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March 2015

Keio University Medical Science Reprint Collection | Web Edition

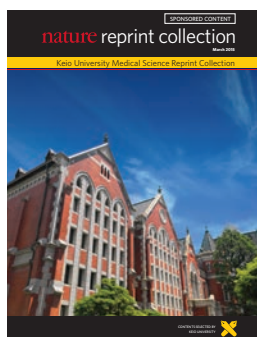


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 Keio University School of Medicine in central Tokyo



**COVER:** The Old University Library located on the Mita Campus was built in 1912 to commemorate the 50th anniversary of Keio University's founding. It has been designated an Important Cultural Property of Japan.

## Nature Reprint Collection

### Keio University Medical Science Reprint Collection | Web Edition

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# Foreword

In the more than 150 years since its founding by renowned educator Yukichi Fukuzawa, Keio University has emphasized research and education based on *jitsugaku*, by which Fukuzawa meant science. Our School of Medicine is a testament to this legacy of critical thinking and the pursuit of knowledge that benefits society, especially during these times of great change.

Keio University maintains a strong and growing international network of over 250 partners, three research hubs in Singapore and France, and a high school in the United States. We also have plans to expand our joint degree programmes and diverse selection of courses in English. The university is ranked ninth in the global *Times Higher Education* Alma Mater Index for the number of degrees awarded to chief executives in top companies, and the prestigious Keio Medical Science Prize has recognized many researchers, six of whom have gone on to win Nobel prizes.

In 2014, Keio University was selected as one of 13 universities under the Top Global University Project funded by the Japanese government. The universities were chosen based on innovation, reputation, international outlook and potential to rise up the global ranks.

Under this project, Keio has committed itself to an important ten-year programme to enhance global sustainability through the principles of *jitsugaku*, specifically in the areas of longevity, security and creativity. Japan has one of the highest proportions of elderly people worldwide, which represents both a challenge and an opportunity for the country to establish itself as a model for health and prosperity supporting citizens of all ages. To develop this resilience, the School of Medicine will further pursue interdisciplinary research under Keio's Longevity Initiative in the areas of regenerative medicine, public policy and robotics.

The *Keio University Medical Science Reprint Collection* contains a selection of 23 papers published by researchers at Keio University in *Nature* and the *Nature* family of primary research journals between 2006 and 2014. The discoveries in these papers have had an important impact on the fields of disease models, genome integrity, immunology, neuroscience and stem cells, as highlighted in the five feature articles written exclusively for this collection. In the coming years, Keio University will continue to make critical advances in medical science and publish research that stands the test of time.



Atsushi Seike   
President, Keio University

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# Keio Research Highlights

## A new website, bringing Keio University science to the world

### Research highlights

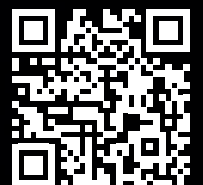
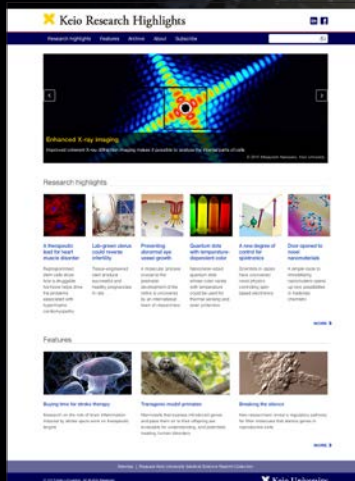
Informative and accessible articles that engage the wider public with some of the groundbreaking research at the university.

### Features

An in-depth look at some of the latest discoveries that contribute to Keio University's 'spirit of science'.

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# A CENTURY-LONG PURSUIT OF EXCELLENCE

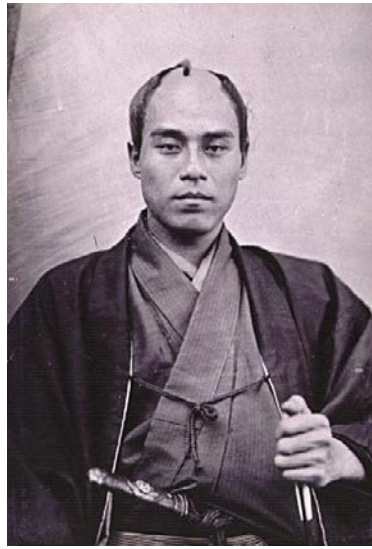
*Formally founded in 1917, Keio University School of Medicine is regarded as one of Japan's top medical schools. Its long-standing reputation for excellence stems from its unique history and its leading role in promoting the practice of advanced Western medicine in Japan. The school's leadership in this area is evidenced by the fact that it has produced two presidents of the Japan Medical Association and one of the two Japanese who have been presidents of the World Medical Association.*

*The School of Medicine has established a formidable reputation in the international medical community, not only for its hospital — the largest university hospital in Japan — but also for its promotion of excellence in medical research through the prestigious annual Keio Medical Science Prize.*

*As it approaches its centenary, the school will build on its past achievements to play a leading role in addressing such global problems as rapidly ageing populations. The construction of a new state-of-the-art hospital building will be key to promoting 'Keio Medicine', an important feature of which is the unique interdisciplinary team approach to patient-oriented medical care currently being realized at Keio.*



Keio founder  
Yukichi Fukuzawa



First dean of Keio  
University School  
of Medicine and  
renowned microbiologist  
Shibasaburo Kitasato



**F**ounded in 1858, Keio University is Japan's oldest institution of higher education, predating even the Meiji-era national imperial universities. Today, Keio University is one of Japan's most popular and prestigious universities, and its alumni include two prime ministers and a long list of prominent political, administrative, legal, medical and corporate leaders.

The university's high standing in Japanese society has much to do with its eminent founder, Yukichi Fukuzawa — a visionary whose face appears on Japan's 10,000 yen note and whose remarkable contribution to Japanese society helped shape the modern nation (see image, top left). A man of remarkable capacity, Fukuzawa founded the original school when he was just 23. Within four years, he had journeyed across Europe and the United States, returning to Japan with texts and concepts that helped modernize Japan. In 1867 he renamed his school after the Keio Era of its foundation and changed its focus to Western-oriented higher education.

Fukuzawa's endeavours defied the established powers of the time. He believed that independence, prosperity and even catching up with Western technology and social organization could be achieved only by making education available to all. By sowing the seeds for the democratization of knowledge, Fukuzawa contributed to the emergence of a large workforce of well-educated

citizens, and ultimately to Japan's rapid industrialization in the twentieth century. For his remarkable accomplishments he is upheld as Japan's luminary of the modern era, and Keio University today embodies his legacy to the Japanese people.

### Modernizing medical training in Japan

Fukuzawa incorporated medical teachings at his school from as early as 1873, and in 1917 the university's School of Medicine was formally established by renowned physician and microbiologist Shibasaburo Kitasato (see image, top right). Himself a recipient of Fukuzawa's generosity in establishing an institute for infectious diseases many years earlier, Kitasato embraced his benefactor's progressive approach to education and was determined to form a medical school at Keio in his honour. Kitasato had always stressed the importance of making medical practice accessible to ordinary citizens and thus strove to establish a medical school that dismantled the boundaries between clinicians and medical scientists. This led to a new, integrated approach to medical training in Japan and laid the foundations for the modernization of Japanese medicine.

Today, as the School of Medicine approaches its centenary, this same spirit of united purpose continues to drive innovation in medical training. Drawing directly from international examples and standards, the school



Keio University Hospital offers minimally invasive treatments for a range of conditions using advanced technologies and surgical techniques

seeks to resolve the key deficiencies in traditional Japanese medical education by introducing universal clinical skills training and emphasizing evidence-based medicine. In this, it is supported by its close academic partnerships and international student exchange programmes with many leading medical schools around the world, including Dana-Farber Cancer Institute, Columbia University and the Karolinska Institute. The university has begun implementing an ambitious programme to reform medical education in Japan, with a nation-leading curriculum incorporating problem-

based learning, observance of strict ethical standards and early clinical exposure.

#### **Innovation in medical research**

Fundamental to the School of Medicine's success are its facilities. Keio's indivisible relationship between research and clinical practice is centred on Keio University Hospital, one of the largest and most well-known general hospitals in Japan. At the forefront of Japanese medicine for almost a century, the hospital offers some of Japan's most advanced medical services and most



## **New Keio University Hospital building**

The original university hospital, established in 1920, is one of Japan's leading institutions of Western medicine. It is also one of its busiest with over 1,000 general beds and 29 specialist departments and other centers. At this hospital, Keio medical researchers and clinicians undertake much of their work together, sharing state-of-the-art facilities to provide the highest level of medical care.

Such is the demand for treatment at Keio that a new hospital building is now under construction. Due to be opened in 2017 as part of the School of Medicine's centenary celebrations, it has been designed to facilitate close collaboration among medical, nursing and pharmaceutical professionals, practition-

ers and researchers to support Keio's world-leading training programmes and to realize a unique style of patient-oriented medical cluster care, one facet of 'Keio Medicine'. The new hospital will also focus on developing core urban-disaster-response capabilities.

The 'Keio Medicine' approach brings together for each patient a tailored team of physicians, nurses, pharmacists, physical therapists and researchers from all specialties. Regarded as the future of leading patient care, this approach ensures that the best possible care is provided to each and every patient, and serves as the basis for Keio's integrated basic and clinical medical programmes, which are among the most advanced in the world. ✕



comprehensive array of facilities for research, development, evaluation and training. A new university hospital building planned for completion in 2017 will facilitate a ‘cluster’ approach, which emphasizes interdisciplinary therapy through cooperation between departments with the latest medical treatments (see “New Keio University Hospital building”).

Two other innovative medical research centres have given Keio a significant edge in global competitiveness. The school’s Center for Integrated Medical Research (CIMR), established in 2001, provides a shared environment for collaborative translational research and scientific work, integrating basic science, clinical research and patient care through the creation of related clusters across academia and industry. The Keio-Med Open Access Facility is part of the CIMR and makes available state-of-the-art technologies such as laser capture microdissection, advanced imaging and genetic sequencing. It has shared facility arrangements with several research partners.

The second of the medical school’s major research facilities, the Center for Clinical Research (CCR), is a government-funded Center of Excellence (COE) for the promotion of global clinical research with a focus on early and exploratory clinical trials. As a flagship medical research centre in Japan, the CCR contributes to the development of novel advanced medical technologies and innovative new drugs through specialized implementation of high-quality clinical trials, large-scale



observational studies, translational studies of new technologies and other biomedical research.

Tokyo's Shinjuku skyline, as seen from Keio University Hospital

In recognition of its research strength, Keio was also awarded generous government funding for two ‘Global COE’ programmes carried out over a period of five years, from 2008 to 2013. The Global COE for Human Metabolic Systems Biology focused on the regulatory mechanisms of metabolism in human physiology and pathology, with the ultimate goal of establishing a world-class

## Keio Medical Science Prize

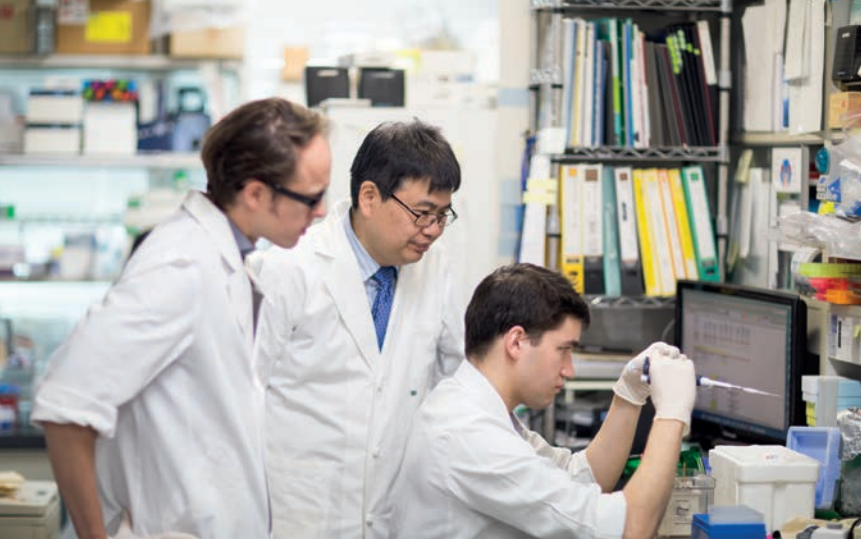
Since 1996, Keio University has been recognizing the outstanding and creative achievements of researchers from around the world in medicine and the life sciences through the annual Keio Medical Science Prize. Established with a generous donation from one of the university’s eminent alumni, Mitsunada Sakaguchi, this distinguished prize acknowledges significant contributions to scientific developments in medicine to promote advances in the field and improve global health. The Keio Medical Science Prize is the only international medical science award bestowed by a Japanese university.

The prize selection committee, consisting of 13 members from Keio University and other leading medical institutions in Japan, is renowned for its ability to recognize truly great advances in medical science across the international research community — in the 19 years of the prize, no fewer than six recipients have subsequently been awarded a



Nobel Prize: Jules Hoffmann, Thomas Steitz, Roger Tsien, Barry Marshall, Elizabeth Blackburn and Stanley Prusiner.

The 2014 award recipients are Karl Deisseroth (see image, centre left) for the development of optogenetics and Hiroshi Hamada (see image, centre right) for his discovery of the molecular and cellular mechanisms of left–right asymmetry. ✕



Hideyuki Okano (centre) and researchers in his laboratory conduct stem cell research to improve our understanding of human diseases and for regenerative medicine

interdisciplinary research and education centre in this field. The Education and Research Center for Stem Cell Medicine was a leading centre for stem cell research in Japan, supporting specialized research in experimental stem-cell regulation, inflammation and tissue regeneration, new cancer treatments targeting cancer stem cells, and regenerative medicine for intractable diseases.

### Towards a new age of medicine

With a rapidly ageing population and more than an estimated 50,000 centenarians, Japan faces significant and growing healthcare challenges. Keio University's current president, Atsushi Seike, a labour economist specialized in population ageing, understands only too well the tests that lie ahead. This situation, however, places Keio in a unique position to conduct cohort studies on the factors contributing to longevity, and a number of studies are now underway exploring the phenotype of centenarians and supercentenarians with obvious implications for us all.

By taking up the challenge of this new age of medicine, Keio University School of Medicine is perpetuating Fukuzawa's legacy through a continuous process of evolution that mirrors the great teacher's doctrine of continuous learning. The new hospital building will be yet another manifestation of this evolution, breaking down the barriers between medical disciplines and further enshrining Kitasato's continuity between medical research and clinical practice. ✕

## Help for victims of the 2011 earthquake and tsunami

The Tohoku–Pacific Ocean earthquake and resulting tsunami that struck on the afternoon of 11 March 2011 was a disaster of unimaginable proportions in which thousands lost their lives and hundreds of thousands were left homeless. Keio University, led by its president Atsushi Seike, immediately rallied in support of those affected. Within a week of the disaster, teams of medical professionals from Keio University School of Medicine were on the ground in the hardest-hit areas to provide medical support as part of the nation's massive response. Doctors, nurses, pharmacists and logistical staff all participated in these teams.

In the ensuing weeks, donations from students and alumni raised the equivalent of about JPY 190 million (US\$1.6 million) to assist disaster relief through the Japanese Red Cross Society. The university also chartered a bus service that allowed over 260 students as well as faculty and staff to contribute to volunteer relief efforts on the ground in one of the most devastated areas, Minamisanriku.

In the year following the disaster, Keio University provided special scholarships to students from affected areas. These scholarships covered tuition and academic fees, as well as entrance fees.

Keio University continues to provide medical support to the disaster-stricken area, with over 500 teams dispatched to the prefectures of Fukushima, Miyagi and Iwate by November 2014. ✕



Doctors provide care for local victims at a temporary medical facility on 20 March 2011



The common marmoset is an ideal model animal for understanding human disease

# Transgenic model primates

*Marmosets that express introduced genes and pass them on to their offspring are invaluable for understanding, and potentially treating, human disorders*

Like humans, marmoset monkeys (*Callithrix jacchus*) are raised by their families. Infants clutch the furry backs of their parents and elder siblings, who also forage to feed them. Group members communicate through direct eye contact and audible calls, taking breaks to listen to each other. “These are highly social behaviors,” says Hideyuki Okano, dean of the Graduate School of Medicine at Keio University, “which makes the common marmoset an excellent model for studying human psychiatric disorders such as autism and schizophrenia.”

Unlike the brains of mice — the model animal most commonly used in research — marmoset brains contain regions essential for higher cognitive functions, Okano explains. Marmosets are New-World natives and valuable candidates for biomedical research due to several practical reasons: they reach sexual maturity shortly after their first birthday, females can produce between 40 and 80 offspring during their lifetime, and the species is smaller and gentler overall. “A cat is much easier to handle than a lion, isn’t it?” says Okano for comparison.

But to exploit these attractive attributes for research, scientists needed to develop marmosets capable of expressing foreign

genes and bequeathing them to their offspring. Erika Sasaki’s laboratory at the Central Institute for Experimental Animals and Okano’s laboratory at Keio University attempted this challenge in early 2006.

They injected a virus carrying a gene for green fluorescent protein (GFP) directly into fertilized marmoset eggs using what Okano describes as a “cheap trick — scientists a century ago could have come up with the idea.” They dipped the fertilized eggs in a sucrose solution, which caused the cytoplasm to shrink, tearing the cell membrane away from the extracellular coating called the zona pellucida. The researchers were then able to inject many of their virus particles into the expanded interstitial zone known as the perivitelline space. The visible green fluorescence of the expressed transgenes allowed them to easily screen candidate embryos up until their transfer into surrogate mothers.

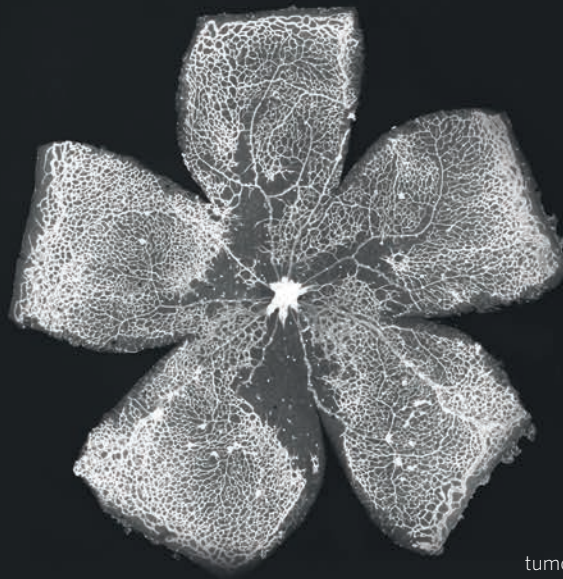
After 144 days of gestation, four transgenic founder marmosets were born with patches of green hair and skin. The researchers waited a year for the animals to reach sexual maturity and then inseminated a normal egg with a sperm from one of the transgenic males. After another transfer to a surrogate mother and another 144 days, an infant marmoset

with green skin and the GFP-transgene in its genome was born. The study, published in *Nature* in 2009, represented the first report of a transgenic non-human primate with germline transmission<sup>1</sup>.

Marmoset research has since expanded exponentially and could soon lead to therapies for as-yet-incurable human disorders. Proving the superiority of the primate for research, Okano’s lab recently found that a marmoset model of an immunological disease captured human pathophysiology much better than mouse models do. Marmosets will also play a central role in a ten-year national project launched in June 2014, for which Okano’s laboratory is mapping the structure and function of the marmoset brain, including models for diseases such as Alzheimer’s and Parkinson’s. The laboratory is also separately screening drugs using induced pluripotent stem cells derived from patients with these diseases and plans to test any promising compounds on their disease models. Okano is hopeful: “In this way, we can identify new drugs that work to cure these diseases.” ✕

## Reference

1. Sasaki, E. *et al.* Generation of transgenic non-human primates with germline transmission. *Nature* **459**, 523–527 (2009).



The retina of mice lacking a key blood vessel enzyme showed almost no production of tumour-like vessels during restricted oxygen flow

# Distinguishing good angiogenesis from bad

*Keio scientists discover a possible target for controlling pathological growth of new blood vessels without hindering healthy processes*

The growth of new blood vessels in tumours has long been a tempting target for cancer treatments. But scientists testing anti-angiogenic agents such as vascular endothelial growth factor (VEGF) inhibitors face a problem: how to inhibit pathological angiogenesis associated with tumours without hindering the healthy growth of blood vessels in the rest of the body. Yoshiaki Kubota from the Laboratory of Vascular Biology at Keio University explains: “The VEGF blockade not only targets tumour vessels but it also damages normal healthy vessels.”

In 2012, his team made an unexpected discovery that revealed a possible way to target pathological blood vessel growth without harming healthy blood vessels<sup>1</sup>. Their finding has revived the prospects of treating cancer and other diseases such as macular degeneration in this way.

Kubota’s team focused on an enzyme called ataxia telangiectasia mutated (ATM) kinase, which plays a key role in the development and maintenance of blood vessels. Mutations in the *ATM* gene in humans are linked with ataxia telangiectasia, an inherited disease whose features include dilated and leaky blood vessels.

To understand the function of ATM in normal and pathological blood vessels,

Kubota’s team induced ischemic retinopathy by limiting oxygen flow to the retina. The resulting accumulation of reactive oxygen species activated *Atm* expression in immature blood vessels that are similar to tumour vessels. Importantly, the hypoxic conditions did not affect *Atm* production in surrounding non-pathological blood vessels. When the researchers repeated this same process in mice engineered to lack endothelial *Atm*, they saw none of the pathological retinal angiogenesis apparent in the normal mice (see image), showing clearly that *Atm* played a pivotal role in the growth of these destructive blood vessels.

The researchers then tested the impact of the relationship between *Atm* and angiogenesis in a mouse model of melanoma, and found similarly that angiogenesis and tumour growth were inhibited in mice lacking endothelial-specific *Atm*. In addition, *Atm* deficiency enhanced the anti-angiogenic action of VEGF inhibitors.

“Most importantly, the disruption of *Atm* signalling prevented pathological neovasculation without affecting normal vascular regeneration,” commented Bethany Kerr and Tatiana Byzova in an article in *Nature Medicine*<sup>2</sup>. “Thus,

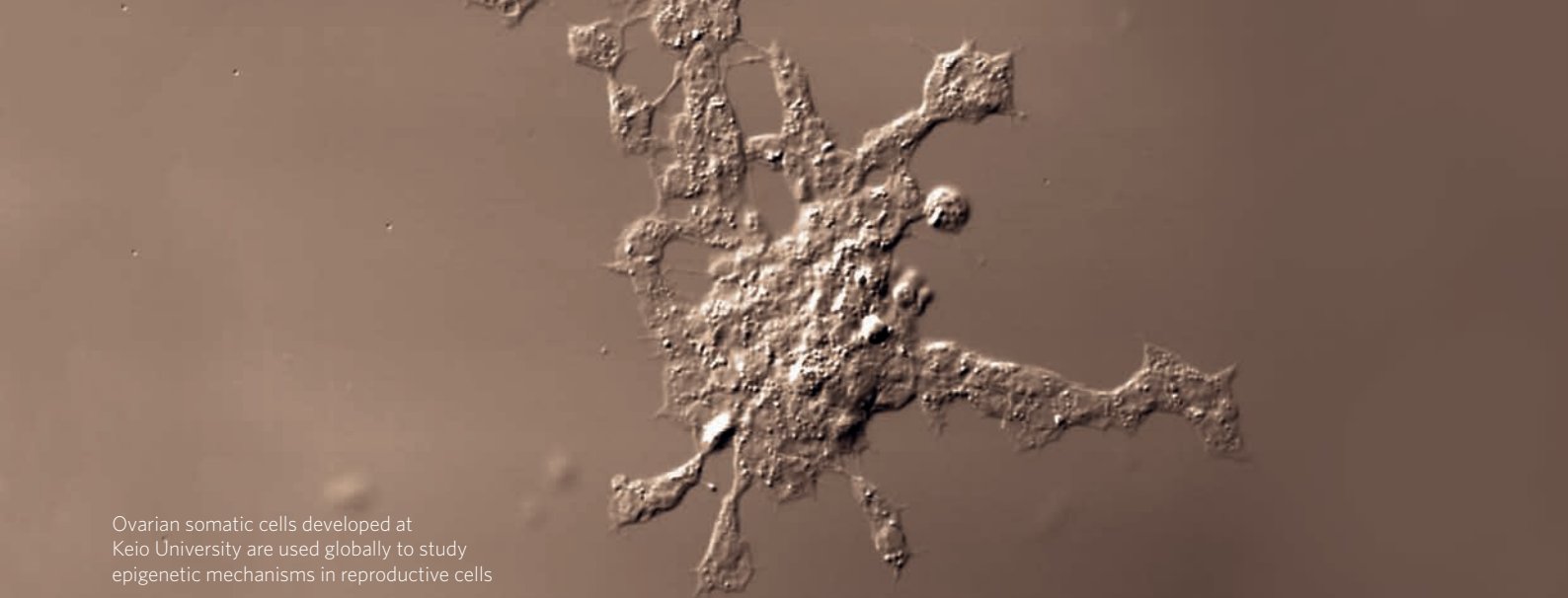
*Atm* activation could be an ideal target for new therapies to combat pathological angiogenesis in a variety of diseases.”

Because ATM kinase is associated with a well-known cellular mechanism for managing the damage caused by free radicals — known as the DNA damage response pathway — the researchers first suspected that loss of this pathway may have been responsible for the lack of pathological blood vessel growth in the knockout mice. But on looking more closely, they found that a completely different pathway was implicated, one involving activation of the stress-associated kinase p38.

“Endothelial metabolism is now being focused on worldwide as a target for anti-angiogenic therapy,” Kubota says. His 2012 paper is cited as a pioneering study in the field, and his lab has been inundated with requests for the mouse lines used in the paper, including the *Atm* knockout mice, by researchers intent on studying the exciting new cancer target. ✕

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2. Kerr, B. A. & Byzova, T. V. The dark side of the oxidative force in angiogenesis. *Nature Medicine* **18**, 1184–1185 (2012).



Ovarian somatic cells developed at Keio University are used globally to study epigenetic mechanisms in reproductive cells

# Breaking the silence

*Keio researchers reveal a regulatory pathway for RNA molecules that silence genes in reproductive cells*

In the reproductive cells of all animals, small RNA molecules known as Piwi-interacting RNA (piRNA) play a key role in the epigenetic control of gene expression. Until recently, however, researchers had only a vague idea of how these molecules are produced and regulated.

In 2009, Haruhiko Siomi from Keio University's School of Medicine and his laboratory helped clear up this picture with a publication in *Nature* that revealed a regulatory circuit that gives rise to both piRNAs and the Piwi proteins they interact with<sup>1</sup>.

Understanding the biogenesis of piRNA is important because these molecules and their associated proteins play such a significant role in reproduction, explains Siomi. Recent studies have shown that they silence DNA sequences known as transposable elements, which can jump from one location to another in the genome. Left to their own devices, these transposable elements can wreak havoc in the genome, potentially leading to chromosome breakage and major mutations that jeopardize the survival and reproductive capacity of germ cells.

"Many men and women have infertility problems of unknown cause," says Siomi. "Maybe these problems are

due to errors or even mutations in the piRNA pathway."

The Keio publication began with "a matter of serendipity," explains Siomi. One day, a researcher in his lab noticed that a small subpopulation of the notoriously fragile cell line used to generate *Drosophila* germline stem cells was spreading vigorously across the dish. He isolated and carefully nurtured the colony, which continued to grow at an even faster pace, and eventually developed a stable population of ovarian somatic cells (see image).

This stable cell line saved researchers from having to meticulously dissect hundreds of flies under a microscope to collect enough ovaries and testes for a decent experiment. "My students used to hate the job," recalls Siomi. Researchers as far flung as the United States and Europe have shared in the relief, using the cells to study the silencing mechanism of piRNAs.

Using this new cell line, Siomi's team was able to show that piRNA stifles the expression of not only transposable elements, but also protein-coding genes. His team established that this new class of piRNA, named 'genetic piRNA', derives from a region of certain protein-coding messenger RNAs that is typically not translated. On closer investigation, a gene

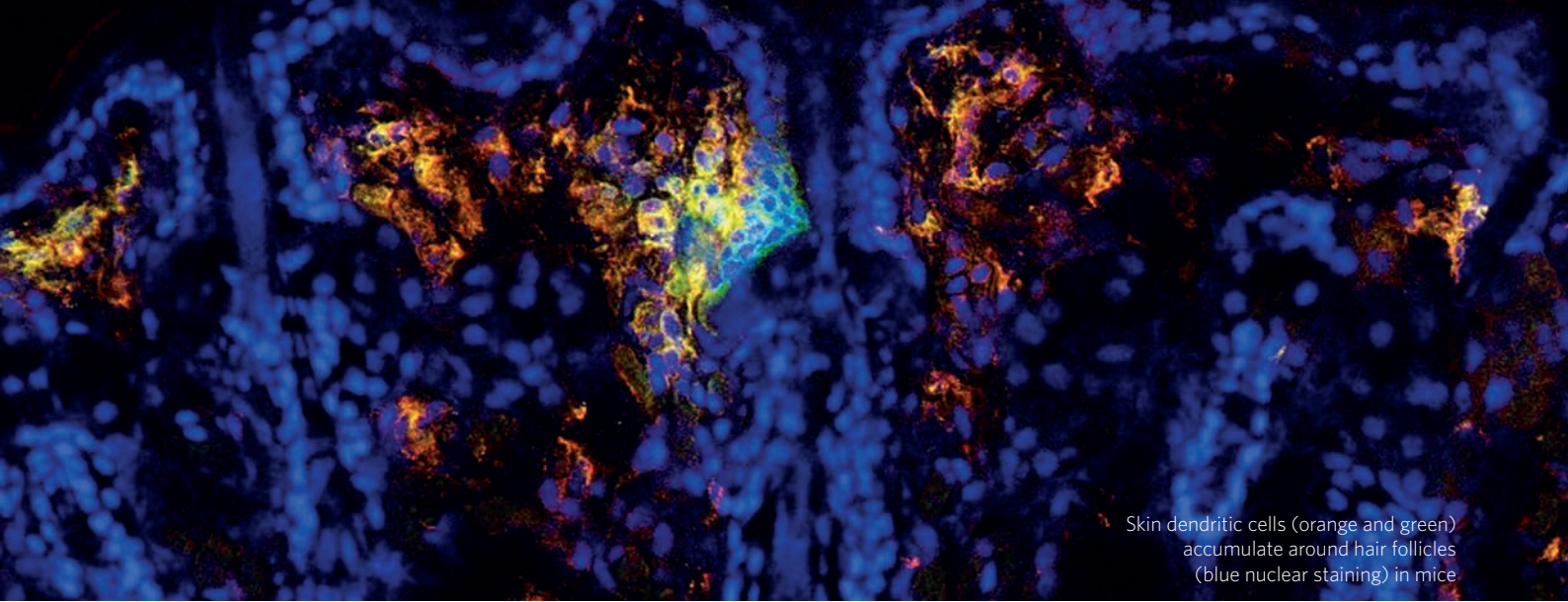
appropriately named *traffic jam* was found to be closely involved with piRNA's fate. *Traffic jam* plays the dual function of producing genetic piRNA and triggering production of Piwi, one of the proteins that piRNA binds with to suppress transposable elements.

The 2009 paper led to more questions, which Siomi's team has since been answering with *in vitro* experiments. They identified several proteins that interact with the Piwi-piRNA complex to silence transposable elements. And most recently, in research that is yet to be published, they determined the sequence within *traffic jam* messenger RNA that directs genetic piRNA production. The implications of this latest finding are enormous, explains Siomi.

"We can now express piRNAs with sequences of interest to target and silence almost any gene without changing the actual gene sequence." What's more, such an artificial system could be applied across the species divide, from egg-laying flies to fast-breeding mice and even larger primates. ✕

## Reference

1. Saito, K. et al. A regulatory circuit for piwi by the large Maf gene *traffic jam* in *Drosophila*. *Nature* **461**, 1296-1299 (2009).



Skin dendritic cells (orange and green) accumulate around hair follicles (blue nuclear staining) in mice

# Hair follicles recruit immune cells

*Combing the epidermis for clues, Keio researchers found that hair follicles are critical gateways in the fight against infection*

**H**air follicles function as entry points to the outer layer of skin for cells that protect against infections, Keisuke Nagao and his team from the Department of Dermatology, Keio University School of Medicine, reported in 2012<sup>1</sup>. The cells in question are members of a specialized class of white blood cells known as Langerhans cells. They form part of the first line of defence in the body's fight against infections, sampling antigens in the epidermis and transporting them to the lymph nodes.

When Nagao first proposed exploring how populations of Langerhans cells are maintained and replenished in the epidermis, Masayuki Amagai, the chair of the Department of Dermatology, was initially very hesitant. "I felt that the question was too fundamental for dermatologists to pursue," he recalls. But after five years of investigation, Nagao was able to discover that the precursors of Langerhans cells enter the skin via hair follicles — a very surprising finding that no one had predicted. "Nagao answered the question beautifully," says Amagai.

The researchers captured images of mouse skin showing Langerhans cells clustering around hair follicles in skin

that was depleted of Langerhans cells (see image). The images clearly showed that colonies of Langerhans cells form around hair follicles, but as they were only snapshots in time, the researchers could not tell whether the cells were being produced at the follicles or recruited from elsewhere.

Nagao's team then used two-photon electron microscopy to obtain videos that showed white blood cells, including Langerhans cells, congregating around hair follicles within 30 minutes to 4.5 hours of applying stress to the skin. The videos also revealed cells entering hair follicles and migrating upward to repopulate the epidermis. "When we saw these movies, we were astonished," Amagai says.

The Keio team went on to find further evidence of the important role of hair follicles in Langerhans cell repopulation. For example, mice that are unable to produce hair follicles show limited repopulation of Langerhans cells after depletion, while human patients with autoimmune disorders that result in the destruction of hair follicles show a similar absence of Langerhans cells. Furthermore, they found that Langerhans cells repopulate the hairless paws of

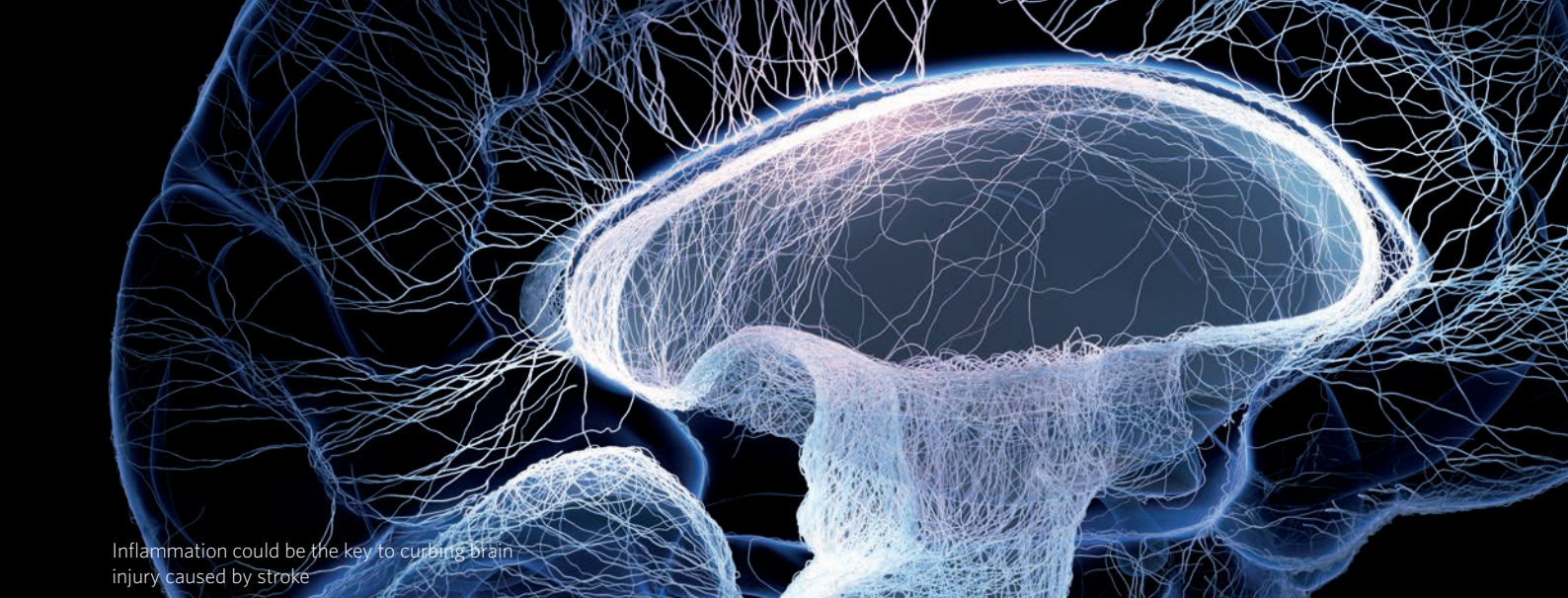
normal mice by migrating from adjacent hairy regions. The team also showed that intercellular signalling proteins known as chemokines are involved in attracting Langerhans cell precursors to hair follicles.

Since its publication two and a half years ago, the paper has been highly cited in the scientific literature — 57 times according to Google Scholar — and has been ranked in the 90th percentile for articles published around the same time in *Nature Immunology*.

The findings have forced scientists to re-evaluate the importance of hair follicles — they are no longer considered merely sites of hair growth; they are now thought of as being important gateways in the body's immune response, Amagai says. The findings also raise the question of whether hair follicles function as conduits between the dermis and the epidermis for other cells and substances. Hair may turn out to be even more critical than even Nagao's research suggests. ✕

## Reference

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Inflammation could be the key to curbing brain injury caused by stroke

# Buying time for stroke therapy

*Research on the role of brain inflammation induced by stroke spurs work on therapeutic targets*

**S**troke is a severe, often fatal, condition that affects an estimated 15 million people worldwide each year. It is the second most common cause of disability and of death in people aged 60 and over. Developing new approaches for treating stroke is particularly critical in Japan, which is rapidly becoming the world's most 'super-aged' nation, with more than one-fifth of its population over the age of 65 as a result of long life expectancies and low fertility rates.

Currently, the only widely approved drug for stroke treatment is tissue plasminogen activator. To be effective, this drug must be administered within approximately three to five hours from the onset of a stroke — a very short time frame in which to diagnose the condition, transport the patient to hospital, and select and administer the drug. Hence, researchers have tried to find other points at which therapeutic intervention is possible.

This question has occupied Akihiko Yoshimura and Takashi Shichita of Keio University's School of Medicine for many years. "Inflammation after stroke was known to promote further injury of the brain, but it was not well understood," notes Yoshimura, "so we decided to clarify the inflammation

mechanism in order to find a new target for stroke therapy."

In 2009, Yoshimura and colleagues published a paper in *Nature Medicine* that established the role of a major inflammation system known as the interleukin-23–interleukin-17 axis in brain injuries resulting from ischemic stroke, the most common form of stroke that occurs when blood vessels in the brain are blocked. The researchers also identified T lymphocytes, a group of white blood cells that localize in infarction areas after brain injury, as a therapeutic target for reducing inflammation and damage resulting from insufficient blood supply<sup>1</sup>.

Using a mouse model, they showed that another class of white blood cells, called macrophages, produced interleukin-23, a protein that is active during the initial phases of brain injury. In addition, and contrary to previous thinking, they discovered that the main source of interleukin-17 was a subset of T lymphocytes known as  $\gamma\delta$ T cells. This was a significant finding since interleukin-17 was found to play an important role in inflammation, which amplifies the damaging effects of an infarction during the delayed phase of ischemic brain injury.

The researchers showed that brain injury can be curbed by reducing the number of  $\gamma\delta$ T cells, even 24 hours after stroke onset. Yoshimura notes that after these results were published, more researchers have begun investigating inflammation after stroke events.

Since the 2009 study, Yoshimura and Shichita's team has been investigating the mechanism of interleukin-23 expression in infiltrated macrophages<sup>2</sup>. They are currently exploring the role of inflammation in order to develop ways to repair damage to the brain. "The pathology of brain injury depends on the balance between destructive tissue inflammation and repairing inflammation," explains Yoshimura.

He hopes that these findings will enable researchers to develop new drugs that will both block fatal strokes and speed the recovery of stroke victims from neural disorders. ✕

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