JSPS Core-to-Core Program
FY2012 Implementation Plan (Project No. : 20002)

Research Theme International Core Research Center for Micro/Nano Chemistry
Duration of Project 2010/4/1 – 2013/3/31 (36 months)
Core Institution in Japan (Co-Chair) School of Engineering, The University of Tokyo
(Takehiko Kitamori)

Implementing Organizations

○ **Japan**

Japan	Core Institution	School of Engineering, The University of Tokyo	
	Co-Chair (name and title)	Takehiko Kitamori, Professor	
	Cooperating Institutions	Kyoto University Nagoya university Waseda University Japan Women's University	Number of Cooperating Institutions 4

○ **Partner Countries**

	Core Institution	Uppsala University, Sweden	
	Co-Chair (name and title)	Ulf Landegren, Professor	
	Cooperating Institutions	Lund University Royal Institute of Technology	Number of Cooperating Institutions 2

	Core Institution	University of South Australia, Australia	
	Co-Chair (name and title)	John Ralston, Professor	
	Cooperating Institutions		Number of Cooperating Institutions 0

	Core Institution	IBM Watson research Center, USA	
	Co-Chair (name and title)	Tze-Chiang Chen, Fellow & Vice President, Science & Technology	
	Cooperating Institutions		Number of Cooperating Institutions 0

	Core Institution	Nangyang Technological University, Singapore	
	Co-Chair (name and title)	Ai-Qun Liu, Professor	
	Cooperating Institutions		Number of Cooperating Institutions
			0

	Core Institution	Swiss Federal Institute of Technology Zurich, Switzerland	
	Co-Chair (name and title)	Petra Dittrich, Assistant Professor	
	Cooperating Institutions		Number of Cooperating Institutions
			0

Objectives of Research Exchange (including the five years after the project finishes)

Recently, many researchers investigate micro and nano chemistry which integrate various chemical functions (experimental rooms) into a ~cm size glass substrate. In this situation, we have pioneered our original methodology and fundamental technology, and we are highly evaluated. However, this field needs combination of various fields and technologies. For example, single molecule detection needs combination of detection and miniaturization, and microfluidics is based on surface chemistry and fluid dynamics. These combinations are really important for both fundamental research and application.

Therefore, we will construct strong collaborations with Rudbeck laboratory in Uppsala University and Ian Wark institution in the University of South Australia, and establish a worldwide core for frontier micro and nano chemistry combining single molecule engineering and surface chemistry for both fundamental research and application.

(1) Collaborations on combination of our methodology and each partner institution's technology such as single molecule engineering and surface chemistry
(2) Construction of single molecule analysis systems and application to medical and biological field
(3) Education of next generation young researchers who can cross several fields such as chemistry, physics and biology

As described above, we will establish a core of micro/nano chemistry to contribute Japanese industry, and educate young researchers to promote next generation science and technology

Results to the present

① Promotion of collaboration research

Recently, single DNA analysis is required in various fields such as bacteria detection and medical diagnosis. For example, circulating tumor cells (CTCs) which exist only 1 cell in 10^9 cells or ES/iPS cells are needed to be analyzed. To realize this, specific cells must be separated from a lot of other cells, and also gene or proteins must be analyzed in single molecule level. That is not easy by conventional methods.

On the other hand, we have integrated various chemical processes on a microchip. Especially, by using extended-nano channels which are smaller than single cells, single cell and single molecule analysis would be realized by combining with various kinds of surface and detection methodologies. Based on this concept, we have been collaborating with the following 5 countries and promoting the research.

· Collaboration with Uppsala University

By using primer immobilized beads prepared in the method described above, RCA processes were integrated onto a microchip by applying our methodology of micro/nano chemical systems. As a result, detection rate was highly improved compared with conventional PCR tubes (90 times), and detection of ultra small number of DNA molecules was realized (zmol(10^{-21} mol)). Also, by using this method, detection of practical genome samples were realized. Moreover, the RCA processes were combined with a nonfluorescent molecular detection method developed by our group, i.e., thermal lens microscopy (TLM). The method realized high sensitive detection of zmol RCA products. The analysis time was dramatically

shortened from hours to minutes, compared with conventional RCA counting individual molecules.

These results were accepted in two journals as co-author papers (Sato et al. Lab Chip, 2010) (Tanaka et al. Anal. Chem., 2011). Furthermore, 8 papers were accepted in an international conference (μTAS) (accept rate: under 60%). One of them was nominated for a poster award from 500 presentations (Tachihara et al., Proc. MicroTAS (2008)).

Based on these results, Sato (Lecturer) promoted to an Associate Professor in Japan Women's University and had an independent laboratory, and she got NEDO project for young researchers (Total 50 million yen).

· Collaboration with South Australia

By exploiting surface chemistry technology of Prof. Ralston in Ian Wark institution, we have developed molecule patterning method such as DNA or proteins toward single cell analysis utilizing extended nanochannels. Also, since they have advantages for hydrodynamics researches, we electrically investigated liquid properties in extended-nano space, and found that ion conductivity in extended nanochannels increase compared with bulk space. In addition, specific fluidic properties have been studied based on capillary filling and mass flow rate measurements. This is a fundamental knowledge for single cell analysis creation.

This result was accepted to a journal (Priest et al. Int. J. Miner. Process., 2011) and accepted in international conference, μTAS (2 papers). Moreover, regarding this result, Prof. Kitamori became a collaborator of a large project in Australia.

· Collaboration with IBM

With IBM, we aim to construct a single cell secretion analysis system using a nanowire originally developed in IBM. To realize that, nanowires must be incorporated onto extended nanochannels. We have developed a low-temperature bonding method that is indispensable for nanowire incorporation. This method enabled to embed functional materials including polymers, biomaterials and electrodes into extended nanochannel, and established fundamental technology for single molecule analysis in extended nanochannel.

· Collaboration with Nangyang Technological University

With Nangyang Technological University, we aim to develop a single cell detection system based on photonics technology. Specifically, by using surface plasmon resonance (SPR) based protein detection system, we aim to construct a sensitive protein detection system in extended-nano channels. We demonstrated the principle using a microchannel, and succeeded biomarker detection by SPR by using a thin bottom glass microchip. On the other hand, a photonic crystal was constructed by droplet array packed in a microchannel. Optical properties can be modified by changing droplet size. This can be an optical system on a microchip.

The results was accepted in 1 journal paper (Guo et al. Lab Chip, 2011) and international conference, μTAS (1 paper).

· Collaboration with ETH

With ETH, we aim to construct a single cell secretion analysis system. Specifically, the goal is to detect single cell secreted molecules fluorescently by laser after chemical reaction in extended nanochannels. We have designed and fabricated an extended nanochannel chip. Also, we have realized multistep mixing, reaction and detection system. On the other hand we discussed concept and design of cell culture system in microchannel in Joint seminar. We aim to develop a method for analysis of single living cell using microfluidics and extended nanofluidics.

As described above, we obtained prominent results with continuously collaborating 2 institutions, and with other 3 institutions, specific direction of collaboration research has been decided through joint seminars, and several preliminary results have been obtained.

② Education of young researchers

To improve English communication skill, our group use English for presentation and discussion in seminars. Owing to such activity, 7 young researchers in our group received awards in international conferences. Moreover, we hold joint seminars in each collaborating country every year, and held a 3 countries' symposium in Japan in March, 2010. Through such exchanging, the number of young researchers' travel to abroad became twice compared with that before this program started. Moreover, we held summer camps in Hakone on 2010 and in Izu on 2011, called about 10 researchers from foreign countries and discussed about collaboration themes to improve discussion and presentation skills in English.

③ Presentations

To exchange research result, our group is active for conference and paper presentations. During 4 years of this program, the number of published papers is 70, the number of presentations in international conferences is 168. Especially, the number of presentations in μTAS conferences is 43 in 4 years. We also invited several researchers from partner countries. Results and collected information are open in this program's home page (http://park.itc.u-tokyo.ac.jp/kitamori/project/).

④ Additional effects

Regarding this program, some of the members received awards and promoted. For example, our group received 15 awards including 7 international awards such as IBM Faculty Award (Prof. Kitamori). In international collaboration systems, we renewed an international exchanging agreement with the University of South Australia, and constructed a joint laboratory in Ian Wark institution. Regarding collaborations with Sweden, we also renewed an international exchanging agreement Uppsala and Lund University. Furthermore, Prof. Landegren was authorized as a fellow in the University of Tokyo. As described above, we obtained results larger than the original aim and constructed the basis for the next program.

Summary of FY 2012 Exchange Plan

Joint Research

Extended from last FY, the basic technologies such as single molecule detection, surface modification and fluidic control will be established to develop the single cell and molecule analysis method on micro- and nano chemical chip. The objectives are creation of new research fields through a promotion of cross-cultural exchange with Uppsala University (medical biology), University of South Australia (surface chemistry) and IBM (IT and MEMS) as pioneers of different fields, and creation of a network to develop young prospects through promotion of exchanges of young researchers with Nangyang Technological University and Swiss Federal Institute of Technology Zurich as groups in same fields. Specific plans are as following. In the University of Tokyo, the whole research is summarized and integrated, the single cell analysis device is developed for medical application and the basis is developed for expanding to analyses of circulating tumor cells (CTCs) and stem cells such as ES and iPS.

In the collaborative research with Uppsala University in Sweden, based on detection and low-temperature bonding methods for glass substrates established previously, detection of a single molecule in an extremely low-volume sample from a single cell will be targeted by a biomolecule measurement using molecule patterning in an extended nanochannel. With University of South Australia in Australia, based on surface modification techniques in micro- and nanochannel developed previously and chemical characteristics of solutions in extended nanochannels clarified previously, fluid dynamic characteristics including flow velocity profile and viscosity will be elucidated. With IBM Watson Research Center in U.S., a detection method of molecules and ions in extended nanochannel will be developed by embedding nanowires in fluidic channels using low-temperature bonding methods. With Nangyang Technological University in Singapore, developments of basic technologies for devices exploiting photonics will be continued and their applications to extended-nano channel are discussed. With Swiss Federal Institute of Technology Zurich in Switzerland, design methodologies of cell-culturing channels based on biophysical knowledge and analytical devices through single molecule fluorescence detection of cell secretion in extended nanochannel will be established to discuss a design policy of single cell and molecule analysis devices.

In addition, young researchers and students in master and doctoral courses will be sent to the partner organizations for about two weeks per man to learn techniques of the partners and deepen exchanges. At the same time, abilities for research accomplishments of the researchers and students will be polished. Moreover, international young researchers and students will be accepted for about one person (one week) from each partner country to teach basic technologies of micro- and nano chemistry in the University of Tokyo. As explained above, young researchers and students will be exchanged with each other, which will results in enough understanding of their methodologies and technologies and promotion of a smooth collaborative research.

Seminar

Extended from last FY, joint seminars will be held once with each partner organization. Researchers and students of Nagoya University, Waseda University and Kyoto University as cooperating institutions of the University of Tokyo will attend the seminars to present their research and share the latest results. Moreover, promotion of stronger collaborative research and their practical plans will be discussed in detail. Opportunities to make English

presentations and discussions will be given to as many students as possible to foster their abilities of communication in English. Furthermore, as the last FY of this program, a joint symposium of the five countries will be held in Japan in order to share the progress of this program and transmit them to the society. In addition, a summer camp inviting young researchers and students from abroad, which was highly appreciated in last FY and FY before last, will be also held in this FY for a training of research proposals and opportunities of exchanges.

Researcher Exchanges

Students will be encouraged to make presentations to foster their presentation and discussion skills in English using the opportunities of the joint seminars, sending researchers and summer camp as explained above. In addition, the research progress of this project will be presented in the largest international conference in this field, The 16th International Conference on Miniaturized Systems for Chemistry and Life Sciences (μTAS2012, Okinawa, Japan), typical conferences in the related fields, The 28th International Symposium on MicroScale Bioseparations (MSB2012, Shanghai, China), The 4th International Symposium on Microchemistry and Microsystems (ISMM2012, Zhubei City, Taiwan), The 38th International Symposium on High Performance Liquid Phase Separations and Related Techniques (HPLC2012, Anaheim, USA), The 19th International Symposium, Exhibit & Workshops on Electro- and Liquid Phase-separation Techniques (ITP 2012, Baltimore, USA), and the largest domestic conference in this field, The 25th Collegium of Society for Chemistry and Micro-Nano Systems. The progress of each organization will be transmitted and exchanged with each other.