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iPS cell clinical research for the heart approved in Japan

This past May, a second clinical project using cells from the Facility for iPS Cell Therapy (FiT) at CiRA has received conditional approval from the Japanese government. Osaka University Hospital Chief of Cardiovascular Surgery, Yoshiki Sawa, will lead a project that differentiates iPS cells made at FiT into cardiomyocytes, which will then be transplanted into patients suffering from heart failure. The project is estimated to require nearly 100 million cells per transplant, significantly more than the 1 million needed for the iPS cell-based therapy done by Dr. Masayo Takahashi of Riken, who announced surgeries to treat age-related macular degeneration (AMD) in the beginning of 2017 using cells from FiT. If successful, the procedure could provide an alternative to heart transplants, which are rarely recommended to elderly patients even if a donor is available. Important from CiRA's perspective, the success of Professor Sawa's project would confirm the versatility of iPS cells from FiT for clinical use.

Making clinical-grade iPS cells is one of CiRA's most important endevours. It is responsible for preparing clinical-grade iPS cells that it distributes to medical organizations and companies. These organizations then differentiate the cells and transplant the products into patients for therapeutic purposes. CiRA's role in the therapy ends with the cell distribution, but its interests remain well into the patient follow-up years later.

Originally, it had been hoped that through iPS cell research, standard therapies could use a patient's own iPS cells. Almost all organ transplantations require the use of immunosuppressant drugs to lower the risk of immune rejection, but these drugs put the patient at risk of infectious disease. It is expected that any iPS cell product prepared from the patient's cells would minimize the risk of an immune rejection. This was the strategy followed by Dr. Takahashi when she conducted the world's first iPS cell therapy, which was also to treat AMD, in 2014. However, because of the time it takes to prepare iPS cells from the patient, CiRA had realized that it would be much more cost and time effective if a facility like FiT existed to provide clinical-grade iPS cells available immediately upon need.

As can be imagined, cardiac therapies are not trivial. Cardiomyocytes are the muscle cells of the heart, but research like that done by CiRA Professor Jun Yamashita has shown that a mixture of cardiomyocytes and non-cardiomyocytes is best for the cell therapy, although the best ratio is still to be determined. At the same time, Associate Professor Yoshinori Yoshida has shown that the maturity of the cells is also a key determinant in the best outcome, but again which maturity is best remains unknown.

While these questions are still to be answered through basic research, when it comes to the patient, sometimes "good enough" is all we want. A therapy that is optimal is always preferred, but the translation from basic to clinical research is not bound by perfection. No matter the outcome of this heart therapy, it is almost certain that it can be improved in the future. It is for this reason that clinically-related research projects being done at CiRA will continue regardless of the outcomes of current and future iPS cell-based therapies. The initial therapy by the Osaka University team will only be done on three patients who satisfy very strict criteria. The first step to iPS cell-based therapies for the heart or any organ is proving their safety in a selected population before expanding the therapy to the whole population.

In response to the announcement, CiRA Director Shinya Yamanaka publically stated that, "we expect this study to lead to new therapies for the heart. We will provide quality iPS cells many more treatments beyond the heart from our iPS cell stock."

Turbulence is good for the blood

The Eto Lab shows that turbulence enhances the production of platelets.

Blood flows through the body smoothly in order to transport its content. In a new study seen in *Cell*, scientists at CiRA show unexpectedly that small levels of turbulence in the blood promotes the generation of platelets, the cells responsible for wound healing. Using this new information, they report a bioreactor that produces more than 100 billion platelets from iPS cells, an amount large enough for patient treatment.

Blood transfusions are the oldest form of cell therapy and have been done for centuries. Platelets are blood cells that stop bleeding and have other healing factors. Platelet transfusions are common for patients suffering from blood diseases or undergoing cancer therapy. However, platelets taken from donors can only be stored for several days, which is why organizations like the Japanese Red Cross hold regular blood drives. While this approach is the global standard, with the number of aging populations increasing, many nations are anticipating severe donor shortages. Japan alone estimates that its platelet supplies will serve only four of every five patients in the next decade.

CiRA Professor Koji Eto, who is also Professor at the Chiba University School of Medicine, has been developing platelets using iPS cell technology to replace the dependency on donors. Platelets are extremely small fragments that blood flow breaks off the surface of much larger cells called megakaryocytes, much like washing debris off a car. Unlike platelets, megakaryocytes can be stored for long periods, but they are extremely rare in the body and therefore difficult to acquire from donors. Eto's research team has found a solution to this problem by making an almost unlimited supply of megakaryocytes from iPS cells.

To produce platelets from megakaryocytes, engineers have constructed bioreactors that recapitulate blood flow. However, for regular patient care, more than 100 billion-order platelets are needed, and no bioreactor comes close to producing this amount.

"There has been lots of work on bioreactors, but they only used laminar flow. Nobody thought about turbulence," said Eto.

The original bioreactors made little effort to recreate blood flow. The next iteration added laminar flow, resulting in a great leap in the number of platelets, but still short for clinical purposes. To reach the numbers needed for patient therapy, the new study shows that besides laminar flow, incorporating turbulent flow into the bioreactors is key.

This realization came from microscopic observations of blood flow in mice. While the blood flow was mostly laminar, Eto's team found turbulence was present around the megakaryocytes.

To generate turbulence, they designed a new bioreactor that behaves like a French Press coffee maker, pushing the flow up and down.

The significance of turbulence was an unexpected finding, since too much turbulence can disrupt blood flow and ultimately be deadly. Eto explained that the turbulence in platelet generation only occurs immediately around the megakaryocytes.

"It's like a flight. Large turbulence is dangerous, but a little turbulence the plane can control. We show the turbulence is only small scale," he said.

Further study revealed that the turbulence stimulates three mediators: macrophage migration inhibitory factor, insulin growth factor binding protein 2, and nardilysin, all of which were previously unknown to have a crucial role in platelet generation.

The bioreactor also includes pillars to which the megakaryocytes attach. Without this attachment, the flow cannot force the shedding of platelets. Further experiments suggested that the first two mediators are crucial for the adhesion properties of the megakaryocytes, thus determining whether the cells attached to the pillars. On the other hand, experiments suggested that nardilysin primes the platelets to break free from the larger megakaryocytes.

Dr. Naoshi Sugimoto, a hematologist and member of the lab who contributed to the study said, "we can use the mediators to make a specialized culture to improve the performance of the bioreactor."

Indeed, while turbulence successfully enhanced the number of platelets shed from a megakaryocyte on average, there was still wide variability in the number of platelets from different megakaryocytes. The inclusion of these mediators, the lab hopes, will optimize the production from all megakaryocytes.

Finally, the platelets were found to behave normally in mouse and rabbits, an important final step before using the platelets in humans.

"Our goal is to produce platelets in the lab to replace human donors," said Eto.

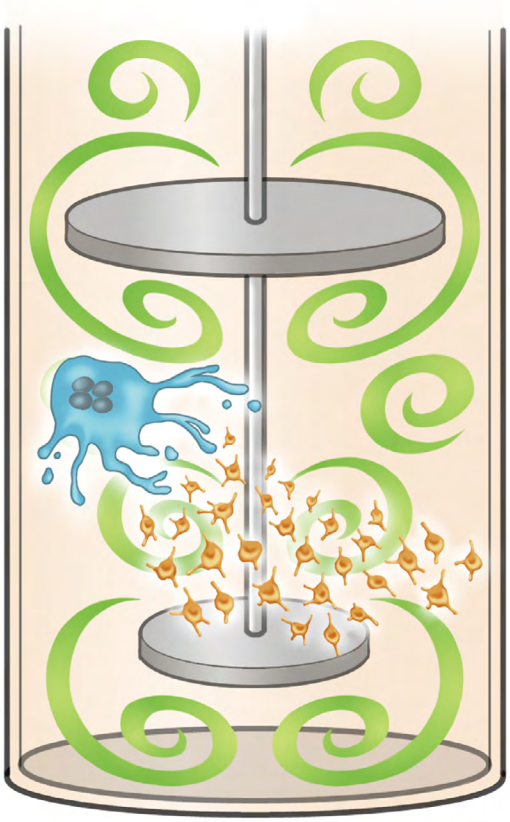


Illustration by Misaki Ouchida (CiRA)

By incorporating turbulence (green) into the bioreactor, researchers can generate a large enough number of platelets (orange) from megakaryocytes (blue) for patient therapy.

Reference

Ito Y, Nakamura S, Sugimoto N et al. (2018) Turbulence activates platelet biogenesis to enable clinical scale *ex vivo* production. *Cell* DOI:10.1016/j.cell.2018.06.011

One gene changes cell identity

The Okita Lab shows serum response factor (Srf) facilitates cell reprogramming into iPS cells by repressing the expression of genes responsible for cell identity.

Cells are defined by their function and shape. Skin cells are different from stomach cells which are different from spleen cells which are different from skeletal cells. Accordingly, each cell type expresses its own set of cell-identity genes, genes that CiRA Junior Associate Professor Keisuke Okita calls "roadblocks."

"The maintenance of cell identity is crucial for health, and its loss is associated with aging and cancer. Roadblocks are factors that maintain cell identity and block reprogramming," he said.

Okita and his CiRA colleague, Dr. Takashi Ikeda, both experts in reprogramming, considered if there are any universal factors that suppress roadblocks. In a new study, they and other CiRA members show that serum response factor (Srf) could be such a factor, as it compromises the identity of several types of mouse cells, including neural progenitor cells, hepatoblasts and uretic bud cells.

Srf responds to mechanical signals in the cell, like changes in cell shape, to activate the expression of other genes.

"In reprogramming, roadblocks are downregulated. We found that downregulating the β-actin gene, Actb, contributed to reprogramming regardless of the cell," said Ikeda.

β-actin is a fundamental molecule for cell morphology. Ikeda found that changes in Actb expression led to changes in Srf activation. Srf consequently bound to roadblock genes through its MADS-box domain, suppressing the expression of the roadblocks and thus compromising cell identity. This compromise made the cell susceptible to being reprogrammed to the pluripotent state, i.e. iPS cells.

The study further shows the nuclear effects of Srf. Roadblock genes were physically displaced from the interior of the nucleus to the periphery. Interestingly, this effect was exclusive; Srf did not show a propensity to displace genes responsible for pluripotency, which would also promote reprogramming.

Finally, Okita and Ikeda show that Srf activation could have pathological repercussions. Overexpressing Srf in mice led to inflammatory conditions such as colitis and metaplasia and dysplasia, which are symptoms associated with cancer. This is not a great surprise, since roadblock genes keep the cell identity, and a loss of which is associated with cancer.

Ikeda explained that Srf could be a common factor in diseases associated with cells behaving unstably.

"During early development, cells undergo many changes. But in the adult body these changes must stop so that each cell type carries its function. In many diseases, cell function is compromised. Srf misactivation could be a cause," he said.

Reference

Ikeda T, Hikichi T, Miura H et al. (2018) Srf destabilizes cellular identity by suppressing cell-type-specific gene expression programs. *Nature Communications*. 9(1):1387 DOI:10.1038/s41467-018-03748-1

Destabilized cells cause pancreatic cancer in mice

The Yamada Lab shows that briefly initiating reprogramming in cells with a cancer mutation is sufficient to trigger pancreatic cancer.

Among cancers, pancreatic cancer has the worst outcome, with only 20% of patients expected to survive one year after the diagnosis. Pancreatic cancer is also distinct in that mutations in the Kras gene can be found in more than 90% of cases, while no other mutation comes close to this frequency in other cancers.

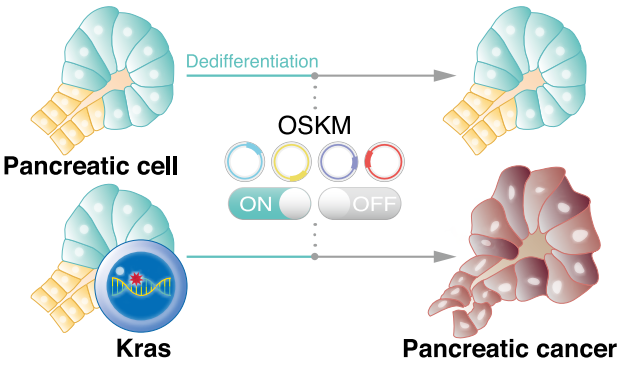
Yet mutations are not enough for the cancer development. University of Tokyo Professor Yasuhiro Yamada, who led the study while at CiRA, says that in many animal models there is "a substantial latency period for cancer development, indicating that additional events are required."

Yamada has been using iPS cell reprogramming technology to identify these additional events.

No genetic mutations are required for a cell to be reprogrammed to an iPS cell, but major epigenetic changes must occur. Epigenetics describe modifications to the gene that expose or conceal the gene to external signals. A crucial first step in reprogramming controlled by epigenetics is dedifferentiation, or the loss of cell identity. Interestingly, dedifferentiation is also frequently seen in cancers.

To study pancreatic cancer, Yamada and his colleagues developed mutant mice in which they reprogrammed pancreatic cells that express Kras mutation. The pancreas is made up of acinar and ductal cells. They found that by activating the reprogramming process transiently in acinar cells with Kras mutation resulted in pancreatic ductal adenocarcinoma, a type of pancreatic cancer.

Looking for a molecular explanation, the study found that the transient reprogramming lowered the acetylation of H3K27 on the enhancer genes responsible for stabilizing acinar cell identity. The result was lowered enhancer activity, which caused the acinar cells to dedifferentiate. Conversely, the cancer could be avoided by forcing the activity of the enhancers despite the transient reprogramming process.



Reprogramming pancreatic cells with a mutation in Kras gene promotes cancer in mice, suggesting dedifferentiation is a trigger for the cancer onset.

Finally, treating the mice with caerulein, a known inflammatory stimulant of the pancreas, also repressed the acinar cell enhancers and led to cancer development. Yamada wonders whether this finding could explain why pancreatic cancer returns in a large proportion of patients following surgery.

"We connected the repression of enhancers with inflammation," he said. "This is totally speculation, but if the operation causes inflammation, that may explain a part of recurrence of pancreatic cancer."

Reference

Shibata H, Komura S, Yamada Y et al. (2018) In vivo reprogramming drives Kras-induced cancer development. *Nature Communications* 9(1):2081 DOI: 10.1038/s41467-018-04449-5

Kidney cells for cell therapy made in the Lab

The Osafune Lab reports a new molecular signature that marks kidney progenitor cells during the differentiation of iPS cells.

Patients with severe kidney diseases have only two options for treatment. One is dialysis therapy, which can now be done at home but still requires two to three treatments a week with each taking several hours. The other is transplantation, which does not need lifelong treatment, but is available only to a small number of patients because of few donors. To compensate for the donor paucity, scientists have considered preparing and transplanting renal progenitor cells from iPS cells for cell therapy and kidney reconstruction.

However, one of the challenges when differentiating to renal progenitor cells from iPS cells is separating the desired cells from other cells that emerge in the production process.

"We can separate renal progenitor cells by detecting nuclear marker gene expression, but the cells are not suitable for clinical therapy because the cells have been genetically modified to express fluorescent reporter proteins that monitor the nuclear marker expression," says CiRA Professor Kenji Osafune.

Typically, processes that separate clinical-grade cells depend on antibodies that bind to surface antigens. The challenge for kidney cell therapies has been identifying which antigens represent renal progenitor cells.

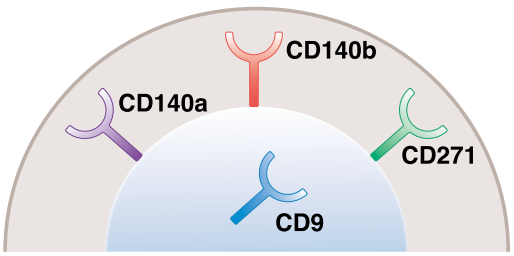
"We know that renal progenitor cells express two nuclear markers, the genes Osr1 and Six2. We looked at cells that expressed these two genes and then mapped their surface markers. We found four antigens were crucial for renal progenitor identity," says Osafune.

The four antigens are CD9, CD140a, CD140b, and CD271. Osafune's team found that the transplantation of cells which express CD140a, CD140b, and CD271, but not CD9 could ameliorate acute kidney injury in mice.

All four antigens are expressed in the embryo, but the expression of CD9 is thought to occur at the earliest stages, while the others are expressed as the embryonic kidneys form.

Osafune stressed that marking renal progenitor cells by their antigens is a big step toward new cell therapies for kidney diseases.

"The isolation of iPSC-derived renal progenitor cells without genetic modification may give a substantial advantage in future cell therapies and disease modeling using patient cells," he said.



The expression of 3 receptors and repression of a 4th marks renal progenitor cells.

Reference

Hoshina A, Kawamoto T, Sueta SI, et al. (2018) Development of new method to enrich human iPSC-derived renal progenitors using cell surface markers. *Scientific Reports* 8(1): 6375. DOI: 10.1038/s41598-018-24714-3

New drug candidates for an orphan disease

The Megumu Saito Lab reports a new iPS cell model that recapitulates the cellular profile of patients with Nakajo-Nishimura Syndrome to reveal new drug targets.

Nakajo-Nishimura Syndrome (NNS) is an incredibly rare disease, with only 30 cases reported, all of which in Japan. It is caused by a mutation in the PSMB8 gene. Patients show symptoms by infancy or early childhood, mostly through fever and other inflammation, but will eventually develop dystrophy in muscles and fat that causes them to emaciate away.

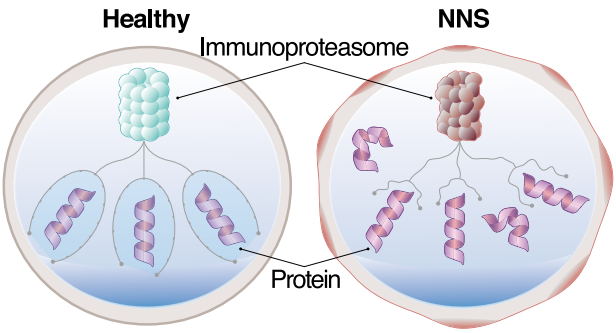
Work at CiRA has already led to a clinical trial on a drug for the rare disease fibrodysplasia ossificans progressiva. Pediatrician and CiRA Associate Professor Megumu Saito hopes to do the same for NNS.

"Corticosteroids are ineffective on lipodystrophy, and most patients die as a result of respiratory or cardiac failure. Because there are few patients, it is hard to build good models. We are making iPS cells and differentiating them into the disease cells," he said.

The PSMB8 mutation in NNS causes dysfunction in the immunoproteasome. The immunoproteasome is responsible for degrading proteins.

Because CiRA is a hub for iPS cell research, Saito's lab had access to 3 NNS patients from whom it prepared iPS cells. The study found that the immunoproteasome in monocytes derived from patient iPS cells had constitutively low activity, which could explain the autoimmune symptoms seen in patients. The accumulation of unwanted proteins caused stress on the cells, triggering an immune reaction and leaving the cells in what Saito calls a "primed state."

"Reactive oxygen species (ROS) were increased in patient iPS cell-monocytes. The primed state coincides with the excessive ROS production," he said.



NNS patient-iPS cell models a dysfunctional immunoproteasome that allows proteins to accumulate, causing stress on the cells.

The excess ROS in the cell was found to activate signaling pathways involving the molecules MAPK and JAK/STAT, which are associated with the secretion of factors that promote inflammation. Encouragingly, applying antioxidant therapy to the monocytes could ameliorate this proinflammatory effect.

Saito is excited that having confirmed this iPS cell model recapitulates the disease symptoms in monocytes, the same iPS cells could be used to produce other inflicted cell types, such as muscle and fat cells, for new drugs to treat NNS.

"Progressive lipomuscular atrophy is an important phenotype that affects the quality of life of NNS patients," he said. "We plan to use our iPS cells to screen for compounds that can treat these symptoms."

Reference

Honda-Ozaki F, Terashima M, Niwa A, et al. (2018) Pluripotent stem cell model of Nakajo-Nishimura syndrome untangles proinflammatory pathways mediated by oxidative stress. *Stem Cell Reports* DOI: 10.1016/j.stemcr.2018.04.004

Artificial cells to battle cancer

The Kaneko Lab uses iPS cell technology to create an artificial type of immune cell that acts against cancer cells.

The immune system is designed to detect and kill cancer cells by recognizing signature peptides on the cancer cell surface. However, cancer has evolved to evade immune cells. In response, cancer researchers are looking for ways that strengthen the detection capability.

According to CiRA Associate Professor Shin Kaneko, among the many types of immune cells, "CD4 T helper cells are effective at preventing the escape of immune surveillance by inducing a polyclonal immune response called antigen spreading." Antigen spreading expands the types of peptides on the cancer cell that immune cells recognize.

Once they recognize the cancer peptide, CD4 T helper cells will activate cytotoxic T lymphocytes, the cells that are ultimately responsible for killing the cancer cells. "CD4 T helper cells activate dendritic cells to induce cytotoxic T lymphocytes that act on the cancer peptide," continued Kaneko.

In previous works, Kaneko's research team demonstrated that by using iPS cell reprogramming technology, they could "rejuvenate" cytotoxic T lymphocytes so that they more effectively kill the cancer. The rejuvenation of immune cells involves reprogramming them into iPS cells and then turning them back to their original form. In the new study, his team applied this strategy to CD4 T helper cells that respond to a leukemia peptide, b3a2. However, differentiation of the iPS cells unexpectedly produced cells more akin to innate lymphoid cells, not rejuvenated CD4 T helper cells.

"That wasn't our goal. Innate lymphoid cells are a new type of cell. They don't have antigen specificity and have very general helper function," said Kaneko. In addition, they have a short lifespan and are localized, whereas CD4 helper T cells have a long lifespan and operate throughout the body.

However, his team showed that manipulating these innate lymphoid cells could convert them to express CD4 T helper cell activity.

"If we force CD4 gene expression and keep the original TCR expression, we can get enough signal for helper activity in an antigen-specific manner," Kaneko added. Keeping the original TCR expression is crucial for the immune cells to respond to the cancer antigen and not to other cells in the body.

To test the effectiveness of their "CD4 T helper-like cells," the scientists used the rejuvenated innate lymphoid cells with forced CD4 expression to prime cytotoxic T lymphocytes. The primed cytotoxic T lymphocytes significantly inhibited tumour growth when transplanted into mice with leukemia.

While Kaneko calls his cells "very artificial," he believes they are just another example of how iPS cell reprogramming technology could be used to fight cancer.

"It is a way to give antigen specificity to innate lymphoid cells," he said.

Reference

Ueda N, Uemura Y, Zhang R et al. (2018) Generation of TCR-expressing innate lymphoid-like helper cells that induce cytotoxic T cell-mediated anti-leukemic cell response. *Stem Cell Reports* DOI: 10.1016/j.stemcr.2018.04.025

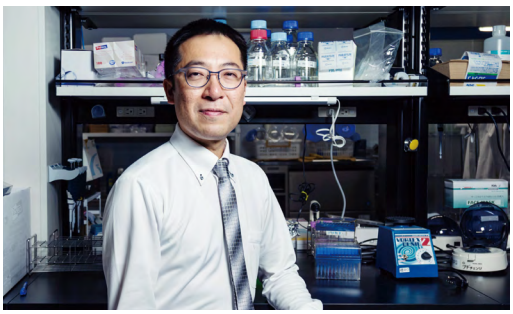
Greetings from the
Hidetoshi Sakurai Lab

Dept. of Clinical Application

Our lab is using patient iPS cells to study myopathies, especially muscular dystrophies, and ways to treat the disease. Muscular dystrophies come in many forms, but they all share the common feature of a loss of muscle mass. Depending on the severity and muscles afflicted, a patient will progressively weaken, eventually losing the ability to do most basic movements such as swallow and breath.

In most cases, the disease is the result of a genetic mutation. iPS cells therefore make for an attractive cellular model, because we can study the effects of the mutation on the muscle cell using patient cells. A large amount of our attention has been towards Duchenne muscular dystrophy, probably the best known of these diseases and was first described in medical chronicles in the 1860s. Patients suffer from mutations in the dystrophin gene, which results in defective dystrophin protein and leaves the muscle cells fragile and easily damaged. In general, the larger the deletion of the gene, the more severe the symptoms. Becker muscular dystrophy is also caused by mutations in the dystrophin gene, but patients show milder symptoms later in life. While all muscles are susceptible to atrophy in these two dystrophies, in other dystrophies only muscles in specific areas are affected. For example, in facioscapulohumeral muscular dystrophy, only the face, shoulder blades and upper arms are affected. Using patient iPS cells, we aim to understand the relationships between mutations and the disease symptoms.

Along with studying the disease development, we are looking at ways to combat the disease, namely through cell therapies and drug discovery. Cell therapies commonly involve transplanting cells into the body to replace the degenerated tissue. Regenerative medicine using iPS cells has already been done for the eye and will soon start for the heart (see p3). Muscle brings a special challenge to regenerative medicine, however, because unlike other organs it is not isolated to just one region of the body. Thus, our laboratory has a distinctive challenge. Besides studying the pathogenesis of myopathies, we are also investigating best cell types for a transplantation and ways to deliver the transplantation including strategic locations in the body for the injection so that the cells disperse to all afflicted muscles.



Hidetoshi Sakurai in open lab

In addition, we are researching alternative and complementary methods to cell transplantation. Drug discovery is one obvious example. CiRA is fortunate to have partnerships with many pharmaceutical companies who provide their infrastructure for drug discovery. The lab has benefited tremendously from these relationships, and is collaborating regularly to identify compounds that can retard or cease the muscle loss. Furthermore, muscular dystrophy degenerates muscle, but the symptoms can quickly worsen due to atrophy, which is the result of the patient reducing movement. Thus, we are considering how rehabilitation improves recovery following cell transplantation therapies.

Overall, our lab seeks scientists with diverse perspectives for the solution of muscular dystrophy.

Monkeying with clones

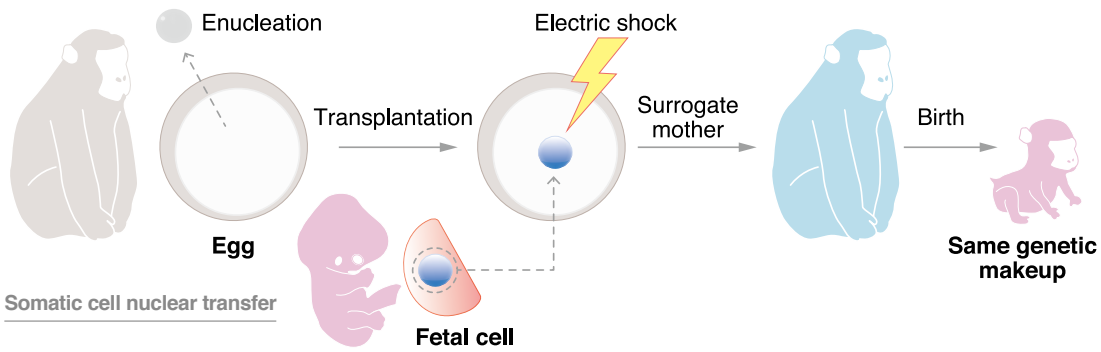
by Assistant Professor Tsutomu Sawai, Uehiro Research Division for iPS Cell Ethics

In February, the journal *Cell* published a paper about the first monkey clone. While other animals have been cloned in the past, including Dolly the Sheep in 1997, none are as evolutionary close to humans as monkeys. The researchers used somatic cell nuclear transfer, the method reported by Dr. John Gurdon in 1962 to clone a frog and led him to share the Nobel Prize with Shinya Yamanaka in 2012. Although the cloning rate remains frustratingly low, the ability to clone monkeys could lead to advanced animal models for the study of human diseases.

Of course, animal cloning is wrought with controversy, and the ability to clone monkeys suggests the ability to clone humans is not too far away. Many people have already looked at cloning as a way to immortalize pets. People may now start sensing an opportunity to clone humans, giving dystopic hope that the preservation of cells could reanimate a tragically lost child. It also would give possibility to someone being cloned unwittingly should their cells be preserved but used in ways without their consent.

Somatic cell nuclear transfer involves the removal of the nucleus of a cell and its insertion into an enucleated egg. The egg provides an environment in which the nucleus is reprogrammed so that the egg can develop into a functional living organism. Interestingly, the research group found that the quality of the somatic cell nuclear transfer depended on the age of the cells from which the nuclei were taken. Nuclei from adult cells led to monkey clones with severe abnormalities, whereas nuclei from fetal cells resulted in healthy clones. However, it should not be assumed that just because monkey clones are possible, we are on the cusp of human clones. It took 30 years to go from frog clones to sheep clones, and another 20 years to reach monkey. Moreover, laws throughout the world strictly prohibit cloning experiments with human cells, and the unestablished risks to both the mother carrying the cloned fetus and the fetus itself only add more weight to the arguments against these experiments.

Nevertheless, the accomplishment reported in Cell has important implications. Monkey research is permitted in Japan if the researcher can establish that no other viable experiments are available. The risks to the monkeys– both the offspring and mother – in these cloning experiments are unknown. Therefore, even these experiments must overcome high ethical standards before receiving permission. Policymakers have an interesting challenge before them.



A volunteer firefighter at CiRA

Assistant Professor Akira Watanabe has an essential role at CiRA. His work includes quantitatively evaluating the safety of clinical iPS cells including those already being used in patient therapies. His research accomplishments have been recognized by his peers, but in June he took home an unusual prize for his contributions outside the lab. Watanabe shared with his team second prize at the Kyoto City Volunteer Fire Corps Competition on June 3. Kyoto City has 217 divisions Volunteer Fire Corps that together constitute nearly 2000 members.

The competition measured the team's performance at fundamental tasks, such as the time it takes to deploy a fire hose. "We trained every day for two months without holidays," he said, "1-2 hours on weekdays and 3-5 hours on weekends."

Volunteers like Watanabe do not get to participate in the photogenic work of firefighting, such as extinguishing fires and rescuing people from the flames. Instead, their work is supportive, and includes basic but important tasks like raising barricades to keep the public and traffic out of emergency areas.

However, in major emergencies such as the Great Hanshin-Awaji Earthquake of 1995, volunteers will be expected to do much more, including first aid

Akira Watanabe

and even rescue people from homes. Watanabe has never been called in these extraordinary situations even though he was speaking just days after an earthquake whose epicenter was a mere 15 km from CiRA.

Watanabe's interest in the volunteer fire corps has some influence from family. "My brother is a firefighter volunteer in Niigata," Watanabe's hometown, he said. His real reason, though, is much more charitable. Many Japanese neighbourhoods including his are disproportionately inhabited by the elderly, and he wants to do his part in helping them.

"I like it better than research," he said half-jokingly. "When I help someone, he or she will be happy. But in research, when we work so hard…" Watanabe finished his sentence with a chuckle.

Science Writing

In May, CiRA sent one of its staff to the Santa Fe Science Writing Workshop. The annual workshop invites approximately 50 people to study under the mentorship of writers and editors with experience at leading U.S. magazines and newspapers, including the New York Times, Washington Post, and Wired. Participants learnt about the basics of journalistic writing, such as the lede, nut graf, and kicker. They were also challenged to write about lectures given at the Santa Fe Institute and the art of pitches. On the last day, they threw their pitches to the instructors.

Congratulations to new faculty in Hong Kong

CiRA is proud to announce that Dr. Becki Yi Kuang has ended her post-doctorate here to become an Assistant Professor this month at the Hong Kong University of Science and Technology where she will run her own laboratory.

Moving countries is natural for Becki, who is from China and came to CiRA from the Brandeis University in Boston after earning her Ph.D.

“I was looking for post-doc positions in the U.S at first. The economy was not great at the time, and it was hard to find a job. So I aimed for Asia or Europe. The advantage is that the change of continent allowed me to apply for the HFSP fellowship,” which she won, she said.

Her Ph.D. advisor, Professor Bing Xu, encouraged her to leave the field of chemistry, explaining that her next job would be the last chance to learn new techniques in the laboratory. That was when he introduced her to CiRA Professor Hirohide Saito.

“Really fortunate to work in [Saito’s] group,” said Becki. “His background is quite broad. We have really good communication. We had two patents and one paper in three years.”

Saito agrees. “She is very talented and very hard working. She has mastered many different topics,” he said.

Being hired by Hong Kong was a combination of both luck and preparation. The newly formed Department of Chemical and Biological Engineering with its new dean, Professor Hsing I-Ming, was aggressively hiring faculty.

Becki did what all applicants did and submitted her application online. But the next day she emailed Prof. Hsing directly and included her application. Job seekers, she said, must take every little effort that gives them an edge.

“We need to be more proactive, because job hunting is hard,” she said.

Even before her arrival, her new colleagues had been contacting her about possible collaborations to benefit from her knowledge on iPS cells. Becki is somewhat incredulous of her recognition as an iPS cell expert and still vividly recalls a stem cell conference shortly after joining CiRA at which one of the attendees found her presence perplexing.

“Why are you here? We’ve been talking all morning about stem cells and I realized you are not a stem cell person at all,” she was told., Becki recalled.

Starting a new lab will bring many new challenges. One of which will be recruitment. Becki is concerned that talented foreign scientists will be intimidated by Hong Kong.

“People see the movies and think, ‘They all speak Cantonese. They all know martial arts,” she said.

There is one thing she does do and wants all prospective researchers to know.

“I’m hiring,” she said.

Becki Yi Kuang (right) with Professors Hirohide Saito (left) and I-Ming Hsing at CiRA last June.

The Temples and Shrines of Kyoto

Eikan-dō Zenrin-ji

The first temple at the southern end of Philosopher's Walk, Eikan-dō (or Zenrin-ji), is far from the biggest temple in Kyoto, but few temples in the city make available as much space publically. That space diffuses the crowd, making it seem less occupied by tourists than it really is. The temple sits on the eastern hills of the city, and a short ascending stairway provides a view of the whole city, albeit not the best but one that does include CiRA.

The temple was founded in 853 for the purpose of building a religious school. The temple was named Zenrin-ji by Emperor Seiwa in 863, but renamed to Eikan-dō in recognition of the eponymous monk's contribution and charity to the poor in the 11th Century. Along with his teachings, Eikan had a hospital built on the grounds.

Friendly faces at Zenri-ji

Best year yet

The iPS Cell Research Fund is an invaluable resource for CiRA. Entirely dependent on private donations, the fund provides money for a number of programs that extend the reach of iPS cell research including internships that train future scientists, both domestic and overseas, and international conferences that bring the best minds in the field to Kyoto.

With the fiscal year ending March 31, the Fund is excited to announce that having collected 3.8 billion yen (approximately USD 41 million), it has had its most successful year yet.

The reason for the increase is simply the number of donors, with no significant increase in the donation per person. Some special events like the charity concert with violinist Ray Chen can explain some of the increase (see Vol. 14). Also, CiRA Director Shinya Yamanaka appeared on television and in other media at higher frequency than previous years.

More than 90% of CiRA staff is hired on fix-termed contracts, meaning independent of performance, employees must leave the institute conditional to research funding. Following the consistent performance of the iPS Cell Research Fund, CiRA has decided to remove this restriction for some of its employees.

"We want to hire and keep the best people at CiRA," said Yamanaka.

The science has stopped.

World Cup! One month of games.

Ganbare Nippon!

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