World Premier International Research Center Initiative (WPI)
FY 2018 WPI Project Progress Report

Host Institution	Kanazawa University	Host Institution Head	Koetsu Yamazaki
Research Center	Nano Life Science Institute (NanoLSI)	Center Director	Takeshi Fukuma

Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2019) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.
* Prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

Summary of State of WPI Center Project Progress (write within **2 pages**)

1. Research Progress

In FY2017, we set up various interdisciplinary research subjects and summarized them into three major projects: (1) development of novel nanoprobe technologies, (2) nano-level understanding of cellular functions and cancer, and (3) establishment of "Nanoprobe Life Science." The efforts to achieve these goals were initiated in FY2017 and have been continued through FY2018. As for (1) and (2), here we mainly report the current status of the long-term and interdisciplinary projects initiated after the launch of NanoLSI. As for (3), we present selected achievements that can highlight the progress of the fusion of the four major research fields: nanometrology, life science, supramolecular chemistry and computational science, leading to the establishment of Nanoprobe Life Science.

(1) Development of novel nanoprobe technologies

- **Scanning probe microscopists** continued to explore various designs and fabrication methods of nanoprobes suitable for novel live cell imaging methods. Some of the probes developed were applied to live cell imaging, which has provided promising results. For example, **Fukuma** established a method to fabricate a Si long nanoprobe suitable for penetration of a cell membrane and thereby succeeded in 3D visualization of intra-cellular structures of a HeLa cell by AFM. This demonstrates the possibility of nanoendoscopic imaging of a live cell for the first time. **Ando** developed a nanopipette with a very thin wall (~6 nm) to improve the spatial resolution of SICM, and a low-noise wideband current amplifier to improve the speed of SICM. **Korchev** developed nanopipette sensors for detecting pH and reactive oxygen species (ROS), and applied them to map the distribution of local proton release at the surface of a gastric parietal cell, and to profile the ROS distribution across the membrane of a live LNCaP cell.
- **Supramolecular chemists** had intensive discussions with life scientists and determined chemicals whose local distribution near and inside a cell is important for understanding specific biological phenomena. They have already started to explore the possibilities of their design and synthesis. This is a relatively long-term project. As a shorter-term project, they started to explore possibilities to modify the functional macromolecules that they have been investigating and integrate them to a nanoprobe. They have already synthesized several kinds of host molecules including macrocyclic compounds (**Ogoshi** & **MacLachlan**), metal complexes (**Akine**), and helical polymers (**Maeda**). The probe functionalization with these molecules is now under investigation. Meanwhile, **Takahashi** and **Asakawa**, who are scanning probe microscopists with chemistry backgrounds, performed a detailed methods survey for chemical functionalization of nanoprobes and started discussions with supramolecular chemists on practical ways to apply these methods to their original macromolecules.
- **Computational scientists** continued to work on the modeling, simulations, and analysis of complex biological systems and their scanning probe microscopy (SPM) measurements. **Foster** set up an SPM database server with some analysis functions, and we have now started to accumulate SPM data for big data analysis in the future. In addition, he developed a method to reproduce a molecular model from AFM data by machine learning (**Nano Lett. 2018, ACS Nano 2018, NPJ Comp. Mater. 2018 (x 2), ACS Nano 2018, Sci. Adv. 2018**). **Mikhailov** performed modeling and simulation of proteins such as myosin V, F1-ATPase and ABC transporter MsbA (**Int. J. Mol. Sci. 2018 (x2)**). In particular, he successfully reproduced HS-AFM observation of myosin V dynamics and clarified the underlying mechanism. He is also working on the modeling of more complicated systems such as biopolymers, biomembranes and cytosol. **Sumikama** developed a simulation method for 2D/3D-AFM imaging of chromosomes. Together with Foster, he also started to develop a method for converting 3D-AFM data to a molecular model by the machine learning approach.

(2) Nano-level understanding of cellular functions and cancer

- **Basic cell biologists** have started to address basic principles of cellular functions by observing

nanostructures and nanodynamics of cells using BioSPM, and several collaboration projects are getting on track. **Matsumoto** proposed a novel model of HGF-induced cell signaling, which was uncovered by HS-AFM, and is now focusing on single-molecule imaging in live cells to validate this model. **Hirao** found that a microbiota-derived metabolite caused dysfunction of self-renewal of hematopoietic stem cells by affecting cytoskeleton dynamics (**Cell Stem Cell, 2018**). To understand the detailed mechanisms, the Hirao group started a collaboration with RIKEN researchers to develop whole bone marrow cell analysis with advanced electron microscopy technology based on intracellular nanostructure analysis, which will be combined with morphologic analysis using Bio-SPM. **Wong** visualized the native nuclear pore complex (NPC) by HS-AFM, and revealed the role of the central channel NPC component Nup62 in regulating the differentiation state of squamous cell carcinoma (SCC) cells (**EMBO Reports, 2018**). **Hanayama** identified a novel regulator of lysosomal exocytosis by phagocytes that promotes heterolysis of tumor cells (**J. Immunol., 2018**), and succeeded in the observation of the internal structure of exosomes including exosomal DNA with high resolution AFM.

- **Cancer researchers** performed interdisciplinary research with scanning probe microscopists and supramolecular chemists to examine the dynamics of cancer-related gene products and intracellular metabolism at the nanoscale. **Wong** discovered that a structural change of nuclear pore complex (NPC) is linked to the process of colon cancer progression. **Hirao** identified that a vitamin metabolite is significantly upregulated in cancer cells, and developed a novel method to detect the metabolite by using a supramolecule pillararene. **Matsumoto** developed an HGF-inhibitory macrocyclic peptide (HiP-8), and identified that HiP-8 specifically recognizes the active HGF and suppresses it (**Nat. Chem. Biol.**, **2019**), indicating HiP-8 is useful for diagnosis and therapy of cancer. **Yano** demonstrated a novel drug resistant mechanism of lung cancer (**Nat. Commun.**, **2019**), and started AFM analysis of EML4-ALK that drives lung cancer development. Moreover, **Nakajima** found a novel regulatory mechanism of cytochrome P450 by RNA editing, and successfully established a P450 detection system by HS-AFM.

(3) Establishment of the novel research field “Nanoprobe Life Science”

We aim to establish the new research field, "Nanoprobe Life Science," by combining our expertise in the four major research fields (①Nanometrology, ②Life Science, ③Supramolecular Chemistry and ④ Computational Science). In FY2017, we decided to start combining two adjacent research fields, and subsequently exploring the fusion of the three or four disciplines. In FY2018, we continued this effort and some of the projects have reached the stage to publish their results as highlighted below.

①×② HS-AFM imaging of nanodynamics of various proteins such as ClpB (**Nat. Commun., 2018**) and KaiC (**Nat. Commun., 2018**); and supercoiled DNA (**ACS Nano, 2018**).

①×③ Self-assembling of pillar[n]arenes visualized by AFM (**Commun. Chem., 2018**).

①×④ Clustering 3D-AFM data by graph-bootstrapping (**Nat. Commun., 2018**); 3D-AFM experiments and simulation of biofouling-resistant interfaces (**ACS Nano, 2018**).

①×②×③ HS-AFM visualizes regulation of HGF dynamics by Hip-8 (**Nat. Chem. Biol., 2019**).

2. Generating Fused Disciplines

Measures to advance research by fusing disciplines: NanoLSI organized 10 T-meetings for intensive discussion between two research groups from different fields, and 2 Colloquiums for all members to inform one another of the progress of their projects. Transdisciplinary research promotion grant with a total of ¥27 million was provided for 22 projects pursued by two or more young researchers in different fields. The 1st advisory board meeting held in last February suggested approach to fused disciplines by facilitating direct communications among young researchers.

3. Realizing an International Research Environment

Enhancing international recognition: NanoLSI organized the Bio-AFM Summer School for junior researchers, Bio-SPM Collaborative Research for established researchers, and NanoLSI Fellow Program for PI-level researchers, in which 23 researchers from overseas participated. NanoLSI held its 2nd Symposium in London, in which 5 invited speakers and 32 researchers participated from UK and other foreign countries.

4. Making Organizational Reforms

Research professorships and evaluation-dependent allowance: The research professors have reduced non-NanoLSI duties as well as enjoy a special allowance depending on their individual evaluation. **Ripple effect**: Based on the above-mentioned pilot scheme of NanoLSI, Kanazawa University has decided to apply the evaluation-dependent annual salary system to all professors/researchers employed by the University from FY2019 onwards.

5. Efforts to secure the Center’s Future Development over the Mid- to Long-term

The university’s commitment: It has provided NanoLSI with research funds of ¥60 million per year, covered the basic salary and social insurance contributions for PIs and researchers who had been employed before the inauguration of NanoLSI, and secured 3000 square meters for the NanoLSI facility. **Fostering the next-generation researchers**: NanoLSI has hired 5 junior PIs who will play important roles in interdisciplinary research. All the junior PIs have been given tenure-track positions.

* Describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 viewpoints, place emphasis on the following:
  (1) Whether research is being carried out at a top world-level (including whether research advances are being made by fusing fields).
  (2) Whether a proactive effort continues to be made to establish itself as a "truly" world premier international research center.
  (3) Whether a steadfast effort is being made to secure the center's future development over the mid- to long-term.

1. Advancing Research of the Highest Global Level

* Among the research results achieved by the center, concretely describe those that are at the world's highest level. In Appendix 1, list the center's research papers published in 2018.
* Regarding the criteria used when evaluating the world level of center, note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

[Outline]

In FY2017, we set up various interdisciplinary research subjects and summarized them into three major projects: (1) development of novel nanoprobe technologies, (2) nano-level understanding of cellular functions and cancer, and (3) establishment of "Nanoprobe Life Science." (Fig. 1). The efforts to achieve these goals were initiated in FY2017 and have been continued through FY2018. As for (1) and (2), here we mainly report the current status of the long-term and interdisciplinary projects initiated after the launch of NanoLSI. As for (3), we present selected achievements that can highlight the progress of the fusion of the four major research fields: nanometrology, life science, supramolecular chemistry and computational science, leading to the establishment of Nanoprobe Life Science. Our achievements in FY2018 include

-Peer-reviewed papers: 81 (43% internationally co-authored; 20 with an IF > 10; 27 with an IF > 7),

-Invited lectures at international conferences: 73,

-Funding procured: ¥866,691,892 overall (incl. 21 major grants in the order of ¥10,000,000 or more).

These achievements are of the highest global level for an institute with 72 researchers (as of March 2019). Of particular note is the finding by Hirao, Oshima and others of "unexpected linkage between self-renewal of stem cells and cytoskeletal dynamics under high fat diet," which made a major impact upon its publication in **Cell Stem Cell (IF: 23.29)**.

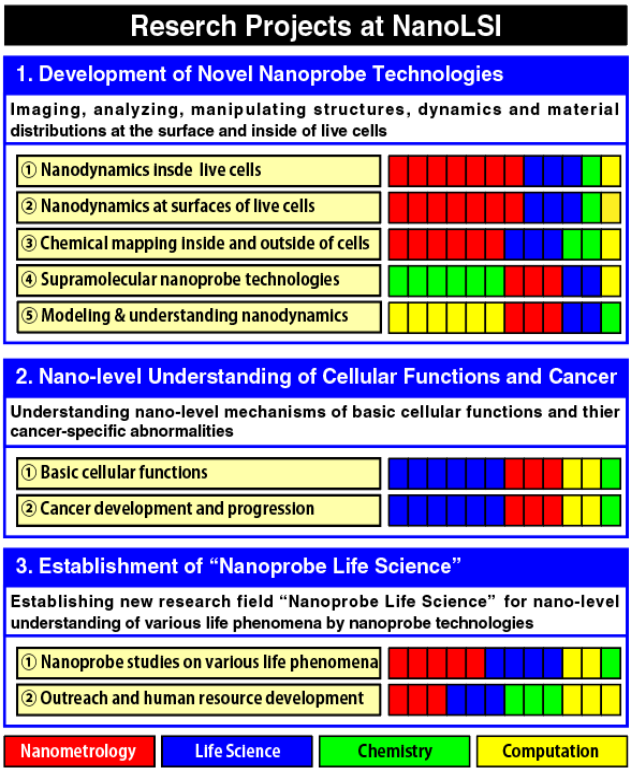


Fig. 1: Research projects at NanoLSI and contributions from the four major disciplines to each project.

[Outline, plan, and progress of each research subject]

(1) Development of Novel Nanoprobe Technologies

Here, we will develop nanoprobe technique to visualize nanodynamics at the surface and inside of live cells. In addition, we will also develop a technique to measure nanoscale distribution of specific molecules or ions using a chemically functionalized probe. Furthermore, we will develop a method for analyzing the measured data and understanding the nanoscale mechanisms of the molecular or cellular functions as well as the measurement principle of the newly developed nanoprobe technologies.

① Visualizing nanodynamics inside live cells (Main PI: Fukuma)

(Objective)

We aim to develop a nanoendoscopic imaging technique to visualize nanoscale structures and dynamics inside live cells.

(Background and Methods)

We will develop 2D/ 3D nanoendoscopic imaging techniques. By scanning a long nanoprobe in a 3D space, including the inside of a live cell, we will visualize intra-cellular nanostructures. In addition, by controlling the tip position inside a cell, we will perform a local 2D imaging on the backside of the cell membrane or on an organelle surface (Fig. 2).

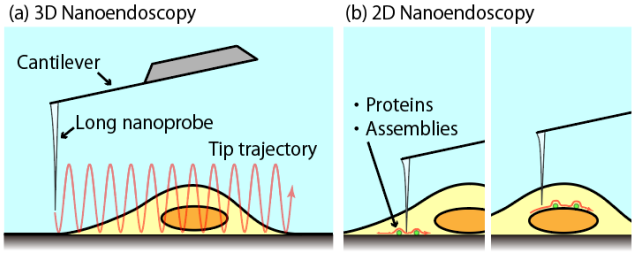


Fig. 2: 2D & 3D nanoendoscopic imaging of a live cell

(Subjects and Plans)

Table 1: Research subjects and plans for the development of nanoendoscopic imaging technique

Subjects	FY2017-2018	FY2019	FY2020	FY2021	FY2022	FY2023-2026
Nanoprobe	**Long nanoprobe** (EBD, FIB-milled, CNT probes)		**Functionalized long nanoprobe** (surface modification, molecular sensors & machines)		**Functionalized long nanoprobe** (improvements in productivity & performance)	・Applications & improvements (usability, productivity, reproducibility) ・Combination with other methods
Microscope	**Prototype I** (combination of 3D-AFM and OM, large scan, FPGA, Tip scan)		**Prototype II** (High speed, large capacity, improved force detection & scanning methods)		**Prototype III** (Usability, analysis software, quantitative capability)	
Measurement Method	2D & 3D imaging of a cell, chromosome, model structures (**Regardless of resolution**)		2D & 3D imaging of a cell, chromosome, model structures (**Spatial resolution< 10 nm**)		2D & 3D imaging of a cell, chromosome, model structures (**Time resolution < 10 s/frame**)	

(Research Progress)

・Development of Long Nanoprobes

(1) To fabricate long nanoprobes for intra-cellular imaging, we installed the focused ion beam - scanning electron microscope (FIB-SEM) with a gas-injection system. With this system, we established the methods for fabricating electron beam deposited (EBD) carbon probes and FIB milled probes with a diameter of 100-300 nm and a length of 5-10 μm. We tested their applicability to the cell membrane penetration and found that an FIB milled probe is more suitable due to its higher toughness and hydrophilicity. However, we also found that the repeated penetration often results in the contamination of the tip apex. This significantly reduces the success rate of the penetration. To solve this problem, we are developing a method to coat the probe surface with an anti-fouling film.

(2) To fabricate long nanoprobes for imaging smaller 3D structures such as chromosomes and other model 3D structures, we used the FIB-SEM with a nano-manipulator. With this system, we succeeded in fabricating a CNT probe with a diameter of 10-50 nm and a length of 100-1,000 nm. We are still optimizing the fabrication conditions to improve the productivity. Meanwhile, to control the apex of the CNT probe with a single-nanometer precision, we installed a transmission electron microscope (TEM) combined with a custom-built nano-manipulator. Although we confirmed that the installed system works fine for observation and manipulation, the small travel ranges of the manipulator did not allow us to attach a CNT inside the TEM chamber. We are now developing a device for the pre-alignment of the positions of the CNTs and the AFM tip before transferring the holder to the TEM chamber. Knowing that the hydrophobicity of the CNTs may cause problems due to the adhesion to the biomolecules, we are also exploring alternative options. One of them is cellulose nano crystals (CNCs), which have mechanical strength similar to that of CNTs yet their surface is hydrophilic. Prof. MacLachlan (PI in supramolecular chemistry and an expert in the field of CNC study) fabricated relatively long CNCs and we just confirmed their molecular-scale structures by AFM.

・Development of Microscope

We designed an AFM head to be combined with a laser confocal microscope (Fig. 3). This AFM has a 100 μm XY sample scanner and a 9 μm Z tip scanner. This scan range is large enough to image a live cell. In addition, a standard size petri dish can be directly mounted on the sample holder and its temperature is kept constant by an integrated heater. We have already installed the confocal microscope and completed the basic AFM design. We are now assembling the parts for testing. Meanwhile, we are developing the AFM control hardware, firmware and software. We installed six SSDs with a RAID0 setup, which enabled high-speed 3D-AFM imaging with a high pixel resolution. We also completed the basic design of the extremely-low-latency IO board for the high-speed FPGA circuit. This will become the platform of the next generation AFM controller. We are now implementing the firmware and software for various cellular imaging modes.

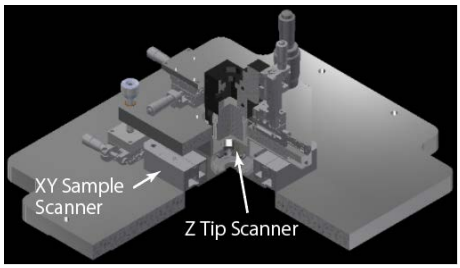


Fig. 3 : AFM head to be combined with a laser confocal microscope.

・Development of Measurement Methods

(1) Intra-cellular imaging: Using the developed FIB-milled probe, we succeeded in the 3D imaging of the inside of a live HeLa cell. This image demonstrates the possibility of 3D nanoendoscopic imaging for the first time in the world. There still remain some issues to be overcome. We found that the cell viability strongly depends on the interval between the cell penetrations and the diameter of the probe. We are now optimizing the conditions for the 3D imaging and the probe fabrication.

(2) Model 3D structures: We are developing a method for fabricating model 3D structures made of CNTs. We have succeeded in fabricating some of the simple models and used them for 3D-AFM imaging. One difficulty we found was that the probe does not necessarily get through the CNTs. To solve this problem,

we are developing a new probe approaching method with a lateral modulation.

(Expected World's Top-level Achievements)

AFM is originally designed for visualizing a 2D height distribution of a surface. While this method allows us to image subnanometer-scale surface structures of biomolecules, the objects to be imaged should be fixed on a hard substrate. Now, we are about to change this concept by introducing 3D-AFM. So far, we have demonstrated that even the 3D distributions of the mobile water (i.e. hydration structures) and flexible molecular chains can be visualized by 3D-AFM (*ACS Nano, 2018*). Here, we further demonstrated that even the floating nanostructures in a live cell can be visualized. This is a major breakthrough in the AFM community. From the biological point of view, fluorescence microscopy has been the most powerful technique for visualizing structures in a live cell. However, it visualizes only the labeled molecules or structures and typically requires a priori knowledge of the objects to be imaged. In contrast, bio-SPM does not require labeling. Therefore, we may be able to visualize unexpected nanostructures. So far, AFM has been used for imaging structures and dynamics of isolated proteins and organelles by postulating the nanodynamics observed are the same in or on a live cell. Once we establish the method to image nanodynamics inside the live cell, we may be able to answer the long-standing questions on the validity of the isolated model systems.

② Measuring nano-dynamics at surfaces of live cells (Principal Investigator: Ando)

(Objective)

We aim to materialize high-speed scanning probe microscopy (HS-SPM) techniques, including (i) HS-SICM enabling *in-situ* observation of protein molecules actively functioning on the membrane surfaces of live cells and intracellular organelles, and in the interior of de-roofed cells, (ii) assay systems enabling observations of purified membrane proteins in asymmetric environments across the membrane, and (iii) devices for further improving the speed performance of HS-AFM. While carrying out these developments, we will reveal the functional mechanism of proteins by HS-AFM imaging.

(Background and Methods)

The Ando group developed HS-AFM enabling real-time, high-resolution imaging of individual biological nano-machines during their functional activity. HS-AFM has displayed a great power in visualizing purified protein molecules in dynamic action. Nevertheless, there are still many interesting targets and phenomena that are unable to be captured with the current HS-AFM. To break through this limitation, we will develop various techniques that will enable the observations described in the Objective.

(Subjects and Plans)

Table 2: Research subjects and plans for developing HS-SICM capable of in-situ imaging

Subjects	FY2017-2018	FY2019	FY2020	FY2021	FY2022	FY2023-2026
Nanoprobes	**Nanoprobes for high-speed/high-resolution SICM**		**Optimization of SICM nanoprobes for low noise, and high resolution**			・Full applications to a variety of biological samples ・Imaging capability other than topography ・Development into a product
Microscope	**HS-SICM I** (towards better spatiotemporal resolution) **HS-AFM I** (extended functionality)	**HS-SICM II** (high spatiotemporal resolution, easier operation, long-time stability) **HS-AFM II** (faster imaging rate, establishment of combined systems)		**HS-SICM III** (polishing up through imaging various biological samples) **HS-AFM III** (established for faster imaging with new functionality)		
Imaging	Preparation of small suspended membranes, membrane proteins and de-roofed cells. Test imaging of cells and proteins by SICM	Test imaging with SICM: De-roofed intracellular architectures, surfaces of cells and intracellular organelles Test imaging with HS-AFM: Imaging membrane-embedded membrane proteins & manipulated proteins		Imaging with SICM: various biological samples, sub-molecular resolution, faster imaging, truly non-invasive imaging Imaging with HS-AFM: biological samples in various environments		

(Research Progress)

・Development of nanoprobes for SICM

We have been trying to improve the pore size and wall thickness of the nano-pipette tip, which limit the spatial resolution of SICM. To this end, we took two approaches: plasma etching of the pipette end and the use of a carbon nanotube (CNT). We succeeded in thinning the wall by etching down to ~6 nm without significantly increasing the pore size, resulting in increased spatial resolution. To insert a CNT into the nano-pore of a glass pipette, we employed two methods: spontaneous insertion into a lipid bilayer formed at the tip end and guiding a CNT into the pore by dielectrophoresis (Fig. 4). We confirmed CNT insertion in both methods. However, the success rate is not high enough in both methods. We are now further improving the preparation of glass pipettes and CNT probes.

・Development of HS-SICM

We have already built a HS-SICM system capable of fast imaging, ~100-times faster than conventional systems. To further increase the speed, noise reduction of ion current detection at high frequencies is

mandatory. To this end, we developed a current amplifier and succeeded in suppressing the current noise at high frequencies (Fig. 5).

・Development of faster HS-AFM

The highest possible imaging rate of our current HS-AFM system is ~15 frames/s (fps) under the conditions of 150 × 150 nm^2 scan range and 100 scan lines. The devices limiting the speed are the Z-scanner and the detector of cantilever oscillation amplitude. We developed a new Z-scanner with a resonant frequency of ~1.4 MHz and a maximum displacement of 300 nm at 100 V (Fig. 6). The speed of Z-scanner displacement is now ~6-times improved. We are now increasing the amplitude detector's speed performance. We expect to achieve 60-80 fps after all.

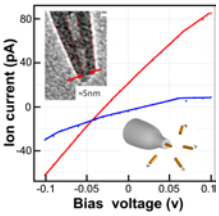


Fig. 4: CNT insertion by dielectroporesis.

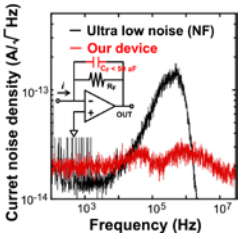


Fig. 5: Low noise amp.

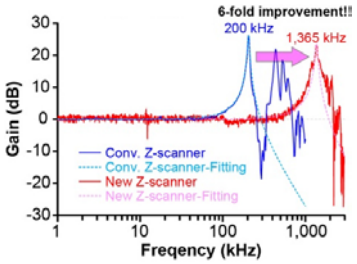


Fig. 6: Faster Z-scanner.

・Development of assay systems for membrane proteins

A variety of purified proteins in dynamic action have been successfully filmed with HS-AFM. Nonetheless, imaging membrane proteins under (near) physiological conditions has been proven to be difficult. This is in part because of the membrane softness and largely because of difficulty in furnishing the assay system with physiologically relevant asymmetric environments across the membrane. To solve this problem, we developed a new assay method. This method allows us to prepare asymmetric environments, including different species and concentrations of ions and molecules and even electric potential across the membrane. To test this assay system, we prepared and characterized a membrane protein (ABC transporter, MsbA) that transports lipid A in bacteria and a membrane-binding protein (pore-forming protein, streptolysin O).

・De-roofing cells and imaging cell interior

One of the keys to successful HS-AFM/ HS-SICM imaging of the exposed interior of de-roofed cells is gentle removal of a part of the cell membrane while keeping the exposed intracellular architectures functional. We combined detergent-based and mechanical de-roofing methods. In the initial phase of this project, we succeeded in exposing and imaging actin/myosin stress fibers with full contractility (Fig. 7). We will develop other de-roofing methods to retain more fragile intracellular architectures by using, for example, membrane pore-forming proteins and amphiphilic polymers used for preparing nanodisks.

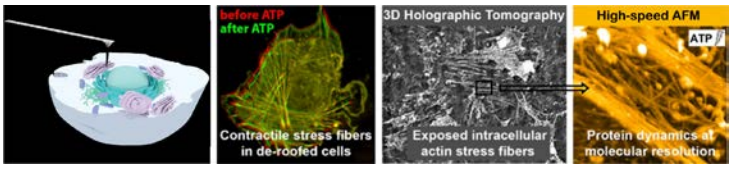


Fig. 7: De-roofing, 3D holographic & HS-AFM imaging of exposed intracellular structures.

(Expected achievements of the highest world level)

The Ando group established the world's fastest HS-AFM for biological studies and developed a fast ion-current detection technique. We will add a high-resolution imaging capability to HS-SICM to materialize the observations mentioned in the Objective. The upcoming technology has the potential to surpass our HS-AFM and have a great impact on the life sciences.

③ Material distribution measurement inside and outside of cells (Principal Investigator: Korchev)

(Objective)

We aim to develop a nanopipette-based measurement method that visualizes the biomolecule distribution inside and outside of live cells.

(Methods)

We are developing a chemical sensor based on scanning ion conductance microscope (SICM). With SICM, voltage is applied between two electrodes—one placed inside and one outside a probe—and the ionic current is recorded while scanning the sample surface, which allows the nanoscale surface shape of live cells to be visualized. Through regulation of the applied voltage and chemical modification of the

nanopipette tip, SICM can be used as a sensor to measure chemical distribution near the cell surface (Fig. 2).

(Subjects and plans)

Table 3: Research subjects and plans for the development of material distribution measurement

Subjects	FY2017	FY2018	FY2019	FY2020	FY2022	FY2023-2026
Chemical sensor	**Nanopore sensor** (modification, method, principle)			**Multi-barrel probe** (measure different chemicals simultaneously)		・Nanobiopsy technique (part of cell, tissue) ・Time-dependent single cell gene expression
Cell function mapping	**Nanoparticle uptake, cell interaction, Lipid imaging**		**Cell metabolites measurement using microelectrodes and ISFETs**		**Signal molecules measurement using nanopore chemical sensors**	
mRNA evaluation	**System for picking up small amount of cytosol**		**Development of high-throughput cytosol collection system**		**System for PCR in the nanopipette**	

To achieve the above objectives, three research subjects are examined (listed in Table 3).

(Research progress)

・Development of a chemical sensor

We developed a nanosensor that is capable of sensing pH by using a nanopipette modified by glucose oxidase and poly-L-lysine. Ion current through the nanopipette is measured as an indicator of the charge of modified molecules, which changes with pH. We succeeded in detecting the pH changes and the proton release near a gastric parietal cell. In addition, we acquired the pH profile and cell topography simultaneously by using scanning ion conductance microscopy (SICM) distance control. Furthermore, the pH measurement based on the nanosensor has a very high temporal resolution, of the order of 1 ms. In the future, we aim to measure cell-derived metabolites by modifying supramolecular polymers that can detect specific chemicals, such as by introducing pillararene into the nanopipette. We also developed an electrode-based new chemical sensor for in vitro study of the toxicity of magnetic nanoparticles (NP) based on the measurement of intracellular reactive oxygen species (ROS) by a novel nanoelectrode. The probe for measuring intracellular ROS using platinized carbon nanoelectrodes with a cavity on the tip was integrated into a micromanipulator on an upright microscope (Fig. 8, *Sci. Rep. 2018*).

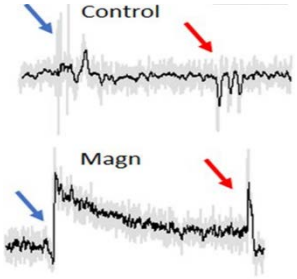


Fig.8: ROS intracellular measurements in individual LNCaP cells.

・Cell function mapping

For the purpose of direct visualization of PM2.5/extracellular vesicle uptake, we collaborated with Prof. Hanayama to measure exosome uptake by using SICM. Since the combination of fluorescence microscopy and SICM is indispensable and measurement throughput is also important, we developed a new SICM equipped with an XY coarse-positioning stage to quickly find target cells. Furthermore, we also developed a new fabrication method for sharper nanopipette. Using the newly developed nanopipette, we succeeded in observing the topography of a single exosome and imaging the endocytosis process as a time-lapse images. We are currently trying to observe exosomes on live cell surfaces. SICM also can be used to map surface charge. We demonstrated the application of this method to an incomplete polystyrene film (neutral) on a glass substrate (negative charge). We are trying to detect phosphatidylserine-derived negative cell surface charges during apoptosis (Fig.9).

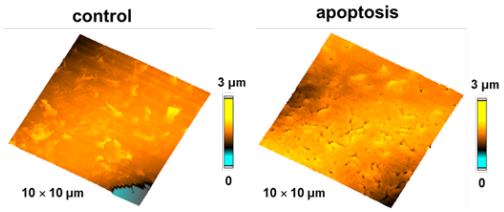


Fig.9: SICM charge mapping of live cell.

(Expected achievement of the world's highest standard)

If the above objectives are achieved, nanoscale measurement of metabolites, hormones, and genes, which was considered impossible using previous technologies, will be possible. The study of those subjects would be facilitated with our newly developed technologies, allowing the achievement of the world's highest standards in nanometrology and life sciences.

④ Supramolecular nanoprobe development (Principal Investigators: Akine, Maeda, Ogoshi, MacLachlan)

(Objective)

We aim to develop new probes for high-performance nano-endoscopy, which are functionalized with the

latest supramolecular technology.

(Methods)

In this study, we develop highly selective probe molecules based on recent advances in supramolecular chemistry and molecular recognition chemistry. Further, we aim to develop nanoprobes with enhanced performance. We develop dual-mode probes functionalized with responsive molecules and probes for molecular observations and manipulations with nanoscale precision.

(Subjects and plans)

Table 4: Research subjects and plans for the development of supramolecular nanoprobes

Subjects	FY2017	FY2018	FY2019	FY2020	FY2021	FY2022	FY2023-2026
Supramolecular nanoprobe	**Design and synthesis of new probe molecules** (responsive helical polymer, photoswitching receptor, surface analysis, bioconjugate probes, etc.)			**Improvement of new probe molecules** (highly sensitive and selective probes, reactive probes, etc.)			・Applications & improvements (in vivo sensing) ・Switching of dual-mode probes
Nanolevel cancer research	**Molecular sensors for biomolecules** (glucose, pH, oxygen, lactate, oncometabolites, etc.)			**Development of new probes modified with sensors** (investigation of sensing ability in cellular environments)			

To achieve the above objectives, we examine two research subjects, as presented in Table 4.

(Research progress)

・Development of fundamental supramolecular nanoprobe technology

To gain a deeper understanding of protein and biomembrane surfaces, analysis of chemical information in addition to morphological information at the nanometer scale is needed. To this end, specialized probe molecules that can detect specific chemical information are necessary. Therefore, the goal here is to identify surface functional groups with high selectivity, sensitivity and nanometer-scale accuracy. It is effective to introduce cyclic molecules, helical polymers, metal complexes, and peptides with highly selective recognition abilities for each target molecule. We successfully developed polymers with chiral recognition abilities (*J. Am. Chem. Soc., 2018*) and macrocyclic compounds with alkane recognition abilities (*Chem. Rev., 2016*), which were studied mainly in homogeneous solutions. Therefore, we will introduce these molecules to a probe tip and study the substrate surfaces (Fig. 10). The ON/OFF switch of molecular recognition ability is also important. At present, different probes need to be used to determine the concentrations of chemical species and surface functional groups following morphological observations of the surface. Thus, we will provide a switching function for the probes that activate their function only when needed. We have successfully developed switching host molecules that change their recognition behavior in response to photoirradiation *(J. Am. Chem. Soc., 2018*), organic anions (*Nature Commun., 2017*), redox reactions (*Chem. Eur. J., 2019*), etc. We have also developed new living polymerization methods to immobilize helical polymers on the substrates and probes. We are now trying to develop new host molecules that can switch the recognition ability toward biofunctional molecules based on the above-mentioned strategy.

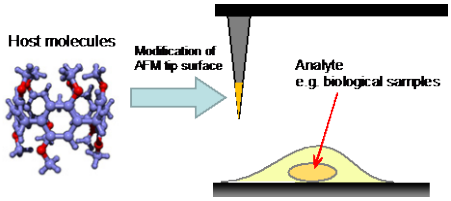


Fig. 10: Development of new selective probe molecules for nanoendoscopy.

・Development of application technology for nanoscale cancer research

The region around cancer cells has chemical properties different from those around normal cells. Therefore, it is important to accurately determine the concentration distributions in real time at the nanometer scale. We are now designing selective sensors for oxygen, pH, and oncometabolites and will evaluate the local concentrations at the nanometer scale by combining these sensors with the nanoprobe technology. We will also use them to analyze biological samples, such as cells. Presently, we have succeeded in the selective recognition of 1-methylnicotinamide, one of the oncometabolites, using a pillararene derivative, and we have started to develop new sensor molecules that can bind O_2 and lactate or measure the temperature to probe the environment of cancer cells using the nanoprobe technology.

(Expected achievement of the world's highest standard)

If we achieve the above objectives, we will be able to determine the local concentrations of various substances at high spatial resolutions that have not been possible using any of the existing technologies. Clarification of these concentration distributions will contribute to a greater understanding of nanoscale substance transport in cancer cells. By comparing cancer cells to normal cells, advancements could be made in the understanding of substance transport in cancer cells and the abnormalities of metabolite production. This imaging study is only possible by combining our supramolecular chemistry sciences with nanoprobe technology, which can result in the world's highest standards in nanometrology and life sciences.

⑤ Elucidating nanodynamics from measured data (Main PIs: Foster, Mikhailov)

(Objective)

We aim to elucidate nanoscale structures and dynamics of biological systems by computational approaches such as mathematical modeling, simulation and machine learning. We also use these approaches to understand the mechanism of bio-SPM measurements.

(Background and Methods)

Bio-SPM provides direct information of the structures and dynamics of proteins and cells. However, due to the complexity of the biological phenomena, it is not always straightforward to understand the mechanisms from the observed bio-SPM images. In this study, we address this issue by using computational approaches. We will perform mathematical modeling of the complicated biological systems. With the developed models, we will simulate the biological phenomena and their bio-SPM measurements. Meanwhile, the images and movies obtained by the bio-SPM measurements will be analyzed by the advanced image processing or machine learning approaches.

(Subjects and Plans)

Table 5: Research subjects and plans for analyses of real models from measured data

Subjects	FY2017-2018	FY2019	FY2020	FY2021	FY2022	FY2023-2026
Simulation	Simulations of myosin, ATPases, dynamin, protein machines, lipid bilayers. Simulations of 3D-AFM images of fibrillar structures.		Simulations of allosteric interactions in protein machines, designed structures, probe penetration into a membrane.			Simulations and mathematical modeling of more complex biomolecular systems with higher functionalities.
Math. Modeling	Coarse-grained models for simulations of proteins. Mesoscopic models for protein assemblies. Multi-particle modeling of active colloids and membranes.		Mechanisms of allosteric interactions in protein machines. Design of protein-like machines' structures.			
Machine Learning	Establish AFM image analysis server and metadata protocols for automated categorization of experimental images.		Develop machine learning toolset for analysis of 3D-AFM images: feature extraction, tip identification, dynamic recognition, including soft systems and systems in solution.			

The NanoLSI machine learning infrastructure has been deployed in Kanazawa, with support for rapid AFM imaging using a graphical user interface, machine learning tools and an initial set of experimental analysis tools. A cycle of robust testing has just begun with a heterogeneous set of users from experiments and simulations across the NanoLSI. In parallel, we have made significant progress in developing a computer vision to molecular recognition in AFM (see Fig. 11) – the first paper for UHV studies has been submitted. We are also already actively developing its capabilities towards imaging of soft systems and for studies in solution. Alongside this, we have further published several key studies in the development of AFM simulations and machine learning in the context of molecular systems *(Nano Lett. (2018), ACS Nano (2018), NPJ Computational Materials (2018), ACS Nano (2018), NPJ Computational Materials (2018), Sci. Adv. (2018))*.

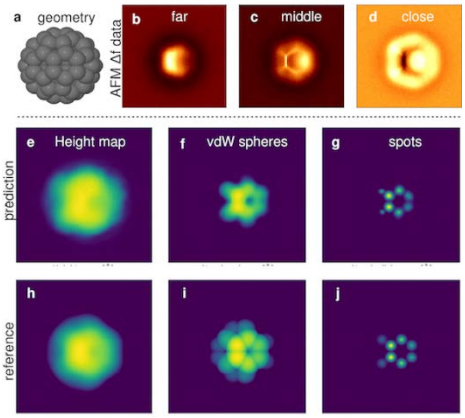


Fig. 11: Comparison of machine learning predictions of 2D image descriptors to reference calculations from AFM images of a C60 cluster.

・**Modeling and Simulation of Biological Systems (Mikhailov)** A. Single biomolecules. Together with T. Ando and N. Kodera, a dynamical model for operation of myosin V was developed and used to interpret experiments on AFM tip-induced myosin translocation; the model also reproduces the natural ATP-driven cycles of myosin (Fig. 12). A molecular model for ABC transporter MsbA was constructed in connection to experiments by T. Ando and K. Ngo. Principles of allosteric regulation and mutation effects in proteins were explored using sequence-specific elastic-network models (together with Y. Togashi from Hiroshima University). A comparative study of functional conformational dynamics in proteins was undertaken by combining high-performance all-atom MD simulations for F1-ATPase at Beijing Computational Science Research Center and coarse-grained simulations for this and other proteins investigated at NanoLSI. Review articles on protein design (Int. J. Mol. Sci., 2018) and coarse-grained modeling of proteins (Int. J. Mol. Sci., 2018) were published and an invited review on

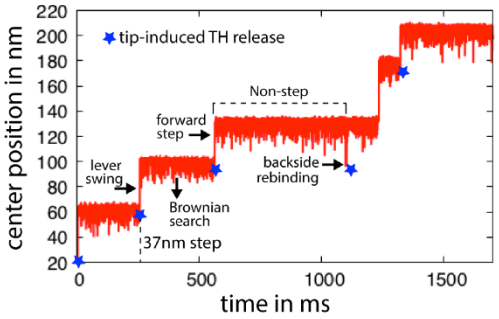


Fig. 12: Modeling tip-induced translocation of myosin.

functional conformational dynamics in protein machines was submitted to J. Royal Soc. Interface.
B. Mesoscale descriptions – polymers and biomembranes. A mesoscopic stochastic polymer model for dynamin filaments on deformable membrane tubes was developed and its parameters were determined from all-atom MD and coarse-grained simulations (in collaboration with Max Delbrück Center for Molecular Medicine and Free University of Berlin). Results are prepared for publication.
C. Cellular level – multiparticle systems. Nonequilibrium collective effects of conformational activity of proteins on transport phenomena in cytoplasm will be studied in multiparticle simulations (collaboration with Sendai, Chiba and Tokyo Metropolitan universities, a joint KAKENHI grant application has been approved). Models and simulation methods were already developed and test simulations have been performed.

・Topography and 3D-AFM Simulation of Chromosomes (Sumikama)

A polymer simulation code to visualize the dynamics of chromosome has been developed, and a theoretical method to compute topographic and 3D-AFM images using the Jarzynski equality was established. While computing the images, the oscillation of probes usually used in the AFM measurements was implemented. Fiber structures of the chromosome are found to be resolved both in the topography and 3D-AFM image. A code to make the well-known x-shaped form of chromosomes is under development.

(Expected World's Top-level Achievements)

Computational approaches such as simulation and machine learning have been a powerful tool for analyzing SPM data. However, their applications have been mostly limited to relatively simple systems consisting of atoms or small organic molecules. By combining these computational approaches with mathematical modeling techniques, we aim to analyze more complicated biological systems, which will lead to a significant development of the interdisciplinary research field Nanoprobe Computational Science. As this research is only possible by combining expertise in three different fields—nanometrology, life science and computational science—the outcomes should have a world's top-level competitiveness.

(2) Nano-level understanding of cellular functions and cancer

Fundamental understanding of the basic functions of cells and cancer-specific abnormalities at the nano level.

① Basic cellular functions (Principal investigators: Matsumoto, Hirao, Wong, Hanayama)

(Objective)

Understanding the basic principles of cellular functions by observing nanostructures and dynamics inside cells.

(Background and Methods)

NanoLSI has decided to engage in this project with a high priority on the integration of its flagship research areas SPM and cancer research. We set out three primary objectives to further understand the basic principles of various cellular functions such as cell proliferation, cellular differentiation, and cell-cell communication. We plan to apply the crowding analytical scanning probe technologies to several cellular nanostructures and dynamics imaging.

(Subjects and Plans)

Table 6: Research subjects and plans for the fundamental cellular functions

Subjects	FY2017	FY2018	FY2019	FY2020	FY2021	FY2022	FY2023-2026
Cell proliferation	Validation of the receptor activation mechanism by dynamic molecular imaging and simulation			Receptor mutation in cancer patients from the aspect of molecular dynamics			・Applications & improvements (usability, productivity, reproducibility) ・Combination with other methods
Cellular differentiation	Identification of regulators of cell differentiation			Nanoscale imaging of cells with EM, AFM & SICM			
Cell-cell communication	Visualization of dynamics of exosome secretion & uptake		Functional analysis of regulators for exosome secretion & uptake		Imaging of exosomal regulators using cancer and healthy cells		

(Research Progress)

・Cell proliferation (Matsumoto)

Matsumoto et al. have been investigating the dynamic mechanisms for hepatocyte growth factor (HGF)-induced MET receptor activation. In FY2018, a split luciferase assay indicated that MET receptor dimerization occurs even if one of MET cannot bind HGF (Fig. 13). Consistent with the results by high-speed AFM analysis, his group proposes a novel model of cell signaling (Fig. 14). The Matsumoto group has been focusing, presently, on single-molecule imaging in live cells, and on computational science to validate the new model.

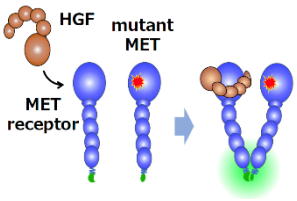


Fig. 13: The model proved by split luciferase.

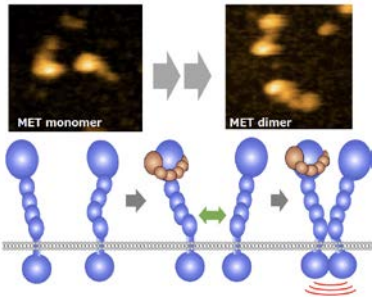


Fig. 14: A new model for HGF-induced MET activation.

・Cellular differentiation (Hirao and Wong)

Hirao et al. discovered that an abnormal diet, such as high-fat diet, causes dysfunction of hematopoietic stem cells by aberrant self-renewal (*Cell Stem Cell, 2018*). To elucidate the mechanisms of how an abnormal diet affects hematopoiesis, we have performed widely targeted metabolomics (over 100 metabolites) and untargeted metabolomics to identify unique functional metabolites in mice fed a high-fat diet. Among detectable metabolites, we found that a microbiota-derived metabolite causes dysfunction of hematopoietic stem cells, suggesting that microbiota dysbiosis may be critical for stem fate decision in hematopoiesis. Interestingly, we found that the microbiota-derived metabolite caused dysfunction of self-renewal by cytoskeleton dynamics. To understand how metabolites affect the morphological change of stem cells, the Hirao group has collaborated with the RIKEN researchers to develop whole bone marrow cell analysis with advanced electron microscopy technology based on intracellular nanostructure analysis. By a combination with morphologic analysis with Bio-SPM, we will seek to understand the detailed mechanisms of how lifestyle controls tissue stem cell homeostasis.

The control of intracellular traffic is vital for cell differentiation. Nuclear pore complexes (NPCs) are multi-protein turnstiles that regulate nucleo-cytoplasmic traffic. Recently, Wong et al. revealed the role of the central channel NPC component Nup62 in regulating the differentiation state of squamous cell carcinoma (SCC) cells. In undifferentiated SCC cells, Nup62 transports the transcription factor p63 into the nucleus to facilitate p63 driving gene expression that maintains the proliferative capacity and stemness of SCCs (*EMBO Rep., 2018*). Also, human influenza virus infects differentiated epithelial cells in the respiratory tract. In a pilot experiment, we captured the nanoscopic conformation dynamics of influenza protein hemagglutinin (HA) precursor using HS-AFM (*BBA Gen. Subjects, 2019*). We have further initiated interdisciplinary research with the Ando group and the Hanayama group to further visualize conformation dynamics of HA binding to liposomes/exosomes in differentiated epithelial cells. The Wong group also collaborated with the Fukuma group, and they plan to develop a novel FM-AFM to examine 4D-genome-architecture in undifferentiated and differentiated cells respectively.

・Cell-cell communication (Hanayama)

Hanayama et al. have been working on the molecular mechanisms underlying the exocytosis of exosomes and lysosomes. We identified several key molecules such as TSG101 that regulate the secretion of exosomes, and their roles in functions of exosomes are under investigation. We also identified myoferlin as a novel regulator that promotes lysosomal exocytosis by phagocytes. Through this process, phagocytes kill cancer cells by lysing them, a mechanism known as heterolysis (*J. Immunol., 2018*). To understand the nanostructures and nano-dynamics of exosomes, collaborations with the Fukuma and Takahashi groups are ongoing. Using high resolution AFM, we observed that exosomes had an unexpectedly distorted structure with many protruding areas. Also, breaking the exosomal membrane with a cantilever enabled the observation of the internal structure, including fibrous substances that are probably DNA (Fig. 15).

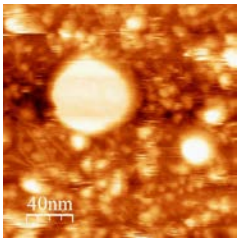


Fig.15: Visualization of the internal structure of exosomes.

(Expected World's Top-level Achievements)

By using an integrated approach with cutting-edge nanoscale imaging technology, we expect to obtain highly valuable information on nanoscopic cellular functions, such as dynamic protein-protein interaction, intracellular localization of metabolites, dynamic regulation of organelle and nanoparticles (exosomes), and the association between non-label stem and niche cells *in vivo*. All this information will provide novel insights to identify core machinery regulating cellular functions at the nanoscale. Therefore, we believe

that the outcome of these interdisciplinary projects will represent the world's top-level competitiveness in life science.

② Development of innovative therapeutic technology based on the understanding of cancer progression mechanism (principle investigators: Oshima, Yano, Hirao, Matsumoto, Nakajima, Wong, and Ando)

(Objective)

We aim to elucidate the nanostructure and dynamic changes associated with cellular transformation and malignant progression of cells. Based on these findings, we develop novel cancer diagnostic and therapeutic methods as well as precision medicine.

(Background and methods)

In this study, we will elucidate structural and biochemical abnormalities of cancer cells due to transformation and malignant progression, and dynamic changes of pharmacokinetics through combination of variety of biological approach together with nano level technique using high-speed AFM and SICM. We also promote metabolic measurement with a newly developed nanoprobe. Based on the novel information, we will develop applied studies that contribute to the development of new diagnostic and therapeutic methods.

(Annual plan)

Table 7: Research subjects and plans for the cancer progression and diagnosis/treatment

Subjects	FY2017	FY2018	FY2019	FY2020	FY2021	FY2022	FY2022-2026
Cancer Progression	**Cell surface structure / nuclear pore** (AFM, SICM etc.)			**Microenvironment / metabolite analysis** (cryoSEM, nanoprobe)			・Establishment of novel concept & mechanistic insight ・Proof of concept for diagnosis and treatment
Cancer Diagnosis	Technology establishment of PET imaging diagnosis for growth factor receptor activation status			Clinical study of PET imaging diagnosis for growth factor receptor activation status			
Cancer Treatment	**Cell surface structure / fusion-protein distribution** (AFM etc.)			**Protein-drug interaction** (cryoSEM, nanoprobe)			
Precision Medicine	**Function and regulation mechanisms of drug-metabolizing enzymes**			**Nanoscale imaging of drug-metabolizing enzymes or related proteins** (HS-AFM)			

To achieve the above objectives, we will examine the four research subjects shown in Table 7.

(Research progress)

・Elucidation of cancer onset mechanisms (Oshima and Wong)

Oshima et al. established tumor-derived organoids (*Cancer Res, 2018*), and found the role of stemness regulation and tumorigenesis by Stat3 (*FASEB J, 2018*), and polyclonal mechanism of metastasis (Fig. 16). They further found that inflammatory signaling induces activation of gastric cancer cell proliferation through NOX1/ROS activation (*Oncogene, 2019*) and miR-135b expression (*Gastroenterology, 2019*).

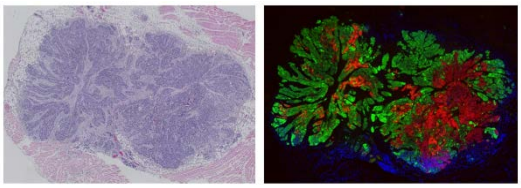


Fig. 16: Polyclonally developed in vivo tumors by different subclones (left, H&E; right, fluorescence image).

Wong et al. showed chromatin structural changes of colon cancers caused by a nucleoporin TPR (*Oncotarget, 2018*). Through interdisciplinary research with the Ando and Oshima groups, using HS-AFM to visualize a nuclear pore complex (NPC), they clarified a mechanism of NPC dynamics that changes with the progression of colon cancer.

・Development of cancer diagnostic technology (Hirao and Wong)

Hirao et al. revealed a role of Ca2+ flux signals in the regulation of cancer stem cells (*Cancer Sci., 2018*). In the downstream of mTOR, they found a critical function of a nicotinamide-metabolizing enzyme, NNMT, for malignant progression. In addition, a vitamin metabolite was significantly up-regulated. They started to discover novel critical nicotinamide-related metabolites for malignancy by metabolomics. Moreover, they found that a pillararene specifically binds to the metabolite. In the future, they plan to develop a clinically available tool for detection of nicotinamide-related metabolites as cancer biomarkers.

Wong et al. showed the NPC changes as a potential new diagnostic marker for colon cancer. They began interdisciplinary research with the Yano group to examine abnormalities of phosphorylated kinase activity and transcriptome to understand drug resistance mechanisms. In the future, they aim to develop a faster diagnostic tool for early detection of cancer.

・Development of cancer diagnosis / therapeutics technology (Matsumoto and Yano)

HGF-MET receptor pathway plays a role in metastasis and drug resistance. HGF is secreted as an inactive single-chain (scHGF), while active two-chain HGF (tcHGF) is formed in cancer. Matsumoto et al. discovered HiP-8 (HGF-inhibitory peptide-8), a macrocyclic peptide, that specifically recognizes tcHGF (*Nat. Chem. Biol., 2019*) (Fig. 17). HS-AFM revealed that HiP-8 restricted the dynamic molecular

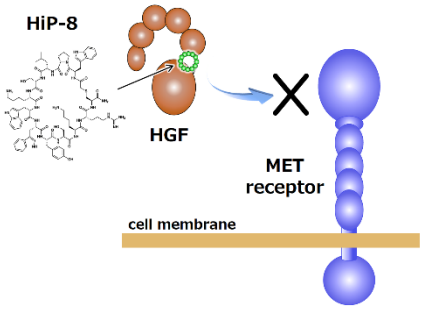


Fig. 17: Structure and outline action of HiP-8.

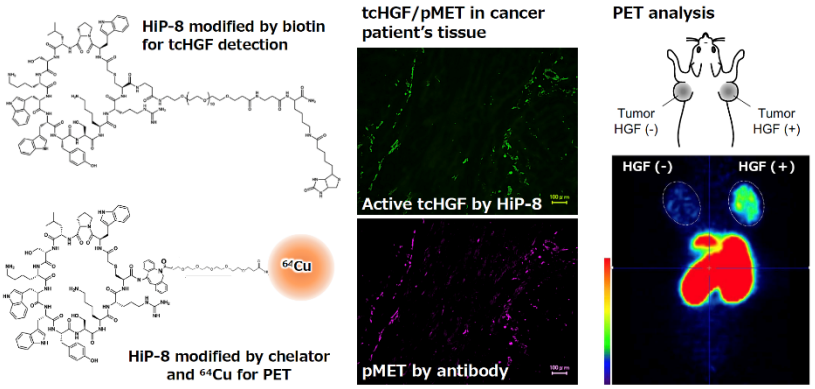


Fig. 18: Chemical modification of HiP-8 (left), detection of tcHGF/pMET in cancer (middle), and HiP-8 accumulation in HGF-positive tumor by PET imaging (right).

movement of HGF into static. tcHGF and active MET (pMET) were detected by HiP-8 in cancer patients' tissues. Positron emission tomography (PET) using HiP-8 as a radiotracer enabled visualization of HGF–MET activation in tumors (Fig. 18). HiP-8 will be a useful tool for diagnosis and therapeutics of cancer.

・Development of cancer therapeutic technology (Yano and Ando)

Yano et al. clarified the intracellular distribution of EML4-ALK oncogenic fusion protein in lung cancer cells. For the next step, the effect of ATP and molecularly targeted drugs on the fusion protein structure will be examined by HS-AFM. They also demonstrated that AXL protein prevented the cancer cell death exposed to molecularly targeted drugs (*Nat. Commun., 2019*).

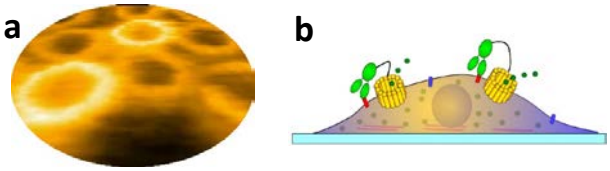


Fig. 19: **a**. HS-AFM images of SLO complexes forming membrane pores. **b**. Membrane perforation by SLO-antibody.

The Ando group has been studying a membrane pore-forming protein, SLO, using high-speed AFM. They are now aiming to create drugs commonly applicable for various types of cancers by conjugating SLO mutants to cancer-specific antibodies or cyclic peptides (Fig. 19). To this end, they attempted to prepare SLO mutants capable of forming and maintaining prepore complexes without membranes.

・Personalized medicine (efficacy and toxicity of anti-cancer drug) (Nakajima)

Nakajima et al. found a novel regulation mechanism of cytochrome P450, a major drug-metabolizing enzyme superfamily, by A-to-I RNA editing (*Pharmacol. Ther., 2018*). They have established a P450 observation system using HS-AFM to elucidate the dynamics of P450 and NADPH-cytochrome P450 reductase interaction. Moreover, they found that anti-cancer drugs such as bosutinib are converted by CYP3A4 to metabolites, which appears to be relevant to an adverse event, liver injury.

(Expected achievement of the world's highest standard)

We have identified that a high-fat diet together with Spred1 deficiency affect hematopoietic stem cell homeostasis, which sheds light on a linkage between intestinal microbiota and stemness (*Cell Stem Cell, 2018*). Moreover, we have shown that microRNA, miR-135b, is upregulated in gastric cancer cells in an inflammation-dependent manner, thus can be a preventive target against gastric cancer (*Gastroenterology, 2019*). We also discovered a novel drug resistance mechanism of EGFR inhibitor in lung cancer by activation of a feedback mechanism, which will contribute to clinical study in the near future (*Nat. Commun., 2019*). These findings provide novel mechanism in cancer research, and we believe that we will be the first in the world to understand the changes in structure and physical properties of cancer cells at the nano level by incorporation of nano-technology. Furthermore, development of diagnostic and therapeutic methods based on our new findings should lead to successful precision medicine at the world's highest standard beyond the existing framework.

(3) Establishment of New Research Field: Nanoprobe Life Science

We aim to establish a new research field “nanoprobe life science” by integrating knowledge from the four research fields: nanometrology, life science, supramolecular chemistry, and computational science. In FY2017, we established two approaches to achieving this objective. The first is to begin with research combining two adjacent fields, with the aim ultimately of developing it into the fusion of three or four disciplines (Fig. 20). The second is to expand the scope for application of nanoprobe technology in the life sciences from biophysics to molecular cell biology, medicine, and pharmacy. In line with these approaches, in FY2018, we vigorously pursued a variety of transdisciplinary research activities. As a result, adding to our pre-existing work combining nanometrology with life science, and nanometrology with computational science, we began working on new fusions of two fields, such as nanometrology with supramolecular chemistry, computational science with life science, and supramolecular chemistry with life science, as well as three-way fusions such as nanometrology, life science, and supramolecular chemistry. Most of them are still works in progress, but some have reached the stage of presenting of findings as highlighted below.

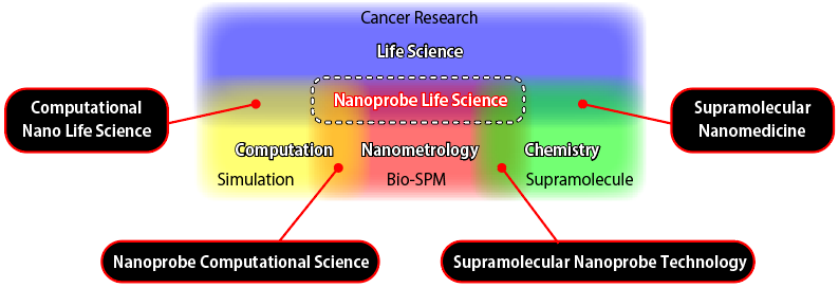


Fig. 20: Relationship between the four major research disciplines.

① Nanometrology x Life Science

Free Energy Landscape and Dynamics of Supercoiled DNA by High-Speed Atomic Force Microscopy (*ACS Nano, 2018*, IF: 13.709)

DNA supercoiling fundamentally constrains and regulates the storage and use of genetic information. While the equilibrium properties of supercoiled DNA are relatively well understood, the dynamics of supercoils are much harder to probe. We directly image supercoil dynamics using high-speed AFM. The dynamic images quantify self-diffusion, branch point flexibility, and slithering dynamics. We demonstrate that reconfiguration of molecular extension is predominantly governed by the bending flexibility of plectoneme arms.

Brouns T., De Keersmaecker H., Konrad S.F., Kodera N., Ando T., Lipfert J., De Feyter S., Vanderlinden W.ACS Nano, 12(12), 11907-11916

Revealing circadian mechanisms of integration and resilience by visualizing clock proteins working in real time (*Nat. Commun., 2018*, IF: 12.353)

The circadian clock proteins KaiA, KaiB, and KaiC reconstitute a remarkable circa-24 h oscillation of KaiC phosphorylation that persists for many days in vitro. Here we use high-speed AFM to visualize and quantify the dynamic interactions of KaiA with KaiC. KaiA transiently interacts with KaiC, stimulating KaiC autokinase activity. As KaiC becomes progressively more phosphorylated, KaiA's affinity for KaiC weakens, revealing a feedback of KaiC phosphostatus onto the KaiA-binding events. These high-frequency binding and unbinding events refine the period of the longer term oscillations. Moreover, this differential affinity explains how the oscillation is resilient in a noisy in vivo milieu .

Mori T., Sugiyama S., Byrne M., Johnson C.H., Uchihashi T., Ando T., Nature Communications, 9(1), 3245

Dynamic structural states of ClpB involved in its disaggregation function (*Nat. Commun., 2018*, IF: 12.353)

An ATP-fueled molecular chaperone ClpB disentangles and reactivates aggregated proteins. Structural dynamics of ClpB during repeated ATP turnover are imaged with high-speed AFM. ClpB forms open and three different closed rings (round, spiral, and newly found twisted-half-spiral). These structures transform from one to another during the ATPase-cycle, indicating that ClpB performs protein disaggregation through these structural changes .

Uchihashi T., Watanabe Y.-H., Nakazaki Y., Yamasaki T., Watanabe H., Maruno T., Ishii K., Uchiyama S., Song C., Murata K., Iino R., Ando T., Nature Communications, 9(1), 2147

② Nanometrology x Supramolecular Chemistry

Ring shape-dependent self-sorting of pillar[n]arenes assembled on a surface (*Commun. Chem. 2018*, IF: to be assigned (new journal from Nature Publishing Group))

Supramolecular chemistry group (Ogoshi et al.) discovered self-sorting behavior based on a principle of geometrical complementarity by shape during our investigation of assembly of pentagonal pillar[5]arenes and hexagonal pillar[6]arenes on a surface. High-resolution AFM measurements by the AFM group (Asakawa and Fukuma et al.) revealed that the lattices formed by assembly of pillar[5,6]arenes were different depending on the pentagonal and hexagonal structures. The lattice difference should contribute to the self-sorting behavior .

Ogoshi T., Takashima S., Inada N., Asakawa H., Fukuma T., Shoji Y., Kajitani T., Fukushima T., Tada T., Dotera T., Kakuta T., Yamagishi T. Commun. Chem.,1(92)

③ Nanometrology x Computational Science

Clustering of force curves constituting a 3D-AFM image by Graph-Bootstrapping (*Nat. Commun., 2018*, IF: 12.353)

The rapid advancement of AFM technologies enabled the recording of high-dimensional large-volume data in a short time. Accordingly, there have been increasing demands for a method to automatically derive physically meaningful information from the AFM data. In this study, we have developed a method for clustering high-dimensional AFM data by Graph-Bootstrapping. With this method, we demonstrated automatic clustering of force versus distance curves constituting a 3D-AFM image of the calcite-water interface. By mapping the 2D distribution of the clusters, we can identify the atomic-scale positions having different surface properties. This technique should greatly improve the speed, accuracy and objectiveness of the 3D-AFM data analysis.

Li X., Collins L., Miyazawa K., Fukuma T., Jesse S., Kalinin S.V., Nature Communications, 9(1), 2428

Hydration Structure of Biofouling-Resistant Nanoparticles (*ACS Nano, 2018*, IF: 13.709)

The Hydrophilic surface chemistries can strongly bind water to produce surfaces that are highly resistant to protein adsorption and fouling. The interfacial bound water and its distinct properties have intrigued researchers for decades, yet the relationship between the water 3D structure and function in antifouling coatings remains elusive. To understand their excellent antifouling properties, 3D-AFM is used to directly observe the interfacial water structure at subnanometer resolution, which we validate using all-atom MD simulations that strikingly predict similar structures of water layers on the original and ultralow fouling surfaces. The convergence of experimental and modeling data reveals that suitably spaced, flexible chains with hydrophilic groups interact with water molecules to produce a connective, quasi-stable layer consisting of dynamic interfacial water that provides a basis for antifouling performance of ultrathin, hydrophilic surface chemistries .

Molino P.J., Yang D., Penna M., Miyazawa K., Knowles B.R., Maclaughlin S., Fukuma T., Yarovsky I., Higgins M.J.,ACS Nano, 12(11), 11610-11624

④ Nanometrology x Life Science x Supramolecular Chemistry

Molecular dynamics suppressed by novel macrocyclic peptide (Nat. Chem. Biol., 2019, IF:13.843)

Through a cross-disciplinary approach, Matsumoto et al. found that HiP-8 (HGF-inhibitory peptide-8), a macrocyclic peptide consisting of 12 amino acids, specifically binds to HGF (*Nat. Chem. Biol., 2019*). Biochemical analysis indicated that HiP-8 binds to HGF through multivalent binding interfaces. High-speed AFM analysis indicated that HiP-8 restricted the dynamic domain movement of HGF into static closed conformations. This study established the novel concept that a small macrocyclic peptide can inhibit the molecular dynamics of a target protein.

Sakai K., Passioura T., Sato H., Ito K., Furuhashi H., Umitsu M., Takagi J., Kato Y., Mukai H., Warashina S., Zouda M., Watanabe Y., Yano S., Shibata M., Suga H., Matsumoto K., Nature Chemical Biology, 15(6), 598-606

2. Generating Fused Disciplines

* Describe the content of measures taken by the Center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields. If any, describe the interdisciplinary research/fused discipline that have resulted from your efforts to generate fused disciplines. You may refer to the research results described concretely in "1. Advancing Research of the Highest Global Level."

Approaches and progress to date on transdisciplinary research is outlined in "1. Advancing Research of the Highest Global Level" above. Here, we report on the development of systems and structures for the promotion of transdisciplinary research. In FY2017, we introduced various new programs including study meetings, seminars, international symposium (held in Tokyo), and tea meetings, in addition to the pre-existing Bio-AFM Summer School. These enabled discussions among researchers from different fields, clarification of the research challenges for the institute as a whole, and formulation of research plans. In FY2018, we continued to pursue the abovementioned programs while making some changes to them, and introducing new ones. Below we report mainly on the changes made since last year.

(1) NanoLSI T-meeting: This program was launched at the start of FY2018 as a weekly, voluntary forum for researchers to engage in free discussion over a cup of tea. It attracted many participants and contributed to the advancement of transdisciplinary research, but with a view to promoting disciplinary fusion more systematically, the approach was altered as follows from the sixth week. Firstly, scheduling was changed to enable individual meetings of two research groups from different fields to be held periodically. Secondly, the format was altered so that a number of young researchers from each discipline could give short presentations, on the basis of which intensive discussion was held on possibilities for joint research. This format proved an extremely worthwhile opportunity for young researchers and PIs to gain direct knowledge of one another's research. Cases are even starting to appear of joint research projects evolving out of encounters at T-Meetings.

(2) NanoLSI Colloquium: Beginning shortly after the WPI was launched, four study meetings were held last year, in order for PIs to learn about one another's research and gain basic knowledge in each of the institute's major fields. These were extremely useful in overall planning of research projects and proposals. In the first half of this year, the focus was placed on fleshing out research projects through individual meetings among research groups. In the second half of the year, the study meetings, which had previously been attended by PIs only, were developed into a colloquium where research groups inform one another of the progress of their projects in the context of the institute's overall research plans. The colloquia are now held periodically and attended by all members of the institute, including young researchers. They involve PIs reporting on their groups' progress and, where necessary, young researchers reporting on progress in relation to specific topics. Each colloquium is followed by an informal dinner gathering to promote exchange among researchers.

(3) NanoLSI transdisciplinary research promotion grant: We established a new grant program under which sums of between ¥0.5-2 million are awarded to transdisciplinary research projects pursued by two or more young researchers in different fields. This year we called for applications in two rounds, spring and fall, as some of the young researchers appointed to the institute had not yet taken up their appointments in the first half of the year. Twenty applications were received in the first round and 13 projects selected, to which a total of ¥19.52 million was granted. In the second round there were 11 applications and 9 projects selected, with a total grant value of ¥7.6 million. At the end of the year, the institute's PIs provided grant recipients with feedback on their projects in the form of written evaluations and advice based on reports and short presentations prepared by the recipients. This grant program was extremely effective in providing researchers with strong encouragement to giving concrete shape to their ideas for transdisciplinary research and begin working on them.

(4) Advisory board meeting: So far, we have appointed 12 researchers from the four major research disciplines as an advisory board member. We had the first advisory board meeting at Kanazawa on 20-21 Feb., 2019. As it was the first meeting, we asked all the advisors to come and familiarize themselves with our strategy and current status of the research and managements. In the meeting, we gave talks on our activities and had intensive discussions. Their comments are mostly encouraging to follow the current direction. In the meanwhile, several advisors suggested to have an event or system to promote direct communications among the young students and post-docs so that they can actively look for an interdisciplinary research subject. This is perfectly in line with our plan and we believe that the aforementioned activities (1)-(3) should facilitate such direct communications.

3. Realizing an International Research Environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:
- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers (in Appendix 2); exchanges with overseas entities (in Appendix 4); number and state of visiting researchers (in Appendix 5)
- Proactive efforts to raise the level of the center's international recognition
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

- Performance of the 16 PIs as world-leading researchers: They published 559 papers during the period 2013-2017, in which 8 papers (1.4%) were rated within the top 1% cited publications and 99 other papers (17.7%) were rated within the top 10%. In addition, 183 papers (32.7%) were internationally co-authored.

- Enhancing international recognition: NanoLSI organized the Bio-AFM Summer School for junior researchers, Bio-SPM Collaborative Research for established researchers, and NanoLSI Fellow Program for PI-level researchers, in which 23 researchers from overseas participated out of 49 participants in total. NanoLSI held its 2nd Symposium in London, in which 5 invited speakers and 29 researchers participated from UK and other countries.

- Overseas research sites: NanoLSI concluded MOUs with Imperial College London, UK, and The University of British Columbia, Canada, in order to sustain long-term research cooperation.

- Number of foreign researchers etc.: Twenty-two researchers (30.6%), namely 5 PIs, 16 project assistant professors and a post-doctoral are non-Japanese out of a total of 72 NanoLSI researchers. A non-Japanese technician is employed who can explain AFM operation in Japanese, Chinese and English. As to the administrative department, 18 members (75%) out of 24 in total speak English.

4. Making Organizational Reforms

* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.
* Describe the center's operation and the host institution's commitment to the system reforms

- **Research professorships and evaluation-dependent allowance**: The research professors have reduced non-NanoLSI duties as well as enjoy a special allowance depending on their individual evaluation. In the evaluation of NanoLSI, one, 9, 11 and 33 researchers were evaluated to be "SS," "S^{+}," "S" and "A," respectively.
- **Meeting of top leaders**: The University President and the NanoLSI Director have been holding regular meetings, once a month, to discuss the status quo, progress and mid/long-term development of NanoLSI as well as organizational reforms of the university.
- **Ripple effect 1**: Based on the above-mentioned pilot scheme of NanoLSI, Kanazawa University has decided to apply the evaluation-dependent annual salary system to all professors/researchers employed by the University from FY2019 onwards.
- **Ripple effect 2**: The University has adopted the research assistant system for masters students implemented by NanoLSI for the entire University.

5. Efforts to Secure the Center's Future Development over the Mid- to Long-term

* Address the following items, which are essential to mid- to long-term center development:
- Future prospects with regard to the research plan, research organization and PI composition; prospects for the fostering and securing of next-generation researchers
- Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure
- Measures to sustain the center as a world premier international research center after program funding ends
- Host institution's organizational reforms carried out for the Center's autonomous administration simultaneously with the creation of the Center..

- **The university's commitment**: It has provided NanoLSI with research funds of ¥60 million per year, covered the basic salary and social insurance contributions for PIs and researchers who had been employed before the inauguration of NanoLSI, and secured 3000 square meters for the NanoLSI facility.
- **New NanoLSI Building**: The University has secured a budget of ¥1,500 million for a new NanoLSI building, giving the top priority for its budgetary request to the Government. Furthermore, the University has decided to spend an additional ¥700 million out of its own budget for the new building.
- **Independency of NanoLSI**: Based on the development of NanoLSI for the past 3 years and upon receipt of approval from the WPI Program Committee, the University will upgrade the status of NanoLSI to that of a research institute directly affiliated to the University as early as possible so as to strengthen the independency and status of NanoLSI in relation to the other departments of the University.
- **Fostering the next-generation researchers**: NanoLSI has hired 5 junior PIs who will play important roles in interdisciplinary research for establishing "nanoprobe life science." All the junior PIs have been given tenure-track positions.
- **Educational entity of NanoLSI**: The doctoral graduate school (5 years), "Division of Nano Life Science," will be launched in FY2020 with six graduate students per year. Kanazawa University has already submitted an application for the new doctoral course to MEXT.
- **Procuring external research funds**: Four PIs have been awarded "CREST" funding. Two PIs have applied for the EU's "Horizon 2020" funding. The Administrative Director has started consultation with researchers inside and outside the institute with a view to applying for larger research grants such as the Grant-in-Aid for Scientific Research on Innovative Areas. Furthermore, the deputy Administrative Director and URAs have been providing technical support for younger researchers to apply for various external funds.
- **Continuation of NanoLSI after the WPI's support period**: The University President and the NanoLSI Director have determined that NanoLSI should remain as a top research institute and that the University will continue to provide sufficient support in terms of permanent positions, space for research and financial support.
- **Securing the budget for research with revenue contribution**: NanoLSI is going to study the successful experience of the preceding WPI centers in order to establish its program and strategy for obtaining a sufficient budget.

6. Others

* Describe what was accomplished in the center's outreach activities in FY 2018 and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.
* In addition to the above 1-5 viewpoints, if there is anything else that deserves mention regarding the center project's progress, note it.

- **Outreach activities**: NanoLSI entails dual approaches to both the research community and the general public. Emphasis has so far been placed on the research community such as the Bio-AFM Summer School, Bio-SPM Collaborative Research, NanoLSI Fellow Program and NanoLSI Symposium in London. Eighty-three researchers from outside have participated in the above activities. Furthermore, "Nature Spotlight on Kanazawa" featuring NanoLSI and its research appeared in Nature Vol.562, No.7726, 11

October 2018. As to the approach to the general public, 35 articles on the research at NanoLSI appeared in newspapers in FY2018.

7. Center's Response to Results of Last Year's Follow-up

* Transcribe the item from the "Actions required and recommendations" section in the site visit report and "Actions required and recommendations" in the Follow-up report, then note how the center has responded to them.
* For the center launched in FY 2018, describe the status of response to the pointed items in "Major points that need to be improved" of "The screening result for WPI centers launched in FY 2018."
* However, if you have already provided this information, indicate where in the report.

Responses to Site Visit Report (Research & Development)

Comment 1 ***"As the center is aware, Bio-SPM is not the only tool for understanding cell biology at the nanolevel. Combining Bio-SPM with other tools should be further pursued to strengthen NanoLSI and its work."***

Development of SPM technologies combined with optical microscopy: Projects are currently underway in areas including (1) fusion of confocal microscopy and 3D-AFM, (2) fusion of optical tweezers and HS-AFM, (3) fusion of fluorescent microscopy and AFM/SICM with a functionalized nanoprobe, and (4) fusion of HS-AFM and tip-enhanced Raman. To advance these projects, we have added researchers with expertise in various methods of optical microscopy to the membership of NanoLSI, including Ichikawa (light-sheet microscopy), Pippulin (Raman microscopy), and Hirata (FRET sensor/microscopy).

Complementary uses of electron microscopes: We have added new Cryo-FIB-SEM and TEM instruments, and are pursuing projects including (1) internal observation of cells and chromosomes using Cryo-FIB-SEM, (2) manufacture of SPM probes using FIB-SEM, and (3) manufacture and evaluation of SPM probe tips using TEM. For this purpose, we also appointed a new technical staff member, Furusho, who has many years of experience as an EM technician in several research institutes.

Comment 2 ***"The proposed nanoendoscope project is very ambitious but questions remain as to its feasibility, for example how damage to cells can be minimized. The use of SICM is very attractive and could be helpful for many applications, which will raise the importance of spatiotemporal resolution. NanoLSI is encouraged to test the usability of these key technologies early in the first 5 years."***

We are aware of the challenging aspects of these technologies and plan to confirm their feasibility in the first five years as described in the original proposal.

Nanoendoscopy: As described in Sec. 1(1)①, we have confirmed that the single insertion and extraction of the thin AFM probe does not cause cell death but repeated insertion in a very short interval will cause fatal damage. We plan to test various surface treatment methods of the nanoprobes to minimize the invasiveness of probe insertion. We also started to explore the feasibility of the local 2D/3D scanning of the tip inside a cell and its influence on cellular activity.

SICM: The main challenges in the SICM development include (1) the molecular-resolution imaging on a live cell surface and (2) chemical mapping at the surface and inside of a live cell. For project (1), we are developing a CNT probe to improve the resolution (see also 1(1)②). For project (2), we have already confirmed that some of the molecular sensors integrated to the SICM probe can detect specific chemicals and the next step will be their application to the mapping of the chemicals around the cells.

Comment 3 ***"The use of supramolecular chemistry as a tool to sense molecules in cells would be excellent, but the current approach, which depends on serendipity, is not sufficient. NanoLSI should consider the systematic designing of supramolecular sensors with a purpose. To accelerate this, the WG strongly recommends including chemists in the NanoLSI Advisory Board who have expertise in molecular designing."***

Following the suggestion, we appointed Prof. Hiroaki Suga at University of Tokyo as a new member of the advisory board. He is a biochemist who can design and synthesize functional molecules applicable to biological research. One of the successful collaborations between him and Matsumoto (PI at NanoLSI) is described in 1(3)④, where he designed a macrocyclic peptide, Hip-8, to specifically regulate the function of HGF. In addition, we also appointed Dr. Arai as a Jr. PI. He is a biochemist who can design molecules that can detect and control the temperature changes inside a live cell.

Comment 4 ***"Setting cancer as a goal is very ambitious and difficult. Ongoing projects on cancer research are in good synergy with the Bio-SPM research; however, a few projects alone will not be sufficient to understand cancer. More effort should be emphasized on nano-level understanding of the cellular functions of normal and cancer cells, which would be an adequate goal for the first 5 years."***

As pointed out, one of the primary objectives of our life science research is to gain a fundamental understanding of the basic functions of cells and cancer-specific abnormalities at the nano-level. In practice, researchers in the field of molecular cell biology such as Hanayama (exosomes), Wong (NPCs),

Hirao (stem cells), and Matsumoto (HGF/MET) are taking the lead in research on cell proliferation, differentiation, and communication. Meanwhile, for medical and pharmaceutical researchers such as Oshima (cancer model), Yano (cancer therapy), and Nakajima (drug metabolism), there are few relevant cases of practical application of SPM, and these researchers face major hurdles in developing projects related to cell function in their respective areas using SPM observation samples. Life science researchers themselves thus need to develop samples through a process of trial and error using SPM. In response to this need, this year we purchased two commercially-available AFMs for cell observation that can be used easily even by beginners, providing an environment in which life scientists can operate SPMs themselves.

Comment 5 ***"The center director Fukuma is playing a very important role as a "hub" in promoting the fusion of different disciplines. However, the question remains as to whether a synergy in understanding among groups can be sustained without him. More direct interactions and candid exchange of ideas among researchers is recommended."***

To promote direct discussions among individual researchers, we set up two types of meetings: (1) T-meeting and (2) NanoLSI colloquium. Detailed explanations are given in 2(1) and 2(2).

Comment 6 ***"It will be very important to create an environment in which researchers and students can enjoy science."***

What we can do as a WPI center in this respect is to furnish an environment in which young researchers, including students, can interact directly with foreign researchers and researchers from other disciplines, and autonomously formulate and pursue transdisciplinary research projects. To date, we have established a system to provide RA funds for doctoral students and master's students seeking to advance to doctoral studies to help them to focus on their research. From this year we also made it possible for not only PDs and assistant professors but also students to participate in NanoLSI colloquia and apply for transdisciplinary research promotion grants (see 2 (3) for details). In practice, one student applied for the grant this year and was successful. We will continue these activities as we work to build an environment in which young researchers can enjoy their research proactively.

Responses to Site Visit Report (Administration)

Comment 1 ***"To push forward the current effort in not only research but also in internationalization and system reform as much as possible, keeping in mind how to plan for the second 5 years of the funding period."***

Comment 2 ***"To make a plan on how to nurture junior researchers into future PIs, for example establishing a tenure track system."***

Comment 3 ***"To make a plan for securing research funding both in Japan and from abroad. In Japan, "Shin-Gakujutsu" and CREST are worth trying. Overseas, the EU has several high-profile funding lines and is promoting collaboration with Japan. Applications that can utilize satellites are worth exploring."***

Comment 4 ***"To make more concrete the plan for making the institute self-sustaining after the funding period ends"***

A response to these comments has been included in "5. Efforts to Secure the Center's Future Development over the Mid- to Long-term."

Responses to Follow-Up Report

Comment 1 ***"Program Committee members mostly agree that NanoLSI has made a good start."***

Comment 2 ***"The leadership of the center director is highly appreciated. Program Committee, however, felt a concern that the discretionary decision-making power of the director may be not sufficient. It will be important for NanoLSI to be as open to new strategic opportunities as the center over the course of a 10-year grant."***

We are still in the early stages of our long ten-year research term, and it is important that the institute's overall research strategy is adjusted whenever necessary under the strong initiative of our Director. Decisions regarding the operation of the institute are discussed by a Steering Board composed of the Director, the Administrative Director, and several key PIs, then tabled and finalized at the NanoLSI conference. We have made it clear that it is the Director who makes the final determinations at each of these meetings. To give effect to the Director's decisions, we have established discretionary elements in the areas of personnel, salaries, and budgeting. In personnel, the Director exercises discretion over seven out of the 25 specially-appointed assistant professor appointments. In salaries, institute members are paid a NanoLSI allowance which varies in line with the results of performance evaluation conducted by the Director. Moreover, from this year, around 20% of the ¥60 million in research funds provided to the institute by the university have been marked as the Director's discretionary funds, to be used or allocated strategically by the Director.

Comment 3 ***"It is not too early to plan of survival after the end of the WPI financial support. NanoLSI should define the missions and milestones during the 10-year period. They will need to include industry beyond academics. At the same time, NanoLSI should stay as a top research institute, the key for which would be the balance between maintaining their own research to push the frontier of the science and technology versus providing services in order to attract revenue contribution. Collaboration with domestic and international institutes, which pursue more or less similar target, is also recommended"***

A response to this comment has been included in "5. Efforts to Secure the Center's Future Development over the Mid- to Long-term."

Appendix 1 FY 2018 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2018. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.

A. WPI papers
List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state "WPI" and the name of the WPI center (WPI-center name)). (Not including papers in which the names of persons affiliated with the WPI program are contained only in acknowledgements.)

B. WPI-related papers
List papers related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (Including papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

Newly selected centers in FY2018 are to list papers under category C below (in addition to categories A and B above).

C. Previously published important WPI-related papers
List previously published papers that provided the basis for the center's research project plan. (Around 30 papers as a yardstick.)

Note: On 14 December 2011, the Basic Research Promotion Division in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. As some WPI-affiliated authors of papers published up to 2011 may not be aware of this requirement, their papers are treated as "WPI-related papers." From 2012, the authors' affiliations must be clearly noted.

(2) Method of listing paper
- List only refereed papers. Divide them into categories (e.g., original articles, reviews, proceedings).
- For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is consistent. (The names of the center researchers do not need to be underlined.)
- If a paper has many authors (say, more than 20), all of their names do not need to be listed.
- Assign a serial number to each paper to be used to identify it throughout the report.
- If the papers are written in languages other than English, underline their serial numbers.
- Order of Listing

A. WPI papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles

B. WPI-related papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles

C. Previously published important WPI-related papers

(3) Submission of electronic data
- In addition to the above, provide a .csv file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
- These files do not need to be divided into paper categories.

(4) Use in assessments
- The lists of papers will be used in assessing the state of WPI project's progress.
- They will be used as reference in analyzing the trends and whole states of research in the said WPI center, not to evaluate individual researcher performance.
- The special characteristics of each research domain will be considered when conducting assessments.

(5) Additional documents
- After all documents, including these paper listings, showing the state of research progress have been submitted, additional documents may be requested.

A. WPI papers

1. Original articles

1) Tadokoro Y., Hoshii T., Yamazaki S., Eto K., Ema H., Kobayashi M., Ueno M., Ohta K., Arai Y., Hara E., Harada K., Oshima M., Oshima H., Arai F., Yoshimura A., Nakauchi H., Hirao A. "Spred1 Safeguards Hematopoietic Homeostasis against Diet-Induced Systemic Stress", Cell Stem Cell 22 (2018) 713-725 (IF=23.29)

2) Jie K., Liu M., Zhou Y., Little M.A., Pulido A., Chong S.Y., Stephenson A., Hughes A.R., Sakakibara F., Ogoshi T., Blanc F., Day G.M., Huang F., Cooper A.I. "Near-Ideal Xylene Selectivity in Adaptive

Molecular Pillar[n]arene Crystals", J. Am. Chem. Soc. 140 (2018) 6921-6930 (IF=14.357)

3) Maeda K., Hirose D., Okoshi N., Shimomura K., Wada Y., Ikai T., Kanoh S., Yashima E. "Direct Detection of Hardly Detectable Hidden Chirality of Hydrocarbons and Deuterated Isotopomers by a Helical Polyacetylene through Chiral Amplification and Memory", J. Am. Chem. Soc. 140 (2018) 3270-3276 (IF=14.357)
4) Ogoshi T., Takashima S., Yamagishi T.-A. "Photocontrolled Reversible Guest Uptake, Storage, and Release by Azobenzene-Modified Microporous Multilayer Films of Pillar[5]arenes", J. Am. Chem. Soc. 140 (2018) 1544-1548 (IF=14.357)
5) Brouns T., De Keersmaecker H., Konrad S.F., Kodera N., Ando T., Lipfert J., De Feyter S., Vanderlinden W. "Free Energy Landscape and Dynamics of Supercoiled DNA by High-Speed Atomic Force Microscopy", ACS Nano 12 (2018) 11907-11916 (IF=13.709)
6) Molino P.J., Yang D., Penna M., Miyazawa K., Knowles B.R., MacLaughlin S., Fukuma T., Yarovsky I., Higgins M.J. "Hydration Layer Structure of Biofouling-Resistant Nanoparticles", ACS Nano 12 (2018) 11610-11624 (IF=13.709)
7) Kawai S., Krejčí O., Foster A.S., Pawlak R., Xu F., Peng L., Orita A., Meyer E. "Diacetylene linked anthracene oligomers synthesized by one-shot homocoupling of trimethylsilyl on Cu(111)", ACS Nano 12 (2018) 8791-8797 (IF=13.709)
8) Schulz F., Ritala J., Krejčí O., Seitsonen A.P., Foster A.S., Liljeroth P. "Elemental Identification by Combining Atomic Force Microscopy and Kelvin Probe Force Microscopy", ACS Nano 12 (2018) 5274-5283 (IF=13.709)
9) Ogoshi T., Tsuchida H., Kakuta T., Yamagishi T.-A., Taema A., Ono T., Sugimoto M., Mizuno M. "Ultralong Room-Temperature Phosphorescence from Amorphous Polymer Poly(Styrene Sulfonic Acid) in Air in the Dry Solid State", Adv. Funct. Mater. 28 (2018) 1707369 (IF=13.325)
10) Mori T., Sugiyama S., Byrne M., Johnson C.H., Uchihashi T., Ando T. "Revealing circadian mechanisms of integration and resilience by visualizing clock proteins working in real time", Nat. Commun. 9 (2018) 3245 (IF=12.353)
11) Li X., Collins L., Miyazawa K., Fukuma T., Jesse S., Kalinin S.V. "High-veracity functional imaging in scanning probe microscopy via Graph-Bootstrapping", Nat. Commun. 9 (2018) 2428 (IF=12.353)
12) Uchihashi T., Watanabe Y.-H., Nakazaki Y., Yamasaki T., Watanabe H., Maruno T., Ishii K., Uchiyama S., Song C., Murata K., Iino R., Ando T. "Dynamic structural states of ClpB involved in its disaggregation function", Nat. Commun. 9 (2018) 2147 (IF=12.353)
13) Shimoi M., Watanabe T., Maeda K., Curran D.P., Taniguchi T. "Radical trans-Hydroboration of Alkynes with N-Heterocyclic Carbene Boranes", Angew. Chem. Int. Ed. 57 (2018) 9485-9490 (IF=12.102)
14) Ogoshi T., Saito K., Sueto R., Kojima R., Hamada Y., Akine S., Moeljadi A.M.P., Hirao H., Kakuta T., Yamagishi T.-A. "Separation of Linear and Branched Alkanes Using Host–Guest Complexation of Cyclic and Branched Alkane Vapors by Crystal State Pillar[6]arene", Angew. Chem. Int. Ed. 57 (2018) 1592-1595 (IF=12.102)
15) Kumar A., Banerjee K., Foster A.S., Liljeroth P. "Two-Dimensional Band Structure in Honeycomb Metal-Organic Frameworks", Nano Lett. 18 (2018) 5596-5602 (IF=12.08)

16) Kawai S., Nakatsuka S., Hatakeyama T., Pawlak R., Meier T., Tracey J., Meyer E., Foster A.S. "Multiple heteroatom substitution to graphene nanoribbon", Sci. Adv. 4 (2018) eaar7181 (IF=11.511)
17) Hirano T., Konno H., Takeda S., Dolan L., Kato M., Aoyama T., Higaki T., Takigawa-Imamura H., Sato M.H. "PtdIns(3,5)P2 mediates root hair shank hardening in Arabidopsis", Nature Plants 4 (2018) (IF=11.471)
18) Ravula T., Ishikuro D., Kodera N., Ando T., Anantharamaiah G.M., Ramamoorthy A. "Real-Time Monitoring of Lipid Exchange via Fusion of Peptide Based Lipid-Nanodiscs", Chem. Mater. 30 (2018) 3204-3207 (IF=9.89)
19) Sakai E., Nakayama M., Oshima H., Kouyama Y., Niida A., Fujii S., Ochiai A., Nakayama K.I., Mimori K., Suzuki Y., Hong C.P., Ock C.-Y., Kim S.-J., Oshima M. "Combined mutation of Apc, Kras, and Tgfbr2 effectively drives metastasis of intestinal cancer", Cancer Res. 78 (2018) 1334-1346 (IF=9.13)
20) Himanen L., Rinke P., Foster A.S. "Materials structure genealogy and high-throughput topological classification of surfaces and 2D materials", npj Computational Mater. 4 (2018) 52 (IF=8.941)
21) Jäger M.O.J., Morooka E.V., Federici Canova F., Himanen L., Foster A.S. "Machine learning hydrogen adsorption on nanoclusters through structural descriptors", npj Computational Mater. 4 (2018) 37 (IF=8.941)
22) Söngen H., Reischl B., Miyata K., Bechstein R., Raiteri P., Rohl A.L., Gale J.D., Fukuma T., Kühnle A. "Resolving Point Defects in the Hydration Structure of Calcite (10.4) with Three-Dimensional Atomic Force Microscopy", Phys Rev Lett 120 (2018) 116101 (IF=8.839)
23) Hazawa M., Lin D.-C., Kobayashi A., Jiang Y.-Y., Xu L., Dewi F.R.P., Mohamed M.S., Hartono, Nakada M., Meguro-Horike M., Horike S.-I., Koeffler H.P., Wong R.W. "ROCK-dependent phosphorylation of NUP62 regulates p63 nuclear transport and squamous cell carcinoma proliferation", EMBO Rep. 19 (2018) 73-88 (IF=8.749)
24) Hirata K., Kitagawa T., Miyazawa K., Okamoto T., Fukunaga A., Takatoh C., Fukuma T. "Visualizing charges accumulated in an electric double layer by three-dimensional open-loop electric potential microscopy", Nanoscale 10 (2018) 14736-14746 (IF=7.233)
25) Uno M., Watanabe-Nakayama T., Konno H., Akagi K.-I., Tsutsumi N., Fukao T., Shirakawa M., Ohnishi H., Tochio H. "Intramolecular interaction suggests an autosuppression mechanism for the innate immune adaptor protein MyD88", Chem. Commun. 54 (2018) 12318-12321 (IF=6.29)
26) Zhou Y., Saito M., Miyamoto T., Novak P., Shevchuk A.I., Korchev Y.E., Fukuma T., Takahashi Y. "Nanoscale Imaging of Primary Cilia with Scanning Ion Conductance Microscopy", Anal. Chem. 90 (2018) 2891-2895 (IF=6.042)
27) Noshiro D., Ando T. "Substrate protein dependence of GroEL–GroES interaction cycle revealed by high-speed atomic force microscopy imaging", Philos. Trans. R. Soc. B Biol. Sci. 373 (2018) 20170180 (IF=5.666)
28) Zaidan M.A., Haapasilta V., Relan R., Paasonen P., Kerminen V.-M., Junninen H., Kulmala M., Foster A.S. "Exploring non-linear associations between atmospheric new-particle formation and ambient variables: A mutual information approach", Atmos. Chem. Phys. 18 (2018) 12699-12714 (IF=5.509)

29) Dewi F.R.P., Domoto T., Hazawa M., Kobayashi A., Douwaki T., Minamoto T., Wong R.W. "Colorectal cancer cells require glycogen synthase kinase-3β for sustaining mitosis via translocated promoter region (TPR)- dynein interaction", Oncotarget 9 (2018) 13337-13352 (IF=5.168)
30) Ogoshi T., Kotera D., Nishida S., Kakuta T., Yamagishi T.-A., Brouwer A.M. "Spacer Length-Independent Shuttling of the Pillar[5]arene Ring in Neutral [2]Rotaxanes", Chem. Eur. J. 24 (2018) 6325-6329 (IF=5.16)
31) Morimoto M., Takatsuji Y., Hirata K., Fukuma T., Ohno T., Sakakura T., Haruyama T. "Visualization of catalytic edge reactivity in electrochemical CO2 reduction on porous Zn electrode", Electrochim Acta 290 (2018) 255-261 (IF=5.116)
32) Kakuchi R., Yoshida S., Sasaki T., Kanoh S., Maeda K. "Multi-component post-polymerization modification reactions of polymers featuring lignin-model compounds", Polym. Chem. 9 (2018) 2109-2115 (IF=4.927)
33) Sakata Y., Yamamoto R., Saito D., Tamura Y., Maruyama K., Ogoshi T., Akine S. "Metallonanobelt: A Kinetically Stable Shape-Persistent Molecular Belt Prepared by Reversible Self-Assembly Processes", Inorg. Chem. 57 (2018) 15500-15506 (IF=4.7)
34) Miyatake Y., Yamano T., Hanayama R. "Myoferlin-Mediated Lysosomal Exocytosis Regulates Cytotoxicity by Phagocytes", J. Immunol. 201 (2018) 3051-3057 (IF=4.539)
35) Asakawa H., Holmström E., Foster A.S., Kamimura S., Ohno T., Fukuma T. "Direct Imaging of Atomic-Scale Surface Structures of Brookite TiO2 Nanoparticles by Frequency Modulation Atomic Force Microscopy in Liquid", J. Phys. Chem. C 122 (2018) 24085-24093 (IF=4.484)
36) Matsumae Y., Takahashi Y., Shiku H., Matsue T. "Quantitative Real-Time Monitoring of Antibody-Induced Internalization of Epidermal Growth Factor Receptor on Single Living Mammalian Cells Using Scanning Electrochemical Microscopy", ChemElectroChem 5 (2018) 3096-3101 (IF=4.446)
37) Vu H.T., Kobayashi M., Hegazy A.M., Tadokoro Y., Ueno M., Kasahara A., Takase Y., Nomura N., Peng H., Ito C., Ino Y., Todo T., Nakada M., Hirao A. "Autophagy inhibition synergizes with calcium mobilization to achieve efficient therapy of malignant gliomas", Cancer Sci. 109 (2018) 2497-2508 (IF=4.372)
38) Mizuno K., Takeuchi K., Umehara K., Nakajima M. "Identification of a novel metabolite of vildagliptin in humans: Cysteine targets the nitrile moiety to form a thiazoline ring", Biochem. Pharmacol. 156 (2018) 312-321 (IF=4.235)
39) Konishi K., Fukami T., Ogiso T., Nakajima M. "In vitro approach to elucidate the relevance of carboxylesterase 2 and N-acetyltransferase 2 to flupirtine-induced liver injury", Biochem. Pharmacol. 155 (2018) 242-251 (IF=4.235)
40) Amano T., Fukami T., Ogiso T., Hirose D., Jones J.P., Taniguchi T., Nakajima M. "Identification of enzymes responsible for dantrolene metabolism in the human liver: A clue to uncover the cause of liver injury", Biochem. Pharmacol. 151 (2018) 69-78 (IF=4.235)
41) Sairenji S., Akine S., Nabeshima T. "Response speed control of helicity inversion based on a "regulatory enzyme"-like strategy", Sci. Rep. 8 (2018) 137 (IF=4.122)
42) Miao W., Sakai K., Ozawa N., Nishiuchi T., Suzuki Y., Ito K., Morioka T., Umitsu M., Takagi J., Suga H., Matsumoto K. "Cellular signaling and gene expression profiles evoked by a bivalent macrocyclic

peptide that serves as an artificial MET receptor agonist", Sci. Rep. 8 (2018) 16492 (IF=4.122)

43) Shibata M., Inoue K., Ikeda K., Konno M., Singh M., Kataoka C., Abe-Yoshizumi R., Kandori H., Uchihashi T. "Oligomeric states of microbial rhodopsins determined by high-speed atomic force microscopy and circular dichroic spectroscopy", Sci. Rep. 8 (2018) 8262 (IF=4.122)
44) Erofeev A., Gorelkin P., Garanina A., Alova A., Efremova M., Vorobyeva N., Edwards C., Korchev Y., Majouga A. "Novel method for rapid toxicity screening of magnetic nanoparticles", Sci. Rep. 8 (2018) 7462 (IF=4.122)
45) Umakoshi T., Udaka H., Uchihashi T., Ando T., Suzuki M., Fukuda T. "Quantum-dot antibody conjugation visualized at the single-molecule scale with high-speed atomic force microscopy", Colloids Surf. B Biointerfaces 167 (2018) 267-274 (IF=3.997)
46) Yang C.-W., Miyazawa K., Fukuma T., Miyata K., Hwang I.-S. "Direct comparison between subnanometer hydration structures on hydrophilic and hydrophobic surfaces via three-dimensional scanning force microscopy", Phys. Chem. Chem. Phys. 20 (2018) 23522-23527 (IF=3.906)
47) Umeda K., Kobayashi K., Minato T., Yamada H. "Atomic-Scale 3D Local Hydration Structures Influenced by Water-Restricting Dimensions", Langmuir 34 (2018) 9114-9121 (IF=3.789)
48) Kakimoto Y., Tachihara Y., Okamoto Y., Miyazawa K., Fukuma T., Tero R. "Morphology and Physical Properties of Hydrophilic-Polymer-Modified Lipids in Supported Lipid Bilayers", Langmuir 34 (2018) 7201-7209 (IF=3.789)
49) Miao W., Sakai K., Imamura R., Ito K., Suga H., Sakuma T., Yamamoto T., Matsumoto K. "MET activation by a macrocyclic peptide agonist that couples to biological responses differently from HGF in a context-dependent manner", Int. J. Mol. Sci. 19 (2018) 3141 (IF=3.687)
50) Akine S., Onuma T., Nabeshima T. "A novel graphite-like stacking structure in a discrete molecule and its molecular recognition behavior", New J. Chem. 42 (2018) 9369-9372 (IF=3.201)
51) Shionoya T., Mizuno M., Tsukamoto T., Ikeda K., Seki H., Kojima K., Shibata M., Kawamura I., Sudo Y., Mizutani Y. "High Thermal Stability of Oligomeric Assemblies of Thermophilic Rhodopsin in a Lipid Environment", J Phys Chem B 122 (2018) 6945-6953 (IF=3.146)
52) Ogiso T., Fukami T., Mishiro K., Konishi K., Jones J.P., Nakajima M. "Substrate selectivity of human aldehyde oxidase 1 in reduction of nitroaromatic drugs", Arch. Biochem. Biophys. 659 (2018) 85-92 (IF=3.118)
53) Miyata K., Fukuma T. "Quantitative comparison of wideband low-latency phase-locked loop circuit designs for high-speed frequency modulation atomic force microscopy", Beilstein J. Nanotechnology 9 (2018) 1844-1855 (IF=2.968)
54) Hirose D., Nozaki S., Kanoh S., Maeda K. "Synthesis of amphiphilic block copolymers containing chiral polythiophene chains and their micelle formation and chiroptical properties", Polym. 10 (2018) 718 (IF=2.935)
55) Ogoshi T., Yamafuji D., Aoki T., Yamagishi T.-A. "An Electric Trap: Electron-Rich Carbonyl Axis Ends Slow Threading/Dethreading Exchange Dynamics of Pillar[5]arene Ring along Axis", Isr. J. Chem. 58 (2018) 1210-1214 (IF=2.607)
56) Li R., Gunarta I.K., Suzuki R., Boldbaatar J., Nakazato R., Yuliana D., Davaakhuu G., Oyunsuren T., Takamatsu N., Kobayashi M., Hirao A., Yoshioka K. "JLP-JNK signaling protects cancer cells from

reactive oxygen species-induced cell death", Biochem. Biophys. Res. Commun. 501 (2018) 724-730 (IF=2.559)

57) Peng H., Kasada A., Ueno M., Hoshii T., Tadokoro Y., Nomura N., Ito C., Takase Y., Vu H.T., Kobayashi M., Xiao B., Worley P.F., Hirao A. "Distinct roles of Rheb and Raptor in activating mTOR complex 1 for the self-renewal of hematopoietic stem cells", Biochem. Biophys. Res. Commun. 495 (2018) 1129-1135 (IF=2.559)
58) Nagata Y., Shimada Y., Nishikawa T., Takeda R., Uno M., Ogoshi T., Suginome M. "A Planar-Chiral Pillar[5]arene-Based Monophosphine Ligand with Induced Chirality at the Biaryl Axis", Synlett 29 (2018) 2167-2170 (IF=2.369)
59) Ogoshi, T., Akutsu, T., Yamagishi, T. "An amphiphilic pseudo[1]catenane: neutral guest-induced clouding point change", Beilstein J. Org. Chem. 14 (2018) 1937–1943 (IF=2.330)
60) Tatsumi N., Tokumitsu S., Nakano M., Fukami T., Nakajima M. "miR-141-3p commonly regulates human UGT1A isoforms via different mechanisms", Drug Metab. Pharmacokinet. 33 (2018) 203-210 (IF=2.087)
61) Zaidan M.A., Haapasilta V., Relan R., Junninen H., Aalto P.P., Kulmala M., Laurson L., Foster A.S. "Predicting atmospheric particle formation days by Bayesian classification of the time series features", Tellus Ser. B Chem. Phys. Meteorol. 70 (2018) 1530031 (IF=2.013)
62) Ogoshi T., Furuta T., Hamada Y., Kakuta T., Yamagishi T. "Solid-state self-inclusion complexation behaviour of a pillar[5]arene-based host-guest conjugate", Mater. Chem. Front. 2 (2018) 597-602 (IF=N/A)
63) Sasai Y., Tsuchida H., Kakuta T., Ogoshi T., Morisaki Y. "Synthesis of optically active π-stacked compounds based on planar chiral tetrasubstituted [2.2]paracyclophane", Mater. Chem. Front. 2 (2018) 791-795 (IF=N/A)
64) Vaneev A.N., Alova A.V., Erofeev A.S., Gorelkin P.V., Aleksashkin A.D., Beznos O.V., Chesnokova N.B., Kost O.A., Majouga A.M., Korchev Y., Klyachko N.L. "Detecting reactive oxygen species in biological fluids by platinum nanoelectrode applying amperometric method", Bull. Russ. State Med. Univ. 7 (2018) (IF=N/A)
65) Ogoshi T., Takashima S., Inada N., Asakawa H., Fukuma T., Shoji Y., Kajitani T., Fukushima T., Tada T., Dotera T., Kakuta T., Yamagishi T. "Ring shape-dependent self-sorting of pillar[n]arenes assembled on a surface" Commun. Chem. 1, (2018) 92 (IF=N/A)

2. Review articles

66) Kakuta T., Yamagishi T.-A., Ogoshi T. "Stimuli-Responsive Supramolecular Assemblies Constructed from Pillar[n]arenes", Acc. Chem. Res. 51 (2018) 1656-1666 (IF=20.955)
67) Song N., Kakuta T., Yamagishi T.-A., Yang Y.-W., Ogoshi T. "Molecular-Scale Porous Materials Based on Pillar[n]arenes", Chem 4 (2018) 2029-2053 (IF=14.104)
68) Fukuma T., Garcia R. "Atomic- and Molecular-Resolution Mapping of Solid-Liquid Interfaces by 3D Atomic Force Microscopy", ACS Nano 12 (2018) 11785-11797 (IF=13.709)
69) Togashi Y., Flechsig H. "Coarse-grained protein dynamics studies using elastic network models", Int. J. Mol. Sci. 19 (2018) 3899 (IF=3.687)

70) Flechsig H., Togashi Y. "Designed elastic networks: Models of complex protein machinery", Int. J. Mol. Sci. 19 (2018) 3152 (IF=3.687)
71) Katayama E., Kodera N. "Unconventional imaging methods to capture transient structures during actomyosin interaction", Int. J. Mol. Sci. 19 (2018) 1402 (IF=3.687)
72) Nakano M., Nakajima M. "Current knowledge of microRNA-mediated regulation of drug metabolism in humans", Expert Opin. Drug Metab. Toxicol. 14 (2018) 493-504 (IF=3.151)
73) Ando T., Bhamidimarri S.P., Brending N., Colin-York H., Collinson L., De Jonge N., De Pablo P.J., Debroye E., Eggeling C., Franck C., Fritzsche M., Gerritsen H., Giepmans B.N.G., Grunewald K., Hofkens J., Hoogenboom J.P., Janssen K.P.F., Kaufman R., Klumpermann J., Kurniawan N., Kusch J., Liv N., Parekh V., Peckys D.B., Rehfeldt F., Reutens D.C., Roeffaers M.B.J., Salditt T., Schaap I.A.T., Schwarz U.S., Verkade P., Vogel M.W., Wagner R., Winterhalter M., Yuan H., Zifarelli G. "The 2018 correlative microscopy techniques roadmap", J Phys D 51 (2018) 443001 (IF=2.373)
74) Kawahara H., Hanayama R. "The role of exosomes/extracellular vesicles in neural signal transduction", Biol. Pharm. Bull. 41 (2018) 1119-1125 (IF=1.694)
75) Akine S. "Dynamic helicity control of oligo(salamo)-based metal helicates", Inorganics 6 (2018) (IF=N/A)
76) Echizen K., Oshima H., Nakayama M., Oshima M. "The inflammatory microenvironment that promotes gastrointestinal cancer development and invasion", Adv. Biolog. Regulation 68 (2018) 39-45 (IF= N/A)
77) Ando T. "High-speed atomic force microscopy and its future prospects", Biophys. Rev. 10 (2018) 285-292 (IF=N/A)

3. Proceedings

78) Voon DC., Yong ZW., Lim KS., Wang HJ., Tan TZ., Oshima H., Oshima M., Ito Y. "Inflammatory and mitogenic signals drive IL23A secretion in intestinal epithelial cells", Cancer Sci. 109 (2018) 647 (IF=4.372)
79) Ueno, M; Hirao, A "mTORC2-mediated metabolic processes contributes drug resistance in leukemia", Cancer Sci. 109 (2018) 747 (IF=4.372)
80) Mizuno K., Sumikama T., Tarnai Y., Tani M. "Origins of Heat Evolution in Mixing Water and Dimethyl Sulfoxide", Int. Conf. Infrared, Millim., Terahertz Waves, IRMMW-THz 2018-September (2018) (IF=N/A)

4. Other English articles

81) Lim KS., Wong RW. "Targeting Nucleoporin POM121-Importin beta Axis in Prostate Cancer", Cell Chem. Biol. 25 (2018) 1056-1058 (IF=5.592)

B. WPI-related papers

1) Spengler M., Dong R.Y., Michal C.A., Hamad W.Y., MacLachlan M.J., Giese M. "Hydrogen-Bonded Liquid Crystals in Confined Spaces—Toward Photonic Hybrid Materials", Adv. Funct. Mater. 28 (2018) 1800207 (IF=13.325)

2) Hiratani T., Kose O., Hamad W.Y., Maclachlan M.J. "Stable and sensitive stimuli-responsive anisotropic hydrogels for sensing ionic strength and pressure", Mater. Horizons 5 (2018) 1076-1081 (IF=13.183)
3) Nakayama M., Kajiyama S., Kumamoto A., Nishimura T., Ikuhara Y., Yamato M., Kato T. "Stimuli-responsive hydroxyapatite liquid crystal with macroscopically controllable ordering and magneto-optical functions", Nat. Commun. 9 (2018) 568 (IF=12.353)
4) Arasada R.R., Shilo K., Yamada T., Zhang J., Yano S., Ghanem R., Wang W., Takeuchi S., Fukuda K., Katakami N., Tomii K., Ogushi F., Nishioka Y., Talabere T., Misra S., Duan W., Fadda P., Rahman M.A., Nana-Sinkam P., Evans J., Amann J., Tchekneva E.E., Dikov M.M., Carbone D.P. "Notch3-dependent β-catenin signaling mediates EGFR TKI drug persistence in EGFR mutant NSCLC", Nat. Commun. 9 (2018) 3198 (IF=12.353)
5) Kang M.-H., Choi H., Oshima M., Cheong J.-H., Kim S., Lee J.H., Park Y.S., Choi H.-S., Kweon M.-N., Pack C.-G., Lee J.-S., Mills G.B., Myung S.-J., Park Y.-Y. "Estrogen-related receptor gamma functions as a tumor suppressor in gastric cancer", Nat. Commun. 9 (2018) 1920 (IF=12.353)
6) Jiang Y., Jiang Y.-Y., Xie J.-J., Mayakonda A., Hazawa M., Chen L., Xiao J.-F., Li C.-Q., Huang M.-L., Ding L.-W., Sun Q.-Y., Xu L., Kanojia D., Jeitany M., Deng J.-W., Liao L.-D., Soukiasian H.J., Berman B.P., Hao J.-J., Xu L.-Y., Li E.-M., Wang M.-R., Bi X.-G., Lin D.-C., Koeffler H.P. "Co-activation of super-enhancer-driven CCAT1 by TP63 and SOX2 promotes squamous cancer progression", Nat. Commun. 9 (2018) 3619 (IF=12.353)
7) Wang P.-X., Hamad W.Y., MacLachlan M.J. "Size-Selective Exclusion Effects of Liquid Crystalline Tactoids on Nanoparticles: A Separation Method", Angew. Chem.-Int. Edit. 57 (2018) 3360-3365 (IF=12.102)
8) Terahara N., Inoue Y., Kodera N., Morimoto Y.V., Uchihashi T., Imada K., Ando T., Namba K., Minamino T. "Insight into structural remodeling of the FlhA ring responsible for bacterial flagellar type III protein export", Sci. Adv. 4 (2018) eaao7054 (IF=11.511)
9) Nishiyama A., Yamada T., Kita K., Wang R., Arai S., Fukuda K., Tanimoto A., Takeuchi S., Tange S., Tajima A., Furuya N., Kinoshita T., Yano S. "Foretinib overcomes entrectinib resistance associated with the ntrk1 g667c mutation in ntrk1 fusion–positive tumor cells in a brain metastasis model", Clin. Cancer Res. 24 (2018) 2357-2369 (IF=10.199)
10) Yu L., Wu D., Gao H., Balic J.J., Tsykin A., Han T.-S., Liu Y.D., Kennedy C.L., Li J.K., Mao J.Q., Tan P., Oshima M., Goodall G.J., Jenkins B.J. "Clinical utility of a STAT3-regulated miRNA-200 family signature with prognostic potential in early gastric cancer", Clin. Cancer Res. 24 (2018) 1459-1472 (IF=10.199)
11) Nguyen T.-D., Tang D., D'Acierno F., Michal C.A., Maclachlan M.J. "Biotemplated Lightweight γ-Alumina Aerogels", Chem. Mat. 30 (2018) 1602-1609 (IF=9.89)
12) Oechsle A.-L., Lewis L., Hamad W.Y., Hatzikiriakos S.G., MacLachlan M.J. "CO2-Switchable Cellulose Nanocrystal Hydrogels", Chem. Mat. 30 (2018) 376-385 (IF=9.89)
13) Deswaerte V., Nguyen P., West A., Browning A.F., Yu L., Ruwanpura S.M., Balic J., Livis T., Girard C., Preaudet A., Oshima H., Fung K.Y., Tye H., Najdovska M., Ernst M., Oshima M., Gabay C., Putoczki T., Jenkins B.J. "Inflammasome adaptor ASC suppresses apoptosis of gastric cancer cells by an IL18-mediated inflammation-independent mechanism", Cancer Res. 78 (2018) 1293-1307 (IF=9.13)
14) Xue L., Cadinu P., Paulose Nadappuram B., Kang M., Ma Y., Korchev Y., Ivanov A.P., Edel J.B. "Gated Single-Molecule Transport in Double-Barreled Nanopores", ACS Appl. Mater. Interfaces 10 (2018) 38621-

38629 (IF=8.097)

15) Dai Y., Pavan Kumar V., Zhu C., MacLachlan M.J., Smith K.J., Wolf M.O. "Mesoporous Silica-Supported Nanostructured PdO/CeO2 Catalysts for Low-Temperature Methane Oxidation", ACS Appl. Mater. Interfaces 10 (2018) 477-487 (IF=8.097)
16) Takeda T., Kozai T., Yang H., Ishikuro D., Seyama K., Kumagai Y., Abe T., Yamada H., Uchihashi T., Ando T., Takei K. "Dynamic clustering of dynamin-amphiphysin helices regulates membrane constriction and fission coupled with GTP hydrolysis", eLife 7 (2018) (IF=7.616)
17) Cao Y., Hamad W.Y., MacLachlan M.J. "Broadband Circular Polarizing Film Based on Chiral Nematic Liquid Crystals", Adv. Opt. Mater. 6 (2018) 1800412 (IF=7.43)
18) Terpstra A.S., Arnett L.P., Manning A.P., Michal C.A., Hamad W.Y., Maclachlan M.J. "Iridescent Chiral Nematic Mesoporous Organosilicas with Alkylene Spacers", Adv. Opt. Mater. 6 (2018) 1800163 (IF=7.43)
19) Hill D.G., Yu L., Gao H., Balic J.J., West A., Oshima H., McLeod L., Oshima M., Gallimore A., D'Costa K., Bhathal P.S., Sievert W., Ferrero R.L., Jenkins B.J., Jones G.W. "Hyperactive gp130/STAT3-driven gastric tumourigenesis promotes submucosal tertiary lymphoid structure development", Int. J. Cancer 143 (2018) 167-178 (IF=7.36)
20) Xu Y.-T., Dai Y., Nguyen T.-D., Hamad W.Y., MacLachlan M.J. "Aerogel materials with periodic structures imprinted with cellulose nanocrystals", Nanoscale 10 (2018) 3805-3812 (IF=7.233)
21) Kotani H., Adachi Y., Kitai H., Tomida S., Bando H., Faber A.C., Yoshino T., Voon D.C., Yano S., Ebi H. "Distinct dependencies on receptor tyrosine kinases in the regulation of MAPK signaling between BRAF V600E and non-V600E mutant lung cancers", Oncogene 37 (2018) 1775-1787 (IF=6.854)
22) Chaudhry M.T., Lelj F., MacLachlan M.J. "Expanded campestarene hosts for tetra- and dinuclear uranyl(VI) complexes", Chem. Commun. 54 (2018) 11869-11872 (IF=6.29)
23) Liang Q., Cui S., Xu S., Yao C., MacLachlan M.J., Li Z. "A porous triptycene-based covalent polymer stabilized binary metal sulfide for enhanced hydrogen evolution under visible light", Chem. Commun. 54 (2018) 3391-3394 (IF=6.29)
24) Ikai T., Yoshida T., Awata S., Wada Y., Maeda K., Mizuno M., Swager T.M. "Circularly Polarized Luminescent Triptycene-Based Polymers", ACS Macro Lett. 7 (2018) 364-369 (IF=6.131)
25) Ikai T., Shimizu S., Awata S., Shinohara K.-I. "Chiral Amplification in π-Conjugated Helical Polymers with Circularly Polarized Luminescence", Macromolecules 51 (2018) 2328-2334 (IF=5.914)
26) Yasuda T., Kagawa W., Ogi T., Kato T.A., Suzuki T., Dohmae N., Takizawa K., Nakazawa Y., Genet M.D., Saotome M., Hama M., Konishi T., Nakajima N.I., Hazawa M., Tomita M., Koike M., Noshiro K., Tomiyama K., Obara C., Gotoh T., Ui A., Fujimori A., Nakayama F., Hanaoka F., Sugasawa K., Okayasu R., Jeggo P.A., Tajima K. "Novel function of HATs and HDACs in homologous recombination through acetylation of human RAD52 at double-strand break sites", PLoS Genet. 14 (2018) e1007277 (IF=5.54)
27) Yamada T., Amann J.M., Tanimoto A., Taniguchi H., Shukuya T., Timmers C., Yano S., Shilo K., Carbone D.P. "Histone deacetylase inhibition enhances the antitumor activity of a MEK inhibitor in lung cancer cells harboring RAS mutations", Mol. Cancer Ther. 17 (2018) 17-25 (IF=5.365)
28) Kobayashi N., Inano K., Sasahara K., Sato T., Miyazawa K., Fukuma T., Hecht M.H., Song C., Murata K., Arai R. "Self-Assembling Supramolecular Nanostructures Constructed from de Novo Extender Protein Nanobuilding Blocks", ACS Synth. Biol. 7 (2018) 1381-1394 (IF=5.316)

29) Ikai T., Minami S., Awata S., Shimizu S., Yoshida T., Okubo M., Shinohara K.-I. "Helicity control of π-conjugated foldamers containing d-glucose-based single enantiomeric units as a chiral source", Polym. Chem. 9 (2018) 5504-5510 (IF=4.927)
30) Ikai T., Awata S., Shinohara K.-I. "Synthesis of a helical π-conjugated polymer with a dynamic hydrogen-bonded network in the helical cavity and its circularly polarized luminescence properties", Polym. Chem. 9 (2018) 1541-1546 (IF=4.927)
31) Haruyama T., Uchihashi T., Yamada Y., Kodera N., Ando T., Konno H. "Negatively Charged Lipids Are Essential for Functional and Structural Switch of Human 2-Cys Peroxiredoxin II", J. Mol. Biol. 430 (2018) 602-610 (IF=4.894)
32) Nguyen T.-D., Nguyen C.D., Hieu N.V., Maclachlan M.J. "Mesoporous Cobalt Tungsten Oxide Heterostructured Nanotoroids for Gas Sensing", Adv. Mater. Interfaces 5 (2018) 1800269 (IF=4.834)
33) Soeta T., Ohashi N., Kobayashi T., Sakata Y., Suga T., Ukaji Y. "Synthesis of Sterically Fixed Phytochrome Chromophore Derivatives Bearing a 15 E- Fixed or 15 E- Anti-Fixed CD-Ring Component", J. Org. Chem. 83 (2018) 10743-10748 (IF=4.805)
34) Carta V., Mehr S.H.M., Maclachlan M.J. "Controlling Ligand Exchange through Macrocyclization", Inorg. Chem. 57 (2018) 3243-3253 (IF=4.7)
35) Enjoji S., Yabe R., Tsuji S., Yoshimura K., Kawasaki H., Sakurai M., Sakai Y., Takenouchi H., Yoshino S., Hazama S., Nagano H., Oshima H., Oshima M., Vitek M.P., Matsuura T., Hippo Y., Usui T., Ohama T., Sato K. "Stemness is enhanced in gastric cancer by a SET/PP2A/E2F1 axis", Mol. Cancer Res. 16 (2018) 554-563 (IF=4.597)
36) Holmström E., Stixrude L., Scipioni R., Foster A.S. "Electronic conductivity of solid and liquid (Mg, Fe)O computed from first principles", Earth Planet. Sci. Lett. 490 (2018) 43788 (IF=4.581)
37) Anetai H., Takeda T., Hoshino N., Araki Y., Wada T., Yamamoto S., Mitsuishi M., Tsuchida H., Ogoshi T., Akutagawa T. "Circular Polarized Luminescence of Hydrogen-Bonded Molecular Assemblies of Chiral Pyrene Derivatives", J. Phys. Chem. C 122 (2018) 6323-6331 (IF=4.484)
38) Ohtsuka J., Oshima H., Ezawa I., Abe R., Oshima M., Ohki R. "Functional loss of p53 cooperates with the in vivo microenvironment to promote malignant progression of gastric cancers", Sci Rep 8 (2018) 2291 (IF=4.122)
39) Hata T., Kanazawa T., Hamada T., Nishihara M., Bush A.I., Yoneda H., Nakajima M., Katsumata T. "What can predict and prevent the long-term use of benzodiazepines?", J. Psychiatr. Res. 97 (2018) 94-100 (IF=4)
40) Beaulieu-Houle G., White N.G., Maclachlan M.J. "Coordination Polymers from Functionalized Bipyrimidine Ligands and Silver(I) Salts", Cryst. Growth Des. 18 (2018) 2210-2216 (IF=3.972)
41) Tran A., Hamad W.Y., MacLachlan M.J. "Tactoid Annealing Improves Order in Self-Assembled Cellulose Nanocrystal Films with Chiral Nematic Structures", Langmuir 34 (2018) 646-652 (IF=3.789)
42) Yoshida T., Maruyama T., Miura M., Inoue M., Fukuda K., Shimazu K., Taguchi D., Kanda H., Oshima M., Iwabuchi Y., Shibata H. "Dietary intake of pyrolyzed deketene curcumin inhibits gastric carcinogenesis", J. Funct. Food. 50 (2018) 192-200 (IF=3.47)
43) Yoshida T., Fukami T., Kurokawa T., Gotoh S., Oda A., Nakajima M. "Difference in substrate specificity of carboxylesterase and arylacetamide deacetylase between dogs and humans", Eur. J. Pharm. Sci. 111

(2018) 167-176 (IF=3.466)

44) Shionoya T., Mizuno M., Tsukamoto T., Ikeda K., Seki H., Kojima K., Shibata M., Kawamura I., Sudo Y., Mizutani Y. "High Thermal Stability of Oligomeric Assemblies of Thermophilic Rhodopsin in a Lipid Environment", J. Phys. Chem. B 122 (2018) 6945-6953 (IF=3.146)
45) Noji T., Matsuo M., Takeda N., Sumino A., Kondo M., Nango M., Itoh S., Dewa T. "Lipid-Controlled Stabilization of Charge-Separated States (P+QB -) and Photocurrent Generation Activity of a Light-Harvesting-Reaction Center Core Complex (LH1-RC) from Rhodopseudomonas palustris", J. Phys. Chem. B 122 (2018) 1066-1080 (IF=3.146)
46) Saga Y., Hirota K., Matsui S., Asakawa H., Ishikita H., Saito K. "Selective Removal of B800 Bacteriochlorophyll a from Light-Harvesting Complex 2 of the Purple Photosynthetic Bacterium Phaeospirillum molischianum", Biochemistry 57 (2018) 3075-303 (IF=2.997)
47) Ikai T., Nagata N., Awata S., Wada Y., Maeda K., Mizuno M., Swager T.M. "Optically active distorted cyclic triptycenes: Chiral stationary phases for HPLC", RSC Adv. 8 (2018) 20483-20487 (IF=2.936)
48) Anand U., Yiangou Y., Akbar A., Quick T., MacQuillan A., Fox M., Sinisi M., Korchev Y.E., Jones B., Bloom S.R., Anand P. "Glucagon-like peptide 1 receptor (GLP-1R) expression by nerve fibres in inflammatory bowel disease and functional effects in cultured neurons", PloS one 13 (2018) e0198024 (IF=2.766)
49) Tanimoto A., Takeuchi S., Kotani H., Yamashita K., Yamada T., Ohtsubo K., Ebi H., Ikeda H., Yano S. "Pulmonary carcinosarcoma showing an obvious response to pazopanib: A case report", BMC Pulm. Med. 18 (2018) 193 (IF=2.721)
50) Kobayashi F., Nishiuchi T., Takaki K., Konno H. "Ubiquitin chain specificities of E6AP E3 ligase and its HECT domain", Biochem. Biophys. Res. Commun. 496 (2018) 686-692 (IF=2.559)
51) Sakai H., Kuroda K., Tsukegi T., Ogoshi T., Ninomiya K., Takahashi K. "Butylated lignin as a compatibilizing agent for polypropylene-based carbon fiber-reinforced plastics", Polym. J. 50 (2018) 997-1002 (IF=2.17)
52) Sakai H., Kuroda K., Muroyama S., Tsukegi T., Kakuchi R., Takada K., Hata A., Kojima R., Ogoshi T., Omichi M., Ninomiya K., Takahashi K. "Alkylated alkali lignin for compatibilizing agents of carbon fiber-reinforced plastics with polypropylene", Polym. J. 50 (2018) 281-284 (IF=2.17)
53) Hossain F., Ohta A., Yamane Y., Shizuka A.-N., Asakawa H., Asakawa T. "Study of Antioxidative Properties of Some Mono Amino-Acid-Type and Dipeptide-Type Surfactants", J. Surfactants Deterg. 21 (2018) 733-744 (IF=1.454)
54) Kamikawa Y., Sakai N., Miyake T., Sagara A., Shinozaki Y., Kitajima S., Toyama T., Hara A., Iwata Y., Shimizu M., Furuichi K., Imamura R., Suda T., Kaneko S., Wada T. "Involvement of p38MAPK in Impaired Neutrophil Bactericidal Activity of Hemodialysis Patients", Ther. Apher. Dial. 22 (2018) 345-354 (IF=1.416)
55) Eguchi Y., Fukumori Y., Taoka A. "Measuring magnetosomal pH of the magnetotactic bacterium Magnetospirillum magneticum AMB-1 using pH-sensitive fluorescent proteins", Biosci. Biotechnol. Biochem. 82 (2018) 1243-1251 (IF=1.255)
56) Asakawa T., Takano Y., Ohta A., Asakawa H. "Aggregation and ph responsive behavior of thioester surfactants and formation of disulfide linkages in aqueous solutions", J. Oleo Sci. 67 (2018) 199-206 (IF=1.182)

57) Asakawa T., Arai N., Fujii A., Takahashi K., Takakuwa K., Honda M., Ohta A., Asakawa H. "Aggregation behavior and thiol-thioester exchange for cationic surfactants with propylthioacetate side chain", J. Oleo Sci. 67 (2018) 969-976 (IF=1.182)
58) Shimizu Y., Mashima-Nemoto T., Hazawa M., Taira Y., Taira I., Ishida I., Isoda K. "The hepatoprotective effect of lycopene on Con A-induced liver injury in mice", Pharmazie 73 (2018) 393-395 (IF=1.016)
59) Back H.-M., Pradhan S., Yoon Y.-R., Kang W., Chae J.-W., Han N., Miki N., Kwon K.-I., Kim S.-K., Yun H.-Y. "Population pharmacokinetic modeling and simulation of afloqualone to predict steady-state exposure levels", Int. J. Pharmacol. 14 (2018) 276-284 (IF=0.765)
60) Ikai T. "Synthesis of optically active polymers containing carbohydrate units as a chiral source and exploration of their functions", Kobunshi Ronbunshu 75 (2018) 406-420 (IF=0.239)
61) Kuo D., Nishimura T., Kajiyama S., Kato T. "Bioinspired Environmentally Friendly Amorphous CaCO3-Based Transparent Composites Comprising Cellulose Nanofibers", ACS Omega 3 (2018) 12722-12729 (IF=N/A)
62) Nguyen T.-D., Hamad W.Y., MacLachlan M.J. "Aerogel templating on functionalized fibers of nanocellulose networks", Materials Chemistry Frontiers 2 (2018) 1655-1663 (IF=N/A)
63) Donatien P., Anand U., Yiangou Y., Sinisi M., Fox M., MacQuillan A., Quick T., Korchev Y.E., Anand P. "Granulocyte-macrophage colony-stimulating factor receptor expression in clinical pain disorder tissues and role in neuronal sensitization", Pain Reports 3 (2018) e676 (IF=N/A)
64) Obata Y., Kita S., Koyama Y., Fukuda S., Takeda H., Takahashi M., Fujishima Y., Nagao H., Masuda S., Tanaka Y., Nakamura Y., Nishizawa H., Funahashi T., Ranscht B., Izumi Y., Bamba T., Fukusaki E., Hanayama R., Shimada S., Maeda N., Shimomura I. "Adiponectin/T-cadherin system enhances exosome biogenesis and decreases cellular ceramides by exosomal release", JCI insight 3 (2018) e99680 (IF=N/A)

2. Review articles

65) Nakano M., Nakajima M. "Significance of A-to-I RNA editing of transcripts modulating pharmacokinetics and pharmacodynamics", Pharmacol. Ther. 181 (2018) 13-21 (IF=10.376)
66) Ikai A., Afrin R., Saito M., Watanabe-Nakayama T. "Atomic force microscope as a nano- and micrometer scale biological manipulator: A short review", Semin. Cell Dev. Biol. 73 (2018) 132-144 (IF=6.138)
67) Wang P.-X., MacLachlan M.J. "Liquid crystalline tactoids: Ordered structure, defective coalescence and evolution in confined geometries", Philos. Trans. R. Soc. A-Math. Phys. Eng. Sci. 376 (2018) 20170042 (IF=2.746)

3. Proceedings

None

4. Other English articles

68) MacLachlan M.J. "Bringing Nanotubes into Line", Angew. Chem.-Int. Edit. 57 (2018) 4838-4839 (IF=12.102)

2. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY 2018 in order from most recent.
- For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
Feb. 12, 2019	Atsushi Hirao	Metabolic Regulation of Stemness in Malignant Hematopoiesis	Eleventh AACR-JCA Joint Conference on Breakthroughs in Cancer Research: Biology to Precision Medicine
Oct. 5, 2018	Miki Nakajima	Significance of post-transcriptional regulation of drug-metabolizing enzymes: perspective insight into future pharmacotherapy	22nd Microsomal and Drug Oxidation/33rd JSSX, **Plenary Lecture**
Oct. 1, 2018	Tomoki Ogoshi	Pillar-Shaped Macrocyclic Compounds "Pillar[n]arenes": from Simple Molecular Receptors to Bulk Supramolecular Assemblies	9th Joint CSJ RSC Symposium
Sep. 10, 2018	Toshio Ando	High-speed AFM: Visualizing protein molecules during their functional activity	19th International Microscopy Congress, **Keynote Speech**
Jul. 31, 2018	Mark J. MacLachlan	Coordination Chemistry in Macrocycles	ICCC Conference, **Plenary Lecture**
Jul. 29, 2018	Takeshi Fukuma	Visualizing Calcite Growth and Dissolution Processes by High-Speed FM-AFM	Gordon Research Conference on Biomineralization
Jul. 5, 2018	Katsuhiro Maeda	Development of Chiral Materials Based on Structural Features of Dynamic Helical Polymers	4th Molecular Chirality Asia (MCAsia 2018)
May 29, 2018	Shigehisa Akine	Novel metallo-molecular containers with open/close feature	101st Canadian Chemistry Conference and Exhibition
Apr. 20, 2018	Masanobu Oshima	Comprehensive phenotype characterization of colon cancer with various combination of driver mutations	The 9th International Conference of Asian Pacific Organization for Cancer Prevention
Apr. 19, 2018	Adam S. Foster	Probing molecular processes at solid-liquid interfaces	7th Multifrequency AFM Conference

3. Major Awards

- List up to 10 main awards received during FY 2018 in order from the most recent.
- For each, write the recipient's name, the name of award, and the date issued.
- In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
Feb.1,2019	Takeshi Fukuma	Japan Society for the Promotion of Science Prize
Oct.,2018	Tatsuki Fukami	JSSX Award for Young Scientists
Sep.,2018	Yutaro Yamada, Hiroki Konno, Katsuya Shimabukuro	Biophysics and Physicobiology Editors' Choice Award 2018
Sep.,2018	Shinji Takeuchi	The Young Investigator Awards of the Japanese Cancer Association
May, 2018	Kazuki Miyata	SSSJ Rising-Researcher Lecture Award
May, 2018	Kenichi Umeda	SSSJ Young-Researcher Lecture Award
May, 2018	Keisuke Miyazawa	SSSJ Student Lecture Award
Apr.,2018	Mikihiro Shibata	The Young Scientists' Prize, The Commendation for Science and Technology by the Ministry of Education, Culture, Sports, Science and Technology

Appendix 2　FY 2018 List of Principal Investigators

NOTE:

*Underline names of principal investigators who belong to an overseas research institution.

*In the case of researcher(s) not listed in the latest report or in the proposal for newly selected centers in FY2018, attach a “Biographical Sketch of a New Principal Investigator”(Appendix 2a).

<Results at the end of FY2018> **Principal Investigators Total: 16**

Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center Director Takeshi Fukuma*	42	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Engineering, Electrical engineering, Nanometrology	90	October, 2017	usually stays at the institute	
Adam Stuart Foster*	43	Department of Applied Physics, Aalto University	PhD in Theoretical Solid State Physics	30	October, 2017	Stays at the institute 30 days or more/per fiscal year	-Promotes understanding of the real image from the observation image while working toward the development of new nanoprobe technology -In charge of NanoLSI Educational Program at the Graduate School - In charge of Selection Committee of Jr.PI
Korchev Yuri*	58	Department of Medicine, Imperial College London	Ph.D. in Biophysics and Cytology, Biophysics	30	October, 2017	Stays at the institute 30 days or more/per fiscal year	-Engaged in measuring the distribution of substances inside and outside the cell while working toward the development of new nanoprobe technology - In charge of the 3rd NanoLSI International Symposium in London held on November 19, 2018
Mark MacLachlan*	45	Department of Chemistry, University of British Columbia	PhD in Chemistry	20	October, 2017	Stays at the institute 30 days or more/per fiscal year	-Engaged in development of supramolecular nanoprobes while working toward the development of new nanoprobe technology - In charge of the 4th NanoLSI International Symposium which will be held on August 8, 2019 at UBC
Alexander S. Mikhailov*	68	Department of Physical Chemistry, Fritz Haber Institute of the Max Planck Society	Doctor of Science, Theoretical Physics, Chemical Physics, Biophysics	40	October, 2017	Stays at the institute 90 days or more/per fiscal year	-Promotes understanding of the real image from the observation image while working toward the development of new nanoprobe technology - In charge of NanoLSI Educational Program at the Graduate School - In charge of Selection Committee of Jr.PI
Richard W. Wong*	44	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Medicine, Molecular cell biology	90	October, 2017	usually stays at the institute	
Toshio ANDO*	68	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Science, Biophysics and Nano-Bioscience	90	October, 2017	usually stays at the institute	
Rikinari Hanayama*	44	Nano Life Science Institute, Institute for Frontier Science Initiative	MD, PhD, Immunology, Cell Biology	80	October, 2017	usually stays at the institute	
Shigehisa Akine*	46	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Science, Supramolecular chemistry, Coordination chemistry	80	October, 2017	usually stays at the institute	
Tomoki Ogoshi*	42	Graduate School of Engineering, Kyoto University / Nano Life Science Institute, Kanazawa Univeristy	Doctor of Engineering, Supramolecular Chemistry, Structural Organic Chemistry	20	October, 2017	Stays at the institute 20% of the total working days / per year based on the cross-appointment agreement between Kyoto univ. and Kanazawa univ.	Engaged in establishment of Nanoprobe Life Science based on supramolecular chemistry
Katsuhiro Maeda*	48	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Engineering, Polymer chemistry	80	October, 2017	usually stays at the institute	
Masanobu Oshima*	57	Nano Life Science Institute, Institute for Frontier Science Initiative	D.V.M., Ph.D., Cancer research, Genetics for Cancer modeling	80	October, 2017	usually stays at the institute	
Miki Nakajima*	49	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Pharmaceutical Sciences, Drug Metabolism and Toxicology, Clinical Pharmacology	70	October, 2017	usually stays at the institute	
Atsushi Hirao*	55	Cancer Research Institute	Doctor of Medicine, Stem Cell Biology	60	October, 2017	usually stays at the institute	
Seiji Yano*	53	Cancer Research Institute	MD, PhD, Medical Oncology, Circumvention of targeted drug resistance	40	October, 2017	usually stays at the institute	
Kunio Matsumoto*	60	Nano Life Science Institute, Institute for Frontier Science Initiative	Doctor of Philosophy, Biological Chemistry, Tumor Biology	90	October, 2017	usually stays at the institute	

Principal investigators unable to participate in project in FY 2018

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken

Appendix 3-1 FY 2018 Records of Center Activities

1. Researchers and center staffs, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Regarding the number of researchers at the Center, fill in the table in Appendix 3-1a.

Special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working on the global circulation of world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

Name	Position	employed since	previous institute
Clemens Franz	Jr. PI, TT Associate prof.	September 19 2018	Karlsruhe Institute of Technology, Germany
Satoshi Arai	Jr. PI, TT Associate prof.	July 1 2019	WASEDA Bioscience Research Institute in Singapore (Research Institute for Science and Engineering, Waseda University)
Satoshi Toda	Jr. PI, TT Assistant prof.	September 1 2019	Department of Cellular and Molecular Pharmacology, University of California San Francisco

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
Imperial College London	Yuri Korchev	Established the Agreement in January 2019 (The effective date is January 15 2019).
University of British Columbia	Mark MacLachlan	Established the Agreement in October 2018 (The effective date is April 2019).

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
RIKEN Center for Biosystems Dynamics Research		Established the collaborative research agreement in May 2018

2. Holding international research meetings

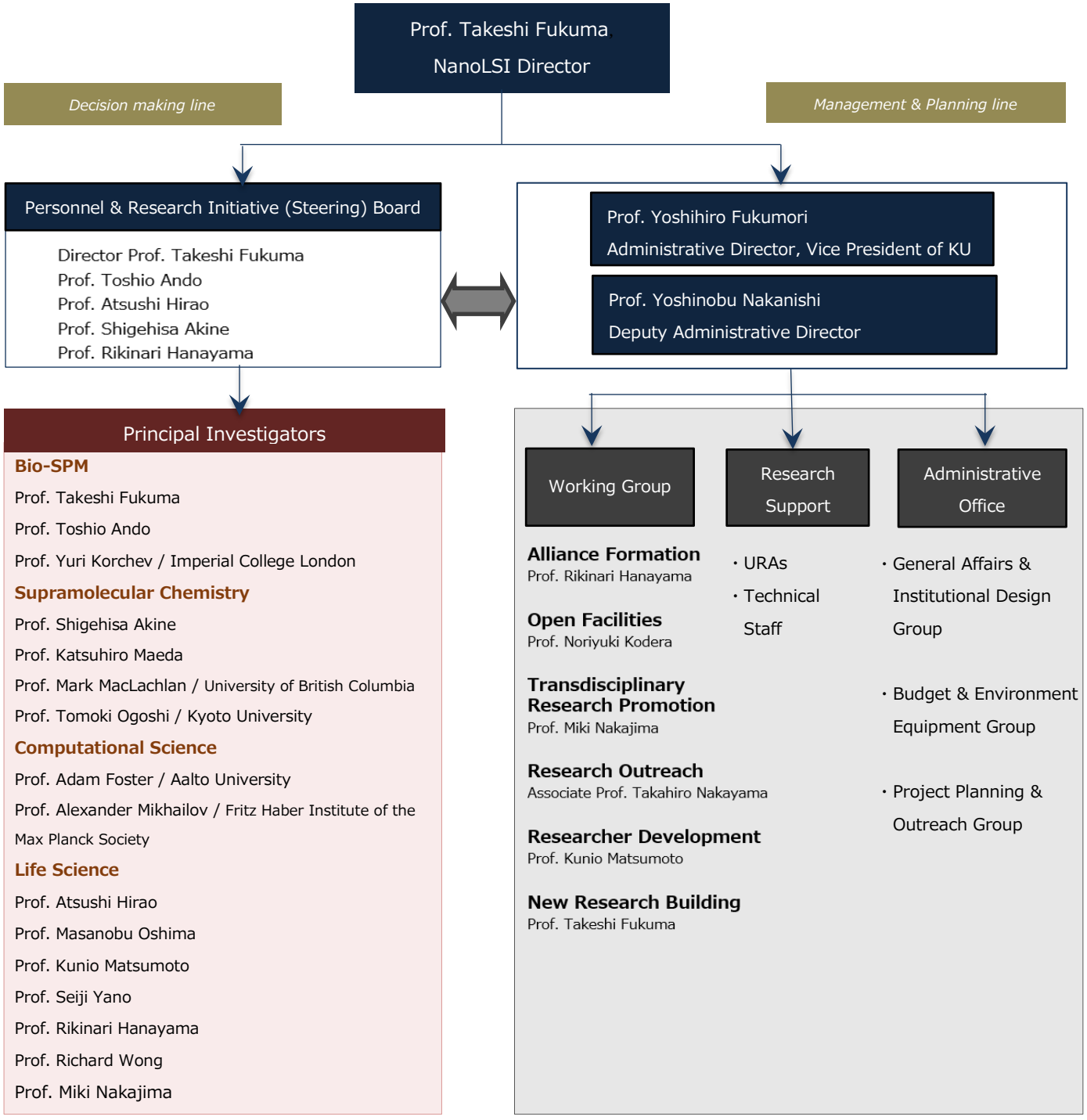
- Indicate the number of international research conferences or symposiums held in FY2018 and give up to three examples of the most representative ones using the table below.

FY 2018: 5 meetings	
Major examples (meeting titles and places held)	Number of participants

The 2nd NanoLSI International Symposium – Towards Establishment of New Research Field: Nanoprobe Life Science– The Cumberland Hotel, London 2018.11.19	From domestic institutions: 16 From overseas institutions: 37
International Symposium on Tumor Biology in Kanazawa Kanazawa University, Kanazawa 2018.5.28	From domestic institutions: 147 From overseas institutions: 8
4th International Symposium on Center of Excellence for Innovative Material Sciences Based on Supramolecules The Kanazawa Theatre, Kanazawa 2018.10.18	From domestic institutions: 216 From overseas institutions: 4

3. Diagram of management system

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any new changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such as the center director, administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research).

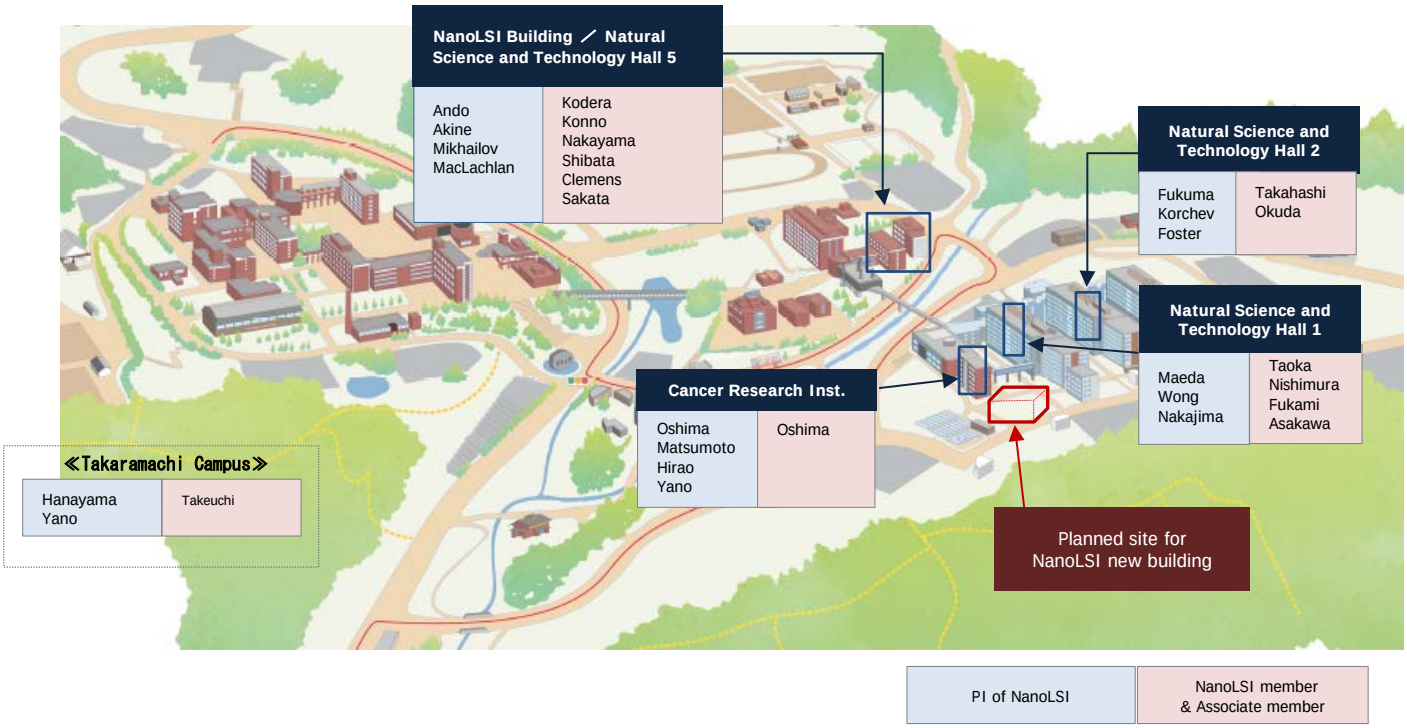


4. Campus Map

- Draw a simple map of the campus showing where the main office and principal investigator(s) are located.

5. Campus Map

- Please draw a simple map of the campus showing where the main office and principle investigator(s) are located.



5. Securing external research funding*

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes “KAKENHI,” funding for “commissioned research projects,” and for “joint research projects” as listed under “Research projects” in Appendix 3-2, Project Expenditures.

External research funding secured in FY2018

Total: 689,475,111 yen

Grant-in-Aid for Scientific Research(S): 33,410,000 yen
Grant-in-Aid for Scientific Research(A): 27,040,000 yen
AMED Practical Research for Innovative Cancer Control: 45,725,000 yen
AMED Practical Research for Innovative Cancer Control: 32,889,653 yen
JST-CREST: 28,600,000 yen

Appendix 3-1a FY 2018 Records of Center Activities

1. Researchers and other center staffs, satellites, partner institutions

1-1. Number of researchers and other center staffs

* Fill in the number of researchers and other center staffs in the table blow.
* Describe the final goals for achieving these numbers and dates when they will be achieved described in the last "center project."

a) Principal Investigators

（full professors, associate professors or other researchers of comparable standing)

(number of persons)

	At the beginning of project	At the end of FY 2018	Final goal (Date: month, year)
Researchers from within the host institution	12	12	12
Researchers invited from abroad	4	4	4
Researchers invited from other Japanese institutions	0	0	0
Total principal investigators	16	16	16

b) Total members

	At the beginning of project		At the end of FY2018		Final goal (Date: month, year)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	49		72		76	
Overseas researchers	7	14.3	22	30.6%	23	30.3%
Female researchers	6	12.2	9	12.5%	16	21.1%
Principal investigators	16		16		16	
Overseas PIs	5	31.3	5	31.3%	5	31.3%
Female PIs	1	6.3	1	6.3%	1	6.3%
Other researchers	33		56		60	
Overseas researchers	2	6.1	17	30.4%	18	30.0%
Female researchers	5	15.2	8	14.3%	15	25.0%
Research support staffs	8		25		20	
Administrative staffs	13		24		25	
Total number of people who form the "core" of the research center	70		121		121	

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the “Total Cost” column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the “Amount covered by WPI funding” column, enter the amount covered by WPI within the total amount.
* In the “Personnel,” “Project activities,” “Travel,” and “Equipment” blocks, the items and details may be changed to coincide with the project’s actual content.

(Million yens)

Cost Items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total Costs	Amount covered by WPI funding
Personnel	Center director and Administrative director	33.4	20.8
	Principal investigators (no. of persons):11	169.2	48.1
	Junior Principal investigators (no. of persons):1	1.6	0.3
	Other researchers (no. of persons):50	213.1	113.6
	Research support staffs (no. of persons):13	42.2	39.7
	Administrative staffs (no. of persons):27	129.4	61.0
	Subtotal	588.9	283.5
Project activities	Remuneration for RA(Research Assistant)	4.4	4.4
	Gratuities and honoraria paid to invited principal investigators (no. of persons):4	10.4	10.4
	Research startup cost (no. of persons):30	77.3	77.3
	Satellite organizations (Europe)	5.5	5.5
	Cost of international symposiums (no. of symposiums):1	4.0	4.0
	Facility expenses	22.1	2.2
	Cost of consumables	14.1	14.1
	Utilities cost	5.1	5.1
	Other costs	64.3	64.0
	Subtotal	207.2	187.0
Travel	Domestic travel costs	2.8	2.8
	Overseas travel costs	15.0	15.0
	Travel and accommodations cost for invited scientists (no. of domestic scientists):9 (no. of overseas scientists):7	11.0	11.0
	Travel cost for scientists on secondment (no. of domestic scientists):9 (no. of overseas scientists):9	4.4	4.4
	Subtotal	33.2	33.2
Equipment	Depreciation of buildings	0.0	0.0
	Depreciation of equipment	5.5	5.5
	Subtotal	5.5	5.5
Research projects (Detail items must be fixed)	Subsidy from the National Government, etc	144.9	0.0
	Grants-in-Aid for Scientific Research, etc.	212.3	0.0
	Commissioned research projects, etc.	197.6	0.0
	Joint research projects	38.0	0.0
	Ohers (donations, etc.)	26.6	0.0
	Subtotal	619.4	0.0
Total		1454.2	509.2

Costs (Million yens)

WPI grant in FY 2018	821.1
Costs of establishing and maintaining facilities	1.0
Establishing new facilities	0.0
Repairing facilities	1.0
Cost of equipment procured	316.4
Nuclear Magnetic Resonance	77.0
Transmission Electron Microscope	54.3
Atomic Force Microscopy System for Life Science	82.6
Cell analyzer	12.7
Laboratory animal breeding rack	8.9
Super-resolution in liquid FM-AFM	15.0
high-speed AFM	15.0
Scanning Ion Conductance Microscope	10.0
High-speed AFM 2	25.2
Others	15.7

*1. Funding sources that include government subsidies (including Enhancements promotion expenses (機能強化促進経費), National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc.), indirect funding, and allocations from the university’s own resources.

*2 When personnel, travel, equipment (etc.) expenses are covered by Grants-in-Aid or under commissioned research projects or joint research projects, the amounts should be entered in the “Research projects” block.

2) Costs of Satellites and Partner institutions

(Million yens)

Cost Items	Details	Total Costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):1	1.5	1.5
	Other researchers (no. of persons):1	1.9	1.9
	Subtotal	3.4	3.4
Project activities	Subtotal	2.1	2.1
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		5.5	5.5

Appendix 4 FY 2018 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2018 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2019 and not described in Appendix 1.

Overseas Satellite 1 **Name** (Total: 1 papers)

1) (Appendix 1 #26) Zhou Y., Saito M., Miyamoto T., Novak P., Shevchuk A.I., *Korchev Y.E.*, Fukuma T., Takahashi Y. "Nanoscale Imaging of Primary Cilia with Scanning Ion Conductance Microscopy", Anal. Chem. 90 (2018) 2891-2895 (IF=6.042)
2)
3)
4)

Overseas Satellite 2 **Name** (Total: 0 papers)

1)
2)
3)
4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2018. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1: Imperial College London

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2018	2				2
	3				3

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2018	1	3			4
					0

Overseas Satellite 2: University of British Columbia

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2018					0
				1	1

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2018	1	2			3
					0

Appendix 5 FY 2018 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.

Total: 46

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
1	Gerhard Wenz	-	Professor, Saarland University, Germany	PhD in Organic Macromolecular Chemistry	Project Professor, Graduate School of Frontier Sciences, The University of Tokyo	2018/4/18	lecture at NanoLSI Open Seminar
2	Matthiew Sollogoub	46	Professor, Sorbonne Universités, UPMC Univ. Paris 06, CNRS, Institut Parisien de Chimie Moléculaire (IPCM)	PhD in Organic, Biological and Supramolecular Glycochemistry	Junior Fellow of the Institut Universitaire de France (2010); Carbohydrate Research Award for Creativity (2011); Alfred Verdaguer Award of the Institut de France, Académie des Sciences (2013); Yoshida lectureship award, International Organic Chemistry Foundation (Japan) (2018); President of the Organic Division of the French Chemical Society (2018)	2018/4/26	lecture at NanoLSI Open Seminar
3	Clemens M. Franz	46	Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany	PhD in Cancer Cell Biology	Karlsruhe Institute of Technology Institute of Zoology Senior Lecturer (2016-2018)	2018/5/10 2018/9/1-2019/3/31 2019/4/1-present	lecture at NanoLSI Open Seminar; Assistant Professor at NanoLSI (2018/9-2019/3), Associate professor at NanoLSI (2019/4-)
4	Mohammad R. K. Mofrad	-	Professor, Departments of Bioengineering and Mechanical Engineering, University of California Berkeley	Ph.D. in Mechanical Engineering and Bioengineering	PI, Molecular Cell Biomechanics Laboratory, University of California, Berkeley	2018/5/18	lecture at NanoLSI Open Seminar
5	Alberto Moreno-Cencerrado	35	PhD student, Institute for Biophysics (DNBT) University of Natural Resources and Life Sciences Vienna (BOKU), Austria	MSc in Physics	IT Technitian (Universidad Autonoma de Madrid) (2011-2012)	2018/5/23	lecture at NanoLSI Open Seminar
6	Dong Ho Lee	71	Professor, Seoul National University Tumor Microenvironment Global Core Research Center	PhD	Board member of Korea Aerospace Industries Ltd	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
7	Young-Joon Surh	62	Professor, Seoul National University Tumor Microenvironment Global Core Research Center	Ph.D., Cancer Research	The 9th Int'l Confrence on Mechanisms of Antimutagenesis & Anticarcinogenesis (Dec. 1-5, 2007) President; Int'l Assoc. Environ. Mutagen Society (Councillor); Int'l Congress on Cell Biology: Chair, Scientific Committee	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa
8	Kyu-Won Kim	65	Professor, Seoul National University Tumor Microenvironment Global Core Research Center	Ph.D. in Biochemistry	President, The Korean Society for Vascular Biology (2001-2003); Full member, The Korean Academy of Science and Technology (2001); Vice-chairman, The Korean Cancer Association (2011 - 2012)	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa
9	Hyewon Youn	-	Clinical associate professor, Seoul National University Tumor Microenvironment Global Core Research Center	Ph.D. in Biological Sciences	American Association of Cancer Research (AACR)(2001-),Korean Society of Molecular Cell Biology, Korean Society of Radiation Bioscience (2007-), Korean Society of Nuclear Medicine, Korean Society of Molecular Imaging (2008-), Korean Association of Immunologists, Korean Vaccine Society (2014-)	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa
10	June-Key Chung	-	Professor, Seoul National University Tumor Microenvironment Global Core Research Center	Ph. D. in Nuclear Oncology	Best paper awards by Korean Association of Science and Technology (1997 and 1999); Outstanding clinical Investigation Award by JNM (1999); Distinguished Service Medal in KSNM (2002); Bumsan Academic Award by Korean Thyroid Society (2009); Beiyer-Schelling Award on Clinical Medicine by Korean Academy of Medical Sciences (2009); SNUH Academic Award in 2009Contribution Award, Asian Regional Cooperative Council on Nuclear Medicine (2011); Life Achievement Award, World Association of Radiopharmaceuticals & Molecular Therapy (2011); Distinguished Service Medal, Korean Society of Molecular Imaging (2012); Cheongbong Award of Nuclear Medicine, KSNM (2014)	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa
11	Jung Weon Lee	-	Professor, Seoul National University Tumor Microenvironment Global Core Research Center	Ph.D. in Pharmacy	The vice director of Research Institute of Pharmaceutical Sciences, SNU	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
12	Byung Woo Han	-	Associate Professor, Seoul National University Tumor Microenvironment Global Core Research Center	PhD in Pharmacy	Award for Infra&Service, Biocon's PI Workshop (2018)	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa
13	Marc Diederich	-	Professor, Seoul National University Tumor Microenvironment Global Core Research Center	PhD in molecular pharmacology	Head of Lab Fondation de Recherche Cancer et Sang (1994-present)	2018/5/28	invited lecture at International Symposium on Tumor Biology in Kanazawa
14	Félix Freire	-	Associate Professor, Centre for Research in Biological Chemistry and Molecular Materials, University of Santiago de Compostela	Ph.D. in Chemistry	The SUSCHEM award (2012); His research was highlighted in the cover of journals such as JACS, Angewandte or Chemical Science	2018/5/30	lecture at NanoLSI Open Seminar
15	Sander J. Wezenberg	-	Assistant Professor, University of Groningen, Stratingh Institute for Chemistry, The Netherland	Ph.D. in Supramolecular Chemistry	The Sandoz Family Foundation professorship (2001)	2018/7/23	lecture at NanoLSI Open Seminar
16	Jerome Lacour	-	Professor, Dé partement de Chimie Organique, Université de Gene `ve, Switzerland	Ph.D. in Organic Chemistry	Associated member of the NCCR Chemical Biology; the Sandoz Family Foundation professorship (2001); a member of the Editorial Advisory Board of Chemical Society Reviews and a Board member of Chirality and CHIMIA; a member of the International Scientific Committee of the International Symposium on Chirality; a member of the Organizing Committee of the EUCHEM "Bürgenstock" Conference on Stereochemistry	2018/7/23	lecture at NanoLSI Open Seminar

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
17	Mark John Macachlan	45	NanoLSI PI / Professor, University of British Columbia	PhD in Chemistry	Fellow of the Royal Society of Chemistry (UK)(2016); Award for Research Excellence in Materials Chemistry (Canadian Society for Chemistry)(2016); Tier 1 Canada Research Chair in Supramolecular Materials (2015-2022); Steacie Prize for Natural Sciences (E.W.R. Steacie Memorial Fund)(2014); Rutherford Memorial Medal (Royal Society of Canada)(2013); Killam Award for Excellence in Graduate Student Mentorship (UBC)(2013); Strem Award for Pure or Applied Inorganic Chemistry (Canadian Society for Chemistry)(2013); Killam Research Prize (UBC)(2011)	2018/7/21-8/3 2018/10/13-10/20 2018/11/17-11/19 2019/2/9-2/23	participation as principal investigator; lecture at NanoLSI Open Seminar; invited lecture at International Symposium on Center of Excellence for Innovative Material Sciences Based on Supramolecules; invited lecure at the 2nd NanoLSI Symposium
18	Julius Rebek, Jr.	75	Professor, Department of Chemistry The Scripps Research Institute, La Jolla, CA, US	Ph.D. in Chemistry	Evans Award, Ohio State University (2006); Univ. of Oregon Creativity Award in Chemistry, Dance and Music (2007); Tau-Shue Chou Award, Academica Sinica (2008); A. von Humboldt Senior Scientist Award, Germany (2009); Fellow, Royal Society of Chemistry (2009); Israeli Chemical Society, Honorary Member (2009); Honorary Doctorate, University of Bonn (2010); Prelog Medal, ETH Zurich (2012); Honorary Doctorate, University Jaume I, Castellon, Spain (2015); Nichols Medal, ACS New York Section (2011)	2018/8/6	lecture at NanoLSI Open Seminar
19	Brendan Jenkins	-	Professor, Hudson Institute of Medical Research Monash University, Melbourne	PhD	The Australian Institute for Policy and Science Tall Poppy Award; publications in the highest-ranking science and medical research journals, including Cancer Cell, Nature Medicine, Nature, Immunity, Journal of Clinical Investigation, Oncogene, Proceedings of the National Academy of Sciences USA, Blood, Molecular and Cellular Biology and Journal of Immunology	2018/10/1	lecture at NanoLSI Open Seminar
20	Luis Sanchez	49	Professor, Universidad Complutense de Madrid	Ph.D. in Organic Chemistry	The Prize to Novel Researchers of the RSEQ (2003); The best Theses in Chemistry at the Community of Madrid (2009 and 2013)	2018/10/18	invited lecture at International Symposium on Center of Excellence for Innovative Material Sciences Based on Supramolecules

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
21	Markus Albrecht	55	Professor, Rheinisch-Westfälische Technische Hochschule Aachen, RWTH Aachen University	Ph.D. in Chemistry	Honoured with the "ADUC-Jahrespreis für Habilitanden" (1998-2001); awarded with the "Landeslehrpreis 2002 des Landes Baden-Württemberg" (2002)	2018/10/18	invited lecture at International Symposium on Center of Excellence for Innovative Material Sciences Based on Supramolecules
22	Tapas K. MANNA	44	Associate Professor, Indian Institute of Science Education and Research, Thiruvananthapuram, India	Ph.D. in Biochemistry	Post-doctoral Fellow: Univ. of Massachusetts Medical School, Worcester; Postdoc-doctoral Fellow: Univ. of California, Santa Barbara	2018/10/26	lecture at NanoLSI Open Seminar
23	Jeffrey Noel	36	Max-Delbrück-Centrum für Molekulare Medizin	PhD in Physics	Computing Awards XSEDE Grant MCB140274 for 4.6MSUs (Co-PI) (2014)	2018/11/2-11/5	discussion for joint research; lecture at NanoLSI Open Seminar
24	Jin Yu	44	Professor, Beijing Computational Science Research Center	PhD in Physics	UC Berkeley Chancellor's Postdoctoral Fellowship (2007)	2018/11/2-11/6	discussion for joint research; lecture at NanoLSI Open Seminar
25	Julia Gorelik	-	Professor, Imperial College London	Ph.D. in Cell Biology	Imperial College Research Excellence Award (2010)	2018/11/19	invited lecure at the 2nd NanoLSI Symposium
26	Joshua Edel	39	Professor, Imperial College London	PhD on the development of single molecule detection	Research fellowship in single molecule biophysics at the Rowland Institute at Harvard University (2005); a prestigious ERC Starting Grant on “Nanoporous Membranes for High Throughput Rare Event Bioanalysis” (2011); an ERC Consolidator Grant related to the development of selective single molecule biosensors (2016)	2018/11/19	invited lecure at the 2nd NanoLSI Symposium
27	David Klenerman	60	Professor, University of Cambridge	PhD in chemistry	RSC Interdisciplinary Award (2007); British Biophysical Society Lecture at the University College Dublin (2008); Fellow of the Royal Society (2012); a Fellow of the Academy of Medical Sciences (2015); the Royal Medal by the Royal Society (2018); knighted in the 2019 New Year Honours for services to science and the development of high speed DNA sequencing technology (2019)	2018/11/19	invited lecure at the 2nd NanoLSI Symposium

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
28	Bart Hoogenboom	-	Professor, LCN, University College London	Ph.D. in Physics	The Student Choice Teaching Award at UCL (2016-2017)	2018/11/19	invited lecure at the 2nd NanoLSI Symposium
29	Patrick Unwin	55	Professor, University of Warwick Branch	Ph.D. in Chemistry	International editors of Journal of Electroanalytical Chemistry (2011-); a member of the international editorial boards of several journals including the ACS journal Langmuir (2014-); Electrochemistry Communications (1999-); Tilden Prize (2012); Geoffrey Barker Medal (2010); Corday-Morgan Medal and Prize (2001); Marlow Medal and Prize (1997)	2018/11/19	invited lecure at the 2nd NanoLSI Symposium
30	Takahiro Ito	-	Assistant Professor, University of Georgia; American Cancer Society Research Scholar	Ph.D., Division of Pharmaceutical Sciences	Member of the Cancer Cell Biology research program at Winship Cancer Institute of Emory University	2018/11/26	invited lecture at International Symposium on Tumor Biology in Kanazawa 2018
31	Jing Chen	-	Professor, Winship Cancer Institute, Emory University	PhD in Biochemistry and Cell Biology	American Cancer Society Basic Research Scholar Award; The Leukemia & Lymphoma Society Scholar Award; Georgia Cancer Coalition Distinguished Cancer Scholar Award; Distinguished Alumnus Award from the Graduate Division of Biological and Biomedical Sciences at Laney Graduate School of Emory University (2016); Winship Research Mentorship Award (2016-2017)	2018/11/26	invited lecture at International Symposium on Tumor Biology in Kanazawa 2018
32	Clemens Schmitt	-	Professor, Max-Delbrück-Centrum für Molekulare Medizin (MDC)	PhD	Group leader of Cancer Genetics and Cellular Stress Responses	2018/11/26	invited lecture at International Symposium on Tumor Biology in Kanazawa 2018

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
33	Danny Porath	57	Professor, Hebrew University of Jerusalem	Ph.D. in Physics	Excellent postdoctoral award of the American Vacuum Society Meeting, Boston 2000 (2000); The Israel Chemical Society Prize for the Outstanding Young Scientist (2007); Erasmus Mundus research scholar for Nanoscience and Nanotechnology (2009); Member of the Editorial Board of "Scientific Report" from Nature Publishing Group (2011); Member of the Editorial Board of "Self Assembly and Molecular Electronics" (2012)	2019/1/25	lecture at NanoLSI Open Seminar
34	Peter Junk	57	Professor, James Cook University	Ph.D in Organometallic Chemistry	Queensland Young Tall Poppy Award - Australian Institute of Political Science (2001); Ecka Granules Visiting Lectureship, University of Tasmania (2003); Terrae Rarae Award: In recognition of outstanding contributions to the coordination chemistry of the rare earth elements. Highlighted in Angewandte Chemie International Edition (2016); Reperio Award (JCU): Best innovative research presentation to investors (2016); Burrows Award, Premier Inorganic Chemistry Award for the RACI. Contributions to Inorganic Chemistry (2016)	2019/1/31	lecture at NanoLSI Open Seminar
35	Ricardo Garcia	59	Professor, Instituto de Ciencia de Materiales de Madrid, CSIC, Spain	Ph.D in Physics	Best PhD Thesis in Physics (Universidad Autónoma de Madrid, Spain) (1990); Fellow American Physical Society (Material Physics), American Physical Society (2007); Technological Innovation Prize (1st), Fundación Madri+d, Madrid Regional Government (2009); Awarded an ERC Advanced grant (2013)	2019/2/20-2/21	participation in advisory board meeting; lecture at NanoLSI Special Seminar
36	Peter Hinterdorfer	56	Professor, Institute of Biophysics, Johannes Kepler University Linz, Austria	Ph.D in Technical Physics	Council Member, Biophysical Society; Postdoctoral Schrödinger Fellowship of the Austrian Science Fund (1992-1993); Research & Development 100 Award (2004); Nomination Nanoaward Austria (2008)	2019/2/20-2/21	participation in advisory board meeting; lecture at NanoLSI Special Seminar

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
37	Francoise Winnik	67	Finnish Distinguished Professor, University of Helsinki, Finland	PhD in organic chemistry and photochemistry	Professor, Faculty of Pharmacy and Department of Chemistry, University of Montreal, Montreal, Canada; Editor-in-chief, Langmuir (a publication of the American Chemical Society); Principal Investigator, International Center for Materials Nanoarchitectonics National (MANA) Institute for Materials Science (NIMS) Tsukuba, Ibaraki, Japan; The 2006 Clara Benson award of the Canadian Institute of Canada; an Executive Editor of Langmuir, the ACS journal of surface and colloid science	2019/2/20-2/21	participation in advisory board meeting; lecture at NanoLSI Special Seminar
38	Carsten Beta	45	Professor, Department of Physics, Potsdam University, Germany	Ph.D. in Physics	Committee member of International Symposium "From Pattern Formation to Turbulence" (2019)	2019/3/6	lecture at NanoLSI Open Seminar
39	Krishna Kanti Dey	38	Assistant Professor, Physics Division, Indian Institute of Technology Gandhinagar, Gujarat, India	Ph.D. in Nanotechnology	First Prize at Postdoc Research Exhibition (2014)	2019/3/6	lecture at NanoLSI Open Seminar
40	Masahiko Negishi	-	Pharmacogenetics Section, Reproductive and Developmental Biology Laboratory,National Institute of Environmental Health Sciences, National Institute of Health, USA	Ph.D. in Biochemistry	Member of the Senior Biomedical Research Service at the National Institutes of Health (2000); Scientific Achievement Award from the International Society for Study of Xenobiotics (2002); an honorary doctorate degree from the University of Kuopio, Finland (2005); a Fellow of the Japanese Society for the Study of Xenobiotics (2012); the Bernard B. Brodie Award in Drug Metabolism by the American Society for Pharmacology and Experimental Therapeutics (ASPET) (2016)	2019/3/11	lecture at NanoLSI Open Seminar

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
41	Alexander V. Neimark	-	Distinguished Professor, Chemical and Biochemical Engineering, Rutgers	Ph.D. in Chemical Engineering	Guggenheim Fellow, Blaise Pascal International Chair, Humboldt Fellow, Fellow of American Institute of Chemical Engineers, Distinguished Visiting Fellow of the Royal Academy of Engineering, and Leverhulme Professorship	2019/3/13	lecture at NanoLSI Open Seminar
42	Adam Stuart Foster	44	NanoLSI PI / Professor, Aalto University	PhD in Theoretical Solid State Physics	Vaisala prize, The Finnish Academiy of Science and Letters (2009)	2018/5/11-5/20 2018/11/9-11/20 2019/1/13-1/25	participation as principal investigator; invited lecure at the 2nd NanoLSI Symposium
43	Alexander S. Mikhailov	69	NanoLSI PI / Professor, Fritz Haber Institute of the Max Planck Society	Doctor of Science/ Theoretical Physics, Chemical Physics, Biophysics	International Solvay Chair in Chemistry (2009)	2018/5/9-5/24 2018/6/15-6/24 2018/7/14-7/31 2018/9/3-9/23 2018/10/30-12/5 2019/1/25-3/15	participation as principal investigator
44	Yuri Korchev	59	NanoLSI PI / Professor, Imperial College London	PhD in Biophysics and Cytology, Biophysics	Editorial Board Member, Pflugers Archiv - European Journal of Physiology	2018/4/9-4/19 2018/6/19-6/25 2018/11/8 2018/11/30-12/9 2019/3/23-3/31	participation as principal investigator; invited lecure at the 2nd NanoLSI Symposium
45	Richard W. Wong	44	NanoLSI PI	Doctor of Medicine, Molecular cell biology	Ambassador of American Sciety for Cell Biology (2017-2019); The Royal Society of Medicine, United Kingdom Fellow (2017-)	usually statys at the center	participation as principal investigator

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
46	Anthony Watts	69	Professor, Department of Biochemistry, University of Oxford	PhD in Biophysics	Managing director of the European Biophysics Journal, a co-opted member of the European Biophysical Societies' Association (EBSA); Royal Society of Chemistry Award for Biomembrane Chemistry for 2001; SERC-CNRS Maxime Hanss Prize for Biophysics (1992); XXV Godnev Annual Lecture and Award, National Academy of Sciences, Belarus (2014); Royal Society of Chemistry Interdisciplinary Prize (2015); Biophysical Society Anantrace Membrane Protein Award and Prize (2015)	2019/3/15	discussion for joint research; lecture at NanoLSI Special Seminar

Appendix 6 FY2018 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2018 by each activity.
* Describe the outreach activities in the “6. Others” of Progress Report, including those stated below that warrant special mention.

Activities	FY2018 (number of activities, times held)
PR brochure, pamphlet	NanoLSI Leaflet (2) (EN/JP), Transdisciplinary Research at NanoLSI (2) (EN/JP), WPI Pamphlet (1) (EN/JP), Nature Spotlight on Kanazawa (1) (EN) (total:6)
Lectures, seminars for general public	Seminar for Kanazawa Medical Association (1 by Fukuma), Kanazawa University 2018 Open Lecture (1 by Fukuma, 1 by Ogoshi, 1 by Oshima) (total: 4)
Teaching, experiments, training for elementary, secondary and high school students	Hakui High school (1 by Akine), Takefu High school (1 by Nakajima) (total:2)
Participating, exhibiting in events	SSH meeting, The Irago Conference, Kagaku-zanmai in Aichi, WPI Science symposium, AAAS Annual Meeting, Science Hills Komatsu temporary exhibition (1 year) (total:6)
Press releases	Ando/Kodera, Hirao/Tadokoro, Ando, Konno, Ando, Fukuma, Foster, Oshima, Hanayama, Ogoshi/Asakawa, Yano, Akine, Matsumoto, Akine, Yano/Fukuda, Ogoshi/Akine, Nakajima, Ogoshi, Yamano/Hanayama (total: 19)
Others（TV Program）	TV Program on Kanazawa University Key Researches "KOKOKARA" （1 by Matsumoto）

*If there are any rows on activities the center didn’t implement, delete that (those) row(s). If you have any activities other than the items stated above, fill in the space between parentheses after “Others” on the bottom with the name of those activities and state the numbers of activities and times held in the space on the right. A row of “Others” can be added, if needed.

Appendix 7 FY 2018 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY2018 resulting from press releases and getting reported.

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	2018.4.26	Newspaper (1)	Research results on Insight into structural remodeling of the FlhA ring responsible for bacterial flagellar type III protein export by Profs. Noriyuki Kodera and Toshio Ando (*Hokkoku Shimbun*)
2	2018.4.27-5.8	Newspaper (1), Website (56)	Research results on protein stabilizing blood-cell production under dietary stress by Prof. Atsushi Hirao and Assist. Prof. Yuko Tadokoro (*Hokkoku Shimbun, The Medical News*)
3	2018.6.1	Website (1)	Research results on HGF by Prof. Kunio Matsumoto (*IMPACT*)
4	2018.6.2	Newspaper (1)	Research results on direct visualization of dynamic structures of protein disaggregation molecular by Prof. Toshio Ando (*Hokkoku Shimbun*)
5	2018.6.17	Website (50)	Research results on the role of lipids in facilitating a functional switch between two forms of Peroxiredoxin by Profs. Noriyuki Kodera, Toshio Ando and Assoc. Prof. Hiroki Konno (*BioTech Gate*)
6	2018.6.27, 9.18, 9.21	Newspaper (3)	Prof. Masanobu Oshima receiving research grant from Hokkoku Cancer Foundation (*Hokkoku Shimbun*)
7	2018.7.11	Website (1)	Research results on inter-ring allosteric communications in chaperonin GroEL by Prof. Toshio Ando (*Phys.org*)
8	2018.7.26	Newspaper (1), Website (1)	Interview of Director Takeshi Fukuma as a pioneer for next generation (*Nikkei Sangyo Shimbun*)
9	2018.8.1	Newspaper (1), Website (1)	Interview of Director Takeshi Fukuma regarding NanoLSI (*Nikkei Shimbun*)
10	2018.8.17	Newspaper (1)	Special lecture for medical students by Prof. Toshio Ando (*Hokkoku Shimbun*)
11	2018.9.15-11.2	Newspaper (7)	Public lecture series by Profs. Takeshi Fukuma, Tomoki Ogoshi and Masanobu Oshima (*Yomiuri Shimbun*)
12	2018.10.2, 10.3	Website (5)	Research results on visualizing charges accumulated in an electric double layer by Prof. Takeshi Fukuma (*New Electronics, Phys.org*)
13	2018.10.2, 10.29, 11.27	Newspaper (3)	Public lecture by Prof. Kunio Matsumoto and Assoc. Prof. Shinji Takeuchi (*Yomiuri Shimbun, Hokkoku Shimbun*)
14	2018.10.26, 10.29	Website (4)	Research results on atmospheric data analysis by Prof. Adam S. Foster (*Phys.org*)
15	2018.12	Magazine (1)	Interview of Director Takeshi Fukuma (*Public Relations Magazine of National Universities*)

16	2018.12.3	Newspaper (2)	Research results on the growth inhibition of gastric cancer cells by GO-Y022 by Prof. Masanobu Oshima (*Hokkoku Chunichi Shimbun, Hokkoku Shimbun*)
17	2018.12.6	Website (1)	Interview of Director Takeshi Fukuma (*Top Researchers*)
18	2018.12.17	Newspaper (1)	Public lecture by Prof. Seiji Yano (*Hokkoku Shimbun)*
19	2018.12.19-2019.1.25	Newspaper (3), Website (15)	Research results on a link between inflammation and gastric cancer by Prof. Masanobu Oshima, Assoc. Prof. Hiroko Oshima and Assist. Prof. Mizuho Nakayama (*Yomiuri Shimbun, Hokkoku Shimbun, ecancer*)
20	2018.12.21, 12.24	Website (2)	Research results on the mechanism that regulates cellular injury by phagocytes during inflammation by Prof. Rikinari Hanayama and Assist. Prof. Tomoyoshi Yamano (*The Medical News, Science Daily*)
21	2018.12.24	Newspaper (1)	Public lecture by Prof. Seiji Yano (*Hokkoku Shimbun)*
22	2018.12.28, 12.30	Newspaper (2)	Director Takeshi Fukuma receiving the 15th Japan Society for the Promotion of Science Award (*Hokkoku Chunichi Shimbun, Hokkoku Shimbun*)
23	2018.12.28, 2019.1.10	Website (19)	Research results on self-sorting through molecular geometries by Prof. Tomoki Ogoshi, Assist. Prof. Takahiro Kakuta, Assoc. Prof. Hitoshi Asakawa and Prof. Takeshi Fukuma (*Phys.org, BioTech Gate, Azonano*)
24	2019.1.17-3.22	Newspaper (5), Television (2), Website (12)	Research results on origin of resistance to lung-cancer drug by Prof. Seiji Yano and Assoc. Prof. Shinji Takeuchi (*Mainichi Shimbun, Yomiuri Shimbun, Nikkei Sangyo Shimbun, Hokkoku Chunichi Shimbun, Hokkoku Shimbun, NHK, Ishikawa Television, ecancer*)
25	2019.1.21-1.30	Website (17)	Research results on a closed cage-like molecule that can be opened by Prof. Shigehisa Akine (*Phys.org, Azonano, Nanotechnology Now*)
26	2019.1.28, 1.29	Website (18)	Research results on artificial HGF by Prof. Kunio Matsumoto and Assist. Prof. Katsuya Sakai (*USA Life Science Database, Phys.org, BioTech Gate, Technology Networks*)
27	2019.2.6, 2.7	Website (10)	Research results on chirality inversion in a helical molecule at controlled speeds by Prof. Shigehisa Akine and Assoc. Prof. Yoko Sakata (*Phys.org, Azonano, Nanotechnology Now*)
28	2019.2.12	Website (14)	Research results on molecular-weight polymer selection by one-dimensional confinement by Profs. Tomoki Ogoshi, Shigehisa Akine, Assoc. Prof. Yoko Sakata and Assist. Prof. Takahiro Kakuta (*Phys.org*)
29	2019.2.13	Newspaper (1)	Research results on acquisition of molecular-targeted drug resistance by lung cancer cells by Prof. Seiji Yano and Assist. Prof. Koji Fukuda (*Hokkoku Shimbun*)
30	2019.2.21	Website (1)	Research results on xeno/endobiotic metabolism potencies vary between strains and sex in rats by Prof. Miki Nakajima and Assoc. Prof. Tatsuki Fukami (*MedicalXpress*)
31	2019.3.25	Website (1)	Research results on the reversible switching of macrocyclic molecules between a liquid and a solid phase upon exposure to vapor by Prof. Tomoki Ogoshi and Assist. Prof. Takahiro Kakuta (*Phys.org*)
32	2019.3.28	Newspaper (1)	Research results on cells related immune tolerance by Prof. Rikinari Hanayama and Assist. Prof. Tomoyoshi Yamano (*Hokkoku Shimbun*)