CiRA Reporter

Center for iPS Cell Research and Application,
Kyoto University

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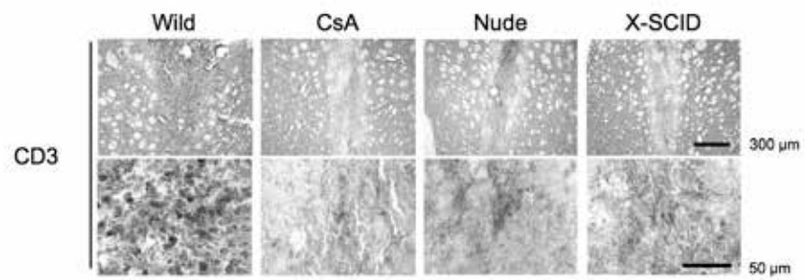
New rat model for Parkinson's disease



X-SCID rats show an immune response to cell transplantation that resembles the use of the immunosuppressant CsA in wild type rats.

Severe combined immunodeficiency (SCID) is a genetic disease that devastates the immune system. Its best known patient is the bubble boy, and its victims cannot come into contact with the physical world. Ironically, this immune phenotype is a great advantage when studying cell therapies for other diseases, since the recipient does not reject transplanted cells. As such, the X-linked SCID (X-SCID) rat was invented. A new study from the Jun Takahashi lab at the Dept. of Clinical Application explores the benefits of this rat model for the study of Parkinson's disease (PD).

Transplantation in the best current model for PD triggers an inflammation response that requires immune suppression. This suppression is normally achieved with cyclosporine A (CsA). However, CsA hinders the maturation of neural progenitor cells and more importantly has serious cytotoxic effects on other organs. On the other hand, X-SCID rats are deficient in receptors that respond to immune signaling. The lab therefore explored whether mature human neurons could survive in X-SCID rats without the use of CsA or other immuno-suppressants.

Dopaminergic neurons were differentiated from human ES cells and human iPS cells using standard protocols and prepared for cell therapy. Injection of these cells into the brains of X-SCID rats triggered an insignificant immune response. In contrast, these cells were rejected 12 weeks after their injection into the brains of wild type rats.

The simple survival of neurons, however, is only necessary but not sufficient to prove X-SCID rats are a good PD model. Therefore, the researchers simulated PD conditions using an established method. Following the development of PD symptoms, DA neurons were injected into X-SCID rats. Not only did the cells show good survival, but the rats tended to recover.

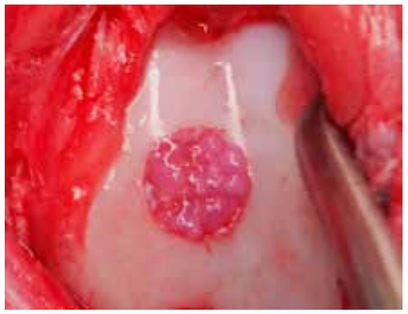
Professor Takahashi believes these results show promise for X-SCID rats as a model for testing PD cell therapies. "These findings show that X-SCID rats exhibited minimal immune response against xeno-transplantation. X-SCID rats have promise as a PD model in preclinical studies of cell transplantation," he said.

Reference

Samata B et al. (2015) X-linked severe combined immunodeficiency (X-SCID) rats for xeno-transplantation and behavioral evaluation. *Journal of Neuroscience Methods* 243: 68-77.
Online publication: Feb. 4, 2015

Scaffold-free iPS cell-based hyaline cartilage for joint repair

Particles consisting of chondrocytes and their secretions, ECM proteins.

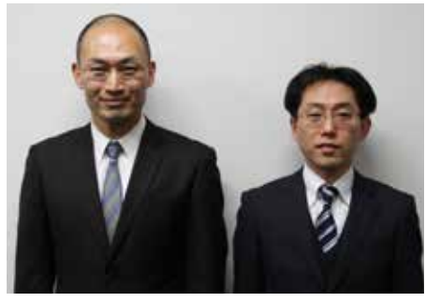


Particles transplanted into the femur of a mini-pig. The particles can be seen in the pinkish circle within the white cartilage.

Cranky knees and other joint pains are normal in the elderly and sometimes even in the young. While these pains are rarely life threatening, those who have them know the burden on quality of life. In many cases, the cause is a loss of hyaline cartilage, which does not have the capacity to regenerate, meaning once gone it is gone forever. Hyaline cartilage is constituted of chondrocytes and their secretions, extracellular matrix (ECM) proteins, which include collagens II and XI. Excluded from these proteins is collagen I, which is the primary collagen in fibrocartilage, or scar tissue. The key to successful recovery then is to introduce into the deteriorated cartilage chondrocytes that secrete only hyaline cartilage ECM proteins.

One of the most common strategies for treating hyaline cartilage damage is autologous chondrocyte transplantation. This technique involves acquiring hyaline cartilage from a biopsy and then transplanting the cartilage to the injured site. Because the biopsy is smaller than the area that needs repair, the chondrocytes must be expanded, a task that requires enzymatic digestion of the ECM proteins. Unfortunately, the expansion causes the chondrocytes to secrete collagen I, which is why the presence of fibrous tissue is inevitable after such operations. “The chondrocytes lose their chondrogenic properties,” says Professor Noriyuki Tsumaki of the Dept. of Cell Growth and Differentiation.

To solve this problem, Tsumaki and his team report a new protocol that expands not chondrocytes, but iPS cells. When a sufficient number of iPS cells are reached, the protocol then calls for the researchers to differentiate the cells into chondrocytes. Because these chondrocytes



Noriyuki Tsumaki and Ahihiro Yamashita

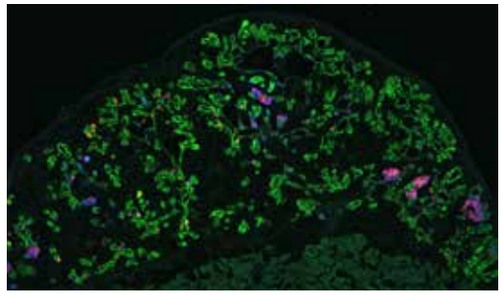
are differentiated directly from iPS cells, there is no need to digest ECM proteins, which avoids the problem of fibrous tissue and allows for only hyaline cartilage to be synthesized.

Another advantage to this method is that it avoids the use of artificial scaffolds. In other studies on ES cell- and iPSC-derived chondrocyte transplantation, artificial scaffolds are included into the transplant to provide support until the chondrocytes begin secreting their own ECM proteins. However, it is unclear if artificial materials prevent optimal integration into the cartilage. Because in the present work the chondrocytes have already begun secreting ECM proteins, they can be transplanted without scaffolds. This feature is attributed to the use of a suspension culture and medium that includes BMP2, TGFβ1 and GDF5 for six weeks. After this time, chondrocytes stop proliferating and begin secreting hyaline cartilage ECM proteins with high purity. This mix of chondrocytes and ECM matrix proteins was harvested as particles 1-2 mm in diameter that could be directly transplanted into the injured tissue. Each particle contained approximately 70,000 chondrocytes, which according to Tsumaki is sufficient for human transplantation. “One million chondrocytes are needed to treat 1 cm^2 defects, and the area of a typical defect is 2-10 cm^2. So we are considering transplanting 30-150 particles. These numbers are quite manageable,” he said.

The team transplanted their particles into three animal models-mouse, rat and mini-pig, finding positive signs for integration and maintenance. These results have only encouraged Tsumaki. “These findings are only preliminary, but they show good indications of safety. The next step is to find the best conditions for transplantation in larger animals before we can consider patient treatment,” he said.

Reference
Yamashita A et al. (2015) Generation of scaffoldless hyaline cartilaginous tissue from human iPSCs. *Stem Cell Reports* 4(3): 404-418.
Online Publication: Feb. 26, 2015

iPS cell-derived pancreatic cells can survive and function in mice



Pancreatic bud cells (green) formed tubular structures post implantation into mice.

One cause of diabetes is insufficient secretion of insulin from β-cells. Researchers have therefore investigated ways to increase and sustain the number of β-cells in the body, which is why the transplantation of progenitor cells is receiving strong consideration. One challenge has been the design of protocols that culture such progenitor cells effectively. Professor Kenji Osafune and his team of the Dept. of Cell Growth and Differentiation has discovered that the physical dimensions of the culture has significant impact on the likelihood ESCs and iPSCs will differentiate into pancreatic bud cells, which are the earliest cells committed to pancreatic lineage. Transplantation of these bud cells in mice resulted in insulin-secreting β-cells.

The intention to experiment with the dimensions of the culture came from observing that in monolayer culture bud cells aggregated in a manner that resembled the pancreatic budding seen in mouse embryos. “The pancreatic bud emerges from a primitive gut tube, which is a monolayer,” notes Osafune. To investigate whether this aggregation facilitated molecular signaling for proper differentiation, the bud cells were harvested in monolayer or aggregation cultures. After examining several human iPSC lines, the authors found that aggregation culture increased the number of bud cells, in some cases several times more.

To become bud cells, the iPSCs first needed to pass through a series of intermediates. The bud cell stage was highlighted by cells bifurcating into those that took the pancreatic lineage and those that died. In other words, it appears the aggregation culture somehow selected desirable cells. Upon transplantation into mice, a number of markers indicated that the aggregate culture bud cells differentiated into functional β-cells. “This is the most important finding,” says Osafune, “that transplanted iPS cell-derived pancreatic cells can survive in mice.”

The outcome of this study provokes a number of questions, as it only demonstrates the benefits of the physical environment on differentiating stem cells to the pancreatic lineage, but gives little insight on the molecular network. Although not sure what contribution the dimension made, Osafune does have his thoughts. “It seems cell contact-mediated signals via extracellular matrices and adhesion molecules and other membrane-bound receptors are important.”

Reference
Toyoda T et al. (2015) Cell aggregation optimizes the differentiation of human ESCs and iPSCs into pancreatic bud-like progenitor cells. *Stem Cell Research* 14(2): 185-197.
Online publication: Jan. 28, 2015

New clues on how adult pancreas regenerates

Yoshiya Kawaguchi and Shinichi Hosokawa

Our bodies have a wonderful way to regenerate after injury or illness. In skin cells it was shown that organ-specific adult stem cells are the source of the regeneration, while in liver it is thought that hepatocytes themselves are. Regarding pancreas, there is great debate about whether adult duct cells differentiate into acinar and/or islet cells. Professor Yoshiya Kawaguchi and his group at the Dept. of Clinical Application report evidence suggesting that adult duct cells have the capacity to differentiate into acinar cells but not into islet cells.

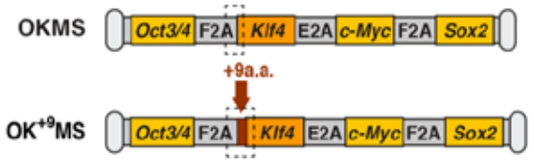
There are three primary factors involved in the differentiation to acinar cells: Sox9, which is present throughout the pancreatic duct but not elsewhere in the pancreas, Notch and Hes1. “Sox9 is very important to keep the identify of duct cells, because it is only expressed there. If Sox9 is reduced, the duct cells lose their identity and differentiate,” explains nephrologist Shinichi Hosokawa, first author of the study. However, while these three factors make an important regeneration network that has been observed in embryonic cells, no study had demonstrated the hypothesis in adult pancreas.

To make such an investigation, the team used mice that were designed to have low Sox9 expression levels. The duct cells of these mice were seen to differentiate into acinar cells after several days, but found no evidence of differentiation to islet cells. Increasing Notch activity significantly reduced the amount of differentiation while at the same time increased the amount of Sox9, suggesting the Sox9 effect is dosage dependent. The effects of Hes1, on the other hand, were only detected when it was completely knocked out, suggesting not a dosage effect but a binary one. From these observations, the authors concluded that Notch regulates Sox9 and Hes1 using independent pathways.

The study thus provides some of the first direct evidence on the plasticity of adult duct cells and the key regulators involved. While insightful, much of the conclusions mirror what has already been observed in embryos. “[The results] are not so surprising. We thought the adult stage and embryonic stage use the same mechanism, but no report proved this,” says Hosokawa.

Reference
Hosokawa S et al. (2015) Impact of Sox9 dosage and Hes1-mediated Notch signaling in controlling the plasticity of adult pancreatic duct cells in mice. *Scientific Reports* 5:8518.
Online publication: Feb. 17, 2015

OSKM stoichiometry determines iPS cell reprogramming



Adding 9 amino acids before Klf4 to switch the isoform from $Klf4_S$ to $Klf4_L$ subtly lengthens the transgene.

Anyone in the field of cell reprogramming recognizes Oct3/4, Sox2, Klf4, and c-Myc, or "OSKM," as the Yamanaka factors that led to the first iPS cells. Originally, these four genes were delivered as individual (monocistronic) viral vectors. In order to simplify protocols, researchers began to deliver them using single polycistronic vectors, where the OSKM genes are linked as mRNA but still produce four separate proteins to induce reprogramming. However, not all vectors are built the same, and it turns out their subtle variations may influence both reprogramming efficiencies and outcomes. Specifically, the length of Klf4 appears to be a significant factor in determining whether a somatic cell is reprogrammed to the pluripotent state. Klf4 was first reported in 1996 by two independent studies. However, despite investigating the same gene, those two reports predicted different locations of the start codon in the mRNA sequences, which when translated result in proteins that differ by nine amino acids in length. Which isoform is used for reprogramming depends on the lab. "Some labs use short Klf4, some labs use long. Some labs have even switched between the two lengths," says Associate Professor Knut Woltjen at the Dept. of Reprogramming Science.

Curious if these amino acids could explain the diverse reprogramming efficiencies that have been reported by different labs, Woltjen and his team employed piggyBac transposons to deliver various polycistronic reprogramming factors, controlling for the Klf4 length. They found that transfection with polycistronic vectors carrying the shorter Klf4 ($Klf4_S$) resulted in more cells that initiated reprogramming, but failed to complete it, leaving them as partially reprogrammed. In contrast, more than twice as many cells transfected with vectors carrying the longer Klf4 ($Klf4_L$) became true iPS cells. Deeper investigation found that polycistronic vectors with the $Klf4_L$ isoform showed much higher Klf4 protein expression, suggesting that the stoichiometry of the reprogramming factors could be the critical factor underlying reprogramming efficiency. According to Woltjen, "The stoichiometry is so important. No matter what system you use to establish it, the stoichiometry has a major impact on the quality of iPS cells." Other studies have noted stoichiometry effects, but Woltjen's team is the first to propose variation in a single factor's mRNA sequence as a determining factor in establishing stoichiometry. Supporting their hypothesis, appending $Klf4_S$ with the missing nine amino acids switched the Klf4 expression and reprogramming dynamics to mirror those seen with $Klf4_L$.

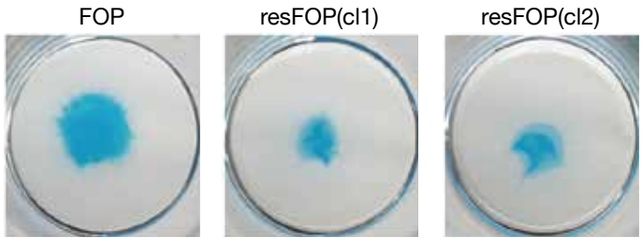
Knut Woltjen and Shin-Il Kim

Moreover, these differences in stoichiometry were reflected in gene expression patterns observed during the reprogramming process. Although reprogramming with either $Klf4_S$ or $Klf4_L$ led to the activation of many hallmark reprogramming genes, the majority of gene regulation was clearly dissimilar. Studying the reprogramming process induced by eight different polycistronic vectors, the team observed that both reprogramming performance and gene expression bifurcated with the Klf4 isoform. This finding may suggest that for popular vectors containing $Klf4_S$, a simple modification of the Klf4 length could augment the number of properly reprogrammed cells. For basic researchers studying the reprogramming process itself, this finding raises caution when directly comparing reprogramming data between labs.

Interestingly, the differences associated with Klf4 length appeared mainly when reprogramming with polycistronic vectors. If instead either $Klf4_S$ or $Klf4_L$ was induced using a monocistronic vector in combination with an OSM polycistronic vector, the isoform dependency of reprogramming disappeared. These results suggest that the polycistronic design of the vector has some innate effect on the expression level of Klf4, while the protein function itself may not be affected. Still, this study warns that inappropriate ratios of monocistronic vectors could also lead to stoichiometry effects. Postdoctoral Fellow Shin-Il Kim, first author of the study, stresses that just recognizing OSKM is not enough when reprogramming and that one must also be aware of the relative expression of the four genes. "Initially, we had no idea how much of a difference it [the 9 amino acids] would make. It goes to show how important it is to really know the materials you are working with," he says.

Reference
Kim SI et al. (2015) KLF4 N-terminal variance modulates induced reprogramming to pluripotency. *Stem Cell Reports* 4(4):727-743
Online publication: Mar. 12, 2015

iPS cell-based disease modeling for Fibrodysplasia Ossificans Progressiva



Rescued FOP cells (resFOP) from two different iPS cell lines (cl1 and cl2) grow to normal size, unlike FOP cells which grow much larger.

Fibrodysplasia ossificans progressiva (FOP), or Stone Man Syndrome, is a rare but devastating disease where the human body solidifies into a statue-like state. FOP is caused by a mutation in the ACVR1 gene and results in tissue ossifying either in response to trauma or idiopathy. Moreover, there is very little available in terms of treatment.

Many groups have investigated the disease by introducing the mutation into animal and human cell models, although the ideal model would use diseased cells from FOP patients. This option is risky, however, because patients are few and the acquisition of these cells could suffice as trauma that stimulates the uncontrolled ossification. iPS cells circumvent this second problem, since non-cartilage cells can be harvested without stimulating the disease.

Accordingly, the Toguchida lab of the Dept. of Cell Growth and Differentiation produced FOP-iPS cells and corrected the mutation in a subset to produce rescued (res) FOP-iPS cells. They then compared the molecular signaling between the two cell types. Both had similar morphology and growth until they were perturbed into chondrogenesis, which was accelerated in FOP-iPS cells. By the end of chondrogenesis, FOP-iPS cells were significantly larger due to enhanced secretion of extracellular matrix proteins, indicating that the disease enhances chondrogenic differentiation and maturation, not cell proliferation.

To identify the molecular triggers of this effect, the team looked at gene expression profiles. FOP-iPS cells and resFOP-iPS cells initially had similar profiles, but these profiles progressively differed as the cells proceeded with chondrogenesis, as nearly 300 genes showed significantly different expression levels in the end. In particular, the SMAD1/5/8 and SMAD2/3 pathways, which regulate a wide variety of cellular functions, were more active. Additional tests recognized PAI1 and MMP genes as two good targets, and application of inhibitors for the gene products reduced chondrogenesis in both cell types such that cell sizes were approximately equal.

Although this work is only preliminary, Associate Professor Makoto Ikeya, one of the first authors of the report, is excited about the prospect, as the identification of certain genes provides promising targets in drug discovery. “That’s the main point of this paper. We are looking for drugs.”

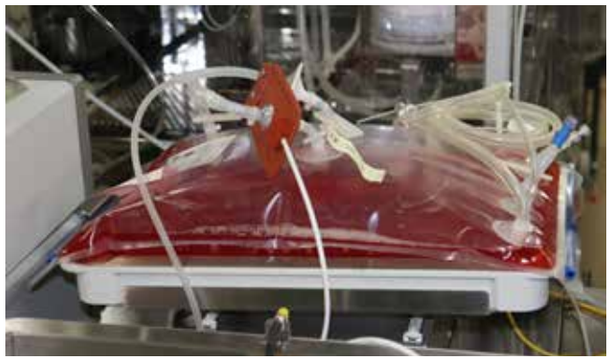
Reference
Matsumoto Y, Ikeya M et al. (2015) New protocol to optimize iPS cells for genome analysis of fibrodysplasia ossificans progressiva. *Stem Cells*
Online publication: Mar. 13, 2015

Greetings from
The Koji Eto Lab
Dept. of Clinical Application

Blood transfusion is the most common form of cell therapy, and blood is just about the easiest type of cell to acquire. However, blood cells like erythrocytes and platelets have a short lifespan, which is why donors are constantly recruited. Almost all countries depend on these donations to supply blood, but developing countries have a hard time recruiting volunteers, and even developed nations are growing concerned. Japan, for example, is anticipating its blood banks to underserve by 20% in the next 10-15 years. In this way, iPS cells are an attractive technology, because they can be expanded indefinitely, which means their supply is not exhausted even when differentiated into blood cells.

One challenge in cell therapies is providing a sufficient number of cells, and blood therapies are extremely demanding in this regard. Whereas cell therapies for the brain, heart, and other systems involve the transplantation of millions of cells, blood transfusions require hundreds of billions of cells, which creates unique challenges in iPS cell expansion. We are exploring ways to achieve these numbers by designing iPS cell-based unipotent progenitors (immortalized progenitors) that can be differentiated into erythrocytes or platelets. These immortalized progenitors can be cryopreserved and expanded when required, allowing us to preserve them for many, many months, unlike the few days in which blood cells can be stored.

To accomplish this goal, our lab is comprehensively investigating hematopoiesis, beginning at the hematopoietic stem cell stage and studying the iterations that lead to myeloid lineage fate. By optimizing the microenvironment, we are expanding and differentiating our immortalized progenitors to supply the requisite numbers of blood cells for patient care. Our aim is to bring this technology to the clinic relatively soon, which is why part of our work involves the industrialization of iPS cell technology. Our lab should therefore appeal to anyone interested in research from the bench to the bedside.



Making blood in the lab

Hundreds attend CiRA's Public Symposium


Tomoki Todo


Yoshiki Sawa


Shinya Yamanaka


Misao Fujita

Since its inception, CiRA has held symposia to inform the general public about iPS cells, including recent developments and discoveries at the institute. These events have happened in multiple cities and offer a rare chance for researchers to interact directly with the people. CiRA Director Shinya Yamanaka is especially committed to these events, as he views them essential for sustaining public support and keeping the public informed so that expectations are within reason. "CiRA's success is dependent on this support," he said.

CiRA had its most recent symposium on March 14 in Kyoto. This year, the institute organized the event in partnership with Advanced Medicine Promotion Organization (AMPO). AMPO invited Professor Tomoki Todo of the University of Tokyo and Professor Yoshiki Sawa of Osaka Univeristy, respectively renown for their work on cancer and cardiac failure therapies, to talk about their progress in their fields. On the CiRA side, joining Yamanaka was Associate Professor Misao Fujita, who leads the Uehiro Research Division for iPS Cell Ethics at CiRA. It was her first time to speak at these symposia and likely the first time for many to hear about the ethics behind the research. "I was surprised many people had never thought about the ethical issues," she said.

Fujita prepared her talk with the intention of giving caution, as she worries that if public expectations become unreasonable, "…once something bad happens, there could be huge backlash." For these reasons, her talk went beyond simply the ethics of iPS cell research, as she also asked the audience to consider the ethics of making animals like pigs chambers for growing human transplant organs and the possibility of growing iPS cells into fully formed humans. In contrast, Yamanaka's talk highlighted the recent findings at CiRA and spoke of the two clinical trials led by CiRA scientists that are expected to begin in upcoming years.

For many of the 755 people in attendance, it was their first detailed lesson about iPS cells. "I knew that iPS cells were some great discovery, but until today I did not understand why," said one attendee.

Ethics of mitochondrial replacement

This past February, the UK parliament passed a law permitting mitochondrial replacement, making the UK the first country in the world to approve this technique. Mitochondrial replacement involves removing the nucleus from one egg that contains defective mitochondrial DNA and transferring it into the cytoplasm of another egg from a different woman with normal mitochondrial DNA but with its nucleus removed. Thus, fertilized eggs using this technique are described as "three-parent babies." Because mitochondrial DNA is always acquired from the mother, mitochondrial replacement offers the best method to date to protect the offspring from mitochondrial DNA defects. However, the ability to prevent a disease from passing specific DNA to offspring has spurned the slippery slope argument about what constitutes acceptable intervention.

Mitochondrial replacement can be seen as a derivation of in vitro fertilization (IVF), which also was once a fascinating and maybe frightening experiment. Since its invention, however, there exist millions of IVF babies, and newspapers around the world celebrated the 35th birthday of Louise Brown, the first IVF baby, two years ago. Nevertheless, mitochondrial replacement does demand we evaluate what is permissible in reproduction science. The manipulation of DNA argues that we are creating designer babies. Designer babies normally spark images of parents selecting a desired height or desired hair/eye colour for their child, but what if we could modify an obesity gene or a dyslexia gene? The faulty mitochondria avoided by mitochondrial replacement can lead to many diseases and is associated with lower life expectancy. Yet so too does obesity, and learning disabilities also have possible detrimental effects on life.

In Japan, there is at the moment no discussion about permitting this technique. However, like IVF, that might change once we see the implications on people's lives. If mitochondrial replacement shows health benefits that dwarf ethical concerns, Japan and many other countries may begin at least reassessing their position.

Tsutomu Sawai, Researcher, Uehiro Research Division for iPS Cell Ethics

Philanthropy

Architect

Famous Japanese architect Tadao Ando and Director Shinya Yamanaka share several qualities. Both are recipients of the Kyoto Prize and both have ensconced themselves to the Kansai region despite endless opportunities to go elsewhere in Japan or the world. In Japan, Ando is almost as well known for his philanthropy as his structures. He is one of CiRA's most ardent supporters and throughout the years has continued to support CiRA not only through his own personal donations, but also by persuading many of his friends to do the same. This year he initiated a fundraiser where over 100 company representatives from Japan assembled to listen to Yamanaka speak about CiRA, its purpose and goals. The result was each committing at least 2.5 million yen over 5 years to the iPS Cell Research Fund. "It's magnificent for us," said Fumitaka Watanabe, one of CiRA's fundraising specialists. "It's a long-term commitment we simply could not acquire without his assistance."

Shinya Yamanaka and Tadao Ando

Athletes

Of all the marathons he runs, none is more important to Director Shinya Yamanaka's heart than the Kyoto Marathon, which occurs every February. No one including himself is sure if it was because of the rain and cold weather, but he finished with a personal best time of 3 hours, 57 minutes and 31 seconds. "I was feeling good and able to pick up the pace in the last half." His run raised 1.75 million yen for CiRA.

Shinya Yamanaka and
CiRA teammate Kentaro Azuma

We are hiring!

Interested in joining CiRA? Along with the numerous fellowships available from national agencies and other sources, CiRA awards exclusive annual post-doctoral fellowships to laboratories that are then used to hire foreign researchers. Candidates should contact the laboratory of interest for details about research projects and potential funding.
For more information, visit: https://www.cira.kyoto-u.ac.jp/e/employment.html

Briefs

CiRA expands

With more research success has come more funding, and with more funding has come more staff. Now with more staff has finally come a new building, as March 16 saw completion of CiRA's second research building. The building is attached by a multi-floor bridge to the inaugural CiRA research complex and it will house the drug discovery unit, bioethics unit, and a number of other laboratories. "Bringing everyone together will help our collaborations and productivity," says Director Shinya Yamanaka.

New building

Kyoto-San Diego

Seeing each other as invaluable partners, this past March Kyoto University and the University of California, San Diego, held their first Joint Symposium, "New Era of Trans-Pacific Knowledge Interactions," in Kyoto. The event was three days and covered a comprehensive spectrum of the sciences. The last day was devoted entirely to biomedical research, with three of the seven Kyoto University speakers coming from CiRA: Professors Yasuhiro Yamada, Jun Takahashi, and Koji Eto. Senior Lecturer Keisuke Okita spoke on the first day.

WIPO comes to CiRA

On February 27, Dr. Francis Gurry, the Director General of the World Intellectual Property Organization (WIPO), visited CiRA to discuss with Shinya Yamanaka and other researchers about patent policy for innovative technologies. Yamanaka believes that the acquisition of patents is an essential part of CiRA's mandate to move iPS cell research to the clinic. "It was a good opportunity to speak directly to WIPO about different patent examinations across countries."

CiRA-ISSCR conference in Kyoto 2016

Next year will mark the 10th anniversary of iPS cells. In recognition of this pivotal moment in stem cell research, ISSCR and CiRA are organizing the International Symposium, "Pluripotency: From basic science to therapeutic applications," on March 22-24, 2016.

Take advantage and come to Kyoto next year to meet top researchers in the stem cell field, to see the home of iPS cells and to visit one of the world's most beautiful and unique cities.

Details will be available on the CiRA and ISSCR webpages later this year.

Sakura season

Everyone in the sun

But me, in the lab

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