

World Premier International Research Center Initiative (WPI) FY2016 WPI Project Progress Report (Post-Interim Evaluation)

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Common instructions:

* Unless otherwise specified, prepare this report from the timeline of 31 March 2017.

* So as to base this fiscal year's follow-up review on the document "Post-interim evaluation revised center project," please prepare this report from the perspective of the revised project.

* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

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

1. Research Progress

The Institute of Transformative Bio-Molecules (ITbM) at Nagoya University (NU) defined its flagship research areas of "**plant chemical biology**", "**chemical chronobiology**", and "**chemistry-enabled live imaging**", and has been conducting interdisciplinary research in the following topics:

(1) Plant chemical biology

- Development of molecules that combat *Striga* and related parasitic plants.
- Development of molecules that control plant stomata.
- Development of molecules that overcome genome barriers to produce new hybrid plant species.
- Discovery of unidentified protein receptors of plant hormones.

(2) Chemical chronobiology

- Development of molecules that control mammalian circadian rhythm.
- Development of molecules that control plant circadian rhythm.

(3) Chemistry-enabled live imaging

- Development of high photo-resistant fluorescent dyes towards 3D/4D super-resolution and single molecule fluorescence imaging.
- Development of fluorescent probes enabling unprecedented visualization of cellular microstructures and biological events.

Among these research objectives, ITbM will place high priority on the development of molecules to combat the parasitic plant *Striga*, taking into consideration its size of impact to the global society. Headed by the Center Director, the team "*Striga*" was organized, consisting of researchers working on the *Striga* project and staff in the Research Promotion Division (RPD)/Strategic Planning Division (SPD). Additional technical staff will be allocated to carry out this project.

Developing molecules to combat *Striga*

With the aim to reduce crop damage caused by the parasitic plant *Striga*, ITbM continues its effort to develop molecules to combat *Striga* via control of *Striga* seed germination. In FY2016, ITbM obtained a lead compound of a germination stimulant that is far more potent than conventional synthetic compounds or natural strigolactones. To make further advances in this project, ITbM will take appropriate measures including hiring of additional researchers and technical staff. In addition, to drive the research and development toward field applications of *Striga* eradication molecules, it is considered crucial to cooperate with local partners and industries in Africa. Coordination with domestic and African local government officials and researchers will enable efficacy studies of ITbM's molecules at local academic institutions and fields, as well as collection of information on the current status of crop damage and needs of local farmers' for practical use of ITbM's molecules. ITbM continues to seek support from industries for the development of effective agrochemicals related to *Striga*.

Summary of Activities in FY2016

Journal publications (Jan. 2016 – Dec. 2016): 139 (22; IF>10, 39; IF>7, 6; Highly cited papers)

Patent filings: 24 (9 cases co-filed among several PI groups)

Commercialization of molecules/catalysts: 4

Awards and honors: 16

Research funds: 963 million yen (Overseas PIs also obtained KAKENHI grants).

2. Advancing fusion of various research fields

ITbM's interdisciplinary research has been promoted under the concept of "Mix". Up to now, 64 collaborative projects have launched at ITbM, including the *Striga* project.

ITbM is implementing various initiatives to promote interdisciplinary research. Namely, the **ITbM Research Award**, which was established to foster interdisciplinary collaboration among young researchers and students. In FY2016, 4 new projects have been launched. In addition, the **ITbM Workshop**, **Mix Lab Seminar**, and **Tea Break Meeting** are being held to share each other's research progress as well as to find seeds of collaboration and possible collaborators.

The members of the Research Promotion Division (RPD) and Strategic Planning Division (SPD) are key players in the promotion of collaborative research. The SPD was established in FY2016 to implement ITbM's research outcomes to the society. ITbM's interdisciplinary research is currently supported from the perspective of research promotion and social implementation activities by the RPD and SPD, respectively.

ITbM's **4 supporting centers** (Molecular Structure Center, Live Imaging Center, Chemical Library Center, and Peptide Protein Center) are also making a major contribution to the promotion of ITbM's interdisciplinary research through their technical support.

In 2016, ITbM has published 9 joint publications among the following research groups: Itami/Higashiyama (1), Itami/Irle (1), Higashiyama/Kinoshita (2), Higashiyama/Yamaguchi (2), Higashiyama/Irle/Yamaguchi (1), Irle/Yamaguchi (1), and Nambo (Crudden group)/Ueda (Higashiyama group) (1). Research accomplishments arising from these joint papers include synthesis of molecules for plant fertilization, bio-imaging, and plant cell division inhibition as well as computational studies on molecules. It is worth mentioning that the development of molecules for plant cell division inhibition by Nambo and Ueda was a result of interdisciplinary collaborative research initiated by the ITbM Research Award.

3. Measures taken to globalize the institute

- Organization of ITbM's annual international symposia (ISTbM-4) and hosting of 3 international awards in chemistry and biology (22nd Nagoya Medal Award of Organic Chemistry, 12th Hirata Award, and 2nd Tsuneko & Reiji Okazaki Award).
- Organization of 2 international joint workshops with ITbM's cooperating institutions (NSF-CCHF & IBS-KAIST, IoC-Academia Sinica)
- Assignment of 2 new non-Japanese PIs at ITbM in FY2016: Florence Tama (NU PI) and Wolf Frommer (overseas PI).
- Exchange of researchers with international partner institutions: 5 students travelled to overseas institutions and 7 students visited ITbM in FY2016.
- In terms of international brain circulation, 6 researchers joined ITbM from overseas institutions, whereas 2 researchers from overseas institutions have been promoted to other institutions.

4. Implementing organizational reforms

- With regard to ITbM's infrastructure, the "WPI-next" program was launched at NU to support world-leading science.
- The University Research Administration (URA) system (started in 2013) was reviewed with respect to the activities of the RPD in ITbM.
- An international public relations taskforce was established at NU following the footsteps of RPD's public relations activities.
- With reference to the English e-mail circulation initiated at ITbM, NU started to distribute notices and information to the whole campus in both English and Japanese.

5. Efforts to secure the center's future development

- In FY2016, ITbM established the Strategic Planning Division (SPD) and employed an Associate Professor (Masters degree in organic chemistry, pharmaceutical science) with prior experience as the head of the chemistry department at a pharmaceutical venture company. Upon establishment of the SPD, the Lecturer (Patent attorney/degree in catalytic chemistry) in charge of intellectual property management was transferred from the RPD to the SPD.
- In order to foster internationally competitive talents, ITbM established a program to actively exchange PhD students with collaborating overseas institutions. A new program that supports the organization of student-initiated symposia was also established.

- * Please describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 criteria, please 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.
 - Please prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

1. Conducting research of the highest world level

- * Regarding the criteria used when evaluating the world level of center, please note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

ITbM defined its flagship research areas of "plant chemical biology", "chemical chronobiology", and "chemistry-enabled live imaging" in late FY2015, and has been continuing its efforts to develop "transformative bio-molecules" that can enhance biotic productivity and quality, and realize innovative bioimaging. To ensure that these targets are achieved, ITbM is developing catalysts that enable efficient synthesis and on demand molecular activation.

While a number of collaborative researches are ongoing, ITbM decided to engage with high priority on the project "Combating *Striga*" considering its size of impact to the global society.

(1) Research progress

(a) Plant chemical biology

Molecules to combat *Striga*

Tsuchiya (Kinoshita group) and Uruguchi (Ooi group) worked in collaboration to develop a strigolactone (SL) mimicking molecule, "super SL" that displays high agonistic activity and selectivity toward the SL receptor ShHTL7. The molecule was developed via structure-activity relationship studies of the initial hit compound SAM-8 discovered in FY2015. The super SL activates the SL signaling in a femtomolar (10^{-15} M) concentration, which is 1,000 times more active than the often-used synthetic SL GR24. Moreover, the cost for synthesis is estimated to be as low as 1/30 compared to the case of GR24. ITbM organized the team "*Striga*" to promote basic science research in *Striga* and application of the developed molecules for practical use to combat *Striga* in Africa.

Molecular control of stomata

The Kinoshita group has been focusing on elucidation of the signaling pathway in stomatal opening and closing through the investigation of the blue-light receptor phototropin (phot 1 and phot 2), plasma membrane (PM) H⁺-ATPase, and plasma membrane K⁺_{in} channels. Through genetic screening of the mutants, it became evident that a lack of PM H⁺-ATPase function resulted in partial insensitivity to blue light-induced stomatal opening (Plant Cell Physiol. 2016). They also found that PM H⁺-ATPase in *Arabidopsis thaliana* leaves was regulated by photosynthesis via sugar accumulation (Plant Physiol. 2016), which provides a new insight into signaling from chloroplasts to PM.

In collaboration with the Itami group and Chemical Library Center, Kinoshita's group discovered several small molecules that induce stomatal opening in the dark and inhibit light-induced stomatal opening, and research to clarify the molecular mechanism is ongoing (JP 2016-194748).

Molecular control of plant growth and development

The Torii-Uchida group has been exploring small molecules that affect the density and/or patterning of stomata through the collaboration with the Itami group, Molecular Structure Center, and Chemical Library Center. Several promising lead compounds were discovered through structure-activity relationship studies, and a molecule that promotes root growth in various plant species such as *Arabidopsis thaliana* as well as edible plants (cucumber, lettuce, etc.) was developed. The group also made a significant discovery in the field of plant development, where they proved that the EPFL2 peptide plays a key role in creating the teeth-like shapes on plant leaves (Curr. Biol. 2016).

In collaboration with the Irlé group, they found that systematic rearrangement of plant hormones leads to a synthetic peptide hormone that can alter plant shape. This approach may lead to the generation of novel synthetic plant peptide hormones, which can effectively control plant growth (Nature Commun. 2017).

Molecular control of plant reproduction

Since the discovery of the LURE peptide as a key molecule for pollen tube guidance, the Higashiyama group has identified several key molecules that function in the process of the pollen

tube guidance and reproduction in plants. In FY2016, the tip-localized pollen-specific receptor-like kinase 6 (PRK6) having an extracellular leucine-rich repeat domain was identified as an essential receptor for the sensing of the LURE1 attractant peptide in *Arabidopsis thaliana* under *semi-in vivo* conditions, and was found to be significant for ovule targeting in the pistil (Nature 2016).

In addition, a methyl-glucuronosyl arabinogalactan polysaccharide derived from the ovule was discovered as an inducer of competency of the pollen tube that responded to the ovular attractant LURE peptide in *Torenia fournieri*. This sugar molecule was named as an **Activation Molecule for Response-Capability (AMOR)**. AMOR has a sugar chain characteristic for plants, and a disaccharide moiety is located at the terminus. In collaboration with the Itami group, a series of isomers of the disaccharide was synthesized, and the β -isomer of the methyl-glucuronosyl galactose (4-Me-GlcA- β -(1-6)-Gal) was found to be essential for AMOR's activity (Curr. Biol. 2016 and Plant Physiol. 2017).

Higashiyama also discovered that the contents in pollen tubes could increase the size of seeds, without fertilization. This new plant phenomenon, named as **POEM (pollen tube-dependent ovule enlargement morphology)**, shows that even in the absence of fertilization (fusion of sperm and egg cells), release of the pollen tube content to the ovule leads to enlargement of the ovule and seed coat formation (Sci. Adv. 2016).

Higashiyama's group also developed a highly efficient CRISPR/Cas9 vector for the widely used model plant *Arabidopsis thaliana*, named pKAMA-ITACHI Red (pKIR). Although the CRISPR/Cas9 system is one of the most popular methods for genetic manipulation, its mutation inducing efficiency for *Arabidopsis thaliana* has remained low. Development of this new pKIR system is expected to become a powerful molecular tool for genome engineering in *Arabidopsis* plants (Plant Cell Physiol. 2016).

In addition, through an international collaboration, Ueda (Higashiyama group) and her colleagues visualized how egg cells in plants divide unequally (asymmetric cell division) after being fertilized for the first time. The direction of this asymmetric cell division determines the body axis of flowering plants, i.e. the top part produces leaves and flowers, and the bottom part develops into roots. This mechanistic discovery on asymmetric cell division in plants provides insight into finding out how flowering plants have evolved to form their body shape (PNAS 2016).

(b) Chemical chronobiology

Molecular control of mammalian circadian rhythm

The Kay-Hirota group has made substantial progress with regard to a molecule called GO289. GO289 was previously discovered as a circadian period-lengthening compound in mammals. In collaboration with the Itami group and a pharmaceutical company, they developed a new GO289-derivative with higher solubility and better metabolic stability, which would be applicable for *in vivo* studies.

Molecular control of plant circadian rhythm

The Kinoshita-Nakamichi group collaborated with the Higashiyama group, and uncovered that clock proteins produced in the morning regulate the clock genes produced during the evening. The team has also discovered that these evening clock genes are responsible for plants to carry out biological processes to respond to the environment during the evening (Plant Cell 2016). Period-lengthening/-shortening molecules for plants were also discovered, and exploration of the biological signaling of the plant circadian rhythm was partly revealed through target protein identification in collaboration with the Molecular Structure Center. A molecule that accelerates the flowering time of the *Arabidopsis* plant was discovered from among the series of period-shortening molecules.

(c) Chemistry-enabled live imaging

Development of fluorescent molecules

The Yamaguchi group previously developed the super photostable dye C-Naphox, which enabled repeated super resolution STED imaging. However, due to its low hydrophilicity, weak fluorescence in aqueous media, and lack of a bio-conjugation site, there remained scope for improving its physical properties for use in biological research. In FY2016, they developed a second-generation dye named PhoxBright 430 (PB430) to overcome the drawbacks of C-Naphox. The properties of the PB430 suggest its promising potential to become a new benchmark probe for STED and other imaging technologies.

Development of photostable dyes emitting in the far-red or near infrared ray (IR) region has also been investigated to enable deep tissue *in vivo* imaging as well as single molecule imaging. For this

purpose, several types of fluorophores were developed; (i) red-emissive polymethine dyes taking advantage of the aromatic stable character of a tropylium ion (Chem. Eur. J. 2016), (ii) a red-emissive cyclic π -conjugated dimer attaining both bright emission and long fluorescent lifetime (Angew. Chem. Int. Ed. 2016); (iii) a rhodamine-type molecule named phosphorhodamine (PR) incorporating an electron-withdrawing phosphine oxide moiety into the π skeleton of the molecule. PR has a strong absorption and intense emission in the far-red region in aqueous solution, and exhibits outstanding photostability compared to the existing cyanine-based dyes.

(d) Development and improvement of ITbM platforms

Catalysis and molecular synthesis

ITbM's synthetic chemistry groups (Itami, Ooi, Crudden and Bode) are developing epoch-making synthetic methodologies that enable synthesis and modification of bioactive molecules, and have been contributing to accelerate ITbM's interdisciplinary research.

The Itami group succeeded in the development of an equimolar C–H/N–H coupling reaction of aromatic compounds, which was reported to be one of the most challenging reactions in C–H activation chemistry. The reaction was applicable to a wide range of arenes, including polycyclic aromatic hydrocarbons (*e.g.* corannulene) and heteroarenes (Chem 2017). Considering that many bioactive molecules contain amino moieties, this reaction would be a useful tool to generate a series of bioactive derivatives. Various new synthetic reactions were also developed such as the **annulative π -extension (APEX)** reaction for the synthesis of soluble sheet-shaped hydrocarbons (Angew. Chem. Int. Ed. 2016) and the *para*-selective C–H borylation of arenes (ACS Catal. 2016).

The Ooi group has developed a variety of asymmetric reactions by using their unique chiral quaternary ammonium catalysts. They developed an enantioselective direct installation reaction of the amine group into carbonyl compounds using a chiral 1,2,3-triazolium catalyst (Chem. 2016). This unprecedented method enables rapid formation of various optically active chiral α -aminocarbonyls, which are structural moieties found in many biologically active compounds and in therapeutics. A new catalytic protocol for the diastereodivergent asymmetric conjugate addition reactions was also developed by the appropriate use of chiral *P*-spiroiminophosphoranes (Nature Commun. 2017). This system could provide access to a complete set of stereoisomers, which are structurally similar but yet often exhibit different biological activities.

The Ooi group is largely contributing to the *Striga* project. Based on the molecule discovered by screening, super SL was developed via structural modification (see above).

The Crudden group has developed a simple direct method to form self-assembled ***N*-heterocyclic carbene (NHC)** monolayers on gold. Using the bench-stable benzimidazolium hydrogen carbonate as a replacement for air-sensitive NHCs or NHC precursors, NHC films were prepared in solution or by vapor-phase deposition from the solid state. This approach will enable researchers from a range of areas including engineers, physicists and biologists to prepare NHC-based films (Nature Commun. 2016).

The Crudden group also developed a new Suzuki-Miyaura cross-coupling type reaction with fluorinated sulfone electrophiles. A series of fluorinated sulfone derivatives behaved as effective electrophiles, leading to the modular and selective synthesis of multiply arylated methanes (ACS Catal. 2016).

A collaborative research between Nambo (Crudden group), Ueda (Higashiyama group) and Ohkawa (Yoshimura group) led to the development of triarylmethane derivatives that selectively inhibit the cell division of plant cells with respect to animal cells (Plant Cell Physiol. 2016).

The Bode group is promoting ITbM's interdisciplinary research through developing effective methods for the chemical synthesis of proteins. Using a powerful chemoselective amide-forming reaction known as α -**ketoacid-hydroxylamine (KAHA)** ligation, the group has succeeded in the syntheses of ubiquitin-like protein NEDD8 (Helv. Chim. Acta 2016) and the exercise hormone Irisin (Helv. Chim. Acta 2016). The group established a user-friendly chiral separation of secondary amines applicable to large-scale synthesis (Angew. Chem. Int. Ed. 2016). The protocol uses a newly developed robust and recyclable hydroxamate polymer resin, and the group demonstrated the production of decagram quantities of enantiomerically pure (+)-mefloquine (an antimalarial drug) from its readily available racemate in a decagram scale. The group had developed "**Sn amino protocol (SnAP)**" reagents, which are available for the convenient one-step synthesis of various saturated *N*-heterocycles, including bicyclic and spirocyclic structures. They are easy to use,

work with a wide variety of aldehydes and ketones including heteroaromatics, and provide predictable access to some of the most valuable structures in modern drug development. Recently, the group has also developed related tin-free **silicon amine protocol** (SLAP) reagents using silicon and light promoted reactions that avoid the need for metals and halogenated solvents (ACS Cent. Sci. 2017). These reagents are commercially available from several suppliers and are used by pharmaceutical companies worldwide.

(e) Theoretical science

The 2 theoretical science groups led by Irle and Tama are establishing multiple collaborations in ITbM, and are promoting interdisciplinary research. Irle and Hijikata are collaborating with team *Striga* and provide insight to the selectivity of active molecules to the *Striga* receptor isoforms. In collaboration with the groups of Yamaguchi and Higashiyama, Irle and Yokogawa made a theoretical approach to elucidate the unique property of Yamaguchi's red-emissive cyclic π -conjugated dimer, which shows both bright emission and long fluorescent lifetime, and concluded that the properties were attributed to unconventional intense excimer emission (Angew. Chem. Int. Ed. 2016).

(f) Four supporting center's activities

The **Peptide Protein Center** headed by Oishi, is actively expanding its network of research with the biology groups at ITbM (Torii-Uchida, Kay-Hirota, and Higashiyama). The center prepared a peptide library consisting of 50 structurally unique cyclic peptides synthesized by KAHA ligation, which will contribute to developing bioactive molecules.

The **Live Imaging Center** headed by Y. Sato, is involved in the majority of ITbM's research projects and has been publishing a number of journal articles. In FY2016, The center has been selected as one of the main 7 facilities for joint usage in Japan, participated in the **Advanced Bioimaging Support (ABiS)** program, and supported 2 major programs in the Grant-in-Aid for Scientific Research on Innovative Areas. The center was also given the honor to receive the most applicants in the ABiS program.

The **Molecular Structure Center** led by Kuwata, has established the proteomics system and succeeded in the identification of target proteins by installing biochemical protocols such as immunoprecipitation, **stable isotope labeling** of amino acids in cell culture (SILAC), phosphoproteomics, and mass spectrometry (MS) imaging. This proteomics system contributed to identifying proteins, carbohydrates such as AMOR as well as DNA.

The **Chemical Library Center** led by A. Sato, has distributed over 300 thousand compounds to more than 30 researchers. The center established a scheme to distribute the library compounds to overseas collaborators under legal compliance, and contributed to strengthening the network of the chemical library center in RIKEN (NP Depo).

(2) Journal publications, press releases, media coverage, international conferences, and awards

In FY2016, 139 (WPI papers: 112) papers were published in peer-reviewed journals (39 (WPI: 28) papers published in journals with an Impact Factor (2015) > 7, 22 (WPI: 13) papers published in journals with an Impact Factor (2015) > 10, and 6 Highly Cited Papers). From January to April 2017, 36 papers have already been published in peer-reviewed journals.

In FY2016, ITbM has held 6 press conferences, and has distributed 11 national/international press releases on its research achievements. In addition, ITbM's research and researchers have been featured over 600 times in a range of national and international media, including newspapers, TV, magazines, and internet sites. ITbM's PIs and researchers have presented their research in a total of 90 international conferences and 227 academic meetings, and a total of 16 awards and honors have been granted to the researchers at ITbM.

(3) Research funds

ITbM has been making marked progress in its research, which is evident in the record of competitive research funds granted to ITbM's researchers. In FY2016, the total amount of research funding obtained was 963 million yen. Representative grants are JST-ERATO (2 projects), JST-CREST (1 project), JST-PRESTO (4 projects), JST-ALCA (1 project), JST-ACCEL-FS (1 project), Grant-in-Aid for Scientific Research on Innovative Areas (2 projects as Area Representative), Grant-in-Aid for Specially Promoted Research (1 project). The overseas PIs have also been successful in obtaining KAKENHI (Grant-in-Aid for Scientific Research) from FY2014. In addition, ITbM applied for the

JSPS Bilateral Program (Joint Research Projects) to strengthen the research collaboration with NSF-CCHF and the project was funded between FY2015-2016.

(4) Patent, technology transfer, and commercialization

Intellectual properties acquired in FY2016 include 17 domestic applications, 3 US provisional applications, 4 PCT applications, and 3 trademark registrations. These applications include 9 inventions generated from the interdisciplinary research between biology and chemistry.

Technology transfer activities led to commercialization of 4 new reagents. LipiDye™, launched in July 2016, is a novel fluorescent dye that stains lipid droplets in cells with high sensitivity. By using LipiDye™ as a lipid stain, non-specific fluorescence emission in the cytoplasm is remarkably suppressed, and live cell imaging of lipid droplets in adipocytes can be performed with a high signal-to-noise (S/N) ratio. Consequently, the new dye received favorable feedbacks from users, and the initial lot of the reagent has almost run out of stock at the supplier. The plant tissue clearing reagent ClearSee®, commercialized in December 2016, enables deep imaging for the whole-plant of various plant species in a simple manner. This reagent rapidly diminishes chlorophyll autofluorescence while maintaining fluorescent protein stability, a feature not provided by conventional reagents, and is expected to contribute to accelerate the discovery of new phenomena in plant biology research. As of the end of FY2016, the number of citations for the publication regarding ClearSee® has reached 16. In addition, ITbM has also launched 2 efficient catalysts for asymmetric synthesis, P-VIP·HCl and M-VIP·HCl, which provide the desired compounds in high selectivity and yield for asymmetric reactions such as the asymmetric aldol reaction, asymmetric Michael addition, and asymmetric hydrophosphonylation.

ITbM focuses on basic research for the creation of innovative scientific and technological outcomes. Accordingly, ITbM has been trying to increase the number of collaborations with companies at an early stage of research, in addition to patent licensing and commercialization of the products developed by ITbM. The number of joint research projects has steadily increased over the years. In FY2016, ITbM has raised a total of 15.4 million yen as research funds from a total of 15 companies, a significant increase of 69% on a year-to-year basis. In addition, during this period ITbM has actively drawn plans for joint research for the subsequent fiscal year, and have already secured 7 collaborations to start in FY2017, where the research funds add up to a total of 13 million yen, which already reaches 86% of the total amount of joint research funds acquired in FY2016.

License agreements were concluded in FY2016 for the aforementioned products ClearSee® and P-VIP HCl, and M-VIP·HCl catalysts. In line with the generation of scientific outputs and securing of intellectual properties, ITbM has continuously made efforts to introduce the center's science and technology to potential partners by disclosing technical information, and providing samples under non-disclosure agreements or materials transfer agreements in a timely manner.

ITbM has been seeking opportunities for collaboration with overseas companies by working closely with NU Tech, a Technology Licensing Organization (TLO) partner of NU in the USA, or through ITbM's own technology transfer activities. In November 2016, 3 researchers from ITbM carried out a technical presentation at the NU Tech Round Table, a technology-matching event held in North Carolina, USA. Discussion for potential collaborations is currently ongoing with 2 companies in the USA. In addition, ITbM has been in contact with European-based pharmaceutical and agrochemical companies. ITbM has also started a joint research project with a pharmaceutical company, and will be concluding an agreement with an agrochemical company for the evaluation of molecules that ITbM has identified so far.

In addition, studies are underway aiming at the development and commercialization of new breeding technologies, which utilizes the efficient grafting ability of tobacco, based on the research outcome by Higashiyama's co-workers. The activities are undertaken in an attempt to turn basic research outputs into agricultural innovation, and are supported by the JST Program for Creating **Start-ups from Advanced Research and Technology (JST-START)**. A university-originated venture start-up will be founded and is scheduled to start its operation in FY2017.

2. Advancing fusion of various research fields

Strategies to promote collaborative research

ITbM's interdisciplinary research has been making notable progress under the concept of "Mix", which is spread throughout ITbM. Up to now, 64 collaborative projects were generated within ITbM,

and each of them has made remarkable progress in promoting interdisciplinary research. Among them, members of the *Striga* project, which was selected by the 2nd ITbM Research Award, identified a receptor of *Striga* that was previously unidentified, leading to the creation of a fluorescent molecule, "Yoshimulactone" and this project is under collaboration with international agrochemical companies. These advances have led to the development of exceptionally active suicide germination and germination-inhibiting molecules for *Striga* during FY2016 (see Section 1). In order to promote interdisciplinary research, ITbM has been implementing various initiatives according to the progress of research. These initiatives include the **Mix Lab Seminar**, which allows newly arrived researchers to introduce their research background and initiate collaborative research projects with ITbM's members; the **ITbM Research Award**, which supports bottom-up interdisciplinary research proposed by young researchers at ITbM; and the **ITbM Workshop**, which is held in conjunction with the annual ITbM international symposium works as a platform for reporting progress on joint research and proposing new joint research. In FY2016, the **ITbM Workshop** has set up a session to propose new collaborative research and to call for potential collaborators.

Members of the **Research Promotion Division (RPD)** and the **Strategic Planning Division (SPD)** are the key players that promote collaborative research at ITbM. While the RPD has been assuming the role to find inventions and scientific discoveries from each research group at an early stage, the SPD was established in FY2016 to socially implement ITbM's research outcomes (see below). Accordingly, ITbM's interdisciplinary research is supported from the perspective of research promotion and social implementation activities by the RPD and SPD, respectively.

ITbM's **4 supporting centers** (Molecular Structure Center, Live Imaging Center, Chemical Library Center, and Peptide Protein Center) are also making a major contribution to the promotion of ITbM's interdisciplinary research. In chemical biology research, although the researchers themselves need to actively collaborate with others who have the necessary skills, it is often the case that misunderstandings occur among researchers from different fields. Therefore, ITbM has established a system for these 4 centers to work together with the researchers to enable the design, supply and visualization of molecules, as well as target identification in a simultaneous manner

ITbM's unique strategies and outcomes have been introduced both inside and outside Japan by ITbM's researchers, and are receiving favorable responses. ITbM is receiving applications for joint research on a regular basis from both domestic and overseas researchers who are interested in ITbM's interdisciplinary research system. Wolf Frommer, who joined ITbM as an overseas PI in FY2016, is a good example of a world-class researcher who was intrigued by ITbM. While Frommer was first planning to start collaborative research with ITbM, he became aware of ITbM's unique research environment and desired closer collaboration. As Frommer's research capabilities were considered to be invaluable for further advancement of ITbM's interdisciplinary research, ITbM decided to employ Frommer as an overseas PI.

Team "*Striga*" to promote the research project "*Combating Striga*"

In FY2016, ITbM has decided to place high priority on the research project "*Combating Striga*" as described in Section 1. Headed by the Center Director, a team was organized consisting of researchers working on the *Striga* project researchers and staff of the RPD/SPD. Tsuchiya (plant biologist) will take lead in this project, and will work in collaboration with synthetic chemists. In FY2017, a technical staff will be allocated to this project. The team holds meetings on a regular basis to share the progress of research and to discuss the strategies to advance the project. Being a non-profit research project, ITbM shares the progress of the project with the NU headquarters to obtain support from relevant government officials.

Interdisciplinary research projects supported by the ITbM Research Award

The four projects have been selected for the ITbM Research Award in FY2016, which are all making notable progresses.

Joint publications and patent applications

In 2016, ITbM has published 9 joint publications among the following research groups: Itami/Higashiyama (1), Itami/Irle (1), Higashiyama/Kinoshita (2), Higashiyama/Yamaguchi (2), Higashiyama/Irle/Yamaguchi (1), Irle/Yamaguchi (1), and Nambo (Crudden group)/Ueda

(Higashiyama group) (1). Research accomplishments arising from these joint papers include synthesis of molecules for plant fertilization, bio-imaging, and plant cell division inhibition as well as computational studies on molecules. It is worth mentioning that the development of molecules for plant cell division inhibition was a result of collaborative research initiated by the ITbM Research Award, mainly conducted by Nambo (synthetic chemist) and Ueda (plant biologist), who are young faculty members of the Crudden and Higashiyama group, respectively. The number of joint publications in ITbM is increasing on an annual basis and a total of 21 publications have been reported through collaborative research at ITbM.

As described in Section 1., among the new patent applications, 9 inventions were created from the results of interdisciplinary research between biology and chemistry, which is about half of the new applications filed in FY2016.

Strategic Planning Division: Function and activities in FY2016

In April 2016, the Strategic Planning Division (SPD) was launched in the Administrative Department to function alongside the Management Division and the Research Promotion Division (RPD). The SPD plays a key role in applying ITbM's research outcomes, such as converting them into intellectual properties, developing alliance strategies such as identification of potential partners, and managing technology transfers and alliances toward social implementation. The SPD has been working to expand and strengthen the collaborations with the industry, by building strong ties with the Academic Research & Industry–Academia–Government Collaboration Department of NU. Interactions between the industry and ITbM's researchers are increasing steadily as ITbM's research outcomes are being effectively communicated to companies via various channels such as presentations at meetings/exhibitions, PR documents, as well as individual contacts.

The basic activities of the SPD in terms of the management of collaborations include creation and proposal of collaboration schemes (patent licensing, material transfer, joint research, and technical consulting), negotiation of terms and conditions in agreements, and progress monitoring of the ongoing joint projects. The SPD prioritizes and proposes the most plausible collaboration schemes through extensive discussions with ITbM's researchers and potential industrial partners.

In order to ensure that ITbM will not devote too many resources into applied research on the short-term needs of its industrial partners, ITbM carefully considers the expected outcomes and benefits arising from the collaboration. Therefore, the roles and responsibilities of each party are shared between ITbM and the partner companies at the planning stage of the collaboration.

As mentioned above, in FY2016, ITbM focused on the increase of joint research projects in order to expand its collaborative network across the industry. In addition to the increase in both the number of projects and the research funds raised, it should be noted that ITbM is seeking new industrial partners including companies abroad.

ITbM has also been seeking opportunities for open innovation programs supported by the industry. In FY2017, ITbM will start a research project that has a contract with a leading domestic pharmaceutical company.

In order to ensure the long-term growth of ITbM, the appropriate selection and prioritization of research themes are considered to be highly significant. ITbM aims to address a variety of global issues using the power of molecules, primarily through basic scientific research for the generation of innovative discoveries and technology seeds that may lead to disruptive innovations.

ITbM believes that the key driver for success is the interdisciplinary research between biology and chemistry, where researchers proactively generate and exchange the ideas and information that arise from curiosity-driven research under the umbrella of the 3 flagship research areas. For this reason, ITbM strongly encourages the researchers to autonomously create research themes and initiate collaborative research by their own approaches. The SPD participates after the initial research outputs are produced, generates a partnering scenario with companies in response to promising opportunities, and thereby keeps a careful balance between basic research and social implementation.

The SPD also monitors global issues of food, agriculture, energy and healthcare, along with industrial trends, in order to create a basis to prioritize research themes and to propose partnering scenarios. Project planning for the *Striga* project has been made accordingly, and continued efforts will be made to promote ITbM's research within a multifaceted framework of industry, government, and academia, including international relations.

3. Globalization of the institution

- * Describe what's been accomplished or recognized in the efforts to raise the center's international recognition as a genuine top world-level 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; number and state of visiting researchers; exchanges with overseas entities
 - 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)

(1) ITbM international symposia and awards

ITbM organized its fourth annual international symposium (ISTbM-4) in December 2016 at NU. The lectures were delivered by 4 ITbM researchers (Dr. Yuichiro Tsuchiya, Professors Jeffrey Bode, Cathleen Crudden, Keiko Torii) along with 8 invited speakers (Professors Kendall Houk (University of California Los Angeles, USA), Azusa Kamikouchi (NU), Marina Kuimova (Imperial College London, UK), Randall Peterson (Harvard Medical School, USA), Shinsuke Sando (University of Tokyo), Peter McCourt (University of Toronto, Canada), Scott Miller (Yale University, USA), Hagan Bayley (University of Oxford, UK)), who are all world-leading international researchers in the fields strongly related to ITbM's research.

ITbM also organized the 12th Hirata Award and the 2nd Tsuneko & Reiji Okazaki Award at the same time as ISTbM-4. The 12th Hirata Award was presented to Professor Emily Balskus (Harvard University, USA), in recognition of her research to discover, understand, and manipulate microbes and microbial communities by integrating the fields of chemistry and biology. The 2nd Tsuneko & Reiji Okazaki Award was presented to Professor Yukiko Yamashita (University of Michigan, USA) for her contribution to the mechanistic elucidation of asymmetric stem cell division and the role of satellite DNA in *Drosophila*. The symposium and the award lectures ended in great success with about 350 participants.

In January 2017, ITbM organized the 22nd Nagoya Medal Award of Organic Chemistry, the third time hosted by ITbM. The Nagoya Gold Medal is awarded every year to an organic chemist who has made significant original contributions to the field in its broadest sense, and the Silver Medal presented every year to a rising scientist based in Japan whose research has had a major impact on the field of synthetic organic chemistry. This year, the Gold Medal was awarded to Professor Stephen Buchwald of the Massachusetts Institute of Technology (USA) and the Silver Medal to Professor Masaya Sawamura of Hokkaido University. Nearly 400 students and researchers across Japan and other international institutes attended the award lectures, including Professor Ryoji Noyori of Nagoya University/JST and Professor Hisashi Yamamoto of Chubu University/University of Chicago (USA), who presented the medals to the winners. The Nagoya Medal is becoming internationally recognized and 2 of 3 recipients of the 2016 Nobel Prize in Chemistry were previous winners of the Nagoya Medal.

(2) ITbM Seminar

ITbM has been holding a series of ITbM Seminars inviting researchers from related fields. In FY2016, ITbM had invited 13 researchers as lecturers. Professor Roald Hoffmann, the 1981 Nobel laureate in Chemistry, also accepted the invitation and presented a talk titled "Two new games for carbon, we hope" in November 2016. Hoffmann has been a honored supporter of ITbM since its establishment, and a meeting with the PIs was held to exchange ideas on the future plan of ITbM during his visit.

(3) Employment of foreign researchers

ITbM employed Florence Tama in April 2016 as a full-time foreign female PI. As a specialist of bio-simulation, Tama is to promote the development of transformative bio-molecules through the elucidation on the functions of bio-molecules. In addition, in October 2016, Wolf Frommer (Carnegie Institution for Science, USA) has also joined ITbM as the fifth overseas PI. As a world-leading plant biologist who was selected as an awardee of the Humboldt Professorship in late October, Frommer is expected to build extensive collaborations with ITbM's members (see Section 2). Frommer is scheduled to move to the University of Düsseldorf in FY2017. A Co-PI who works with Frommer has already been appointed, and will join ITbM in April 2017.

Both Tama and Frommer were the invited lecturers of ITbM's previous international symposia (ISTbM), and the invitations had led to these appointments. Thus, ITbM's symposia are contributing to expand ITbM's international network and provide opportunities to attract overseas researchers. ITbM has also employed many postdoctoral researchers from overseas countries. The ratio of

non-Japanese researchers is 33% as of March 31, 2017.

(4) "Omotenashi" Support

While the RPD has staff to provide support to foreign researchers and their families, ITbM signed a contract with a company in FY2016 to provide advanced medical service information anytime 24 hours a day.

(5) International public relations and outreach activities

In order to gain an understanding of ITbM's research by the international community, ITbM has been releasing international press releases on research accomplishments, notices of international events and other relevant information. As a result of these releases, ITbM has been highlighted in various national/international media and is gradually receiving increased recognition from the international science community. A recent release includes coverage of ITbM and Nagoya University's overseas postdoctoral researchers to share their experience about research in Japan and views in comparison to overseas institutes.

ITbM has also been exhibiting at international events, including BioJapan, Science Agora and the AAAS Annual Meeting, to present its research activities, establish networks and nurture the next generation of scientists. These endeavors are envisaged to increase the international recognition of ITbM and the overall awareness of Japanese research.

(6) International partner institutions

Overseas PIs' host institutions are important partners of ITbM. In addition to ETH-Zürich (Switzerland), Queen's University (Canada), University of Washington (USA), and the University of Southern California (USA), the Carnegie Institution for Science (USA) newly became a partner of ITbM in October 2016 as the host institution affiliated with Frommer. While extensive collaboration is ongoing with these partner institutions, ITbM accepted 4 students from ETH (Bode group) in FY2016.

ITbM is also collaborating with the NSF Center for Selective C-H Functionalization (USA). While CCHF was awarded a Science Across Virtual Institute (SAVI) from NSF (USA) to enable its international collaboration, ITbM's application to the JSPS Bilateral Joint Research Project for FY2015-FY2016 was also successful, which strengthened the partnership. In FY2016, ITbM has sent 3 PhD students to CCHF (University of Michigan; Professor John Montgomery, University of Utah; Professor Matthew Sigman, Scripps Research Institute; Professor Jin-Quan Yu), and accepted 2 students from CCHF (Emory University and University of Washington). ITbM has expanded this network to include other related institutes such as the Institute for Basic Science (IBS, KAIST, Korea). In June 2016, ITbM hosted a joint international workshop "2016 International C-H Functionalization Workshop", inviting members of CCHF (7 faculties, 3 postdoctoral researchers, 12 students, and 1 staff), and IBS (2 faculties, 4 postdoctoral researchers, and 11 students).

ITbM also decided to enter a partnership with the Institute of Chemistry (IoC), Academia Sinica (Taiwan) in FY2016. ITbM and IoC co-organized a joint workshop at NU to initiate collaborative research in November 2016. The Director of IoC and 8 faculties visited ITbM and discussed potential collaborations with ITbM's researchers. In FY2017, ITbM members are scheduled to visit IoC to strengthen the partnership and promote collaborative research between the institutes.

ITbM also started collaboration with the University of Freiburg (UoF). In 2015, the Institute of Advanced Research (IAR) of NU and Freiburg Institute for Advanced Studies (FRIAS) of UoF jointly launched a "Joint Freiburg-Nagoya Project Group" and a call for collaborative research. A joint proposal organized by the Ooi and Itami groups of ITbM and Professor Breit in UoF was selected, and collaborative research in synthetic chemistry launched in FY2016. A researcher from the Ooi group visited the Breit lab to start the experiments from June 2016, and ITbM accepted a researcher from the Breit group in September 2016. The researcher's exchange in this framework will be continued, and a joint symposium is scheduled in FY2017 at UoF.

(7) National/international conferences organized by ITbM PIs

ITbM's PIs are world-leading scientists in their respective science fields, and have been contributing to the organization of various international conferences. In October 2016, Frommer organized the "Cold Spring Harbor Asia Conference on Latest Advances in Plant Development & Environmental Responses" at Awaji, Japan. In December 2016, Yoshimura organized "The 23rd Annual Conference of Japan Society for Chronobiology". In both conferences, the Director Itami was invited as a

keynote lecturer, which was a good opportunity to show the presence of ITbM's chemists to world-leading biologists.

(8) Promotion of ITbM's researchers

The international visibility of ITbM is indicated by how ITbM is involved in international brain circulation. In FY2016, 6 researchers joined ITbM from overseas institutions, whereas 2 researchers from overseas institutions have been promoted to the other institutions. The records are listed in Appendix 3-1.

(9) Visitors from overseas institutions

ITbM actively hosts visitors from overseas institutions as an endeavor to improve its international visibility. In FY2016, ITbM co-hosted 2 of the JST-SAKURA Exchange Program in Science (Harbin Institute of Technology and Nanjing University) and attended undergraduate students. ITbM also hosted a visit of undergraduate students from the Dalian University of Technology and high school students from the Bard High School Early College.

Many officials of overseas universities and governments have visited ITbM. In FY2016, ITbM hosted the delegates from the following institutions; University of Minnesota and North Carolina State University (USA), University of Strasbourg (France), University of Freiburg (Germany), University of Western Australia, Universities Australia, Australian National University, Curtin University, La Trobe University, Macquarie University, Monash University, University of Queensland, and University of Tasmania (Australia), Ministry of Education and POSTECH (South Korea).

4. Implementing 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.

(1) Innovative system reform of ITbM

(a) Decision making system

The Director has the authority to make final decisions over all matters concerning the operation and management of ITbM, such as the appointment of personnel, the Center's budget and research priorities. The role of the President of NU is limited to the appointment of the Director according to suggestion by the WPI program committee.

(b) Evaluation system and incentives

ITbM established a system to provide incentives to the Director, the Vice Director, PIs, and the Administrative Director based on evaluation of their performance. The determination of eligible persons and the amount of incentive is left to the discretion of the Director.

(2) Ripple effect to NU

(a) "WPI-next" program

In reference to ITbM's unique personnel structure such as the Co-PI system, the "WPI-next" program was launched at NU to support world-leading science. There were 2 projects awarded in FY2014, and 2 more projects were selected in FY2016.

(b) Department for "Academic Research & Industry-Academia-Government Collaboration"

In order to promote efficient use of intellectual properties and research outcomes from ITbM and other NU's institutes, NU conducted organizational reform of research supporting units to establish the department.

(c) Revision of the URA system

The URA system that started in 2013 was reviewed extensively in reference to the role of the RPD at ITbM. The URA was categorized into 5 groups and their functions were defined as follows: "Planning & Strategy Group", "Regional Collaboration & Communication Group", "Project Promotion Group", "Intellectual Property & Technology Transfer Group", and "International Industry-Academia-Collaboration & Human Resource Development Group".

(d) International Public Relations Taskforce

ITbM has been sharing its expertise and experience on international public relations to the Academic Research and Industry-Academia-Government Collaboration Department at NU. As a result, NU now has a system to send out international press releases on research accomplishments for the entire

university and has started a taskforce to establish an international public relations department at the university. Members of the RPD are involved in this taskforce as advisors to promote these activities and the internationalization of the university as a whole.

(e) Venture business support

NU launched a "Venture Fund of Nagoya University and Tokai Area's Universities". Establishment of these systems strongly supports ITbM's activity.

(f) Information distributed in English

In reference to the English e-mail distribution of ITbM, NU started to circulate information of grants, funding and other information in both English and Japanese from the end of FY2013.

5. Efforts to secure the center's future development over the mid- to long-term

* Please 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 (including measures of support by the host institution)

(1) Strategic Planning Division (SPD, see Section 2)

The SPD was established as a new division of the Administrative Department, and began its operation in April 2016. The SPD plays a key role in realization of the practical use of the research outcomes at ITbM. An Associate Professor (Masters degree in organic chemistry, pharmaceutical science) with prior experience as the head of the chemistry department at a pharmaceutical venture company was employed as of April 2016. A Lecturer (Patent attorney/ degree in catalytic chemistry) in charge of intellectual property management was transferred from the RPD to the SPD.

(2) Employment of new PIs (see Section 3)

According to ITbM's research progress, the need for bio-simulation had increased. ITbM decided to invite Florence Tama as a PI and a specialist in the field from April 2016. A postdoctoral researcher and a secretary have already been allocated to the Tama group. In September 2016, Wolf Frommer joined ITbM as a new overseas PI. Frommer is a world-leading plant biologist, and is expected to promote ITbM collaborative research via development of biosensors. A Co-PI of the Frommer group was appointed, and international open recruitment for postdoctoral researchers in his group has started.

(3) Improvement of platforms that support ITbM's research

While ITbM has been developing and improving various platforms needed to conduct interdisciplinary research, a target identification platform remained to be developed. The Molecular Structure Center is working with biologists of the Kay group, who are experienced in target identification, and has succeeded in the identification for several projects. In addition, collaboration with the Institute of Chemistry (IoC), Academia Sinica will be started to set up a wide range of target identification methods. The director of IoC is a specialist of target identification, and has developed several identification methods that can be applicable to ITbM's research. Moreover, ITbM is also collaborating with RIKEN CSRS. ITbM and CSRS have already entered a collaboration agreement in January 2015, and several collaborative research projects are ongoing. The joint workshop between the research centers is being held on an annual basis, and ITbM hosted the 3rd workshop in January 2017.

(4) Mentoring of young researchers

Fostering young researchers is a key mission of ITbM. In order to foster internationally competitive talents, ITbM prepared a program and continued to exchange faculties and PhD students with collaborating overseas institutions (see Section 3). ITbM is also utilizing the international programs run by NU for researcher exchange and collaboration.

Mix Labs and Mix Offices, which have been established to promote interdisciplinary research, are serving as places for the young researchers to learn about other research fields. In FY2016, ITbM

started a lecture course series on chemical biology to establish the education system for students to conduct interdisciplinary research in chemistry and biology.

In 2015, ITbM started a program that supports the organization of student-initiated symposia. The students from several PI groups form a team, and organize small events. While the program provides an opportunity to experience a series of tasks needed for event organization, it also allows the students to become visible to academic researchers. In December 2016, a student team organized a one day symposium titled "Chemistry Workshop: Student-Centered Symposium of Forefront Chemistry", inviting 6 researchers from academia and industries.

(5) Initiatives to be taken after the support of WPI grant ends

As it is evident in the total amount of competitive research grants collected by ITbM's researchers (see Section 1), it is highly likely that the budget to conduct research will be secured. ITbM will take the necessary actions to secure the budget to operate ITbM. The SPD will cooperate with NU to acquire intellectual property rights and conduct business matching with companies for beneficial outcomes. ITbM will also take all means to work out strategies to collect donations. Nevertheless, NU's strong support is crucial to sustain ITbM at the current level. While the WPI program financially supports ITbM, NU conducts system reform of the university to ensure that ITbM is maintained. NU will include ITbM as part of the Institute of Advanced Research to secure the employment of ITbM's faculties and staffs by providing the necessary financial support.

6. Others

* In addition to the above 1-5 evaluation items, only if there is anything else that deserves mention regarding the center project's progress, please note it.

(1) Outreach activities

In order to promote ITbM's activities to the science community and to the general public, ITbM has been preparing various brochures and novelty goods. Many of the researchers at ITbM are involved in public lectures, teaching to high school/university students and exhibitions at public events. ITbM puts particular emphasis on nurturing the young generation and has been carrying out science demonstrations for the public, including the Science Agora at the Miraikan. ITbM is actively involved in open house events, hosting visitors during the NU Homecoming Day and Festival.

(2) Concern for the environment and safety

ITbM had set up the Environment and Safety Committee so that researchers at ITbM are constantly aware of the appropriate issues when conducting their research. Its 4th annual meeting was held in February 2017. The Director presented the recent progress of ITbM's research projects and the report of the Ames test to check the mutagenicity of molecules created at ITbM to secure their safety.

7. Center's response to the site-visit report

* Transcribe each item from the "Actions required and recommendations" section and note how the center has responded to them. However, if you have already provided this information, please indicate where in the report.

Comments in the Site Visit Report

Comment 1: A strategic plan for ITbM research for the next several years

Now that ITbM has proven that the concept of transformative bio-molecules is valuable in plant biology and chronobiology, the science direction and challenges that ITbM should pursue over the next 5 years should be laid out more clearly than the simple statement of the three flagship research areas.

<Action of ITbM>

ITbM will tackle the following research objectives under the following 3 flagship research areas stated below and will work to actively promote chemical biology research to "understand", "see", and "regulate" living organisms by establishing new interdisciplinary research fields between chemistry and biology. This is expected to lead to the creation of transformative bio-molecules.

Plant chemical biology

- Development of molecules that combat *Striga* and related parasitic plants.
 - Development of molecules that control plant stomata.
 - Development of molecules that overcome genome barriers to produce new hybrid plant species.
 - Discovery of unidentified protein receptors of plant hormones.
- Chemical chronobiology
- Development of molecules that control mammalian circadian rhythm.
 - Development of molecules that control plant circadian rhythm.
- Chemistry-enabled live imaging
- Development of high photo-resistant fluorescent dyes towards 3D/4D super-resolution and single molecule fluorescence imaging.
 - Development of fluorescent probes enabling unprecedented visualization of cellular microstructures and biological events.

To accomplish these objectives, ITbM will also improve and develop its platforms of small molecule synthesis, peptide and protein synthesis, chemical library, laser microscopy, omics and molecular analysis, phenotypic assay, theoretical design, and bio-simulation.

Comment 2: Target identification

Target identification remains the bottleneck for many of the projects, and it would be advisable to recruit a chemical biologist with expertise in target identification.

<Action of ITbM>

ITbM recognizes that target identification is indispensable to elucidate the mechanisms of molecular biological functions and to develop transformative bio-molecules. The Molecular Structure Center has been working along with the Kay group of ITbM, and has achieved identification of the target proteins at several projects. In addition to this endeavor, ITbM has started collaborations with experienced biologists of IoC, Academia Sinica to accelerate the target ID process. ITbM will also collaborate with RIKEN CSRS. ITbM and CSRS entered an agreement for the two centers to collaborate and coordinate on January 2015 (see Section 5).

Comment 3: Education and career paths for young researchers

For maintaining or even increasing the amount of external funding, it is also necessary to make strategic plans for personal visibility. Although ITbM has already been globally visible, chemists are not well acknowledged in the biology societies and vice versa. Overseas or foreign researchers are not well recognized in the communities in Japan, which may impede a successful grant application.

<Action of ITbM>

In order to improve the visibility of overseas PIs, NU PIs have continued to spread the word of the overseas PIs' scientific activities and great contribution to ITbM. NU PIs have also been inviting overseas PIs to domestic symposia as lecturers. As a result, the number of invitations for the overseas PIs from domestic universities and symposia has increased. Moreover, 3 overseas PIs, who applied to the JSPS Grants-in-Aid for Scientific Research (KAKENHI), were successful in securing the grant for FY2017; "KIBAN (A)" for Bode, "KIBAN (B)" for Crudden, and "Innovative Area" for Torii. A similar strategy will work to improve the visibility of ITbM's researchers in other fields. Accordingly, biology PIs are inviting chemistry PIs to present their results of interdisciplinary research.

Comment 4: ITbM graduate program

The WG previously recommended the creation of an ITbM graduate program, in which graduate students are co-supervised by PIs from different disciplines, because the educational aspect of ITbM will ultimately determine its long-term global visibility and sustainability. Although ITbM will start a new chemical biology lecture series, it would be of greater impact to establish an independent graduate program or at least to have dual mentorship (i.e., chemistry and biology) for graduate students at ITbM. Serious discussions and planning are needed on how ITbM can participate in graduate education. ITbM has been doing very well in fostering young researchers. In order to

encourage them and to nurture future core members, it is important to establish a tenure-track system or some other systems for securing their future.

<Action of ITbM>

NU currently places a top priority on strengthening graduate school education, and is working on systematic reform. NU is pursuing an institutional design that remove barriers among departments and allow graduate students to participate in the state-of-the-art research. Through these endeavors of NU, a system will be established that allows ITbM to accept graduate students. At the same time, efforts toward establishing a program for application centered on ITbM are under way for the "Excellent Graduate School" which is scheduled for FY2017. The continuous employment of ITbM's faculties is also being discussed, along with the establishment of ITbM as a permanent institute. ITbM has established a cooperative relationship with the departments of NU PIs, and has partially achieved the assignment of graduate students to ITbM. From FY2017, a few undergraduate students will also be allocated to overseas PI groups. In addition to these efforts at the department level, the reform of the graduate school at the university level as mentioned above is expected to lead to development of a system that allows many students to participate in ITbM.

Comment 5: Strategies for commercialization of the most promising molecules

It is obviously important to make strategic plans for translational research. For instance, field studies are an essential step to apply transformative bio-molecules in plant biology to practice. At the same time, while it is very attempting to invest in commercialization of the potential leads, critical balance in both manpower and resources have to be maintained to ensure that the quality of science and reputation of excellency at ITbM are not compromised. In this regard, it is welcome news that ITbM will establish a consortium by enrolling firms of related fields and expand its network for collaboration with industry. On the other hand, prioritization of the leads for advancement and strategically planning in partnership are clearly needed.

<Action of ITbM>

To address the purposes above, ITbM has established the Strategic Planning Division (SPD). The SPD is strategically advancing effective partnerships with companies, while maintaining a strong partnership with the department of Academic Research & Industry–Academia–Government Collaboration of NU. ITbM will establish partnerships with companies that are taking the lead in processes necessary for practical use, and will not devote too many resources to research aimed at practical uses (see Section 2).

Comment 6: Additional organizational reform

NU is very supportive of ITbM by adopting many of the new practices, and has used WPI to drive internal changes, which often are difficult with only role models but without organizational or financial incentives. NU is committed to continue ITbM after the end of the WPI program, which will be of considerable benefit considering the visibility and attention that ITbM has brought to NU already. However, additional organizational reform is needed to accommodate visiting graduate students and ultimately to establish an independent graduate program and a tenure-track system at ITbM.

<Action of ITbM>

ITbM has established a system to accept visiting graduate students in cooperation with the departments of NU PIs, and has been accepting many graduate students from overseas collaborating institutions to conduct collaborative research. On the other hand, the system of assigning graduate students to ITbM will be established alongside the graduate school reform of NU, as described above. ITbM is positioned under the Institute for Advanced Research and has been permanently established at NU as an international research base to advance cutting-edge basic research. NU promises to provide the necessary support, which includes the continuous employment of ITbM's faculties.

A comment in the Interim Evaluation (MEXT)

A guideline for collaboration with industry is needed. As ITbM moves forward, it will be important for them to find creative ways to engage with the public, especially NPOs and other interest groups that are concerned with sustainability and environmental impact. Otherwise, ITbM runs the risk of appearing (to the public or to policy makers) as being driven too much by industry relationships. It would be good if the center creates some programs to discuss and prioritize problems for their research to address from the standpoint of world needs.

<Action of ITbM>

Since the launch of the center, ITbM's general principle has been to conduct curiosity-driven cutting-edge basic research. As a consequence, the center does not necessarily customize or prioritize its research projects according to industrial needs. Following the center's general principle, ITbM does not plan to extensively use its resources for technological applications. Instead, the center will focus on establishing relationships with industries, where the industries take initiative in implementing ITbM's research outcomes.

ITbM realizes that its research projects should be prioritized according to the needs of societies. Therefore, ITbM established the SPD in 2016, which plays a key role in realization of ITbM's research outcomes. In collaboration with the department of Academic Research & Industry-Academia-Government Collaboration of NU, the SPD will take initiatives to prioritize the projects through various measures (see Section 2).

World Premier International Research Center Initiative (WPI)

Appendix 1 FY2016 List of Center's Research Results and Main Awards

A. Refereed Papers

- List only the Center's papers published in 2016. (Note: The list should be for the calendar year, not the fiscal year.)

- (1) WPI papers
List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state the name of his/her WPI center) (Not including papers whose acknowledgements contain the names of persons affiliated with the WPI program.)

Order of Listing

1. Original articles
2. Review articles
3. Proceedings
4. Other English articles
5. Articles written in other than English

- (2) Method of listing paper
- List only referred 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 the same. (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.
- If the papers are written in languages other than English, divide them into language categories when listing them.
- Assign a serial number to each paper to be used to identify it throughout the system.
- (3) Submission of electronic data
- In addition to the above, for each paper 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 in FY 2016.
- They will be used as reference in analyzing the trends and states of research in all the WPI centers, 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 (Jan 1, 2014 – Dec 31, 2014)

1. Original Articles

- (1) Takehisa Maekawa, Hiroshi Ueno, Yasutomo Segawa, Michael M. Haley and Kenichiro Itami, *Chem. Sci.*, 2016, 7, 650-654. "Synthesis of open-shell ladder p-systems by catalytic C–H annulation of diarylacetylenes" (DOI: 10.1039/c5sc03391h)
- (2) Jiao Jiao, Kei Murakami, and Kenichiro Itami, *ACS Catal.* 2016, 6, 610–633. "Catalytic Methods for Aromatic C–H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules" (DOI: 10.1021/acscatal.5b02417) **Highly Cited Paper**
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- (81) Kohsuke Ohmatsu, Yuichiro Ando, Tsubasa Nakashima, Takashi Ooi, *Chem* 2016, 1, 802–810. "A Modular Strategy for the Direct Catalytic Asymmetric α -Amination of Carbonyl Compounds" (DOI: 10.1016/j.chempr.2016.10.012)
- (82) Toshiaki Tameshige, Satoshi Okamoto, Jin Suk Lee, Mitsuhiro Aida, Masao Tasaka, Keiko U. Torii, Naoyuki Uchida, *Curr. Biol.* 2016, 26, 2478–2485. "A Secreted Peptide and Its Receptors Shape the Auxin Response Pattern and Leaf Margin Morphogenesis" (DOI: 10.1016/j.cub.2016.07.014)
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- (84) Keisuke Ikegami, Takashi Yoshimura, *General and Comparative Endocrinology* 2016, 227, 64–68. "Comparative analysis reveals the underlying mechanism of vertebrate seasonal reproduction" (DOI: 10.1016/j.ygcen.2015.05.009)
- (85) Xuan Zhao, Tsuyoshi Hirota, Xuemei Han, Han Cho, Ling-Wa Chong, Katja Lamia, Sihao Liu, Annette R. Atkins, Ester Banayo, Christopher Liddle, Ruth T. Yu, John R. Yates III, Steve A. Kay, Michael Downes, and Ronald M. Evans, *Cell* 2016, 165, 1644–1657. "Circadian Amplitude Regulation via FBXW7-Targeted REV-ERBa Degradation" (DOI: 10.1016/j.cell.2016.05.012)
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2. Review Articles

- (1) Yasutomo Segawa, Hideto Ito and Kenichiro Itami, *Nature Reviews Materials* 2016, 1, 15002. "Structurally uniform and atomically precise carbon nanostructures" (DOI: 10.1038/natrevmats.2015.2)
- (2) Yasutomo Segawa, Akiko Yagi, Katsuma Matsui, and Kenichiro Itami, *Angew. Chem. Int. Ed.* 2016, 55, 5136–5158. "Design and Synthesis of Carbon Nanotube Segments" (DOI: 10.1002/anie.201508384)
- (3) Junichiro Yamaguchi, Kei Muto, Kenichiro Itami, *Top. Curr. Chem.* 2016, 374, 55. "Nickel-Catalyzed Aromatic C–H Functionalization" (DOI: 10.1007/s41061-016-0053-z)
- (4) Daisuke Maruyama, Mina Ohtsu, Tetsuya Higashiyama, *Seminars Cell Dev. Biol.* 2016, 60, 127–135. "Cell fusion and nuclear fusion in plants" (DOI: 10.1016/j.semcdb.2016.07.024)
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- (6) Daisuke Uruguchi, Takashi Ooi, *Top. Curr. Chem.* 2016, 372, 55–83. "Site-Selective Conjugate Addition through Catalytic Generation of Ion-Pairing Intermediates", *Topics in Current Chemistry: Site Selective Catalysis*, T. Kawabata Ed. Springer (2016). (DOI: 10.1007/128_2015_655)
- (7) Jennifer L. Nemhauser & Keiko U. Torii, *Nat. Plants* 2016, 2, 16010. "Plant synthetic biology for molecular engineering of signalling and development" (DOI: 10.1038/nplants.2016.10)
- (8) Taeko Nishiwaki-Ohkawa and Takashi Yoshimura, *J. Endocrinol.* 2016, 229, R117–R127. "Molecular basis for regulating seasonal reproduction in vertebrates" (DOI: 10.1530/JOE-16-0066)
- (9) Masashi Ryo, Takuya Matsuo, Takafumi Yamashino, Mizuho Ichinose, Mamoru Sugita & Setsuyuki Aoki, *Plant Signal. Behav.* 2016, 1, e1116661. "Diversity of plant circadian clocks: Insights from studies of *Chlamydomonas reinhardtii* and *Physcomitrella patens*" (DOI: 10.1080/15592324.2015.1116661)

3. Proceedings

4. Other English Articles

- (1) Yoko Mizuta, Daisuke Kurihara and Tetsuya Higashiyama, *Cytologia* 2016, 81, 1–2. "Visualization of Plant Sexual Reproduction in the Whole-mount Pistil by ClearSee" (DOI: 10.1508/cytologia.81.1). Editorial
- (2) Thibault J. Harmand, Claudia E. Murar and Jeffrey W. Bode, *Nature Protocols* 2016, 11, 1130–1147. "Protein chemical synthesis by α -ketoacid–hydroxylamine ligation" (DOI: 10.1038/nprot.2016.052). Protocol
- (3) Masaki Okumura and Toshinori Kinoshita, *Bio-protocol* 2016, 6, e2044. "Measurement of ATP Hydrolytic Activity of Plasma Membrane H⁺-ATPase from *Arabidopsis thaliana* Leaves" (DOI: 10.21769/BioProtoc.2044). Protocol
- (4) Koji Takahashi and Toshinori Kinoshita, *Molecular Cell Biology of the Growth and Differentiation of Plant Cells*, 156-173, CRC Press. "The regulation of plant cell expansion: Auxin-induced turgor-driven cell elongation" (DOI: 10.1201/b20316-13). Book

5. Articles written in other than English

- (1) Yoshikatsu Sato, Chenguang Wang, Aiko Fukazawa, Masayasu Taki, Tetsuya Higashiyama, Shigehiro Yamaguchi, *Plant Morphology* 2016, 28, 9–13. "A super photostable fluorescent dye that survives in repeated STED laser irradiation" (in Japanese)
- (2) Daisuke Maruyama and Tetsuya Higashiyama *Plant Morphology* 2016, 28, 43–47. "Termination mechanism of pollen tube guidance in *Arabidopsis thaliana*" (in Japanese)

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

- List up to 10 main presentations during FY2016 in order from most recent.
- For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

- 1) Tetsuya Higashiyama, "Signaling in Pollen Tube Guidance", Cold Spring Harbor Asia Conference on Latest Advances in Plant Development & Environmental Response, Awaji Island, Japan, November 29–December 2, 2016
- 2) Kenichiro Itami, "Exploring Nanocarbon Materials and Plant Biology by C-H Activation" The Holger Erdtman Lecture, KTH, Sweden, October 31, 2016
- 3) Steve Kay, Circadian Rhythm Networks in Health and Disease, Nobel Prize Laureate Summit, Chengdu, China, September 2016
- 4) Cathleen Crudden, "New Trends in Organometallic Chemistry leading to Organic Synthesis," 252nd American Chemical Society National Meeting & Exhibition, Philadelphia, PA, USA, August 2016
- 5) Takashi Yoshimura, "Universality and diversity in the photoperiodic signal transduction in vertebrates", 28th Conference of European Comparative Endocrinologists Leuven, Belgium, August 25, 2016 (plenary lecture)
- 6) Jeffrey Bode, "Synthesis of N-Heterocycles", Tetrahedron Symposium, Barcelona, Spain, June 2016 [Plenary Lecture]
- 7) Toshinori Kinoshita, "Regulation of the plasma membrane H⁺-ATPase in response to physiological signals" Agriculture Resources and Environment: Science and Technology, Nanjing Agricultural University, China, May 21–24, 2016
- 8) Takashi Ooi, "Molecular Design of Organic Ion Pairs for Asymmetric Catalysis", Columbia University, New York, USA, May 12, 2016
- 9) Shigehiro Yamaguchi, "Main Group Strategy for Photo- and Electro-Functional Materials", Sino-German Main Group Chemistry Symposium, Beijing, China, April 10–15, 2016
- 10) Keiko Torii, 1st CRC1101 Symposium, Molecular encoding of specificity in plant processes. Univ. Tübingen and Heidelberg, Max Planck Institute for Developmental Biology, Tübingen, Germany, April 4–6, 2016

C. Major Awards

- List up to 10 main awards received during FY2016 in order from the most recent.
- For each, write the recipient's name, name of award, and year issued.
- In case of multiple recipients, underline those affiliated with the center.

- 1) Steve Kay, Funding Award: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases, 2016
- 2) Kenichiro Itami, The SYNLETT Best Paper Award 2016, Thieme, 2016
- 3) Keiko Torii, Distinguished Lecture, Institute of Plant Molecular Biology, Academia Sinica, Taipei
- 4) Masakazu Nambo, CSJ Presentation Award, The 97th CSJ Annual Meeting, March 2017
- 5) Takashi Yoshimura, Ishizuki Yoshimochi Memorial Lectureship Award, Japan Thyroid Association, November 2016
- 6) Kenichiro Itami, The Holger Erdtman Lecture, KTH, Sweden, October 2016
- 7) Kenichiro Itami, The Nagase Prize, Japan, September 2016

- 8) Tetsuya Higashiyama, Best Paper Award, Journal of Plant Research, The Botanical Society of Japan, September 2016
- 9) Tetsuya Higashiyama, Hirase Award, Japanese Society of Plant Morphology, September 2016
- 10) Shigehiro Yamaguchi, Nagase Foundation Award, April 2016

World Premier International Research Center Initiative (WPI)

Appendix 2 FY 2016 List of Principal Investigators

NOTE:

- Underline names of principal investigators who belong to an overseas research institution.
- In case of researchers not listed in the latest report, attach "Biographical Sketch of a New Principal Investigator".

<Results at the end of FY2016>			Principal Investigators Total: 13						
Name (Age)	Affiliation (Position title, department, organization)	Academic degree specialty	Working hours				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			(Total working hours: 100%)						
			Work on center project		Others				
Research activities	Other activities	Research activities	Other activities						
Center director <u>Kenichiro ITAMI*</u> (45)	Director, Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr.Eng <u>Specialties</u> : Organic Synthesis, Catalysis, Pharmaceuti-cal Science, Nanocarbon Chemistry	50%	30%	10%	10%	from the beginning	usually stays at the center	
Tetsuya <u>HIGASHIYAMA*</u> (45)	Vice-Director, Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr.Sci <u>Specialties</u> : Live Cell Biology, Plant Reproduction, Bio-active molecules, Peptides	70%	20%	0%	10%	from the beginning	usually stays at the center	
<u>Jeffrey W. BODE*</u> (43)	Professor of Organic Chemistry Department of Chemistry and Applied Biosciences, ETH Zürich, Switzerland	Doctoral of Natural Science <u>Specialties</u> : Organic Synthesis, Peptide and Protein Chemistry, Catalysis, Ligation and Bioconjugati-on reactions	16%	5%	64%	15%	from the beginning	Stayed at the center one month in FY2016. Connected 24 hours through iPad to the center. Holds on-line group meeting once a week. Joins PI meeting online.	sent four young scientists to the center (three months each)
<u>Cathleen M. CRUDDEN*</u> (50)	Professor Department of Chemistry, Queen's University, Canada	Ph.D <u>Specialties</u> : Catalysis, Organic Synthesis, Materials Chemistry, Chirality	16%	5%	64%	15%	from the beginning	Stayed at the center one month in FY2016. Holds Skype group meeting once a week. Joins PI meeting online.	
Stephan IRLE* (49)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Ph.D. <u>Specialties</u> : Electronic Structure Theory, Computation-al Materials Science, Quantum Chemistry of Complex Systems	80%	10%	0%	10%	from the beginning	usually stays at the center	

Toshinori KINOSHITA* (48)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Sci <i>Specialties</i> : Plant Molecular Physiology	80%	10%	0%	10%	from the beginning	usually stays at the center	
Takashi OOI* (51)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Engineering <i>Specialties</i> : Organic Synthesis, Catalysis, Molecular Recognition	80%	10%	0%	10%	from the beginning	usually stays at the center	
Keiko TORII* (51)	Distinguished Professor Department of Biology, University of Washington Investigator Howard Hughes Medical Institute and Gordon and Betty Moore Foundation (HHMI-GBMF)	Ph.D. <i>Specialties</i> : Plant Development, Signal Transduction, Stem Cell Maintenance/Differentiation in Plants	16%	5%	64%	15%	from the beginning	Stayed at the center one month in FY2016. Holds on-line plant biology meeting "Mixplant meeting" once a week. Joins PI meeting online.	
Shigehiro YAMAGUCHI* (48)	Vice-Director, Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Engineering <i>Specialties</i> : Main Group Chemistry, Physical Organic Chemistry	70%	20%	0%	10%	from the beginning	usually stays at the center	
Takashi YOSHIMURA* (47)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Agriculture <i>Specialties</i> : Animal Physiology, Systems Biology, Neuroendocrinology	60%	10%	20%	10%	from the beginning	usually stays at the center	
Steve A. Kay* (57)	Dean and Anna H. Bing Dean's Chair, Professor of Biological Sciences, Professor of Neurology, Physiology and Biophysics, Dornsife College of Letters, Arts and Sciences, University of Southern California	Ph.D. <i>Specialties</i> : Chronobiology, Genetics, Biochemistry, Systems Biology	16%	5%	64%	15%	from April 1st 2014	Holds on-line meeting on an as-needed basis. Joins PI meeting online.	
Florence Tama* (42)	Professor Institute of Transformative Bio-Molecules / Department of Physics, Graduate School of Science, Nagoya University	Ph.D <i>Specialties</i> : computational biophysics	45%	5%	40%	10%	from April 1st 2016	usually stays at the center	
Wolf B. Frommer* (59)	Staff Member and Dir. emerit., Carnegie Science, Stanford Professor (by Courtesy) Dep. Biology, Stanford University	Dr. rer. nat. <i>Specialties</i> : Biology	16%	5%	64%	15%	from October 16th 2016	Stayed at the center for four days in FY2016 in order to discuss research activity at the Institute from next fiscal year. Joins PI meeting online.	

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Appendix 2- attachment
FY2016 Biographical Sketch of a New Principal Investigator

Name (Age)	Florence Tama (41)
Affiliation (Position title, department, organization)	Professor, Department of Physics, Graduate School of Science, Nagoya University
Academic degree, specialty	Ph.D in computational biophysics

[Research and education history]

Education

1996	B.S., Paul Sabatier University, France (Physical sciences)
1997	M.S., Paul Sabatier University, France (Chemistry of Biomolecules)
2000	Dr. Sci., Paul Sabatier University, France (Computational Biophysics)

Professional experience

2000-2005	Post-doctoral research, The Scripps Research Institute, USA
2006-2012	Assistant Professor, University of Arizona, USA
2013-present	Unit Leader, AICS, RIKEN, Japan
2015-present	Full Professor, Department of Physics, Nagoya University, Japan
2016-present	Associate Editor for 'Biophysics and Physicobiology'

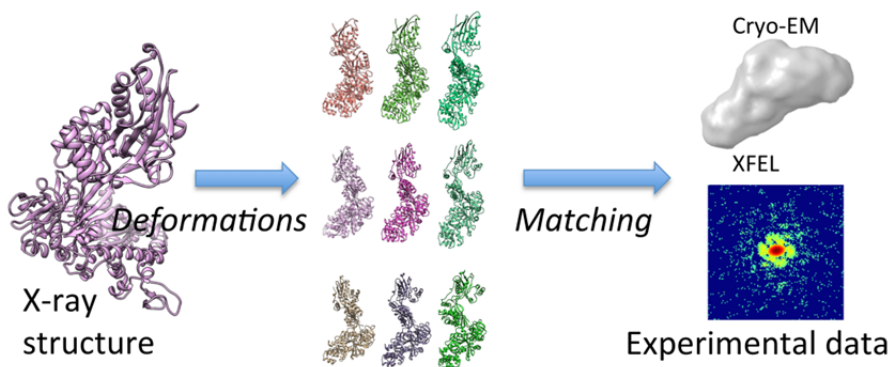
[Achievements and highlights of past research activities]

(* Describe qualifications as a top-caliber researcher if he/she is considered to be ranked among the world's top researchers.)

Structural characterization of macromolecular complexes and their functional states is a crucial task in molecular biology, since such molecular machines accomplish many important cellular functions. My research focus on the development of new computational methods to obtain atomic level descriptions of conformational transitions occurring in macromolecular complexes using a variety of low-resolution experiments and X-ray crystallography. In addition, we work in close collaboration with experimental groups to study function of specific biological systems.

Method development

Normal mode analysis (NMA) is commonly used to study the motions of biological systems that occur on time scales not accessible via standard molecular dynamics simulation. Such an ability of NMA to predict the thermal fluctuations of molecules has been utilized to analyze experimental data. NMA consists in the decomposition



of the motion into vibrational modes. This approach extends the time scale accessible to theoretical work and has proven to be extremely useful for studying collective motions of biological systems. Our

studies have enabled the extension of applications of NMA to large macromolecular assemblies. Applications of these approaches have focused on several macromolecular assemblies and their functional motions: the swelling transition of viruses, the ratchet-like motion of the ribosome and the conformational transition of the myosin.

In addition, I developed methods to analyze data arising from cryo Electron Microscopy (cryo-EM) experiments using both 2D and 3D data. Indeed, cryo-EM has become an essential tool for structural biology research. Cryo-EM experiments can produce medium resolution structures (usually in the range between 20 and 5 Å) but allows studying large and flexible macromolecular complexes inaccessible to X-ray and NMR techniques.

However, as its resolution is not sufficient to derive atomic models, it requires data from other experiments and/or computation. For bridging the resolution gap and extract structure and dynamics from cryo-EM data, we have developed hybrid methods, combining high-resolution structure with NMA or MD simulations. Such methods were also extended to Small Angle X-ray Scattering (SAXS) experiments.

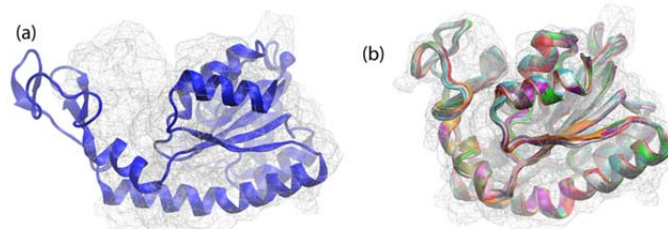


Illustration of flexible fitting by molecular dynamics simulation. (a) Initial fit of the X-ray structure (blue ribbon) onto the cryo-EM data at 4 Å resolution (gray envelop). (b) Ribbon representation of twelve conformations of the protein obtained from simulations and the low-resolution cryo-EM structure. A better fit with the cryo-EM data is observed after refinement with our approach.

(b) is the cover image of the Dec 15th 2008 issue of the Biophysical Journal

More recently, we have started to work with X-ray free-electron laser (XFEL). Recent developments of XFEL light sources offer a new possibility for the imaging of biological macromolecules (RIKEN/SPring 8). It is anticipated that extremely strong XFEL laser allows the X-ray imaging of biological systems without crystallization. Since crystallization is not necessary, it could be applied to a wider variety of the systems under various physiological conditions or to observe elementary steps of a biochemical function. Currently, laser technology and experimental techniques are still being developed, thus atomic level resolution, such as obtained by X-ray crystallography, is not yet available. However, new data on biological systems at sub μm scale are emerging. Therefore computational tools are needed to interpret data becoming available. As collaboration with Dr. Song at Spring-8, we constructed a hypothetical model of a RNA-sponge, a biomaterial with possible medical application. In addition, we have demonstrated that dynamics of biological molecules can be extracted from single molecule XFEL experiments under specific experimental conditions.

Studies of proteins structure, function, dynamics

My research group is also interested in understanding protein functions. Therefore we have been studying biological systems in collaboration with several experimental groups. In most cases, we are using computer modeling to interpret existing experimental data at an atomic level scale. Observations made from the simulations are also used to drive new experiments

- **Anthrax:**

In collaboration with Dr Fisher (U. of Kansas Medical Center) and Dr Collier (Harvard Medical School), we have probed the conformational dynamics of the Protective Antigen pore, which mediates pH gradient-driven translocation of the enzymatic components of anthrax toxin across membranes. Our calculation predicts conformational rearrangements in regions that are known to catalyze protein translocation.

- **Membrane transporter proteins:**

In collaboration with Dr. Stephen Wright (U. of Arizona Physiology Dept), our group is interested in developing a predictive model of substrate/transporter interactions for a family of membrane proteins known as organic cation transporters (OCTs). We have simulated the dynamics of EmrD, a membrane transporter similar to OCT, to obtain a better understanding of the functioning of these systems. We

have also shown that proposed homology models are stable during MD simulations. This line of research was supported by the National Institute of Health (PI: S. Wright, Co-PI: F. Tama).

- Small heat shock proteins:

With Dr. Vierling (U. of Mass.), we are studying the active form of the small heat shock proteins (sHSP) that are critical proteins to rescue unfolded/misfolded proteins. The sequence and predicted conformational flexibility of the N-terminal arm of sHSP have been suggested to determine sHSP chaperone efficiency. Molecular dynamics simulations have revealed that the N-terminal arm can adopt several conformations (open and closed), which could explain the difference observed in efficiency between species. This line of research was supported by the National Institute of Health (PI: E. Vierling, Co-I: F. Tama).

- Pilus IV:

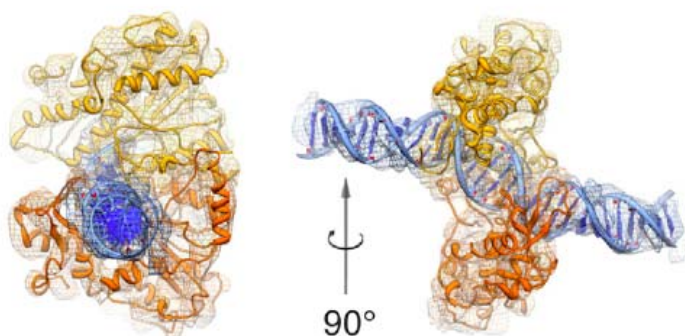
Type IV pili (T4P) are long protein assemblies associated with a variety of bacteria. They are long and flexible appendages that are associated with a wide variety of bacterial functions, including motility, colony formation, genetic recombination, and infection. Our collaborator, Dr. Nicolas Biais (Brooklyn College New York), is conducting single molecule AFM experiments on T4P. We are aiming to complement his experimental observations with a more atomic detailed picture of the response of T4P to external forces.

We have investigated structure of a T4P segment derived from cryo-EM using molecular dynamics simulations. Forces were applied to the system in order to induce stretching of the pilus (that had been observed experimentally). The stretching of the T4P system leads us to an understanding, at an atomic level of detail, of the T4P responds to tension forces.

In particular, we have been able to identify sequences in T4P that become exposed to the filament's external environment. More specifically, a sequence in GC-T4P, known to become exposed upon the application of pulling forces, also becomes exposed in our simulations. Our simulations also enable us to predict a second exposed region of the GC-T4P filament under tension. Our collaborator, Dr. Biais, was able to confirm the exposure of this region experimentally.

- Restriction endonuclease SgrAI:

SgrAI is a sequence specific DNA endonuclease that functions through an unusual enzymatic mechanism. In collaboration with Dr. Horton (U. of Arizona), who used single-particle transmission EM to reconstruct distinct populations of SgrAI, we built an atomic model of the structure of SgrAI at 8.6 Å resolution, demonstrating the conformational state of SgrAI in its activated form. This hybrid approach revealed an unusual mechanism of enzyme activation that explains SgrAI's oligomerization and allosteric behavior.



Atomic model of SgrAI obtained after flexible fitting

[Achievements]

(1) International influence

a) Guest speaker, chair, director, or honorary member of a major international academic society in the subject field, b) Holder of a prestigious lectureship, c) Member of a scholarly academy in a major country, d) Recipient of an international award(s), e) Editor of an influential journal etc.

a) Invited Lectures at international meetings since moving to Japan:

RIKEN joint symposium with INSA, Lyon, France May 2013

Workshop on "modeling of biomolecular systems in cellular environments" Kyoto University Oct 31- Nov 1, 2013

Novel measurement techniques for visualizing 'live' protein molecules at work - Kickoff Symposium, Kyushu University, Oct 3 2014

Large-scale biological simulations using supercomputers, RIKEN Advanced Institute for Computational Science, Apr 1-2, 2015

3. The 3rd International Symposium on Transformative Bio-Molecules, Nagoya University, May 25-26 2015

Colloque de la Société Française de Microscopie, Nice, June 29–July 3 2015

Japanese Biophysical society meeting, Kanazawa, Sept 13-15 2015

Symposium: Integrative Structural Biology with Hybrid Methods, Osaka University, Oct 3, 2015

Cutting Edge of Technical Innovations in Structural and Systems Biology, Kyushu University, Nov 13-14, 2015

American Chemical Society Meeting, San Diego, March 13-17, 2016

Workshop Organization

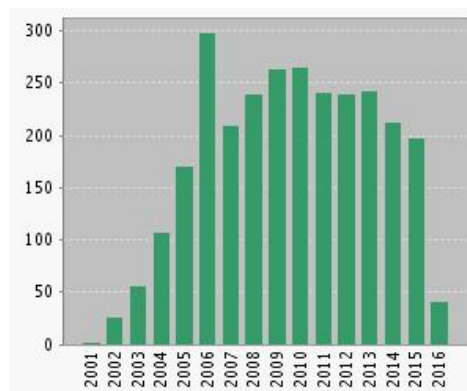
Co –organizer of “ Coarse-Grained Modeling of Structure and Dynamics of Biomacromolecules” Telluride workshop, CO, USA in 2010, 2012, 2014, 2016

(2) Receipt of large-scale competitive fundings (over past 5 years)

National Science Foundation	\$450,000	2007 - 2012
National Institute of Health – Co-PI	\$100,000	2009 - 2012
National Institute of Health – Co-I	\$100,000	2010 – 2012
National Institute of Health – Co-I	\$100,000	2011 – 2012

(3) Article citations (Titles of major publications, and number of citations.)

Total papers: 45, Total citation: 2821, h-index: 22, Researcher ID: A-7077-2016



Most-cited papers

1. F. Tama and Y.H. Sanejouand. (2001)Conformational change of Proteins arising from Normal Mode Analysis.**Protein. Eng. 14: 1-6 [531 times cited]**

2. F. Tama, F.X. Gadea, O. Marques and Y.H. Sanejouand. (2000) A building block approach for determining low-frequency normal modes of macromolecules. **Proteins** 41: 1-7 [320 times cited]
3. F. Tama, M. Valle, J. Frank and CL Brooks III. (2003) Understanding the ratchet-like inter-subunit reorganization of the ribosome. **Proc. Natl. Acad. Sci. USA** 100: 9319-9323 [239 times cited]
4. K. Mitra, C. Scaffitzel, T. Shaikh, F. Tama, S. Jenni, CL. Brooks III, N. Ban and J. Frank. (2005) Structure of the E. coli protein-conducting channel bound to a translating ribosome. **Nature** 438: 318-324 [210 times cited]
5. F. Tama and CL. Brooks III. (2006) Symmetry, form and shape: guiding principles for robustness in macromolecular machines. **Annual Review of Biophysics & Biomolecular Structure** 35: 115-133 [170 times cited]

Recent important papers

1. J. Baker, N. Biais and F. Tama. (2013) In silico studies of Pilus IV, **Plos Computational Biology** 9(4):e1003032
2. Hybrid Electron Microscopy Normal Mode Analysis graphical interface and protocol. (2014) CO. Sorzano, J.M. de la Rosa-Trevín, F. Tama, S. Jonić. **J. Struct. Biol.** 188:134-41
3. M. Gallagher-Jones, Y. Bessho, S. Kim, J. Park, S. Kim, D. Nam, C. Kim, Y. Kim, Y. Noh do, O. Miyashita, F. Tama, Y. Joti, T. Kameshima, T. Hatsui, K. Tono, Y. Kohmura, M. Yabashi, SS. Hasnain, T. Ishikawa, C. Song. (2014) Macromolecular structures probed by combining single-shot free-electron laser diffraction with synchrotron coherent X-ray imaging. **Nat Commun.** 2:5:3798
4. S. Patel, E. Vierling and F. Tama. (2014) Replica exchange molecular dynamics simulations provide insight into substrate recognition by small heat shock proteins. **Biophys J.** 10:2644-55
5. Tokuhsa, A, Tama, F., Jonic, S. & Miyashita, O (2016). Hybrid Approach to Identify Conformational States from X-ray Free Electron Laser Diffraction Patterns **J. Struct. Biol**, *in press*

(4) Others (Other achievements that indicate qualification as a top-caliber researcher, if any.)

World Premier International Research Center Initiative (WPI)
Appendix 2- attachment
FY2016 Biographical Sketch of a New Principal Investigator

Name (Age)	Wolf B Frommer (58)
Affiliation (Position title, department, organization)	Staff Member and Dir. emerit., Carnegie Science, Stanford Professor (by Courtesy) Dep. Biology, Stanford University
Academic degree, specialty	Dr. rer. nat., Dipl. Biol., Biology

[Research and education history]

Education

1981 Diploma, Biology, University of Cologne, Germany
 1987 Dr. rer. nat. Biology, University of Cologne, Germany

Professional Experience

1987 Short postdoctoral fellowship at the Shanghai Institute for Plant Physiology, Chinese Academy of Sciences, China
 1988-1989 Postdoctoral fellow at the Institut für Genbiologische Forschung, Berlin, Germany
 1990-1991 Head of a research group in the department of Prof. Dr. Lothar Willmitzer, Institut für Genbiologische Forschung, Berlin
 1992-1996 Head of Independent Young Investigator Group at Genzentrum Berlin (BMBF-funded), Institut für Genbiologische Forschung, Berlin
 1996-2003 Professor and Chair, Plant Physiology, Tübingen University
 2000-2004 Founder and Board Member, Sympore GmbH Tübingen
 1997-2001 Cofounder and Director of Center for Plant Molecular Biology, Tübingen University
 2003-2007 Staff Member, Carnegie Science, Stanford
 2003-2011 Prof. by Courtesy, Dep. Biology, Stanford University, Stanford
 2007-2009 Vice President and Cofounder, Joint Bioenergy Institute, Emeryville
 2007-2016 Director, Dep. Plant Biology, Carnegie Science, Stanford
 2011-2016 Professor, Dep. Biology, Stanford University, Stanford
 2016-present Staff Member and Dir. emerit., Carnegie Science, Stanford; Prof. by Courtesy, Stanford University

[Achievements and highlights of past research activities]

(* Describe qualifications as a top-caliber researcher if he/she is considered to be ranked among the world's top researchers.)

9/1/2010-8/31/2013	NSF	EAGER: A microfluidic platform for accelerated co	\$350,804	to WBF
9/1/2010-8/31/2015	NSF	Arabidopsis 2010: The role of nutrient sensing an	\$876,845	to WBF
4/15/2011-3/31/2016	NSF	The Membrane-based Protein Interactome	\$1,834,557	to WBF, subcontract to Rhee, Carnegie
4/1/2012-3/31/2015	USDA	Biochemical Function of the Type III TAL Effectors	\$138,660	Subcontract to WBF
11/1/2012-10/31/2014	Bill & Melinda Gates	Transformative strategy for controlling rice blight	\$100,000	to WBF, subaward of 30k to B. Yang, Iowa State University
2/12/2013-2/11/2015	Carnegie Canada	Mapping the newly discovered sugar translocation	\$14,370	to WBF, subaward to UBC, Canada

5/1/2013-4/30/2017	NSF	Collaborative Research: The role of host nutrient	\$563,326	to WBF
5/22/2014-5/21/2017	Syngenta	SWEET Transporters as Key for Maize Yield Improvements	\$1,222,798	to WBF
9/1/2014-8/31/2019	NSF	Novel Biosensors for Monitoring Nitrogen Uptake	\$879,403	to WBF, addtl. funds in remaining years
10/28/2014-10/31/2016	Bill & Melinda Gates	Transformative Strategy for Controlling Rice Blight	\$505,912	to WBF, addtl. funds in remaining years
3/18/2015-1/14/2017	NIH	A novel drug detection assay using fluorescent sensors	\$145,943	to WBF, addtl. funds in remaining years
04/01/2016-03/31/2017	Carnegie		\$100,000	Coll. with Embryology Dep., Carnegie

[Achievements]

(1) International influence

a) Guest speaker, chair, director, or honorary member of a major international academic society in the subject field, b) Holder of a prestigious lectureship, c) Member of a scholarly academy in a major country, d) Recipient of an international award(s), e) Editor of an influential journal etc.

Wolf B. Frommer has delivered more than 100 invited lectures over the past 10 years at conferences, universities and companies worldwide. The following list are representative recent keynote, plenary, and invited lectures.

a) Guest Speaker (2015-2016)

- 04/16 EMBO Practical Course: *In Vivo* Plant Imaging, "The iterative 'evolution' of genetically encoded sensors". Heidelberg, Germany.
- 04/16 ZMBH, Heidelberg: "SWEET transporters – from bacteria to plants to humans, and from molecules to new technologies to applications" Heidelberg, Germany.
- 05/16 German Academy of Sciences: "Fluoreszierende Picosensoren als Spione in lebenden Zellen", Halle, Germany
- 05/16 University of Regensburg: "Transport of sugars: from classical physiology to atomic structures and application in medicine and agriculture"; Regensburg, Germany
- 06/16 XVII International Workshop on Plant Membrane Biology, Maryland. "Seeing what the plant sees" (Co-organizer)
- 07/16 ITbM, Nagoya University: "Visualizing nutrient and hormone transport", Nagoya, Japan
- 09/16 Max Planck Institut für Züchtungsforschung, Köln: "Sugar Translocation: from atomic structures to applications in the field"; Köln, Germany
- 09/16 CEPLAS, Heinrich Heine University Düsseldorf: "In vivo biochemistry - fluorescent biosensors for measuring metabolite dynamics and transporter activity", Düsseldorf, Germany
- 09/16 Max Planck Institut für Entwicklungsbiologie, Tübingen: "Sugar Translocation in crop plants: from atomic structures to biotech applications". Tübingen, Germany
- 09/16 UC San Diego, La Jolla, CA. "Sugar allocation – from the field to atomic structures and back"
- 03/15 Amgen, San Francisco. "In vivo biochemistry built on genetically encoded fluorescent sensors for ions, metabolites and protein activity"
- 04/15 University of California, Davis, CA. "Competing paths and interests - mapping steps in sugar translocation in plants."
- 05/15 3rd International Symposium on Transformative Bio-Molecules (ISTbM-3), Nagoya, Japan. "The next generation of fluorescent biosensors for monitoring enzyme/transporter activity in vivo."
- 06/15 The 5th PanAmerican Plant Membrane Biology Workshop, San Pedro de Atacama, Chile. "Measuring transporters in action with fluorescent activity reporters."
- 07/15 26th International Conference on Arabidopsis Research (ICAR), Paris, France. "The role of sugar transporters in carbon allocation."
- 09/15 University of Wisconsin-Madison, WI. "In vivo biophysics and biochemistry: Measuring transport in action"
- 09/15 Distinguished Lecturer. Boyce-Thompson Institute for Plant Research (BTI), Cornell University, Ithaca, NY. "In vivo biophysics and biochemistry: Measuring transport in action"

09/15 University San Francisco, CA. "Carbon allocation in plants - from molecules to the field".
 12/15 9th Mexico-USA Plant Biology Symposium, Cancun, Mexico. "Sugar allocation – from the field to atomic structures and back"

b) Holder of prestigious lectureships (since 2011)

12/15 9th Mexico-USA Plant Biology Symposium, Cancun, Mexico. "Sugar allocation – from the field to atomic structures and back" (Plenary Lecture)
 09/15 Distinguished Lecturer. Boyce-Thompson Institute for Plant Research (BTI), Cornell University, Ithaca, NY. "In vivo biophysics and biochemistry: Measuring transport in action"
 10/14 The 38th Naito Conference on "Molecule-based biological systems" Sapporo, Japan. "Novel approaches for visualization of transport processes in vivo." (Plenary Lecture)
 07/14 Introduction as Chair of the Cell Biology Session, 25th International Conference on Arabidopsis Research (ICAR), University of British Columbia, Vancouver, Canada. (Plenary Lecture)
 05/14 2014 Plant Protein Phosphorylation Symposium, University of Missouri, Columbia, MO. Keynote Speaker: "Watching biochemistry live".
 06/13 UMDF Mitochondrial Medicine, Newport Beach, CA. "Optical sensors and in vivo biochemistry." (Plenary Lecture)
 06/13 Arabidopsis Conference (ICAR), Sydney, Australia. "Biosensors for recording transporter and enzyme activities in plants." (Plenary Lecture)
 02/13 Pennsylvania State University, University Park, PA. Distinguished Lectures in Life Science, The Huck Institutes for the Life Sciences: "A multi-pronged approach to plant nutrition: pico-sensors for transport gene discovery and regulation."
 02/13 Michigan State University, MI. Nathan Edward Tolbert Lectureship in Plant Biochemistry: "In vivo biochemistry with the help of genetically encoded sensors."
 02/13 University of Illinois, Urbana, IL. Pioneers in Genomics Lecture: "A multi-pronged approach to plant nutrition: pico-sensors for transport gene discovery and regulation."
 03/13 International Workshop on Plant Membrane Biology (IWPMB2013), Kurashiki, Japan. "A multipronged approach for unraveling nutrient uptake and translocation." (Plenary Lecture)
 03/12 Japan Society for Bioscience, Biotechnology and Agrochemistry (JSBBA), Kyoto, Japan. "Raiding the SWEET shop – how pathogens gain access to the plants nutrient resources."
 11/12 Clayton Pearson Lecturer, University of British Columbia, Vancouver, Canada. "Molecular Diagnostics: Genetically encoded sensors for subcellular analysis of metabolite dynamics and transport activity in live cells."
 06/11 2th International Conference on Plant Metabolism, Qingdao, China. "Raiding the SWEET shop- how pathogens gain access to the plants nutrient resources." (Plenary Lecture)

c) Member of a scholarly academy in a major country

German National Academy of Sciences Leopoldina, 2015
 Faculty of 1000 Biology, Section Head, since 2001
 Max Planck Institute, Scientific Advisory Board member, 2003-2008
 North American Arabidopsis Steering Committee, Elected Member, 2009-2014
 American Association for the Advancement of Science (AAAS); Fellow

d) Recipient of an international award(s)

- Young Investigator Award; 1992-1996 (Nachwuchsgruppe am Genzentrum Berlin, Institut für Genbiologische Forschung)
- Gottfried-Wilhelm-Leibniz Award from Deutsche Forschungsgesellschaft; 1998, www.dfg.de/en/news/scientific_prizes/leibniz_preis/
- Körber Award for European Science; 2001, www.koerber-stiftung.de/
- Fellow of American Association for the Advancement of Science AAAS; 2003
- Laurence Bogorad Award for Excellence in Plant Biology, 2012 (American Society of Plant Biologists)

e) Editor of an influential journal

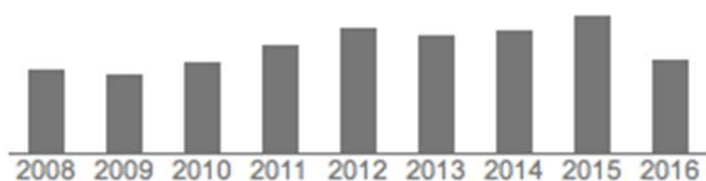
Advisory Board, The Plant Journal (1998-2003), Trends in Plant Science (1998-2002); Guest Editor: Curr. Opin. Plant Biotechnol., Annu. Rev. Plant Biol. (2003-2004); Co-Editor J. Plant Physiol. (1996-1998); Co-Editor The Plant Cell (1998-2006); Section Editor Plant Biology (2000-2003); Co-Editor J. Biol. Chem. (2004-2006); Editorial Board: Plant Methods (2004-2008); Editorial Board Annual Rev. Plant Biol. (2007-2012); Editorial Board

BMC Biol. (since 2009); Editor-in-Chief *Frontiers in Plant Physiology* (2009-2012); Guest Editor *Curr. Opin. Plant Biology* (2010). Editor-in-Chief *Frontiers in Plant Science* (2010-2012).

(2) Receipt of large-scale competitive fundings (over past 5 years)

(3) Article citations (Titles of major publications, and number of citations.)

Citation indices	All	Since 2011
Citations	22224	9623
h-index	87	55
i10-index	216	184



Over 275 publications and 40 patent applications; Personal Top 15 Profiled Publications

- Sosso D., Li Q.B., Luo D., Schläpfer J., Gendrot G., Suzuki M., Koch K.E., McCarty D.R., Ross-Ibarra J., Rogowsky P., Chourey P.S., Yang B. & **Frommer W.B.** (2015) Seed filling in domesticated maize depends on SWEET-mediated *trans*-epithelial hexose transport. *Nature Genet.* **47**, 1489-93 (PMID: 26523777)
- Tao Y., Li S., Xu Y., Lily S. Cheung L.S., Eom J.S., Chen L.Q., **Frommer W.B.** & Feng L. (2015) Structure of a eukaryotic seven transmembrane SWEET transporter in a homo-trimeric complex. *Nature* **527**, 259-63 (PMID: 26479032).
- Jones A.M., Xuan Y, Xu M., Wang R.S., Ho C.H., Lalonde S., You C.H., Sardi M.I., Parsa S.A., Smith-Valle E., Pilot G., Pratelli R., Grossmann G., Acharya B.R., Hu H.C., Engineer C., Villiers F., Takeda K., Assmann S.M., Chen J., Kwak J.M., Schroeder J.I., Albert R., Rhee S.Y. & **Frommer W.B.** (2014) Border control - a membrane-linked interactome of Arabidopsis. *Science* **344**, 711-16. (PMID: 24833385).
- Ho C.H & **Frommer W.B.** (2014) Fluorescent sensors for activity and regulation of the nitrate transceptor CHL1/NRT1.1 and oligopeptide transporters. *eLife* **3**, e01917. (DOI: 10.7554/eLife.01917; PMID: 24623305).
- Lin I W., Sosso D., Chen L.Q., Gase K., Kim S.G., Kessler D., Klinkenberg P., Qu X.Q., Hou B.H., Carter C., Baldwin I.T. & **Frommer W.B.** (2014) Nectar secretion requires sucrose phosphate synthases and the sugar transporter SWEET9. *Nature* **508**, 546-9. (PMID: 24670640).
- Chen L.Q., Qu X.Q., Hou B.H., Osorio S., Fernie A.R. & **Frommer W.B.** (2012) Sucrose efflux mediated by SWEET proteins as a key step for phloem transport. *Science* **335**, 207-211.
- Chen L.Q., Hou B.H., Lalonde S., Takanaga H., Hartung M., Qu X.Q., Guo W.J., Kim J.G., Underwood W., Chaudhuri B., Chermak D., Antony G., White F.F., Somerville S.C., Mudgett M.B. & **Frommer W.B.** (2010) Sugar transporters for intercellular exchange and nutrition of pathogens. *Nature* **468**, 527-32.
- Loqué D., Lalonde S., Looger L.L., von Wirén N. & **Frommer W.B.** (2007) A cytosolic trans-activation domain essential for ammonium uptake. *Nature* **446**, 195-98.
- Okumoto S., Looger L.L., Micheva K.D., Reimer R.J., Smith S.J & **Frommer W.B.** (2005) Detection of glutamate release from neurons by genetically encoded surface-displayed FRET nanosensors. *Proc. Natl. Acad. Sci. USA* **102**, 8740-45.
- Bürkle L., Cedzich A., Döpke C., Stransky H., Okumoto S., Gillissen B., Kühn C. & **Frommer W.B.** (2003) Transport of cytokinins mediated by purine transporters of the PUP family expressed in phloem, hydathodes and pollen of Arabidopsis. *Plant J.* **34**, 13-26.
- Kühn C., Franceschi V., Schulz A., Lemoine R. & **Frommer W.B.** (1997) Macromolecular trafficking indicated by localization and turnover of sucrose transporters in enucleate sieve elements. *Science* **275**, 1298-300.

12. Ninnemann O., Jauniaux J.C. & **Frommer W.B.** (1994) Identification of a high affinity ammonium transporter from plants. *EMBO J.* **13**, 3464-71.
13. Riesmeier J.W., Willmitzer L. & **Frommer W.B.** (1994) Evidence for an essential role of the sucrose transporter in phloem loading and assimilate partitioning. *EMBO J.* **13**, 1-7.
14. **Frommer W.B.**, Hummel S. & Riesmeier J.W. (1993) Expression cloning in yeast of a cDNA encoding a broad specificity amino-acid permease from *Arabidopsis thaliana*. *Proc. Natl. Acad. Sci. USA* **90**, 5944-48.
15. Riesmeier J.W., Willmitzer L. & **Frommer W.B.** (1992) Isolation and characterization of a sucrose carrier cDNA from spinach by functional expression in yeast. *EMBO J.* **11**, 4705-13.

(4) Others (Other achievements that indicate qualification as a top-caliber researcher, if any.)

009 Highly Cited Researcher, ISI

As PI, Wolf B Frommer has mentored over 70 postdoctoral fellows and many have gone on to hold current positions such as Director, Department of Physiology & Cell Biology, Leibniz-Institute for Plant Genetics and Crop Plant Research; Associate Dean and Professor, Department of Plant Biology, U. Minnesota, Prof. University Hohenheim (2); Prof. University Heidelberg; Prof, University College Station TX; Prof. Virginia Tech; Prof. University of Washington (2); CEO Direvo; etc.

Laboratory Research

Our laboratory studies metabolite transport and signaling. We deem transporters to be positioned at strategic control points and their regulation as critical for the coordination of metabolic processes in different tissues and organs of a multicellular organism (plant or animal). Metabolite levels are also used as critical information for the organism to coordinate physiological processes as best exemplified by glucose regulation of insulin secretion. In both plant and animal systems we have identified key transporters for small molecules such as sugars (glucose and sucrose), amino acids, peptides, ammonium, and nucleobases. We use these genes/proteins as tools to get at the regulatory processes that coordinate flux in the organism. To be able to monitor ion and metabolite dynamics, as well as the activity of proteins in vivo, we have developed a tool set, genetically encoded biosensors for in vivo biochemistry.

Microbial studies

We engineered yeast strains as a tool for suppression cloning of eukaryotic transporters. We developed genetically encoded fluorescent sensors and monitored sugar dynamics and fluxes in yeast cells. We systematically identified regulatory networks that control the preparedness of yeast cells to changes in glucose supply. We used sensors to identify a new class of sugar transporters, named SWEETs (SLC50), and showed that bacteria have similar transporters that function as dimers of a triple-helix bundle as demonstrated by crystallography (coll. Liang Feng, Stanford University).

Mammalian Studies

We developed sensors for glucose, lactate (coll. Felipe Barros), tryptophan and the neurotransmitter glutamate. We used the sensors to analyze processes such as glucose flux in cancer cells, the contribution of GLUT transporters to Arion's cycle, the potential role of amino acid exchangers in cancer, and the release of neurotransmitters from neurons. We currently study the role of the newly identified SWEETs (SLC50) sugar transporters in zebrafish, mouse and human systems. We have developed improved calcium sensors suitable for applications in a wide range of organisms. We pioneered the first transport activity sensors, for example for peptide transporters, a concept that can be expanded to mammalian transport proteins.

Plant Studies

We identified many of the key transporters for sugars, amino acids, ammonium and nucleobases. We could show that SUT sucrose proton cotransporters are essential elements of phloem loading and this assimilate allocation in a variety of plants. We pioneered the development of fluorescent sensors for metabolites including sugars, amino

acids, and hormones. Recently, we identified a new class of sugar transporters, the SWEETs, using FRET sensors expressed in human cells. We demonstrated that these transporters play essential roles in nectar secretion, in phloem loading, seed filling and importantly, pathogen susceptibility in crop plants. We have or are developing activity sensors for ammonium, nitrate, peptide, hormone and sugar transporters and have begun to implement these sensors for studying the regulation of transporters. We developed the split ubiquitin membrane interaction trap into a high throughput screening tool and systematically analyzed the interactions between membrane and signaling proteins as a means to get at the regulation of transporters.

World Premier International Research Center Initiative (WPI)

Appendix 3-1 FY2016 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

- Enter the total number of people in the columns below. In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [] brackets.
- In the "Administrative staffs" column, put the number and percentage of bilingual staffs in the () brackets.
- In the "Final Goal" column, enter the currently projected goal and the estimated date for achieving it [00 month, 00 year].

	Goal set in the "Post-interim evaluation revised center project"	Results at end of FY 2016	Final goal (Date: March, 2022)
Researchers	80 <27, 34%> [21, 26%]	72 <24, 33%> [20, 28%]	80 <27, 34%> [21, 26%]
Principal investigators	13 <6, 46%> [3, 23%]	13 <6, 46%> [3, 23%]	13 <6, 46%> [3, 23%]
Other researcher	67 <21, 31%> [18, 27%]	59 <18, 31%> [17, 29%]	67 <21, 31%> [18, 27%]
Research support staffs	50	47	50
Administrative staffs	13 (7, 54%)	13 (6, 46%)	12 (6, 50%)
Total	143	132	143

Other matters of 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 to mobilize/circulate the 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.

Prof. Stephen Irle, one of Non-Japanese Nagoya University PIs at the Institute transfers to Oak Ridge National Laboratory as of end-March, 2017 with a position title of Senior Research Leader. ITbM plans to seek a new PI to succeed to Prof. Irle's post.

Examples of researchers involved in the global brain circulation:

Position at ITbM	Period of project participation	Previous Affiliation (organization, *country)	Next Affiliation (Position title, organization, *country)
Research Fellow	11/1/2013 ~8/31/2016	Okayama University, Japan	Lecturer, Xi'an Jiaotong University, China
Research Fellow	9/1/2013 ~3/31/2017	Monash University, Australia	Assistant Professor, Gakushuin University, Japan
Research Fellow	4/1/2016 ~Present	Indian Institute of Science Education and Research, India	—
Research Fellow	4/1/2016 ~Present	Technische Universität München, Germany	—

Research Fellow	10/1/2016 ~Present	Institute of Pharmacy, Freie Universität Berlin, Germany	—
Research Fellow	1/1/2017 ~Present	Washington University School of Medicine, USA	—
Research Fellow	1/1/2017 ~Present	Indian Institute of Technology Tirupati, India	—
Research Fellow	1/16/2017 ~Present	The University of Manchester, UK	—

* The country in which the organization is physically located.

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
n/a		

< Partner institutions >

Institution name	Principal Investigator(s), if any	Notes
ETH Zurich	Jeffrey W. BODE	
Queen's University	Cathleen M. CRUDDEN	
University of Washington	Keiko TORII	
University of Southern California	Steve A. KAY	
Carnegie Institution for Science	Wolf B. FROMMER	From FY2016
NSF Center for Selective C-H Functionalization		
University of Freiburg		
RIKEN Center for Sustainable Resource Science (CSRS)		

2. Securing competitive research funding

Competitive and other research funding secured in FY2016

Total: 962,602,302 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.

<Major external funds>

- Name: Strategic Basic Research Programs (ERATO), JST
Total Amount: 220,960,000 JPY (Kenichiro Itami)
- Name: Strategic Basic Research Programs (ERATO), JST
Total Amount: 65,000,000 JPY (Tetsuya Higashiyama)
- Name: Grant-in-Aid for Scientific Research on Innovative Areas (Research in a proposed research area), JSPS
Total Amount: 171,730,000 JPY (Tetsuya Higashiyama)
- Name: Grant-in-Aid for Scientific Research on Innovative Areas (Research in a proposed research area), JSPS
Total Amount: 88,660,000 JPY (Toshinori Kinoshita)

3. International research conferences or symposiums held to bring world's leading researchers together

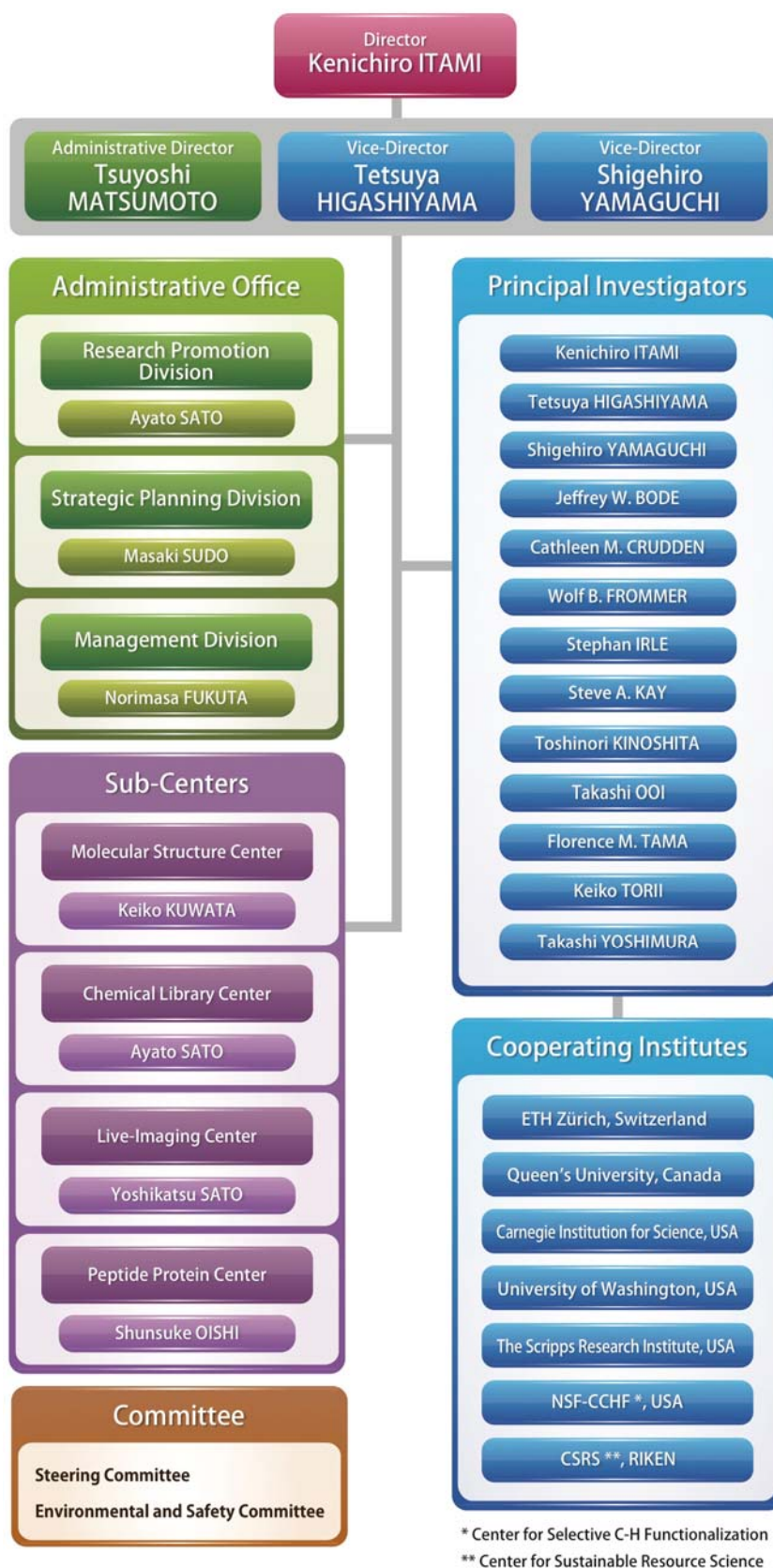
- Indicate the number of international research conferences or symposiums held in FY2016 and give up to three examples of the most representative ones using the table below.

FY 2016: 5 meetings	
Major examples (meeting titles and places held)	Number of participants
The 22nd Nagoya Medal of Organic Chemistry Noyori Conference Hall, Nagoya University January 27, 2017	From domestic institutions: 370 From overseas institutions: 3
The 4th International Symposium of Transformative Bio-Molecules (ISTbM-4), Hirata Award, Okazaki Award Noyori Conference Hall, Nagoya University December 12-13, 2016	From domestic institutions: 330 From overseas institutions: 13
2016 International C–H Functionalization Workshop ITbM, Nagoya University June 16-18, 2016	From domestic institutions: 39 From overseas institutions: 39

Other meetings: The 3rd CSRS-ITbM Joint Workshop, ITbM-IoC Joint Workshop

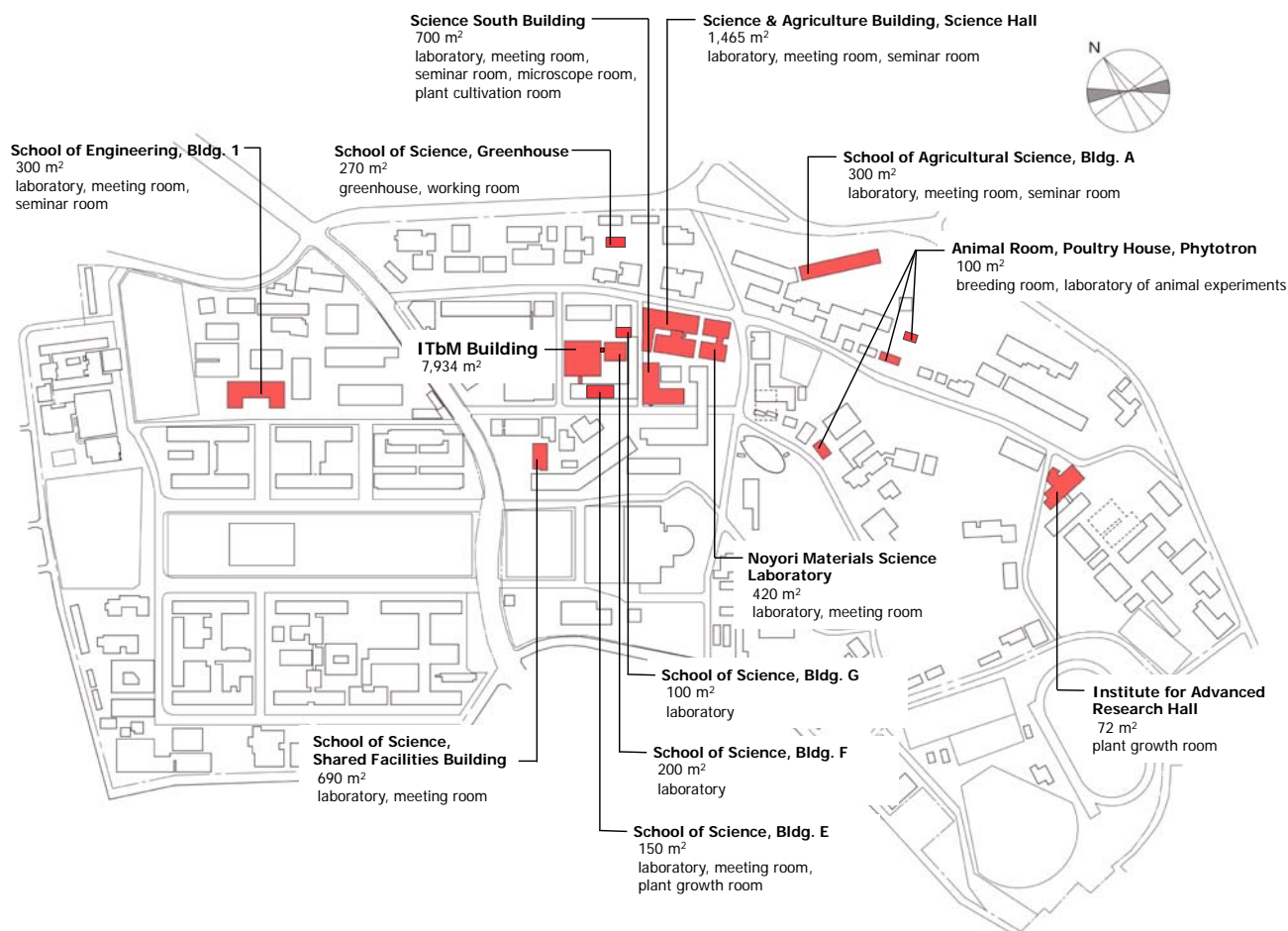
4. Center's management system

- Please diagram management system in an easily understood manner.
- If any changes have been made in the management system from that in the "Post-interim evaluation revised center project," please describe them. Please describe any changes made in the administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research)



5. Campus Map

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



The offices of the Center Director, All the PIs, and Administrative Department are located in the "ITbM Building"

World Premier International Research Center Initiative (WPI)

Appendix 3-2 6. Project Expenditures (the exchange rate used: 1USD= 100JPY)

1) Overall project funding

Cost Items	Details	Costs	WPI grant	Costs (Ten thousand dollars)
		(Ten thousand dollars)		
Personnel	Center director and Administrative director	32		
	Principal investigators (no. of persons):9	99		
	Other researchers (no. of persons):42	207		
	Research support staffs (no. of persons):23	44		
	Administrative staffs (no. of persons):25	75		
	Total	457		672
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0		
	Cost of dispatching scientists (no. of persons):9	11		
	Research startup cost (no. of persons):14	11		
	Cost of satellite organizations (no. of satellite organizations):0	0		
	Cost of international symposiums (no. of symposiums):7	1		
	Rental fees for facilities	23		
	Cost of consumables	13		
	Cost of utilities	48		
	Other costs	76		
	Total	183		
Travel	Domestic travel costs	2		
	Overseas travel costs	11		
	Travel and accommodations cost for invited scientists (no. of domestic scientists):13 (no. of overseas scientists):23	8		
	Travel cost for scientists on secondment (no. of domestic scientists):3 (no. of overseas scientists):5	4		
	Total	25		
Equipment	Depreciation of buildings	36		
	Depreciation of equipment	312		
	Total	348		
Other research projects	Projects supported by other government subsidies, etc.	227		
	Commissioned research projects, etc.	599		
	Grants-in-Aid for Scientific Research, etc.	377		
	Total	1203		
Total		2216		
			Cost of equipment procured	189
			Costs of establishing and maintaining facilities	0
			Name of equipment:Analytical System of Biomolecular Interactions	39
			Number of units: 1 Set	Costs paid
			Name of equipment:Ultra High-Speed Liquid Chromatograph System	12
			Number of units: 1 Set	Costs paid
			Name of equipment:Nano-Flow Liquid Chromatography-Fourier-Transform Mass Spectrometry System	50
			Number of units: 1 Set	Costs paid
			Name of equipment:Parallel Peptide Synthesis System	14
			Number of units: 1 Set	Costs paid:
			Name of equipment:Inverted Research Microscope	14
			Number of units: 1 Set	Costs paid:
			Name of equipment:Laser Scanning Modules	16
			Number of units: 1 Set	Costs paid:
			Name of equipment:STED laser	16
			Number of units: 1 Set	Costs paid:
			Others	28

2) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (Ten thousand dollars)
Personnel	Principal investigators (no. of persons):0	/
	Other researchers (no. of persons):0	
	Research support staffs (no. of persons):0	
	Administrative staffs (no. of persons):0	
	Total	
Project activities		
Travel		
Equipment		
Other research projects		
Total		0

Nagoya University -2

Institute of Transformative Bio-Molecules

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Appendix4 FY2016 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY2016 that were coauthored between the center's researcher(s) in domestic institution(s) 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. 2017 and not described in Appendix 1.

Overseas Satellite 1 (Total: OO papers)

- 1)
- 2)
- 3)
- 4)

Overseas Satellite 2 (Total: OO papers)

- 1)
- 2)
- 3)
- 4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY2016. 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:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016					

Overseas Satellite 2:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016					

World Premier International Research Center Initiative (WPI)
Appendix 5 FY 2016 Visit Records of World Top-caliber Researchers from Abroad

Researchers Total: 39

	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 symposia)
1	Cathleen Crudden	50	Principal Investigator, ITbM / Professor, Department of Chemistry, Queens University	Ph.D. Chemistry	<ul style="list-style-type: none"> The Aldrich Lecture Award Clara Benson Award, CSC Catalysis Lectureship Award, Catalysis Society 	1 month	<ul style="list-style-type: none"> participation as principal investigator
2	Keiko Torii	51	Principal Investigator, ITbM / Professor, Department of Biology, Washington University	Ph.D. Biochemistry	<ul style="list-style-type: none"> JSPS Prize SJWS Award Fellow, AAAS 	1 month	<ul style="list-style-type: none"> participation as principal investigator
3	Jeffrey W. Bode	43	Principal Investigator, ITbM / Professor, Department of Chemistry and Applied Bioscience, ETH Zurich	Dok. Nat. Sci.	<ul style="list-style-type: none"> E.J. Corey Award Novartis Lectureship Hirata Gold Award 	1 month	<ul style="list-style-type: none"> participation as principal investigator
4	Wolf B. Frommer	59	Director, Carnegie Institution	Dr. rer. Nat	<ul style="list-style-type: none"> Young Investigator Award, German Federal Ministry for Science and Technology (1992) Gottfried-Wilhelm-Leibniz Preis, German Research Foundation (DFG) (1998) European Science Award, Körber Foundation (2001) Fellow, American Association for the Advancement of Science (2003) Laurence Bogorad Award for Excellence in Plant Biology Research, American Society of Plant Biology (2012) Member, German Academy of Sciences, Leopoldina (2015) 	5 days	<ul style="list-style-type: none"> research discussion
5	Roald Hoffmann	79	Professor, Cornell University	Chemistry	<ul style="list-style-type: none"> Nobel Prize in Chemistry (1981) National Medal of Science (1983) ForMemRS (1984)[1] NAS Award in Chemical Sciences (1986) Priestley Medal (1990) Lomonosov Gold Medal (2011) 	3 days	<ul style="list-style-type: none"> lecture @ seminar research discussion
6	Chen, Yu-Ju	N/A	Director, Academia Sinica	Ph.D., Physical Chemistry	<ul style="list-style-type: none"> Young Chemists Award, The Chinese Chemical Society, 2006. Distinguished Young Chemist Award, Federation of Asian Chemical Societies, 2007. Junior Research Investigators Award, Academia Sinica, 2008. Ta-You Wu Memorial Award, National Science Council, 2008. Outstanding Scholar Award, Taiwan Society for Mass Spectrometry, 2012. Outstanding Research Award, National Science Council, 2012. 	3 days	<ul style="list-style-type: none"> participation in 2016 ITbM-IoC Joint Workshop on Biomolecules and Materials
7	Sun, Shih-Sheng	N/A	Deputy Director, Academia Sinica	Ph.D., Chemistry	<ul style="list-style-type: none"> ACS Zappert Award, 2002 K. Keith Innes Summer Research Award, 2001 Graduate Student Award for Excellence in Research, State University of New York at Binghamton, Binghamton, New York, 2001 Outstanding Research Assistant Award, Department of Chemistry, State University of New York at Binghamton, Binghamton, New York, 2001 Ministry of Education Fellowship, Taiwan, 1989-1991 Mr. Chung-Ya Wu Foundation Scholarship, National Cheng Kung University, Tainan, Taiwan, Fall, 1988 	3 days	<ul style="list-style-type: none"> participation in 2016 ITbM-IoC Joint Workshop on Biomolecules and Materials
8	Cyril Zipfel	N/A	Professor, The Sainsbury Laboratory	Plant immunity, signaling, receptor kinases	<ul style="list-style-type: none"> The Charles Albert Shull Award (2015) 	2 days	<ul style="list-style-type: none"> lecture @ ITbM seminar
9	Peter Mccourt	59	Professor, University of Toronto	Biotechnology, Genetics, Molecular Biology	<ul style="list-style-type: none"> Silver medal winner, International Plant Growth Substance Association (2013) University of Toronto, Inventors of the year (2012) Canada Research Chair in Plant Molecular Biology (2004 – present) NSERC-Industrial Chair in Plant Biotechnology (2000-2010) 	9 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
10	Randall Peterson	45	Associate Professor, Harvard Medical School	Systems Biology	<ul style="list-style-type: none"> NIH EUREKA award (2009) Nature Biotechnology SciCafe Award (2010) Sanders MGH Research Scholar (2011) Charles Addison and Elizabeth Ann Sanders Endowed Chair (2014) 	7 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
11	Kendall Houk	74	Professor, University of California, Los Angeles	Organic Chemistry	<ul style="list-style-type: none"> Fellow, American Chemical Society (2009); Arthur C. Cope Award, American Chemical Society (2009) Member, National Academy of Sciences (2010) Robert Robinson Award of the Royal Society of Chemistry (2012) Fellow of the Royal Society of Chemistry (2012) UCLA Society of Postdoctoral Scholars Mentoring Award (2013) UCLA Glenn T. Seaborg Medal (2013) Honorary Professor, University of Queensland, Brisbane, 	6 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
12	Hagan Bayley	66	Professor, University of Oxford	Chemical Biology	<ul style="list-style-type: none"> 2010: British Biophysical Society 50th Anniversary Lecture 2011: Fellow of the Royal Society of Biology; Edward Teller Distinguished Lecture Series, University of California Davis; Fellow of the Royal Society; William E Mahoney Seminar, University of Massachusetts Amherst 2012: Fellow of the Learned Society of Wales; Royal Society of Chemistry Interdisciplinary Prize; Honorary Member of the British Biophysical Society 2013: Honorary Fellow of Balliol College 2014: UK's 100 leading practising scientists 2016: The Menelaus Medal of the Learned Society of Wales. 	9 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
13	Marina Kuimova	37	Associate Professor, Imperial College London	Chemical Physics	<ul style="list-style-type: none"> The IUPAP C6 Young Scientist Prize in Biological Physics (2014); ChemComm Emerging Investigator Lectureship (2013) RSC Harrison-Meldola Prize (2012) British Biophysical Society Young Investigator Award (2012) Grammaticakis-Neumann Prize of the Swiss Chemical Society (2011) EPSRC Career Acceleration Fellowship (2010) SET for Britain Roscoe and Westminster Medals, UK Parliament (2009) EPSRC Life Science Interface Fellowship (2007) 	5 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)

14	Yukiko Yamashita	45	Associate Professor, University of Michigan	Developmental Biology	<ul style="list-style-type: none"> Searle Scholar (2008) Women In Cell Biology, Junior Career Recognition Award, American Society for Cell Biology (2009) MacArthur Fellow (2011) University of Michigan, Basic Science Research Award (2013) Rackham Graduate School Faculty Recognition Award (2016) 	9 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
15	Emily Balskus	37	Associate Professor, Harvard University	Chemical Biology	<ul style="list-style-type: none"> HIMI-Gates Faculty Scholar (2016) Chemical and Engineering News Talented Twelve (2015) Camille Dreyfus Teacher-Scholar Award (2015) NSF CAREER Award (2015) MIT Technology Review Innovator Under 35 (2014) Damon Runyon-Rachleff Innovation Award (2014) Packard Fellowship for Science and Engineering (2013) NIH Director's New Innovator Award (2012) 	10 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
16	Scott J. Miller	50	Professor, Yale University	Ph.D. in Chemistry	<ul style="list-style-type: none"> Yoshimasa Hirata Memorial Gold Medal of Nagoya University (2009) National Institutes of Health MERIT Award (2011) Fellow of the American Association for the Advancement of Science (2012) American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (2016) Member, American Academy of Arts and Sciences (2016) 	5 days	<ul style="list-style-type: none"> Invited lecturer @ 4th International Symposium on Transformative Bio-Molecules (ISTbM-4)
17	Stephen Buchwald	61	Professor, Massachusetts Institute of Technology	Chemistry	<ul style="list-style-type: none"> Honorary Doctorate (University of South Florida, 2015) BBVA Frontiers in Knowledge Award in Basic Sciences (2014) Linus Pauling Award (2014) Ulysses Medal (University College Dublin, 2014) Arthur C. Cope Award (2013) Gustavus J. Esselen Award for Chemistry in the Public Interest (2010) Siegfried Medal Award in Chemical Methods which Impact Process Chemistry (2006) American Chemical Society's Award for Creative Work in Synthetic Organic Chemistry (2006) CAS Science Spotlight Award (2005) Bristol-Myers Squibb Distinguished Achievement Award (2005) 	5 days	<ul style="list-style-type: none"> Invited lecturer @ 22nd Nagoya Medal of Organic Chemistry
18	Erker Gerhard	70	Professor, The University of Munster	Organic Chemistry	<ul style="list-style-type: none"> Japan Society for the Promotion of Science (JSPS) Invitation Fellowship Award, Japan 2005 Eugen und Ilse Seibold-Prize 2011 ERC Advanced Grant 2011 Elhuyar-Goldschmidt Award of the Real Sociedad Espanola de Quimica 2013 Member of the Senate of the National Academy of Sciences Leopoldina 2015 - present Honorary Member Chemical Society of Japan 2017 - present 	4 days	<ul style="list-style-type: none"> lecture @ ITbM seminar research discussion
19	Michael M. Haley	N/A	Professor, University of Oregon	Ph.D. Chemistry	<ul style="list-style-type: none"> American Chemical Society, Division of Organic Chemistry Fellowship, 1990-91 NSF Postdoctoral Fellowship, 1991-93 NSF CAREER Award, 1995-1998 US-Israel BSF Ernst D. Bergmann Memorial Award, 1997 Richard A. Bray Faculty Fellow, 1998 	4 days	<ul style="list-style-type: none"> lecture @ ITbM seminar research discussion
20	Li Deng	N/A	Orrie Friedman Distinguished Professor of Chemistry, Brandeis University	Ph.D. Chemistry	<ul style="list-style-type: none"> Chan Memorial Award in Organic Chemistry, 2008 Japan Society for the Promotion of Science (JSPS) Fellow, 2007 Negishi-Brown Distinguished Lectureship, 2007 	3 days	<ul style="list-style-type: none"> lecture @ seminar research discussion
21	Géraldine Masson	N/A	Professor, Institut de Chimie des Substances Naturelles, ICSN	Ph.D. Chemistry	<ul style="list-style-type: none"> Liebig Lectureship of the German Chemical Society Japan Society for Promotion of Science (JSPS) Fellowship Médaille de Bronze du CNRS Prix DIVERCHIM de la DCO Bourse Marie-Curie 	2 days	<ul style="list-style-type: none"> lecture @ seminar
22	Johanna Meijer	58	Professor, Leiden University	Chronobiology	<ul style="list-style-type: none"> 2013-present Visiting professorship Oxford University 2014-present: Member of the Koninklijke Hollandse Maatschappij der Wetenschappen (Royal Dutch Society of Sciences) 2014 Highlight in the journals Nature and Science: Meijer and Robbers, Proc Royal Acad Science 2015 Ariens Kappers Lecture at the European Biological Rhythms Society, Manchester 2016: Aschoff and Honma Prize in Biological Rhythm Research (International Selection Committee, chaired by Dr. Takao Kondo) 	1 day	<ul style="list-style-type: none"> lecture @ symposium
23	Carl Johnson	N/A	Professor, Department of Biological Sciences, Vanderbilt University	Chronobiology	<ul style="list-style-type: none"> President of the Society for Research on Biological Rhythms (2012-2014) Chancellor's Research Award, Vanderbilt University (2005) Aschoff and Honma Prize in Biological Rhythms Research (2014) Secretary and Treasurer, Society for Research on Biological Rhythms Phi Beta Kappa Society 	5 days	<ul style="list-style-type: none"> lecture @ symposium research discussion
24	John O'Neil	N/A	Group leader, Medical Research Council, Laboratory of Molecular	Chronobiology	N/A	1 day	<ul style="list-style-type: none"> lecture @ seminar research discussion
25	Achim Kramer	N/A	Professor, Charité – University Medicine Berlin	Chronobiology	N/A	3 days	<ul style="list-style-type: none"> lecture @ seminar research discussion
26	Ueli Schibler	69	Professor, University of Geneva	Chronobiology	N/A	4 days	<ul style="list-style-type: none"> lecture @ seminar research discussion
27	Mario Guido	55	Professor, the National University of Córdoba	Chronobiology	N/A	3 days	<ul style="list-style-type: none"> research discussion
28	Enrico Martinola	N/A	Professor, University of Zurich	Molecular Plant Physiology	<ul style="list-style-type: none"> 1983 Humboldt fellowship 1998 Award for foreign specialists, Japanese Ministry of Forestry and Agriculture 2001 Körber Preis for European Science 2001, together with Prof. W. Frommer, Prof. R.Hedrich, Prof. D. Sanders and Prof. N. Sauer 2003 Election to the "Deutsche Akademie der Naturforscher Leopoldina" 2010-2012 Distinguished Visiting Professor, Postech University, Pohang, South Korea 2011 Cozzarelli Prize of the the National Academy of Sciences of the USA 	1 day	<ul style="list-style-type: none"> research discussion
29	Yiyong Zhu	43	Professor, Nanjing Agricultural University	PhD, Agriculture	N/A	20 days	<ul style="list-style-type: none"> research discussion

30	Grossniklaus Ueli	53	Professor, Institute of Plant Biology, University of Zürich	PhD in Drosophila developmental biology	<ul style="list-style-type: none"> • 1995-1996 Human Frontiers of Science Program Fellowship • 1997 Scholarship of the "Janggen-Poehn-Stiftung" • 1998 Demerec-Kaufmann-Holländer Fellowship in Developmental Genetics • 1998-2002 Searle Scholarship (http://www.searlescholars.net) • 2007 Elected as Member of the European Molecular Biology Organization (EMBO) 	1 day	<ul style="list-style-type: none"> • lecture @ seminar
31	Jose F. Gutierrez-Marcos	N/A	Associate Professor, University of Warwick	PhD Genetics	<ul style="list-style-type: none"> • 2002, 2004, 2006 Research Merit Award, University of Oxford • 2011, Teaching Excellence Award, University of Warwick • 2016, Research Merit Award, University of Warwick 	11 days	<ul style="list-style-type: none"> • lecture @ seminar • research discussion
32	Simon Blakey	N/A	Associate Professor, Department of Chemistry, Emory University	PhD, Chemistry	<ul style="list-style-type: none"> • Phi Beta Kappa, Recognition for Excellence in Teaching and Mentorship (2010) • NSF Career Award (2009) • Thieme Synlett/Synthesis Journal Award (2009) • Lilly New Faculty Award (2005) • Commonwealth Scholarship to the University of Cambridge (2001) • Trinity College External Research Scholarship (2001) 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
33	Huw Davies	60	Asa Griggs Candler Professor/Director of Graduate Studies, Department of Chemistry, Emory University	PhD, Chemistry	<ul style="list-style-type: none"> • American Chemical Society Cope Scholar Award (2005) • Fellow of the Royal Society of Chemistry (2007) • Fellow of the American Chemical Society (2009) • Fellow of the American Association for the Advancement of Science (2013) • eEROS Reagent of the Year Award (2013) • Fellow of the National Academy of Inventors (2015) 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
34	Christine Luscombe	N/A	Adjunct Associate Professor of the Department of Chemistry, University of Washington	PhD, Chemistry	<ul style="list-style-type: none"> • Fellow of the Royal Society of Chemistry, 2016 • Editorial Advisory Board Member, Journal of Applied Physics, 2016 • Chemistry of Materials Reviewer Award, 2015 • Robert J. Campbell Associate Professor, 2015 • Finalist, Clean Energy Education & Empowerment (C3E Award), 2015 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
35	Cora MacBeth	N/A	Assistant Dean for Sciences, Emory University	PhD, Chemistry	N/A	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
36	John Montgomery	N/A	Professor of Chemistry, University of Michigan	Chemistry	<ul style="list-style-type: none"> • Fellow of the American Association for the Advancement of Science (AAAS) 2011 • Pfizer Michigan Green Chemistry Award, 2007 • ACS Arthur C. Cope Scholar Award, 2001 • Johnson and Johnson Focused Giving Grant, 2001 • Camille Dreyfus Teacher Scholar Award, 1998 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
37	Jamal Musaev	N/A	Principal Scientist and Director of the Emerson Center, Emory University	Ph.D., Quantum Chemistry	<ul style="list-style-type: none"> • Visiting Professor award from the European Committee: Universitat de les Illes Balears, Palma de Mallorca, Spain, (Oct. 2007) • Visiting Professor award of the University of Tokyo, Tokyo, Japan (2002-2003) • Japan Society for Promotion of Science (JSPS) Fellowship (1991-1993) • Azerbaijan Republic Fellowship for Promotion of Science (1978-1981) 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
38	Mu-Hyun Baik	N/A	Professor, Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST)	Inorganic / Organometallic / Computational Chemistry	<ul style="list-style-type: none"> • 2013, Scialog Innovation Award (Research Corporation) • 2010, Scialog Fellow Award (Research Corporation) • 2009, Kavli Fellow Award (National Academy of Sciences USA & Kavli Foundation) • 2007, Alfred P. Sloan Fellow, Alfred P. Sloan Foundation • 2007, NSF-CAREER Award, National Science Foundation USA 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop
39	Sung-Woo Hong	N/A	IBS-KAIST	Organic, Medicinal Chemistry	<ul style="list-style-type: none"> • Marquis Who's Who in the World (2013) • Asian Core Program (ACP) • Lectureship Award, Taiwan & Malaysia (2013) • Young Organic Chemist Award, Div. of Organic Chemistry, KCS (2012) • Thieme Chemistry Journal Award, Thieme Publishers (2012) 	4 days	<ul style="list-style-type: none"> • participation in 2016 International C-H Functionalization Workshop

World Premier International Research Center Initiative (WPI) Appendix 6 FY2016 State of Outreach Activities

Using the table below, show the achievements of the Center's outreach activities in FY2016(number of activities, times held).

※Describe those activities that have yielded novel results or that warrant special mention in the "Special Achievements" space below.

※In appendix 7, list and describe media coverage (e.g., articles published, programs aired) in FY2016 resulting from press releases and

Activities	FY2016(number of activities, times held)
PR brochure, pamphlet	5: ITbM A4 Pamphlet, ITbM B4 Pamphlet, ITbM Mid-term Booklet (Press releases), Asia Research News 2017 (ITbM Research), NU Topics, NU Research
Lectures, seminars for general public	G7 Ibaraki Tsukuba Symposium (Itami), Yomiuri Science-Technology Forum (Itami), Nagase Prize Lecture (Itami), WPI 10th Anniversary Symposium (Itami), Plant Science Symposium (Higashiyama), NHK Taiga Seminar (Yoshimura), Student Visitors from Harbin Institute of Technology and Dailian University of Technology
Teaching, experiments, training for elementary, secondary and high school students	Meiwa High School (Irlle), NU High School (Higashiyama), Hamamatsu City High School, Bard High School, Zuiryo High School (Yoshimura), Kariya High School (Ichinose), International Summer School (Italy, Bode), Fujishima High School (Taki, Itami)
Science café	NU School of Science Fresher's Science Café, Meidai Café (Notaguchi)
Open houses	School of Science Alumni, NU Co-op, NU Homecoming Day, NU Festival
Participating, exhibiting in events	NU Fresher's Training, Chemistry Gran-Prix, Aeon Science Event, Super Science High School Event, BioJapan, Science Agora, AAAS Annual Meeting
Press releases	11 Press releases (Higashiyama, Itami, Uchida, Kasahara, Ueda, Ooi, Kinoshita) 6 Press conferences (Higashiyama, Uchida, Kasahara, Ueda, Ooi)

<Special Achievements>

11 International Press releases

Established New Chemical Outreach Program on "Antibiotic Kits for All", will begin work with high school students in 20

**World Premier International Research Center Initiative (WPI)
Appendix 7 FY 2016 List of Project's Media Coverage**

	Date	Types of Media (e.g., newspaper, television)	Description
1	Apr 3, 2016	Newspaper	Prof. Kenichiro Itami's interview featured in Asahi Shimbun.
	Apr 6, Jun 29, 2016	Web (International: 2)	Dr. Norihito Nakamichi and Prof. Toshinori Kinoshita research on the plant circadian rhythm, published in the Plant Cell. Featured in Global Plant Council and Crop Biotech website.
	Apr 8 – Jun 9, 2016	Newspaper (4), Web (Domestic: 21, International: 34)	Prof. Tetsuya Higashiyama's research on the discovery of AMOR, a sugar chain molecule that increases the fertilization efficiency in plants, published in Current Biology. Featured in Asahi, Chunichi, Kagaku, Nikkei Shimbun, Kyodo News, JST Science Portal, and Chinese Media.
	Apr 11 – Jun 1, 2016	Magazine (1), Web (Domestic: 1)	Prof. Tetsuya Higashiyama's research on the discovery of a receptor in pollen tubes that is required to detect a LURE peptide for fertilization in plants, published in Nature. Featured in Newton magazine and Life Science Reviews website.
2	Apr 11, 2016	TV	Prof. Takashi Yoshimura's research on rooster crow, published in Scientific Reports. Featured in NHK News.
	Apr 12, 2016	Web (International: 1)	Dr. Daisuke Maruyama and Prof. Tetsuya Higashiyama's research on plant cell fusion, published in Cell. Featured in Phys.Org.
3	May 13 – Aug 18, 2016	Newspaper (1), Web (Domestic: 1, International: 1), Magazine (1)	Drs. Yuichiro Tsuchiya and Shinya Hagihara's research on the parasitic plant, Striga, published in Science. Featured in Kagaku Kogyo Nippo, Scientific Research on Innovative Areas, a MEXT Grant-in Aid Project FY2015-2019 website, Monthly Kagaku magazine, Nature Chemical Biology.
4	May 23 – Nov 12, 2016	Web (Domestic: 70)	Profs. Kenichiro Itami and Takashi Yoshimura's research on the biological rhythm, published in Angewandte Chemie. Featured in Huffington Post, MSN, Fox News, UK, Canadian, Indian and Dutch Media.
5	May 26, 2016	Newspaper	Prof. Kenichiro Itami's lecture at the Yomiuri Techno Forum featured in Yomiuri Shimbun.
6	Jun 1, 2016	Magazine	Prof. Keiko Torii's research on plant peptides featured in Monthly Kagaku magazine.
7	Aug 5, 2016	Newspaper	Prof. Tetsuya Higashiyama's initiation of his new research project featured in Kagaku Shimbun.
	Aug 8 – 30, 2016	Newspaper (3), Web (Domestic: 25, International: 40)	Prof. Kenichiro Itami's research on the synthesis of organic nanotubes, published in the Journal of the American Chemical Society. Featured in Nikkei Sangyo, Chunichi, Kagaku Shimbun, Yahoo News, Mynavi News, Brazilian, Russian, Chinese, Spanish Media.
	Aug 9 – Oct 11, 2016	Web (Domestic: 8, International: 35)	Prof. Kenichiro Itami's research on the synthesis of semiconductors, published in the Journal of the American Chemical Society. Featured in Nikkei Technology, EETimes, ChemEurope.
	Aug 16, 2016	Web (International: 1)	Prof. Kenichiro Itami's research on benzene featured in ACS Central Science.
	Sep 2 – 29, 2016	Newspaper (3), Magazine (1), Web (Domestic: 50, International: 21)	Drs. Toshiaki Tameshige and Naoyuki Uchida, and Prof. Keiko Torii's research on the zig-zag of leaves, published in Current Biology. Featured in Chunichi, Nikkei, Kagaku Shimbun, Kodomono Kagaku magazine, Kyodo News, Indian Media.
8	Sep 12, 13, 2016	Web (International: 2)	Prof. Cathleen Crudden's research on gold carbenes, published in Nature Communications. Featured in Phys.Org.
8	Sep 30, 2016	Newspaper	Prof. Kenichiro Itami's research group featured in Chunichi Shimbun.
9	Oct 2, 2016	Newspaper	Prof. Tetsuya Higashiyama's interview featured in Asahi Shimbun.
	Oct 8, 15, 2016	Newspaper	Prof. Kenichiro Itami's comment regarding the Nobel Prize in Chemistry and Nagoya Medal featured in Chunichi Shimbun.
	Oct 20 – 28, 2016	Newspaper (3), Magazine (1)	Dr. Keiko Kuwata's collaborative research featured in Nikkei Sangyo, Kagaku Shimbun, Kagaku Kogyo Nippo, Nikkei Biotech magazine
	Oct 24, 25, 2016	Newspaper (1), Web (International: 1)	Nagoya Medal (hosted by ITbM) featured in Japan Times.
	Oct 27, 2016 – Jan 1, 2017	Newspaper (4), Magazine (2), Web (Domestic: 4, International: 12)	Dr. Ryushiro Kasahara and Prof. Tetsuya Higashiyama's research on the fertilization of plants, published in Scientific Reports. Featured in Chunichi, Nikkan Kogyo, Kagaku Shimbun, Kagaku Kogyo Nippo, Newton magazine, Asian Scientist.
	Nov 11, 2016	Magazine	Prof. Kenichiro Itami's winning of the Nagase Award featured in Toshin Times.
	Nov 11 – 25, 2016	Newspaper (4), Web (Domestic: 1, International: 12)	Prof. Takashi Ooi's research on synthetic chemistry, published in Chem. Featured in Chunichi, Nikkei Sangyo, Nikkan Kogyo, Kagaku Shimbun, Chem Europe.
	Nov 7, 2016	Magazine (1), Web (International: 1)	Prof. Kenichiro Itami's research on synthetic chemistry featured in ACS Chemistry & Engineering (C&EN) News.
	Nov 21 – Dec 12, 2016	Newspaper (1), Magazine (1), Web (Domestic: 2, International: 52)	Prof. Tetsuya Higashiyama's research on genetic engineering, published in Plant and Cell Physiology. Featured in Nikkei Sangyo Shimbun, Nikkei Biotech, Chinese Media.
	Nov 22 – Dec 19, 2016	Newspaper (4), Web (Domestic: 13, International: 15)	Dr. Minako Ueda and Prof. Tetsuya Higashiyama's research on plant cell division, published in PNAS. Featured in Asahi, Chunichi, Nikkei Sangyo, Mainichi Shimbun, Kyodo News, Global Plant Council.
	Nov 25, 2016	Web (International: 12)	Drs. Minako Ueda, Masakazu Nambu and Keiko Kuwata's research on cell division, published in Plant Cell Physiology. Featured in Phys.Org and Breaking News.
	Dec 1, 2016	Magazine	Prof. Kenichiro Itami's research on synthetic chemistry featured in Synfacts.
	Dec 4, 2016, Jan 3, 5, 7, Mar 25, 2017	Newspaper (5)	Prof. Takashi Yoshimura's research on roosters featured in Chunichi, Nikkei, Yomiuri KODOMO Shimbun.
	Feb 22, 2017	Newspaper	ITbM featured in Nikkei Shimbun.
10	Mar 17, 23, 2017	Newspaper (2)	Prof. Kenichiro Itami's winning of the Yomiuri Techno Gold Medal featured in Yomiuri Shimbun.