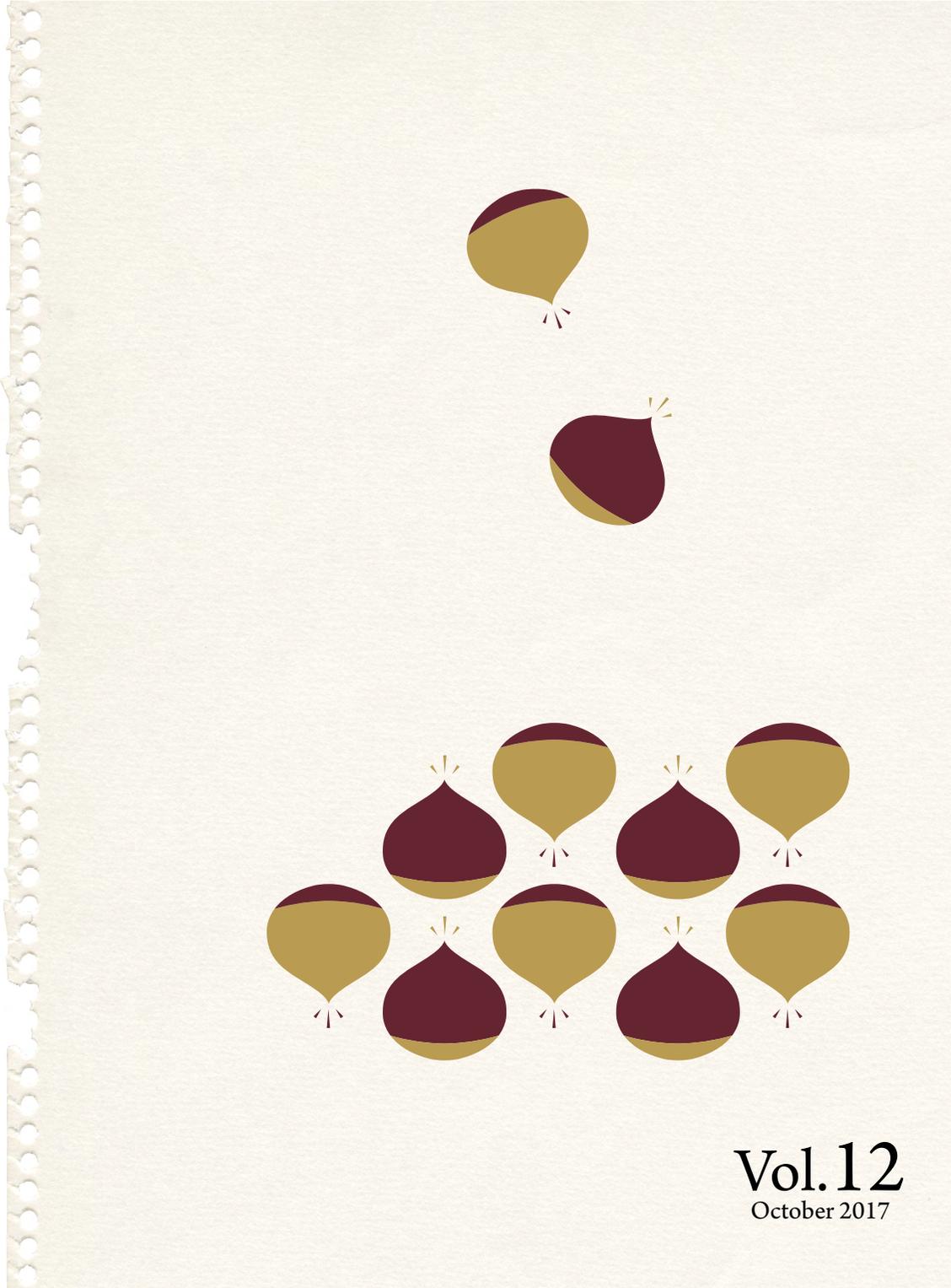


# CiRA

# Reporter

Center for iPS Cell Research and Application,  
Kyoto University



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International Public Communications Office  
Center for iPS Cell Research and Application (CiRA)  
Kyoto University  
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto  
606-8507 Japan

### Writing and editing

Peter Karagiannis (CiRA)

### Layout and figures

Masaya Todani (CiRA)

### Cover design

Ohmukai Design Office

### Print

Tani Printing Corporation

### Contact

ips-contact@cira.kyoto-u.ac.jp  
Website: [www.cira.kyoto-u.ac.jp/e/](http://www.cira.kyoto-u.ac.jp/e/)  
Tel: +81-75 366 7005  
Fax: +81-75 366 7185

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# Bacteria change mammalian cell identity

*The Shinji Masui lab shows proteins from bacteria can be used to reprogram mouse cells.*

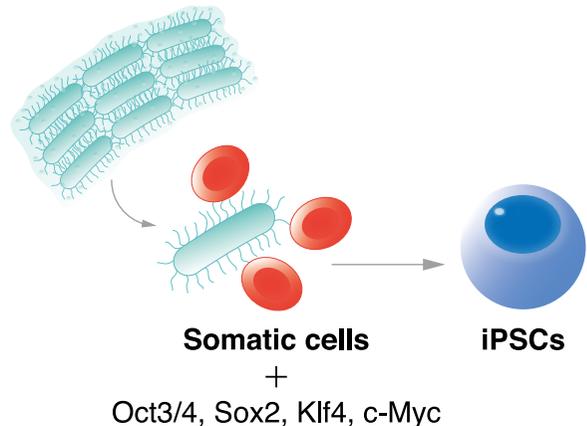
The discovery of iPS cells demonstrated that a cell's identity could be changed through the activation and repression of certain genes. While it is now possible to reprogram cells from one identity to another, the low efficiency limits the type of experiments and medical applications. In its latest study, the Shinji Masui lab reports that proteins from bacteria can enhance the reprogramming efficiency, giving light to how xenoproteins can regulate cell behavior and cell identity.

Masui notes that even though a number of chemical compounds have been found to improve reprogramming efficiency, the efficiency remains dissatisfactory, and finding new compounds is not trivial.

“Several small molecules are known to enhance reprogramming, but the search is laborious. Bacterial proteins are easier to screen and prepare,” he said.

According to Masui, scientists must screen tens of thousands of small molecules to find one reprogramming candidate, whereas they need only screen tens of bacterial proteins.

Cell reprogramming to iPS cells was first demonstrated by transducing into mouse cells the four Yamanaka factors. In the new study, Masui and his colleagues tested 30 genes from the bacterium *Wolbachia pipientis* and found that introducing the protein coded from one of these genes with the Yamanaka factors into mouse cells significantly raised the reprogramming efficiency. However, the effect depended on the cell type, as both mouse fibroblasts and mouse neural progenitor cells could be reprogrammed more efficiently, but



**Bacterial proteins enhance the reprogramming of mouse cells to iPS cells.**

mouse hepatoblasts became more resistant to reprogramming when the bacterial protein was added.

Further analysis showed that the xenoprotein-enhanced reprogramming was the result of repressing genes that sustain cell identity, suggesting that how xenoproteins interact with specific genes in the cell accelerates reprogramming.

“*Wolbachia pipientis* proteins downregulated cytoskeletal genes. Cell morphology is very important for cell identity. It determines how the cell interacts with its environment,” said Masui.

The discovery that xenoproteins bind to cytoskeletal proteins suggests other methods that suppress these proteins could also benefit cell reprogramming science.

## Reference

Ikeda T, Uchiyama I, Iwasaki M et al. (2017) Artificial acceleration of mammalian cell reprogramming by bacterial proteins. *Genes to Cells* DOI: 10.1111/gtc.12519

# Stem cells lose their shine

*The Yasuhiro Yamada and Takuya Yamamoto labs show the gold standard for embryonic stem cells does not replicate cell behavior in the embryo. The discovery indicates a need for scientists to reconsider how stem cells are made.*

**B**ecause they can form any cell in the body, ES cells have tremendous potential for regenerative medicine. These artificial cells are also expected to give great insights on the very beginnings of human development, which would explain how a small number of cells in the embryo grow into a whole body. A new study from the CiRA laboratories of Professor Yasuhiro Yamada and Junior Associate Professor Takuya Yamamoto shows ES cells have abnormal epigenetics that limits their usefulness in scientific research and clinical application. The findings, which can be read in *Nature*, suggest more attention is needed on how ES cells are made.

From a scientific perspective, a key feature of ES cells is pluripotency, which allows the cells to differentiate into any cell type. This same property is true of embryonic cells and is considered essential for development.

One way to study pluripotency is by injecting ES cells into mouse embryos. There, they mix with embryonic cells to form chimeric (genetically-modified) mice.

“When we transplant ES cells into a mouse embryo, the cells will mix with the host embryonic cells. That is how we make chimeric animals,” explained Yamada.

“The original ES cells were made using serum (S)+LIF. Many years later it was shown that ES cells made using 2i+LIF have better pluripotent

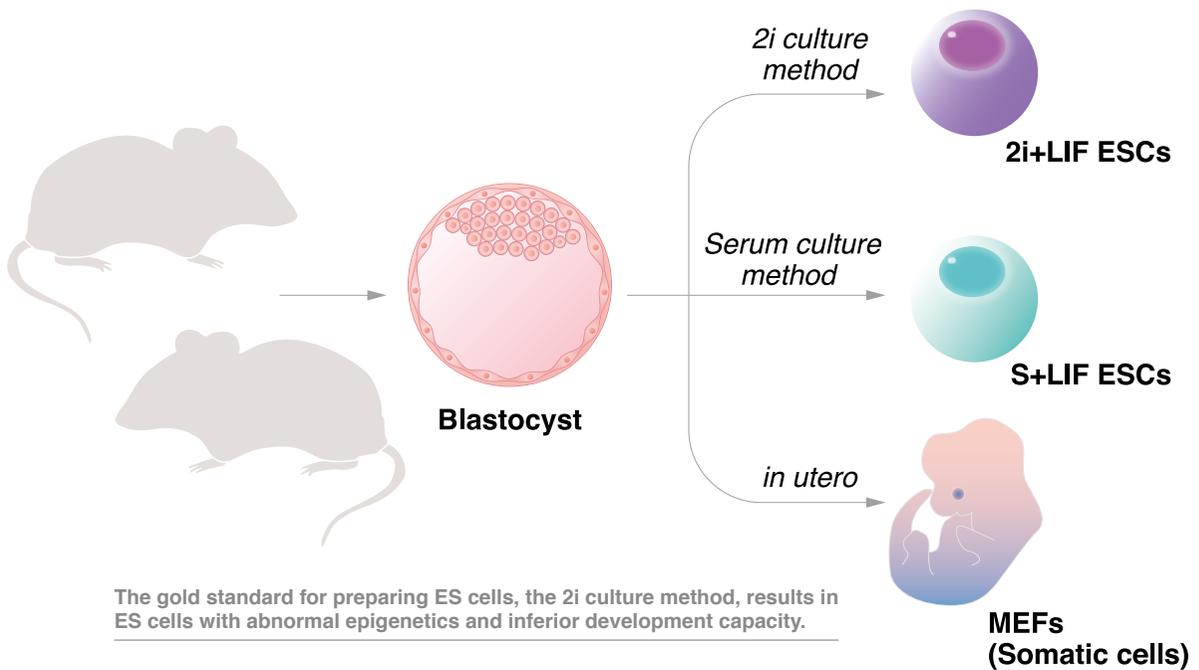
features. These ES cells are the gold standard. ES cells are identical genetically, but different epigenetically,” he added.

One way in which the epigenetics of 2i+LIF ES cells and S+LIF ES cells differ is in the methylation of DNA.

“DNA of 2i+LIF ES cells is more hypomethylated. Hypomethylation is an important event that happens after an egg is fertilized. The methylation levels in the embryo change with development,” says Masaki Yagi, first author of the study.

The methylation levels of 2i+LIF are thought to better recapitulate the methylation levels of embryonic cells during development, which is one reason 2i+LIF ES cells are preferred by scientists.

Like in every mouse cell, every gene in a mouse ES cell consists of one allele from the mother and one allele from the father. For most genes, during the very earliest stages of development, demethylation will occur on both alleles. The one exception is genes within imprinting control regions (ICRs). Here, only one allele will undergo demethylation. Having one methylated allele and one demethylated allele in the ICRs is considered essential for proper development. Yagi found that in female mouse ES cells prepared in 2i+LIF, both alleles in ICRs are demethylated, a phenomenon not seen in ES cells prepared in S+LIF. Moreover, this difference has a big impact on the developmental potential of the ES cells.



“We did two types of tests. One is nuclear transfer and the other is tetraploid embryo complementation. Both are stringent ways to test ES cell development potential. Only S+LIF ES cells could develop into mice,” said Yagi.

This finding is significant, because it forces researchers to reassess ES cells. If 2i+LIF ES cells are truly equivalent to embryonic cells, they should have the same developmental capacity. While countless experiments have confirmed that 2i+LIF ES cells are pluripotent by creating chimeric mice, the experiments by the two CiRA labs suggest the quality of the pluripotency does not match the quality in embryonic cells and that 2i+LIF ES cells may not be as well suited for the study of development as first believed.

“Because 2i+LIF ES cells successfully make chimeras, many laboratories have not considered the possibility that the pluripotency is substandard. Our findings show that scientists must select the ES cell derivation protocol carefully,” said Yamada.

Further experiments indicated the addition of inhibitors for MEK1/2 or Src, which are included in other ES cell derivation protocols, could preserve the epigenetic quality of ES cells made with 2i+LIF.

While Yagi admits most of the excitement about these findings will come from a select group of stem cell biologists, he stresses that pluripotency quality is a major determinant in how quickly stem cell-based therapies will reach patient care.

“Our findings are helpful for generating high-quality and safer pluripotent stem cells. We demonstrated imprint-losing ES cells have lower pluripotency potential. Further research can improve stem cell derivation and propagation,” he said.

#### Reference

Yagi M, Kishigami S, Tanaka A et al. (2017) Derivation of ground-state female ES cells maintaining gamete-derived DNA methylation. *Nature* 548: 224  
DOI: 10.1038/nature23286

# Curing Parkinson's disease is not for monkey brains

*The Jun Takahashi lab has published a series of reports that show iPS cell-based therapy benefits monkeys with Parkinson's disease and other neurodegenerative diseases.*

**B**efore an experimental cell therapy for brain diseases can be tested on patients, it must first be confirmed in monkeys. In the past few months, the Jun Takahashi lab has published several papers that are considered last steps before announcing the first iPS cell-based therapy for neurodegenerative diseases.

Parkinson's disease degenerates a specific type of cells in the brain known as dopaminergic (DA) neurons. It has been reported that when symptoms are first detected, a patient will have already lost more than half of his or her DA neurons. Several studies have shown the transplantation of DA neurons made from fetal cells can mitigate the disease. The use of fetal tissues is controversial, however. On the other hand, iPS cells can be made from blood or skin, which is why Professor Takahashi, who is also a neurosurgeon specializing in Parkinson's disease, plans to use DA neurons made from iPS cells to treat patients.

"Our research has shown that DA neurons made from iPS cells are just as good as DA neurons made from fetal midbrain. Because iPS cells are easy to obtain, we can standardize them to only use the best iPS cells for therapy," he said.

To test the safety and effectiveness of DA neurons made from human iPS cells, Tetsuhiro Kikuchi, a neurosurgeon working in the Takahashi lab, transplanted the cells into the brains of monkeys.

"We made DA neurons from different iPS cell lines. Some were made with iPS cells from healthy donors. Others were made from Parkin-

son's disease patients," said Kikuchi, who added that the differentiation method used to convert iPS cells into neurons is suitable for clinical trials.

It is generally assumed that the outcome of a cell therapy will depend on the number of transplanted cells that survive, but Kikuchi found this was not the case. More important than the number of cells was the quality of the cells.

"Each animal received cells prepared from a different iPS cell donor. We found the quality of donor cells had a large effect on the DA neuron survival," Kikuchi said.

To understand why, he looked for genes that showed different expression levels, finding 11 genes that could mark the quality of the progenitors. One of those genes was *Dlk1*.

"*Dlk1* is one of the predictive markers of cell quality for DA neurons made from embryonic stem cells and transplanted into rat. We found *Dlk1* in DA neurons transplanted into monkey. We are investigating *Dlk1* to evaluate the quality of the cells for clinical applications," said Kikuchi.

Another feature of the study that is expected to extend to clinical study is the method used to evaluate cell survival in the host brains. The study demonstrated that magnetic resonance imaging (MRI) and position electron tomography (PET) are options for evaluating the patient post surgery.

"MRI and PET are non-invasive imaging modalities. Following cell transplantation, we must

regularly observe the patient. A non-invasive method is preferred,” said Takahashi.

The group is hopeful that it can begin recruiting patients for this iPS cell-based therapy before the end of next year. “This study is our answer to bring iPS cells to clinical settings,” said Takahashi.

In a related study, the lab reports a strategy that improves the survival of the transplanted cells in monkeys. For a transplantation to succeed, the donor and patient must have matching human leukocyte antigens (HLA) to prevent tissue rejection. The equivalent to HLA in monkeys is MHC, or major histocompatibility complex. The study, first authored by CiRA Assistant Professor Asuka Morizane, shows that dopamine neurons derived from MHC-matched monkey iPS cells stimulated far less neuroinflammation when transplanted into monkey brains than did dopamine neurons derived from MHC-unmatched monkey iPS cells. While this difference did not completely eliminate the need for immunosuppressants, it did lower the dosage so as to reduce the risk of infection. The findings suggest HLA matching for iPS cell therapies will improve outcomes in

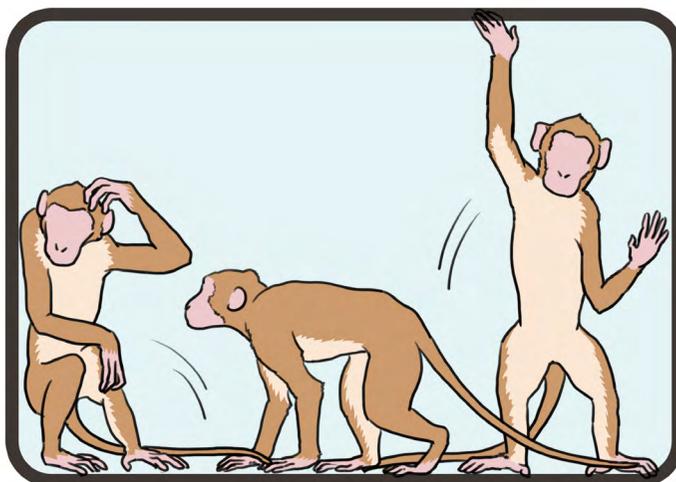


Illustration by Misaki Ouchida (CiRA)

**Monkeys show reduced Parkinsonian symptoms following a donor-matched iPS cell-based therapy.**

patients with neurodegenerative diseases.

“The combination of MHC-matching and immunosuppression will reduce the dose and duration of the immunosuppressive drug and be the best strategy for the transplantation,” said Morizane.

Finally, Noritaka Sano, another neurosurgeon in the group, has discovered the molecule neuropilin-1 (NRP-1) could mark cells that have good therapeutic benefit in cell transplants for patients who have suffered stroke or other trauma. These patients are at risk of losing vital communication between the nervous system and muscle. One reason therapies have not advanced as quickly as they have for Parkinson’s disease is the uncertainty about which cell populations are best for the transplant. Sano found cells that express NRP-1 tend to send axons to the corticospinal tract (CST), indicating these could convalesce the damage.

#### Reference

Kikuchi T, Morizane A, Doi D et al. (2017) Human iPS cell-derived dopaminergic neurons function in a primate Parkinson’s disease model. *Nature* DOI: 10.1038/nature23664

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Sano N, Shimogawa T, Sakaguchi H et al. (2017) Enhanced Axonal Extension of Subcortical Projection Neurons Isolated from Murine Embryonic Cortex using Neuropilin-1. *Frontiers in Cellular Neuroscience* 11:123 DOI: 10.3389/fncel.2017.00123

## Advances in pancreas research

*The Kenji Osafune lab has published a series of papers that reveal biomechanical and biochemical factors for pancreas differentiation and disease.*

The heart is designed optimally to pump blood, the lungs are designed optimally to exchange air, and even the brain, with its many folds and regions, is designed to control thought. In general, organs have one structure to maximize one function. Not the pancreas. It has one shape that gives it two distinct functions: the production of hormones and the digestion of foods.

This feature has made the pancreas an exceptionally difficult organ to synthesize in the lab. The dramatic increase in diabetes and other related diseases, however, has created a high demand for cell therapies that use pancreatic cells.

Two types of culture systems, cell aggregation (3D) and monolayer (2D), are used to make insulin-secreting islet cells for cell therapies, but they vary significantly in their differentiation efficiency. In a project led by Junior Associate Professor Taro Toyoda, the Osafune lab has found the different efficiencies can be attributed to the different expressions of proteins responsible for cell biomechanics.

“Aggregation cultures cause mechanical stress on cells that does not exist in monolayer cultures,” said Toyoda.

Scientists have had much more success generating pancreatic progenitor cells in aggregation culture systems, but monolayer culture systems offer an easier and stable way to produce the cells.

The study shows that adding inhibitors for non-muscle myosin II and ROCK into monolayer

culture leads to an efficiency that is comparable with aggregate culture.

In another study, the lab reports that the molecule AT7687 promotes the differentiation of iPS cells to pancreatic progenitor cells.

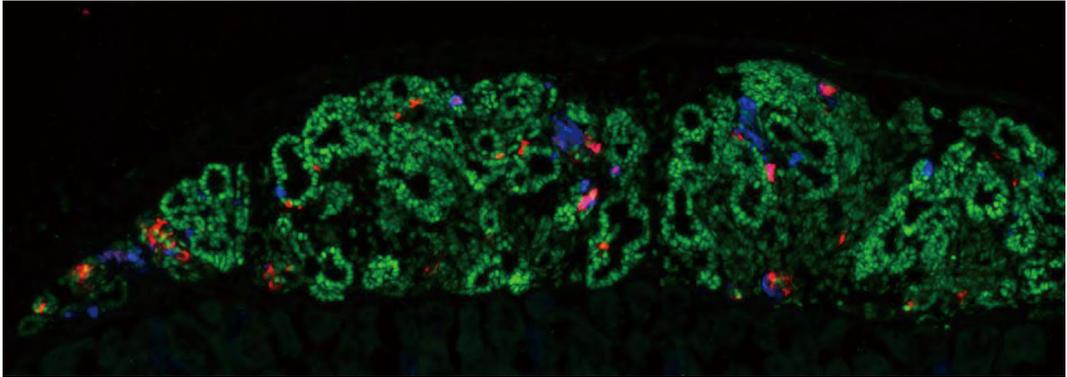
“We tested over a thousand compounds on iPS cells. We found adding AT7867 to standard differentiation protocols enhanced pancreatic progenitor cell levels,” said Prof. Osafune.

While the pancreatic progenitor cells themselves do not produce insulin, the study shows that with further manipulation the cells could be differentiated into islet cells that do.

“It is difficult to store islet cells for a long time. We can store iPS cells and pancreatic progenitor cells, but pancreatic progenitor cells are advantageous because they shorten the handling period,” he said.

The induction of pancreas lineage differentiation by the lab has also led to a new disease model. In fulminant type 1 diabetes (FT1D), the cell loss is so rapid that patients can die within a day if ketoacidosis is untreated. In a collaborative effort with Osaka University, the group reports pancreatic beta cells derived from iPS cells made from FT1D patients.

Scientists depend on samples of inflicted cells to study disease development and test experimental drugs. In FT1D, however, almost all the pancreatic beta cells are destroyed. Skin cells from



The addition of chemical inhibitors simplifies the culture method used to generate pancreatic progenitor cells from iPSCs.

three FT1D patients and three healthy donors were reprogrammed into iPS cells and then differentiated into insulin-producing beta cells. Because the immune system is responsible for the cell death in FT1D, the researchers added three standard immune cell secretions (the cytokines TNF $\alpha$ , IL-1 $\beta$ , and IFN $\gamma$ ) that activate apoptosis.

“iPS cells from patient or healthy donors were equally likely to differentiate into beta cells using our protocol. The patient cells showed more caspase-3 activation. Caspase-3 is a marker of apoptosis,” said Osafune, which makes the patient cells more sensitive to stimuli that promote apoptosis.

These cells will be the basis of new human FT1D models to study experimental drug compounds.

**E**PO (erythropoietin) has gained notoriety as the drug of choice in cycling. For anemia patients, however, EPO doping is essential,

as it is the primary hormone responsible in the body for producing red blood cells. Patients with chronic kidney disease are especially susceptible to anemia, because the kidney is the primary site of EPO production. The Osafune lab shows iPS cells can be induced into cells that secrete EPO and when transplanted convalesce anemic mice.

To date, no EPO cells have been isolated from the kidney. Although EPO is produced by the kidney in adults, the liver is responsible for EPO during the fetal stage. The researchers modified methods used to differentiate iPS cells into fetal hepatic cells that produce EPO.

The study found that EPO secretion could be increased by treating iPS cells with insulin-like growth factor 1 (IGF-1), which was named for its structural resemblance to insulin but contributes to growth and anabolic processes, and with prolyl hydroxylase domain-containing enzyme inhibitors, which regulate oxygen levels.

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# iPS cells lead to a new drug clinical trial

*CiRA shows rapamycin may inhibit excessive bone growth in the orphan disease fibrodysplasia ossificans progressiva.*

With an estimated 1,200 patients worldwide, fibrodysplasia ossificans progressiva (FOP) is an extremely rare disease. In FOP patients, soft tissues like muscles and ligaments are replaced with bone following damage. The excessive bone literally causes the body to ossify to the point that patients cannot move. Because of its rarity, there is little understanding of the disease and thus little in terms of treatment. In a new study, Professor Junya Toguchida and Associate Professor Makoto Ikeya report a new drug screening system using iPS cells that reveals one drug candidate, rapamycin, could prevent the ossification seen in FOP.

The abnormal bone growth in FOP is because of a mutation in the ACVR1 gene, which causes soft tissue to respond abnormally to trauma.

“The body reacts like it has a broken bone even though soft tissue is damaged. Bone grows in the soft tissue, and the patient loses mobility. Eventually the bone growth spreads so it is hard to swallow or breathe,” explains Ikeya.

Toguchida and Ikeya have long worked together to study how the ACVR1 mutation causes FOP by using patient iPS cells. Although the disease is rare, Toguchida, who is also an orthopedic surgeon at Kyoto University Hospital, has had access to about half of Japan’s FOP patients through patient advocacy groups, while Ikeya, a developmental biologist, has been studying the abnormal bone growth by differentiating these iPS cells into bone or soft tissue cells.

In the current study, to find candidate drug com-



(Left to right) Junya Toguchida, Makoto Ikeya and Kyosuke Hino

pounds, Kyosuke Hino used a high-throughput drug screening (HTS) system that hit rapamycin. Rapamycin is an approved drug that is used to suppress immune reactions during transplants and other treatments.

“Our HTS system is unique because we can study the effect of the drug on patient cells in animal models. Usually, patient cells are tested outside a body. Plus, we searched currently marketed drugs. These drugs should accelerate clinical trials because we already know their dose levels and side effects,” said Ikeya.

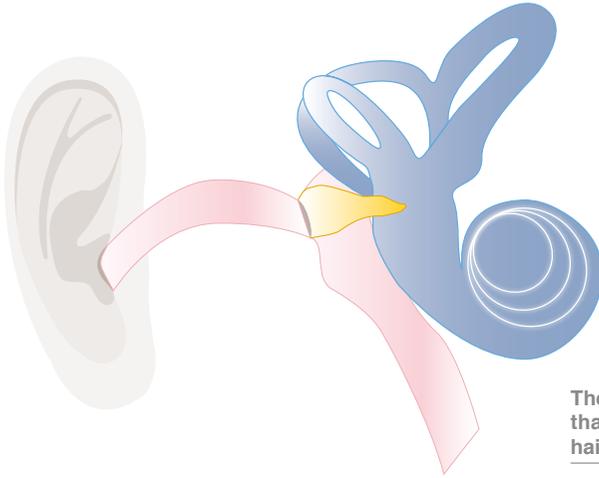
Toguchida and a team of researchers received approval from Kyoto University for a clinical trial of rapamycin to treat FOP. The trial began Oct. 5 at Kyoto University Hospital.

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# A stem cell population in the ear

*The Megumu Saito lab identifies genes that could promote cochlear regeneration.*



The M. Saito lab has found gene candidates that could promote the regeneration of lost hair cells responsible for hearing in the ear.

An amazing 1 in 20 people around the world suffer from hearing loss, and 10% of them are children. In many cases, especially the elderly, the loss is not due to any disease but the loss of hair cells in the ear. Otolaryngologist Takehiro Iki of the Saito lab believes that iPS cell technology could lead to new therapies to regenerate these cells.

“Hair cells in the cochlear sensory epithelium (CSE) sense sounds. These cells do not regenerate in mammals. As we age, we lose these cells and our hearing,” he said.

Scientists have been able to regenerate mammalian hair cells in the lab, suggesting that the CSE contains a small population of stem cells that could regenerate the lost hair cells. Iki sought to identify these stem cells by comparing their gene expressions with those of ES cells. He prepared cells from the CSE of newborn mice, since hair cell regeneration is lost at about 3 weeks after birth in these animals.

Iki had expected CSE stem cells to express genes

that are associated with the stemness of ES cells. Instead, he found three genes that associated with the cell cycle.

“*Nabp1* is essential for a variety of DNA processes including replication. *Cdkn2a* encodes proteins that induce cell cycle arrest in response to stress. *Gadd45a* also encodes proteins that respond to stress,” he said.

These factors could contribute to the proliferation of cells, but they do not necessarily indicate stemness and therefore do not confirm whether the cells can go on to differentiate into hair cells. A second search revealed the transcription factors *Trib3*, *Klf5* and *Hmga2*, which have a role in pluripotency, were upregulated.

The manipulation of these factors could enable the reprogramming of CSE hair cells.

## Reference

Iki T, Tanaka M, Kitajiri SI et al. (2017) Microarray analyses of otospheres derived from the cochlea in the inner ear identify putative transcription factors that regulate the characteristics of otospheres. *PLOS ONE* DOI: 10.1371/journal.pone.0179901

# Greetings from the Knut Woltjen Lab

*Dept. of Life Science Frontiers*

**E**ach lab in CiRA focuses on some specific aspect of human health which can be addressed by iPS cell research. Some are interested in the derivation and banking of iPS cells, while others prioritize specific organs or disease and use iPS cells to study the development processes along with related pathologies. Still others apply iPS cells and their differentiated derivatives in the search for cellular or pharmacological treatments for disease. In this primarily clinical-focused environment, our lab is distinct in that our interests lie in the development of biological tools that help expose the underlying answers to these challenging scientific questions.

Genetics often lies at the core of human health issues. Our research therefore centers around genome engineering with CRISPR-Cas9 and TALENs, which are molecular scissors used to tailor genome sequences. Motivated to enhance the precision of gene modification, we develop methods to create and correct subtle genetic changes including small deletions and single-base mutations. Adding new function to the genome, our piggyBac transposons can introduce large synthetic genetic circuits. In this way we have established methods for consistent and scalable transgene expression, simplifying the selection and tracking of cells with desired functions, and revealed the influence of reprogramming factor stoichiometry, all for the purpose of clarifying the molecular

mechanisms of iPS cell production.

Looking to biology for inspiration, we consider ourselves primarily a bioengineering lab. We're proud to see our technology used broadly, and most of our projects involve collaborations that test the potential of our innovations. With our technologies in hand, our collaborators have accomplished drug discoveries for neurodegenerative diseases, in vitro human germ cell development, and new insights into cancer progression.

Thus, we fulfill a unique position in CiRA that has allowed us to establish strong scientific relationships within Japan and across multiple countries, which is best represented by the global diversity of our lab members. Overall, our lab offers an excellent environment for anyone who wants to build new technologies that have far-reaching impact in multiple biological and medical disciplines.



Knut Woltjen

# The symbiosis of the artificial and the natural

by Associate Professor Jusaku Minari, Uehiro Research Division for iPS Cell Ethics

The news has been giving lots of attention to artificial intelligence recently. AI has spread to all sorts of industries, from entertainment to business, law and order, national defense, and of course medicine. Arguably the biggest news about AI, and certainly news that caught attention in Japan, was its prospect in playing popular Japanese board games like Igo and Shogi. Although these games were considered extraordinary if not impossible challenges for AI, accomplishments this year proved otherwise. But not the “intelligence”, I want to stress the “artificial” of AI in this essay.

I stress “artificial” because of its basis in CiRA. iPS cells are cells not found in nature, which makes them artificial. Much like how many researchers are using AI to solve complex problems related to nature, researchers at CiRA and similar institutes are using artificial cells (iPS cells) to solve complex problems related to

health and disease.

The point I want to convey is that we depend on the artificial to understand the natural, especially humans and their abilities and potentials. This realization should give us a positive impression of the artificial, but one that should not come unconditionally.

Our challenge is to incorporate the artificial seamlessly into our lives. Certainly one group of people responsible for this task is the experts who are designing, refining and managing artificial systems like AI and iPS cells. But these people are not enough. The artificial is impacting almost every facet of our lives in ways that is making us question our values. AI is seen encroaching into almost all professions, and iPS cells are changing our views of life. We need all members of society to take active involvement in our evaluation of these innovations.



Jusaku Minari at symposium

## CiRA Outreach

**O**n August 3 and 4, CiRA took part in MIRAI SUMMER CAMP 2017 in Tokyo. The annual camp goes one month long and provides a number of educational activities for school-aged children during the summer holidays. Participants had opportunities to learn about the science of water, the manufacturing of coffee, and, of course, iPS cells. Approximately 90 children attended the CiRA workshop. Kenji Ito, a scientist in the Yasuhiro Yamada lab, gave a presentation about the basics of cell reprogramming. Students were also given a chance to play a board game that models iPS cell reprogramming and differentiation.

Kanazawa was one of the more dominant cities in Japan during the Edo period and today continues to retain much of the architecture from that era. The city lies between mountains and the Japan Sea about 250 km due north of Kyoto. CiRA Professor Kenji Osafune visited July 9 to take part in a CiRA Café, which allowed the general public to learn about iPS cells. His talk covered

the application of iPS cells to study regenerative medicine for diseases such as kidney disease, diabetes, and liver failure.



iPS cell board game



Kenji Ito



Kenji Osafune (right) and CiRA colleague Hiroyuki Wadahama

## Awards

**P**rofessor Yoko Hamazaki was one of two researchers awarded the Kao Foundation for Arts and Science Prize on June 16. The foundation recognized Hamazaki for her work on the development and maintenance of thymic epithelial cells in immune self-tolerance. Hamazaki only joined CiRA this summer, but hopes the award is a harbinger of her future research.

“My research career has focused on thymic epithelial cells. The next step is to expand research to cure diseases and understanding of human

immunology with various approaches including the use of iPS cell technology” she said.



Yoko Hamazaki (center)

# The Temples and Shrines of Kyoto

## Toji-in

**T**oji-in lies a little south of Kinukakenomichi, a road home to Kinkakuji and other popular temples in northern Kyoto. Despite this location, the narrow roads leading to the temple discourage tourist buses from reaching it, and the surrounding residential neighborhood even hides it from pedestrians. This makes the temple a rarity in the city, in that the absence of crowds gives an aural serenity that matches the visual serenity. As a home for Shoguns, the temple was the target of military assaults that have had it burned to the ground and rebuilt many times. While the garden captures all the aesthetics associated to Japan, the temple is relatively modest and seems unworthy of its violent past.



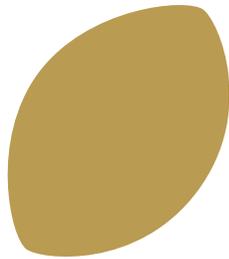
Main entrance

## CiRA International Symposium

**M**ark the date. November 6-8, CiRA will host its next international symposium in Kyoto. Please check the CiRA website for information about speakers and the program.



[http://www.cira.kyoto-u.ac.jp/e/international\\_symposium](http://www.cira.kyoto-u.ac.jp/e/international_symposium)



*Autumn is coming  
Many colours from one, green  
Can we change them back?*



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## **CiRA Reporter**

Center for iPS Cell Research and Application (CiRA), Kyoto University  
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan  
[www.cira.kyoto-u.ac.jp/e/](http://www.cira.kyoto-u.ac.jp/e/)  
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