October 2017 Issue No.15

QBiC

NEWSLETTER OF RIKEN Quantitative Biology Center

QBiTs

Autumn in Osaka

The leaves are changing colors in front of RIKEN QBiC B-building in Suita, Osaka. The gate and building have been a fixture of Suita's Furuedai neighborhood for the last thirty years. The B-building was designed by Pritzker Prize wining architect Kenzo Tange, and was originally known as the Osaka Bioscience Institute.

Inside This Issue

CATCHING UP WITH

Cardiomyocytes Connect Japan and Europe

by Lorenzo Marcucci

In 2014, I worked in the Yanagida group at QBiC. Yanagida-sensei has been leading the development of single molecule detection techniques to study molecular motors since late 80's. I was exposed to a very exciting and top-level environment in the field of single molecule characterization of muscle contraction. This was extremely useful to define the working hypotheses of the mathematical models which I was developing, but even more peculiar, was our collaboration with the developers of the University of Tokyo Heart simulator (UT-Heart).

In this project, we had the possibility of linking the single molecule properties to the macroscopic heart contraction to explore the "physiological meaning", to quote Yanagida-sensei, of new discoveries at the microscopic level. In this multi-scale approach, the modeling of the single fiber, or cardiomyocyte, was somehow a weak point. Therefore, in the 2015 I accepted a European reintegration grant at the Department of Biomedical Sciences at the University of Padova, in Italy, where Prof. Carlo Reggiani and his group contributed to the single muscle fiber characterization for several decades.

Director Toshio Yanagida enjoying the park with Lorenzo

In doing so, I have maintained a tight collaboration with QBiC, where I still have a visiting researcher position and which I visit several times per year. This collaboration led to our manuscript [see: Hot off the press] which proposes the recently discovered mechano-sensing mechanism in the myosin filament as one molecular basis of the Frank-Starling law, over which researchers are still puzzling, despite it being discovered more than 100 years ago.

I personally believe that the mechano-sensing mechanism will lead muscle research for the next years, and so these days I am applying for a "Global Fellowship", a European grant which would allow me to be in QBiC and continue this fruitful collaboration for the next three years. ■

HOT OFF THE PRESS

◆Lorenzo Marcucci with Toshio Yanagida in *Scientific Reports,* "Titin-mediated thick filament activation, through a mechanosensing mechanism, introduces sarcomere-length dependencies in mathematical models of rat trabecula and whole ventricle."

◆Takaaki Horinouchi and Chikara Furusawa in *Nature Communications,* "Time-programmable drug dosing allows the manipulation, suppression and reversal of antibiotic drug resistance in vitro" and in *J. Biotechnology*, "Improvement of isopropanol tolerance of *Escherichia coli* using adaptive laboratory evolution and omics technologies."

◆Hiroki Ueda with Etsuo Susaki and Hideki Ukai in *Systems Biology and Applications,* "Next-generation mammalian genetics toward organism-level systems biology" and with Etsuo Susaki in *Scientific Reports,* "CUBIC pathology: three-dimensional imaging for pathological diagnosis" and *Cell Reports,*"Whole-body profiling of cancer metastasis with single-cell resolution" and with Yuta Shinohara and Yohei Koyama in *Molecular Cell,* "Temperature-sensitive substrate and product binding underlie temperature-compensated phosphorylation in the clock."

Recent Science Events

• Sep 28, 2017, QBiC-CDB Joint Seminar
Luis Morelli, Biomedicine Research Institute Buenos Aires

• Sep 28, 2017, QBiC Seminar
Ilaria Testa, KTH, Stockholm, Sweden

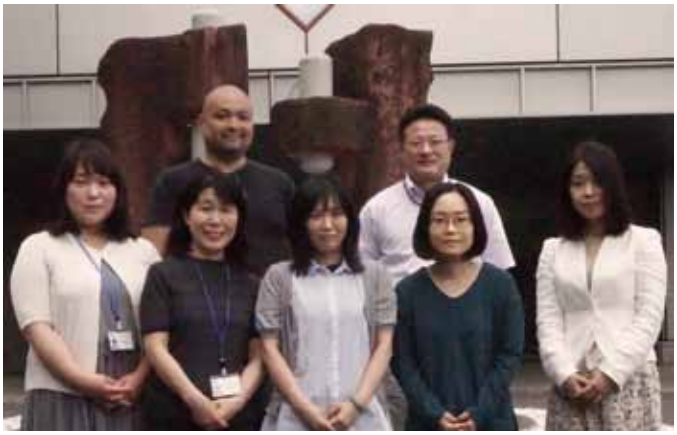
• Sep 27, 2017 , QBiC Seminar
David D. Thomas, University of Minnesota

• Sep 27, 2017, QBiC Seminar
L. Michel Espinoza-Fonseca, University of Minnesota

MEET THE LAB

Quantum Dots are Simple Chemistry in

Takashi Jin's Laboratory for Nano-Bio Probes



Takashi Jin (back right) and his team pose in front of the Gate of Hope sculpture at the entrance of QBiC B-building

The laboratory for Nano-Bio Probes aims to develop chemical and biological probes for bio-imaging based on nano- and bio-technology. Bio-imaging has become an indispensable tool for life science research and clinical diagnosis. The technologies allow investigators to observe, in real-time, the dynamics and structures of molecules in living cells and of cells in living tissues. One reason this is possible has been improved fluorescent probes.

Organic dyes and fluorescent proteins are common fluorescent labels that are attached to a molecule of interest and observed. However, they are not well suited for long-term in vitro and in vivo observations, because they undergo rapid photodegradation and photobleaching. Thus, the need for alternative probes has led researchers to consider nano-particle based imaging probes (nanoprobes) such as semiconductor nanoparticles (quantum dots: QDs).

Our research develops highly fluorescent and robust nanoprobes, which can be widely used for the visualization of molecular and cellular dynamics in living systems. For single-molecule imaging, we synthesize highly fluorescent QD-based nanoprobes combined with fusion protein/tag technology. We also synthesize cellular-imaging nanoprobes that are sensitive to perturbations in light or magnetic fields for

continued on page 7

Recent publications from QBiC researchers

◆Nobuyuki Tanaka and Yo Tanaka in *Sensors and Actuators A: Physical,* "Ultra-thin glass sheet integrated transparent diaphragm pressure transducer" and joined by in *ROBOMECH Journal,* "Contamination-free non-contact wettability assessment system."

◆Yoshihiro Morishita, Takashi Jin and Daisuke Ohtsuka in *Nature Communications,* "Reconstructing 3D deformation dynamics for curved epithelial sheet morphogenesis from positional data of sparsely-labeled cells."

◆Setsuko Tsuboi, Akira Sasaki and Takashi Jin in *Chem Commun (Camb),* "Immunoglobulin binding (B1) domain mediated antibody conjugation to quantum dots for in vitro and in vivo molecular imaging."

◆Arno Germond, Vipin Kumar, Taro Ichimura, Tomonobu Watanabe and Chikara Furusawa explained, "Raman spectroscopy as a tool for ecology and evolution" in the *Journal of the Royal Society Interface*.

◆Yasushi Okada in *Molecular Cell,* "Dynamic organization of chromatin domains revealed by super-resolution live-cell imaging."

Recent Science Events

• Aug 8, 2017, QBiC Seminar
Adrian W. Moore, RIKEN Brain Science Institute, Wako, Japan

• Jun 23, 2017, QBiC Seminar
Piotr Fajer, Florida State University

Synthetic Biology over Coffee

Miki Ebisuya does science cafe

On May 31, Miki Ebisuya, led an English language Science cafe at Nescafe Sannomiya, Kobe. Ebisuya, who is Unit Leader of QBiC Laboratory for Reconstitutive Developmental Biology, explained her field, the meaning of “synthetic biology.” She let the audience in on the challenges of engineering cells to form patterns, one of the major projects of her lab.

She also challenged the audience to think of their own ideas for synthetic biology. The audience, which included local high school students and young adults was encouraged not to worry about useful or practical ideas but merely think about interesting biological phenomenon. There were group discussions and the audience presented some interesting ideas.

Ebisuya said, "The event was fun. I enjoyed talking with the high-schoolers and the people who love science. And I was really impressed by their questions and ideas for synthetic biology. I wouldn't be surprised if biologists were working on similar projects."

Miki Ebisuya schooling science enthusiast on synthetic biology in English at Nescafe in Kobe

Some of their more memorable ideas were a band-aid or first-aid adhesive tape made of living cells that can heal a wound quickly and an in vitro meat named "Kobe-cultured beef."

Ebisuya added, "I really appreciate the efforts of the organizers, the high-school teachers, and the language teachers." ■

QBiC was there

078 Kobe Calling Shuichi Onami

Kobe's inaugural town festival 078 KOBE featured art, music, film, fashion, food, and science! Several information technology related programs were included among a smorgasbord of productions in this two day event on May 6 and 7.

QBiC's Shuichi Onami and RIKEN K computer scientist Tatemasa Miyoshi headlined the "Big data x Science - new tide in the front of research". They explained their research and had a casual discussion about their own experience in the field. They discussed the prospects of future research and fielded questions from the audience on the importance of data-driven approaches in science.

078 is Kobe’s telephone area code and the 078 KOBE festival featured all things from the area, including RIKEN’s Kobe facilities on the Port Island.

Engineering to Eliminate Barriers

Nobuyuki Tanaka discusses his work and his work philosophy

Nobuyuki Tanaka is a research scientist in Yo Tanaka's Laboratory for Integrated Biodevice. He spoke with QBiTs at the conclusion of the RIKEN Kansai Joint Retreat 2017.

Tell us about the lab and your work.

There are two main axes of work in our lab. In one direction, we are developing cutting-edge devices and another direction is application of basic devices, which is what I'm mostly working on. I also develop a new technique for assessing the wettability of surfaces such as cellular tissues, biomaterials, industrial products, etc, with a company [see hot off the press].

Some of the devices have gained a fair amount of attention in Japanese popular media. The pump made from earthworm muscle and an electricity generating device made from electric rays come to mind. Were you involved in these projects?

Nobuyuki Tanaka on bicycle

Those are examples of the cutting edge work, which is led by Yo-sensei. He published the proof of concept studies and now I collaborate on related projects looking for practical applications such as using the heart muscle in a drug testing microdevice.

Your recent publication with a group from ETH Zurich was also a microdevice collaboration. Tell us about that work.

We developed an agarose gel based confinement system for studying stem cell differentiation. We shared a micro-cast silicone mold with our collaborators in Switzerland and we provided protocols for creating the agarose gel confinement in the mold. Agarose is widely used material in biology.

And now you're doing similar collaborations within QBiC. What kind of equipment do the labs need?

The labs need no special equipment. That is a very important point. A key point in my mind is eliminating barriers to application of our technology. So, we focus on improving our protocols and procedures to eliminate the need for special equipment, or special procedures that may be difficult.

At this retreat, we had a lot of requests for collaboration and the things these researchers request are all a little different but my philosophy is the same. I think these collaborations will be successful because we focus on eliminating the barriers to successful implementation, such as special equipment.

What kind of barriers have you found surprising?

As an engineer with experience in microfabrication I don't see the barriers in advance at all. Trouble is our teacher, so when the researchers comeback with problems that's the only way to discover the barriers.

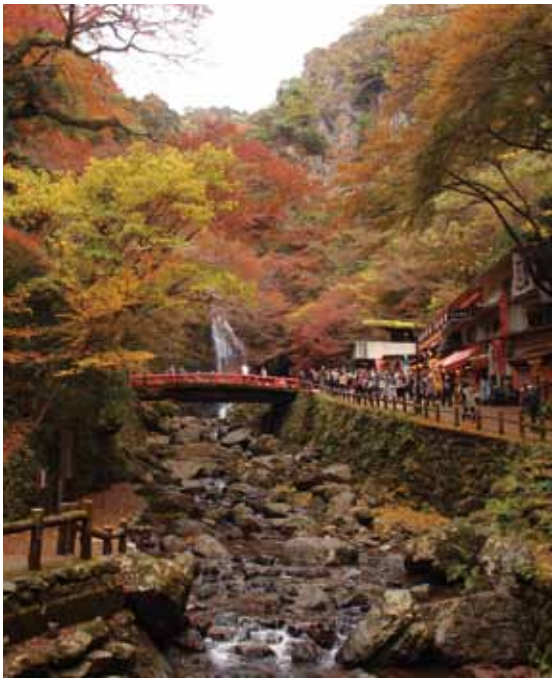
We are also developing cutting edge technology in our lab and of course there is always trouble with cutting edge technology so that trouble can be our teacher too. Both axes of the work in our lab are important.

QBiC and QBiTs reader are in a wide variety of fields including AI and supercomputing. Do you have anything to say to them?

Communication is the most important thing. We also used machine learning in our work [Tanaka et al., doi: 10.1371/journal.pone.0173647] but very basic methods. We don't need the cutting-edge machine learning at the start. It's important to start with easy to use and easy to understand techniques in biology. Keeping the communication simple is also important. We have to understand each other's field so the retreat is very important opportunity for us. ■

Monkeys and Waterfalls and Foliage

Enjoy the autumn colors in Minoh



The Minoh Waterfall nature trail is a paved, wheelchair accessible path through the Minoh Quasi-National Park in the foothills just north of QBiC. The hardest part of the walk is figuring out when to go. In short, the answer is autumn.

With copious maple foliage, snacks and drinks along the way and a free natural hot spring to soak your aching feet at the end of the trail, there is no better walk in the area or for the season. On weekends and holidays locals join the hordes of tourists for a walk in the woods and it gets crowded. The trail is more than just a walk in the woods though.

It starts right at Hankyu Minoh station. Hankyu for their part have made the nomenclature as confusing as possible and while the city of Minoh has settled on this phonetic spelling Hankyu railway signs are in complete disagreement and it can be seen spelled, Mino, Minō, Minoo, Mino-O and Minoh depending on where you look. Nonetheless there is no other similarly named location of any import for hundreds of kilometers so you can feel confident that you're headed in the right direction despite the attempt by the railway to confuse you.

Alphabetization of Japanese words is always up for debate and local variation is par for the course so furrowing your brow at confusing signage is a common experience for those of us using alphabetized signage in Japan. Moving past that and the Minoh station brings you immediately to the start of the trail.

Straight ahead out of the only ticket gate is the trail, which starts with souvenir shops, a standing only bar on the right, and beer vending machines on the road. Alcoholic beverage vending machines are becoming less and less common in Japan and semi-rural tourist attractions such as this waterfall are great opportunity to see this bit of old-time Japan. Restaurants and souvenir shops continue for the first few hundred yards and the free foot bath is in this area as well.

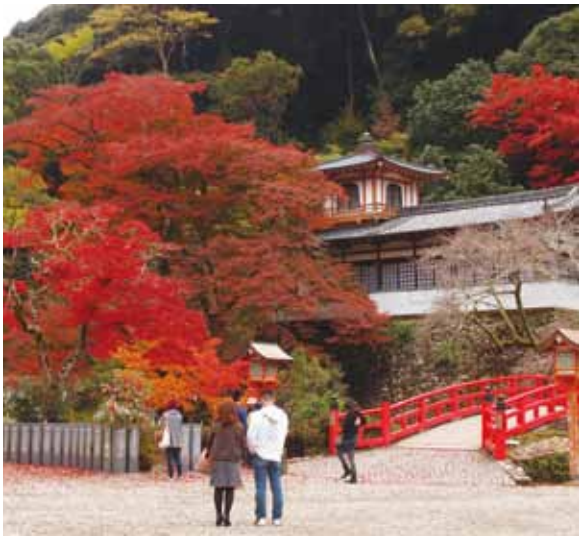
The trail follows the Minoh River with a paved path on one side and an unpaved path on the other side for most of the way to the falls. Bicycles are not allowed on the majority of the trail but joggers are common as are selfie-stick wielding tourist. To get away from the crowds simply switch to the other side of the river at one of several bridges.

A number of traditional buildings including the Ryu-An-Ji temple, make the trail picturesque. For those interested in wildlife there are monkeys frequently looking for handouts in the area and plenty of signs warning not to feed the monkeys.

Roasted chestnuts and maple leaf tempura are sold in many places along the trail as is the local specialty Minoh beer. There isn't a better brewery in Japan and everything they make tastes right. To get the stuff right from the tap, the brewery is a long walk in the other direction from Minoh station but there is a wide-open tasting room and plenty of the best beer in Japan once you've gotten there.

For those who'd like to go further into the mountains rather than back towards civilization. The Minoh Waterfall also marks the start of the Tokai Walking Trail which connects Osaka to Tokyo. That walk will take several weeks but the waterfall trail can be done in a half day.

Transport: One-way transport from Yamada Station near QBiC ¥520. From Yamada Station take an Osaka Monorail to Hotarugaike Station. Change to a northbound Hankyu Takarazuka line train one stop to Ishibashi Station. Take a Mino-O bound Mino line train to the terminus.



Quantum Dots

continued from page 3

the purpose of controlling the cellular state. Furthermore, for the non-invasive visualization of cellular dynamics in living tissues, we synthesize near-infrared (NIR) emitting nanoprobes in the second biological window (1000-1500 nm), a wavelength region that has a high transparency in living tissues. Accompanying these technologies, we also develop efficient probe-delivery techniques that allow us to target specific cells, tissues and organs.

Near infrared (NIR) fluorescence imaging is one of the most popular modalities for the non-invasive visualization of biological process in vitro and in vivo. In the case of deep-tissue imaging, visible-emitting fluorescent probes cannot be applied because of the strong absorption and scattering of visible light by intrinsic chromophores (e. g., hemoglobin, melanin and flavin) and organelles (e.g. mitchondoria and cytoskeleton) in tissues. Compared with visible light (400-700 nm), NIR light (700-1400 nm) is highly permeable in living tissues.

In addition, tissue autofluorescence and scattering induced by NIR light excitation are much lower than those by visible light excitation in tissue imaging. In most of the commercially available in vivo imaging systems, the NIR region ranging from 700 to 900 nm (1st-NIR optical window) has been used for deep tissue imaging. This is because the conventional NIR photodetectors (silicon CCD camera) are sensitive in the 1st-NIR region, and 1st-NIR emitting probes (e. g. Indocyanine green, Cy 7, and CdSeTe QDs) are commercially available.

Although 1st-NIR fluorescence imaging is useful for the non-invasive visualization of organs and tissues at the whole body level, its spatial resolution is not enough to observe cellular dynamics in vivo. As autofluorescence and light scattering by tissues significantly decrease in the NIR region ranging from 1000 to1400 nm (second optical window), NIR fluorescence imaging in the 2nd-NIR region is expected to offer better spatiotemporal resolution in deep tissue imaging.

To achieve deep-tissue imaging with high spatiotemporal resolution, we have developed and patented 2nd-NIR emitting probes, PbS Quantum Dots for non-invasive fluorescence imaging of lymph nodes, cerebral blood vessels, breast tumors and phagocytic cell migration.

WELCOME

QBiC received visitors from Ritsumeikan University for tours of the MDGRAPE-4 supercomputer and the Watanabe and Takahashi labs.

Ph.D. students from the University of Cambridge and Osaka University also visited QBiC for tours of the MDGRAPE-4 supercomputer and the microscope rooms of the Okada and Taniguchi labs. This was part of an Osaka University sponsored international exchange program. The students interests included electron microscopy and sushi!

Awards

Mitsuhiro Iwaki, research scientist in the Laboratory for Cell Dynamics Observation received a Japan Bioindustry Association Award for development of DNA nanodevices directed to mechanical control of stem cell differentiation.

RIKEN CENTENNIAL
Since 1917

NEWCOMERS at QBiC

Reiko Yamamoto

Team Shiroguchi
Sports: Baseball
(only watching, no play)
Hobbies: Playing with my daughter
Food: Sweet-n-sour chicken

Yuhei Ashida

Team Ebisuya
Sports: I like walking
Hobbies: Reading novels
Food: Steak

Naoko Komai

Team Taiji
Sports: Skiing and snowboarding
Hobbies: Traveling, watching movies and comedy shows
Food: Sushi

The Chow Down

Reiko Yamamoto's Sweet-n-Sour Chicken

Ingredients

6 pieces of fried chicken (from a delicatessen or supermarket)
1 pack of baby leaf salad mix
8 Small tomatoes
120 g sugar
2 Tbsp ketchup
100 cc vinegar
50 cc soy sauce
100 cc plus 1½ tsp water
1½ tsp potato starch

Have a recipe you want to share? Contact us at: **qbits@riken.jp**

Recipe

1. In a pan, mix the 100 cc water, vinegar, soy sauce, sugar and ketchup.
2. Heat over low heat until hot but not boiling. Add the fried chicken, mix with the sauce and heat for about 2 minutes.
3. In a separate small container mix the potato starch and remaining 1½ tsp water.
4. Remove the pan from heat and immediately mix in the potato starch-water to stop the cooking process.
5. Transfer the chicken and sauce to a plate garnished with baby leaf salad mix.
6. Add the small tomatoes and serve.

Find us on the web: http://www.qbic.riken.jp/ Follow us on twitter: @QBiC_RIKEN

Published by the Office for Science Communications, RIKEN Quantitative Biology Center.
Editor: Kylius Wilkins
If you have any suggestions, comments, or would like to contribute to the newsletter, please send an email to: qbits@riken.jp