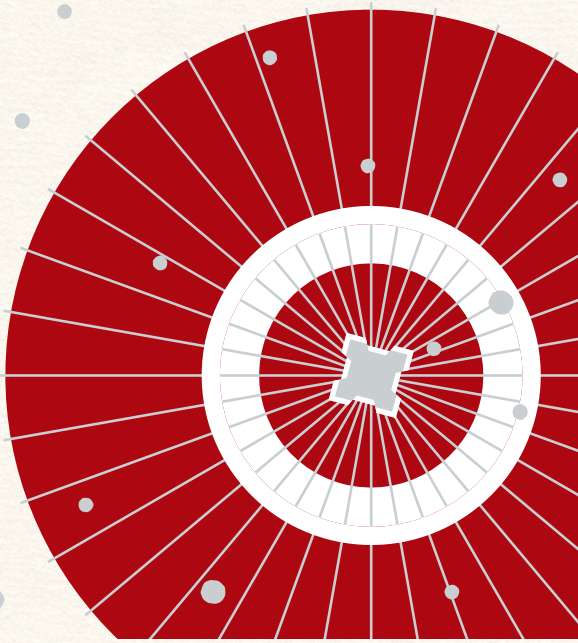
CiRA Reporter

Center for iPS Cell Research and Application,
Kyoto University



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Patient stem cells reveal a new drug target in Pompe Disease

The Hirohide Sakurai lab uses patient iPS cells to study the development of Pompe disease in muscle cells.

Pompe disease is a metabolic disorder in which a defective enzyme prevents the conversion of glycogen into glucose in lysosomes. As a result, cells suffer from accumulated glycogen that weakens and eventually kills muscles cells especially. Of the two types of Pompe disease, children with infantile-onset Pompe disease (IOPD) will rarely reach their second birthday. Using iPS cell technology, CiRA researchers have reprogrammed the skin cells of three IOPD patients into muscle cells and found a new drug target for the disease.

"Pompe disease is caused by a defect in lysosomal acid α–glucosidase (GAA). The defect causes an accumulation of glycogen in lysosomes in skeletal and heart muscles," explains CiRA Associate Professor Hidetoshi Sakurai, who led the study.

Enzyme replacement therapy with recombinant GAA is standard treatment. Recombinant GAA improves symptoms and extends lifespans, but for unknown reasons skeletal muscle is less responsive to the therapy than heart muscle, such that patients still develop a need for artificial respiration.

Because the muscle cells in Pompe disease patients are already extensively damaged by the time of diagnosis, animal models have been used to test experimental drugs, but according to Sakurai none adequately replicate IOPD.

"The symptoms in mouse models are more like late-onset Pompe disease (LOPD). The onset of muscle weakness is slower, and the animals live longer," he said.

Noting that human cells are preferred, the Sakurai lab compared muscle cells prepared from the iPS cells of IOPD patients and healthy donors. The patient iPS cell-derived muscle cells showed characteristics consistent of the disease. The cells had depleted GAA, and lysosomes were enlarged and carried high glycogen content.

Additional study confirmed that the disease particularly afflicts the mitochondria to change the metabolism of muscle cells. Further, the scientists found that the signaling of mTORC1, a molecule that has a role in cell growth and cell metabolism, was affected. mTORC1 is indispensable for cell function and unlikely to make a suitable drug target, since changes in its activity can have deleterious effects on other organs. However, Sakurai notes other molecules regulated by mTORC1 could make promising targets and that these molecules could be found with patient iPSC-muscle cells.

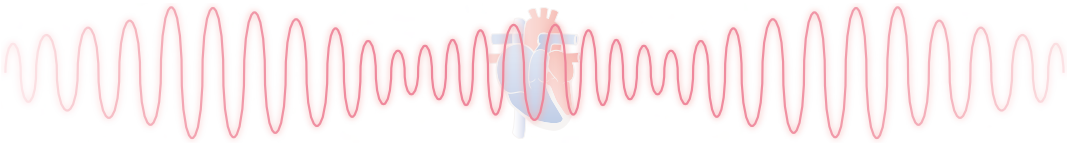
"The relationship between mTORC1 signaling and the patho-mechanism of Pompe disease has not been fully elucidated. Further study could help us find new targets to replace or improve enzyme replacement therapy," he said.

Reference

Yoshida T, Awaya T Jonouchi T et al. (2017) A skeletal muscle model of infantile-onset Pompe disease with patient-specific iPS cells. *Scientific Reports* 7(1):13473. DOI:10.1038/s41598-017-14063-y

Detecting heart arrhythmias before they happen

The Jun Yamashita lab presents a new iPS cell model that can predict if a drug will trigger the fatal arrhythmia Torsade de Pointes.



CiRA researchers use iPS cells to model Torsade de Pointes, a type of tachycardia.

It is estimated that one drug will cost several billion dollars before it will be approved for sale to patients. These costs can be permanently lost if a drug that is approved is then withdrawn, as was the case for cisapride and flecainide, two drugs that were discovered to induce heart arrhythmias in patients. These unexpected effects were because none of the experiments done to test drug safety sufficiently recapitulated behavior in the human heart.

One type of arrhythmia of interest to Professor Jun Yamashita is Torsade de Pointes (TdP).

"TdP are drug-induced lethal arrhythmias. They appear in electrocardiograms as twisted waves. Our three-dimensional (3D) cardiac sheets derived from iPS cells showed TdP when treated with cisapride and flecainide. No other human heart model does this," he said.

In the new study, Yamashita and his team report a new iPS cell-based model that accurately predicts whether a drug will induce TdP. The model depends on two conditions. First, it includes a mixture of cardiomyocytes (heart muscle cells) and non-cardiomyocytes (other heart cells). Second the model is 3D, not 2D, which had been the standard.

"TdP are seen as spiral waves that have a meandering pattern," said Yamashita. "We saw the meandering pattern much less in 2D models." However, even 3D conditions were not sufficient, as the researchers never saw TdP if the 3D model only consisted of cardiomyocytes.

"New phenomenon that has never occurred in normal 2D culture condition can suddenly emerge if we prepare 3D and heterogeneous cell populations. That is the most surprising outcome in this study," he added.

The 3D shape and mixture of cardiomyocytes and non-cardiomyocytes changes the electrical conduction of the heart. Cisapride was originally approved for gastric illnesses. On the other hand, flecainide was originally prescribed for patients with heart illnesses. Coronary patients normally show a loss of cardiomyocytes, thus increasing the proportion of non-cardiomyocytes in their hearts. The new 3D model can modify the ratio of cells to test for TdP in different patient demographics like those seen in patients taking the two aforementioned drugs.

"Our protocol can adapt the cardiomyocyte ratio. We can use the model to understand TdP. Our results suggest electrophysiology and structure features contribute to TdP generation," he said.

Reference

Kawatou M, Masumoto H, Fukushima H et al. (2017) Modelling Torsade de Pointes arrhythmias *in vitro* in 3D human iPS cell-engineered heart tissue. *Nature Communications* 8(1):1078. DOI:10.1038/s41467-017-01125-y

Gene interactions and positions in the nucleus determine cell identity

The Takuya Yamamoto lab reports a new technology, ms4C-seq, that shows how gene interactions and gene translocations in the nucleus are coordinated during cell reprogramming.

To successfully reprogram cells into iPS cells, a series of nuclear events must occur. Among these is the movement of specific genes from the nuclear membrane to the nuclear interior. In a new study seen in *Nature Communications*, the Takuya Yamamoto lab describes new technology, ms4C-seq, and uses it to show the translocation of these genes is accompanied by an increase in their interactions with other genes. The study gives important insights on the structural and spatial gene changes necessary for cell reprogramming.

"Bivalent domains are regions in a gene that have active and repressive marks for transcription. They mark genes that are silent but poised to undergo transcription rapidly," explains Hiroki Ikeda, who conducted the experiments.

The maintenance and differentiation of iPS cells depends on the regulation of bivalent genes. Ikeda reasoned that much like the morphological and functional changes that occur in a cell during reprogramming, bivalent genes too undergo structural and spatial gene changes when cells are reprogrammed.

"Chromatin interactions regulate gene expressions. If a gene interacts with repressor regions it is repressed. If a gene interacts with an activator region it is activated," he continued.

Using public data, the study shows that bivalent genes move from the nuclear membrane to the nuclear interior during reprogramming. Ikeda considered whether this nuclear translocation is accompanied by changes in chromatin interactions between bivalent genes. To study the interactions, the lab developed ms4C, which is a modified version of standard chromatin conformation capture (CCC) technology. ms4C lowers both the amount of DNA needed to study multiple interaction sites and the noise in the signal to enhance detection of chromatin interactions.

Comparisons of public data and ms4C data revealed that as bivalent genes translocate from the nuclear periphery to the nuclear interior during reprogramming, their interactions with each other increase.

Yamamoto believes that change in the nuclear position from the periphery to the interior during reprogramming provides the transcription machinery easy access to bivalent genes.

"The changes in interactions with nuclear translocation may open interaction sites between bivalent genes for rapid response to extracellular differentiation cues," he said.

Reference

Ikeda H, Sone M, Yamanaka S et al. (2017) Structural and spatial chromatin features at developmental gene loci in human pluripotent stem cells. *Nature Communications* 8:1616. DOI:10.1038/s41467-017-01679-x

in vitro trials and informatics find new drugs for Alzheimer's disease

The Haruhisa Inoue lab finds a combination of 3 FDA-approved drugs has positive effects on neurons derived from the iPS cells of 13 different Alzheimer's disease patients.

CiRA researchers have conducted a new approach for discovering drugs to treat Alzheimer's disease. By screening and chemoinformatics of existing drugs, they show a cocktail of three drugs reverses the molecular indications of Alzheimer's disease in an *in vitro* trial using multiple patients' neurons. The chemical structures of the drugs suggest independent modes of action that together give a synergistic effect.

At the molecular level, Alzheimer's disease is associated with the formation of amyloid β (Aβ) plaques and progressive impairment of the neuronal integrity. Many experimental drugs have shown preventive effects on the Aβ accumulation, however, none have passed clinical trials. CiRA Professor Haruhisa Inoue says the reasons are simple.

"Patients are heterogeneous, and Aβ accumulation starts 20 years before the onset."

Inoue believes effective treatments can best be found by studying human-specific cells from multiple patients and compounds that have long been studied for safety.

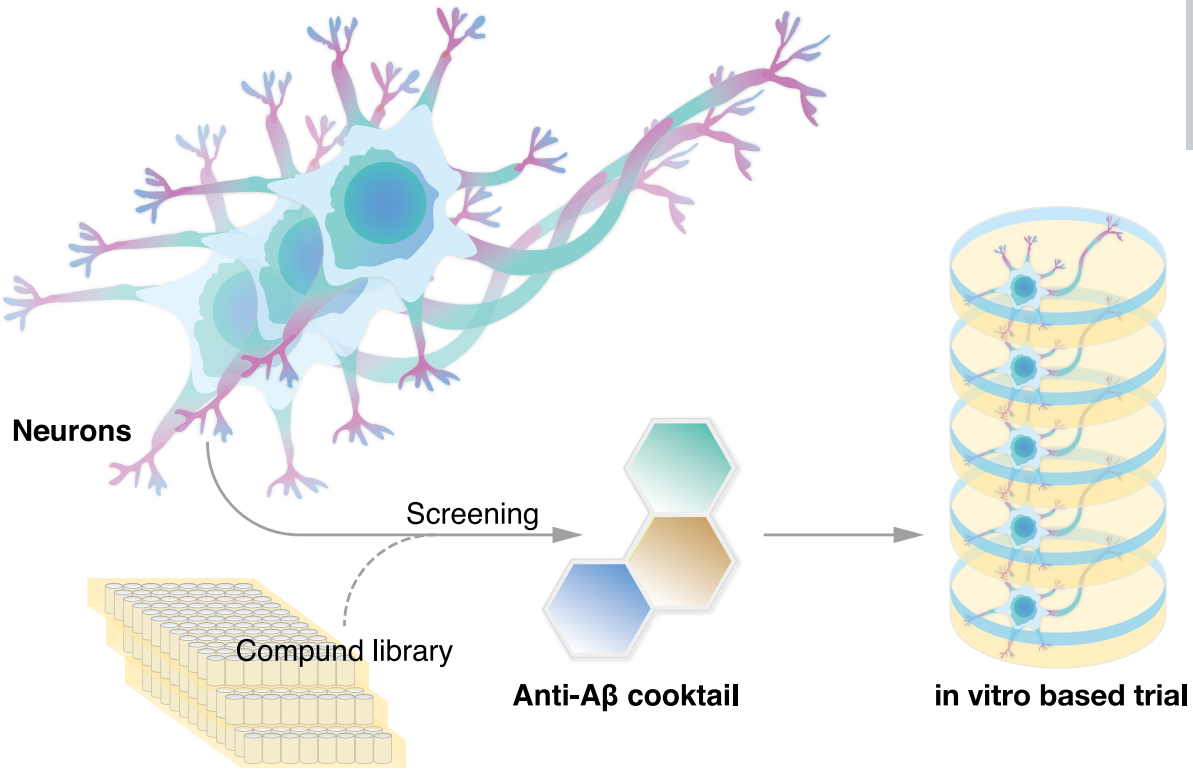
In its newest study, his group tested over 1,000 drug compounds on neurons made from the iPS cells of Alzheimer's disease patients. The researchers used chemoinformatics to cluster the best candidates into different groups based on the chemical structures. One drug, bromocriptine, was found to lower Aβ accumulation through its ergoline structure by altering Aβ metabolism. Ergoline drugs are common, and the best known is LSD. Bromocriptine, on the other hand, is approved for use against Parkinson's disease.

"Bromocriptine is used in Parkinson's disease because it is an agonist for the dopamine receptor and other receptors. We attribute our findings to changing Aβ metabolism, which is a new mechanism," said Inoue.

Further study considered a combination of the candidates, with the most effective including bromocriptine and two other drugs, topiramate, which is used to treat epilepsy, and cromolyn, which is an anti-inflammatory drug used to treat asthma. Chemoinformatics analysis found that the three drugs clustered differently.

"Each of these drugs have different structures and target different molecules," noted Inoue.

Patients with Alzheimer's disease can be divided into familial (patients who express a gene mutation that is associated with the disease) and sporadic (patients who do not express a causal mutation) groups, and even these groups can be divided further into subgroups. The different molecular causes of Alzheimer's disease suggests many experimental drugs will show positive effects on only subsets of Alzheimer's diseases patients. In the study, the initial discovery of the drug combination was made using cells from a familial Alzheimer's disease patient. However, an *in vitro* trial confirmed the same combination had positive effects on cells made from 13 different familial and sporadic patients.



Drug screening and in vitro trials of iPS cell-derived cortical neurons.

Inoue attributes these findings to the fact that the drug cocktail has multiple targets, which could expand the number of patients who benefit from the treatment. At the same time, he cautions that while encouraging, the study is only a first step.

"Our tests show bromocriptine, cromolyn and topiramate work on isolated neurons, but we do not know if the same effects will be seen inside brains where neurons interact with many other cells," he said.

In addition to the above paper, the lab has published three papers that describe iPS cell lines made from the blood of patients suffering from one of several diseases. Patients expressed a mutation associated with autosomal dominant lateral temporal epilepsy, dystonia, or familial idiopathic basal ganglia calcification (also known as Fahr disease). The lines provide new human cell models to study the respective diseases.

Reference

Kondo T, Imamura K, Funayama M et al. (2017) iPSC-based compound screening and *in vitro* trials identify a synergistic anti-amyloid β combination for Alzheimer's disease. *Cell Reports* 21(8): 2304. DOI: 10.1016/j.celrep.2017.10.109

T GW, Kondo T, Murakami N et al. (2017) Induced pluripotent stem cells derived from an autosomal dominant lateral temporal epilepsy (ADLTE) patient carrying S473L mutation in leucine-rich glioma inactivated 1 (LGI1). *Stem Cell Research* 24:12 DOI: 10.1016/j.scr.2017.07.030

Murakami N, Ishikawa T, Kondo T et al. (2017). Establishment of DYT5 patient-specific induced pluripotent stem cells with a GCH1 mutation. *Stem Cell Research* 24:36. DOI: 10.1016/j.scr.2017.07.029

Sekine SI, Kondo T, Murakami N et al. (2017) Induced pluripotent stem cells derived from a patient with familial idiopathic basal ganglia calcification (IBGC) caused by a mutation in *SLC20A2* gene. *Stem Cell Research* 24:40. DOI: 10.1016/j.scr.2017.07.028

Nano-sized RNA molecular machines kill cells

The Hirohide Saito lab has constructed geometrical shapes out of RNA that assemble proteins and kill unwanted cells.

RNA is an essential molecule for the conversion of genes to proteins. It is also a very useful molecule to make various nano-sized shapes with function. These RNA architectures in turn can be used to detect, assemble, and activate proteins that have very specific effects on a cell, such as programmed cell death.

"RNA is made up of four ribonucleotide bases: adenosine, guanine, cytosine, and uracil. This makes the RNA structure easy to engineer and is why I use RNA to make nanosized structures," said CiRA Professor Hirohide Saito.

Regardless of how much protein is in the cell, to function properly, many proteins must assemble into complexes with other proteins or nucleic acids like RNA. Therefore, to optimally control a protein inside a cell, bioengineers like Saito aim to not only control gene expression, but also the localization and assembly of proteins.

"Caspase-8 is an apoptosis protein that kills cells, but only when it oligomerizes," he said.

Because of its apoptotic nature, Saito wondered if he could control caspase-8 oligomerization using RNA to kill off undesired cells such as cancer cells.

His lab prepared nano-sized RNA scaffolds that can attach and assemble caspase-8 through RNA-binding proteins (RBPs).

L7Ae has been the preferred RBP in the Saito lab for nearly a decade. Using prediction software, Saito has shown that L7Ae can force desired angles in RNA, which allows for the creation of different shapes that exert different functions in a cell.

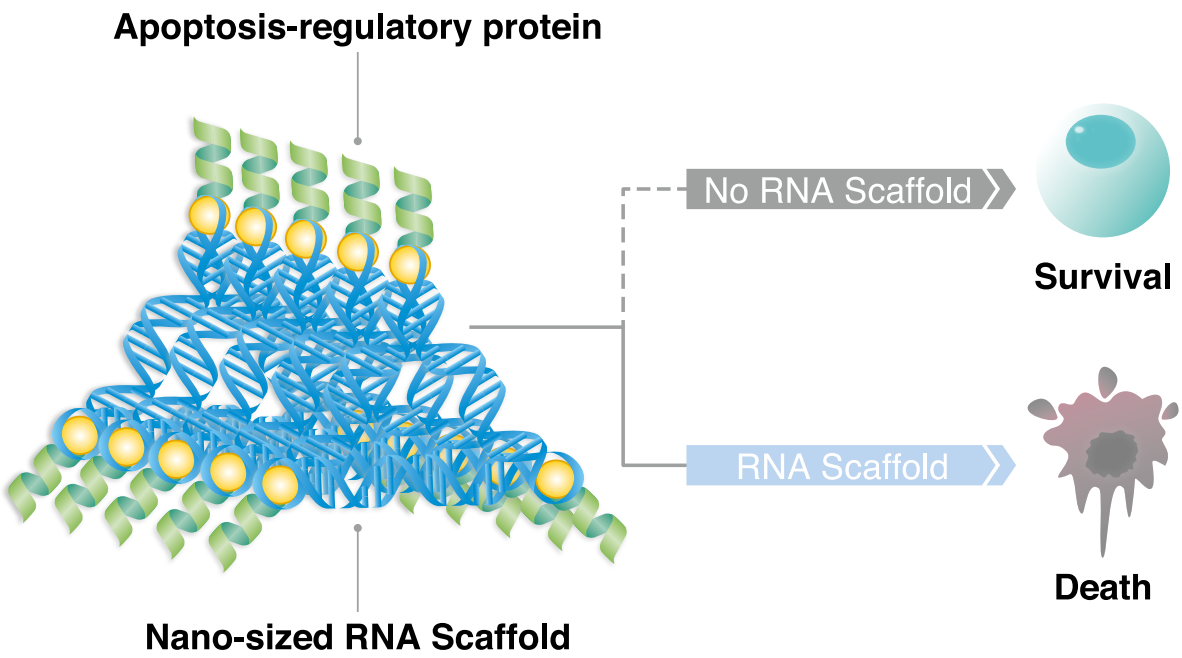
Tomonori Shibata, a researcher in the lab, used L7Ae to construct multiple caspase-8-spiked assemblies inside HeLa cells, a type of cancer cell commonly used in laboratories to test new biotechnology.

"When we transfected only caspase-8, we found a minority of cells died. However, when we transfected caspase-8 via our nanostructure, we found over 70% of the cells died," said Shibata, confirming that the assembly of caspase-8 was critical for apoptosis activity.

Because L7Ae is not expressed in human cells, the L7Ae-caspase 8 system will kill all cell types with equal efficiency. To make a system that targets specific cell types, Shibata and Saito considered other RBP-RNA combinations.

"Switching the RBP to a protein that is high in only target cells allows us to control cell fate selectively," said Saito.

Shibata demonstrated this point by switching L7Ae to LIN28A. Lin28A has a role in cancer and tissue regeneration and is more highly expressed in iPS cells than in HeLa cells. He bound caspase-8 to LIN28A (LIN28A-caspase-8) and transfected the complex along with RNA that has high affinity for LIN28A into iPS cells and HeLa cells. In HeLa cells, the interaction be-



RNA scaffolds regulate the activity of apoptosis proteins to kill cells.

tween LIN28A-caspase-8 and this synthetic RNA formed a nanostructure that activated caspase-8, killing most of the cells. In contrast, because endogenous LIN28A in iPS cells can compete with LIN28A-caspase-8 for binding to the synthetic RNA, a far higher number of iPS cells survived.

Nevertheless, LIN28A is expressed in both cell types, albeit it at different levels, meaning the system kills both cell types to some degree. As an alternative design, Shibata considered the lab's miRNA technology, miRNA switch, which was first reported in 2015. An miRNA switch is an RNA machine that either turns on or off a molecular action depending on its interaction with miRNA. Using his L7Ae-caspase-8 device, Shibata attached an additional synthetic RNA component that bound one of two miRNA, miRNA-21 or miRNA-302, which are expressed differently in iPS and HeLa cells. Adding miRNA switch to the design led to more efficient killing of the targeted cell type.

Saito stresses that it is the selectivity of his RNA nanotechnology that makes it a potentially powerful tool in synthetic biology.

"In any therapy, we want to target the diseased cells without damaging healthy ones. Our RNA nanotechnology may be refined for this targeting," he said.

Reference

Shibata T, Fujita Y, Ohno H et al. (2017) Protein-driven RNA nanostructured devices that function *in vitro* and control mammalian cell fate. *Nature Communications* 8(1):540. DOI:10.1038/s41467-017-00459-x

Greetings from the
Takuya Yamamoto Lab

Dept. of Life Science Frontiers

The rapid success of iPS cell application to the clinic – the first iPS cell-based therapy was commenced more than two years ago and recently a drug discovered through an iPS cell-based model at CiRA has received permission for study in a clinical trial – has stimulated a vibrant energy in clinicians seeking new experimental treatments for intractable diseases. This enthusiasm is shared at CiRA, where the majority of our scientific labs are using iPS cells to study development and disease. However, to reach this clinical potential, scientists who study the reprogramming mechanism in order to produce iPS cells efficiently and safely are necessary.

The discovery of iPS cells was a landmark finding that opened the door to a new field of cell biology. At the same time, those in the field of cell reprogramming know the efficiency of the reprogramming remains frustratingly low, in large part because of our poor understanding about the molecular networks that regulate the process. Thus, despite the above, iPS cell applications will be limited unless we uncover much more detail about these networks. Reprogramming occurs through a hierarchy that includes regulation at the chromatin level, transcription level, and post-transcriptional level. We study these different levels using a wide range of techniques including standard molecular biology and biochemistry experiments, comprehensive genome-wide analyses, and bioinformatics. Our hope is to build a comprehensive roadmap of the genetic and epigenetic events required for a somatic cell to begin and complete the reprogramming process. As one example, we reported this year a mechanism through which two factors regulate the metabolic transition essential for reprogramming.

Takuya Yamamoto

Although not a large group compared to others at CiRA, our experimental techniques demand that the lab be diverse in terms of expertise. This diversity and our scientific approach make us a unique node in CiRA such that, along with conducting our own independent studies, we are involved in a number of collaborative projects. Such projects have revealed insights on disease development and maintenance of the pluripotent state.

Because we are not aspiring to cure a disease or innovate a breakthrough biotechnology, some may perceive us a one of the less sexy groups at CiRA. Nevertheless, our goal is to elucidate the fundamentals of iPS cells, making us a basis for all other related discoveries and an excellent location to learn about reprogramming.

The need for dialogue

by Researcher Mika Suzuki, Uehiro Research Division for iPS Cell Ethics

Recently, the word "dialogue" has been on my mind. For example, the other morning I was watching the news and heard that a disagreement between two parties would be resolved by dialogue. But the news never explained what type of dialogue. Is it chatting while enjoying tea together? The Cabinet Office has announced its initiative, Science and Technology Dialogue with the public. This dialogue is defined as interactive communication in which researchers explain their research outcomes and activities to society in an easy-to-understand manner. The Cabinet Office recognizes the importance of dialogue to gain public understanding and support for further development of science and technology. Even CiRA uses the word. The Uehiro Research Division for iPS Cell Ethics at CiRA states on its Japanese website that it wishes to have dialogue with the public to understand all perspectives about human iPS cells.

In all these cases, dialogue aims to gain the understanding and support of the general public, and then resolve concerns by providing explanations and answers. It is based on the assumption that if people understand the issues and satisfy their questions, then they are likely to support the idea. But is this assumption true? Dialogue involves not only explaining but also listening.

For me, dialogue is about an exchange of ideas with the purpose of reaching new ideas, not convincing other people to agree with you. In this concept, dialogue removes positions or titles. First and foremost, researchers are human beings before they are scientists.

If researchers have dialogue with the public on the use of iPS cells, they should share their values and what they think is appropriate use of iPS cells while providing a scientific, rational and objective explanation. And the public should be granted the opportunity to talk about their values and not only ask questions that satisfy their scientific curiosity. I think such dialogue is necessary to find where both sides can agree. It is important for scientists to remember that especially in the field of iPS cells, all people are affected by this science and technology. Many of the opinions from the general public will not be based on science, but on how lives will be impacted. Science alone cannot answer these concerns.

Have we had this type of dialogue about iPS cells? I am not sure that we have. It has been 10 years since the discovery of human iPS cells, and I have been working as a bioethicist at CiRA for five years. Now more than ever, I feel strongly the form of dialogue needs to change. This is a goal of mine at CiRA.

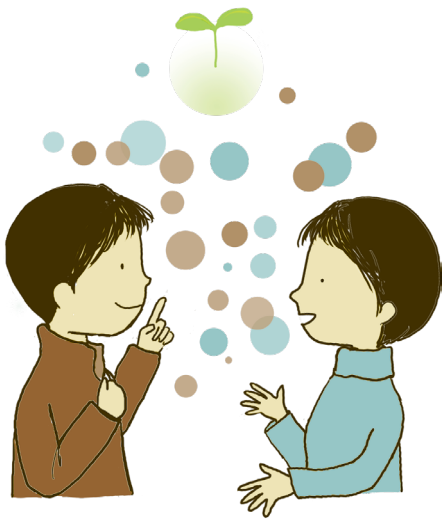


Illustration by Maiko Tanaka, *dialogue*

CiRA 2017 International Symposium

For the last several years, CiRA has organized international symposia that bring leading stem cell scientists to Kyoto. CiRA Director Shinya Yamanaka says that these symposia provide a rare opportunity to young researchers.

"Geographically, it is difficult for many students in Japan to visit institutes in the United States and Europe and hear stem cell leaders," he said.

Juan Carlos Izpisua Belmonte

Shinya Yamanaka

These symposia are a high priority at CiRA, and Yamanaka wants them to be recognized as equals to other similarly sized academic symposia around the world. Indeed, CiRA has received cooperation from some of the biggest non-profits and industrial players in the field. In 2016, CiRA jointly hosted its symposium with the International Society for Stem Cell Research in Kyoto, and in 2014 with Takeda Science Foundation in Osaka. The most recent symposium, A Decade of Human iPSCs: From Bench to Bedside, took place last November 6-8 near Heian Shrine, one of the largest shrines in Kyoto and a 15 minute walk from the institute. Talks were divided into the study of pluripotency, disease modeling with stem cells, regenerative medicine, new stem cell technologies, and finally the preparation of stem cell lines for clinical application. In total, 21 scientists spoke about their work including 7 from CiRA and 11 from overseas. Among the speakers was Juan Carlos Izpisua Belmonte of the Salk Institute, who made arguably the biggest splash in stem cell news last year with his reports about growing xeno organs in mice and rats and about gene editing the human embryo. Kazutoshi Takahashi, who first authored the original iPS cell papers as a post-doctoral scientist in the Yamanaka lab, also spoke as a representative of the Gladstone Institutes where he now works. Yasuhiro Yamada, an expert on cancer research, gave his last talk as a professor at CiRA, having moved to the University of Tokyo last December.

For the opportunity to organize these international symposia, CiRA is greatly indebted to its numerous benefactors who support the iPS Cell Research Fund, which funded the symposium. As a result, students were able to attend for free.

"It is very important that young researchers should have as many opportunities as possible to meet with leading scientists," said Yamanaka.

Taking advantage of the long list of elite stem cell scientists who attended the symposium, CiRA followed the symposium the next day with its annual retreat. Most of the symposium speakers attended the closed event, at which CiRA students had an opportunity to discuss their research and receive feedback with the guests.

The world is coming to Japan

Beginning with CiRA Director Shinya Yamanaka, whose passion for running is well known in scientific circles, CiRA staff has been running local marathons as a way to fundraise. The most recent was the 7th Osaka Marathon on November 26. Professors Hirohide Saito and Jun Takahashi, who both ran their first marathons in 2016, proudly ran personal bests. “It does not get easier, but it does get fun,” said Takahashi.

Yamanaka has plans to run two marathons in February, including the 6th Kyoto Marathon on February 18. As a way to tie together the 2020 Tokyo Olympics and CiRA, CiRA fundraiser Aiko Tokunaga made a suggestion. “We spoke to a representative of Misato Michishita to ask if she would like to run the marathon together with Dr. Yamanaka,” she said. .

Michishita earned the silver medal in the 2016 Paralympics marathon and set a world record last year. She met Yamanaka in 2016 at a marathon in which both were competing. She will be 43 by 2020, but according to NHK she aspires to qualify for the Tokyo Games.

Regarding the Kyoto Marathon, the plan is to have her run the first two thirds of the race and Yamanaka the remainder. Add the Rugby World Cup in 2019, and Japan will be host to a number of grand international events in the near future. The city of Osaka, which is about a marathon’s distance from Kyoto, seeks to add the list, as it submitted its bid last year to host World Expo 2025. CiRA showed its support by welcoming delegates of the Bureau International des Expositions, who will decide the winning bid. Four countries are vying for the opportunity (Azerbaijan, France, and Russia). Osaka has hosted the quinquennial event before. World Expo 1970 took place in what was then the barren northern part of Osaka, but is now the city’s most popular residential area for families. The influx of families followed the large infrastructure projects including parks and trains that were made in preparation of the World Expo. Osaka hopes being host in 2025 can similarly revitalize other regions of the prefecture.

Hirohide Saito

Jun Takahashi

Open house celebrates 10 years of iPS cells

To mark the 10th anniversary of the first report on human iPS cells, CiRA held an open house on December 17, in which the public was given the chance to see the facilities, learn about the science and even do some experiments.

Because of the number of visitors and their nationalities, tours were held in Japanese and English throughout the day. For many guests, the chance to see the laboratories was not only the first time to see the inner workings of an iPS cell institute, but also the first time to see a cell biology institute. Included in the tour was access to the Facility for iPS Cell Therapy (FiT), which is preparing iPS cells for clinical application and provided contrast to the laboratory conditions for general experiments. The tour ended with a chance to see iPS cells under a microscope.

“It was eye-popping to learn about the important research taking place at CiRA. I appreciated the opportunity to see the laboratory and to meet some of the people behind this organization,” said Evelyn Gunn, a visitor from Canada.

Besides the tour, CiRA had arranged many activities for visitors to learn about iPS cell science. Assistant Professor Shin-Ichi Mae demonstrated experiments in an open lab that included how scientists attach a fluorescent protein to Sox2. The expression of Sox2 marks a cell as pluripotent and is also one of the four factors used to make the original iPS cells. Science Illustrator Misaka Ouchida, a member of the CiRA International Public Communications Office (IPCO), which organized the open house, ran a seminar for elementary school children in which she taught some of the basics about cells through drawings. These basics included a realization that different cells take different shapes and the many different shapes of proteins and organelles inside the cell. Junior Associate Professor Keisuke Okita, who was a scientist in the Yamanaka lab when the iPS cell discovery was made, gave a lecture about the theory of cell reprogramming.

Akemi Nakamura, Manager of IPCO, explained that these events are crucial for sustaining public support.

“People in Japan are very excited about iPS cell research, but they have never seen an iPS cell or an iPS cell laboratory,” she said.

Misaki Ouchida at the Science Illustration Workshop

Shin-Ichi Mae at the iPS cell experimental laboratory

The Temples and Shrines of Kyoto

Yasaka Shrine

The Yasaka Shrine is relatively modest, especially when considering its location – Gion, the renowned Geisha district. Yet it is the first shrine many visitors to Kyoto encounter, as it sits at the every end of the longest commercial street as a gateway into the mountains and the rustic part of the city. Because of its location, the temple serves more as a meeting spot than destination and is host to many festivals that go long into the night. The shrine predates Kyoto becoming the capital of Japan in 794. With the exception of the main gates, which can be seen a mile away, architecturally the shrine is rather modest. Although all shrines are Shinto, Buddhist influence in the design can be seen, a testament to the power struggles between the two religions throughout Japan's history until the Meiji Restoration in 1868.

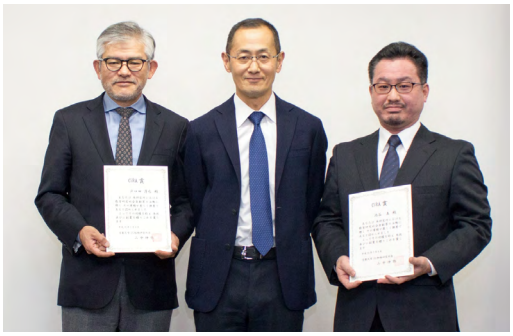
Yasaka Shrine Gates (Center)

Komainu guarding the shrine entrance

Photos by Robert Milewski

CiRA Awards

Each new year at CiRA begins with a short speech by CiRA Director Shinya Yamanaka about last year's accomplishments and this year's goals. At the end, Yamanaka recognizes the CiRA faculty members deemed by their peers to have had the biggest impact. This year, the award was given to Professor Junya Toguchida and Associate Professor Makoto Ikeya, whose work on fibrodysplasia ossificans progessiva, a rare bone disease, led to a clinical drug trial beginning last October.

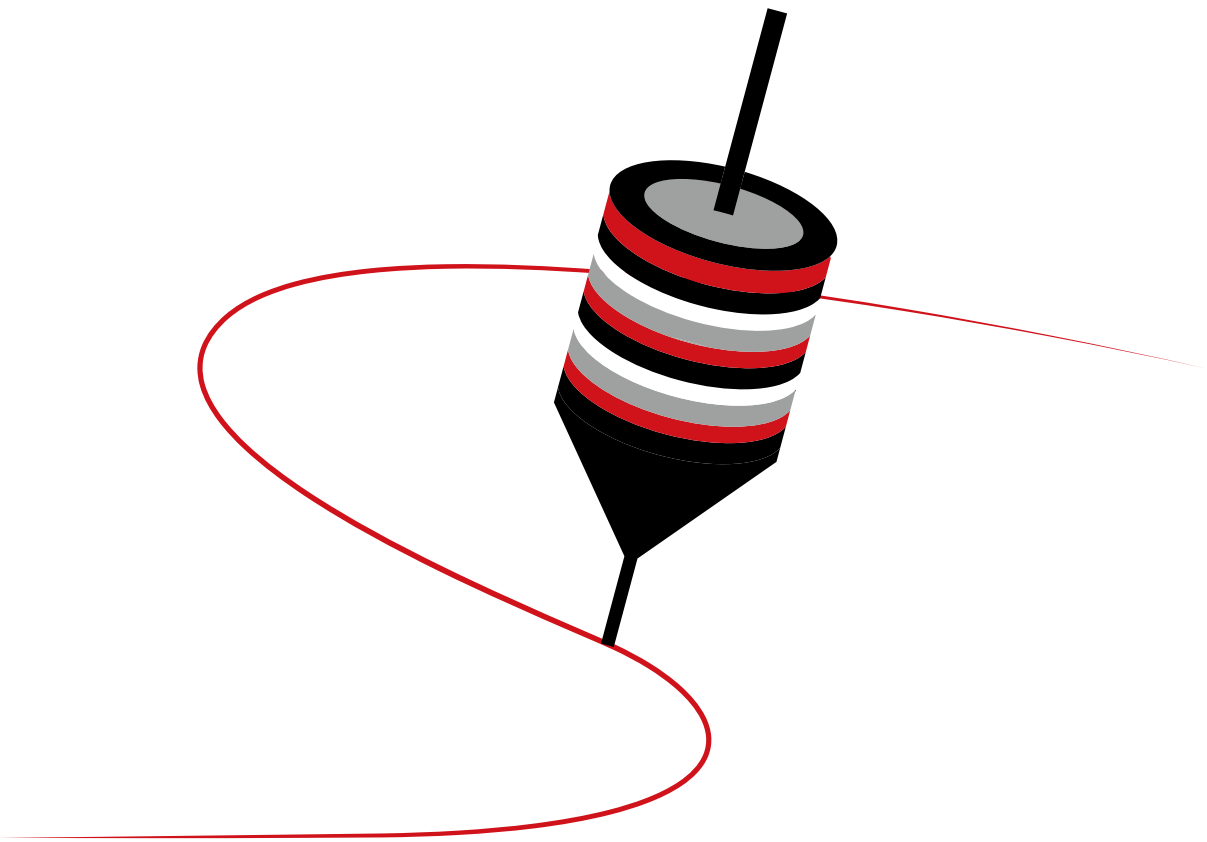


(from left) Junya Toguchida, Shinya Yamanaka and Makoto Ikeya

New resolution.

Go to the gym? Nope, the lab.

My goal: a paper.



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