in Wako has elucidated which neurons are responsible for carrying olfactory information about amino acids in the aquatic environment from the nose to the brain of zebrafish. They found that the activity of these neurons is required to elicit zebrafish attraction towards amino acids in their environment[1].

Olfactory sensory neurons (OSNs) project from the nose to the olfactory bulb, which is the first relay station for olfactory information in the brain. Each OSN expresses only one type of odorant receptor and responds to a particular set of closely related odors. The OSNs that express the same odorant receptor send their axons together to a specific part of the olfactory bulb.

Yoshihara and colleagues used genetic approaches to express a fluorescent protein in various populations of OSNs. They found that only one of these populations projected to the lateral part of the olfactory bulb, which is known to fire in response to amino acid signals.

When hungry zebrafish were placed into a tank of water with amino acids pumped into one corner, the fish tended to spend more time in the portion of the tank near the amino acids. This suggests that zebrafish are attracted towards the amino acids as a potential source of food. When the researchers blocked synaptic transmission in the population of OSNs that projected to the lateral olfactory bulb, this blocked the so-called 'attractive behavior' of the zebrafish towards the amino acids. Blocking synaptic transmission in other populations of OSNs had no effect on this behavior, but did reduce attractive responses of zebrafish to a putative social pheromone in the environment.

According to Yoshihara, "a combination of genetic, anatomical, and behavioral approaches enabled us to provide a direct functional link between different odor inputs and distinct behavioral outputs through segregated olfactory neural circuits from the nose to the brain." Using similar approaches, Yoshihara says that he and his colleagues "are now investigating neural circuit mechanisms underlying other olfactory behaviors such as escape from predators and memory of mates or related individuals."

1. Koide, T., Miyasaka, N., Morimoto, K., Asakawa, K., Urasaki, A., Kawakami, K. & Yoshihara, Y. Olfactory neural circuitry for attraction to amino acids revealed by transposon-mediated gene trap approach in zebrafish. *Proceedings of the National Academy of Sciences USA* **106**, 9884-9889 (2009).

Natural suppressors of a treatment-induced disease

A naturally occurring population of dendritic cells reduces the incidence and severity of graft-versus-host-disease in mice

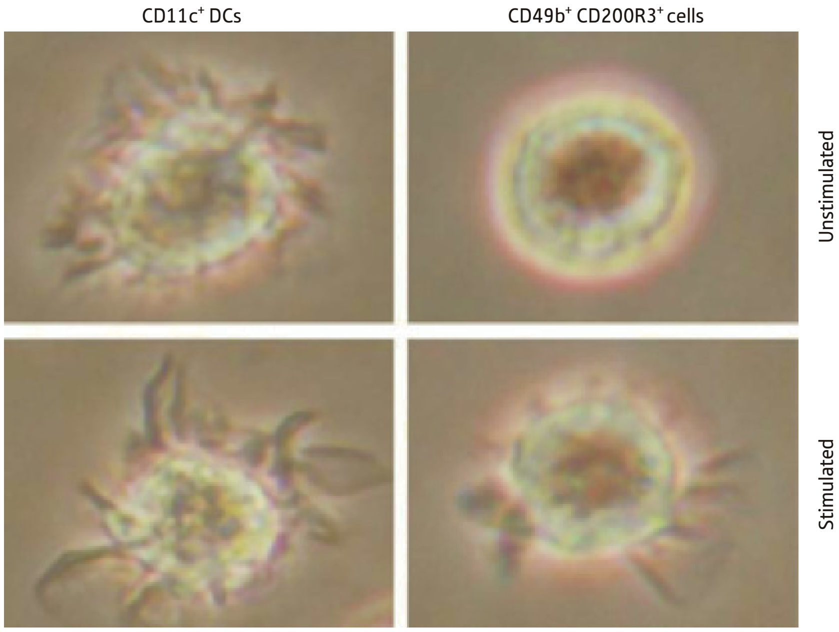


Figure 1: Phase contrast microscopy images (original magnification × 400) showing the morphology of non-regulatory (CD11c$^+$) DCs (left column) and CD200R3$^+$ DC$_{regs}$ (right column) before and after stimulation with a pro-inflammatory agent.

Researchers in Japan have shown that mouse dendritic cells (DCs), which can promote or inhibit inflammation depending on the proteins displayed on their surface, include a subpopulation that exerts beneficial effects during a treatment for leukemia and other malignancies. The treatment—known as allogeneic hematopoietic stem cell transplantation (alloHSCT)—can, in some situations, result in graft-versus-host-disease (GVHD). Acute and chronic GVHD occur when donor immune cells called T lymphocytes recognize and become activated by proteins present on recipient but not donor tissues. The resulting T lymphocyte-driven immune response can result in severe damage to the recipient skin, gastrointestinal tract and liver.

Previous work by these researchers described the generation of regulatory DCs from mouse bone marrow (BM-DC$_{regs}$) that, when injected after alloHSCT, reduce the severity and incidence of acute and chronic GVHD. The team, led by Katsuaki Sato at the RIKEN Research Center for Allergy and Immunology in Yokohama, has now shown that naturally occurring counterparts of BM-DC$_{regs}$ exist and influence the outcome of alloHSCT in mice[1].

The researchers started by searching for genes associated with immunosuppressive DC function. A comparison of the genes expressed in BM-DC$_{regs}$ and non-regulatory DCs revealed that the gene encoding the surface protein CD200R3 is expressed exclusively in BM-DC$_{regs}$. They found that blockade of CD200R3 impaired the ability of BM-DC$_{regs}$ to suppress proliferation of T lymphocytes, whereas forced expression of CD200R3 in non-regulatory DCs reduced their ability to promote T lymphocyte cell division. This indicates that CD200R3 contributes to the immunosuppressive function of BM-DC$_{regs}$.

Reasoning that naturally occurring regulatory DCs might also express CD200R3, the researchers screened blood and spleen cells for CD200R3 expression. They identified a small population of CD200R3-expressing cells that, like BM-DC$_{regs}$, produced immunosuppressive cytokines, which are regulators of the immune system, and inhibit T cell proliferation. These CD200R3$^+$ DCs exhibited a different morphology than non-regulatory DCs (Fig. 1).

When injected after alloHSCT, Sato and colleagues found that these CD200R3$^+$ DCs—like BM-DC$_{regs}$—suppressed the onset and severity of GVHD. Recipients of CD200R3$^+$ DCs contained lower amounts of serum proinflammatory proteins, and higher numbers of immunosuppressive regulatory T lymphocytes. Further highlighting the biological importance of CD200R3$^+$ DCs, pre-treatment with a CD200R3-blocking antibody prior to alloHSCT exacerbated GVHD.

"The functional identification of naturally occurring human DC$_{regs}$, as well as their counterparts generated in the laboratory, may provide an advantageous means of intervening to prevent chronic GVHD after alloHSCT" says Sato. ■

1. Sato, K., Eizumi, K., Fukaya, T., Fujita, S., Sato, Y., Takagi, H., Yamamoto, M., Yamashita, N., Hijikata, A., Kitamura, H., Ohara, O., Yamasaki, S., Saito, T. & Sato, K. Naturally occurring regulatory dendritic cells regulate murine cutaneous chronic graft-versus-host disease. *Blood* **113,** 4780–4789 (2009).

Day in and day out

Fluctuations in the levels of various molecules in the blood provide a reliable indicator of the body's internal clock

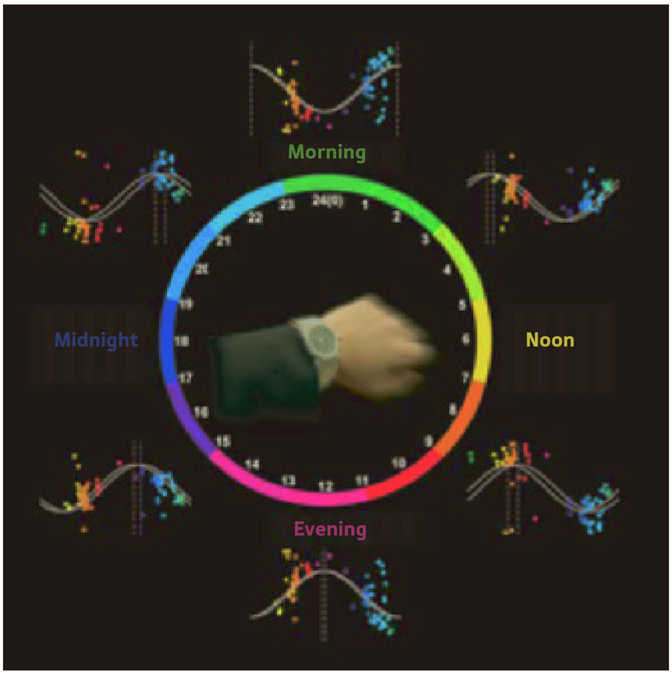


Figure 1: Oscillations in the levels of a number of blood metabolites correlate directly with the passage of internal 'body time' in mice. Each dot in this figure corresponds to an individual metabolite, and its color represents the peak time for that molecule relative to the central 'clock'.

Without consciously checking your watch, your body knows the time by maintaining its own internal clock that tracks the day–night cycle through so-called circadian rhythms. Accordingly, disruption of these cycles, whether due to transient effects of jet-lag or disorders such as familial advanced sleep-phase syndrome, can profoundly affect an individual's ability to maintain a normal pattern of sleeping and waking.

Circadian rhythms also affect a number of other physiological activities, including manifestations of disease and the body's response to therapeutics. "Interestingly, some cancer growth is under circadian clock control," says Yoichi Minami of the RIKEN Center for Developmental Biology in Kobe. "This suggests that if we take drugs with precise timing, we can reduce unwanted effects."

Inspired by the work of 18th Century botanist Karl Linné, who assembled a literal circadian clock composed of flower species that open and close their petals at specific times of day, Minami and colleagues Takeya Kasukawa, Yuji Kakazu, Tomoyoshi Soga and Hiroki Ueda recently set about constructing an analogous 'body clock' for mammals.

To achieve this, they applied sophisticated analytical chemistry techniques to characterize time-of-day-specific fluctuations in the levels of a broad variety of small molecules circulating in the mouse bloodstream[1]. They performed their analysis with mice that were maintained either in fixed light–dark cycles, or in constant darkness, to distinguish variability resulting from external environmental time cues versus purely internal circadian timetables.

Depending on the analytical method applied, the researchers were able to detect between 150 and 300 compounds that appeared to show circadian regulation under both conditions. Once the oscillations of these various metabolites had been characterized, they were able to apply these patterns to determine the body-time at which a blood sample was collected (Fig. 1). Importantly, the accuracy of these measurements was not affected by differences in age, sex or food consumption, and the team was even able to directly observe relative shifts in the circadian clock resulting from simulated jet-lag.

These findings now clear the way for constructing an equivalent internal timetable for people. "One of our main goals is translation of circadian clock research from lab to clinic," says Kasukawa. "If we can show the validity of our method in human beings … our method will contribute to the diagnosis of disease caused by circadian clock dysfunction [and] speed up development of circadian clock-conditioning drugs." ■

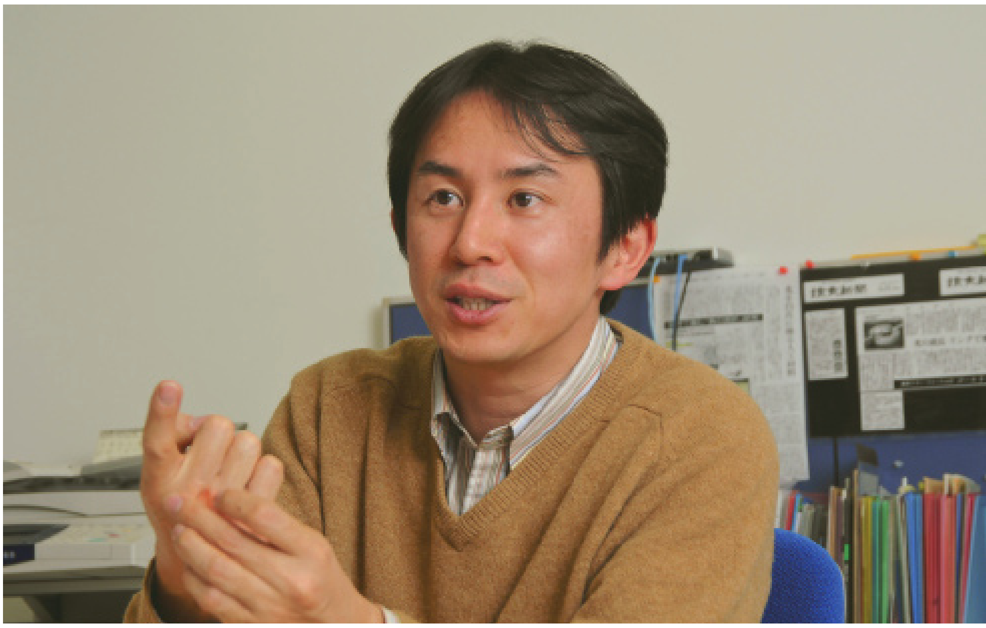
1. Minami, Y., Kasukawa, T., Kakazu, Y., Iigo, M., Sugimoto, M., Ikeda, S., Yasui, A., van der Horst, G.T.J., Soga, T. & Ueda, H.R. Measurement of internal body time by blood metabolomics. *Proceedings of the National Academy of Sciences USA* **106**, 9890–9895 (2009).

Using metamaterials to defy our common understanding of light

Takuo Tanaka

Associate Chief Scientist
Metamaterials Laboratory
RIKEN Advanced Science Institute

'Metamaterials' — artificially created materials with nanostructures designed to control light — are attracting considerable attention for the development of a range of new technologies, such as very thin eyeglass lenses, optical microscopes that will allow the observation of atoms, optical fibers with no transmission loss, and technologies that could make a person invisible. The functions of metamaterials are beyond our common understanding of natural phenomena. Amid intensifying global competition over the development of metamaterials, Takuo Tanaka, Associate Chief Scientist at the RIKEN Advanced Science Institute, and his colleagues succeeded in February 2009 in developing a technology that uses light to fabricate metal into a three-dimensional nanoscale structure, thus making significant progress in metamaterials research. "Metamaterials will surely be able to expand the world of light," says Tanaka. Attention is now being focused on research into how to use metamaterials to defy our common understanding of light.



Technology that will make a person invisible?

In 2006 John Pendry of the Imperial College London, UK, and his colleagues published a paper stating that an object can be made invisible by covering it with a material having special refractive index properties. In their paper, they asserted that an object can be made invisible by diverting light coming from behind the object such that it is no longer blocked by the object. This proposal made headlines throughout the world as a possible technology for making a person invisible. However, the technology requires a material that can be used to arbitrarily control the traveling direction of light.

Light traveling through air changes direction when it enters a lens made of glass or plastic by a process called refraction. The degree of refraction, or the amount of deviation in the traveling direction of light at a boundary between two media, is determined by the refractive index (n), which is a constant for each medium. Light is an electromagnetic wave composed of interacting electric and magnetic components, which in turn interact with the medium through which the light is traveling. The degree of interaction between a material and the electric component is given by the relative permittivity (ε), while the interaction with the magnetic component is determined by the relative magnetic permeability (μ) of the material. The refractive index is then given by the product of the square roots of these two physical quantities: $n = \sqrt{\varepsilon}\sqrt{\mu}$. It is common knowledge in optics, however, that at the wavelengths of visible light, natural substances only interact with the electric component of the electromagnetic wave, and not with the magnetic component; that is, the relative magnetic permeability of natural substances is fixed at unity, and the refractive index is determined solely by the relative permittivity.

"Creating metamaterials that interact with the magnetic wave of the light enables us to obtain various refractive indices," says Tanaka. "'Meta' means 'transcend', and a metamaterial is a material that transcends the limits of our common understanding of optics."

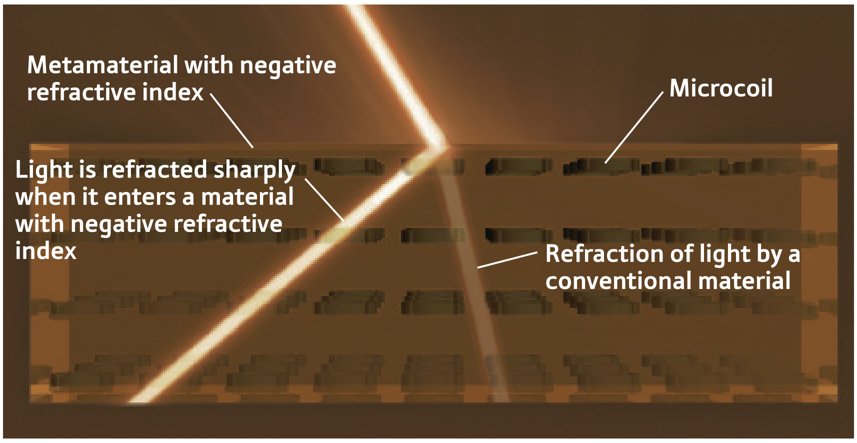


Illustration by Nariyuki Yoshihara

Figure 1: Metamaterials with negative refractive index.
Microcoils in a metamaterial interact with the magnetic component of the light wave to refract the beam at a sharper angle.

Using metamaterials with negative refractive index to observe atoms and molecules

How can we create metamaterials? "The principle is not difficult to understand. Just try to remember the phenomenon of electromagnetic induction you learned in your junior high school science class," says Tanaka. Moving a magnet near a coil of wire causes an electric current to flow through the coil: that is the phenomenon of electromagnetic induction. "An electric current flows through the coil so that the changes in the magnetic field caused by the motion of the magnet can be canceled out. Use of this principle makes it possible to generate magnetism in a material in the form of coils even if the material is not itself magnetic. For example, nanoscale metal coils smaller than the wavelength of light could be incorporated into a transparent plastic or glass material. These coils would then interact with the magnetic waves of light to cause an electric current to flow through them in accordance with the principle of electromagnetic induction, changing the macroscopic magnetic permeability of the material."

Metamaterials are now attracting worldwide attention, triggered by the paper published in 2000 by Pendry and his colleagues, who claimed, "A material with a negative refractive index would make it possible to use light to observe infinitesimally small objects." Visible light has wavelengths of about 400–700 nm, and structures smaller than half the wavelength are not visually observable. This is the common understanding of light. However, the paper by Pendry and his colleagues has defied this common understanding; the use of light to observe living cells at the atomic or molecular level would greatly contribute to the development of life sciences. Furthermore, use of light to pattern a semiconductor circuit with a line width of several nanometers would dramatically improve the performance of computers.

"Professor Pendry and his colleagues claimed in their paper that a lens made of a metamaterial with a negative refractive index could be used to amplify the 'near-field light' that includes the information of structures that are smaller than the wavelength of light, and make the light reach our eyes. Near-field light can be generated when an object is irradiated with light, but it immediately diminishes without reaching our eyes. Thus, the successful amplification of near-field light would be a landmark event."

As early as 2000, a research group at the University of California at San Diego, USA, successfully used microwaves, which are longer in wavelength than visible light, to fabricate a metamaterial with a negative refractive index, prompting global competition over the development of metamaterials with negative refractive indices for visible-light applications.

Metamaterials that do not reflect light

"A microscope is an optical instrument that combines various optical techniques. Based on the microscope techniques, I have studied how to use light to observe and fabricate three-dimensional structures. When I joined RIKEN in 2003, I began exploring a new research theme, and I became interested in metamaterials around 2004."

Tanaka and his colleagues started by theoretically confirming the feasibility of developing metamaterials that can interact with the magnetic component of visible light. In 2005 they demonstrated theoretically, for the first time, that a metamaterial with a negative refractive index throughout the entire visible-light wavelength region can be created by fabricating nanoscale silver coils and arranging them in a special pattern (Fig. 1). Tanaka and his colleagues soon started to explore theoretically what can be achieved with metamaterials.

"The creation of negative refractive index materials requires negative values in terms of both relative permittivity and relative magnetic permeability. However, the creation of negative refractive index materials is not the only application of metamaterials. Since global attention was focused on negative refractive index, we attempted to investigate what would happen if the relative magnetic permeability is increased to a value larger than 1.0."

In 2006 Tanaka and his colleagues proposed an idea for a metamaterial that eliminates light reflection completely by introducing a relative magnetic permeability of larger than 1.0. A material that does not completely reflect light would contribute significantly to the development of light-based information technology. "Light can maintain 99.9% of its intensity even if it

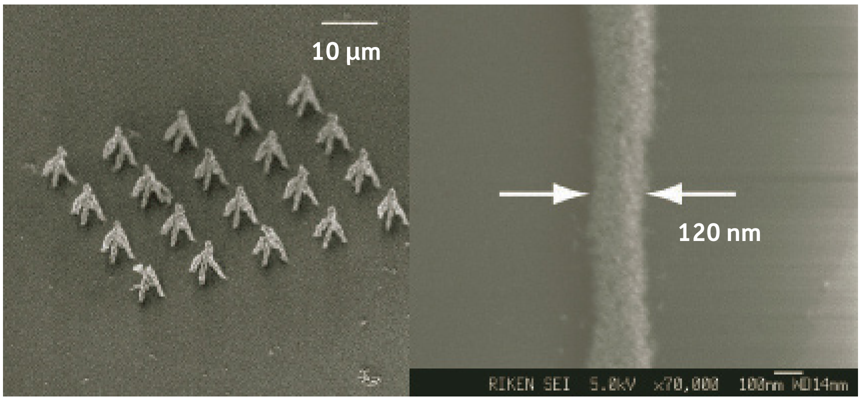


Figure 2: Fabricated three-dimensional metal structure (left), and a fine wire (right).
It is expected that three-dimensional micro-fabrication techniques will allow microcoils to be incorporated into transparent materials with all orientations, thus providing a metamaterial that can interact with the magnetic component of light.

is transmitted through 1 km of optical fiber. However, it loses as much as 4% of its intensity at the ends of the optical fiber. If a metamaterial that does not reflect light is used at the ends of the optical fiber, all of the light can be made to enter and exit the optical fiber."

A more familiar example is a dramatically thinner lens with a larger relative magnetic permeability. A metamaterial with a refractive index five times greater than glass can be used to create a lens five times thinner than conventional lenses. This will also lead to the development of small, lightweight lenses for optical equipment such as cameras. Furthermore, a significantly greater demand for metamaterials with larger refractive indices is expected in various fields.

Three-dimensional nanoscale metal fabrication

How is it possible to create metamaterials that can interact with the magnetic component of light? The answer is to create a multitude of nanoscale coils smaller than the wavelength of light passing through the material.

In August 2008 a research group at the University of California at Berkeley, USA, announced that it had successfully fabricated metamaterials with a negative refractive index at near-infrared and visible wavelengths. One of the metamaterials consists of multiple layers of two-dimensional net-like structures, thus forming a number of coils. "The metamaterial can interact only with the magnetic waves from a certain direction. Creating a metamaterial that can interact with magnetic waves coming from various directions requires a number of coils arranged in every direction. This cannot be satisfied by a metamaterial consisting of multiple layers of two-dimensional net-like structures. Use of semiconductor processing techniques makes it possible to fabricate metal into nanoscale structures, but only two-dimensional structures. Thus, three-dimensional processing techniques are required to arrange coils in every direction."

In February 2009 Tanaka and his colleagues attracted public attention when they announced that they had successfully used a light-irradiation method to fabricate metal into nanoscale three-dimensional structures. In this process, a transparent material is first mixed with gold or silver ions, which can be reduced to metal atoms when excited by ultraviolet light (wavelength: 100–400 nm). Tanaka and his colleagues showed that near-infrared lasers with a wavelength of about 800 nm can be used to selectively metalize ions at the laser focal point, which can be moved progressively to fabricate a three-dimensional nanostructure (Fig. 2).

Metallization usually occurs by ultraviolet irradiation, so how can metallization also be induced using a near-infrared laser? It is known that when near-infrared laser light is converted into ultra-short laser pulses of approximately 100 femtoseconds (1 femtosecond = 10^{-15} seconds) and focused into a very narrow beam using a microscope objective lens, the photon density at the focal point can be increased remarkably, triggering a phenomenon known as 'two-photon absorption' — the absorption of two photons (packets of light) instead of the usual one by each ion. As ultraviolet photons have twice the energy of near-infrared photons, the absorption of two near-infrared photons provides the same energy as a single ultraviolet photon, inducing metallization of the silver or gold ions.

"As far as I know, there are no facilities besides those at RIKEN that can provide techniques that make it possible to fabricate metal into three-dimensional nanoscale structures." Thus, Tanaka and his colleagues have made a great step toward creating metamaterials that can interact with the magnetic component of light regardless of the incoming direction.

"However, we need to fabricate tens of trillions of microcoils for a cube of even 1 mm in size. There are many technical challenges to overcome, but I am really determined to fabricate metamaterials that can interact with the magnetic waves of light on my own."

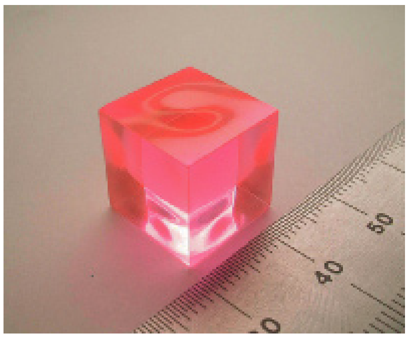


Figure 3: Optical memory in which information is recorded three-dimensionally.
A cube of memory 1.0 cm per side can store about 250 gigabytes of information. This technique can be extended to the development of an optical disc 12 cm across and 1.2 mm thick that could store as much as 1 petabyte (one million gigabytes) of information.

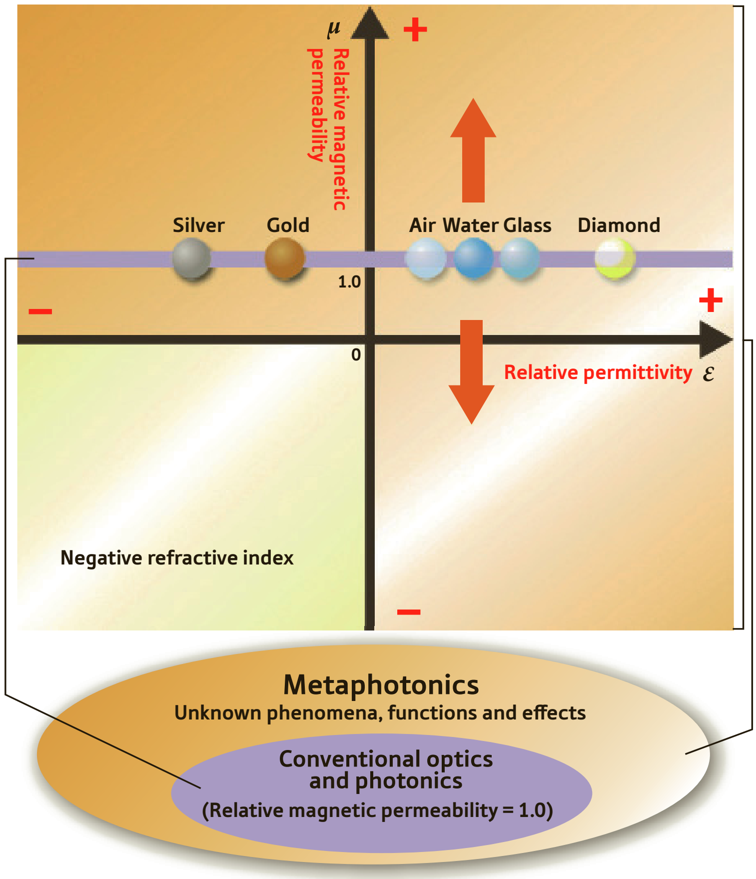


Figure 4: Metaphotonics.
Naturally occurring materials have a relative magnetic permeability of 1.0, and do not interact with the magnetic component of light. Conventional optics and photonics deal with a narrow definition of light. Metamaterials can expand our understanding of light by making it possible to realize a range of relative magnetic permeabilities. The study of metamaterials for the control of light is called 'metaphotonics'.

Video recording of a complete lifespan of 80 years

Tanaka and his colleagues are also working toward the development of optical disks with extremely large storage capacity by taking advantage of their light-based three-dimensional processing technology (Fig. 3). "A DVD is 1.2 mm thick, but only a layer with a thickness of about 1 μm is used for data storage. Thus, 99.9% of the disk is only a circular plastic board that supports the thin recording layer. If these thin layers are stacked into a single structure so that data can be stored three-dimensionally, we can possibly create a disk with extremely large storage capacity more than one million times that of a conventional DVD. In addition, the data retrieval speed will be drastically improved if information is stored three-dimensionally."

Current DVDs have a data storage capacity of about 4.7 gigabytes, allowing for a maximum video recording time of about two hours. "If the data storage capacity is increased up to one million times that of the current DVD, we will be able to store a video recording with the same picture quality for a complete lifespan of 80 years, from birth to death. If the data storage capacity were increased by that amount it would eliminate the need to select the data to be stored. I think that the impact would be significant."

Metaphotonics: beyond conventional light theory

Although Tanaka and his colleagues are currently working toward the development of optical disks with extremely large storage capacity, Tanaka also says, "I want to be fully engaged in science through research into metamaterials. I decided to engage in research into metamaterials because I thought that I could write a new textbook on optics. Conventional optics deal only with materials having a relative magnetic permeability of 1.0. This is a one-dimensional, very small world. Use of metamaterials with various relative magnetic permeabilities would greatly expand the world of light."

Tanaka named the new field of academic study that deals with the wide world of optics 'metaphotonics', because the new field transcends the world of conventional optics and photonics (Fig. 4). "Conventional textbooks on optics are written on the assumption that materials do not interact with the magnetic waves of light. However, nobody knows what will happen if materials interact with the magnetic waves of light. Thus, I think we need to actually create metamaterials, and to verify the content of textbooks on optics. I am sure that we will be able to discover unknown phenomena and unexpected treasures buried in the wide world of light."

Metaphotonics is emerging as a new field of study that takes advantage of metamaterials to explore the world of light. ■

About the researcher

Takuo Tanaka was born in Hyogo, Japan, in 1968. He graduated with a BSc from the department of Applied Physics, Faculty of Engineering, Osaka University, in 1991, and later obtained his MSc and PhD in Applied Physics from the same university in 1993 and 1996. He then joined the Department of Electrical Engineering, Faculty of Engineering Science, Osaka University, as Assistant Professor. In 2003 he moved to the RIKEN Nanophotonics Laboratory where he worked as a research scientist. He was promoted to Senior Research Scientist in 2005, and to Associate Chief Scientist in 2008, and is now working as head of the Metamaterials Laboratory in the RIKEN Advanced Research Institute. His research background is in three-dimensional microscopy, and his current research interests include nanophotonics, plasmonics and metamaterials, and their applications in functional photonics devices.

Brains interact at the 2009 RIKEN BSI Summer Program

Now in its 12th year, the summer program at the RIKEN Brain Science Institute (BSI) again this year offered its participants a unique introduction to the field of brain science, with a high-profile lecture series and hands-on laboratory internships. Under the theme of 'Interacting Brains', this year's lecture program focused on how brains of diverse animals are specialized for interaction.

The internship program ran from July 1 to August 26, with an 11-day lecture course taking place from July 13 to July 24. While some participants attended only the lectures, others in the internship program had the option of enrolling in both the lecture and laboratory components of the program.

Stella Barth, an undergraduate neurobiology major at Harvard University, expressed enthusiasm about her experience. "The researchers here were very welcoming and supportive," Barth said of Kazuo Okanoya's Laboratory for Biolinguistics. "As an undergraduate, I was also granted more independence than I've ever had before."

For undergraduate interns, the program offers a unique introduction to laboratory research. Barth, whose research focus is on the biology of birdsong, described her excitement at being invited to participate in brain surgery on a Bengalese finch. "I've never had that chance before," she said. "It was a bit scary, but also really amazing."

Ai-hong Song, another participant in this year's summer program, remarked on the institutional connection she had established through the internship component of the program. Song's research in the BSI program followed on her recent findings (published in the March issue of *Cell*) on cytoplasmic transport in neurons.

"For me, this is just the beginning," she said. "The program has provided a great chance to initiate collaborative research between Atsushi Miyawaki's Laboratory for Cell Function Dynamics, where I did my internship here, and my home institution, the Institute of Neuroscience in Shanghai," she explained.

The program also included a language component, with interns offered 1.5-hour Japanese classes twice a week, as well as cultural outings in areas around Tokyo. Support for the internship program comes from the Edwin O. Reischauer Institute of Japanese Studies.

A high-resolution spectrometer to unravel the secrets of nuclear structure

The exploration of nuclear structures serves not only to advance our understanding of the most basic elements of our physical world, but also to explain the origins of our universe and to spawn groundbreaking industrial applications. Producing beams of high-energy radioisotopes has become the most effective technique for conducting such investigations, enabling researchers to study states well beyond the range of stable nuclei.

The Radioisotope Beam Factory (RIBF) at the RIKEN Nishina Center for Accelerator-Based Science was built with the goal of generating the world's highest-energy radioisotope beams for use in nuclear experiments. The SHARAQ spectrometer, short for 'spectroscopy with high-resolution analyzer and radioactive quantum beams', designed by the Center for Nuclear Study (CNS) at the University of Tokyo, is the first facility to use an unstable nuclei beam as a measurement probe. The name 'SHARAQ' was inspired by the famous Japanese woodblock artist Toshusai Sharaku.

In March of this year, the first RIBF beam line was connected to the SHARAQ spectrometer, together forming a high-resolution radioisotope beam analyzer. Experiments have confirmed that the system is performing correctly, and plans are on track toward the execution of new cutting-edge nuclear science experiments.

In commemoration of the successful commissioning of experiments at SHARAQ, a ceremony was held on June 30 at the conference room of the RIBF building, co-hosted by the RIKEN Nishina Center and the CNS.

Designed to meet demanding requirements for precision and resolution, the newly commissioned SHARAQ spectrometer promises to produce exciting results over the next few years that will greatly expand the landscape of nuclear science.

RIKEN and J-TEC collaborate in joint research on retinal regeneration

Age-related macular degeneration, a medical condition of the eye resulting from damage to the retina, is the leading cause of visual acuity loss among elderly populations in America and Europe, and is increasingly prevalent in Japan. Despite signs that the transplant of pigment epithelial cells may be effective in treating this condition, difficulties in preparing cell sources and problems of immune rejection have prevented further advances in this field.

A new form of treatment for this condition may now be on the horizon, however, with the conclusion of an agreement on July 23 between RIKEN and Japan Tissue Engineering Co. Ltd (J-TEC). Groundbreaking new research, to be conducted by J-TEC together with the Laboratory for Retinal Regeneration at the RIKEN Center for Developmental Biology (CDB), will focus on the application of human induced pluripotent stem (iPS) cells to the manufacture of retinal pigment epithelial cells.

In circumventing problems of immune rejection associated with retinal pigment epithelial cell transplantation, the iPS cell approach offers renewed hope that a safe and effective treatment for visual conditions such as age-related macular degeneration will be found. Paired with J-TEC's pioneering tissue-engineering technology, research on the manufacture of iPS cell-derived retinal cells at the Laboratory for Retina Regeneration promises to chart a course toward the world's first regenerative treatment for retinal diseases.

As a first step toward the new joint research initiative, a protocol is to be developed within the next three to five years setting out a framework for clinical application of retinal pigment epithelium cells derived from human iPS cells. Once this protocol is decided, clinical studies will begin at the medical institution next to the RIKEN CDB.

Dr Kathleen S. Rockland
Laboratory head
Cortical Organization and Systems Laboratory
Brain Science Institute, RIKEN
2-1 Hirosawa, Wako-shi,
Saitama 351-0198, Japan

Dear Dr Rockland,
How have you been doing? I hope that things in the laboratory are going smoothly and that everyone is doing well.

It has been quite a while since I visited your laboratory as part of the Riken BSI Summer Internship program and it is amazing how time flies by. However, my memories from four summers ago are still crystal clear. Upon my arrival, I was very warmly greeted by you and the members in your laboratory, all of whom had gone out of their way to make me feel welcomed. I also still remember walking into your laboratory and being instantly impressed by how clean and well-maintained it was.

The working environment was a very pleasant one, with everyone always ready to help and to give me the support I needed. During my stay there, my original apprehension of not being able to converse in Japanese was unfounded, as it never became an issue. I then went on to learn so much over the next few months. My techniques in various immunohistochemical and zinc stains had vastly improved, and they now form a core portion of my dissertation. Without all the help that you and Dr Noritaka Ichinohe have given me, my dissertation research would not be going on as smoothly as it is now. For that you have my sincerest gratitude.

Apart from gaining experience in the laboratory, I also got to see parts of Tokyo while I was there. I would like to thank both you and Charles for taking time off your busy schedules to show me around Ueno and the Tokyo Bay area. In addition, I managed to snatch glimpses into the Japanese way of life, as at various points during my stay, people from the laboratory had invited me to their homes for dinners and to enjoy the stunning displays of fireworks that are put up during the summer.

I am very fortunate to have been given the opportunity to work in your laboratory as part of the internship program. This experience has not only allowed me to enrich myself professionally, it has also given me some insights into the Japanese culture, which I find absolutely fascinating. All these experiences that I have had in Japan are unforgettable and the memories formed are very dear to me.

Finally, I would like to wish you all the best, and perhaps I will see you soon!

Best regards

Peiyan Wong
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Vanderbilt University
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