CiRA Reporter

Center for iPS Cell Research and Application,
Kyoto University

Vol.10
April 2017

CONTENTS

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

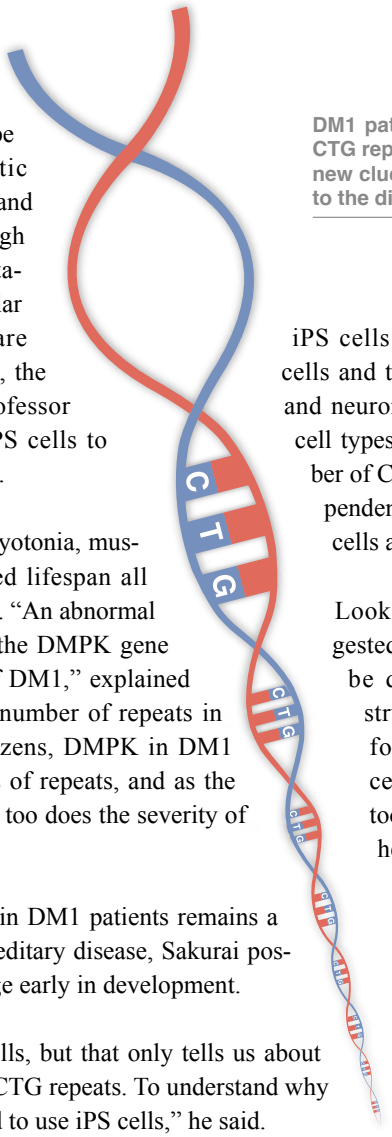
Cover design
Ohmukai Design Office

Print
Tani Printing Corporation

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

A new cause of muscular dystrophy

The Hidetoshi Sakurai lab uses iPS cells to reveal epigenetic changes trigger a rare form of muscular dystrophy, DM1.



DM1 patients have an extraordinarily long CTG repeat. Patient iPS cells have provided new clues on how these repeats contribute to the disease.

Myotonic dystrophy type 1 (DM1) is a genetic disease that targets muscle and other organ systems. Although the effects of the gene mutation are known, the molecular mechanisms responsible are not. In its latest publication, the laboratory of Associate Professor Hideotoshi Sakurai uses iPS cells to identify a possible candidate.

DM1 patients suffer from myotonia, muscle atrophy, and a shortened lifespan all because of a single mutation. "An abnormal number of CTG repeats in the DMPK gene is the causative mutation of DM1," explained Sakurai. While the normal number of repeats in the gene is in the small dozens, DMPK in DM1 patients can have thousands of repeats, and as the number of repeats grows, so too does the severity of the disease.

Why these repeats increase in DM1 patients remains a mystery. Because it is a hereditary disease, Sakurai postulated that the causes emerge early in development.

"We can examine patient cells, but that only tells us about the current condition of the CTG repeats. To understand why the repeats grow, we decided to use iPS cells," he said.

iPS cells were prepared from DM1 patient cells and then differentiated into muscle cells and neurons. Although DM1 affects different cell types differently, unexpectedly, the number of CTG repeats increased with time independent of the cell type (iPS cells, muscle cells and neurons).

Looking for explanations, Sakurai suggested that "the increase in repeats could be due to changes in the chromatin structure." Indeed, his research group found that the chromatin in muscle cells prepared from patient iPS cells took a closed state, whereas those from healthy donors were in the open state.

"This difference is a new clue on how CTG repeats form in DM1 patients," he concluded, proposing that manipulating the status of the chromatin could offer a therapeutic strategy.

Reference

Ueki J., Nakamori M., Nakamura M. et al. (2017) Myotonic dystrophy type 1 patient-derived iPSCs for the investigation of CTG repeat instability.
Scientific Reports 7: 42522. DOI:10.1038/srep42522

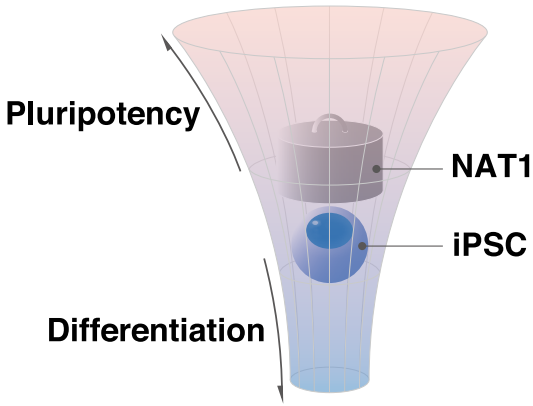
The makings of better human stem cells

The Shinya Yamanaka lab finds Nat1 may improve stem cell quality.

Although they have come to define his career, CiRA Director Shinya Yamanaka describes iPS cells as an outcome of a much greater scientific interest. "My scientific research has been about cell pluripotency. I have been searching for factors like *Nat1* (Novel APOBEC1 target #1, also known as eIF4G2) that regulate pluripotency," he said.

Many people do not associate *Nat1* with Yamanaka, but it has been a major theme in his research for more than two decades, dating back to the time he was first identified *Nat1* while working as a post-doctorate at the Gladstone Institutes. In its most recent publication, his lab at CiRA reports new insights on how *Nat1* regulates pluripotency in mouse ES cells.

Pluripotency describes a state in which a cell can differentiate into any other cell type. Scientists have since discovered many states of pluripotency. Based on the condition the cell is cultured, a mouse ES cell can take one of three pluripotent states: ground, naïve, or primed.



***Nat1* promotes differentiation and blocks reprogramming to the pluripotent state.**

"The ground state is best for regenerative medicine, because it has the highest pluripotency and efficiency at differentiating into other cells," said Hayami Sugiyama, a researcher in the Yamanaka lab and first author of the study. In humans, however, no ground state ES cells are known, and naïve state ES cells have only recently been created. "We are using mouse cells to find factors that could help us acquire ground pluripotency in human cells," said Sugiyama.

Previous work from the Yamanaka lab and others has already revealed *Nat1* as such a factor. In particular, mouse ES cells in which *Nat1* was deleted (*Nat1*-null cells) showed properties similar but not identical to those of ground state even though the cells were cultured in conditions appropriate for the naïve state. In the current study, Sugiyama identifies two gene targets of *Nat1* that were suppressed in *Nat1*-null cells, Map3k3 and Sos1. Interestingly, the translation but not the transcription of these genes was changed. This observation suggests that inhibiting the activity of the proteins could be crucial in acquiring the ground state in mouse cells.

Because mouse and human ES cells behave differently, these findings do not assure that *Nat1* will clarify ground pluripotency in human cells. Nevertheless, Sugiyama believes that by using *Nat1* he can find signaling pathways in mouse cells that might also work in human cells.

Reference

Sugiyama H., Takahashi K., Yamamoto T. et al. (2017) *Nat1* promotes translation of specific proteins that induce differentiation of mouse embryonic stem cells.
Proceedings of the National Academy of Sciences 114:340-345
DOI: 10.1073/pnas.1617234114

New drug for the prevention of bleeding

The Koji Eto lab reports a new drug that enhances the production of platelets from iPS cells.

Platelet therapies depend on blood donations, but many countries are realizing this dependency is unsustainable. In Japan, it has been estimated that there will be a crippling undersupply of platelet donors in a generation. CiRA Professor Koji Eto and his team have been developing an iPS cell-based system that produces platelets independent of donors. In their latest work, they describe a new drug, TA-316, that enhances the production of platelets from iPS cells and brings this form of treatment closer to the clinic.

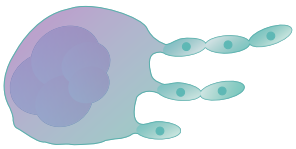
"There is an urgent need for systems that are independent of donors. The Japanese Red Cross Society estimates Japan will have an undersupply of 20%," says Eto. "But platelets cannot be stored for more than a week. We are preparing immortalized megakaryocyte progenitors [from iPS cells] that produce platelets and can be stored for more than half a year."

Megakaryocytes are the cells responsible for producing platelets, and one megakaryocyte can make over 1,000 platelets in the body. However, in the lab, this number drops precipitously to just 10 or so. One reason is TPO.

A cousin to EPO, the renown performance enhancing drug that increases the number of red blood cells, TPO is the hormone most responsible for stimulating megakaryocytes to produce platelets. "Many drugs that target the TPO receptor have been made," says Eto, "but they are not good enough."

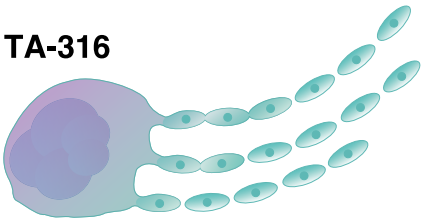
There are already several drugs approved for clinical use to counter low platelet count. Among these drugs, Eto and his group compared TA-316 with the one it most resembled structurally, Eltrombopag, finding TA-316 was superior in two ways. First, it enhances the number of immortalized megakaryocyte progenitors made from iPS cells, but this effect was relatively mild, as it only doubled the amount of progenitors compared with Eltrombopag. Second, and more significant, was that it was ten times more productive at producing platelets from a single megakaryocyte compared with the approved drug. Furthermore, their findings indicated that the effect could be synergized by combining TA-316 with other drugs that enhance platelet levels.

FDA-approved drug



FDA-approved drugs only stimulate a modest amount of platelets from megakaryocytes.

TA-316



TA-316, on the hand, stimulates multiple times more.

Along with improving platelet numbers, Eto is excited that TA-316 could reveal how platelets form, saying, "Many factors determine platelets. We can use TA-316 to study these factors and diseases."

Reference

Aihara A., Koike T., Abe N., et al. (2017) Novel TPO receptor agonist TA-316 contribute to platelet biogenesis from human iPS cells. *Blood Advances*. DOI: 10.1182/bloodadvances.2016000844

Skin cells halt blindness

CiRA and Riken scientists use iPS cell technology to stop vision degeneration in patients.

A team of scientists led by ophthalmologist Dr. Masayo Takahashi at Riken Center for Developmental Biology (CDB), Kobe, and Dr. Shinya Yamanaka at CiRA has reported the world's first iPS cell-based therapy. Skin cells from a patient going blind were reprogrammed into eye cells using iPS cell technology and then transplanted back to the patient, stabilizing her vision. CiRA contributed to this work by evaluating the safety of the cells prior to transplantation.

The patient suffers from wet age-related macular degeneration (AMD), a disease that leads to the progressive degeneration of vision due to an impairment of retinal pigment epithelial (RPE) cells. While some patients can be treated with drugs, surgical intervention that transplants retinal cells is the only option for others.

The researchers took a skin biopsy from the patient and reprogrammed the cells into iPS cells, which were then differentiated into retinal pigment epithelial cells and prepared for transplantation.

However, the creation of iPS cells requires manipulating the DNA of the skin cells, which sometimes can cause mutations associated with cancer. Therefore, the cells used for the transplantation had to undergo exhaustive evaluation to confirm they were safe.

"Because this was the first iPS cell-based therapy, we were extra vigilant in checking the safety of the cells," said Dr. Akira Watanabe, who with Yamanaka, performed genomic analyses of the iPS cells at CiRA.

Yamanaka and Watanabe looked for abnormal changes in the chromosomes, DNA copy numbers and other irregularities in the DNA. Because these were the first ever human transplantation experiments, they made their stringency very high.

iPS cell-derived retinal pigment epithelial cells that passed CiRA's tests were transplanted into one of the patient's eyes in order to compare the therapy with the untreated eye. One year after the surgery, the patient's vision in the treated eye had stabilized and even showed improvement.

AMD was selected as the first disease for iPS cell-based therapy, because the eye is relatively easy to diagnose post-surgery and because the number of cells needed for the transplant was relatively few compared to that needed for larger organs.

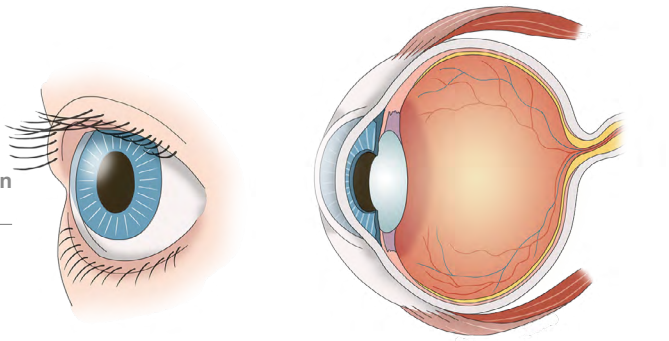
This therapy is the beginning of what Yamanaka envisions as the future for iPS cells. A major program at CiRA is the preparation of clinical-grade iPSCs that can be used by clinicians like Takahashi to treat patients. "This is a brilliant work by Dr. Masayo Takahashi. We are working with her and other clinicians and scientists to treat a wide range of diseases. AMD is the important proof of concept," he said.

Reference

Mandai M., Watanabe A., Kurimoto Y. et al. (2017) Autologous induced stem cell-derived retinal cells for macular degeneration. *N Engl J Med* 376 (11): 1038-1046. DOI:10.1056/NEJMoa1608368

A master transcription factor for eye cells

The Shinji Masui lab shows PAX6 expression is essential for corneal epithelial cells.



Development of the eye depends on master transcription factors.

Illustration by Misaki Ouchida (CiRA)

The ability of a cell to preserve its identity is crucial for healthy function. When essential transcription factors function abnormally, proper regulation of the gene expression is lost, potentially leading to degeneration and disease. Although the cornea is exclusively expressed in the eye, transcription factors that preserve its identity are of high interest, in part because of the success using stem cells to treat related diseases. For example, the first and only transplant of iPS cell-derived tissues in a patient was done to treat age-related macular degeneration (see p6). In its latest report, the Shinji Masui lab shows that the transcription factor PAX6 is essential for the identity of corneal epithelial cells, which cover the surface of the cornea.

To demonstrate PAX6 necessity, the lab used CRISPR-Cas9 technology to modify PAX6 expression. Cells in which PAX6 was repressed were still corneal epithelial cells, but the cells were larger than normal and the expression of crucial genes associated with this cell identity was repressed. To compensate, the cells overexpressed genes responsible for other epidermal cells, suggesting that function was compromised. "The function of epithelia depends on the expression of different keratin genes," explained Masui. "We found that by modifying the PAX6 expression, the cells would change their expression of keratin isoforms. These changes probably mean the function of the epithelia changed too."

These findings should have implications beyond the identity of cells in the eye. Epidermal cells like those in the skin have been extraordinarily difficult to prepare from stem cells compared with other cell types. The finding that PAX6 repression stimulates compensatory expression of keratin genes more affiliated with skin epidermis could provide insights on how to prepare these cell types in the lab.

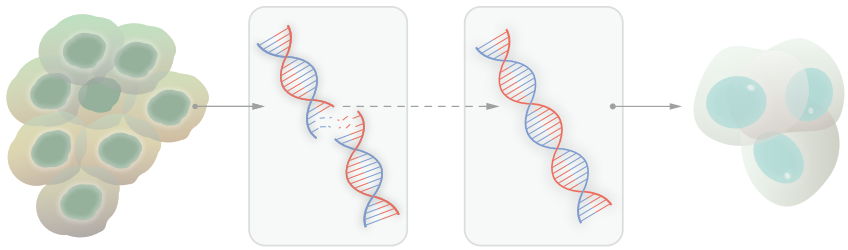
"Our goal is to build a library of transcription factors that determine cell identity," said Masui. "While this study was about corneal epidermal cells, we are interested in understanding the principles stipulating cell identity in general."

Reference

Kitazawa K., Hikichi T., Nakamura T. et al. (2016) PAX6 regulates human corneal epithelium cell identity. *Experimental Eye Research* 154:30-38. DOI: 10.1016/j.exer.2016.11.005

The organ determines if a gene is cancerous

The Yasuhiro Yamada lab demonstrates that the malignancy of an oncogene varies with the organ.



CiRA researchers show the tumorigenicity a cancer gene can be modified by gene correction following reprogramming.

Oncogenes are genes in which mutations are associated with cancer. Hundreds of oncogenes exist, but in most cases, how they initiate the cancer is poorly understood.

"Mutations in the *Apc* gene are interesting because they cause cancer only in the intestine even though they are found throughout the body," said CiRA Professor and Pathologist Yasuhiro Yamada.

To understand why, Yamada and his team of researchers used iPS cell technology to reprogram cancer cells caused by the *Apc* gene. "Reprogrammed tumor cells (RTCs) are like iPS cells, but have some important differences," he noted.

One difference is pluripotency. By definition, pluripotency gives a cell the ability to differentiate into any cell type equally, but RTCs were biased to form placental cells.

"We attributed this to the *Apc* mutation," said Kyoichi Hashimoto, one of the lead authors of the new study. "We therefore rescued the mutation and looked at the effects in mice."

Indeed, rescuing the gene resulted in RTCs that were pluripotent and had a gene expression profile that was consistent of ES cells. At the same time, forcing the *Apc* mutation in ES cells compromised pluripotency and converted the gene expression profile to one akin of RTCs.

When injected into mice, RTCs with the rescued *Apc* gene contributed to producing all the organs in the body, and no tumors were found. On the other hand, when the gene was disrupted in fully developed mice, tumors formed, but only in intestine, suggesting that something in the intestine itself triggered the malignancy.

"Our results suggest that genetic changes are not enough to cause the cancer in intestine," said Yamada. Additional study showed that the intestinal tumors expressed a methylation pattern that was absent in both RTCs and rescued RTCs. "Controlling these epigenetic changes may control the cancer," he added.

Reference

Hashimoto K., Yamada Y., Semi K. et al. (2017) Cellular context-dependent consequences of *Apc* mutations on gene regulation and cellular behavior.
Proceedings of the National Academy of Sciences 114:758-763.
DOI: 10.1073/pnas.1614197114

Gene inactivation in liver causes diabetes-like symptoms

The Yoshiya Kawaguchi lab shows how Prox1 gene can cause glucose intolerance in mice independent of fat accumulation.

Obesity and damaged liver are considered the main causes of type 2 diabetes. However, studying the degree each has on the disease has been difficult. In its newest publication, the Yoshiya Kawaguchi lab describes a new mouse model that explains how insulin intolerance develops with only hepatocyte injury. This finding could provide new therapeutic strategies for patients without obesity.

Diabetes is typically associated with obesity, but a new mouse model gives insight on diabetes development absent obesity.

The risk of diabetes has been well associated with a person's genes. "People with a specific variant of the Prox1 gene show more fat and are more at risk of diabetes," said CiRA Professor Yoshiya Kawaguchi.

The role of Prox1 on fat is relatively well established, but its role in hepatocyte injury is relatively unknown. "We know how Prox1 regulates liver development," he added, "but we do not know its role in adult liver," which is when type 2 diabetes is more likely to occur.

Members from his lab therefore prepared mutant mice in which the Prox1 gene could be inactivated exclusively in hepatocytes. The mice showed glucose intolerance and impaired liver function but no additional fat accumulation. The liver dysfunction was attributed to hepatocyte injury, but surprisingly to a very specific region of the liver.

"Hepatocytes can be divided into regions based on their metabolic function," explains surgeon Dr. Toshihiko Goto, who first authored the study. "Perivenous hepatocytes conduct glycolysis, and periportal hepatocytes conduct OXPHOS (oxidative phosphorylation)," he said.

The inactivated Prox1 caused injury to the perivenous region of the liver, where hepatocytes showed defective glycolysis and energy starvation, which stimulated autophagy to meet the energy demand. On the other hand, periportal hepatocytes showed no morphological changes.

Interestingly, mitochondria in the perivenous hepatocytes resembled those in periportal mitochondria, which suggested a change in energy metabolism. "We think hepatocyte injury in the perivenous hepatocytes caused glycolysis to switch to OXPHOS," said Goto.

Because the glucose intolerance was only accompanied by changes in hepatocyte metabolism, Kawaguchi proposes the study could indicate the possibility of diabetes treatment for non-obese patients.

"Our findings suggest if we can find drugs that control the liver metabolism, we may be able to prevent or even reverse glucose intolerance," he said.

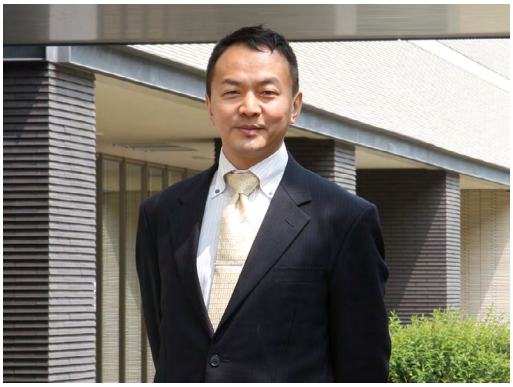
Reference

Goto T., Elbahrawy A., Furuyama K. et al. (2017) Liver specific Prox1 inactivation causes hepatic injury and glucose intolerance in mice. *FEBS Letters* 591:624-635
DOI: 10.1002/1873-3468.12570

Greetings from the
Wataru Fujibuchi Lab

Dept. of Cell Growth and Differentiation

In the model of development, a single cell, the zygote, proliferates and eventually differentiates into all the cell types of the body. When looking through a microscope, the difference between a hepatocyte, cardiomyocyte and keratinocyte is pretty clear. However, these distinctions quickly break down when we talk about similar cell types. The inability to well define a cell type reduces both the efficiency and safety of cell therapies. In response, our lab is devoted to establishing methods that give a quantitatively rigorous definition of cells.



Wataru Fujibuchi

There are currently over 20 stem cell banks and registries around the world that store information on human cells. These sites provide comprehensive information, including omics and cellular assays. However, they have not been standardized, leaving variation in essential details about the cells, such as measurement techniques and sample details, making it difficult to exchange data between sites. As more metadata are collected, this problem will only exasperate, which threatens international collaborations like those involving the iPS Cell Stock at CiRA.

As a first step, it is essential the community establish minimum information standards (MIS). MIS already exist for numerous methods related to the biosciences, all going by an alphabet of abbreviations. MIAME is used for gene expression microarray, MIAPE for proteomics, and MIACA for cell-based assays. MIACA, however, is not well suited for single-cell analysis or next generation sequencing. To extend this category of MIS to regenerative medicine, we have introduced MIACARM. We have applied MIACARM to SHOGoiN, a repository we developed that integrates disparate human cell information at single-cell resolution and was designed for the quality control of cells used in regenerative medicine.

While there is a great deal of informatics in our laboratory, we also do wet experiments. In our most recent work, we report a scheme to predict toxicology in pluripotent stem cells and those differentiated from them. The novelty in this work, however, was that the stem cells were never differentiated. Instead, we employed Bayesian gene networks as well as machine learning analyses and found remarkable accuracy at predicting the late-onset toxicity, which represents later stages of development, of chemicals in three different categories. We are now testing the same method on iPS cells.

Overall, the lab offers opportunities for scientists interested in wet and dry experiments. The lab was originally based on theoretical studies, but the people and opportunities at CiRA are well suited for combining bioinformatics with cell and molecular biology.

The future of infertility medicine

by Dr. Tsutomu Sawai, Uehiro Research Division for iPS Cell Ethics

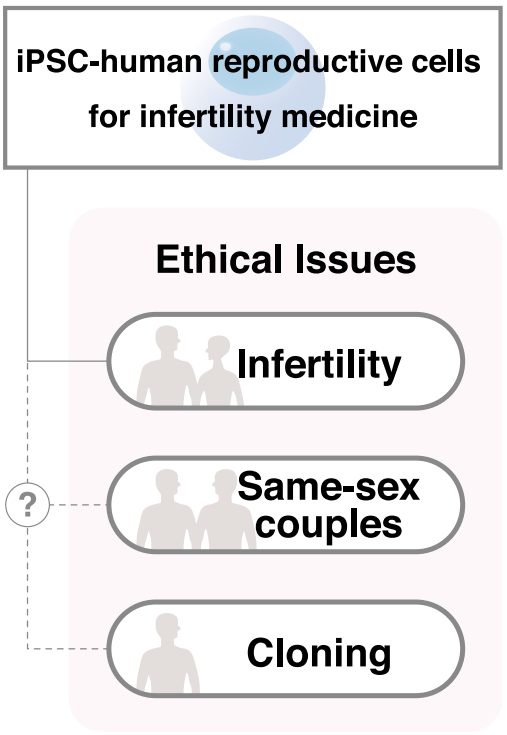
Science is making great strides in creating germ cells, like sperm and eggs, in the lab. This research has been instrumental in understanding how reproduction works, leading to new discoveries about the causes of infertility and possible treatments.

In October of last year, scientists from Kyushu University (Hikabe et al., 2016), Japan, reported the first direct creation of eggs from mouse iPS cells. Previously, mouse iPS cells had been used to create primordial germ cells (PGCs), which are the progenitors of sperm and eggs, but to acquire actual germ cells, the PGCs had to be injected into the ovaries of a mouse. The research from Kyushu goes a step further by showing how to acquire eggs without any animal transplantation.

Around the same time, the World Health Organization (WHO) released new criteria for the definition of infertility: couples that have tried but failed to conceive for at least one year. Some sources reported that the WHO extended this definition farther to include people who want children but are without partners, a claim the WHO has denied.

The incident brings to light questions about who has the authority to decide the definition. It is almost a certainty that in the future iPS cells will be used to make human reproductive cells for infertility medicine. While it is safe to assume that infertile couples will be eligible for this treatment, which other demographics will qualify remains debatable. Same sex couples, individuals without partners, and women beyond an age where they can conceive are all examples. These arguments will depend on what rights society decides people have to children.

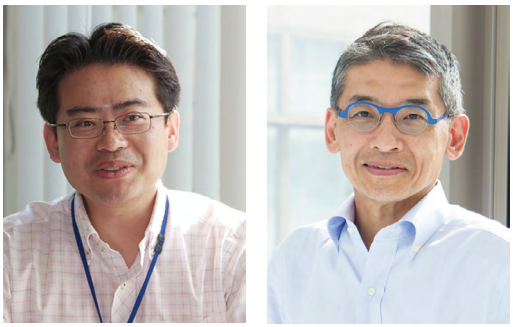
Current science is still a long way from germ cells derived from human iPS cells, and iPS cell research has taught us that mouse cells are much easier to manipulate than human cells. Nevertheless, what has been accomplished in mouse cells has proven true for human cells in most cases, and it is thought to be only a matter of time until the exceptions disappear. Therefore, it is not premature to begin consideration of our definition of infertility and which patients will have access to future infertility medicine.



Prizes to CiRA Professors

Professor Yasuhiro Yamada received the 13th Japan Academy Medal last February. The prize was in recognition of his research on epigenetic factors that regulate cancer cells and their reprogramming. The medal is awarded annually to six of Japan's best young researchers (under 45 years of age) in any academic field. Yamada is grateful for the award and believes it represents the invaluable efforts of all his lab members, saying, "It is an honor to receive this prize. It reflects the hard work from everyone in the lab."

In March, Professor Koji Eto was received an award from the Terumo Foundation for Life Science and Arts, which is given annually to two exemplary Japanese scientists. Eto was recognized for his work on the preparation of clinical-grade platelets using iPSC technology. After giving an honorary talk to the foundation, he remarked, "I am very excited to see the wide interest in our work."



Yasuhiro Yamada (Left) and Koji Eto

iPS cells across the country

The Yamaguchi Center for Arts and Media (YCAM) sits in the most western part of Honshu, about 500 km away from Kyoto. The center serves the community by hosting events that explain the synthesis of technology and society. The theme of its most recent Bioresearch Open Day, held last February, was "Cells and Genes". Junior Associate Professor Takuya Yamamoto participated by giving a talk on iPS cells and showcasing some of the educational material produced by CiRA including iPS Master, a software application, and Karuta, a card game about iPS cells.

"We get support from all over the country," said Yamamoto. "I appreciate it and want to show I am grateful."

CiRA in the News

Last March, Scientific American visited CiRA for an article about the future of iPS cell-based therapies. And in January, Director Shinya Yamanaka sat down with the New York Times to discuss his vision of iPS cells. Read the articles at the links below.

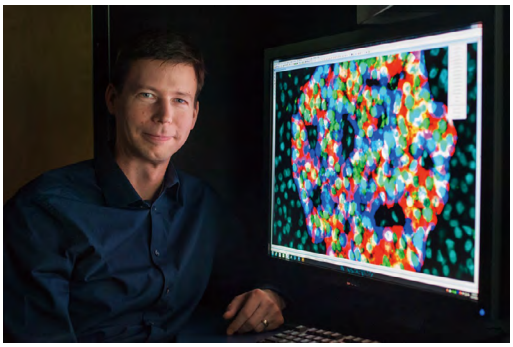
Scientific American (https://www.scientificamerican.com/article/waiting-to-reprogram-your-cells-dont-hold-your-breath/)
The New York Times (https://www.nytimes.com/2017/01/16/science/shinya-yamanaka-stem-cells.html?_r=0)

Taking iPSCs to School

Professor Timothy Kieffer of the University of British Columbia is spending a year-long sabbatical at CiRA to learn more about iPSCs and advance his diabetes research. “I believe a stem cell based cure for diabetes is close,” he said. He and his graduate student, Mitchell Braam, are collaborating with Professor Kenji Osafune and Associate Professor Knut Woltjen to make iPSCs from patients with rare monogenic forms of diabetes and applying CRISPR to correct the genetic mutations before differentiating the iPSCs to insulin producing cells.

As part of the agreement for funding his sabbatical, the Japan Society for the Promotion of Science (JSPS) asked Kieffer to visit a school and share his research and Canadian experiences. February 18, he visited Koshi High School in Fukui Prefecture, which is designated a Super Science High School by the government of Japan. These schools receive special funding for science education.

In addition to providing an overview of stem cells and his diabetes research, Kieffer discussed CiRA and the opportunities available for learning more. He was accompanied by Osafune to translate as needed. “I was not sure what to expect, but despite their young age, the students were keenly interested in iPSCs and asked excellent questions,” said Kieffer.



Timothy Kieffer

Kyoto Marathon

Without fail, CiRA was well represented at the Kyoto Marathon on Feb. 19, with ten of its faculty and staff running to fundraise. Director Shinya Yamanaka ran his fourth consecutive personal best time, while Deputy Director Junya Toguchida also ran a personal best. Both coincidently were ardent rugby players in medical school, but Toguchida attributed the personal bests to a simpler reason. “I run, run and run,” he said.

Shinya Yamanaka at the Kyoto Marathon 2017

The Temples and Shrines of Kyoto

Tō-ji Temple

Tō-ji Temple, which literally translates to "East Temple," was one of the first architectures erected following the transfer of Japan's capital to Kyoto in 794. It was joined by Saiji Temple ("Western Temple"), which together welcomed visitors from the south through the main gate of the city. Of the two, Tō-ji became the favourite, and the Emperor gave it more atention. Conversely, Saiji was not given equal attention. Consequently, despite both having suffered many fires and other natural destructions, only Tō-ji remains today.

The Buddhism proselytized at Tō-ji from its very beginnings was radical, as it claimed the Buddhist faith was available to all, including women, and not just aristocrats. The temple therefore devoted its attention to all residents and began implementing programs that would benefit all, including schools and medicines. The temple was also committed to art, and its halls are adorned by many examples.

Although Tō-ji remains, its current design differs from its original, and it has been estimated that the temple is only one-fourth its largest size. The temple is marked by a large pagoda that dominates the landscape of southern Kyoto. The pagoda too has seen a number of reconstructions, but the current version has stood since 1644.

Five-story pagoda of Tō-ji

CiRA International Symposium

Mark the date. Nov. 6-8, CiRA will host its next international symposium in Kyoto. Please check the CiRA website regularly for announcements about speakers and abstract deadlines.

New spirit with spring

Motivation in the lab

Graduation near

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/
Vol.10 | April 2017