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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 7023

Cell therapies in Japan

CiRA researchers investigate stem cell therapies at private clinics in Japan

In the late autumn of 2014, Japan enacted a new law, the Act on the Safety of Regenerative Medicine (ASRM), which changed the regulation of cell therapies. Before this change, private clinics in Japan operated cell therapies with little regulation. In fact, CiRA Associate Prof. Misao Fujita states in a new paper describing the implications of ASRM that before the enactment of this law "there were no rules in place for performing cell therapies in private practice in Japan." The Japanese government had little data about the number of clinics conducting cell therapies and what types of cell therapies were being offered.

To evaluate the effects of ASRM reliably requires information on the cell therapy environment prior to its passing. Accordingly, Fujita led an investigation by the Uehiro Research Division for iPS Cell Ethics at CiRA of private clinics in Japan that offered cell therapies as of May 2014. The study identified 74 clinics offering 247 types of cell therapies that covered a wide range of disease and disorders. Somewhat unexpectedly, the vast majority of cell therapies were intended to treat ailments that had alternative therapies available. "This is an important observation," says Fujita. "The Helsinki Declaration and ISSCR [International Society for Stem Cell Research] only allows unproven cell therapies in extraordinary circumstances to patients with no effective alternatives, but never in cases where alternatives exist."

One purpose of ASRM is to gain control of those private clinics that provide cell therapies in order to prevent exploitation and even tragedy. In 2010, a medical tourist from Korea died of pulmonary embolism following stem cell therapy from a Japanese private clinic. Moreover, because these therapies are not entitled to reimbursement from Japan's national health insurance, they can put exorbitant financial burden on the patients. While ASRM may be imperfect, one of the reasons for the imperfections is a lack of knowledge about the cell therapies available. Fujita hopes that new data acquired from the implementation of ASRM will lead to better policies. "I expect we will see changes to ASRM after a few years," she said.

In a separate paper published by *Cell Stem Cell*, the Uehiro Research Division and collaborators explain the first civil lawsuit brought by a patient against a private clinic in Japan under ASRM. The courts concluded that the doctor did not adequately consult the patient on the risks of the stem cell therapy and may have gone so far as to dismiss the risks despite the patient's concerns. The authors suggest that medical societies as a whole, and in particular the Japanese Society for Regenerative Medicine, must be more vigilant at disseminating information about questionable practices. Fujita, who is also an author on this paper remarks, "We hope that this case will lead to more responsibility by the medical field against reckless stem cell clinics in Japan."

Reference

Fujita M, Hatta T, Ozeki R et al. (2015)
The current status of clinics providing private practice cell therapy in Japan. *Regenerative Medicine,* doi:10.2217/rme.15.64

Ikka T, Fujita M, Yashiro Y et al. (2015)
Recent court ruling in Japan exemplifies another layer of regulation for regenerative therapy. *Cell Stem Cell* 17: 507-508.

Inflammation is associated with bone growth

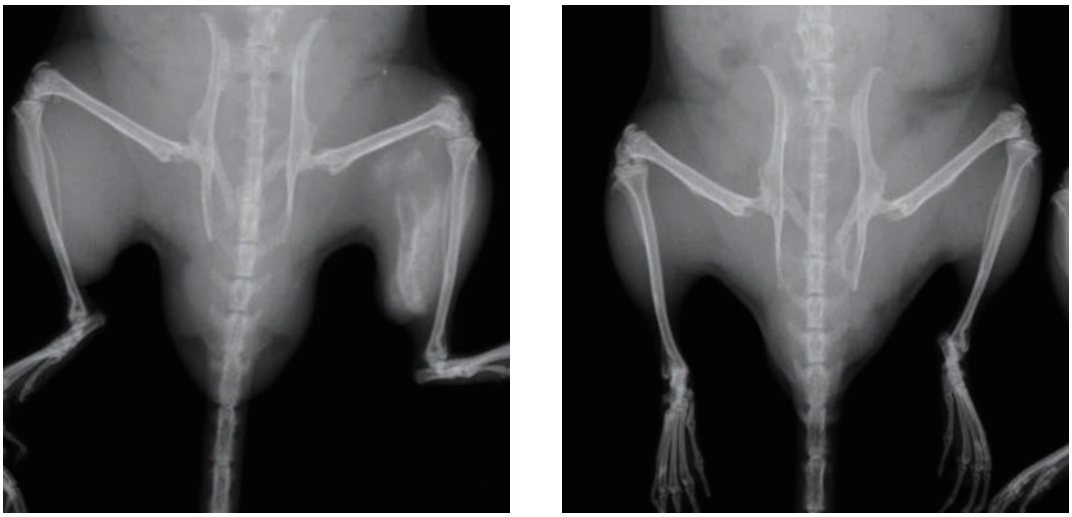
(Left to right) Junya Toguchida, Kyosuke Hino (first author) and Makoto Ikeya at CiRA press conference.

New results from the Toguchida lab show an unexpected link between inflammation and uncontrolled bone growth

Fibrodysplasia Ossificans Progressiva (FOP) is a rare, but devastating disease where bone is grown within soft tissue. Accordingly, it is also known as Stone Man Syndrome, since the patient's body ossifies into a statue-like state. It is a genetic disease, but patients normally do not show symptoms until their school-aged years. Normally, inflammation or trauma triggers the disease. This complicates study of FOP because the trauma associated with acquiring patient cells could stimulate the irregular bone growth. For the same reason, surgery that removes excessive bone is not an option, because it too risks more bone growth in the post-operation healing period.

At the molecular level, the FOP mutation is thought to cause irregular function of bone morphogenetic proteins (BMP). BMP are what stimulate bone healing after a fracture or break. In the case of FOP, however, hyperactive BMP activity is commonly seen, which is why scientists are seeking drugs that can suppress BMP signaling. In particular, FOP patients hold a mutation in the BMP receptor, ACVR1. How this mutation leads to dysfunctional BMP signaling remains unclear. "There are two popular theories," explains CiRA Associate Prof. Makoto Ikeya, one of the project leaders of the study. "In one, BMP signaling is always active. In the other, BMP signaling is abnormally strong when activated."

Although most researchers have focused their attention on factors associated with early stages of the BMP signaling cascade, CiRA researchers in Prof. Junya Toguchida's lab took advantage of the large number of patient iPS cells they could generate to consider how molecules primarily



FOP-iPS cells and resFOP-iPS cells were transplanted into the right and left legs of mice, respectively. Stimulation with Activin-A resulted in excessive bone growth by the FOP-iPS cells (left mouse, right leg), but not by resFOP-iPS cells (left mouse, left leg). No Activin-A stimulation resulted in no excessive bone growth by either cell type (right mouse).

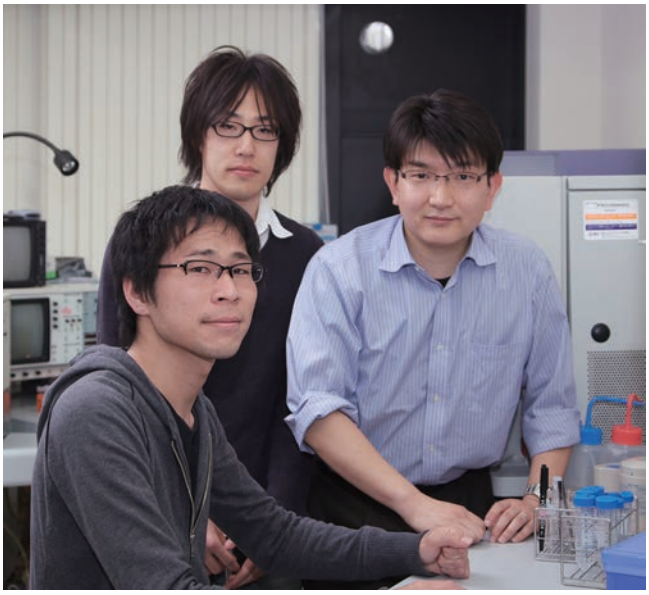
involved in immune responses could also have a role. “Because patients show FOP symptoms after trauma or inflammation, we thought this would be a good strategy,” explains Ikeya. They therefore examined the effects of Activin-A, a molecule better known for its transduction of TGF-β signaling.

The researchers made two types of FOP-iPS cells, those that retained the ACVR1 mutation (FOP-iPS cells) and those that had the mutation corrected (resFOP-iPS cells) and transplanted them into mice. Activin-A stimulation caused excessive BMP activity and increased the expression of several factors associated with chondrogenesis only in the transplanted FOP-iPS cells, resulting in excessive bone growth. Comparatively, no excessive bone growth was seen in the absence of Activin-A stimulation. Importantly, the addition of Activin-A inhibitors was found to have an ameliorating effect, pointing towards a new target for FOP drug discovery. However, TGF-β signaling is essential for cartilage, which suggests that Activin-A could have undesirable side effects. Toguchida therefore believes other drug targets should be the goal. “We want to find a drug that acts somewhere downstream of Activin-A but before bone formation,” he said. The group expects that their model will be advantageous for finding new drug candidates.

Reference

Hino K, Ikeya M, Horigome K et al. (2015) Neofunction of ACVR1 in fibrodysplasia ossificans progressiva. *PNAS* 112: 15438-15443.

New tissue engineering to treat heart disease



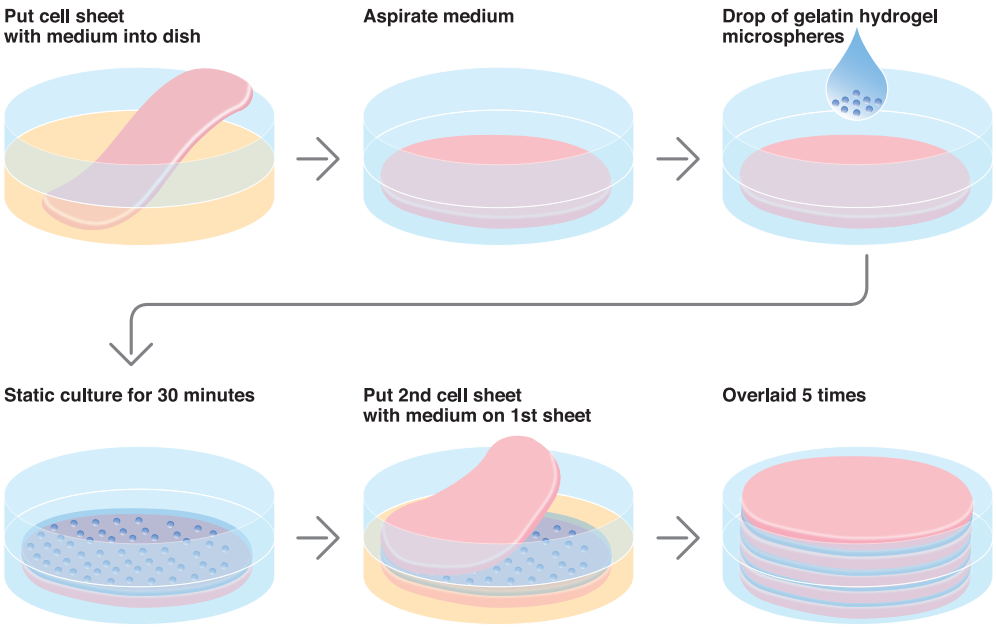
Jun K. Yamashita (right) and colleagues.

CiRA researchers show the use of biodegradable microspheres simplifies cell preparation for therapies against heart disease

In cell therapies for heart disease, heart cells are transplanted as cell sheets that are laid over the heart. To minimize both the preparation time of the heart cells and the surgery time, several sheets are stacked onto each other and transplanted at the same time. However, in this scenario, the sheets in the inner stacks are deprived of oxygen and other nutrients, thus their cells will often die before or shortly after transplantation compromising the therapy. A possible solution to this problem would be to insert tiny pillars that create enough space between sheets so that all would have access to the surrounding environment and sustain cell survival. Prof. Jun K. Yamashita and his lab have found that gelatin hydrogel microspheres, an invention of Prof. Yasuhiko Tabata at Kyoto University, could act as these pillars and that transplanting stacks of cell sheets with these microspheres between significantly increased the survival of mice with infarcted heart.

The method is remarkably easy and iterative, as stacks of any number of sheets is possible. A single sheet is first cultured in a petri dish and then layered with the microspheres. This process is repeated until the desired number of sheets is stacked. Further, stacks can be stacked onto other stacks, allowing for even faster preparation of the cell therapy. This approach is exactly the one the Yamashita lab took, as it made three separate 5-sheet stacks that together made one stack (15 sheets) about 1 mm thick. “This allows us to deliver a large number of cells than otherwise,” explained Yamashita.

An important component of the stacks for maximal therapeutic effect is to have a mix of necessary heart cells, including cardiomyocytes,



Schematic of sheet stacking. Sheets are layered individually. Before the next sheet is introduced, the medium is aspirated and gelatin hydrogel microspheres are added. This process was repeated until 5 sheets were stacked. Large stacks could be made by mixing smaller stacks and applying the same strategy.

endothelial cells and vascular mural cells. Getting the right proportion of cell types has been a major focus of the Yamashita lab along with the delivery of these cells. "We are still improving our system, but the ratios we get are effective in mouse models," says Yamashita. Despite the separation between sheets caused by the microspheres, the sheets in a given stack showed good electro-coupling with each other. Further, the researchers confirmed months after the transplantation that the microspheres had vanished and that the grafts had induced neovascularization and reorganization into mature cardiac tissue.

As mice are relatively small animals, the number of cells needed for the transplantation is dwarfed by the number that will be required in humans, but there is reason to believe that the same system will apply. "We have already made these stacks using human heart cells and found better survival in petri dishes," explains Yamashita, "but we have yet to transplant the cells into larger animals for confirmation."

The transplantation of cell sheets is used for organs besides the heart, such as the liver or kidneys, and the same problem of cell death in the inner layers of stacked sheets exists. For this reason Yamashita is eager to share his technique with other researchers. "My lab studies the heart, but there is no reason the same method cannot be used to study other organs," he says.

Reference

Matsuo T, Masumoto H, Tajima S et al. (2015) Efficient long-term survival of cell grafts after myocardial infarction with thick viable cardiac tissue entirely from pluripotent stem cells. *Scientific Reports* 5: 16842.

Greetings from the
Haruhisa Inoue Lab

Dept. of Cell Growth and Differentiation

The greatest risk factor for many neuro-degenerative diseases is age. This makes it very difficult to study the disease development, since by the time a patient is diagnosed the disease will have already progressed to its late stages. Animal models have provided some important clues on the pathogenesis, but they fail to comprehensively recapitulate the disease, which may explain why so many promising drug compounds inevitably prove to be false positives. For these reasons, there is great excitement surrounding iPS cells. Using cell reprogramming science, we can literally take somatic cells from the patient, reprogram them into iPS cells and then using the proper culturing conditions differentiate them into neurons and watch them degenerate as they mature. Based on this ability, we hope to identify key early-stage targets that will help identify new therapeutics.

Our lab focuses on neuro-degenerative diseases, like Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Interestingly, over 90% of cases for these diseases are sporadic, meaning they show no genetic cause. Consequently, although these patients may be diagnosed with the same disease, there is good reason to think that how the disease develops varies between patients, which may help explain why different patients respond differently to a given experimental treatment. iPS cells are expected to provide a way that identifies which patients are most likely to respond positively, which would significantly lower drug and other health costs.

Accordingly, we are interested in how AD, ALS and similar diseases develop and finding drug candidates for retarding or reversing this development. The scope of our research requires us to not only investigate these diseases, but to also understand how neurons develop and how associating cell types, such as microglia and astrocytes, interact with neurons, since there is evidence that dysfunctional behavior in these cells causes the pathology in some cases. We are also partnering with several pharmaceutical companies, as Japan is heavily invested in neuro-degenerative disease therapeutics, since it is anticipated that the number of patients will intensify with the nation's aging population.

Haruhisa Inoue

Gene editing the human embryo

by Associate Prof. Misao Fujita, Uehiro Research Division for iPS Cell Ethics

In the previous newsletter, I described some of the special ethical issues regarding the genome editing of human embryos, namely the use of human embryos for research and the potential of creating living human beings from edited embryos. In this essay, I would like to delve deeper into this second consideration.

The idea of genome edited embryos being nurtured to birth is fraught with risk, since the technology is far from being established as safe. Currently, it is impossible to predict what effects genomic changes to the embryo will have on health. Further, who will have authority for permitting these changes and who will be responsible should unforeseen effects occur?

However, there is reason to believe that with proper development in the technology, genome editing of the embryo can be an effective treatment for genetic diseases that exist before birth, literally giving a life that would not be given otherwise. At the same time, as these methods become safer and cheaper, there will undoubtedly be pressure on parents to have the embryo modified before birth in the case a deleterious mutation is identified. There is also reason to worry that for children who have not had their genes edited, they risk being marginalized since society may view them as people who have chosen their own burden.

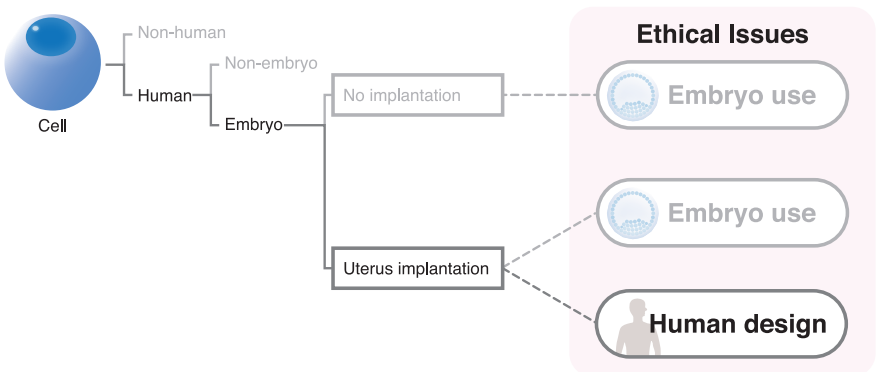
Another concern often considered in these discussions is designer babies, as genome editing of the embryo allows for one to choose skin color, eye color, and pretty much anything else that is inscribed in our genetic code. It might even be possible to eventually design one's talent or personality. Moreover, how specific can we be? Will we be designing children with specific muscle development explicitly to win Olympic medals or, even more dystopic, maybe wars? How far can this technology go and how far will we let it?

Finally, one major difference about genome editing the embryo compared with other cells in the body is the inter-generational effect of the change. Changing the genome of the embryo means that these changes will be passed to the offspring. Thus, any unexpected effects will be difficult to remove from the population.

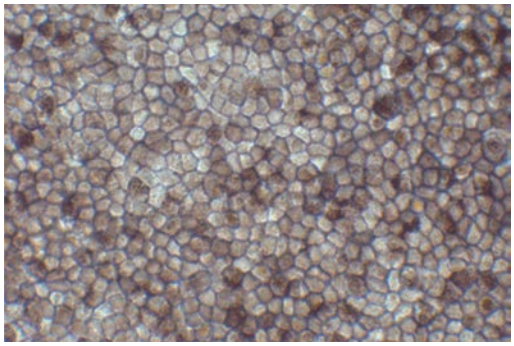
This past Dec. 3rd, several academies and societies declared current genome editing of embryos that can be returned to the uterus and nurtured to birth as irresponsible. However, as this technology advances, these same concerns will emerge again.

(The second of a two-part series)

Ethical issues associated with gene editing



Positive results on iPS cell clinical research



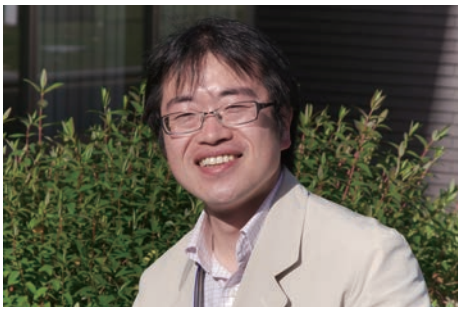
iPSC-derived retinal pigment epithelium cell sheet.
(Photo from RIKEN Center for Developmental Biology.)

Last autumn, Dr. Masayo Takahashi of the Riken Center of Developmental Biology (CDB) gave the latest report on the condition of the first patient to have ever received a transplant of cells derived from iPS cells. The patient, who suffers from age-related macular degeneration (AMD), had her own skins cells reprogrammed into iPS cells, which were then differentiated into retinal cells and transplanted back into her eyes. At a recent press conference about the surgery, the Japan News on Oct. 2 quotes a spokesperson of the project as having said, "As the first clinical study of its kind, with the main aim of confirming the safety of the patient, this can be deemed a good result."

While the patient's eyesight was reported to have stabilized, the quote alludes to the main purpose of the trial, which is not to cure the patient but rather to demonstrate the safety of iPS cell-based therapies. Seeing that this was the first operation of its kind, the surgery is establishing criteria for satisfactory safety of iPS cells.

"All kinds of cell therapies evaluate the integrity of the cells," explains CiRA Assistant Prof. Akira Watanabe of the Shinya Yamanaka lab who was responsible for evaluating the quality of the iPS cells used for the AMD surgery. "The reference is cancer cells. So if we find any oncogenic mutations in the iPS cells that are also present in cancer cells, we deem the cells unsafe." In the case of the AMD patient, the cells passed all the requisite safeguards, but since this is only one patient for one specific disease, the best criteria for evaluating the quality of iPS cells is an ongoing study.

Now that the cells have been transplanted, CiRA has essentially no direct involvement in the evaluation of the therapy, since the patient's care is entirely the responsibility of the CDB and the associated hospital. Nevertheless, CiRA is heavily invested in the outcome and was very excited to see the patient's recovery progressing favorably. The public too is carefully watching, since a successful operation would be the prototype for an entirely new type of cell therapy – iPS cell-based therapy. However, the standards for success are different, since scientists will be enthusiastic about the results so long as the cell therapy is safe even if the AMD is not ameliorated, whereas the public is expecting much more and may be disappointed anything short of healing. Moreover, now that the cells are inside the patient, a failed outcome could be the result of numerous causes besides the iPS cells. For example, tumors could still emerge but be the result of the patient's genetic background or of contaminating undifferentiated cells. Once the cells are inside the patient, "no one knows which part is the failure," said Watanabe.



Akira Watanabe

Dr. James Watson visits CiRA

James Watson with Peter Karagiannis of CiRA.

CiRA is frequently humbled by the list of notable people who visit. These visitors include not only Nobel laureates, but also a prime minister and royalty. Despite these famous names, it is arguable that CiRA's most legendary guest, at least in terms of science, only visited last October, as CiRA was honored to welcome Dr. James Watson. Watson was given a tour of the facilities, which included the opportunity to see fibroblasts that had been differentiated into functional cardiomyocytes via iPS cells. Along with touring CiRA, Watson shared many stories with his two hosts, Profs. Shinya Yamanaka and Jun Takahashi. Especially, he spoke of his time at Cold Springs Harbor Laboratory, citing the Cold Spring Harbor Courses as the biggest contribution the institute has made despite the exceptional science produced there. Conversation also veered to the contributions Francis Crick made to England winning the war and his belief that Jennifer Doudna and Emmanuelle Charpentier should soon win the Nobel Prize for their work on CRISPR/Cas9.

"CiRA is very lucky to welcome so many esteemed guests. But everyone at our institute has had their research influenced in some way by Watson. It was a true privilege to have him visit," said Yamanaka.

Genome editing conference

CiRA Associate Prof. Knut Woltjen teamed with Prof. Junji Takeda of Osaka University to organize the Conference on Transposition and Genome Engineering (TGE), 2015, this past November in Nara, marking only the third time the biennial event was held outside the United States. TGE is intentionally kept small, with just over 100 participants. "The opportunity for interaction is one reason I really like this event and wanted to bring it to Japan," said Woltjen. TGE is not sponsored by any society, but is instead planned by a cooperative of dedicated scientists who develop and share new technologies. "The field is changing so quickly," Woltjen said. "Last time TGE was dominated by transposons, but this year there are fewer discussions on the topic." He added that while there was clear excitement in 2013 over a then relatively new genome technology, CRISPR/Cas9, that previous meeting focused mainly on TALE nucleases. Indicating the rapid change in the field, this year Woltjen invited Prof. Emmanuelle Charpentier, co-discoverer of Cas9 gene editing applications, as a plenary speaker in her first visit to Japan. Several of the invited speakers also took advantage to give talks at CiRA, including Profs. Keith Joung of Harvard University, William Skarnes of the Sanger Institute, and Bruce Conklin of the Gladstone Institutes.

T-CiRA labs officially open

Earlier this year, CiRA announced an agreement to form T-CiRA, a grand collaboration with Takeda Pharmaceutical Company Limited that is easily the largest partnership the institute has made with a pharmaceutical company (see CiRA Reporter, July 2015, Vol 3). T-CiRA had its opening ceremony on Dec. 15 at the Shonan Research Center of Takeda, 50 km south of Tokyo, where all T-CiRA projects will be conducted. Over 50 media members attended the press conference. There, CiRA Director, Prof. Shinya Yamanaka introduced the first six labs to operate at T-CiRA, all of which will be run by CiRA faculty: Drs. Makoto Ikeya, Haruhisa Inoue, Shin Kaneko, Kenji Osafune, Hidetoshi Sakurai and Yoshinori Yoshida. T-CiRA is one response to CiRA's vision of translating iPS cells into clinical therapies and aims to expand its number of groups to 10-12 before the end of 2016.

Lab leaders of T-CiRA with executives of the program. (Left to right) Ikeya, Inoue, Osafune, Kaneko, Takeda CEO and President Christophe Weber, Prof. Yamanaka, Takeda Global Head of Regenerative Medicine Izumo, Sakurai and Yoshida.

Science Agora

Science Agora is an annual event organized by JST (Japan Science and Technology Agency) since 2006 in Tokyo as a way to promote science to the general public. The 3-day event normally occurs the second weekend of November and has seen its attendance increase by nearly 500% since its founding. CiRA participated its first time last year and came home awarded as one of the best exhibits. This year it did the same. This time CiRA prepared a quiz that visitors were asked to take. "It was a clever way to get the public to read our posters carefully", said Dr. Hiroyuki Wadahama, one of the CiRA representatives hosting the exhibit.

CiRA Café in Osaka

The city of Osaka has built Knowledge Capital, a venue at the heart of its downtown for experts to bring their ideas to the general public. CiRA has taken advantage by holding three CiRA Cafés there. The most recent was Dec. 18, when Prof. Noriyuki Tsumaki discussed his use of iPS cells to study cartilage formation and new therapies for related illnesses. The capacity only allows 50 people to attend, which is why a lottery was held to select from the hundreds of applicants for the event.

iPS Cell Research Fund

Despite the fiscal year not completing until the end of March, the iPS Cell Research Fund has already had its most successful year. CiRA depends on this fund to provide a variety of programs that help train future iPS cell scientists, including the iPS cell training course (see article below) and CiRA/ISSCR International Symposium (Mar. 2016). To express our gratitude, CiRA organizes several annual thank-you events across the country that welcomes all donors. The latest was held in Tokyo on Nov. 30. To provide greater access to the host, Prof. Shinya Yamanaka, the event was split into a morning and afternoon session that each invited just under 100 attendees. As an expression of the how well CiRA is held in the public's eye, the rooms for this event were also donated. At each session, Yamanaka gave presentations that updated the audience on the latest of CiRA research and also details on how its support has strengthened the institute.

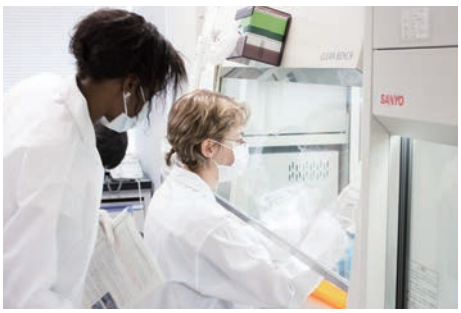
Shinya Yamanaka in Tokyo.

iPS Cell Training Course

Since its inception, an important objective of CiRA's has been the promotion of iPS cell technology. As part of this effort, CiRA has held annual training programs that welcome people from around the world. At three days, the course is short, but comprehensive. "One of the best, interesting courses I have done," said Akram Al Labbar, a post-doctorate who came from the University Putra Malaysia to take part in the most recent class, which was held on Oct. 21-23.

As the course has grown in popularity, it has become increasingly international. "We have never had people come from this far before," said Prof. Isao Asaka, who runs the program and was remarking on students travelling from the U.K. and the U.S. this year. Along with the quality education, an important factor that attracts students is cost; the class is free. For this reason, and the limited space for training, however, it also means that the number of participants is strict. "Unfortunately, we always have no choice but to turn down many applicants," comments Asaka.

The class is held normally in the autumn and is open to scientists of any level, including students.



Students at the iPS Cell Training Course.

Runner first, scientist second

It is not unusual to pass a bookstore in Japan and find Prof. Shinya Yamanaka's picture on the cover of a science magazine. However, as testament to his popularity, you can find his face on a number of non-scientific publications too. Most recently, in preparation of the Osaka Marathon, the national athletics magazine Number Do had a picture of Yamanaka on the cover of its running issue published Sept. 30, 2015. As would be expected for a sports magazine but unusual for Yamanaka, the article ignores the science of cell reprogramming and instead focuses on his passion for running. In it, one can read how Yamanaka has devoted himself to running for over 30 years and considers it his best remedy for stress. He also explains his admiration for countries like the United States that have a culture of private citizens directly supporting science by donating to research institutions and universities. Yamanaka wants to bring this culture not only to CiRA, but also Japan, and uses his marathon runs as campaigns for the iPS Cell Research Fund, bringing together his passion and this goal.

Shinya Yamanaka at the Osaka Marathon 2015.

Osaka Marathon

One reason Prof. Yamanaka's face was on the cover of Number Do (see article above) was anticipation of the Osaka Marathon, which was run on October 25. Each year, CiRA members take part, both as a personal goal and also to represent the institute. This year had the largest CiRA contingent, as joining Yamanaka were Profs. Junya Toguchida, Noriyuki Tsumaki, Kenji Osafune, and Assistant Prof. Akira Watanabe along with several other CiRA staff. This was Prof. Tsumaki's first time to run for CiRA. "I was nervous so I trained hard. It was not easy, but I will run it again," he said. The CiRA runners were not only able to raise the profile of CiRA, they also motivated other marathoners to the cause. In total, 103 participants selected CiRA as their choice charity, making it the most represented of all fundraising groups for the race. About the run itself, earlier this year Yamanaka ran a personal best at the Kyoto Marathon, eclipsing the 4-hour mark. Whatever his training regimen, it continues to pay off as he ran another personal best by over 30 seconds in Osaka.

For those interested in supporting CiRA, please see the CiRA webpage and click on the iPS Cell Research Fund link.

Noriyuki Tsumaki at the Osaka Marathon 2015.

The Temples and Shrines of Kyoto

Shimogamo Shrine

The Kamo River cuts through Kyoto, providing a favorite place of reprieve for tourists and endurance for runners. Near where it and the Takano River confluence and a walk from Kyoto University sits the Shimogamo Shrine, which has inhabited Kyoto since before the city was founded. Despite its size and mere steps from the river, the shrine is easy to miss by the fortress of trees that surround it. The history of the shrine is obscure, but based on its age unsurprisingly mythology is involved. The area on which the shrine is built is thought to be where Princess Tamayori is to have been impregnated by a god that would eventually lead to a divine son. While that record is without certainty, the shrine's significance with the rise of Kyoto during the Heian Period (794-1185) is not. It was during this era, when the Shimogamo Shrine was at its most prestigious, that the Aoi Matsuri became, an annual festival that is one of Kyoto's biggest event today. Presently, the shrine serves as a community center, hosting markets and lectures.

Shimogamo Shrine

Don't forget next March

ISSCR CiRA

Hope to see you here

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