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Waseda University pushes forward with global academic network

Innovative programs and prioritized funding have propelled Waseda University to record highs in world university rankings, underscoring the university’s reputation for openness, dynamism, and diversity.

The role of mathematics in science and technology
—Multiscale Analysis, Modelling and Simulation

"Some people may wonder about the importance of mathematics in society," says Yoshihiro Shibata, head of the Multiscale Analysis, Modelling and Simulation Unit. “However, it is difficult to initially test complex new ideas and concepts using experiments alone, such as investigating the flow of blood in arteries. The development of science and technology often requires a cycle of mathematical analysis, computer simulations, and experimental verification."

In this unit, members collaborate with international partners to apply nonlinear partial differential equations, geometry, and quantum mechanics to practical applications such as fluidics, or the flow of gas and liquids. As part of their activities, Shibata and his colleagues also started a doctoral course at the Faculty of Science and Engineering in April 2017, with lectures in quantum mechanics, quantum mathematics, fluid mathematics, numerical fluid dynamics, experimental hydrodynamics, and geometry. Students participate in international symposia as well.

The course is run in collaboration with researchers from Imperial College London, Technical University Darmstadt, the University of Pisa, Rice University, the University of Pittsburgh, and the University of Hamburg. “Students must spend at least three months at one of our partner institutes,” explains Shibata. “Beginning in 2018, we will offer co-teaching courses with the University of Pisa and intend to expand our network to include institutes from China.”

Specific research topics include mathematical modeling based on imaging the interaction of molten metals with concrete, related to the decommissioning of nuclear reactors destroyed in the Fukushima accident; analyzing cloud formations to better understand climate change; and observing blood flow for early diagnosis of cardiovascular issues such as aneurysms.

“The emphasis of our education and research is to combine expertise in mathematics and physics to produce useful models to solve major problems facing mankind.”

Multiscale Analysis, Modelling and Simulation Unit

Integrating methodology of political science and economics for innovative models solving global issues
—Positive/Empirical Analysis of Political Economy

“Raising taxes is both a political and economic decision. So is importing rice or fruit products. But universities in Japan teach politics and economics as separate subjects. Waseda University has combined these subjects in the Faculty of Political Science and Economics.”

Aiji Tanaka

Advanced Study could complete their studies entirely in English. “We are hiring international faculty members to teach and conduct research at Waseda,” explains Tanaka. “It’s a stringent selection process, assessing both publications and teaching ability. We hired six international faculty in 2016, and are interviewing more for the coming year.”

Tanaka and colleagues are also collaborating with Stanford University and the University of Essex to organize summer schools at the Waseda campus in Tokyo. Plans include expanding courses to contain wider global perspectives, hiring more international staff, and collaborating on positive theory/empirical analyses of the behavior of political/economic actors and the governance of political systems and multinational corporations with the Said Business School at Oxford University, the School for Advanced Studies in the Social Sciences, the University of California, San Diego, and other universities abroad.

“Waseda University has a 130-year history of pioneering political economics-based education and research,” says Tanaka. “Our faculty members are training our students to be fluent in the languages of both economics and politics, and we will continue this tradition on a global scale to resolve the challenges of the 21st century.”

Positive/Empirical Analysis of Political Economy Unit

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In vitro veritas: Biosensors and microarrays come to life

Advances in biosensors and microfluidic devices are driving a quiet revolution in biomedical research, which could lead to the reduction or elimination of animal use in many experiments. By Alan Dove

For decades, laboratory biologists have regarded animal models as a necessary evil. While some activists decry their use on moral grounds, even the most practical-minded researchers acknowledge fundamental problems with them. Animals are expensive, provide only imperfect replicas of human biology, and introduce numerous variables into experiments that can be difficult or impossible to control.

These flaws aren’t purely academic. Pharmaceutical researchers have struggled for years with late-stage development failures, in which drugs that look promising in multiple animal systems turn out to be useless or even toxic in humans. Nonhuman models have simply been the least bad tool for detailed studies on human biology.

Thanks to advances in completely unrelated fields, though, that grim situation is starting to change. Using improved biosensors that can monitor microscopic compartments, and microfluidic devices that combine the miniaturized features of computing chips with living cells and tissues, researchers are now building systems that can reduce or even eliminate the need for laboratory animals while simultaneously yielding better data.

Diamonds are for sensors

Pharmacokinetics researchers have been among the most enthusiastic proponents of improving on animal models. Ideally, researchers would like to know exactly where a drug goes in the body and how and when it’s processed, generating a detailed history from dosing to metabolism to excretion. In practice, that has entailed cumbersome techniques such as medicating numerous animals and sacrificing them for analysis at different times. Besides being laborious and expensive, these experiments give only coarse measures of drug metabolism across time and body compartments.

In recent years, investigators have implanted tiny, electrochemical carbon-based sensors into animals, which provide measurements of metabolic changes in real time in a single animal. That’s worked for natural signals such as dopamine and serotonin levels in the brain, but the high background noise and low dynamic range of carbon probes make them poor choices for studying drug metabolism.

Chemists and biologists are collaborating to overcome those limitations. Yasuaki Einaga, professor of chemistry at Keio University in Yokohama, Japan, has worked on electrochemical sensors for decades. Einaga’s group has found that boron-doped diamond probes are particularly good at detecting electrochemical changes in solutions. His researchers have tested these probes in systems ranging from wastewater treatment to chemical synthesis.

“To further explore their biological applications, in 2007 [we] succeeded in downsizing the ... probes to micro scale,” says Einaga. Hiroshi Hibino, professor of molecular physiology at Niigata University School of Medicine in Niigata, Japan, saw the system’s potential for pharmacokinetics applications, and began collaborating with Einaga in 2011.

The two labs have since found that boron-doped diamond probes can detect electrochemical changes caused by several classes of drugs in live animals and explanted organs, cont.>

Upcoming features

providing real-time data on drug concentrations. "The number of drugs measurable by these sensors is much more than that of any conventional electrode," says Einaga. In one recent paper, for example, the team accurately measured concentrations of a diuretic, an anticonvulsant, and a chemotherapeutic agent in guinea pigs' inner ears.

"[We] have a plan to test the kidney, [and] both groups are discussing a further collaboration to develop an implantable microsensing system to track [a drug] and its effects longitudinally in organs such as the brain," says Hibino. He adds that the two labs are now in discussions with several other researchers who want to use the technology in fields ranging from oncology to psychopharmacology.

**Plumbing codes**

While improved biosensors can extract more and better data from each animal, they can also be combined with microfluidic devices to replace an animal outright, at least for some types of experiments. Microfluidic device makers borrow techniques from the electronics industry to manufacture miniature laboratories on chip-like wafers. The small size of the chips' channels and chambers means that fluids can flow through them rapidly. Microfluidic devices can also include complex structures that mimic biological compartments, making cultured cells behave more naturally. Finally, the chips can be mass-produced on semiconductor manufacturing equipment, making them relatively cheap.

Over the past few years, biologists have built a series of progressively more complex microfluidic devices, which have essentially evolved into artificial, miniaturized human organs. Biosensors built into these systems allow researchers to watch in real time as, for example, a tiny human-like liver or kidney reacts to an incoming dose of a drug.

The power of these new systems can be intimidating, though. "The biggest challenge for us instrument providers is to educate people," says Fabien Crespo, head of marketing and sales at Elveflow in Paris, France. Crespo adds that "people are kind of afraid of microfluidics, which is a lot about plumbing."

Elveflow and a few other companies have made this microscopic "plumbing" their main focus. "Researchers can now find microchips suited to their applications, and we are providing everything to control liquid flow inside those microchips," says Crespo. Because the microfluidics field has standardized the different types of fittings that go into and out of chips, a single liquid-handling system can adapt to changing laboratory needs. In Elveflow's setup, for example, a point-and-click computer interface allows researchers to build multistep protocols controlling liquid flows. More advanced users can use a scripting interface to drive the system programmatically.

Such flexible, modular systems are undoubtedly one reason microfluidics are becoming so popular. "We are seeing a lot of expansion in the field, especially over the last two years," says Crespo. He adds that while the first users of microfluidics were mostly in academic research laboratories, he's seen increasing demand from industrial scientists. That's likely driven by interest in developing new preclinical drug screening assays, but Crespo also expects microfluidics to start showing up in point-of-care diagnostic tests within the next few years.

**The government chips in**

The groundwork for the new boom in microfluidics began nearly a decade ago, through a combination of basic research and farsighted government assistance. When researchers in a few academic laboratories began building "organ-on-a-chip" systems, administrators at the U.S. National Institutes of Health (NIH), the U.S. Food and Drug Administration, and the Defense Advanced Research Projects Agency took notice. "It became apparent... that this was going to be a promising tool and technology," says Danilo Tagle, associate director for special initiatives in the Office of the Director at NIH in Bethesda, Maryland.

Tagle and his counterparts at other agencies convened a meeting with researchers in 2011 to discuss turning the new tissue and organ chips into practical models for drug testing and regulatory approval. "Numerous studies in the past few years have indicated that as much as 90% of the attrition in drug development is caused by failure to predict safety as well as efficacy when using [cell] culture systems and in vivo animal models," says Tagle. "What we’re hoping [is that] these tissues on chips or organs on chips can fill in the missing information we need in order to have better success in drug development."

To help make that happen, NIH created the Tissue Chip for Drug Screening program in 2012. Collaborating with several academic labs, the initiative’s five-year goal was to build organs on chips that could yield accurate predictions about drug responses in humans. Researchers funded by the program had to build devices that could keep cells alive in a setting that would mimic specific organs or tissues, and incorporate biosensors to measure the cells' physiology. The program has now established several independent testing centers for organ chips, using over 100 drugs that cleared traditional preclinical testing only to fail in clinical trials. "We’re asking the question, 'Would a given chip have predicted the adverse event that the 2D culture systems and the animal models were unable to predict?'" says Tagle. Organ chips
that do well in these tests could be used to supplement or even replace animal data in future regulatory filings by drug makers.

Having concluded its first phase in July, with several promising systems being tested for assaying drug toxicity, the Tissue Chip program is now focusing on models for drug efficacy. These single- and multiorgan systems will be built to mimic particular diseases, including Parkinson’s disease, amyotrophic lateral sclerosis, and osteoarthritis.

Deep breaths

The main advantage organ chips have over traditional cell culture systems is their ability to simulate the complex structures and dynamics of intact organs. Instead of being restricted to flat, solid surfaces, chip makers can incorporate microscopic channels, curves, pores, and layers for the cells to populate. The carefully controlled, programmable fluid flows of a microfluidic device add to the realism of the technology, recreating the forces those same cell types would encounter in living humans.

Lungs provide a good example of both the challenges and the potential of this approach. In the human lung, cells maintain a semipermeable barrier with two distinct sides, allowing gas exchange between air and blood, while keeping the two fluids separate and withstand regular cycles of flexing with each breath. Researchers at Harvard University’s Wyss Institute first mimicked this system with a lung chip in 2010. Emulate in Boston, Massachusetts, is continuing development on that and other organ chips.

The Boston team isn’t alone, though. “We saw this very interesting paper from the Wyss Institute, [and] we wanted to go further [with the concept],” says Olivier Guenet, CEO of AlveoliX in Bern, Switzerland. Guenet is also a group head at the University of Bern’s ARTORG Center for Biomedical Engineering Research, where his lab collaborates with clinical teams treating patients with lung diseases.

To simulate the structure and three-dimensional deformation of a lung, Guenet’s team developed a platform that seeds cells onto thin layers of silicone containing regularly spaced holes. Only 3 micrometers thick, the layers are nonetheless strong enough to withstand repeated, breath-like flexing. Having accomplished that, “the second biggest challenge was that we wanted ... to develop something that is very easy to use,” says Guenet.

After several design iterations, AlveoliX now has a prototype system that maintains 12 lung chips on a standard-size multiwell plate. This arrangement enables users to handle and test the chips with existing microscopes, plate readers, and other common laboratory equipment. Ultimately, “we want to be able to take cells from a patient and test them ... and see which therapy is going to be best for that patient,” says Guenet.

The chips should also prove useful for preclinical studies, allowing scientists to control fluid flows, mechanical stresses, and other parameters with far greater precision than they can in living models, while simultaneously eliminating the challenges of animal handling. “I don’t know any biologist who likes to sacrifice animals, and with organs on chips [now available], we really want to reduce animal testing,” says Guenet.

Concerto for organs

As organ chips become more established, scientists in the field are already pushing microfluidics and biosensor technology to the next logical step: multiorgan systems. In theory, one could simply pump culture medium through different chips in series, circulating drugs and metabolites within a high-tech homunculus. The reality turns out to be considerably more challenging.

“There’s just a lot of things that can go wrong when somebody tries to do this,” says Mike Shuler, president and CEO of Hesperos in Orlando, Florida. The company specializes in multiorgan chip systems. Shuler, who is also a professor of engineering at Cornell University in Ithaca, New York, says even people intimately familiar with multiorgan chip systems can have trouble getting them running. “When I’m transferring technology from my [academic] lab down to the company, sometimes it takes a few iterations for us to get it to work right,” he says.

As a result, Hesperos has built its business on offering multiorgan models as a service, rather than trying to sell and support them as stand-alone products. To date, the company has collaborated with several pharmaceutical companies interested in testing drug leads on chips. Shuler says Hesperos typically builds systems with four or five interconnected organs. “The liver is almost always the critical one, then cardiac and neuromuscular junctions ... are probably the [next] most popular,” he says, adding that the company has also built systems incorporating artificial skin, gastrointestinal tracts, and blood-brain barriers.

One of the biggest challenges has been keeping the systems running long enough for extended metabolic testing. “We try to operate out to 28 days,” says Shuler. At that timescale, the difference in solubility between oxygen and carbon dioxide in the cells’ medium can cause gas bubbles to accumulate, disrupting the system’s tightly controlled fluid flows. Hesperos has addressed that problem by eliminating the pumps normally used to control microfluidic devices, and using a carefully designed gravity flow system instead.

As the technology continues to develop, proponents of microfluidic systems expect their popularity to skyrocket in the next few years. “We’re already being put into workflows for large and small pharma, [and] at this point we’ve been able to meet just about every single milestone that people have set out for us,” says James Hickman, Hesperos’ chief scientific officer. Shuler projects that human organ chips “eventually will, I think, replace animals [or] so greatly reduce animal use that it’s a much less significant part of the drug development process, because you are getting data on human systems.”

Alan Dove is a science writer and editor based in Massachusetts.
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Based at both Wenzhou Medical University and Wenzhou University the research team led by Prof. Xiaokun Li is devoted to FGF basic and translational research with their clinical application as an ultimate goal. The therapeutic modalities using FGF formulations have evolved from the initial external and topical administration to implantable medical device as well as injection. The clinical indications have expanded from trauma and diabetic ulcer treatment, to neurological repair/regeneration. In the immediate future, FGFs will also be instrumental in the treatment of major metabolic diseases, such as diabetes and atherosclerosis.

The fibroblast growth factor (FGF) family is comprised of a group of structurally related protein ligands that signal through FGF receptor tyrosine kinases (FGFRs) to carry out a plethora of vital functions in development, metabolism, tissue homeostasis and repair after injury. Historically, translational research of FGF/FGFR has focused on the oncology aspect in the West, whereas the research team led by Prof. Xiaokun Li based at both Wenzhou Medical University and Wenzhou University is devoted to FGF biotechnology and the delivery of engineered clinical grade FGFs for tissue repair and regeneration.

The FGF family consists of 18 mammalian FGFs divided into 6 subgroups on the bases of their sequence homology, phylogenetics and structural characteristics. Five of the subgroups are considered canonical FGFs capable of high affinity binding to heparin sulfate (HS) and acting locally as paracrine molecules. The potential of FGFs in promoting cell proliferation, survival, angiogenesis, migration, and differentiation, have been explored for therapeutic applications in the setting of tissue repair/regeneration and also cancer therapy. Li’s team, which started from Jinan University, Guangzhou, overcame several major bottlenecks for FGF protein engineering and recombinant production such as poor protein solubility and stability, enabling them to develop and license the first FGF protein drug (FGF2) in the world for clinical use. The clinical trial of the topical FGF2 biologics, led by Prof. Xiaobing Fu and first reported in the Lancet, proved its beneficial effect in accelerating healing of burn wound, skin flap transplantation, and diabetic ulcers. As of June 2017, in China alone, FGF biologics have been used in 80 million cumulative patients/cases with great clinical and socioeconomic benefit. Importantly, the safety record of this treatment has been excellent: during a 20-year period post-FGF treatment of clinical follow-up, no excessive hyperplasia or other major adverse effects have been observed. The FGF biologics have transformed the clinical practice of trauma management from the traditional anti-infection and anti-inflammation therapies to include FGF-induced coordinated pro-active repair and functional regeneration. In the past 10 years, Li and his colleagues have also successfully developed novel formulations for FGF1 and FGF2, as well as FGF7 and FGF10 biologics, which are currently in different phases of clinical evaluation. A non-mitogenic mutant FGF1 formula is also under preclinical evaluation for the treatment of Type 2 Diabetes.

The endocrine FGFs are relatively new members of the FGF family with much reduced affinity toward HS and activate FGFRs with Klotho as a cofactor and exhibit distinct regulatory activity in various metabolic processes including glucose, lipid, bile acid, vitamin D and phosphate metabolism and energy homeostasis. These atypical FGFs, as exemplified by FGF21, present therapeutic potentials for a myriad of major metabolic diseases such as diabetes, obesity, cardiovascular and renal diseases, amongst others. Besides the aforementioned paracrine FGFs, Li’s team has also undertaken major effort on basic and translational research on endocrine FGFs, particularly FGF21 and more recently FGF23. Li and his colleagues first discovered the role of adiponectin in mediating the metabolic effect of FGF21 on energy metabolism and insulin sensitivity, as well as protection against atherosclerosis. Currently the team has completed preclinical studies and is in the process of applying for CFDA approval for clinical trial on FGF21 for the treatment of diabetes. In collaboration with Prof. Mohammadi from New York University, Li’s team provides structural insight into the activation of Phospholipase C by the concerted action of two FGF receptor molecules. A recent Nature publication further solved the atomic structure of the α-Klotho/FGFR1c/FGF23 ternary complex providing a basis for understanding how klothos and endocrine FGFs interact, therefore opening up new avenues for structure-based drug design. Studies from Li’s team have already unveiled unexpected therapeutic activity of FGF1 toward diabetic nephropathy and demonstrated that mitogenic and metabolic activities can be uncoupled by tuning FGF1/FGFR dimer stability. These mechanistic findings will likely lead to future drug discoveries targeting FGFs for the treatment of a variety of human diseases.

Armed with the rich and validated experience of “Chinese Style” protein drug development, the Wenzhou FGF team and its network of international collaborators, which together constitute the “Wenzhou FGF family” is pushing ahead to make significant contributions to translate FGF research discoveries into clinical application in the years to come.
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