CiRA Reporter

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Kyoto University
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto
606-8507 Japan

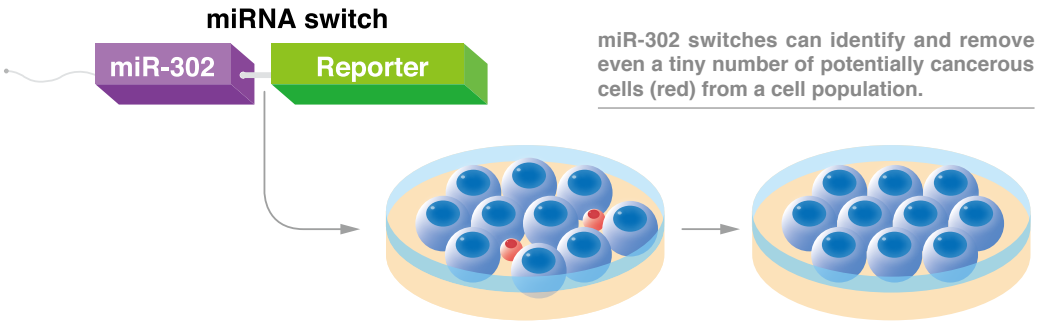
Cover design
Ohmukai Design Office

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

RNA detects and eliminates undifferentiated cells

The Hirohide Saito labs uses RNA-based technology to remove potentially cancerous cells from a heterogeneous population.



miR-302 switches can identify and remove even a tiny number of potentially cancerous cells (red) from a cell population.

Pluripotent stem cells (PSCs) allow scientists to create any number of cell types for regenerative medicine. However, the transformation is not 100%, resulting in residual PSCs and other undifferentiated cells. Because these residual cells proliferate, they risk creating tumors, which means they must be removed before the cell therapy is applied to the patient. Typically, removal involves the use of antibodies that bind to surface receptors on the PSCs, but the efficiency of this method for some cell types precludes clinical application. Therefore, Professor Hirohide Saito believes, "Alternative strategies for cell purification are important to facilitate some cell therapies."

For one strategy, the Saito lab is seeking unique signatures from inside rather than outside the cell. "We are separating cells by micro RNA (miRNA), not surface receptors," explains Dr. Callum Parr, a researcher in the Saito laboratory and first author of a new study in *Scientific Reports* that describes miRNA-based technology. In a previous publication, the group had reported miRNA switches, a biotechnology that turns a gene on or off depending on the miRNA found inside the cell. The body has thousands of miRNAs, but one in particular, miR-302, is especially associated with proliferation. "Undifferentiated cells specifically express miR-302 and as they differentiate they lose this expression," said Parr.

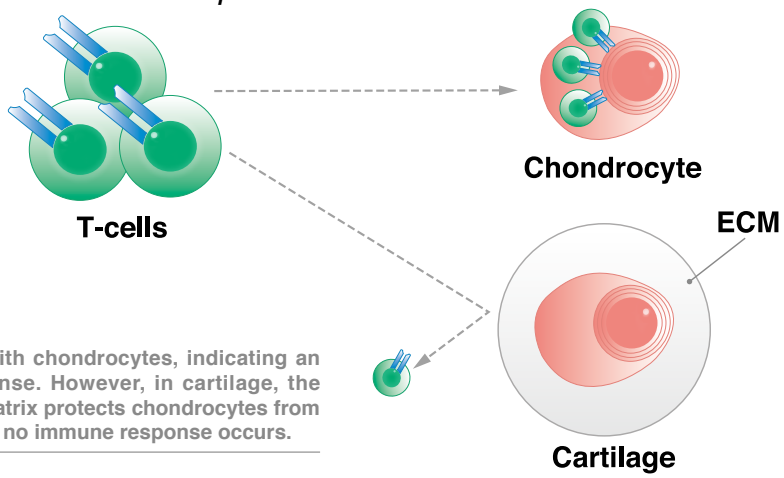
The paper shows that miR-302 switches are more sensitive to the presence of undifferentiated cells in a heterogeneous cell population than methods that depend on antibodies. Indeed, they could identify and separate undifferentiated cells that constituted as little as 0.05% of the cell population. Based on this finding, Parr believes, "We can control cell survival using this miR-302 switch to setup a gene circuit that will automatically kill undifferentiated cells. This is a major advantage because with previous methods we have to sort the cells out using expensive equipment in a process that is both time-consuming and damaging to live cells."

Reference

Parr C, Katayama S, Miki K et al. (2016) MicroRNA-302 switch to identify and eliminate undifferentiated human pluripotent stem cells.
Scientific Reports 6. DOI: 10.1038/srep32532

Cartilage prepared from iPS cells does not activate immune cells

The Noriyuki Tsumaki lab shows iPS cell-derived cartilage does not trigger an immune response.



T cells react with chondrocytes, indicating an immune response. However, in cartilage, the extracellular matrix protects chondrocytes from the T cells, and no immune response occurs.

In most cell transplantations, it is imperative to match the donor and patient to avoid immune responses that reject the transplant. Cartilage is an exception, and several thousand transplantations without matching are known. The reason for this exception is the nature of cartilage. "Cartilage consists of chondrocytes and extracellular matrix (ECM)," explains CiRA Professor Noriyuki Tsumaki. Chondrocytes are responsible for secreting ECM proteins. When cartilage is transplanted the ECM protects the chondrocytes from the host's immune cells, thus preventing an immune response.

However, even though the above feature relaxes the conditions for donor eligibility, cartilage donors remain woefully insufficient. Tsumaki and his team have therefore been seeking other sources for cartilage, focusing on iPS cells. While it was expected that cartilage derived from iPS cells should also be immune privileged, the Tsumaki lab reports the first proof in *Tissue Engineering Part A.*

Like chondrocytes from normal cartilage, the study shows that iPS cell-derived chondrocytes express limited amounts of HLA, and iPS cell-derived cartilage does not stimulate T cells.

Tsumaki is an orthopedic surgeon who aims to translate his research to patient treatment for knee ailments. "This finding will influence our strategy for clinical care," he said. The lab is already at the forefront of creating both chondrocytes and cartilage using iPS cells and has already tested the effects of their transplantation in a number of animals.

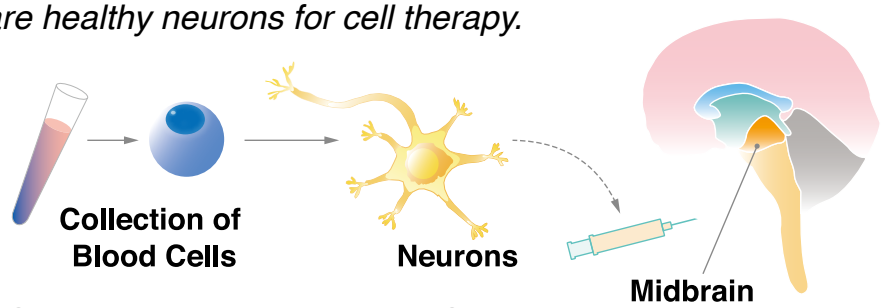
Donor matching can be a painstakingly long process, especially if the patient has the misfortune of a rare HLA type. The immuno-privilege of iPS cell-derived cartilage, on the other hand, suggests any healthy donor is sufficient. Tsumaki anticipates this work to expedite the use of iPS cells for cartilage injuries. "I hope to start patient care in the next few years," he said.

Reference

Kimura T, Yamashita A, Ozono K et al. (2016) Limited immunogenicity of human iPS cell-derived cartilages. *Tissue Engineering* 22 (23 and 24).
DOI: 10.1089/ten.tea.2016.0189

High cell purity for Parkinson's disease therapy

The Jun Takahashi lab reports a new molecule used to prepare healthy neurons for cell therapy.



General schematic of neurosurgery using iPS cells.

Parkinson's disease is a neurodegenerative disorder that causes a debilitating loss of midbrain dopaminergic (mDA) neurons. Much evidence supports stem cell therapies as effective treatment for this degenerative effect. Research is still needed, however, to identify which neural subpopulations derived from the stem cells leads to best outcomes. A new study from CiRA shows that LRTM1, a protein that may contribute to synapse formation and axon guidance, could be an invaluable marker of the ideal cells.

Professor Jun Takahashi and his team are aiming to lead the first clinical iPS cell-based therapy for Parkinson's disease in Japan. "We have reported other markers for mDA neurons. Because we plan the first patient trials, we want to make the population as pure as possible," said Takahashi. By preparing neurons from stem cells and then selecting those that expressed LRTM1, the scientists could increase the number of transplanted cells that survived in rats and also improve Parkinsonian symptoms.

The discovery of LRTM1 was based on gene studies. Based on its previous work, the group already knew which genes indicated stem cells that were likely to differentiate into mDA neurons. Further analysis revealed that five genes coded for proteins on the cell surface, but "LRTM1 was the only protein exclusively expressed in the brain region that produces mDA neurons," said Takahashi. Important was that these cells did not express genes consistent with proliferation, which suggests they are not susceptible to growing tumors, a risk that must be considered in all stem cell-based therapies. Instead, when transplanted into rat and monkey brains, the cells developed into mature mDA neurons and extended more neuronal fibers to the host brain than did the transplantation of populations that did not express LRTM1. "All our data indicated cells expressing LRTM1 give better results," Takahashi said.

LRTM1 adds another marker to the list of indicators Takahashi's team is using to prepare mDA neurons from stem cells. Each stem cell has the potential to differentiate into all neuron types in the brain, but the specific loss of mDA neurons means only a very select group of cells should be used in the therapy. Based on these findings, Takahashi is optimistic the list of markers will soon be sufficient for patient treatment. "We hope to start our first patient trials in the next two to three years," he said.

Reference

Samata B, Doi D, Nishimura K et al. (2016) Purification of functional human ES and iPSC-derived midbrain dopaminergic progenitors using LRTM1.
Nature Communications 7. DOI: 10.1038/ncomms13097

Unprecedented purity and yield of endothelial cells in the lab

The Megumu Saito lab shows the environment in which stem cells are cultured heavily influences the ability to produce endothelial cells.

Endothelial cells are responsible for communication between blood and tissues and are found throughout the body. In terms of disease, their dysfunction is associated with an assortment of disorders, including hypertension and thrombosis. Several researchers have prepared endothelial cells from pluripotent stem cells, but the yield and purity is not satisfactory for clinical purpose. A collaboration between the Megumu Saito lab and the Kiyotoshi Sekiguchi lab at Osaka University has shown that changing the environment in which the stem cells are cultured during the differentiation process can improve these outcomes.

"When preparing endothelial cells, we culture the stem cells on laminin-coated extracellular matrix," explained Saito. It is not uncommon for one laminin to be selected throughout the whole culture process. There are at least 15 different types of human laminin. LM511 is normally used to culture stem cells, but Saito observed, "We show switching the type of laminin increases the number of endothelial cells." His team found that using LM511 for the first three days of culture and then LM411 for the next four significantly improved the differentiation to endothelial cells.

Assistant Professor Akira Niwa, a member of the lab, noted that LM511 reacts well with stem cells, but as the stem cells differentiate, LM411 is more effective at specifying the lineage towards endothelial cells. "We noticed LM411 has very specific distribution in the body. LM411 is located around blood vessels and bone marrow," he remarked. LM511 was appropriate to promote the early stages of differentiation, whereas LM411 could steer the later stages of differentiation to endothelial cells. Moreover, using a LM411 derivative, LM411-E8, achieved a purity of endothelial cells that was over 95%, more than twice the purity of any previous report.

The improvement was likely due to the type of molecules laminin binds. "LM411-E8 binds to specific types of integrin, which promotes endothelial cell differentiation," said Niwa. Further study revealed this molecule to be VEGF. "VEGF is a common hormone used to promote endothelial growth," he added. Accordingly, the new protocol includes VEGF during the LM411-E8 stage. It also uses another compound, CHIR99021, during the LM511 stage to promote the early stages of differentiation.

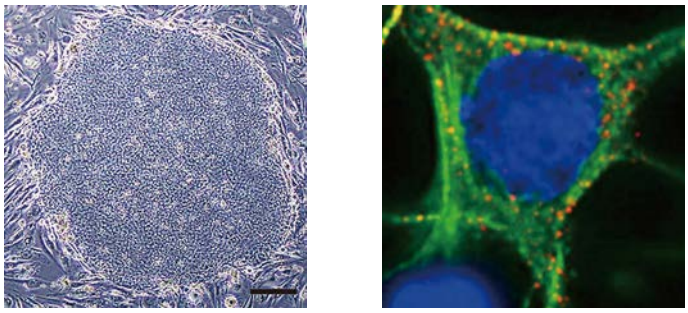
"These are very exciting findings," said Saito. "Since many diseases are linked to poor endothelial function, the derivation of highly purified functional PSC-derived endothelial cells provides a platform for future cell therapy and disease modeling."

Reference

Ohta R, Niwa A, Taniguchi Y et al. (2016) Laminin-guided highly efficient endothelial commitment from human pluripotent stem cells. *Scientific Reports* 6. DOI: 10.1038/srep35680

Calcium contributes to neurodegeneration in cognitive disorders

The Haruhisa Inoue lab shows evidence for a candidate drug target to prevent age-related dementia.



(left) Colony of patient iPS cells. (right) A neuron derived from patient iPS cells shows an accumulation of tau (red), which is consistent with the molecular phenotype of FTLD.

As the average age of society rises, so too does the incidence of neurodegenerative diseases, especially those that affect cognition. In many of these diseases, like Alzheimer's disease, the loss of neurons is accompanied by accumulations of the protein tau (tauopathies). The relationship between the neuronal loss and accumulation of misfolded tau is not well understood, however, especially the molecular events that precede both. The Haruhisa Inoue lab reports in *Scientific Reports* that iPS cells can be used to show that abnormal calcium regulation could modulate the degeneration.

"Frontotemporal lobar degeneration tauopathy (FTLD-Tau) is a subtype of familial neurodegenerative disorder," said Inoue. Patients show behavior and personality changes and memory loss. Sometimes they are incorrectly diagnosed with a psychiatric disorder."

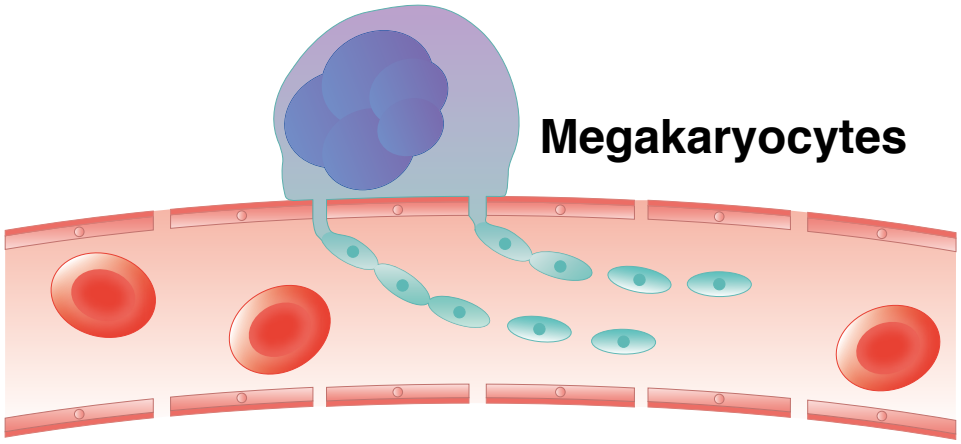
To investigate the neuronal loss in FTLD-Tau, Inoue's team prepared iPS cells from FTLD-Tau patients who showed different mutations in the gene responsible for tau protein, *MAPT*. Previous iPS cell models have shown that patient neurons show a larger accumulation of tau protein than do normal cells. The lab went one step further by looking at potential molecular causes. "We found patient cells had accumulated levels of misfolded tau and dysregulated Ca^{2+} transients evoked by electrical stimulation," explained Inoue. To determine if the increased activity contributed to the tau accumulation, the lab took advantage of Designer Receptors Exclusively Activated by Designer Drugs, or DREADD. According to Inoue, "These systems enable us to modulate activity-relevant Ca^{2+} influx by inserting chemical receptors into the neurons." By inhibiting the Ca^{2+} influx with DREADD, the researchers could suppress the neuronal degeneration, suggesting neuronal activity was triggering neurodegeneration. These results further suggest a new candidate target for preventing or at least delaying FTLD-Tau progression.

Reference

Imamura K, Sahara N, Kanaan NM et al. (2016) Calcium dysregulation contributes to neurodegeneration in FTLD patient iPSC-derived neurons.
Scientific Reports 6. DOI:10.1038/srep34904

A new drug compound pushes artificial blood closer to the clinic

Inhibition of a specific enzyme maintains platelets.



Megakaryocytes extend proplatelets into the blood vessels. Platelets (turquoise) are fragments of proplatelets sheared by the blood flow.

Platelet transfusion is crucial for a number of disease treatments and surgical interventions. Most platelet supplies depend on human donors, but aging populations are causing a demand for platelets that is not being matched by donors. Professor Koji Eto and his team are therefore using iPS cells to prepare an alternative platelet source. “Platelets from human donors must be used within a few days,” said Eto, “but our iPS cell technology provides a consistent supply.”

Effective platelets must express a specific receptor in order to function properly. Eto explains that to cause coagulation, the receptor “GPIbα keeps platelets attached to the injured blood vessel.” During the generation of platelets in the lab using iPS cell technology, specific enzymes are known to shed GPIbα, resulting in suboptimal platelet performance. It turns out a number of enzymes can contribute to the shedding, but Eto’s team show that inhibiting just one significantly improves platelet performance. “Many of the enzymes that shed GPIbα have multiple roles that should not be inhibited. But we found inactivating ADAM17 gave best results,” he said. Indeed, platelets transfused into mice showed better coagulation effects when treated with an ADAM17 inhibitor, a molecule identified as KP-457.

The discovery of KP-457 is but one key step to recapitulate human platelet development in the lab. Eto and his team are seeking more chemicals that enhance the platelet phenotype so that platelets from human donors can be completely replaced with those made from iPS cells.

Reference

Hirata, S, Murata T, Suzuki D et al. (2016) Selective inhibition of ADAM17 efficiently mediates glycoprotein Ibα retention during ex vivo generation of human induced pluripotent stem cell-derived platelets.
Stem Cells Translational Medicine.
DOI: 10.5966/sctm.2016-0104

Greetings from the
Masato Nakagawa Lab

Dept. of Life Science Frontiers

My research career became very clear in 2006, as I was a member of the Yamanaka lab when the first iPS cell paper was published. I have since remained with Professor Shinya Yamanaka and focused on the science of reprogramming. Mainly, my questions surround issues regarding the safety and efficiency of reprogramming. One of the major advances my lab has made in reprogramming is the recognition that c-Myc, one of the original Yamanaka factors and an oncogene, can be replaced with L-Myc to significantly reduce the risk of tumorigenesis and increase the reprogramming efficiency. CiRA has incorporated this substitution as part of its standard production of iPS cells. Why L-Myc has this effect is not clear, however. We are therefore investigating the mechanisms with which L-Myc promotes regeneration.

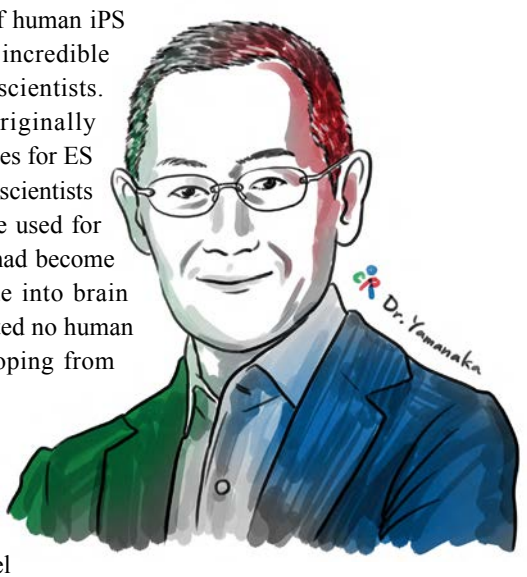
Secondary to the activation and deactivation of genes in reprogramming is the microenvironment in which the cells are cultured. The original iPS cells were prepared using feeder cells. Feeder cells simplify the reprogramming, but they also risk contaminating the iPS cells, which means any protocol that uses feeder cells disqualifies the iPS cell product from clinical application. Working with Professor Kiyotoshi Sekiguchi of Osaka University, we have demonstrated that laminin 511-E8 fragments can eliminate the requirement of feeder cells for iPS cell preparation. Complementing this material is the use of xeno-free constituents in the culture, which allows us to prepare iPS cells in a manner that should satisfy the strict demands for clinical application. Like L-Myc, the use of laminin 511-E8 fragments is also part of standard protocol at CiRA.

The above are two practical examples of our work for the translation of iPS cells to patient care. These discoveries, especially the case of L-Myc, are the result of basic research. In this way, we are conducting intense study of the transcriptome and proteome. We have designed a high-sensitivity mass spectrometer (MS)-based shotgun-proteomic analytical system that is coupled with capillary liquid chromatography (LC). The use of its meter-long monolithic column increases the separation and identification efficiency of proteins. This allows us to compare mRNA and protein copy numbers at global levels. Interestingly, there exist a surprising number of proteins that are highly expressed in iPS cells compared with fibroblasts even though the mRNA levels are approximately the same in the two cell types. We speculate that the copy numbers of these proteins might be regulated post-transcriptionally in a cell-specific manner. We are targeting these proteins as candidates with vital roles in the reprogramming mechanism.

The Nakagawa Lab members

Happy Birthday iPS cells!

CiRA faculty reflect on how iPS cells have changed their research.



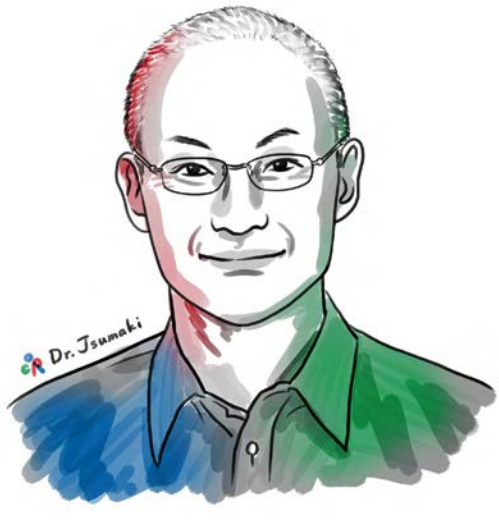
2017 marks the 10th anniversary of human iPS cells. Their creation has had an incredible impact, not just on science but also scientists. Although the international media originally focused mostly on iPS cells as substitutes for ES cells in research on new cell therapies, scientists quickly realized that iPS cells could be used for much more. Suddenly, science fiction had become science, as blood cells could be made into brain cells, and diseases for which there existed no human models could now be watched developing from their beginnings in real time.

The speed of iPS cell research has been almost dizzying, making iPS cells the root of several prestigious awards, including, of course, the Nobel Prize given to Professor Shinya Yamanaka in 2012. 2016 saw several organizations plan special events to recognize this landmark moment. Nature Reviews devoted an entire issue to pluripotent stem cells last March. That same month, the International Society for Stem Cell Research (ISSCR) celebrated iPS cells by partnering with CiRA to hold the symposium, Pluripotency: From Basic Science to Therapeutic Applications in Kyoto. Last autumn, Cell Press, which published the first iPS cell papers, hosted a similar symposium in California.

Furthermore, CiRA has found a significant uptick in the number of foreign media requests for comments by Professor Shinya Yamanaka. Most inquiries have asked for reflections on how iPS cells will change medicine in the future. On the other hand, far fewer have asked how iPS cells will change people's lives, like that of the patient who received the first iPS cell-based therapy in Kobe, Japan, in 2014.

While the ultimate aim of CiRA is new iPS cell-based therapies for intractable diseases, the institute has already had an impact on a large number of people. CiRA, which itself is the result of iPS cells, will surpass 500 employees this year after launching with a total of 150 in 2010. Furthermore many of CiRA's current faculty were scientists at the early stages of their careers, working as post doctorates and in some cases having just finished graduate school when Yamanaka and Dr. Kazutoshi Takahashi published the first iPS cell papers. Suddenly, the announcement of iPS cells made these researchers into pioneers who not only sought to learn this new technology, but also discover new ways to use it.

One example is Professor Kenji Osafune, who saw a dramatic change in the job market after the announcement of iPS cells. In 2006, Osafune was working at Harvard University in



the Doug Melton lab. Being a nephrologist, Osafune was using human ES cells to study relevant diseases. “My original goal was to develop regenerative medicine for kidney disease,” he said. To him, stem cells were a tool to treat patients.

Coincidently, human ES cells had yet to celebrate their 10th anniversary when human iPS cells were reported. During this interim, many scientists, including Osafune, can recall a period of conservative policies that limited research using human ES cells. Policies in the United States got arguably the most attention, but other countries had even more onerous restrictions, including Japan. Osafune’s plan was always to return to Japan following his time in the Melton lab, but the country’s laws for ES cell research made him pessimistic. “People in Japan told me to look for jobs outside Japan,” he said. After iPS cells, however, Osafune found an encouraging job market for anyone interested in working with this Japanese innovation. It did not hurt when right next door to the Melton lab during Osafune’s stay there, Dr. Kevin Eggan and his team reported iPS cells from an ALS patient, demonstrating a further advantage over ES cells in that iPS cells could be used for human disease modeling. Suddenly, not only did iPS cells seem equal to ES cells, the added opportunities for disease modeling and drug discovery suggested they could be superior.

Professor Noriyuki Tsumaki was much closer physically to the discovery of iPS cells, working at Osaka University, which is less than an hour away from CiRA. Tsumaki at the time was researching chondrocyte differentiation. “I was studying cartilage development in embryogenesis,” with the aim of innovating regenerative medicine to treat cartilage damage, he said. Initially Tsumaki had only casual interest in the report, since his research focus was not pluripotency. “I read about iPS cells in the newspaper,” he said. Because iPS cells were made from fibroblasts, Tsumaki wondered if it would be possible to directly reprogram fibroblasts to cartilage, a hypothesis he would prove in a publication a few years later. To learn about iPS cells, “I contacted Professor Yamanaka to teach us to transduce genes into fibroblasts. He said ‘yes’ and Dr. Takahashi taught us,” recalled Tsumaki. Despite the close geographical proximity, it was a bit surprising to hear that Yamanaka and Takahashi were so cooperative, as they were effectively the only iPS cell gurus in the country at the time. “We went to the same junior and senior high school,”

Tsumaki confessed. It turns out Yamanaka and Tsumaki attended the same high school together, where they both took up judo, leading to careers in orthopedic surgery after occasionally breaking bones in the same dojo.

Neither Osafune nor Tsumaki were expecting iPS cells, since their research was in indirectly related fields. On the other hand, those closer to the study of cell development and pluripotency were waiting with anticipation. “I heard a rumor from my colleagues that Shinya was successful at iPS cells,” said Professor Yasuhiro Yamada about a talk given by Yamanaka before the publication. Yamada had to wait for the magic formula, however, until the Cell publication. When the paper was finally released, Yamada was about one year into a post at Gifu University (Japan) after an extended stint in the Rudolf Jaenisch lab at MIT. Yamada is a pathologist by training whose interest is primarily in cancer cells. He had joined the Jaenisch lab because he wanted to expand his research in cancer cell epigenetics. There he learned cancer cell nuclear transfer experiments, but realized this technique would demand many years of training before he could be independent. “[Nuclear transfer] requires very high expertise and is very difficult to do even in two years,” he said about his tenure at MIT. iPS cells provided a much easier and some ways better model to study the cancer cell epigenome. “I saw the domed shape, ES-like colony. I was so excited, because I never thought I could change somatic cells to stem cells,” Yamada claimed about his first successful creation of iPS cells. Yamada would later become one of the first cohorts, along with Osafune and Junior Associate Professor Shinji Masui, another faculty member at CiRA, to earn national grants specific to iPS cell research.

Professor Junya Toguchida, who has been with CiRA since its inception, remembers hiring Yamanaka at Kyoto University. “Shinya joined us in 2004. I think in the [job interview] presentation he mentioned he wanted to make pluripotent stem cells from differentiated cells,” he said. Toguchida had long been using mesenchymal stem cells to study bone regeneration and sarcomas. He had no experience using pluripotent stem cells, but was eager to try. “It was a miracle and I wanted to be involved. At the time we did not know how much we can do,” he said. iPS cells allowed him to branch out his research to the study of fibrodysplasia ossificans progressiva (FOP), an extremely rare but devastating bone disease that is thought to inflict less than 5,000 people worldwide. “Mesenchymal stem

cells are good for regenerative medicine, but not disease modeling," explained Toguchida. Since transitioning to iPS cells, Toguchida estimates he has met about half of Japan's FOP patients, and his group is now preparing a clinical trial to treat the disease based on patient iPS cell studies.

Associate Professor Knut Woltjen had just moved to Toronto, Canada, to join the Andras Nagy lab as a post-doctoral fellow when the mouse iPS cell paper was published. In fact, Woltjen still remembers that "the original iPS cell paper by Takahashi and Yamanaka was pinned outside our post-doc office for months, " but he actually gave it relatively little thought. He had been working with mouse ES cells throughout his Ph.D. studies, because he was developing new transposon and gene targeting biotechnologies to study genetics. "To me, ES cells were a tool to work with the genome," he said. Since mouse ES cell lines were abound, mouse iPS cells just represented a surplus in the toolbox. "The mouse was not that exciting for me, but if it was human," he said, "that could be cool."

Woltjen's work switched from mouse ES cells to human iPS cells when Nagy returned from a conference. Woltjen remembers, "Andras came into the lab all excited and said 'let's try reprogramming with piggyBac transposons.'" At the time there was still uncertainty as to whether reprogramming could be done safely, but the piggyBac system offered a possibility. Woltjen started the project in February 2008, and by April he already had his first reprogrammed cells. He still expresses disbelief at his success, saying, "Literally the first experiment worked. It was so easy to do." The paper would be published a year later and a few months after that he was presenting it at ISSCR in 2009. There he met Yamanaka, who, according to Woltjen, told him, "Oh, I know you. I wanted to tell you about a new institution [CiRA] we are opening. You should apply."

Woljten's decision to join CiRA had to be carefully weighed, as it required him and his family move to another country. Even for the Japanese, accepting a post at CiRA was not obvious. Osafune said, "Japanese think of our undergraduate university as our hometown," which is why he was very excited to join CiRA and Kyoto University, from which he graduated. On the other hand, for someone like Yamada, who had graduated from Gifu University, the decision was not so easy, but that opinion changed when Yamanaka called. "[At CiRA], I could think about research from morning to evening," he said. In contrast, because of teaching and clinical responsibilities, "in Gifu, I could only think about two to three hours [a day] about research." Similarly, Tsumaki was not only employed at Osaka University, he had graduated from there too. In the end, though, his success in direct reprogramming and personal relationship with Yamanaka won out.

Interestingly, none of the labs view themselves as iPS cells labs. Rather, they see iPS cells as tools that advance their own research interests. Working at CiRA though, they sometimes have to be reminded that other cells exist. "Some of my students complained, because I was so into iPS cells I forgot about somatic cells," admitted Toguchida.

Learn more about the 10th anniversary at
http://www.cira.kyoto-u.ac.jp/10th/e/

Osaka Marathon

The city of Osaka held its 6th annual marathon the day before Halloween, and as usual CiRA was well represented. Ten CiRA members ran, with many running personal bests including Shinya Yamanaka. “It was warmer than expected, making it a hard run,” he was quoted. Each year the number of CiRA runners taking part in the marathon has increased. “I ran my first marathon earlier this year in Kyoto,” said CiRA Professor Hirohide Saito. “I was surprised at how good I felt after and now want to run more, but this time I could not run after 30 km. I need to practice more.”

Moreover, another 136 runners choose CiRA as their charity for fundraising. “Every year we are humbled by the number of people who run on behalf of CiRA,” said Aiko Tokunaga, a fundraiser at CiRA.

Shinya Yamanaka at the Osaka Marathon 2016.

Science Agora

CiRA participated in Science Agora last November, the third time it has taken part in Japan’s largest annual science exhibition for the public. This year it released the English version of iPS Master, an app for the iPad that simulates the original experiments done by Professor Shinya Yamanaka and Dr. Kazutoshi Takahashi to create iPS cells (https://www.cira.kyoto-u.ac.jp/e/faq/ips-master.html). The Uehiro Division for iPS Cell Ethics at CiRA also participated by presenting a poster on the ethics behind xeno stem cell transplantation for the harvesting of human organs in animals.

CiRA Internships

The CiRA internship program invites undergraduate and graduate students from around the world to CiRA for 8 consecutive weeks between May and October to work in a host lab. The internships act like lab rotations and are intended to result in longer stays, either through matriculation to Kyoto University or hiring as a post doctorate. Candidates are encouraged to first contact their preferred labs about potential projects before applying. Successful applicants will receive a stipend for their stay and travel to Kyoto.

Calls for applications will begin mid-February and end March 10. Please see the CiRA website for details.

The Temples and Shrines of Kyoto

Myōshin-ji

Myōshin-ji Temple is relatively young by Japanese standards, as its history only reaches back to the 14th Century. Its founding emperor, Hanazono, was a passionate practitioner of Zen and requested on his deathbed that the shrine become an education centre for Zen teachings. That influence has remained, as the temple is the headquarters of the Myōshin-ji Temple School of Rinzai Zen Buddhism and has spawned several Zen programs with local schools and universities.

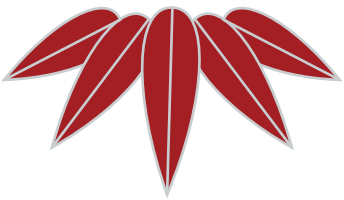
Inside the temple grounds

Myōshin-ji is actually a compound of 48 sub-temples, one of which is Taizo-in. Daiko Matsuyama is the vice priest of Taizo-in and a few years ago befriended CiRA Professor Junya Toguchida. According to Toguchida, Matsuyama followed a slightly odd trajectory to his final career, as he graduated from Tokyo University with a degree in engineering, but then followed the footsteps of his father, who was a Buddhist priest. Toguchida was struck by Matsuyama's interest in iPS cells, especially the idea of making haploid cells like sperm and eggs. As someone active in the local and global community, Matsuyama did not surprise Toguchida when he suggested CiRA host an iPS night at the temple.

Shihori Yokoyabashi

The event happened on October 22, at which over 60 guests learned about iPS cells from CiRA staff including Dr. Shihori Yokoyabashi of the Yamanaka lab and bioethicist Dr. Misao Fujita. Also joining the list of speakers was Dr. Hiroshi Hatayama, a gynecologist at Adachi Hospital, one of the oldest hospitals in Kyoto, and expert in infertility. Because of Matsuyama's interests, the speakers focused on efforts to make sperm and egg cells from iPS cells, discussing the science, potential medical applications, current status, and bioethics. Toguchida attended as a moderator.

(Left to right) Junya Toguchida, Hiroshi Hatayama, Misao Fujita and Daiko Matsuyama



It quickly turns dark

White blankets cover the roofs

All the temples glow

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/
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