World Premier International Research Center Initiative (WPI)
Executive Summary（Interim Evaluation）

Host Institution	Nagoya University	Host Institution Head	Seiichi Matsuo
Research Center	Institute of Transformative Bio-Molecules (ITbM)	Center Director	Kenichiro Itami

*Summarize the Self-Evaluation Report for Interim Evaluation (**within 4 pages** including this page).

1. Summary of State of WPI Center Project Progress

ITbM was launched as a unique research center to develop “transformative bio-molecules” that make a marked change in the form and nature of biological science and technology. Many interdisciplinary research projects have been launching rapidly in the “Mix Lab”, and a number of new bio-functional molecules and molecular technologies have been developed. Many of the research outcomes have been filed for patents and published as joint publications between different research groups. According to the research progress, ITbM has defined its flagships as “Plant Chemical Biology”, “Chemical Chronobiology”, and “Chemistry-enabled Live Imaging”.

The Center’s remarkable activity has been supported by the Administrative Department. In addition to Management Division and the Research Promotion Division (RPD), the Strategic Planning Division (SPD) will be newly established in April 2016, playing a key role in realization of ITbM’s research outcomes by working out strategies for the acquisition of IP rights and business matching with companies.

As an international institute, the Administrative Department has been organized to support foreign researchers. ITbM enrolls 4 overseas PIs, 1 full-time foreign PI at NU, and many foreign postdoctoral researchers. In April 2016, another full-time female foreign PI (Florence Tama) will be enrolled.

Exchange of young faculties and students between ITbM and the host institutes of the overseas PIs or the international partner institutions have been leading to ITbM’s internationalization.

ITbM’s annual international symposia and international awards are also contributing to increase ITbM’s international visibility.

ITbM’s challenges are contributing to the system reform of NU. NU established a new department through organizational reform to promote efficient use of IPs and research outcomes. NU also launched a venture fund. Establishment of these systems strongly supports ITbM’s activity.

2. Center’s Research Activities

Molecule-initiated biology (chemical biology) to create transformative bio-molecules has made remarkable progress, and is currently shifting to the next phase, i.e., understanding and controlling biological processes by utilizing the molecules developed at ITbM.

At such a turning point, ITbM has defined the following flagship research areas based on the Center’s research achievements so far along with its future perspectives: **Plant chemical biology**, **Chemical chronobiology**, and **Chemistry-enabled live imaging**. ITbM will focus on these flagship research areas 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, to lead to the creation of transformative bio-molecules.

[1] Molecular control of plant growth: Novel functional molecules that control plant growth and differentiation based on direct chemical transformation of the plant hormones have been developed. Molecules modulating stomatal opening/closure have also been discovered, i.e., modulate the number and density of stomata, accelerate stomatal opening/closure, and restrict stomatal dynamics reversibly.

[2] Molecular control of plant reproduction: ITbM has succeeded in discovering several key biomolecules (LURE, AMOR, and CALL1) that control plant reproduction and identifying the corresponding receptors (*Nature*). The detailed mechanism of plant reproduction (*Cell*) has also been disclosed at a molecular level in order to control the designed hybridization by molecules.

[3] Molecular control of animal/plant biological clock: A number of potent molecules controlling the animal/plant biological clocks have been discovered. Based on the identification of the target

proteins, X-ray crystal structures, and evaluation of biological functions, some of the discovered molecules are under further investigation with a pharmaceutical company. Researchers have also demonstrated that modulation of the plant biological clock by molecules may lead to the development of an optimized variety of crops.

[4] Molecular control of *Striga*: ITbM has succeeded in developing a fluorescent probe molecule "Yoshimulactone" (YLG) that enables disclosure on the mechanism of germination and elongation of the *Striga* parasite that causes huge damage on crop production in Africa (*Science*). Researchers have also identified strigolactone receptors in *Striga* by the use of YLG. YLG became available on the market at the beginning of 2016. In addition, molecules that induce or inhibit *Striga* germination have been developed.

[5] Imaging molecules: ITbM has developed molecules that exhibit exceptionally high resistance to photobleaching that can accelerate cutting-edge and super-resolution bio-imaging such as STED microscopy. Researchers have also developed molecules that exhibit high responsive property to environment polarity and have discovered near infrared emissive phospha-fluoresceins. These super high performance molecules may serve a significant role in leading the bio-imaging field.

[6] Catalysis and rapid molecule synthesis: ITbM has established epoch-making synthetic methodologies that allow rapid synthesis and modification of biologically active molecules. These include next-generation cross-coupling catalysts, C-H coupling catalysts, asymmetric reactions, and rapid peptide/protein synthesis. These synthesis technologies have been applied to ITbM's interdisciplinary research, and towards developing candidate molecules for medicines and agrochemicals.

ITbM has been conducting national/international joint research projects. The **Center for Sustainable Resource Science (CSRS) at RIKEN** is a national partner of ITbM. The collaborative research outcome on the improvement of plant biomass by modifying the plant biological clock was published as a joint paper. An international collaboration with **Freiburg University, Germany** has recently started. The joint program titled "Multicomponent Supramolecular Catalysts for Sustainable Chemical Synthesis" has been organized by Ooi and Itami of ITbM and Prof. Breit of Freiburg University, where they work together towards the development of new catalysts according to the new concept of organic synthesis. The **National Science Foundation Center for Selective C-H Functionalization (NSF-CCHF), USA**, which consists of top leading synthetic chemists in USA and giant firms of pharmaceuticals and agrochemicals, is also an important international partner of ITbM. So far, three joint papers have been published in top journals (*Nature Commun., JACS*).

ITbM researchers are being widely recognized by the international science community and society. This is evident by the significant number of prestigious international awards and honors as well as invitations to major international symposia that have been granted to ITbM's PIs. All of the PIs serve as editorial boards of major scientific journals.

ITbM's researchers have been constantly obtaining competitive funding. Overseas PIs have also been successful in obtaining KAKENHI (Grant-in-Aid for Scientific Research) from FY2014.

The numbers of IP filings and technological transfers have significantly increased over the years. ITbM has filed 39 national patent applications including 11 PCT and 3 US applications. In addition, ITbM has filed 7 national patent applications derived from ITbM's interdisciplinary research between chemistry and biology.

ITbM has concluded 15 license contracts to date. So far, 5 molecules/catalysts developed at ITbM became commercially available through the technology transfers.

ITbM's plant biology research by Higashiyama and his co-worker was adopted in the program for Creating Start-up from Advanced Research and Technology from JST (START program) and this will accelerate the start-up for the venture company in 2018.

Summary of 2012.11~2016.3 (papers: 2012.11~2015.12)
Papers: 385 (IF>10: 103, IF>7: 160, Hot papers (top 0.1%): 2, Highly cited papers (top 1%): 22)
Patent files: 39 (including 7 cases that were co-filed among several PI groups)
Technology transfers: 14 compounds (including commercialization of 5 molecules/catalysts)
Awards and honors: 49
Research grants: Over 20 projects including 2 JST-ERATO. Overseas PIs also received KAKENHI.

3. Interdisciplinary Research Activities

Mix Labs and Mix Offices that merges various departments and lab groups play a key role for interdisciplinary research at ITbM. Researchers and students from different fields share the same space and discuss on a daily basis. Over 30 new interdisciplinary research projects have been generated across 11 research groups and 4 centers, and have resulted in 12 papers and 7 patent files (see Section 2 for the details of outcomes). The **ITbM Research Award**, established to foster interdisciplinary collaboration among young researchers and students is another key. So far, 10 proposals among the 20 applications were selected, and the selected proposals were each awarded 2 million yen over 2 years. In addition, the **ITbM Workshop**, **Mix Hour**, and **Tea Break Meeting** are being held to share each other's research progress and to find seeds of collaboration and possible collaborators.

Contribution by the **Research Promotion Division (RPD)** towards facilitating interdisciplinary research is also notable. RPD takes up a role of a catalyst to initiate collaboration through attending all PI's group meetings to follow up on the research progress and sharing the potential seeds with other groups in different research fields. Based on these endeavors, the RPD follows each research from the start, which makes it possible to make strategic plans at an early stage by filing research outcomes as intellectual properties and to carry out transfer of technology by finding matches that meets the needs of the firms.

4. International Research Environment

ITbM has several international partner institutions. An important partner is the **NSF-CCHF**. ITbM collaborates with CCHF in the field of C-H activation chemistry constituting an important area of ITbM's research. Since 2013, ITbM has sent 8 PhD students and accepted 5 students plus 1 faculty with a duration of 3-6 months. The exchange envisaged to foster young scientists has been successful up to now. So far, 3 collaborating papers have already been published. ITbM has also expanded the network to include other related institutes such as the Institute for Basic Science (IBS, KAIST, Korea). ITbM will host a joint international workshop in June 16-18, 2016, inviting the members of CCHF and IBS to Nagoya.

Collaborations including researcher exchange with the **Broad Institute** and **The Scripps Research Institute, USA** has also recently started. ITbM will further expand its international network and improve ITbM's visibility. For this purpose, ITbM utilizes the international programs available at NU.

ITbM enrolls 4 world-leading overseas PIs, 1 full-time foreign PI at NU, and many foreign postdoctoral researchers. In April 2016, another full-time female foreign PI (Florence Tama) will be enrolled. All the 4 overseas PIs continue to actively contribute to the various activities at ITbM. They are staying in Nagoya for 1-2 months per year and attending the site-visits and annual international symposia. Even when they are absent from Nagoya, they have a close contact with their respective Co-PIs and postdoctoral researchers through regular TV conferences or e-mails. They also send 2-3 young researchers to ITbM.

In order to support researchers from overseas, the Administrative Department consists of staff with good correspondence in both English and Japanese. The RPD has a staff to provide a wide range of support for the daily lives of foreign researchers and their families. Halls of international residence are allocated to ITbM foreign researchers with high priority.

ITbM has organized 8 international symposia and workshops over the past 3 years, including 3 international awards, such as the **Hirata Award** and **Nagoya Medal** to recognize the outstanding accomplishments of world-class chemists, and the **Tsuneko and Reiji Okazaki Award** for molecular biologists. ITbM's annual international symposium (ISTbM) along with the RIKEN CSRS-ITbM joint workshops have led to fruitful discussions and the initiation of new research collaborations.

5. Implementing Organizational Reforms

The Director has the authority to make final decisions over all matters concerning the operation and management of ITbM. NU has established a rule to provide incentives to the Director, the Vice Director, PIs, and the Administrative Director based on their performance and evaluations, the determination of eligible persons and the amount of incentive is left to the discretion of the Director. The Executive Board of NU will evaluate the Director in reference to the Center's achievement and the WPI committee's report.

In order to promote efficient use of intellectual properties and research outcomes from ITbM and other NU institutes, NU has conducted the organizational reform of research supporting units to establish the "Department for Academic Research & Industry-Academia-Government Collaboration". NU launched a "Venture Fund of Nagoya University and Tokai Area's Universities". Establishment of these systems strongly supports ITbM's activity.

NU has been strongly supporting ITbM. Representative concrete measures are 1) provision of space, 2) financial support toward construction of ITbM's new building, 3) support towards the operation of the new building, 4) covering salaries, 5) ITbM's high priority to use the halls of residence. NU is working to reform structures, strengthen financial base, and improve university-wide communication to more effectively and flexibly assign resources. Through these measures, ITbM will be sustained at NU.

NU has been actively engaged in developing female leaders and young female researchers. Due to its efforts, the President of NU was selected as one of the 10 world universities that have made advanced efforts to promote gender equality under the IMPACT 10x10x10 program of **United Nation Women's HeForShe movement**. ITbM is fully utilizing these platforms to support female researchers.

6. Future Vistas

ITbM's next challenge is how to utilize its outcomes and to contribute to the society. Upon the development of novel products based on ITbM's molecules and molecular technologies, this will largely improve ITbM's international/national visibility and recognition by the general public. To achieve this, the **Strategic Planning Division (SPD)** will be established in April 2016, by hiring experienced personnel. The SPD will make strategies and a roadmap to contribute to the scientific community and society.

ITbM has several industrial partners of chemicals, pharmaceuticals, and agrochemicals. In order to achieve the best matching with these industries, ITbM will launch a consortium by enrolling firms of related fields and expand its network. The consortium also functions to collect the needs of industries and of societies.

Fostering young researchers is also a key mission. ITbM has started educational activities for students. As part of NU's graduate school of science, faculties of ITbM and related departments will provide a new chemical biology lecture series from FY2016.The class will be open to the whole University.

ITbM will continue its challenge toward internationalization. Through expansion of its international network, exchange of researchers and PhD students with overseas institutions will be promoted by using various resources available at ITbM and NU. Especially during 2016, ITbM will make even stronger bonds with the Broad Institute and the Scripps Research Institute through collaborating research and exchanging researchers and students.

NU reorganizes the research centers/institutes and supports frontier research led by the "Institute for Advanced Research" for fundamental research and the "Institute of Innovation for Future Society" for applied research. Under the umbrella of the "Institute for Advanced Research", ITbM will be supported as an international research institute conducting frontier basic chemistry and biology.

7. Others

Safety is an important issue especially to ITbM. Special safety training suitable for interdisciplinary environments is provided to all ITbM researchers. The training also provides an opportunity to explain to the foreign researchers about the difference among the safety rules of Japan and their countries.

It is also essential for ITbM to communicate to the general public widely that ITbM always addresses the environmental and safety issues carefully, and to gain the understanding from the international/domestic societies and local community. Accordingly, ITbM has set up an **Environment and Safety Committee** so that researchers at ITbM are constantly aware of these issues when conducting their research.

8. Center's Response to Results of FY2015 Follow-up (including Site Visit Results)

ITbM's identity: Remarkable progress of interdisciplinary research through close collaboration by ITbM's compact nature.

Strategic plan for the next several years: Concentrate on advancing and disseminating ongoing interdisciplinary research in the next 3 years (see also Section 6).

Education of different disciplines: ITbM's faculty starts a new chemical biology lecture series from FY2016, as part of NU's graduate school.

Strategies for spin-off companies and commercialization: Some of the research outcomes by ITbM have already been commercialized as products and license agreements with industries are also in progress. ITbM is considering of establishing a consortium-like organization that will be responsible for the overall commercialization of the molecules developed at ITbM.

World Premier International Research Center Initiative (WPI)
Self-Evaluation Report for Interim Evaluation

Host Institution	Nagoya University	Host Institution Head	Seiichi Matsuo
Research Center	Institute of Transformative Bio-Molecules (ITbM)	Center Director	Kenichiro Itami

Common Instructions:
* Please prepare this report based on the current (31 March 2016) situation of your WPI center.
* As a rule, keep the length of your report within the specified number of pages. (The attached forms are in addition to this page count.)
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

1. Summary of State of WPI Center Project Progress (write within 2 pages including this page)

Describe the center's identity and the achievement status of its initially stated goals.

- On the sheets in Appendix 1~5, list the Principle Investigators, and enter the number of center personnel, a chart of the center's management system, a campus map showing the center's locations on the campus, and project funding.

High-impact, interdisciplinary research at ITbM

ITbM was launched at Nagoya University (NU) as a unique research center to develop innovative functional molecules that make a marked change in the form and nature of biological science and technology. By taking full advantage of ITbM's cutting-edge molecular synthesis expertise and intense interactions with leading plant/animal biology research, "transformative bio-molecules" will be developed that can (1) enhance biotic productivity and quality, and (2) realize innovative bio-imaging. To ensure that these targets are achieved, ITbM will (3) develop catalysts that enable efficient synthesis and on demand molecular activation. The ultimate goal of ITbM is to have a positive impact on major global issues such as food production. In late 2015, the following research areas were defined as ITbM's flagships: "**Plant Chemical Biology"**, "**Chemical Chronobiology"**, and "**Chemistry-enabled Live Imaging"**.

The combination of ITbM's researchers high research profile with the new research style at ITbM has facilitated interdisciplinary research at a pace more rapidly than initially expected. ITbM's "Mix Labs" that mix different disciplines has been highly effective, and has led to the development of a number of new bio-functional molecules and molecular technologies. The ITbM Research Award, established to promote interdisciplinary research proposed by young researchers, has accelerated collaborations in a bottom-up manner and most of the proposals have been making good progress to mature into ITbM's representative projects. Many of the research outcomes have been filed for patents and published as joint publications between different research groups. The main research outcomes are shown below (details in Section 2-1).

[1] Molecular control of plant growth: Novel functional molecules that control plant growth and differentiation based on direct chemical transformation of the plant hormones have been developed. Molecules modulating stomatal opening/closure have also been discovered, i.e., modulate the number and density of stomata, accelerate stomatal opening/closure, and restrict stomatal dynamics reversibly.

[2] Molecular control of plant reproduction: ITbM has succeeded in discovering several key biomolecules (LURE, AMOR, and CALL1) that control plant reproduction and identifying the corresponding receptors. The detailed mechanism of plant reproduction has also been disclosed at a molecular level in order to control the designed hybridization by molecules.

[3] Molecular control of animal/plant biological clock: A number of potent molecules controlling the animal/plant biological clocks have been discovered. Based on the identification of the target proteins, X-ray crystal structures, and evaluation of biological functions, some of the discovered molecules are under further investigation with a pharmaceutical company. Researchers have also demonstrated that modulation of the plant biological clock by molecules may lead to the development of an optimized variety of crops.

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microscopy. Researchers have also developed molecules that exhibit high responsive property to environment polarity and have discovered near infrared emissive phospha-fluoresceins. These super high performance molecules may serve a significant role in leading the bio-imaging field.

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Administrative Department supporting ITbM's research

The Administrative Department consists of the Administrative Director leading the Management Division (General Affairs Unit and Accounting Unit) and the Research Promotion Division (RPD). Many of the RPD members hold either a PhD or Masters degree in science and conduct public relations and outreach activities along with a science designer. An experienced intellectual properties (IP) manager also joined ITbM to file for patents and strategically exploit ITbM's research outcomes for industrial applications. The Strategic Planning Division (SPD) will be newly launched in April 2016, playing a key role in realization of ITbM's research outcomes by working out strategies for the acquisition of IP rights and business matching with companies. An Associate Professor with prior experience as the head of the chemistry department at a pharmaceutical company will be employed as of April 2016.

Internationalization

ITbM was launched initially with 3 overseas PIs (Crudden, Bode, Torii), and invited an additional overseas PI (Kay) in 2014. ITbM also has one full-time foreign PI (Irle) at NU, and will employ another full-time female foreign PI (Florence Tama) in April 2016. Most of ITbM's postdoctoral researchers are from abroad. The ratio of non-Japanese researchers is 34% as of March 31, 2016.

The Administrative Department consists of staff with good correspondence in both English and Japanese to handle various tasks. The RPD has staff to provide support to foreign researchers and their families. Faculties and students have been exchanged between ITbM and the host institutes of the overseas PIs or with international partner institutions such as the NSF Center for Selective C-H Functionalization, USA.

ITbM has been hosting annual international symposia (ISTbM) and three international awards (Hirata Award, Tsuneko & Reiji Okazaki Award, Nagoya Medal of Organic Chemistry), which have been contributing to increase ITbM's international visibility. ITbM also utilizes the international programs run by NU such as Top Global University Project to promote international collaborative research.

System reform

NU revised its rules to give executive authority to the director to make top-down decisions over the appointments of ITbM's personnel, budget, research priorities, and incentive-based bonuses.

As represented by the e-mails distributed in both English and Japanese, ITbM's efforts to support foreign researchers are spreading across the university. ITbM's Co-PI system, forming a team of top-level overseas PI in overseas institutes and a full-time Co-PI in NU, was incorporated to the WPI-next program established to support top-level science of NU.

NU established "Department for Academic Research & Industry-Academia-Government Collaboration" through organizational reform to promote efficient use of intellectual properties and research outcomes. NU also launched "Venture Fund of Nagoya University and Tokai Area's Universities". Establishment of these systems strongly supports ITbM's activity.

ITbM has been working effectively towards accomplishing the missions set by the WPI. On top of its substantial research outcomes, ITbM's endeavors are contributing to the system reform of NU.

2. Center's Research Activities (within 8 pages)

2-1. Research results to date

Provide an overall picture of the Center's research activities and select 5~10 representative results achieved during the period from 2012 through March 2016. Number the results [1] to [10] and provide a description of each.

- In Appendix 2-1, list the papers underscoring each research achievement and provide a description of each of their significance.

Since ITbM's establishment in 2013, the novel synthetic small molecules designed and synthesized by the synthetic chemistry groups and the Chemical Library Center at ITbM have been screened and provided to the biologists at ITbM. Thus, within three years, all the biologists at ITbM now have their desired molecules for further studies. Molecule-initiated biology (chemical biology) to create transformative bio-molecules is currently shifting to the next phase, i.e., understanding and controlling biological processes by utilizing the molecules developed at ITbM.

At such a turning point, ITbM has defined the following flagship research areas based on the Center's research achievements so far along with its future perspectives.

1. **Plant chemical biology**
2. **Chemical chronobiology**
3. **Chemistry-enabled live imaging**

ITbM will focus on these flagship research areas 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, to lead to the creation of transformative bio-molecules.

[1] Molecular control of plant growth

Plants are capable of changing into a form suitable for their growth, by perception and response of the signals from the surrounding environment such as water, nutrients, light, gravity and so on. Such plant responses are orchestrated by transmitting the signals perceived locally and to the whole body. Plant hormones are known to play a central role in the signal transduction. Itami, Kinoshita and Torii have developed novel functional molecules that control plant growth and differentiation based on chemical modification of the plant hormones. For example, auxin has been known as a plant hormone involved in plant growth (Plant Physiol. 2012), and the discovery of auxin dates back to Darwin's pioneering work in the 1880's. Itami has constructed a focused library by modification of auxin with his unique C-H coupling reactions. This library consists of structurally unique auxin derivatives that classical synthetic chemistry could never approach. They succeeded in discovery of the novel functional molecules that control plant growth, differentiation and stomata function precisely (Patent 2013). In addition, they have succeeded in obtaining biological evidence of an auxin receptor related to cell elongation, which has been unknown for over 130 years since Darwin's report.

Stomata in plants play a key role in the regulation of gas-water exchange between the plant and the atmosphere to conduct photosynthesis/transpiration. To have complete control over plant stomata is considered important not only to increase the production of biomass and provide drought tolerance for crops, but also to prevent global warming by reduction of a greenhouse gas (CO_2).

Kinoshita has been focusing on biological research of stomata to elucidate plant responses to its surrounding environment. He has reported that the blue light receptor phototropin, membrane H^+-ATPase and other factors play a role as key regulators for stomatal opening/closure. Among the several factors that were identified, he showed that transgenic *Arabidopsis* plants overexpressing H^+-ATPase using the guard cell promoter *GC1* exhibited enhanced light-induced stomatal opening and photosynthesis, by approximately 25% and 15%, respectively, thus leading to a 1.5 times increase in plant growth compared to the wild type. In addition, the transgenic plants exhibited drought tolerance in a similar manner to the wild type (PNAS 2014). In addition, Kinoshita has developed a convenient chemical screening method using a small leaf disc. His group has also discovered several promising molecules having stomatal opening/closure functionality, among over more than 20,000 of molecules, through the extensive collaboration with the Itami group and the Chemical Library Center. The team is currently focusing on elucidating the detailed mechanism of the biological phenomena triggered by molecules, and application of IP rights and technological transfer of the research outcomes.

Torii has been making a number of remarkable discoveries on the receptors and the transcription factors involved in the control of the number and density of plant stomata, and has been leading the field of

developmental biology of plant stomata at the molecular level, which includes genes, proteins, and peptides. Recently, she explored both EPF2 and Stomagen, known as inhibitory and acceleratory regulators of stomatal development, respectively, directly bind to ERECTA-family receptor kinases, and showed antagonism on the receptor to fine-tune tissue patterning on the plant epidermis (Nature 2015). To advance her research on stomatal chemical biology at ITbM, Torii and Uchida are collaborating with the Bode-Oishi group to uncover the peptide signaling orchestration of tissue patterning. In addition, she has been exploring small molecules that affect the density and patterning of stomata through the collaboration with the Itami group, the Molecular Structure Center, and the Chemical Library Center. The team has discovered several promising lead compounds through structure-activity relationship studies. Moreover, they were successful in demonstrating that one of the lead compounds was applicable to hydroponic culture/soil cultivation. Development of molecules that control stomatal development has been making progress in research at both the basic (developmental biology and chemical biology) and applied level (towards social implementation).

[2] Molecular control of plant reproduction

Higashiyama group has discovered the LURE peptide, known as a long-standing mystery for pollen tube guidance (Nature 2009). He has demonstrated the possibilities of overcoming the genome barrier and of analyzing the real-time cellular/molecular dynamics during the plant reproduction process. By utilizing LURE, he has reported a significant progress on rare interspecies-crossing between different families of plants (PLoS Biol. 2012), and identified LURE receptors and their dynamics (Nature 2016). At ITbM, he has discovered several key molecules including a peptideglycan AMOR, which activates pollen tubes for fertilization to occur (Curr. Biol. 2016) and a novel peptide CALL1, which attracts pollen tubes from a long distance, through the extensive collaborations with ITbM's synthetic chemists (Itami, Bode) and the Molecular Structure Center. In addition, he was successful in the real-time analyses by deep imaging of the plant tissue, live cell imaging of embryogenesis, and optical tweezers. Based on these achievements, he was able to realize an artificial heterofertilization (Dev. Cell 2013), live imaging of calcium spikes during double fertilization (Nature Commun. 2014), and elucidate the prevention mechanism of multiple fertilization (Cell 2015) with the Live Imaging Center. Furthermore, he is trying to investigate further details of pollen tube attraction, fertilization, and embryogenesis at the molecular level by using the unique fluorescent probes developed by Yamaguchi (ACIE 2015, 2016).

[3] Molecular control of the animal/plant biological clock

Since the identification of the small molecule KL001 from a cell-based circadian phenotypic screening (Kay and Hirota, Science 2012), Kay-Hirota and Yoshimura's groups have discovered novel small molecules continuously through the extensive collaboration with ITbM's synthetic chemists (Itami, Ooi) and the Chemical Library Center. Based on these discoveries, Kay-Hirota and Yoshimura have conducted chemical biology research to uncover the mystery of the biological clock at the molecular and the organism level, respectively.

Kay and Hirota discovered a more potent molecule, KL044 through the structure-activity relationship (SAR) study of KL001 and were able to provide a rational design of a molecule that binds to the clock protein cryptochrome (CRY) by 3D-QSAR analysis through the collaboration with the Irle group (ChemMedChem 2015). Kay-Hirota and Itami have also identified a promising molecule, GO289 that inhibits Casein Kinase 2 (CK2) strongly and selectively *in vitro* (IC_{50} 7 nM). In addition, they obtained the CK2-GO289 co-crystals and provide a possible mechanism to account for the extremely high potency and selectivity of GO289.

Yoshimura has conducted animal physiology studies on the sleep-wake rhythm, secretion of hormones, and seasonal breeding triggered by the biological clock at the organism level. The collaborative team by Yoshimura and Itami has demonstrated that transformation of a period-lengthening molecule KL001, resulted in the development of period-shortening derivatives synthesized via catalytic C-H coupling reactions developed by the Itami group (ACIE 2015). Yoshimura's group has also conducted research on seasonal clocks, and showed that the thyroid-stimulating hormone (TSH) acts as a spring hormone (Nature 2003, 2008, PNAS 2008, Nature Commun. 2013). In addition, he has also demonstrated that the thyroid hormone (T3) secreted by stimulation of TSH acted not only as key regulator of thermoregulation in a homoisothermic animal, but also as a trigger molecule for seasonal breeding (Endocrinol. 2015).

Kinoshita and Nakamichi have been working on how various biological responses are brought about by

the plant's complex clock network. They demonstrated that one of the plant clock proteins CCA1, directly affects the key gene expressions for plant responses such as drought stress, signal transduction of plant hormones, and opening/closure of stomata (Plant Cell 2016). Moreover, the collaborative team of Kinoshita-Nakamichi, Itami, and the Chemical Library Center has discovered several molecules exhibiting period-lengthening activity. Through structure-activity relationship studies, the team also demonstrated that one of the derivatives showed period-shortening activity. Many of the present crops have been selected species with optimized properties that are regulated by their circadian clock. To be able to modulate plant circadian clock by molecules is expected to lead to the development of an optimized variety of the crops. Finally, the team succeeded in identification of the first-in-class molecule that controls the plant's biological clock (Patent 2014).

[4] Molecular control of parasitic plant *Striga*

The parasitic plant *Striga hermonthica*, so-called witchweed, has been causing huge damage on crop production in Africa. Huge losses in agriculture due to *Striga* are estimated to be worth 10 billion US dollars every year. *Striga* is able to geminate by sensing strigolactones released from host plants at a pico-molar range and is parasitic on host plants. The genetic intractability of *Striga* has been the main barrier for identifying its germination mechanism. Tsuchiya (Kinoshita group) and Hagihara (Itami group) have developed a fluorescence turn-on probe, Yoshimulactone (YLG), which activates strigolactone signaling and illuminates signal perception by strigolactone receptors. Yoshimulactone enabled the identification of 10 strigolactone receptors in *Striga* as well as visualization of the *in vivo* strigolactone perception during its germination (Science 2015). Yoshimulactone became available on the market at the beginning of 2016 and researchers in the world now have access to use Yoshimulactone in their research not only for studying *Striga* germination but also for modulation of plant development.

The discovery of strigolactone receptors and the development of a fluorescent probe (Yoshimulactone) together with the high-throughput screening facilities developed by the Chemical Library Center allowed ITbM to quickly discover new molecules that can potentially combat *Striga*. For example, the Ooi group and the Chemical Library Center have developed highly active molecules for suicide germination of *Striga* (agonists), which have almost equal activities to those of natural strigolactones (Patent 2015). On the other hand, the Itami group identified the molecules that inhibit *Striga* germination (antagonists) from their chemical library constructed by their own C-H coupling reactions. ITbM is currently in a unique position to advance its research to save *Striga*-affected crops in Africa.

[5] Imaging molecules

Yamaguchi group has created a series of unique photo/electron functional molecules by introducing main group elements (boron, phosphorus and others) into their aromatic system. Yamaguchi has actively applied his own fluorescent molecules to biological research through the collaborations with Higashiyama and the Live Imaging Center at ITbM. Among the molecules that he has developed, he demonstrated that one of his fluorescent probes Ph-Bphox showed high responsive property to environment polarity, and C-Naphox, a structurally reinforced Ph-Bphox derivative, exhibited exceptionally high resistance to photobleaching (ACIE 2015). Impressively, the intracellular fluorescent intensity of C-Naphox remained at 83% of the initial value even after recording 50 images in STED imaging, whereas a significant decrease in signal intensity was detected for cells stained with conventional Alexa 488 and ATTO 488 used frequently in bio-imaging under the same conditions (ACIE 2015). These characteristics enable 3-dimensional stimulated emission depletion microscopy and time-lapse STED imaging, and accelerate practical application of microscopic technology.

Yamaguchi's fluorescent molecules (Ph-Bphox and C-Naphox) are open to be commercialized and the Strategic Planning Division is working on the strategic and multifaceted utilization of these fluorescent probes through collaboration with the world's leading institutions and biologists. Yamaguchi has also developed the red-emitting fluorescent molecules applying the excited-state intramolecular proton transfer (ACIE 2014) and near infrared emissive phospha-fluoresceins.

At ITbM, Yamaguchi, who designs and synthesizes unique fluorescent molecules, has collaborated with Higashiyama, who is one of the leaders in the field of imaging for plant biology, and the Live Imaging Center that manages the world's leading microscopes, to make unexplored molecular dynamics and phenomena of life visible at the molecular level.

[6] Catalysis and rapid molecule synthesis

ITbM's synthetic chemistry groups (Itami, Ooi, Crudden and Bode) have established epoch-making synthetic methodologies that enable synthesis and modification of indispensable bioactive molecules, and have contributed to facilitate ITbM's interdisciplinary research at a rapid pace.

Itami group has developed more than 20 unique catalysts for various types of C-H coupling reactions, and has demonstrated that these catalysts could activate C-H bonds existing in aromatic compounds with a high degree of efficiency and regioselectivity. In recent years, he has accomplished not only coupling reactions of aromatic compounds but also various functionalization reactions such as aromatic ester activation (Nature Commun. 2015), aromatic borylation (JACS 2015) and aromatic amination (JACS 2015). These effective molecule transformation reactions have been applied globally as common synthetic methods in chemical, pharmaceutical, and agrochemical companies, and 11 joint researches have been conducted with various companies as of April 2016. At ITbM, his unique and rapid synthetic technologies enabled the discovery of various bioactive molecules such as molecules that alter the mammalian circadian rhythms (ACIE 2015) and modulate stomata functions. In addition, his group has conducted chemical biology research, and also discovered molecules that accelerate plant growth (Patent 2013) and develop biologically valuable probe molecules, Yoshimulactone (Science 2015). Moreover, he has achieved the synthesis of structurally uniform carbon nanotubes (Nature Chem. 2013), graphene nanoribbons (Nature Commun. 2015), and warped nanographene having an unparalleled 3-dimensional structure (Nature Chem. 2013). These results have led to the creation of a novel research area of "molecular nanocarbon" and his new molecules are expected to be integrated in ITbM's research in the near future.

Ooi group has developed various types of reactions, which enabled the rapid generation of structurally diverse chiral molecules with his unique chiral quaternary ammonium catalysts, so-called onium catalysts. With these catalysts, he has reported various "otherwise-difficult-to-achieve" reactions, including the asymmetric allylation reaction (Nature Chem. 2012), construction of contiguous quaternary stereocenters (JACS 2013, Nature Chem. 2013), reductive multicomponent coupling reaction (Chem. Sci. 2015), diastereoselective Michael addition reaction (ACIE 2015) and unprecedented asymmetric coupling reaction (JACS 2015). These reactions enabled rapid access to structurally complex molecules such as natural products and were supplied to the biologists at ITbM. Through the extensive collaboration at ITbM, he has developed suicide germination molecules of *Striga* (with Kinoshita-Tsuchiya) and molecules that alter the mammalian biological clock (with Kay-Hirota and Yoshimura).

Crudden and co-workers have developed various types of next generation cross-coupling reactions and established methodologies to install various functional groups into the organic compounds at will. As an example, she has achieved the novel cross-coupling reaction without conventional and time-consuming process such as protection and deprotection of functional groups in organic molecules (ACIE 2014, Org. Lett. 2015). With this methodology, she has demonstrated that three-dimensionally organized and highly selective biologically active molecular structures can be created efficiently (Nature Commun. 2016). In addition, she has established a truly game-changing methodology to modify metal surfaces and particles precisely (Nature Chem. 2014). This new technology is thought to be indispensable for high-sensitivity bio-imaging and sensing.

Bode and co-workers have developed epoch-making methodologies of peptide/protein syntheses known as KAHA ligation that enables to the synthesis of not only large bio-molecules such as proteins but also medium size cyclic peptides rapidly at a large scale. At ITbM, he has developed the KAHA ligation further and succeeded in the synthesis of the calcium-binding protein S100A of which the synthesis was conventionally difficult (Nature Chem. 2015). The KAHA ligation has improved the reaction rate dramatically and has opened up new possibilities of peptide ligation reactions. In addition, he proposed the concept "synthetic fermentation" based on microbial fermentation that microorganism can rapidly provide potent molecules and use them for different purposes. By utilizing KAHA ligation fully, he was able to construct a chemical library consisting of tens of thousands of peptides rapidly and discover a potent inhibitor of viral protease from the library (Nature Chem. 2014). Furthermore, Bode has achieved unprecedented successes in the area of synthetic chemistry of small molecules. The reagents and building blocks developed by the Bode group are now available on the market, and his synthetic methodology is now utilized extensively through the pharmaceutical companies in western countries.

2-2. New Challenges

Describe the new challenges befitting a WPI center that have been undertaken.

Mix-Labs: Key to interdisciplinary research

At ITbM's Mix Labs, researchers and students from different fields share the same space and are able to discuss and communicate about science, education and other administrative matters on a daily basis. Two Mix Labs were established in April 2013, and students and researchers in the fields of synthetic chemistry, animal/plant biology, and theoretical sciences were situated so that they are evenly arranged in the Mix Labs. The effects of the Mix Labs have been extremely positive and have become far beyond ITbM's initial expectation, as these labs have been working well as a place where new unique ideas in research are being generated from daily communications. This Mix Lab concept has been reflected in ITbM's new building that was constructed in April 2015, where over 30 new interdisciplinary research projects are being generated across 11 research groups and 4 centers, some of which have already led to patent applications, journal publications and technology transfers. The continuous merging and reassembling of research projects that have arisen from the Mix Lab effect, have led to the establishment of new interdisciplinary research fields at ITbM, such as plant chemical biology, chemical chronobiology, and chemistry-enabled live imaging.

Research Promotion Division: Full support for ITbM's research

The Research Promotion Division (RPD) was established in March 2013 at ITbM to play a key role in creating a bridge between the university's faculty and administrative staff. The RPD carries out seamless activities for ITbM to become established as an independent and internationally visible institute. Characteristic activities of the RPD include management of symposia and seminars, carrying out international public relations, science visualization, public outreach, construction of a broad network with other universities, institutes, and companies, providing wealth and safety training, daily-support for overseas researchers including their family, promotion of intellectual properties and research collaborations, consultation of interdisciplinary research, and promotion of social implementation.

Most members in the RPD hold either a PhD or Masters degrees in a related research field of ITbM (chemistry or biology), and their expertise in these fields makes the RPD a reliable existence at ITbM. Arising from the RPD's contribution in promoting ITbM's activities, NU is now considering to incorporate the ITbM-RPD model into the university's infrastructure as a third group in addition to the existing faculty and administrative office platform in the near future.

Co-PI system

ITbM introduced the Co-PI system to enable world-class researchers in related research fields (synthetic chemistry and plant/animal biology) participate in ITbM's research activities within the limited budget. In addition to 3 overseas PIs, Keiko Torii (Univ. Washington, Howard Hughes Medical Institute), Cathleen Crudden (Queen's Univ.), and Jeffrey Bode (ETH) who were present from the beginning of ITbM, Steve Kay (now serving as the President of the Scripps Research Institute since 2015) has joined ITbM as an overseas PI from 2014. To make the PIs' research at ITbM possible, ITbM decided to employ young researchers as Co-PIs who stay full time at ITbM and cooperate with the overseas PIs. The current institutions of overseas PIs' are cooperative organizations of ITbM by agreeing to a Memorandum of Understanding (MOU). These agreements enable young researchers to visit and conduct their research in ITbM, and accelerate ITbM's globalization. The invitation of world-leading researchers as overseas PIs at ITbM, has led to increased attention of ITbM's research results and activities from the international science community, and has contributed to improving the global visibility of ITbM.

2-3. Joint Research Advanced

Describe the joint research that the Center has undertaken with research organizations in and outside Japan.

- In Appendix 2-3, list and describe the cooperative research agreements that the Center has with other organizations.

Center for Sustainable Resource Science (CSRS) at RIKEN, Japan

CSRS, focusing on plant biology and synthetic chemistry was established at almost the same time as ITbM. In 2013, ITbM invited Dr. Kazuo Shinozaki (Director of CSRS) as an invited speaker at the International Symposium on Transformative Bio-Molecules (ISTbM-1) in May and CSRS also invited Itami (ITbM) in CSRS' inauguration ceremony in October. Following these ventures, both institutes concluded the "Agreement on the Association and Cooperation" and held the 1st CSRS-ITbM Joint Workshop in

January 2014. The workshop takes place annually in either Nagoya or Wako. In January 2016, both directors made a joint statement on the joint use of the research support platform, and confirmed further promotion of collaboration between CSRS and ITbM. Joint projects have been initiated between CSRS and ITbM, and Dr. Sakakibara (CSRS) and Kinoshita (ITbM) have worked together to improve plant biomass by modifying the plant biological clock (Plant Cell Physiol. 2016).

Freiburg University, Germany
NU and Freiburg University concluded a MOU for further promotion and collaboration, and they started a call for collaborative research. The proposal titled "Multicomponent Supramolecular Catalysts for Sustainable Chemical Synthesis" organized by Ooi and Itami of ITbM and Prof. Breit of Freiburg University was selected in 2015, and collaborative research towards the development of new catalysts according to the new concept of organic synthesis has been recently launched (see also Section 4-1-1).

National Science Foundation Center for Selective C-H Functionalization (NSF-CCHF), USA
ITbM became a partner of NSF-CCHF that consists of top leading synthetic chemists in USA and giant firms of pharmaceuticals and agrochemicals. While a MOU is under construction, collaborating research projects are ongoing, and three joint papers have been published in top journals as shown below (see also Section 4-1-1).

(1) "Key mechanistic features of Ni-catalyzed C-H/C-O biaryl coupling of azoles and naphthalen-2-yl pivalates", H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami, D. G. Musaev, *J. Am. Chem. Soc.* 2014, 136, 14834-14844.
(2) "Concise syntheses of dictyodendrins A and F by a sequential C-H functionalization strategy", A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami, H. M. L. Davies, *J. Am. Chem. Soc.* 2015, 137, 644-647.
(3) "Decarbonylative organoboron cross-coupling of esters by nickel catalysis", K. Muto, J. Yamaguchi, D. G. Musaev, K. Itami, *Nature Commun.* 2015, 6, 7508.

2-4. Appraisal by Society and Scientific Organizations

Describe how society and/or scientific organizations in and outside Japan have recognized the Center's research achievements.
・ In Appendix 2-4, list the awards received and invitational lectures given by the Center's researchers.

ITbM's researchers are being widely recognized by the international science community as well as by the society. This is evident by the significant number of prestigious international awards and honors as well as invitations to major international symposia that have been granted to ITbM's PIs.

Yoshimura became the first Japan-based animal biologist to receive the Van Meter Award, which was established in 1930 by the American Thyroid Association, and Itami became the youngest Japanese chemist to receive the Arthur C. Cope Scholar Award by the American Chemical Society in 2015. Crudden has received the 2015 Killam Research Fellowship from the Canada Council in recognition of her exceptional career achievements, and Torii has been awarded the 35th Saruhashi Award in 2015, which is granted each year to a female scientist in recognition for their distinguished research in natural sciences. Torii's accomplishments have been widely covered in the media, including 12 national newspapers, and over 60 websites and magazines.

Since the launch of ITbM in December 2012, ITbM's PIs have been invited to give lectures at nearly 200 international conferences held worldwide and at over 300 academic meetings, as well as at public workshops, where they have successfully promoted their research along with the activities of ITbM. All of the PIs serve as editorial boards of major scientific journals and many of them are on the organizing committee of various international conferences, thus reflecting their presence in the science community.

2-5. Center's Research Environment including Facilities and Equipment

Describe the Center's research environment including facilities and equipment and the state of its utilization.

NU has provided 5,165 m^2 of research space for ITbM, which contains 2,165 m^2 of new space on top of the existing 3,000 m^2 of space designated to Nagoya PIs. Communal equipment to conduct Mix-Lab's interdisciplinary research were purchased and installed. A high performance computer was also purchased in the server room to conduct theoretical calculations and the set up for all the servers has been completed during FY2014. In addition, large-scale equipment was purchased for the research centers. As the 3 overseas PIs, Crudden, Bode and Torii were initially not eligible to apply for research grants within Japan, ITbM provided research funds for the overseas PI's groups for start-up. Upon appointment of Steve Kay of the University of Southern California (USA) as an overseas PI from FY2014,

an additional 134 m^2 of new space was allocated to accommodate his research group. A total of 5,357 m^2 of research space was provided to ITbM from NU during FY2014. In FY2015, a new six-storied building (7,934 m^2) that reflects the Mix Lab concept, which was designed based on the experience and achievements in the two Mix Labs, was constructed for ITbM. In the new building, Mix Labs are located on the second and fourth floor, and Mix Offices are located on the third and fifth floor. There are no barriers within the Bio Mix Labs and the Chem Mix Labs, along with the Mix Office spaces located directly above. This removes the conventional barriers between research groups, thus creating huge Mix Labs and Mix Offices to promote interdisciplinary research. Such a two-level structure for offices and laboratories is rare and very few examples with a similar type of structure are present in the world. Researchers at ITbM can have an open view of the Mix Labs through the windows of the Mix Offices. In addition to the Mix Labs and Offices, ITbM's building is equipped with a children's room, kitchen space, discussion space, and terrace, for all members to feel comfortable and freely discuss their research.

2-6. Non-WPI Project Funding

Describe the results in securing non- WPI project funding.

- In Appendix 2-6, draw of graph showing the Center's transition in securing non-WPI project funding and list external funding warranting special mention.

ITbM researchers have been constantly obtaining competitive funding from the time of the center's establishment. The total amount of competitive funding obtained in FY2013 was 1,141 million yen, which is more than double the amount obtained in FY2012 (528 million yen). The amount of funding further increased in the following years (FY2014: 1,290 million yen, FY2015: 1.185 million yen). Major competitive funding obtained in FY2015 are JST-ERATO (2 projects), JST-CREST (2 projects), JST-PRESTO (2 projects), Grant-in-Aid for Scientific Research on Innovative Areas (1 project as Area Representative), JST-ALCA (1 project), Grant-in-Aid for Specially Promoted Research (1 project) etc. 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 (cf. 2-3) and the project was selected for FY2015-2016.

2-7. Applications of research results

Describe the applications created from research results, their effect in spawning innovation, intellectual properties (IPs) obtained, and joint research activities conducted with corporations, etc.

To create strong patents and transfer technology globally for the sustainable operation of ITbM, ITbM employed an IP manager affiliated to ITbM in June 2014. As a result, the activities related to IP and technological transfer have made significant progress.

Patent application:

To remove the barrier that often hinders the rapid promotion for basic research caused by patent filing, which has a relatively long period of obligation of confidentiality, ITbM has established an effective application system for IP. This system works by the IP manager who collects information on each group's research progress and has discussions with researchers at an early stage in research. As a result, ITbM has achieved active IP-related activities without slowing down the submission of journal publications and presentations at academic conferences. Since ITbM's establishment, ITbM has filed 39 national patent applications (33 and 6 applications in chemistry and biology, respectively). Among them, 11 and 3 applications were transferred to a PCT and US applications, respectively. In addition, ITbM has filed 7 national patent applications derived from ITbM interdisciplinary research between chemistry and biology. This became possible as the strategies of interdisciplinary research and intellectual properties were able to merge at the right stage.

Technology transfer:

ITbM has concluded 15 license contracts to date (12 and 3 contracts in chemistry and biology, respectively). This includes 9 contracts that were newly concluded in 2015. This indicates the good progress in ITbM's technology transfer and social contribution. So far, 5 molecules/catalysts developed at ITbM became commercially available through technology transfers.

Joint research and development with company:

Since the establishment of ITbM, 17 joint projects with companies have been continuing up to date (joint R&D in chemistry, in biology, and in theoretical sciences are 10, 6, and 1, respectively). ITbM has also continued to engage actively for innovation through the cooperation with industries, governments, and

schools towards social implementation.

Venture start-up:
One of ITbM's plant biology research (Higashiyama and his co-worker) was adopted in the program for Creating Start-up from Advanced Research and Technology from JST (START program) and this will accelerate the start-up for the venture company in 2018.

Formation of the consortium:
To gain recognition in ITbM's research and bring about social implementation, ITbM has established the working group of the general incorporated association. The group has been collecting information on the pre-existing association at NU and other universities, and is making the plan for the association.

2-8. Achievements of Center's outreach activities

- In Appendix 2-8, list and describe media coverage resulting from press releases and reporting.

ITbM has distributed over 40 press/event releases, held over 10 press conferences about their research activities and has been covered over 1400 times in the media, including in international and domestic websites, newspapers, magazines, television, and radio. The use of international press release services such as EurekAlert!, ResearchSEA and AlphaGalileo has been greatly successful in reaching out to audiences in North America, Asia and Europe, respectively, which is evident by the increase in international media coverage. A number of ITbM's research news have been translated in various languages, such as Chinese, Dutch, French, Germany, Indonesian, Korean, Portuguese, Russian, and Spanish. ITbM is also working together with its partner institutes, Emory University and RIKEN CSRS to release joint press releases and strengthen the collaboration.

The distribution of press releases and subsequent media coverage are considered to have led to effective dissemination of ITbM's activities, thus leading to increased attention from the academia, industry, public and media. For example, a press release on C-Naphox, a fluorescent molecule for live cell imaging, developed by the collaboration between Yamaguchi and Higashiyama's groups in 2015, has received a number of inquiries from both the academia and industry, within and outside Japan. In addition, Kinoshita's press release on increasing the photosynthesis in plants in 2013 has led to research collaboration with an overseas organization. ITbM has also been approached by NHK to create a one-hour TV program, 'Chikyu (Earth) Agora', featuring ITbM's research in 2014.

ITbM has also been involved in various outreach activities including science experiment demonstrations at high schools (Konko, Sendai Daiichi, Ichinomiya, Kikuzato, and Nanzan High School) and at the Science Agora (Miraikan, Tokyo) to nurture the future generation of scientists. Lab tours and seminars to introduce ITbM are also held for students and teachers from local and overseas high schools (Bard, Eleanor Roosevelt (USA), Sendai, Kikuzato, Sugiyama (Japan) High Schools) as well as for visitors from abroad including the Minister of Education, Culture and Science from Mongolia. ITbM's activities are also introduced to the academic community by means of booth exhibitions at international events, including the International Symposium on Homogeneous Catalysis (Ottawa, Canada) and to the public at the AAAS Annual Meetings (USA), Super Science High School Presentation (Yokohama) and the WPI Joint Symposia. Many of the PIs and staff are also involved in holding public lectures to high school students and to adults interested in science.

3. Interdisciplinary Research Activities (within 2 pages)

3-1. State of Strategic (or "Top-down") Undertakings toward Creating New Interdisciplinary Domains

Since the launch of ITbM, all members continue to work under the slogan, "changing the world with molecules" to develop molecules to "understand", "see" and "regulate" biological systems. While ITbM had initially selected four interdisciplinary researches as core projects in a top-down style, many bottom-up research projects have emerged during the last three years, stimulated by the Mix Lab environment, and in 2015 ITbM has defined 3 flagship research areas as "Plant Chemical Biology", "Chemical Chronobiology", and "Chemistry-enabled Live Imaging" as denoted in Section 2-1.

The research projects are enabled by support of the unique set of platforms available at ITbM; (i) small-molecule synthesis, (ii) phenotypic assay development, and (iii) theoretical design and biosimulation are the platforms posed by each PI group, while the (iv) chemical library (Chemical Library Center), (v) laser microscopy (Live Imaging Center), and (vi) omics and molecular analysis (Molecular Structure Center), and (vii) peptide and protein synthesis (Peptide/Protein Center) are covered by each sub-center established at ITbM (the Peptide/Protein Center was newly launched in 2015 according to the growing needs of peptides and proteins). These platforms are shared among all ITbM's researchers and interdisciplinary research is strongly promoted by them.

There was a big challenge in introducing Mix Labs and Mix Offices that have no physical walls across various departments and lab groups, because it required mixing of different cultures furnished at each group. Practical problems were also encountered during the sharing of common resources. These issues were solved by communicating and understanding each other, and the Mix Lab concept started to work positively. This has led to promotion of interdisciplinary research much faster than initially expected. Different technical terms were also a serious problem, but this was overcome by using "molecules" as a common keyword.

3-2. State of "Bottom-up" Undertakings from the Center's researchers toward Creating New Interdisciplinary Domains

Mix Labs and Mix Offices have also significantly contributed to promote bottom-up interdisciplinary projects among young researchers as a place where new unique ideas in research are being generated from daily communications among the researchers from different fields working side-by-side. Other strategic measures listed below are also contributing effectively to facilitate interdisciplinary research.

ITbM Research Award: *promoting bottom-up research proposed by young researchers*

This award was established to foster interdisciplinary collaboration among young researchers and students. All ITbM members (except PIs) including postdoctoral researchers and students are eligible to apply. Selected proposals are each awarded 2 million yen over 2 years. The proposals prepared in English are pre-evaluated, and finally selected through oral presentation in English. The referees are all NU PIs, several overseas PIs, and in cases visiting professors with a high research profile. Through the three-time offers, ten proposals among the twenty were selected after careful evaluation, and most of the proposals have been making a good progress to mature into ITbM's representative research projects. The award also contributes to encourage young researchers to apply for external grants in the near future.

ITbM Workshop: *sharing research progress and find seeds of collaboration*

The workshop is held annually to follow-up, share research progress and to provide an opportunity for new collaboration. Members who participated in the workshop are those engaged in ITbM research including faculties, postdoctoral researchers, technical staff, students, and administrative staff, and extensive discussions about the details and plans of research were held across one or two days. The workshop functions to expand the bottom-up collaboration generated during daily discussions around his/her bench to the whole of ITbM members and invite further participants in the fields of synthetic chemistry, biology, and theoretical science.

ITbM Mix Hour: *sharing the background of each member and support team-up*

The ITbM Mix Hour started off as a small meeting to get to know each other, and has been expanded as a full ITbM seminar to share the background and specialty among ITbM researchers. Those who newly joined ITbM provide a self-introduction to share their background, which helps in devising new research plans and launching collaborative research. It also provides an opportunity for those who leave ITbM to present a summary of their research conducted at ITbM.

ITbM Tea Break Meeting: *promoting "Mix" by casual discussion*

ITbM started the Tea Break Meeting from 2015 to promote "Mix" through casual discussions such as on research progress and Mix Lab/Mix Office management. The meeting has been providing an important opportunity to mix the researchers, technical staff, and administrative staff situated on different floors of ITbM's building.

Research Promotion Division (RPD): *providing seamless research support and catalyzing collaboration*

RPD's activity, as denoted in Section 2-2, has been largely contributing to collaboration. RPD is playing a role of a catalyst to initiate collaboration through attending all PI's group meetings to follow-up the research progress and sharing the potential seeds with other groups of different research fields. This represents an asset of ITbM's RPD, consisting of highly motivated members holding higher degrees in related fields. As a result of this endeavor, the RPD follows each research from the beginning and is able to make strategic plans earlier about filing outcomes as intellectual properties and to carry out transfer of technology by finding matches that meets the needs of the firms. By being able to understand the science, the RPD is able to carry out effective international public relations, science visualization, and public outreach.

Chemical Library Center: *promoting ITbM's collaboration by providing biologically active molecules*

This center is playing an important role for collaboration by finding and providing active lead molecules toward specific biological assays. The importance of this center is evident as many of the research results denoted in Section 2-1 were achieved by a large contribution from this center. The center is preparing unique sets of libraries composed of selected commercial natural products, pharmaceutical compounds, and original synthetic compounds. Despite its limited size, it has been providing hit molecules to all the interdisciplinary research projects at ITbM, which means the project-based hit rate is 100%. The compound-based hit rate is also 0.5%, which is higher compared to the usual hit rate of 0.01-0.1%. The Chemical Library Center has made the collaborations between chemists and biologists to proceed smoothly. The size of the library expands by incorporating small compounds, peptides, and proteins synthesized at ITbM, and the center is envisaged to become a powerful and important entity for ITbM.

4. International Research Environment (within 4 pages)

4-1. International Circulation of the Best Brains

4-1-1. Results of International Joint Research (other than with the satellite)

National Science Foundation Center for Selective C-H Functionalization (NSF-CCHF), USA

As an international partner in the field of C-H activation chemistry constituting an important area of ITbM's research, ITbM started to collaborate with CCHF in 2013. CCHF is a virtual institute with top leading 23 PIs and their research groups working in the field of C-H activation chemistry in 14 universities/institutes across the USA. Around 4 to 5 researchers per year (duration: 3-6 months) are being exchanged between the institutes, which is envisaged to foster young scientists. So far, 3 collaborating papers have already been published in top journals (see Section 2-3), and further collaborations are ongoing. 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 selected, which will strengthen the partnership. This collaboration between CCHF and ITbM was highly evaluated by NSF. ITbM has also expanded the network to include other related institutes such as the Institute for Basic Science (IBS, KAIST, Korea). Now the three institutes hold online meetings and virtual symposia through TV conferences on a regular basis. ITbM will host a joint international workshop in June 16-18, 2016, inviting the members of CCHF and IBS to Nagoya. Many researchers, including graduate students from these centers will come to ITbM as participants.

The exchange record with CCHF:
From ITbM to CCHF
FY2013: 1 PhD student (Emory Univ.)
FY2014: 3 PhD students (Scripps Research Institute, Caltech, Emory Univ.)
FY2015: 4 PhD students (Emory Univ., Stanford Univ., Georgia Tech, Caltech)
From CCHF to ITbM
FY2014: 1 faculty (Scripps Research Institute), 3 students (Emory Univ., Georgia Tech)
FY2015: 2 students (Emory Univ.)

Freiburg University, Germany

NU's European Center was established in Freiburg and strong collaborative relationships already exist with Freiburg University. In 2014, both universities signed a MOU for further promotion and collaboration across various research fields, and the PhD joint degree program was launched at the Medical Schools. At ITbM, Higashiyama (Vice-Director) and Ueda (Lecturer) have started collaborative research in plant biology with Freiburg University (Prof. Laux). ITbM will conduct further collaborative research in biochemistry and chemistry with Freiburg University. In 2014, ITbM and the Department of Natural Science of Freiburg University held a joint symposium at Freiburg to initiate collaborative research. In 2015, Nagoya IAR of NU and FRIAS of Freiburg University jointly launched a "Joint Freiburg-Nagoya Project Group" and a call for collaborative research. A proposal organized by Ooi and Itami of ITbM and Prof. Breit in Freiburg University was selected, and the collaboration was recently launched. A researcher from the Ooi group will be visiting the Breit lab to start experiments from June, while ITbM will accept a researcher from Freiburg in September 2016.

Broad Institute of MIT & Harvard, USA

Prof. Stuart Schreiber (Director of Broad Institute, USA), who has initiated the field of chemical biology, visited ITbM as the winner of Nagoya Gold Medal in January 2016. During his stay, Itami had a discussion with Prof. Schreiber, in which they discussed on various issues including chemical biology and the future of science (the interview was published in "Chemistry Today" in April 2016 and will be on-air in YouTube in the near future). In their discussion, they concluded to run together to develop frontier research of chemistry and biology. A collaborative research will start from June 2016 by sending a PhD student from the Itami group to the Broad Institute.

The Scripps Research Institute, USA

ITbM has already been collaborating with NSF-CCHF researchers as denoted above. In addition, the collaboration in biology will start as initiated by the Presidency of ITbM's overseas PI Steve Kay from 2015.

4-1-2. State of Top World-level Researchers residing at the Center

Describe the participation of overseas Principle Investigators, the short-term stays of joint researchers, and the state of participation in symposiums sponsored by the Center.

- In Appendix 4-2, enter the number of researchers from abroad within the total number of the Center's researchers, and their

annual transition

All of the 4 world-leading ITbM overseas PIs continue to actively contribute to the various activities of ITbM. They are staying in Nagoya for 1-2 months per year and attending the site visits and annual international symposia, ISTbM. Even when they are absent from Nagoya, they have close contact with their respective Co-PIs and postdoctoral researchers through regular TV conferences or e-mails. They also send two – three young researchers of his/her institutes to ITbM.

One of the overseas PIs set-up a "clone-lab" having the same equipment, instruments, and software as his own lab and shares their database, which is significantly contributing to carrying out effective research. Both labs are connected over Face-Time for 24 hours and have good tools for communication.

While Irle was only a full-time foreign PI, Florence Tama joins in April 2016 as a full-time female PI.

ITbM launched a short-stay program of international top-level researchers. This program will contribute to improve international visibility and to launch new international collaborations.

4-1-3. Utilization and Employment Situation of Young Researchers

Describe the utilization and employment situation of young researchers including postdoctoral researchers.

- In Appendix 4-3, enter the state of international recruitment for postdoctoral researchers, applications received, and selections made
- In Appendix 4-4, enter the percentage of postdoctoral researchers from abroad
- In Appendix 4-5, enter the state of postdoctoral researchers' employment

In order to enable NU's 7 PIs to focus on their research, NU provided permission to employ 7 Associate Professors and Lecturers to provide lectures and handle educational affairs in the place of the PIs. Recruitment started from FY2012. To start with, 3 faculty members were employed in April 2012 and the remaining 4 faculty members were employed during FY2013. One of them became an Associate Professor (tenure) of Nagoya University in March 2015.

In addition, 3 Co-PIs to work with overseas PIs were employed in February (1) and April 2013 (2), and 1 additional Co-PI was employed to work with Steve Kay in May 2014.

The 3 Chief Coordinators for the 3 centers (Live Imaging Center, Chemical Library Center and Molecular Structure Center) started up upon establishment of ITbM for the purpose of research support were employed in March, April and May 2013, respectively.

To enhance ITbM's research, 2 Assistant Professors, one in Irle's group in September 2014 and another in Kinoshita's group in April 2015 were employed. Also, one of the postdoctoral researchers, who had been achieving significant results in one of the core research projects at ITbM, was promoted to an Associate Professor in December 2015.

ITbM has been widely advertising its public recruitment of postdoctoral researchers worldwide. The advertisements have been posted not only on the websites of ITbM, NU and overseas PIs' institutions, but also on major journals such as Science and Nature, and job search sites such as JREC-IN. As a result, ITbM has received 103 applications (including 25 female applicants), and has been able to employ excellent non-Japanese researchers as postdoctoral researchers (15 in FY2013, 4 in FY2014 and 9 in FY2015).

Promotion activities for ITbM postdoctoral researchers and faculty have been showing positive outcomes. Amongst them, 2 ITbM researchers were awarded with JSPS Postdoctoral Fellowships for Overseas Researchers and 14 researchers have left ITbM for new positions. Fortunately, 8 researchers succeeded in gaining positions as Associate Professor, Assistant Professor or equivalent positions at universities and research institutions both within and outside Japan. In addition, 1 postdoctoral researcher has been selected for the YLC (Young Leaders Cultivation) Program by the Institute for Advanced Research in NU (both assistant professors) and 1 researcher has been assigned as a Designated Assistant Professor in the Graduate School of Medicine, NU.

4-1-4. Other

Describe the Center's policy for sending Japanese researchers overseas to gain international experience, and give examples of how the Center is working to create career paths for its researchers within a global environment of researcher mobility.

Fostering young researchers is a key mission of ITbM. In addition to ITbM's programs to exchange faculty and graduate students with collaborating overseas institutions such as NSF-CCHF, ITbM is utilizing the international programs run by NU. The main examples are shown below.

Top Global University Project (MEXT)
The project is aiming to promote the globalization of Japanese universities, and strongly supports the collaborative research of ITbM and Freiburg University as shown in Section 4-1-1.

Dispatching Young Researchers Abroad Program at the Graduate School of Science (NU)
The program is aiming to foster young researchers including PhD students through research experiences (2-6 months) in overseas institutions. As of March 2016, 2 young faculties of ITbM and 1 PhD student have been supported and have conducted their international collaborative research abroad.

Long-term collaboration with University of Münster, Germany
The long-term mutual exchange of PhD students and young faculties with the University of Münster (Germany) had started as an "International Research Training Group (IRTG)" Program (FY2005-2011), and was followed by another Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation, "Innovative Molecular Catalysis and Novel Functional Materials" (FY2011-2014). In this program, ITbM's young faculties had the experience to give intensive course lectures in English, and PhD students conducted collaborative research. This program is further expanded by including Queen's University, Canada, and Kyoto University as the Core-to-Core Program "Elements Function for Transformative Catalysis and Materials" (FY2014-2018).

4-2. Creating the Center's Environment

4-2-1. Holding International Research Meetings

Describe the results obtained from holding the Center's main international research meetings.

- In Appendix 4-6, enter the number of international research conferences or symposiums held and give up to two examples of the most representative ones.

International Symposium on Transformative Bio-Molecules (ISTbM)
ITbM is organizing its annual international symposium (ISTbM), by inviting prestigious researchers from around the world, who are closely related to ITbM's research fields of systems biology, biochemistry, synthetic chemistry, and theoretical science. ITbM has organized its first symposium (ISTbM-1) in April 2013 to commemorate the launch of the institute. At ISTbM-1, 8 invited speakers along with ITbM's starting 10 PIs, presented their research. Amongst the invited speakers were Professor Huw Davies of Emory University, Director of NSF-CCHF (USA) and Professor Kazuo Shinozaki, Director of RIKEN CSRS, which led to interactive discussions and initiation of research collaborations between the institutes.

ITbM organized its second symposium (ISTbM-2) in May 2014. At ISTbM-2, the following 5 speakers who are closely related to ITbM's research fields of systems biology, biochemistry, synthetic chemistry, and theoretical science were invited to present their research: Professors Robert E. Campbell (University of Alberta), David C. Nelson (University of Georgia), David J. Craik (University of Queensland), Sukbok Chang (KAIST) and Hisashi Yamamoto (University of Chicago/Chubu University).

ITbM organized its third symposium (ISTbM-3) in May 2015. At ISTbM-3, the following 6 speakers were invited to present their research: Professors Yoshinori Fujiyoshi (School of Pharmaceutical Science, Nagoya University), Makoto Fujita (University of Tokyo), Gregory A. Voth (University of Chicago), Wolf Frommer (Carnegie Institute), Christopher H. Chang (University of California, Berkeley), and Sean Cutler (University of California, Riverside). In addition, the following speakers from NU also spoke about their research: Professors Yoshikatsu Matsubayashi (plant biology), Hiroshi Abe (bio-probes), and Florence Tama (bio-simulation). From ITbM, Yamaguchi, Yoshimura and Ooi reported on their progress at ITbM.

Hirata Memorial Lecture and Hirata Award
In memory of NU's late honorary professor Yoshimasa Hirata, the Hirata Memorial Lecture had been held each year. ITbM became the organizer of the Hirata Memorial Lecture on its 10th anniversary year and held the symposium in February 2014. Professor Martin Burke (University of Illinois) was selected as the winner in 2014 and was invited to present his research along with the following special invited speakers: Professors Yoshito Kishi (Harvard University), Justin DuBois (Stanford University) and Daisuke Uemura (Kanagawa University).

From 2015 onwards, the Hirata Memorial Lecture was renamed as the Hirata Award and the 11th award lecture was carried out at the same time as ISTbM-3 (see above). The 11th Hirata Award was presented to Professor Ashraf Brik (Technion-Israel Institute of Technology), in recognition of his research to elucidate the mechanism of protein decomposition through ubiquitin, using a chemically synthesized protein.

Tsuneko and Reiji Okazaki Award
The Tsuneko and Reiji Okazaki Award was established to recognize rising stars in the field of molecular biology, and ITbM organized the 1st award along with ISTbM-3 (see above). The 1st Tsuneko and Reiji Okazaki Award was presented to Professor Feng Zhang (Broad Institute of Harvard and MIT), in recognition of his impressive research accomplishments in the development and application of genome editing. The award was presented by Honorary Professor Tsuneko Okazaki (Nagoya University) after Professor Zhang's award lecture.

Nagoya Medal of Organic Chemistry
From 2014, Itami was selected to become the chair of the Nagoya Medal of Organic Chemistry, which is an international award in organic chemistry that has been granted to many prestigious researchers across the world. The Nagoya Medal was established in 1995 by Professors Hisashi Yamamoto (University of Chicago/Chubu University) and Nobel Laureate Ryoji Noyori and is held each year with the financial support by the Banyu Life Science Foundation International. In October 2014, ITbM organized the 20th Nagoya Medal of Organic Chemistry at Nagoya University and invited Professors John Hartwig (University of California, Berkeley) and Itaru Hamachi (Kyoto University) as the Nagoya Gold and Silver winners, respectively. The 21st Nagoya Medal of Organic Chemistry was organized by ITbM and held at NU in January 2016, inviting Professors Stuart Schreiber (Broad Institute of Harvard and MIT) and Zhaomin Hou (RIKEN) as the Nagoya Gold and Silver medalists, respectively. This event had more than 400 attendees, including the founders of the Nagoya Medal, Professors Yamamoto and Noyori.

4-2-2. Support System for Overseas Researchers

To allow the researchers from abroad to settle down in Japan and focus on their research, ITbM has assigned a staff in RPD to support the daily lives of foreign researchers and their families. The staff provides a wide range of support such as assistance in registrations at city council and banks, linguistic support (interpretation and translation) and giving advice on daily lives, education and health care.

On Campus
As ITbM has been sending all notices from the university to researchers in both English and Japanese, NU realized the importance of this endeavor from ITbM, and the university administration office took over this process and started to send grants and funding information in both languages from the end of FY2013. All meetings at ITbM with participation of non-Japanese-speaking researchers are held in English and all documents and meeting minutes are prepared in both English and Japanese. Many documents for university administrative procedures have been translated into English by ITbM's Administrative Department. The Administrative Department especially focuses on providing attentive support in the employment and resignation of non-Japanese researchers and provides detailed explanations of Japanese tax and the social insurance system in English. Based on these experiences, ITbM has joined the English Translation Promotion Project in NU from FY2015.

Daily Life
In order to provide a better environment for foreign researchers to focus on their research, arrangements have been made with the university's accommodation facilities, and university rules have been revised so that ITbM postdoctoral researchers can stay in the accommodation facilities for up to 2 years (initially 1 year before changing the regulations). Also, ITbM helps foreign researchers who are looking for an apartment outside the campus by providing linguistic support when signing an apartment lease contract and other procedures required for living, and helps them settle in the neighborhood.

Education
ITbM has also been cooperating with the Nagoya City Board of Education and other universities in the region by providing assistance to enter local public schools in Nagoya, supporting communications between school and families and introducing private Japanese teachers and educational materials to learn Japanese. ITbM has also negotiated with the international schools near NU to accept preschool children of the researchers arriving from overseas.

Health Care
ITbM's staff has collected information of hospitals with English services in Nagoya to cover major 9 medical departments. ITbM supports the health care of foreign researchers and their families by accompanying them to hospitals, supporting pregnant mothers for childbirth, along with providing advice in selecting hospitals, and providing information on vaccination for children. To provide advanced medical service information, ITbM plans to sign a contract with International SOS in the near future.

5. Implementing Organizational Reforms (within 3 pages)

5-1. Operation carried out under the Center Director's Leadership

Describe the division of roles and authority between the Center and its host institution, and the state of the Center director's presence at the Center.

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 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.

The Steering Committee has been held once a month to discuss and consider important matters of the center, including research plans, operation and management, personnel affairs and the budget.

The Steering Committee is a place for discussion and provides advice for the Director to make the final decisions. The Committee members include the Director, 2 Vice-Directors, Administrative Director, Head of Research Promotion, 5 NU PIs, and the Trustee of NU (in charge of WPI affairs). The Director operates and manages the Center in consultation with the Steering Committee.

The Director has been holding a regular meeting with the President of NU once a month to discuss over any issues related to the management of ITbM.

5-2. Administrative Personnel who facilitate the use of English in the Work Process

The Administrative Department led by the Administrative Director, consists of the following 2 divisions, with 2 Associate Administrative Directors (the Head of Management and the Head of Research Promotion) to assist the work of the Administrative Director. In FY2016, the Strategic Planning Division will be newly established as part of the Administrative Department.

Management Division

With the Head of Management, the Management Division consists of the General Affairs Unit (4 staff) and the Accounting Unit (5 staff). The 9 staff in the Management Division consists of 4 full-time administrative staff from the university (including 2 competent English speakers), 4 contract employees (including 3 competent English speakers) and 1 part-time employee.

Research Promotion Division

With the Head of Research Promotion (Associate Professor, PhD in synthetic chemistry and chemical biology), the Research Promotion Division consists of an Assistant Professor (PhD in organometallic chemistry) and a science designer (Masters degree in plant biology) to conduct international promotion of research, research administration, public relations, outreach activities, along with event management, and a University Research Administrator (PhD in bioinorganic chemistry holding a concurrent post), a Lecturer (Patent attorney/ degree in catalytic chemistry) in charge of intellectual property management, and a contract employee (Bachelors degree in plant biology) to support the daily living of foreign researchers at the center. Many of the members at the RPD are proficient in English.

Strategic Planning Division (Established in April 2016)

In strong cooperation with the Research Promotion Division, the Strategic Planning Division plays a key role in realization of the practical use of the research outcomes at ITbM by working out strategies for the acquisition of intellectual property rights and business matching with companies. This will enable ITbM to enhance the value of research outcomes and share the benefit to the society. At the Strategic Planning Division, 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 and a good fluency in English will be employed as of April 2016.

Secretaries for PIs and Overseas PIs

ITbM has employed 5 secretaries to support NU PIs (3 of them are competent in English) and 2 secretaries for the 4 overseas PIs (both competent in English).

5-3. System Reforms and Their Ripple Effect within the Host Institution

Describe the following:
- Reforms to the Center's research operation advanced by way of the WPI Program's research-results evaluation system
- Reforms to the Center's operation made by introducing a merit-based salary system
- Ripple effects of the Center's system reforms within the host institution

Evaluation system and Incentives

According to the "Implementation Guidelines for the Special Bonus System for Persons in the Service of Nagoya University Institute of Transformative Bio-Molecules", which is the system to provide incentives to the Director, the Vice Director, PIs, and the Administrative Director based on their performance and evaluations, the determination of eligible persons and the amount of incentive is left to the discretion of the Director. The Executive Board of NU will evaluate the Director in reference to the Center's achievement and the WPI committee's report.

All researchers at ITbM including postdoctoral researchers are evaluated every year through an annual report to be submitted at the end of each fiscal year. While the evaluation is reflected on the incentives for PIs and others as stated above, other designated faculties and postdoctoral researchers are subject to a salary increase based on their evaluation upon renewal of their contract.

"WPI-next" program

In reference to ITbM's unique personnel structure such as Co-PI system, the "WPI-next" program was launched at NU to support the world-leading science. There were 2 projects that were selected in 2014.

"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 institutes, NU conducted the organizational reform of research supporting units to establish the "Department for Academic Research & Industry-Academia-Government Collaboration".

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.

Information Distributed in English

As grants and funding information from the university were initially provided in Japanese, these were translated into English by the ITbM administrative office. NU realized the importance of these endeavors and subsequently, the university administration decided to take over this activity and started to distribute information of grants and funding and other information in both English and Japanese from the end of FY2013. This reflects ITbM's efforts to support foreign researchers are spreading across the university.

5-4. Support by Host Institution

Besides the state and effectiveness of the host institution's support for the Center, describe the Center's positioning within the host institution's mid- to long-term plans.
- In Appendix 5-1, describe specific support measures being taken by the host institution.

NU has been strongly supporting ITbM. President Matsuo and Director Itami have a regular meeting once a month and discuss ITbM's management including the future plan to establish ITbM as a sustainable research center. NU is working to reform structures, strengthen financial base, and improve university-wide communication to more effectively and flexibly assign resources. Through these measures, ITbM is expected to become sustained at NU.

NU has amended its mid-term plans by adding the following statement "Establishment of core research centers by promoting the projects including the World Premier International Research Initiative and the International Science Innovation Center Development Project (COI)" and includes promotion of ITbM's research in the FY2014 plan. In addition, the previous Hamaguchi Plan of NU specified that "Establishment of the World Premier International Research Initiative (WPI) – Institute of Transformative Bio-Molecules" for the promotion of world-class research, and the NU's support to ITbM is further emphasized in the Matsuo Plan "NU MIRAI 2020".

Representative concrete measures are 1) provision of space, 2) financial support towards construction of ITbM's new building, 3) support towards the operation of the new building, 4) covering salaries, 5) ITbM's priority to the use of hall of residence. More details are available in Appendix 5-1.

5-5. Others

5-5-1. Efforts to Foster Young Researchers (e.g., start-up funding)

The ITbM Research Award was established in FY2013 to promote interdisciplinary research proposed by young researchers, postdoctoral researchers, and students. Applicants can apply for the award annually, and 20 applications of the newly proposed interdisciplinary research have been received in 3 rounds of offerings up to now. Among them, 10 proposals were adopted through careful consideration. Among the proposals, 2 of them have already led to the discovery of molecules having potent and selective activities, filed for patents, and submitted their papers to journals. In the research related to *Striga*, the research group rapidly developed a novel fluorescent probe "Yoshimulactone" and introduce it into the market through patent application and licensing. Soon after its publication (Science 2015), this research was covered by the media in the world and was chosen for "Signaling Breakthroughs of the Year 2015".

Personnel exchange between overseas bases, such as NFS-CCHF has been active year by year, ITbM has exchanged 13 students with NSF-CCHF up to date. In the next fiscal year, ITbM will hold the Joint Workshop in the middle of June 2016 (from 16 to 18 June, 2016) with NSF-CCHF and the Institute of Basic Science (Korea), and with Academia Sinica (Republic of China) in the middle of November 2016 (from 15 to 17 Nov, 2016), at NU. Many synthetic chemists, biochemists, and biologists including graduate students are scheduled to visit ITbM and have interactive discussions.

On the educational front, to establish the education system for students to learn "chemical biology", ITbM has decided to start a lecture course series on chemical biology. In addition, ITbM tours for high schools and universities in USA and Asian countries have also been ongoing.

Thus, ITbM has supported young students and researchers both in research and education, and has actively promoted their development in the interdisciplinary area of synthetic chemistry, plant/animal biology, and theoretical sciences.

5-5-2. Appointment of Female Researchers

- In Appendix 5-2, give the transition in the number of female researchers.

At ITbM, 2 female PIs (Torii, Crudden) have been in roll, and they are leading the world by conducting cutting-edge science. Their remarkable achievements are evident in their collected number of awards (see Section 2-4 and Appendix 2-4). ITbM also has 7 female faculties and 8 female postdoctoral researchers, with 17 in total, counting to 26% among all the researchers. In addition, one foreign female PI (Florence Tama) joins ITbM as of April 2016.

The activity of female PhD students is also remarkable. For example, Ms. Akiko Yagi in the Itami group and Ms. Maki Hayashi in the Kinoshita group were awarded the "L'Oreal-UNESCO Award for Women in Science, Japan Encouragement Prize" in 2014 and 2015.

NU has been actively engaged in developing women leaders and young female researchers who can play a leading role in the world, by preparing nursery schools and after-school childcare center on campus ahead of other universities in Japan. Due to their efforts, the President of NU was selected as one of the 10 world universities that have made advanced efforts to promote gender equality under the IMPACT 10x10x10 program of United Nation Women's HeForShe movement. ITbM is fully utilizing these platforms to support female researchers.

6. Future Vistas (within 2 pages)

6-1. Future Policies and Plans for Advancing the Center's Operation and Project

ITbM is placed as a significant research institute conducting frontier basic research at NU in the University's mid-term plans and President Matsuo's Initiative. Under the strong support of NU, ITbM's challenge to create "transformative bio-molecules" is making remarkable progress. A number of interdisciplinary research projects are ongoing through a good collaboration of synthetic chemists, plant/animal biologists, and theoretical scientists. Several outcomes have been filed as patents and published in journals, and in FY2016, their numbers should increase significantly.

An important key to promote interdisciplinary research is ITbM's "Mix" strategy. In the new building designed to reflect the "Mix Lab" concept, interdisciplinary research is further enhanced to produce many seeds for transformative bio-molecules.

The next challenge is how to utilize ITbM's outcomes and to contribute to the society. Upon the development of novel products based on ITbM's molecules and molecular technologies, this will largely improve ITbM's international/national visibility and recognition by the general public. To achieve this, the "Strategic Planning Division (SPD)" will be newly established in April 2016, by hiring experienced personnel. The SPD will make strategies and prepare a roadmap to contribute to the scientific community and society.

Molecules developed at ITbM are classified into two main types of use; one as research tools and another for general use. The research-based molecules will be immediately filed for patents, published in journals, and subject to technology transfer to the appropriate reagent companies and major institutes to be available to any researcher, as was the case of "Yoshimulactone". For those molecules of general use, such as the *Striga* killer and plant growth promoters, ITbM will start collaborations with a suited firm through matching immediately after finding bioactive lead compounds, and will proceed to make a plan of IP and further development towards its wide use in general society. The collaboration with firms is essential to advance the development process adequately under regulations and laws.

ITbM has several industrial partners of chemicals, pharmaceuticals, and agrochemicals. In order to achieve the best matching with industries, ITbM will launch a consortium by enrolling firms of related fields and expand its network. The consortium also functions to collect the needs of industries and of societies.

Fostering young researchers who carry out ITbM's interdisciplinary research is also a key mission. ITbM started educational activities for students. As part of NU's graduate school of science, faculties of ITbM and related departments will provide a new chemical biology lecture series from FY2016. The class will be open to the whole University.

ITbM will continue its challenge toward internationalization. Through expansion of its international network, exchange of researchers and PhD students with overseas institutions will be promoted by using various resources available at ITbM and NU as stated in Section 4-1-4. Especially during 2016, ITbM will make even stronger bonds with the Broad Institute and the Scripps Research Institute through collaborating research and exchanging researchers and students.

6-2. Measures to sustain the center as a World Premier International Research Center after Program Funding Ends

As clearly indicated in President Matsuo's Initiative "NU MIRAI 2020", NU reorganizes the research centers/institutes and supports frontier research led by the "Institute for Advanced Research" for fundamental research and the "Institute of Innovation for Future Society" for applied research. Under the umbrella of the "Institute for Advanced Research", ITbM will be supported as an international research institute conducting frontier basic chemistry and biology. ITbM's target fields should flexibly revised according to the social needs, and accordingly the Director, PIs, and researchers may change in the future. NU will continue the ongoing supports towards ITbM, and will provide additional support to manage the center even after termination of funding from the WPI program. For this purpose, NU will reform structures and strengthen its financial base (Section 5-4 and Appendix 5-4). ITbM also continues its effort to obtain expenditures through every measure as stated in Section 6-1. ITbM will also apply to grant opportunities of overseas foundations.

7. Others (within 1 page)

* In addition to the above 1-6 evaluation items, only if there is anything else that deserves mention regarding the center project's progress, please note it.

ITbM's wealth and safety training for interdisciplinary research

While the interdisciplinary research is rapidly in progress at the Mix Labs, ITbM has to provide special safety training suitable for interdisciplinary environments. The training also provides an opportunity to explain to the foreign researchers about the difference among the safety rules of Japan and their countries. ITbM started the original safety training in FY2014. The course consists of 3 sections; general safety lecture, specific lab safety lecture, and practical training. All the researchers of ITbM learn about safety of both chemistry and biology labs/experiments, such as safe use/disposal of chemicals in the Chem Mix-Lab and contamination of exogenous germs and seeds in the Bio Mix-Lab. Differences in domestic and foreign regulations of chemicals and biological materials, such as a color and contents of a gas cylinder are covered. The ITbM safety course has been authorized as the official training of NU from FY2015.

Concern for the environment and safety

Upon development of molecules that modulate biological system in plants/animals, it is essential for ITbM to communicate to the general public widely that ITbM always addresses the environmental and safety issues carefully, and to gain the understanding from the international/domestic societies and local community. Accordingly, ITbM has set up an Environment and Safety Committee (see below) so that researchers at ITbM are constantly aware of these issues when conducting their research. The committee also contributes to prepare and improve the ITbM's safety training course stated above. In addition, ITbM has been actively involved in public outreach events (Science Agora, science café, open lectures) to explain ITbM's concern for safety and environmental issues. In the media, ITbM also expresses its consideration towards safety. Upon being featured in Japan national TV program, NHK "Chikyu (Earth) Agora" (broadcasted in December 2014), ITbM emphasized the significance on the safety of new species and molecules created at ITbM.

ITbM has been conducting Ames test to check mutagenicity of molecules created at ITbM to secure their safety since FY2014. In the past 2 years, 11 compounds were examined, and their safety information were fed back to the researchers.

Environmental and Safety Committee

As ITbM aims to create chemical compounds that affect plants and animals, as well as generate new plant and animal species, the Environmental and Safety Committee was established to seek the counsel of experts for ITbM's research to be conducted competently whilst complying with the laws and regulations.

Mission:

To evaluate whether new compounds and species generated through ITbM's research along with their methods address environmental and safety issues appropriately, comply with laws and regulations, and thus provide relevant advice to the Director.

Members:

1 Nagoya University PI
- Toshinori Kinoshita, Director of Center for Gene Research, Nagoya University

1 Internal Expert within Nagoya University
- Associate Professor of Jurisprudence, Graduate School of Law, NU

4 External Experts outside Nagoya University
- Trustee/Vice-President of Okayama University
- Senior Research Administrator, Strategic Program Support Unit, Okayama University
- Head of Natural Environment Division, Department of the Environment, Aichi Prefecture
- Senior Councilor, Life & Bio Plaza 21 (NPO)

8. Center's Response to Results of FY2015 Follow-up (including Site Visit Results) (Use as Many Pages as needed.)

Describe the Center's Response to Results of FY2015 Follow-up. Note: If you have already provided this information, please indicate where in the report.

Recommendations to ITbM by the Working Group:

1. ITbM should create a strong identity that distinguishes it from other national and international centers with similar research focuses. Considering the fact that fusion is ITbM's hallmark in creating transformative biomolecules, the number of joint publications is an important parameter for measuring the center's success and identity.

<ITbM's response>

As stated by the Working Group, ITbM's identity is to create a new interdisciplinary research field through the fusion between animal/plant biology and synthetic chemistry. This is brought about by ITbM's compact nature, which enables close collaboration between research groups. Outputs from collaborative research can been seen by the increasing number of joint publications and patent applications as follows: 2 patent applications in 2013, 3 journal publications and 2 patent applications in 2014, 7 journal publications and 2 patent applications in 2015, 2 journal publications and preparation of 1 patent application in 2016.

The ITbM Research Award, which was established to promote interdisciplinary research proposed by young researchers, has shown to be highly successful. For example, the following 2 projects proposed in 2013, "Synthetic compounds that alters plant circadian clock and flowering time"[*1] and "Discovery of new molecules that control the cell cycle: Understanding the mechanism of animal and plant"[*2], have already led to the discovery of effective molecules, which have been filed for patents and prepared for journal publications. Moreover, the "Fluorogenic probes for strigolactone receptors" project, which was selected in 2014, has led to the development of a new fluorescent probe "Yoshimulactone". This outcome was published in the journal, *Science*, filed for a patent and has been commercialized as a visualizing reagent. The research was also featured in various media and was selected as a "Signaling Breakthroughs of the Year 2015" in *Science*.

*1 Project members: Norihito Nakamichi, Saori Takao (Kinoshita Group), Junichiro Yamaguchi, Takahiro Uehara (Itami Group), Kohsuke Ohmatsu, Yukino Furukawa (Ooi Group)

*2 Project members: Masakazu Nambo (Crudden Group), Taeko Ohkawa (Yoshimura Group), Daisuke Kurihara, Minako Ueda (Higashiyama Group), Keiko Kuwata (Molecular Structure Center)

*3 Project members: Masahiko Yoshimura, Shinya Hagihara (Itami Group), Yuichiro Tsuchiya (Kinoshita Group), Yoshikatsu Sato (Live-Imaging Center), Keiko Kuwata (Molecular Structure Center), Ayato Sato (Chemical Library Center)

*4 http://stke.sciencemag.org/content/9/409/eg1.full

2. Development of a strategic plan for the next several years is important..

<ITbM's response>

Since the finishing of ITbM's new research building, ITbM has finally established an environment where researchers can fully concentrate in their research. ITbM plans to concentrate on advancing and disseminating its ongoing interdisciplinary research in the next 3 years. This is currently of significant priority for ITbM. ITbM is also under preparation to launch new research projects and discover new seeds.

Plans for the ITbM's flagship research areas for the next 3 years:

(1) Plant chemical biology

- Development of highly active and selective molecules that either suppress or promote the

germination of the parasitic plant *Striga*.
- Development of highly active and selective molecules that control the number and/or opening/closing of plant stomata, along with elucidation of the molecular mechanism and effect of the molecules towards plant growth.
- Identification of molecules that controls pollen tube guidance and elucidation of its molecular mechanism.
- Discovery of unidentified protein receptors of plant hormones.

(2) Chemical chronobiology
- Development and commercialization of tool molecules that control mammalian circadian rhythm, as well as elucidation of its molecular mechanism. Application towards clinical uses (currently under collaboration with RaQualia).
- Development of synthetic molecules that control plant circadian rhythm, as well as elucidation of its molecular mechanism.

(3) Chemistry-enabled live imaging
- Development and commercialization of high photo-resistant fluorescent dyes with practical applications and super-resolution fluorescence imaging.

The next challenge is how to utilize ITbM's outcomes and to contribute to the society. Upon the development of novel products based on ITbM's molecules and molecular technologies, this will largely improve ITbM's international/national visibility and recognition by the general public. To achieve this, the "Strategic Planning Division (SPD)" will be newly established in April 2016, by hiring experienced personnel. The SPD will make strategies and prepare a roadmap to contribute to the scientific community and society.

Molecules developed at ITbM are classified into two main types of use; one as research tools and another for general use. The research-based molecules will be immediately filed for patents, published in journals, and subject to technology transfer to the appropriate reagent companies and major institutes to be available to any researcher, as was the case of "Yoshimulactone". For those molecules of general use, such as the *Striga* killer and plant growth promoters, ITbM will start collaborations with a suited firm through matching immediately after finding bioactive lead compounds, and will proceed to make a plan of IP and further development towards its wide use in the general society. The collaboration with the firms is essential to advance the development process adequately under regulations and laws.

ITbM has several industrial partners of chemicals, pharmaceuticals, and agrochemicals. In order to achieve the best matching with industries, ITbM will launch a consortium by enrolling firms of related fields and expand its network. The consortium also functions to collect the needs of industries and of societies.

3. It would be worthwhile to consider a summer school and a graduate program, which would further increase the center's international visibility and promote interdisciplinary education that will enhance the effectiveness of its Mix-Lab strategy..

<ITbM's response>

ITbM is currently starting educational activities for students in order for the next generation of scientists to carry out ITbM's interdisciplinary research.

ITbM's faculty will start a new chemical biology lecture series from FY2016, as part of NU's graduate school.

ITbM is scheduled to hold a joint international workshop in June 16-18, 2016 with its international partner institutes, NSF Center for Selective C-H Functionalization (CCHF, USA) and Institute for Basic Science (IBS, Korea). Many researchers, including graduate students from these institutes will come to ITbM as participants. These researchers have already expressed an interest in ITbM's interdisciplinary research between chemistry and biology, and ITbM plans to share its activities as well as carry out discussions to start new international research collaborations.

4. Strategies for spin-off companies and commercialization of the most promising molecules should be established for the translation of basic achievements.

<ITbM's response>

Some of the research outcomes by ITbM have already been commercialized as products and license agreements with industries are also in progress. One representative example is Yoshimulactone, which has become available as a reagent on the market by Tokyo Chemical Industries in January 15, 2016. Currently, the PIs are involved in commercializing their own compounds with the help of ITbM's IP manager. In the near future, ITbM is considering of establishing a consortium-like organization that will be responsible for the overall commercialization of the molecules developed at ITbM. In order to do so, discussions with the university's office for industrial-academic collaborations are ongoing.

One of ITbM's plant biology research (Higashiyama and his co-worker) was adopted in the program for Creating Start-up from Advanced Research and Technology from JST (START program) and this will accelerate to start up a venture company in 2018.

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Appendix 1-1. FY 2015 List of Principal Investigators

NOTE:
・Underline names of investigators who belong to an overseas research institution. Place an asterisk (*) by names of investigators considered to be ranked among world's top researchers.
・In case of researchers not listed in the latest report, attach "Biographical Sketch of a New Principal Investigator".

<Results at the end of FY2015>

Principal Investigators Total: 11

Name (Age)	Affiliation (Position title, department, organization)	Academic degree, specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Center director Kenichiro ITAMI* (44)	Director, Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr.Eng *Specialties*: Organic Synthesis, Catalysis, Pharmaceuti-cal Science, Nanocarbon Chemistry	50%	30%	10%	10%	from the beginning	usually stays at the center	
Tetsuya HIGASHIYAMA* (44)	Vice-Director, Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr.Sci *Specialties*: Live Cell Biology, Plant Reproduction , Bio-active molecules, Peptides	70%	20%	0%	10%	from the beginning	usually stays at the center	
Jeffrey W. BODE* (41)	Professor of Organic Chemistry Department of Chemistry and Applied Biosciences, ETH Zürich, Switzerland	Doctoral of Natural Science *Specialties*: 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 FY2015. Connected 24 hours through iPad to the center. Holds on-line group meeting once a week. Joins PI meeting every two weeks online.	sent three young scientists to the center (three months each)

Cathleen M. CRUDDEN* (49)	Professor Department of Chemistry, Queen's University, Canada	Ph.D *Specialities*: Catalysis, Organic Synthesis, Materials Chemistry, Chirality	16%	5%	64%	15%	from the beginning	Stayed at the center one month in FY2015. Holds Skype group meeting once a week. Joins PI meeting every two weeks online.	sent one young scientist to the center (three months)
Stephan IRLE* (48)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Ph.D. *Specialties*: 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* (47)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr.Sci *Specialities*: Plant Molecular Physiology	80%	10%	0%	10%	from the beginning	usually stays at the center	
Takashi OOI* (50)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Engineering *Specialties*: Organic Synthesis, Catalysis, Molecular Recognition	80%	10%	0%	10%	from the beginning	usually stays at the center	
Keiko TORII* (50)	Distinguished Professor Department of Biology, University of Washington Investigator Howard Hughes Medical Institute and Gordon and Betty Moore Foundation (HHMI-GBMF)	Ph.D. *Specialties*: Plant Development, Signal Transduction, Stem Cell Maintenance/ Differentiati-on in Plants	16%	5%	64%	15%	from the beginning	Stayed at the center six weeks in FY2015. Holds on-line plant biology meeting “Mixplant meeting” once a week. Joins PI meeting every two weeks online.	

Shigehiro YAMAGUCHI* (47)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Engineering Specialties: Main Group Chemistry, Physical Organic Chemistry	80%	10%	0%	10%	from the begining	usually stays at the center	
Takashi YOSHIMURA* (46)	Professor Institute of Transformative Bio-Molecules, Nagoya University	Dr. Agriculture *Specialties*: Animal Physiology, Systems Biology, Neuroendoc-rinology	60%	10%	20%	10%	from the begining	usually stays at the center	
Steve A. Kay* (56)	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. *Specialties*: Chronobiolo-gy, Genetics, Biochemistry, Systems Biology	16%	5%	64%	15%	from April 1st 2014	Stayed at the center four days in FY2015. Holds on-line meeting on an as-needed basis	

Researchers unable to participate in project in FY 2015

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

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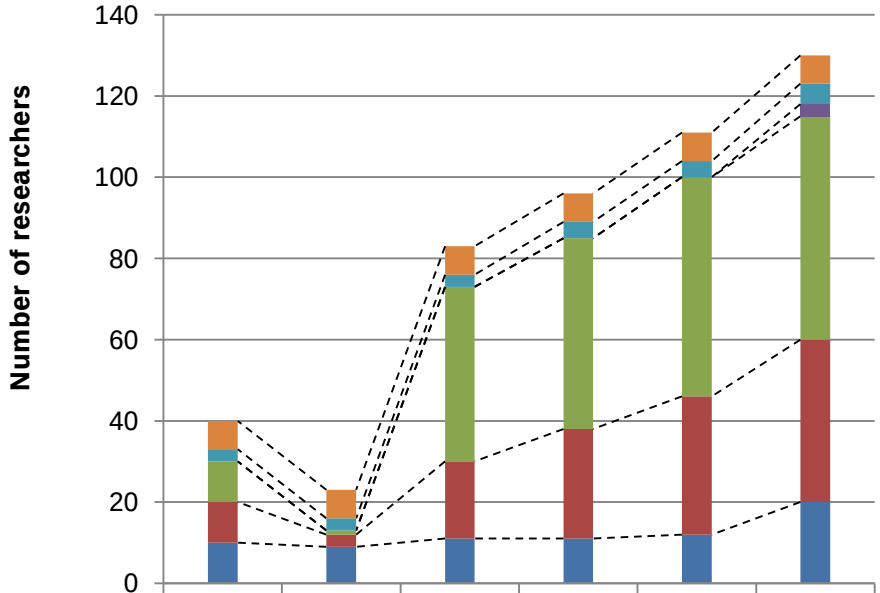
Appendix 1-2. Number of researchers in the "core" established within the host institution

*Make a graph of the annual transition in the number of center personnel since the start of project.

Annual Transition in the Number of Members



	At beginning	FY2012	FY2013	FY2014	FY2015	Final goal
PI: Researchers from within host institution	7	7	7	7	7	7
PI: Foreign researchers invited from abroad	3	3	3	4	4	5
PI: Researchers invited from other Japanese institutions	0	0	0	0	0	3
Other researchers	10	1	43	47	54	55
Research support staffs	10	3	19	27	34	40
Administrative staffs	10	9	11	11	12	20

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.

An additional female non-Japanese PI, Prof. Florence Tama is planned to join ITbM as a Nagoya University PI in April 2016.

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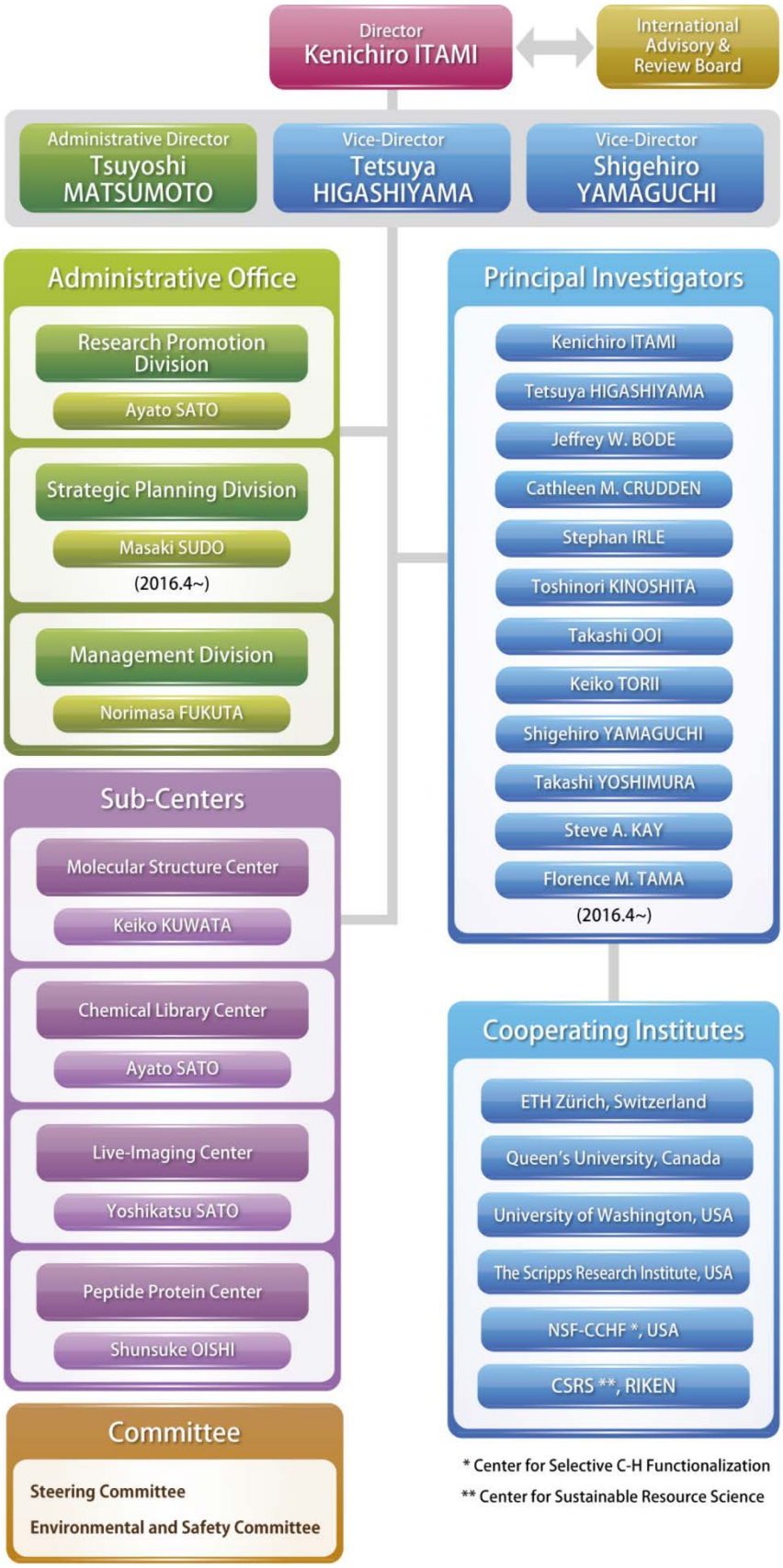
Appendix 1-3. Center's Management System

- Please diagram management system in an easily understood manner.



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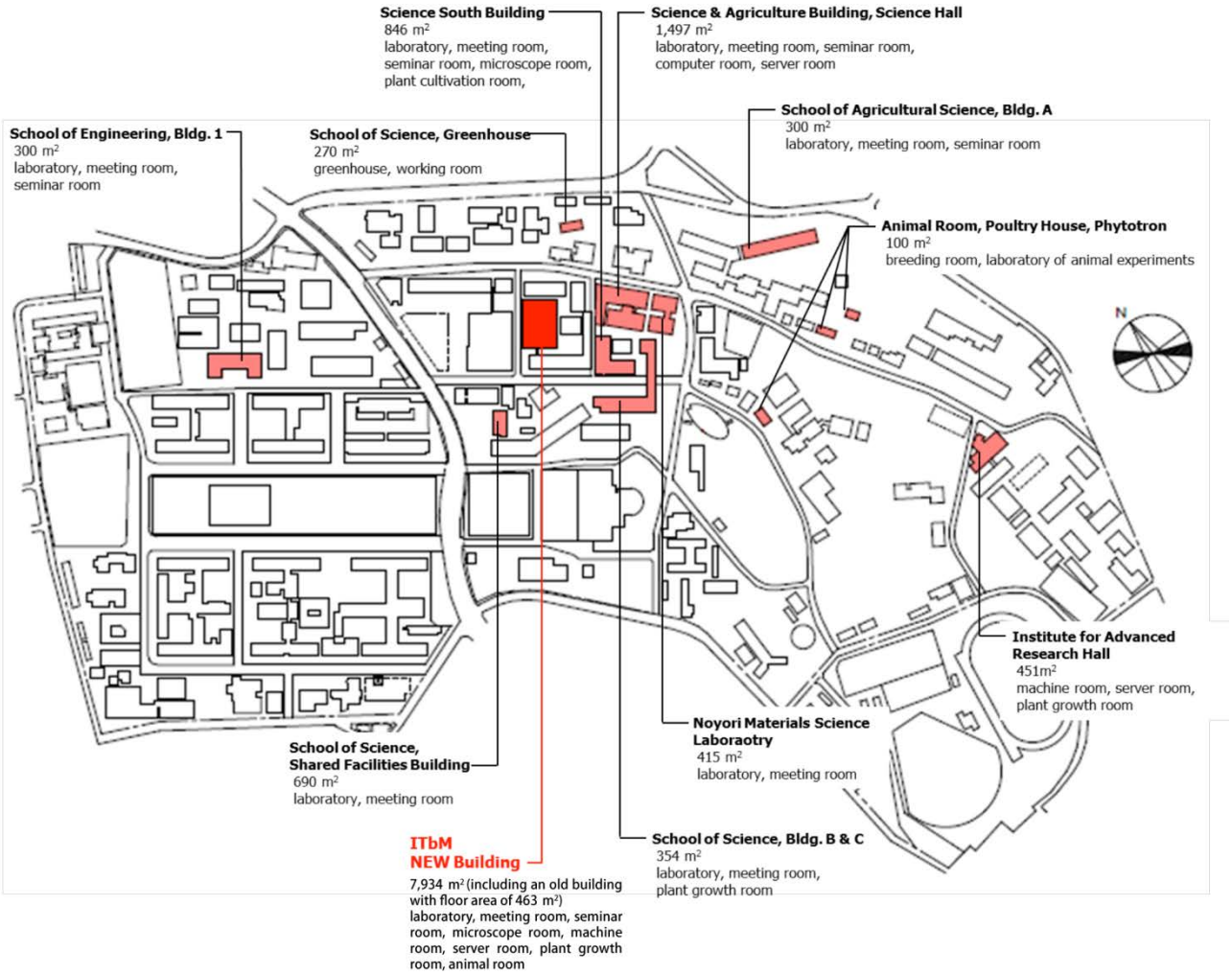
Appendix 1-4. Campus Map

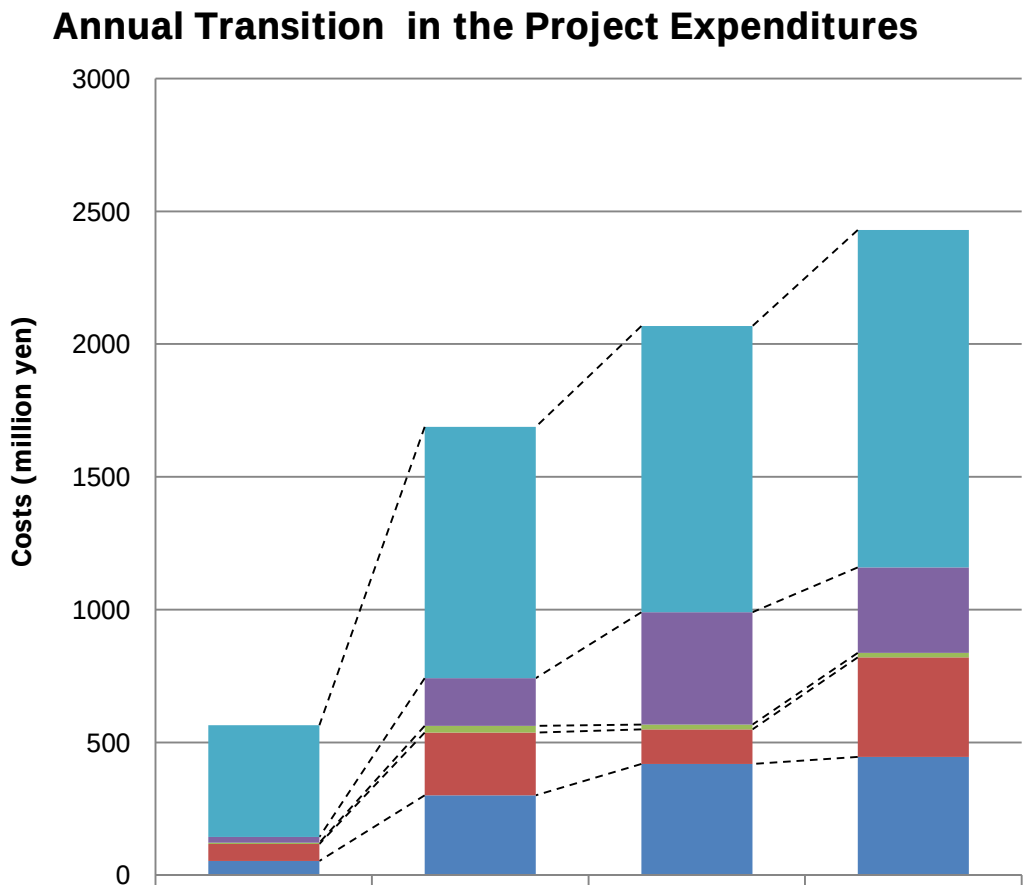
- Please draw a simple map of the campus showing where the main office and principle investigator(s) are located.



World Premier International Research Center Initiative (WPI)

Appendix 1-5-1. Annual transition in the project expenditures

*Make a graph of the transition in the number of overall project funding.



	FY2012	FY2013	FY2014	FY2015
Researchprojects	421	946	1078	1271
Equipment	22	180	423	322
Travel	4	25	18	17
Projectactivities	65	236	130	375
Personnel	53	301	419	445

- To date, what has the Center's thinking been about spending project funding, and how has the funding been spent?

WPI subsidy has been spent on management and improvement cost for the center, personnel expenses for researchers (Co-PIs and postdocs etc.) and research support staff (members in Research Promotion Division etc.), start-up cost, purchase of large-scale facilities for the shared use in the center and maintenance cost (utilities etc.). It is also spent on project promotion cost and travel allowance required for the promotion in building the research center.
For the research cost, it is covered by the competitive funding obtained by each researcher.

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Appendix 1-5-2. FY2015 Project Expenditures (the exchange rate used: 1USD= JPY)

i) Overall project funding

Cost Items	Details	Costs (million yen)
Personnel	Center director and Administrative director	29
	Principal investigators (no. of persons):8	87
	Other researchers (no. of persons):43	223
	Research support staffs (no. of persons):19	34
	Administrative staffs (no. of persons):23	72
	Total	445
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0
	Cost of dispatching scientists (no. of persons):1	1
	Research startup cost (no. of persons):20	134
	Cost of satellite organizations (no. of satellite organizations):0	0
	Cost of international symposiums (no. of symposiums):4	4
	Rental fees for facilities	27
	Cost of consumables	5
	Cost of utilities	46
	Other costs	158
	Total	375
Travel	Domestic travel costs	3
	Overseas travel costs	7
	Travel and accommodations cost for invited scientists (no. of domestic scientists):13 (no. of overseas scientists):8	4
	Travel cost for scientists on secondment (no. of domestic scientists):0 (no. of overseas scientists):7	3
	Total	17
Equipment	Depreciation of buildings	40
	Depreciation of equipment	282
	Total	322
Other research projects	Projects supported by other government subsidies, etc.	236
	Commissioned research projects, etc.	759
	Grants-in-Aid for Scientific Research, etc.	276
	Total	1271
Total		2430

million yen

WPI grant		652
Costs of establishing and maintaining facilities		0
Establishing new facilities (Number of facilities: , m²)	Costs paid:	
Repairing facilities (Number of facilities: , m²)	Costs paid:	
Others		
Cost of equipment procured		199
Name of equipment: Glove Box Number of units: 1 Set	Costs paid:	10
Name of equipment: Organic Solvent Purification Equipment Number of units: 1 Set	Costs paid:	6
Name of equipment: Office Furniture and Laboratory Benches Number of units: 1 Set	Costs paid:	31
Name of equipment: AV System Number of units: 1 Set	Costs paid:	12
Name of equipment: Automated Washing Machine Number of units: 1 Set	Costs paid:	4
Name of equipment:TV Conference System Number of units: 1 Set	Costs paid:	2
Name of equipment: Automated Peptide Synthesizer Number of units: 1 Set	Costs paid:	13
Name of equipment: Mass Spectrometry System Number of units: 1 Set	Costs paid:	30
Name of equipment: Auto-sampler Number of units: 1 Set	Costs paid:	13
Others		78

ii) Costs of Satellites and Partner institutions

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

Nagoya University

Institute of Transformative Bio-Molecules

World Premier International Research Center Initiative (WPI)

Appendix 2-1. List of papers underscoring each research achievement

- List papers underscoring each research achievement listed in the item 2-1 "Research results to date" (up to 40 papers) and provide a description of the significance of each (within 10 lines).
- 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.
- If a paper has many authors, underline those affiliated with the Center.
- If a paper has many authors (say, more than 10), all of their names do not need to be listed.

[1] Molecular control of plant growth

1. Koji Takahashi, Ken-ichiro Hayashi, Toshinori Kinoshita, *Plant Physiol*. **2012**, *159*, 632-641.
Auxin activates the plasma membrane H^+-ATPase by phosphorylation during hypocotyl elongation in *Arabidopsis thaliana*

The phytohormone auxin is a major regulator of diverse aspects of plant growth and development. However the ubiquitin-ligase complex SCFTIR1/AFB, which includes the TRANSPORT INHIBITOR RESPONSE1/AUXIN SIGNALING F-BOX (TIR1/AFB) auxin receptor family, has recently been demonstrated to be critical for auxin-mediated transcriptional regulation, the mechanism by which auxin mediates H^+-ATPase activation has yet to be elucidated. Kinoshita and coworkers succeeded to exhibit direct evidence for H^+-ATPase activation in *Arabidopsis thaliana* by auxin through phosphorylation during early-phase hypocotyl elongation. In addition, he also demonstrated α-(phenylethyl-2-one)-auxin known as the auxin antagonist specific for the TIR1/AFBs had no effect on IAA-induced H^+-ATPase phosphorylation. His results suggest that the TIR1/AFB auxin receptor family is not involved in auxin-induced H^+-ATPase phosphorylation. This is the long-sought mechanism that is central to the acid-growth theory.

2. Yin Wang, Ko Noguchi, Natsuko Ono, Shin-ichiro Inoue, Ichiro Terashima, Toshinori Kinoshita, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 533-538.
Overexpression of plasma membrane H^+-ATPase in guard cells promotes light-induced stomatal opening and enhances plant growth

Stomatal pores in the plant epidermis control gas exchange between plants and the atmosphere in response to light, CO_2, and the plant hormone abscisic acid. Light-induced stomatal opening is mediated by at least three key components: the blue light receptor phototropin, plasma membrane H^+-ATPase, and plasma membrane inward-rectifying K^+ channels. Very few attempts have been made to enhance stomatal opening of increasing photosynthesis and plant growth. Kinoshita and coworkers succeeded to demonstrate that stomatal aperture is a limiting factor in photosynthesis and plant growth, and that manipulation of stomatal opening by overexpressing H^+-ATPase using the strong guard cell promoter GC1 in guard cells is useful for the promotion of plant growth, and, in contrast, the overexpression of phototropin or inward-rectifying K^+ channels in guard cells had no effect on these phenotypes.

3. Jin Suk Lee, Marketa Hnilova, Michal Maes, Ya-Chen Lisa Lin, Aarthi Putarjunan, Soon-Ki Han, Julian Avila, Keiko U. Torii, *Nature* **2015**, *522*, 439-443.
Competitive binding of antagonistic peptides fine-tunes stomatal patterning

Plant stomata have been known to develop according to positional cues, which include a family of secreted peptides called epidermal patterning factors (EPFs). However, how these signaling peptides orchestrate pattern formation at a molecular level remains unclear. Torii and coworkers succeeded to demonstrate one of the key hormones Stomagen, which promotes stomatal development, binds to ERECTA (ER)-family receptor kinases and interferes with the inhibition of stomatal development by the EPIDERMAL PATTERNING FACTOR 2 (EPF2)–ER module, and both EPF2 and Stomagen directly bind to ER and its co-receptor TOO MANY MOUTHS. In addition, they disclosed EPF2 induces rapid phosphorylation of downstream signaling components in vivo. Their findings demonstrate how a plant receptor agonist and antagonist define inhibitory and inductive cues to fine-tune tissue patterning on the plant epidermis at a

molecular level.

[2] Molecular control of plant reproduction

4. Hidenori Takeuchi, Tetsuya Higashiyama, *PLoS Biology* **2012**, *10*, e 1001449.
A species-specific cluster of defensin-like genes encodes diffusible pollen tube attractants in *Arabidopsis*

The flowering plant *Arabidopsis thaliana* has more than 300 defensin-like (DEFL) genes for positive selection of male/female and host/parasite interactions. However, little is known of the relationship between the molecular evolution of DEFL genes and their functions. Higashiyama and coworkers succeeded to identify a cluster of DEFL genes and in *A. thaliana* and demonstrate that these DEFL peptides (cysteine-rich peptide), named AtLURE1 peptides (**LURE peptides**), are pollen tube attractants guiding pollen tubes to the ovular micropyle. They demonstrated down-regulation of the expression of these peptides impaired precise pollen tube attraction and recombinant AtLURE1 peptides attracted *A. thaliana* pollen tubes at a higher frequency compared to *A. lyrata* pollen tubes, suggesting that these peptides are species-preferential attractants in micropylar guidance. Their results indicated that these peptides are sufficient to overcome interspecific barriers in gametophytic attraction and penetration.

5. Daisuke Maruyama, Yuki Hamamura, Hidenori Takeuchi, Daichi Susaki, Moe Nishimaki, Daisuke Kurihara, Ryushiro D. Kasahara, Tetsuya Higashiyama, *Dev. Cell* **2013**, *25*, 317-323.
Independent control by each female gamete prevents the attraction of multiple pollen tubes

In flowering plants, double fertilization is normally accomplished by the first pollen tube and the fertilized ovule subsequently inhibits the attraction of a second pollen tube. However, the mechanism of second-pollen-tube avoidance remains unknown. Higashiyama and coworkers succeeded to disclose second-pollen-tube avoidance is ceased by the two female gametes and the cessation of pollen tube attraction initiates before synergid cell death. In addition, they succeeded to demonstrate hetero-fertilization, second-pollen-tube attraction induced by half-successful fertilization allowed the ovules to complete double fertilization, producing a genetically distinct embryo and endosperm.

6. Yuki Hamamura, Moe Nishimaki, Hidenori Takeuchi, Anja Geitmann, Daisuke Kurihara, Tetsuya Higashiyama, *Nature Commun*. **2014**, *5*, 4722-4780.
Live imaging of calcium spikes during double fertilization in *Arabidopsis*

Ca_2^+ waves and oscillation are key signaling elements during the fertilization process of animals, and are involved, for example, in egg activation. In the unique double fertilization process in flowering plants, both the egg cell and the neighboring central cell fuse with a sperm cell each. Higashiyama and coworkers succeeded in imaging cytosolic Ca_2^+ in these two cells, and in the two synergid cells that accompany the gametes during semi-*in vivo* double fertilization. Following pollen tube discharge and plasmogamy, the egg and central cells displayed transient Ca_2^+ spikes, but not oscillations. Only the events in the egg cell correlated with the plasmogamy. In contrast, the synergid cells displayed Ca_2^+ oscillations on pollen tube arrival. The two synergid cells showed distinct Ca_2^+ dynamics depending on their respective roles in tube reception. These Ca_2^+ dynamics in the female gametophyte seem to represent highly specific signatures that coordinate successful double fertilization in the flowering plants.

7. Daisuke Maruyama, Ronny Völz, Hidenori Takeuchi, Toshiyuki Mori, Tomoko Igawa, Daisuke Kurihara, Tomokazu Kawashima, Minako Ueda, Masaki Itoh, Masaaki Umeda, Shun-ichi Nishikawa, Rita Groß-Hardt, Tetsuya Higashiyama, *Cell*, **2015**, *161*, 907-918.
Rapid elimination of the persistent synergid through a cell fusion mechanism.

In flowering plants, fertilization-dependent degeneration of the persistent synergid cell ensures one-on-one pairings of male and female gametes. Higashiyama and coworkers succeeded to prove that the fusion of the persistent synergid cell and the endosperm selectively inactivates the persistent synergid cell in *Arabidopsis thaliana*. In the article, they demonstrated the synergid-endosperm fusion causes rapid

dilution of pre-secreted pollen tube attractant in the persistent synergid cell and selective disorganization of the synergid nucleus during the endosperm proliferation with preventing attractions of excess number of pollen tubes. They also demonstrated the synergid-endosperm fusion is induced by fertilization of the central cell, while the egg cell fertilization predominantly activates ethylene signaling. They concluded that two female gametes (the egg and the central cell) control independent pathways yet coordinately accomplish the elimination of the persistent synergid cell by double fertilization.

8. Hidenori Takeuchi, Tetsuya Higashiyama, *Nature* **2015**, *531*, 245-248.
Tip-localized receptors control pollen tube growth and LURE sensing in *Arabidopsis*

In the sexual reproduction of flowering plants, the tip growth of the male gametophyte (the pollen tube) is precisely guided by female cues to achieve fertilization. Several female-secreted peptides such as LURE1 have recently been identified as species-specific attractants that directly control the direction of pollen tube growth. However, the way by which pollen tubes precisely and promptly respond to the guidance signal from their own species is unknown. Higashiyama and coworkers succeeded to demonstrate tip-localized pollen-specific receptor-like kinase 6 (PRK6) is an essential for sensing of the external LURE1 attractant peptide in *Arabidopsis thaliana* under semi-*in-vivo* conditions, and recruits the core tip-growth machinery such as pollen-expressed ROPGEFs (Rho of plant guanine nucleotide-exchange factors), including ROP signaling proteins.

9. Akane G. Mizukami, Rie Inatsugi, Jiao Jiao, Toshihisa Kotake, Keiko Kuwata, Kento Ootani, Satohiro Okuda, Subramanian Sankaranarayanan, Yoshikatsu Sato, Daisuke Maruyama, Hiroaki Iwai, Estelle Garénaux, Chihiro Sato, Ken Kitajima, Yoichi Tsumuraya, Hitoshi Mori, Junichiro Yamaguchi, Kenichiro Itami, Narie Sasaki, Tetsuya Higashiyama, *Curr. Biol.* **2016**, *26*, 1-7.
The AMOR arabinogalactan sugar chain induces pollen-tube competency to respond to ovular guidance

Precise directional control of pollen-tube growth by pistil tissue is critical for successful fertilization of flowering plants. Ovular attractant peptides, LURE, which are secreted from two synergid cells on the side of the egg cell, have been identified. Emerging evidence suggests that the ovular directional cue is not sufficient for successful guidance but that competency control by the pistil is critical for the response of pollen tubes to the attraction signal. However, the female molecule for this competency induction has not been reported. Higashiyama and coworkers succeeded to identify ovular arabinogalactan, named Activation Molecule for Response-Capability (AMOR), induces competency of the pollen tube to respond to LURE peptides in *Torenia fournieri* and they demonstrated the terminal disaccharide of AMOR of which was essential for its activity. In addition, they also demonstrated only the beta isomer of methyl-glucuronosyl galactose disaccharide exhibited AMOR activity through extensive collaboration with Itami and coworkers.

[3] Molecular control of the animal/biological biological clock

10. Tsuyoshi Hirota, Jae Wook Lee, Peter C. St. John, Mariko Sawa, Keiko Iwaisako, Takako Noguchi, Pagkapol Y. Pongsawakul, Tim Sonntag, David K. Welsh, David A. Brenner, Francis J. Doyle III, Peter G. Schultz, Steve A. Kay, *Science* **2012**, *337*, 1094-1097.
Identification of small molecule activators of cryptochrome

Impairment of the circadian clock has been associated with numerous disorders, including metabolic disease. Although small molecules that modulate clock function might offer therapeutic approaches to such diseases, only a few compounds have been identified that selectively target core clock proteins. From an unbiased cell-based circadian phenotypic screen, Kay and Hirota identified KL001, a small molecule that specifically interacts with cryptochrome (CRY). KL001 prevented ubiquitin-dependent degradation of CRY, resulting in lengthening of the circadian period. In combination with mathematical modeling, their studies using KL001 revealed that CRY1 and CRY2 share a similar functional role in the period regulation. Furthermore, KL001-mediated CRY stabilization inhibited glucagon-induced gluconeogenesis in primary hepatocytes. KL001 thus provides a tool to study the regulation of CRY-dependent physiology and aid

development of clock-based therapeutics of diabetes.

11. Jae Wook Lee, Tsuyoshi Hirota, Anupriya Kumar, Nam-Jung Kim, Stephan Irle, Steve A. Kay, *ChemMedChem* **2015**, *10*, 1489-1497.
Development of small-molecule cryptochrome stabilizer derivatives as modulators of the circadian clock

Small-molecule probes have been playing prominent roles in furthering our understanding of the molecular underpinnings of the circadian clock. Kay and Hirota previously discovered a carbazole derivative KL001 as a stabilizer of the clock protein cryptochrome (CRY). In this article, they described an extensive structure–activity relationship analysis of KL001 derivatives leading to the development of a highly active derivative KL044. They demonstrated subsequent 3D-QSAR analyses identified critical features of KL001 derivatives and provided an understanding of their interaction with CRY at the molecular level.

12. Tsuyoshi Oshima, Iori Yamanaka, Anupriya Kumar, Junichiro Yamaguchi, Taeko Nishiwaki-Ohkawa, Kei Muto, Rika Kawamura, Tsuyoshi Hirota, Kazuhiro Yagita, Stephan Irle, Steve A. Kay, Takashi Yoshimura, Kenichiro Itami, *Angew. Chem. Int. Ed.* **2015**, 54, 7193-7197.
C-H activation generates period-shortening molecules that target cryptochrome in the mammalian circadian clock

Itami, Yoshimura, Kay-Hirota, and Irle succeeded to reveal biological aspects of KL001 derivatives, which are modulators of the mammalian circadian clock. By using cutting-edge C**-**H activation chemistry developed by Itami, a focused library of KL001 derivatives was rapidly constructed, which enabled the identification of the critical sites on KL001 derivatives that induce a rhythm-changing activity along with the components that trigger opposite modes of action. The first period-shortening molecules that target the cryptochrome (CRY) were thus discovered (Yoshimura and Kay-Hirota). Detailed studies on the effects of these compounds on CRY stability implicate the existence of an as yet undiscovered regulatory mechanism (Irle).

13. Yusuke Nakane, Keisuke Ikegami, Masayuki Iigo, Hiroko Ono, Korenori Takeda, Daisuke Takahashi, Maiko Uesaka, Meita Kimijima, Ramu Hashimoto, Natsumi Arai, Takuya Suga, Katsuya Kosuge, Tomotaka Abe, Ryosuke Maeda, Takumi Senga, Noriko Amiya, Teruo Azuma, Masafumi Aman, Hideki Abe, Naoyuki Yamamoto, Takashi Yoshimura, *Nature Commun.* **2013**, *4*, 2108-2114.
The saccus vasculosus of fish is a sensor of seasonal changes in day length

The pars tuberalis of the pituitary gland is the regulatory hub for seasonal reproduction in birds and mammals. Although fish also exhibit robust seasonal responses, they do not possess an anatomically distinct pars tuberalis. In this article, Yoshimura and coworkers succeeded to discover the expression of key genes regulating seasonal reproduction and rhodopsin family genes in the saccus vasculosus of masu salmon. Immunohistochemical studies demonstrated that all of these genes were expressed in the coronet cells of the saccus vasculosus, suggesting the existence of a photoperiodic signaling pathway from light input to neuroendocrine output. In addition, isolated saccus vasculosus had the capacity to respond to photoperiodic signals, and its removal abolished photoperiodic response of the gonad. Although the physiological role of the saccus vasculosus has been a mystery for several centuries, their findings indicate that the saccus vasculosus acted as a sensor of seasonal changes in day length in fish.

14. Ryosuke Maeda, Takayuki Shimo, Yusuke Nakane, Nobuhiro Nakao, Takashi Yoshimura, *Endocrinol.* **2015**, *156*, 4238-4243.
Ontogeny of the saccus vasculosus, a seasonal sensor in fish

The ontogeny of thyrotrophs and the regulatory mechanisms of TSH are apparently different between the TSH secreted from the pars distalis (PD) and the one from pars tuberalis (PT). Interestingly, fish do not have an anatomically distinct PT, and the saccus vasculosus (SV) of fish have been suggested to act as a seasonal sensor. In this article, Yoshimura and coworkers examined the ontogeny of the pituitary gland and SV using rainbow trout, identified parvalbumin (*Pvalb*) as a marker for SV development through a

microarray analysis, and exhibited the morphological differentiation of SV occurs during the embryonic stage but that the functional differentiation into a seasonal sensor occurs in a later developmental stage.

15. Mari Kamioka, Saori Takao, Takamasa Suzuki, Kyomi Taki, Tetsuya Higashiyama, Toshinori Kinoshita, Norihito Nakamichi, *Plant Cell* **2016**, *28*, 696-711.
Direct repression of evening genes by CIRCADIAN CLOCK-ASSOCIATED1 in the *Arabidopsis* circadian clock

The circadian clock is a biological timekeeping system that provides organisms with the ability to adapt to day-night cycles. Timing of the expression of four members of the *Arabidopsis thaliana* PSEUDO-RESPONSE REGULATOR (PRR) family is crucial for proper clock function, and transcriptional control of PRRs remains incompletely defined. In this article, Kinoshita and Nakamichi demonstrated that one of the plant clock protein CIRCADIAN CLOCK-ASSOCIATED (CCA1) directly affects the key gene expressions of PRR5 for plant responses such as drought stress, signal transduction of plant hormones, and opening/closure of stomata. They also exhibited the interaction between CCA1 and PRR5 is regulated temporally, that is, direct binding by CCA1 in the morning provides strong repression of PRR5, and repression by CCA1 also temporally regulates an evening-expressed gene set that includes PRR5.

[4] Molecular control of *Striga*

16. Yuichiro Tsuchiya, Masahiko Yoshimura, Yoshikatsu Sato, Keiko Kuwata, Shigeo Toh, Duncan Holbrook-Smith, Hua Zhang, Peter McCourt, Kenichiro Itami, Toshinori Kinoshita, Shinya Hagihara, *Science* **2015**, *349*, 864-886.
Probing strigolactone receptors in *Striga hermonthica* with fluorescence

Elucidating the signaling mechanism of strigolactones has been the key to controlling the devastating problem caused by the parasitic plant *Striga hermonthica*. To overcome the genetic intractability that has previously interfered with identification of the strigolactone receptor, Hagihara (Itami G) and Tsuchiya (Kinoshita G) developed a fluorescence turn-on probe, Yoshimulactone Green (YLG), which activates strigolactone signaling and illuminates signal perception by the strigolactone receptors. They exhibited how strigolactones bind to and act via their receptors *ShHTLs*, the diverged family of α/β hydrolase-fold proteins in *Striga*. Live imaging using YLGs revealed that a dynamic wavelike propagation of strigolactone perception wakes up *Striga* seeds. These results suggested that *ShHTLs* function as the strigolactone receptors mediating seed germination in *Striga.* Their findings enable access to strigolactone receptors and observation of the regulatory dynamics for strigolactone signal transduction in *Striga.*

[5] Imaging molecules

17. Eriko Yamaguchi, Chenguang Wang, Aiko Fukazawa, Masayasu Taki, Yoshikatsu Sato, Taeko Sasaki, Minako Ueda, Narie Sasaki, Tetsuya Higashiyama, Shigehiro Yamaguchi, *Angew. Chem. Int. Ed.* **2015**, *54*, 4539-4543.
Environment-sensitive fluorescent probe: a benzophosphole oxide with an electron-donating substituent

Phosphole oxide derivatives exhibited high thermal and chemical stabilities, and these materials have been widely applied in organic electronics. However, biological applications have not yet been explored exhaustively. In this article, Yamaguchi and coworkers succeeded to discover novel fluorescent molecules based on the design of which an electron-donating substituent is introduced into electron-accepting benzophosphole oxide skeleton. These molecules exhibited high fluorescence quantum yields even in polar and protic solvents, and a drastic color change of its fluorescence spectrum as a function of the solvent polarity. They also demonstrated the phosphole-based compounds to stain adipocytes, in which the polarity of subcellular compartments could then be discriminated on the basis of the color change of the fluorescence emission.

18. Chenguang Wang, Aiko Fukazawa, Masayasu Taki, Yoshikatsu Sato, Tetsuya Higashiyama, Shigehiro Yamaguchi, *Angew. Chem. Int. Ed.* **2015**, *54*, 15213-15217.
A phosphole oxide based fluorescent dye with exceptional resistance to photobleaching: a practical tool for continuous imaging in STED microscopy

The development of stimulated emission depletion (STED) microscopy represented a major breakthrough in cellular and molecular biology. However, the intense laser beams required for both excitation and STED usually provoke rapid photobleaching of fluorescent molecular probes, which significantly limits the performance and practical utility of STED microscopy. In this article, Yamaguchi and coworkers reported a photo-resistant fluorescent dye C-Naphox as a practical tool for STED imaging. Pleasingly, the intracellular fluorescent intensity of C-Naphox remained at 83% of the initial value even after recording 50 images using identical laser intensities, whereas a significant decrease in signal intensity was detected for cells stained with conventional Alexa 488 and ATTO 488 used frequently in bio-imaging under the same conditions. The physico-chemical characteristics of C-Naphox are expected to accelerate practical application of the microscopic technology.

19. Naoya Suzuki, Aiko Fukazawa, Kazuhiko Nagura, Shohei Saito, Hirotaka Kitoh-Nishioka, Daisuke Yokogawa, Stephan Irle, Shigehiro Yamaguchi, *Angew. Chem. Int. Ed.* **2014**, *53*, 8231-8235.
A strap strategy for construction of an excited-state intramolecular proton transfer (ESIPT) system with dual fluorescence

The excited-state intramolecular proton transfer (ESIPT) chromophores exhibit a dual emission originating from both the initial excited form and its proton-transferred tautomer, which covers a broad wavelength range. However, the ESIPT chromophores have been limited structurally to only a few variations. In this article, Yamaguchi and coworkers succeeded to discover a novel ESIPT chromophore based on a novel “strap strategy” making use of a functional and flexible alkyl chain, and the molecules exhibited dual emission bands with high luminescence quantum yields, which cover a wide range in the visible region depending on the solvent polarity, even in aqueous medium. Their “functional strap” strategy endows remarkable features totally different from those of the conventional ESIPT system based on the keto-enol tautomerism.

[6] Catalysis and rapid synthetic approach

20. Yutaro Saito, Yasutomo Segawa, Kenichiro Itami, *J. Am. Chem. Soc.* **2015**, *137*, 5193-5198.
***para*-C-H borylation of benzene derivatives by a bulky iridium catalyst**

The **“***para***”** modifications of aromatics can only be effected via lengthy synthetic sequences that lack modularity and often require separate starting materials/reagents for each proposed derivative. Upon these problems, Itami and coworkers succeeded to achieve *para*-selective catalytic C-H borylation with sterically bulky diphosphine ligand Xyl-MeO-BIPHEP on iridium. In addition, they also succeeded to transform anticholinergic drug Caramiphen into various derivatives via the *para*-borylated reaction. The [Ir(cod)OH]2/Xyl-MeO-BIPHEP catalyst represents a unique, sterically-controlled, *para*-selective, aromatic C–H borylation system that should find use in streamlined, predictable chemical synthesis, in the rapid discovery, and optimization of pharmaceuticals and materials.

21. Takahiro Kawakami, Kei Murakami, Kenichiro Itami, *J. Am. Chem. Soc.* **2015**, *137*, 2460-2463.
Catalytic C–H imidation of aromatic cores of functional molecules: ligand-accelerated Cu catalysis and application to materials- and biology-oriented aromatics

Itami and coworkers achieved versatile C**-**H imidation of arenes that can be applied to a range of materials- and biology-oriented aromatics. In the combination of copper and 6,6’-dimethyl-2,2’-bipyridyl as a ligand, a wide range of aromatics, such as polycyclic aromatic hydrocarbons, aromatic bowls,

porphyrins, heteroaromatics, and natural products, can be imidated. With a direct method for activating/converting otherwise difficult aromatic substrates in hand, they are now in a position to synthesize a range of new functional arylamine materials.

22. Haruka Omachi, Takuya Nakayama, Eri Takahashi, Yasutomo Segawa, Kenichiro Itami, *Nature Chem.* **2013**, *5*, 572-576.
Initiation of carbon nanotube growth by well-defined carbon nanorings

Carbon nanotubes (CNTs) are currently produced as mixtures that contain tubes of various diameters and different sidewall structures. The electronic and optical properties of CNTs are determined by their diameters and sidewall structures, and so a controlled synthesis of uniform-diameter, single-chirality CNTs–a significant chemical challenge–would provide access to pure samples with predictable properties. Itami and coworkers achieved a rational bottom-up approach to synthesize structurally uniform CNTs using carbon nanorings (cycloparaphenylenes) as templates and ethanol as the carbon source. The average diameter of the CNTs formed is close to that of the carbon nanorings applied, which supports the operation of a 'growth-from-template' mechanism in CNT formation. This bottom-up organic chemistry approach is intrinsically different from other conventional approaches to making CNTs and, if it can be optimized sufficiently, offers a route to the programmable synthesis of structurally uniform CNTs.

23. Katsuaki Kawasumi, Qianyan Zhang, Yasutomo Segawa, Lawrence T. Scott, Kenichiro Itami, *Nature Chem.* **2013**, *5*, 739-744.
A grossly warped nanographene and the consequences of multiple odd-membered-ring defects

Graphite, the most stable form of elemental carbon, consists of pure carbon sheets stacked upon one another like reams of paper. Individual sheets, known as graphene, prefer planar geometries as a consequence of the hexagonal honeycomb-like arrangements of trigonal carbon atoms that comprise their two-dimensional networks. Defects in the form of non-hexagonal rings in such networks cause distortions away from planarity. Itami and coworkers succeeded to synthesize, isolate, and fully characterize spectroscopically a novel type of carbon allotrope, $C_{80}H_{30}$ nanographene consisting of 26 rings that incorporates five seven-membered rings and one five-membered ring embedded in a hexagonal lattice. In addition, they also achieved an independent synthetic route to a freely soluble derivative of this new type of 'nanocarbon' and revealed how the properties of such a large graphene subunit are affected by multiple odd-membered-ring defects.

24. Kyohei Ozaki, Katsuaki Kawasumi, Mari Shibata, Hideto Ito, Kenichiro Itami, *Nature Commun.* **2015**, *6*, 6251.
One-shot K-region-selective annulative π-extension for nanographene synthesis and functionalization

The optoelectronic nature of two-dimensional sheets of sp^2-hydridized carbons such as graphenes and nanographenes can be dramatically altered and tuned by altering the degree of π-extension, shape, width, and edge topology. Among various approaches to synthesize nanographenes with atom-by-atom precision, Itami and coworkers developed one-shot annulative π-extension (APEX) reactions of polycyclic aromatic hydrocarbons and demonstrated significant potential of the reactions not only to achieve a 'growth from template' synthesis of nanographenes, but also to fine-tune the properties of nanographenes. They also exhibited APEX reactions occurred at the K-region (convex armchair edge) of silicon-bridged polycyclic aromatic hydrocarbons as π-extending agents. Theoretical calculations suggest that the complete K-region selectivity stems from the olefinic character of the K-region. The protocol is applicable to multiple APEX and sequential APEX reactions, to construct various nanographenes in a rapid and programmable manner.

25. Kohsuke Ohmatsu, Mitsunori Ito, Tomoatsu Kunieda, Takashi Ooi, *Nature Chem.* **2012**, *4*, 473-477.
Ion-paired chiral ligands for asymmetric palladium catalysis

Conventional chiral ligands rely on the use of a covalently constructed, single chiral molecule embedded

with coordinative functional groups. Ooi and coworkers developed a new strategy for the design of a chiral ligand for asymmetric transition-metal catalysis; their approach is based on the development of an achiral cationic ammonium–phosphine hybrid ligand paired with a chiral binaphtholate anion. This ion-paired chiral ligand imparts a remarkable stereocontrolling ability to its palladium complex, which catalyzes a highly enantioselective allylic alkylation of α-nitrocarboxylates. By exploiting the possible combinations of the achiral onium entities with suitable coordinative functionalities and readily available chiral acids, this approach should contribute to the development of a broad range of metal-catalyzed, stereoselective chemical transformations.

26. Kohsuke Ohmatsu, Naomichi Imagawa, Takashi Ooi, *Nature Chem.* **2013**, *6*, 47-51.
Ligand-enabled multiple absolute stereocontrol in metal-catalysed cycloaddition for construction of contiguous all-carbon quaternary stereocentres

The development of a general catalytic method for the direct and stereoselective construction of contiguous all-carbon quaternary stereocenters remains a formidable challenge in asymmetric synthesis. Ooi and coworkers achieved a highly enantio- and diastereoselective [3+2] annulation reaction of 5-vinyloxazolidinones and activated trisubstituted alkenes catalyzed by a palladium complex bearing a newly devised phosphine ligand with a chiral ammonium salt component, which enables the single-step construction of three contiguous stereocenters, including vicinal all-carbon quaternary stereocenters, in a five-membered heterocyclic framework. This stereoselective cycloaddition protocol relies on the remarkable ability of the chiral ligand to rigorously control the absolute stereochemistry of each chiral center associated with the multiple bond-forming events, and provides a reliable catalytic process for the asymmetric synthesis of densely functionalized pyrrolidine natural products and pharmaceuticals.

27. Daisuke Uraguchi, Kohei Yamada, Takashi Ooi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9954-9957.
Highly *E*-selective and enantioselective Michael addition to electron-deficient internal alkynes under chiral iminophosphorane catalysis

Conjugate addition of enolates (known as Michael addition) to electron-deficient alkynes offers an extremely powerful tool for incorporating a vinylic component at the α-position to carbonyl functionalities. In some cases, however, stereochemical control involving facial recognition of both the enantiocontrol and the geometry control poses an important yet difficult challenge. Ooi and coworkers disclosed the first broadly useful, highly *E*-selective, and enantioselective conjugate addition of prochiral enolates to β-substituted alkynyl carbonyl compounds under the catalysis of a *P*-spiro chiral iminophosphorane, and achieved simultaneous control of the newly generated central chirality and olefin geometry with a wide array of the alkynyl Michael acceptors possessing different aromatic and aliphatic β-substituents. This protocol provides access to structurally diverse, optically active α-amino acids bearing a geometrically defined trisubstituted olefinic component at the α-position.

28. Daisuke Uraguchi, Natsuko Kinoshita, Tomohito Kizu, Takashi Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768-13771.
Synergistic catalysis of ionic Brønsted acid and photosensitizer for a redox neutral asymmetric alpha-coupling of *N*-arylaminomethanes with aldimines

Numerous efforts have been devoted to the development of synthetically useful and selective radical reactions. In particular, significant advances have been made in the arena of photoredox catalysis, providing a number of otherwise unachievable modes of molecular transformations. However, precise absolute stereocontrol in light-driven photochemical reactions still constitutes a formidable challenge. Ooi and coworkers developed a redox neutral, highly enantioselective coupling by harnessing the efficient *P*-spiro chiral arylaminophosphonium catalyst and a transition-metal photosensitizer under visible light irradiation, and they achieved to synthesize desired 1,2-diamines in high yield and enantioselectivity. The mode of synergistic catalysis in this reaction provides a powerful strategy for controlling the bond-forming processes of reactive radical intermediates.

29. Masakazu Nambo, Cathleen M. Crudden, *Angew. Chem. Int. Ed*. **2014**, *53*, 742-746.
Modular synthesis of triarylmethanes through palladium-catalyzed sequential arylation of methyl phenyl sulfone

Crudden and Nambo achieved the programmed synthesis of triarylmethanes, which are valuable structures in materials, sensing and pharmaceuticals, from methyl phenyl sulfone as an inexpensive and readily available template without conventional and time-wasting process such as protection and deprotection of functional groups in organic molecules. They demonstrated to install three aryl groups through two sequential palladium-catalyzed C-H arylation reactions, followed by an arylative desulfonation. This method provides a new synthetic approach to multi-substituted triarylmethanes through Pd-catalyzed sequential arylations using readily available haloarenes and aryl boronic acids, and is also valuable for the preparation of unexplored triarylmethane-based materials and pharmaceuticals.

30. Masakazu Nambo, Muhammad Yar, Joel D. Smith, Cathleen M. Crudden, *Org. Lett.* **2015**, *17*, 50-53
The concise synthesis of unsymmetric triarylacetonitriles via Pd-catalyzed sequential arylation: a new synthetic approach to tri- and tetraarylmethanes

Crudden and Nambo also achieved the synthesis of tetrarylmethanes through palladium-catalyzed sequentiall arylations from an inexpensive and readily available chloroacetonitrile. They demonstrated to install the three aryl groups via a Pd-catalyzed Suzuki-Miyaura cross coupling reaction followed by back-to-back C-H arylations to afford triarylacetonitriles in three steps with no over-arylation at any step at first and then succeeded to covert triarylacetonitrile into highly functionalized tetraarylmethanes. This new strategy provides rapid access to a variety of unsymmetrical tri- and tetraarylmethane derivatives from simple, readily available starting materials.

31. Cathleen M. Crudden, J. Hugh Horton, Iraklii I. Ebralidze, Olena V. Zenkina, Alastair B. McLean, Benedict Drevniok, Zhe She, Heinz-Bernhard Kraatz, Nicholas J. Mosey, Tomohiro Seki, Eric C. Keske, Joanna D. Leake, Alexander Rousina-Webb, Gang Wu, *Nature Chem*. **2014**, 6, 409-414.
Ultra stable self-assembled monolayers of *N*-heterocyclic carbenes on gold

The oxidative and thermal instabilities of thiol-based self-assembled monolayers (SAMs) are widely known and are an impediment to their widespread commercial use. Crudden and coworkers achieved the generation of N-heterocyclic carbene (NHC)-based SAMs on gold that demonstrate considerably greater resistance to high temperatures, boiling water, organic solvents, pH extremes, electrochemical cycling above 0 V and 1% hydrogen peroxide, than the thiol-based counterparts. This increased stability is related to the increased strength of the gold–carbon bond relative to that of a gold–sulfur bond, and to a different mode of bonding in the case of the carbene ligand. In particular, benzimidazole-derived carbenes provide films with the highest stabilities and evidence of short-range molecular ordering. Chemical derivatization can be employed to adjust the surface properties of NHC-based SAMs.

32. Yi-Lin Huang, Jeffrey W. Bode, *Nature Chem*. **2014**, *6*, 877-884.
Synthetic fermentation of bioactive non-ribosomal peptides without organisms, enzymes or reagents

Microbial fermentation can rapidly provide potent compounds that can be easily screened for biological activity, and the active components can be isolated. Its success in drug discovery has inspired extensive efforts to modulate and control the products. Bode and coworkers document a ‘synthetic fermentation’ of bioactive, unnatural peptides ‘grown’ from small building blocks in water using amide-forming ligations without any organisms, enzymes or reagents. The sequences, structures and compositions of the products can be modulated by adjusting the building blocks and conditions. The ‘fermentations’ can be conducted in arrays and screened for biological activity without isolation or workup. As a proof-of-concept, about 6,000 unnatural peptides were produced from just 23 building blocks, from which a hepatitis C virus NS3/4A protease inhibitor with a half-maximum inhibitory concentration of 1.0 microM was identified and characterized.

33. Ivano Pusterla, Jeffrey W. Bode, *Nature Chem*. **2015**, *7*, 668-672.
An oxazetidine amino acid for chemical protein synthesis by rapid, serine-forming ligations

Amide-forming ligation reactions allow the chemical synthesis of proteins by the union of unprotected peptide segments, and enable the preparation of protein derivatives not accessible by expression or bioengineering approaches. The native chemical ligation (NCL) of thioesters and *N*-terminal cysteine is unquestionably the most successful approach, but is not ideal for all synthetic targets. Bode and coworkers developed the synthesis of an Fmoc-protected oxazetidine amino acid for use in the alpha-ketoacid–hydroxylamine (KAHA) amide ligation. When incorporated at the *N*-terminus of a peptide segment, this four-membered cyclic hydroxylamine can be used for rapid serine-forming ligations with peptide alpha-ketoacids. This ligation operates at low concentration (100 microM – 5 mM) and mild temperatures (20–25°C). The utility of the reaction was demonstrated by the synthesis of S100A4, a 12 kDa calcium-binding protein not easily accessible by NCL or other amide-forming reactions due to its primary sequence and properties.

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Appendix 2-3. List of the cooperative research agreements in and outside Japan

1. Counterpart of an Agreement : Queen's University
   Name of an Agreement : Memorandum of Understanding
   Dates of an Agreement : April 1, 2013
   Summary of an Agreement : The MOU is to affiliate Dr. Cathleen M. Crudden (Queen's Univ) to NU with the position of Overseas Principal Investigator to be engaged in collaborative research at NU. The MOU includes relationship, commitment, MTA, IP, publications and so on.
2. Counterpart of an Agreement : University of Washington and Howard Hughes Medical Institute
   Name of an Agreement : Memorandum of Understanding
   Dates of an Agreement : April 1, 2013
   Summary of an Agreement : The MOU is to affiliate Dr. Keiko Torii (University of Washington, Howard Hughes Medical Institute) to NU with the position of Overseas Principal Investigator to be engaged in collaborative research at NU. The MOU includes relationship, commitment, MTA, IP, publications and so on.
3. Counterpart of an Agreement : ETH Zurich
   Name of an Agreement : Memorandum of Understanding
   Dates of an Agreement : September 1, 2013
   Summary of an Agreement : The MOU is to affiliate Dr. Jeffrey Bode (ETH Zurich) to NU with the position of Overseas Principal Investigator to be engaged in collaborative research at NU. The MOU includes relationship, commitment, MTA, IP, publications and so on.
4. Counterpart of an Agreement : Albert-Ludwigs-Universität Freiburg
   Name of an Agreement : The Memorandum of Understanding on the promotion and collaborations
   Dates of an Agreement : March 18, 2014
   Summary of an Agreement : This MOU is to enable mutual exchange of students and researches and to promote joint research in such as medical sciences, chemistry and life sciences, and Institute for advanced studies and research.
5. Counterpart of an Agreement : The RIKEN Center for Sustainable Resource Science (CSRS)
   Name of an Agreement : Memorandum of Understanding on collaboration and cooperation
   Dates of an Agreement : January 7, 2015
   Summary of an Agreement : This MOU is to promote researches in biology, chemistry, and their interdisciplinary fields under collaboration and cooperation.
6. Counterpart of an Agreement : The RIKEN Center for Sustainable Resource Science (CSRS)
   Name of an Agreement : Memorandum of Understanding on Joint Workshop
   Dates of an Agreement : January 7, 2015
   Summary of an Agreement : The MOU is to hold Joint-Workshop under non-disclosure agreement.
7. Counterpart of an Agreement : The Freiburg Institute for Advanced Study, Albert-Ludwigs-Universität Freiburg
   Name of an Agreement : Agreement concerning joint activities between FRIAS/University of Freiburg and Nagoya IAR/Nagoya University
   Dates of an Agreement : May 14, 2015
   Summary of an Agreement : The agreement is to deepen the collaboration and contribute to strategic partnership. The Institutes will call for joint research groups and jointly fund to the groups selected in a joint FRIAS-Nagoya IAR call.
8. Counterpart of an Agreement : Emory University by and on behalf of its Center for Selective C-H Functionalization and Center for Catalytic Hydrocarbon Functionalization, Institute for Basic Science-Korea Advanced Institute of Science and Technology
   Name of an Agreement : Academic Exchange and Cooperation Agreement
   Dates of an Agreement : TBD
   Summary of an Agreement : The agreement is to develop academic exchange and cooperation in education and research.

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Appendix 2-4. Major Awards, Invited Lectures, Plenary Addresses (etc.)

1. Major Awards

- List main internationally-acclaimed awards received/unofficially announced 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) Kenichiro Itami, 2016 Ta-Shue Chou Lectureship Award, Institute of Chemistry, Academia Sinica, 2016
2) Kenichiro Itami, Arthur C. Cope Scholar Award, American Chemical Society, 2015
3) Kenichiro Itami, Swiss Chemical Society Lectureship Award, 2015
4) Shigehiro Yamaguchi, 33rd Academic Award, Chemical Society of Japan, 2015
5) Cathleen Crudden, Killam Research Fellowship, 2015
6) Keiko Torii, 35th Saruhashi Award, 2015
7) Keiko Torii, 2015 ASPB Fellow Award, American Society of Plant Biologists, 2015
8) Takashi Yoshimura, 2015 Van Meter Award, American Thyroid Association, 2015
9) Keiko Torii, 31st Inoue Prize of Science, 2015
10) Shigehiro Yamaguchi, Mukaiyama Award, 2015
11) Tetsuya Higashiyama, NISTEP Award 2014, 2014
12) Tetsuya Higashiyama, Yomiuri Techno Forum Gold Medal Prize, 2014
13) Takashi Ooi, Fellow of the Royal Society of Chemistry, 2014
14) Cathleen Crudden, The Aldrich Lectureship Award, 2014
15) Kenichiro Itami, The Aldrich Lectureship Award, 2014
16) Takashi Ooi, Inoue Prize for Science, 2013
17) Kenichiro Itami, Mukaiyama Award, 2013
18) Kenichiro Itami, Novartis Chemistry Lectureship Award, 2013
19) Kenichiro Itami, The JSPS Prize, 2013
20) Kenichiro Itami, Asian Rising Star Award, 2013
21) Jeffrey Bode, Fellow of the Royal Society of Chemistry, 2013
22) Kenichiro Itami, German Innovation Award, Gottfried Wagner Prize, 2012
23) Shigehiro Yamaguchi, The JSPS Prize, 2012
24) Keiko U. Torii, Elected Fellow, American Association for the Advancement of Science, 2012
25) Kenichiro Itami, Fellow of the Royal Society of Chemistry, UK, 2012

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

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

1) Takashi Yoshimura, "Novel roles for TSH and TH identified by discovery-driven approach", 15th International Thyroid Congress, Orlando, Florida, U.S.A., October 19, 2015

2) Kenichiro Itami, "Catalyst-Enabling Nanocarbon Science & Plant/Animal Biology" The Arthur C. Cope Scholar Award, Boston Convention & Exhibition Center, Boston, USA, August 18, 2015

3) Shigehiro Yamaguchi, "Main Group Strategy for Photo- and Electronic Functions", The 14th International Symposium on Inorganic Ring Systems (IRIS-14), Regensburg, Germany, July 27-31, 2015

4) Jeffrey Bode, "Cross Coupling 2.0", 44th National Organic Symposium, Washington, D. C., June 28-July 2, 2015

5) Stephan Irle, "Super-reduced POM27-: An Excellent Molecular Cluster Battery Component and Semipermeable Molecular Capacitor", The 19th International Annual Symposium on Computational Science and Engineering (ANSCSE19), Ubon Ratchathani, Thailand, June 17-19, 2015

6) Takashi Ooi, "Asymmetric Catalysis of Designer Chiral Organic Ion Pairs", 16th Tetrahedron Symposium: Challenges in Bioorganic and Organic Chemistry, Berlin, Germany, June 16-19, 2015

7) Cathleen Crudden, "Mild, Easy Deposition Method for the Production of Highly Ordered, Ultra Stable NHC-based Films on Gold," 98th Canadian Society for Chemistry Conference, Ottawa, ON, June 13-17, 2015

8) Keiko Torii, "Receptor Kinase Specificity and Integration in Stomatal Patterning" Gordon Research Conference, Plant Development, Holderness, NH, USA, July 20-25, 2014

9) Toshinori Kinoshita, "ABA regulates hypocotyl elongation via dephosphorylating plasma membrane H^+-ATPase in Arabidopsis thaliana" Plant Biology 2014, Oregon Convention Center, USA, July 13, 2014

10) Tetsuya Higashiyama, "Cell-to-cell communication and key molecules in pollen tube guidance and early embryogenesis" Mittwochs-Kolloquium, Max Planck Institute for Developmental Biology and Friedrich Miescher Laboratory in Tübingen, Germany, June 18, 2014

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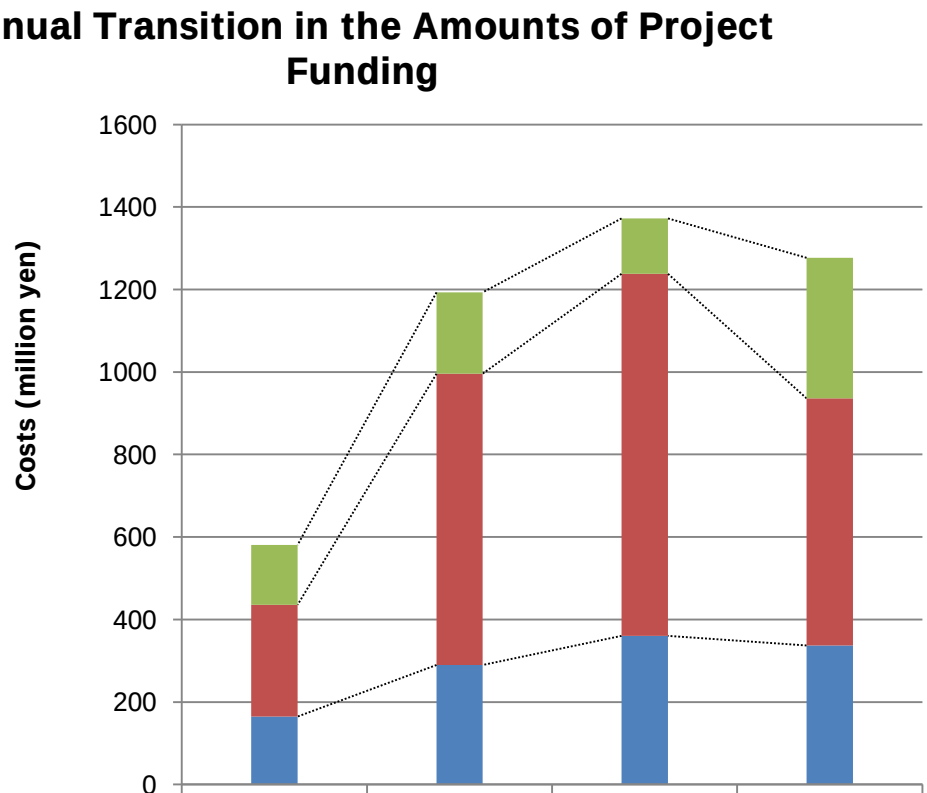
Appendix 2-6. Amounts of Non-WPI project funding (grants)

*Make a graph of the annual transition in non-WPI project funding (grants).



	FY2012	FY2013	FY2014	FY2015
Grants-in-Aid for Scientific Research, etc.	145	197	134	341
Commissioned research projects, etc.	271	706	878	599
Projects supported by other government subsidies, etc.	165	290	360	337

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

FY2012
- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 256,768,000 JPY (acquired by Tetsuya Higashiyama)

FY2013
- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 470,884,000 JPY (acquired by Kenichiro Itami)
- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 326,172,000 JPY (acquired by Tetsuya Higashiyama)

FY2014
- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 555,611,000 JPY (acquired by Kenichiro Itami)
- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 261,587,000 JPY (acquired by Tetsuya Higashiyama)
- Name: Strategic Basic Research Programs (CREST), JST
  Total Amount: 155,480,000 JPY (acquired by Takashi Ooi)

FY2015

- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 324,864,000 JPY (acquired by Kenichiro Itami)
- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 235,323,000 JPY (acquired by Tetsuya Higashiyama)
- Name: Grant-in-Aid for Scientific Research on Innovative Areas (Research in a proposed research area), JSPS
  Total Amount: 207,220,000 JPY (acquired by Toshinori Kinoshita)

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Appendix 2-8. FY 2015 List of Project's Media Coverage

- Select main items of coverage, and list them within these 2 pages.

No.	Date	Type media (e.g., newspaper, television)	Description
1	Apr 2, 2015 – Mar 4, 2016	Newspaper (13): Chunichi Shimbun	Prof. Takashi Yoshimura's monthly series about research on animal behavior
2	Apr 6 – 27, 2015	Web (5): ASPB Plant Science Today	Prof. Keiko Torii's winning of the 2015 Fellow of ASPB Award
3	Apr 14 – May 1, 2015	Newspaper (1); Web (International: 47, Domestic: 6)	Prof. Kenichiro Itami's research on selective functionalization of benzene rings, published in the Journal of the American Chemical Society. Featured in Kagaku Shimbun, Science Daily, Dutch news
4	Apr 21 – Nov 3, 2015	Newspaper (12); Magazine (6); Web (International :3, Domestic: 64)	Prof. Keiko Torii's winning of the 35th Saruhashi Prize Featured in Asahi, Chunichi, Sankei, Mainichi, Yomiuri, Nikkei, Nikkan Kogyo, Nikkei Sangyo Shimbun, Nature Digest, Nikkei Science, Yahoo, Jiji, Wall Street Journal
5	Apr 23 – May 7, 2015	Newspaper (6); TV (1); Web (International: 29, Domestic: 29); Magazines (2)	Dr. Daisuke Maruyama's research on plant reproduction, published in Cell. Featured in Chunichi, Yomiuri, Mainichi, Nikkei Sangyo, Nikkan Kogyo Shimbun, NHK News, Science Daily, Yahoo, Nikkei Biotech
6	May 9 – Jun 19, 2015	Newspaper (1); Web (International: 53, Domestic: 7); Magazine (2)	Prof. Itami, Yoshimura, Irle, and Kay's interdisciplinary research on molecules that can change the circadian rhythm, published in Angewandte Chemie. Featured in Chunichi Shimbun, Science Daily, Chemisch2Weekblad (Dutch), Social News (Spanish), Yahoo, Chemistry
7	May 18, 2015	Newspaper (1): Yomiuri Shimbun	Prof. Toshinori Kinoshita's research on plant stomata, published in PNAS
8	May 26, 2015	Newspaper (3); Web (4); TV (1)	Construction of ITbM's new building. Featured in Asahi, Yomiuri, Chunichi Shimbun, Nikkan Kogyo; CBC News
9	Jun 10, 2015	TV (1): NHK	Okazaki Award Ceremony
10	Jun 18, 2015	Newspaper (1); Web (International: 24, Domestic: 5)	Prof. Keiko Torii's research on plant stomata, published in Nature. Featured in Kagaku Shimbun
11	Jun 23 – 30, 2015	Web (International: 25): Science Daily, Biotech (Chinese)	Prof. Jeffrey Bode's research on chemical synthesis of proteins, published in Nature Chemistry
12	Jun 25, 2015	Magazine/Web: Fortune	Prof. Steve Kay's research on the circadian clock
13	Jun 29, 2015	Web (International: 27)	Prof. Kenichiro Itami's research on a new nickel catalyst, published in Nature Communications. Featured in Phys.Org, Science Daily, Emory Chemistry News
14	Jul 2015	Magazine: Toyo Keizai	ITbM and Prof. Itami's research group highlighted as part of Nagoya's special issue
15	Jul 10, 2015	Magazine/Web: Science	Prof. Keiko Torii's comments on women in science

16	Jul 10, 2015	Newspaper (7); Website (Domestic: 10)	Prof. Tetsuya Higashiyama's research on plant reproduction, published in Developmental Cell. Featured in Chunichi, Asahi, Yomiuri, Mainichi, Nikkei Sangyo, Nikkan Kogyo Shimbun, Yahoo, Jiji, WSJ, Nikon
17	Jul 17, 2015	Newspaper/Web: Asahi Shimbun	Prof. Tetsuya Higashima's family featured in women's leadership program at Nagoya University
18	Jul 23 – Sep 2, 2015	Newspaper (2); TV (2); Web (International: 129; Domestic: 11)	Prof. Takashi Yoshimura's research on roosters' crowing behavior, published in Scientific Reports. Featured in Chunichi, Mainichi Shimbun, Fuji, Nihon TV, AFP, Yahoo, MSN, Discovery News, Daily Mail (other news translated into German, French, Spanish, Chinese, Indonesian, Russian, Portuguese)
19	Aug 21 – Sep 28, 2015	Newspaper; Web (International: 34, Domestic: 7)	Drs. Hagihara and Tsuchiya's interdisciplinary research on the development of a molecule to probe the growth of parasitic plants, published in Science. Featured in Chunichi, Nikkei Sangyo, Kagaku, Yomiuri Shimbun, Science Daily, Nature Chemical Biology, Science
20	Jul 28, 2015	Newspaper (1)	Prof. Tetsuya Higashiyama's interview in Nikkei Sangyo
21	Aug 3, 2015	Newspaper (1)	Prof. Takashi Yoshimura highlighted in Nikkan Kogyo
22	Aug 25, 2015	Web: Nature Asia	Prof. Shigehiro Yamaguchi's research on graphene
23	Oct 19 – 30, 2015	Web (International: 12): News Medical	Prof. Takashi Yoshimura's winning of the 2015 Van Meter Award
24	Oct 23, 2015	Newspaper (1); Web (International: 27, Domestic: 3); Magazine (1)	Profs. Shigehiro Yamaguchi and Tetsuya Higashiyama's research on a new fluorescent molecule for live cell imaging, published in Angewandte Chemie. Featured in Nikkei Sangyo Shimbun, Microscopy Analysis, Photonics
25	Oct 27, 2015	Web: Nature Asia	Prof. Kenichiro Itami's research on benzene rings
26	Oct 29, 2015	Newspaper (6); TV (1); Radio (1); Web (International: 1, Domestic: 17)	Prof. Tetsuya Higashiyama's research to see through plants, published in Development. Featured in Yomiuri, Asahi, Chunichi, Nikkei, Kagaku Shimbun, NHK News; CBC Radio, Yahoo News, Chemistry
27	Nov 18, 2015	Web (International: 4)	Research collaboration between ITbM and RaQualia. Featured in Asian Scientist and Sleep Review.
28	Feb 8, 2016	Web (International: 9)	Profs. Irle, Hirota, Kay's research on the mammalian circadian clock, published in ChemMedChem. Featured in Atlas of Science, Phys.Org, Open Science EU.
29	Mar 1, 2016	Magazine (1)	Prof. Shigehiro Yamaguchi and Dr. Kohsuke Ohmatsu's CSJ award featured in Chemistry and Chemical Industry
30	Mar 10, 2016	Newspaper (2); Web (International: 32, Domestic: 3); TV (1); Radio (1)	Prof. Tetsuya Higashiyama's research on plant fertilization, published in Nature. Featured in Science Daily, Global Plant Council, Chunichi, Kagaku Shimbun, Nature News & Views, NHK News, NHK Radio
31	Mar 22, 2016	Web: Chemistry World (RSC)	Prof. Kenichiro Itami's research highlight on aromatic rings, published in JACS
32	Mar 23, 2016	Web (International: 19, Domestic: 1)	Dr. Norihito Nakamichi's research on the plant circadian clock, published in the Plant Cell.
33	Mar 30, 2016	Web: Nature Japan	Prof. Kenichiro Itami's research highlight on nanocarbons, published in Nature Review Materials
34	Mar 2016	Magazine (1)	Prof. Kenichiro Itami interview with Prof. Schreiber in Gendai Kagaku

Covered 765 times in the media during FY2015 in international and domestic websites, newspapers, magazines, television, and radio

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Appendix 3. List of papers of representative of interdisciplinary research activities

- List up to 10 papers that underscoring each interdisciplinary research activity and give brief accounts (within 10 lines).
- 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.
  If a paper has many authors, underline those affiliated with the Center.
- If a paper has many authors (say, more than 10), all of their names do not need to be listed.

1. Tsuyoshi Oshima, Iori Yamanaka, Anupriya Kumar, Junichiro Yamaguchi, Taeko Nishiwaki-Ohkawa, Kei Muto, Rika Kawamura, Tsuyoshi Hirota, Kazuhiro Yagita, Stephan Irle,* Steve A. Kay, Takashi Yoshimura,* and Kenichiro Itami*, *Angew. Chem. Int. Ed.* **2015**, *54*, 7193–7197. "**C-H activation generates period-shortening molecules that target cryptochrome in the mammalian circadian clock**" (DOI: 10.1002/anie.201502942)

   <Interdisciplinary research between organic chemistry, animal biology and theoretical chemistry>
   The biological clock regulates various daily rhythms, such as sleep/wake rhythm, body temperature, and metabolism. Disruption of the circadian rhythm may lead to sleep disorders, cancer and other diseases. Kenichiro Itami, Takashi Yoshimura, Stephan Irle, Tsuyoshi Hirota and Steve Kay and their groups have come together to discover for the first time, a rhythm-changing molecule with period-shortening activities that targets the clock protein, CRY, which open doors to molecule-based solutions for circadian-related diseases and improving food production in animals.

2. Yuichiro Tsuchiya, Masahiko Yoshimura, Yoshikatsu Sato, Keiko Kuwata, Shigeo Toh, Duncan Holbrook-Smith, Hua Zhang, Peter McCourt, Kenichiro Itami, Toshinori Kinoshita and Shinya Hagihara, *Science* **2015**, *349*, 864–868 "**Probing strigolactone receptors in *Striga hermonthica* with fluorescence**" (DOI: 10.1126/science.aab3831)

   <Interdisciplinary research between organic chemistry, plant biology and live cell imaging>
   A molecular approach has been used to identify the protein responsible for germination of *Striga* seeds through visualization by green fluorescence. *Striga*, a parasitic plant known as witchweed has seriously affected millions of hectares of crop fields in Africa that poses a major threat to food security. Nevertheless, the exact mechanism on how *Striga* seeds detect host crops has not been fully clear up to now. In a new study reported in *Science*, Shinya Hagihara and Yuichiro Tsuchiya and their team have come together to develop a new visualizing molecule to examine the process of *Striga* germination. The outcome of this study is expected to accelerate research to control *Striga* growth and to save crop losses worth of billions of U.S. dollars every year.

3. Chenguang Wang, Aiko Fukazawa,* Masayasu Taki,* Yoshikatsu Sato, Tetsuya Higashiyama,* and Shigehiro Yamaguchi*, *Angew. Chem. Int. Ed.* **2015**, *54*, 15213–15217. "**A phosphole oxide based fluorescent dye with exceptional resistance to photobleaching: a practical tool for continuous imaging in STED microscopy**" (DOI: 10.1002/anie.201507939)

   <Interdisciplinary research between organic chemistry, biology and live cell imaging>
   A new photostable fluorescent dye for super resolution microscopy has been developed to serve as a powerful tool to visualize biological events and structural details in living cells at real-time for prolonged recording periods. Bio-imaging by fluorescence microscopy is a useful technique to study the localization and movement of molecules in living cells by fluorescence. Yet, the gradual degradation of fluorescent dyes when exposed to the high intensity light necessary for super resolution microscopy has been a major obstacle for long-term observations. Shigehiro Yamaguchi and Tetsuya Higashiyama's group has developed a new fluorescent dye, "C-Naphox" with enhanced photostability to enable continuous live cell imaging by STED microscopy, which opens doors to observe real-time biological events for extended time periods with high resolution.

4. Wook Lee, Tsuyoshi Hirota*, Anupriya Kumar*, Nam-Jung Kim, Stephan Irle and Steve A. Kay*, *ChemMedChem* **2015**, *10*, 1489–1497. "**Development of small-molecule cryptochrome stabilizer derivatives as modulators of the circadian clock**" (DOI: 10.1002/cmdc.201500260)

<Interdisciplinary research between organic chemistry, animal biology and theoretical chemistry>
Tsuyoshi Hirota, Stephan Irle, and Steve Kay and their group have come together to develop a small molecule that slows down the circadian clock rhythm through binding to the CRY clock protein. The structure-activity relationship of the small molecules was examined at the atomic level and the group identified the structural basis of CRY-acting compounds. In other words, they were able to identify which parts of the small molecule can be modified to make it more effective, for example, making it bigger or smaller in certain directions. The group discovered a 10 times more potent derivative relative to a previously discovered molecule. Using this information will enable studies to virtually screen a relatively large collection of compounds with the computer and test the most potent molecules in the lab. Through a combination of organic synthesis, biological screening and computational modeling, the group was able to find the most potent CRY-acting molecule so far.

5. Eriko Yamaguchi, Chenguang Wang, Aiko Fukazawa,* Masayasu Taki, Yoshikatsu Sato, Taeko Sasaki, Minako Ueda, Narie Sasaki, Tetsuya Higashiyama,* and Shigehiro Yamaguchi*, *Angew. Chem. Int. Ed.* **2015**, *54*, 4539–4543. "**Environment-sensitive fluorescent probe: a benzophosphole oxide with an electron-donating substituent**" (DOI: 10.1002/anie.201500229)

<Interdisciplinary research between organic chemistry, biology and live cell imaging>
Shigehiro Yamaguchi and Tetsuya Higashiyama's groups have developed an environment-sensitive fluorescent probe by attaching electron-donating aryl groups to electron-accepting benzophosphole skeletons. Among the several derivatives that were prepared, one benzophosphole oxide was particularly interesting, as it retained high fluorescence quantum yields even in polar and protic solvents. This phosphole-based compound exhibited a drastic color change of its fluorescence spectrum as a function of the solvent polarity, while the absorption spectra remained virtually unchanged. Based on these features, this phosphole-based compound was used to stain adipocytes, in which the polarity of subcellular compartments could be distinguished by the color change of the fluorescence emission.

6. Masayasu Taki,* Hiroaki Ogasawara, Hiroshi Osaki, Aiko Fukazawa, Yoshikatsu Sato, Kimi Ogasawara, Tetsuya Higashiyama and Shigehiro Yamaguchi*, *Chem. Commun.* **2015**, *51*, 11880–11883. "**A red-emitting ratiometric fluorescent probe based on a benzophosphole P-oxide scaffold for the detection of intracellular sodium ions**" (DOI: 10.1039/c5cc03547c)

<Interdisciplinary research between organic chemistry, biology and live cell imaging>
Shigehiro Yamaguchi and Tetsuya Higashiyama's groups have developed a ratiometric fluorescent probe based on a benzophosphole *P*-oxide and demonstrated its application for the detection of intracellular Na^+ ions. Excitation by visible light induced red emission from this probe in water, which was subjected to a hypsochromic shift upon complexation with Na^+. Based on this change, a ratiometric analysis enabled visualization in the changes of Na^+ concentration in living mammalian cells.

7. Eriko Yamaguchi, Aiko Fukazawa, Youhei Kosaka, Daisuke Yokogawa, Stephan Irle, Shigehiro Yamaguchi, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 1545–1552. "**A benzophosphole P-oxide with an electron-donating group at 3-position: enhanced fluorescence in polar solvents**" (DOI: 10.1246/bcsj.20150238)

<Interdisciplinary research between organic chemistry, and theoretical chemistry>
Fluorophores with intramolecular charge-transfer (ICT) character in the excited state exhibit significant solvatochromism of their fluorescence. Stephan Irle and Shigehiro Yamaguchi's groups report an example of such compounds, a benzophosphole *P*-oxide bearing an electron-donating *p*-(diphenylamino)phenyl group at the 3-position. While this compound shows only subtle dependence of the absorption maximum on the solvent polarity, its emission maximum is significantly red-shifted upon increasing the solvent polarity. Most notably, the fluorescence quantum yields gradually increase with increased Stokes shifts. In this study, the origins of this difference are examined by a combined experimental and theoretical approach.

8. Naoya Suzuki, Aiko Fukazawa, Kazuhiko Nagura, Shohei Saito, Hirotaka Kitoh-Nishioka, Daisuke

Yokogawa, Stephan Irle,* and Shigehiro Yamaguchi*, *Angew. Chem. Int. Ed.* **2014**, *53*, 8231–8235. "**A strap strategy for construction of an excited-state intramolecular proton transfer (ESIPT) system with dual fluorescence**" (DOI: 10.1002/anie.201404867)

<Interdisciplinary research between organic chemistry and theoretical chemistry>
An amine-embedded flexible alkyl strap has been incorporated into an emissive boryl-substituted dithienylpyrrole skeleton as a new entity of excited-state intramolecular proton transfer (ESIPT) chromophores. The π-electron system shows a dual emission, which covers a wide range of the visible region depending on the solvent polarity. Stephan Irle and Shigehiro Yamaguchi's groups have shown that the incorporation of the aminoalkyl strap as well as the terminal boryl groups efficiently stabilize the zwitterionic excited-state species resulting from the ESIPT even in an aqueous medium.

9. Tomokatsu Kushida, Cristopher Camacho, Ayumi Shuto, Stephan Irle,* Masayasu Muramatsu, Tetsuro Katayama, Syoji Ito, Yutaka Nagasawa, Hiroshi Miyasaka,* Eri Sakuda, Noboru Kitamura, Zhiguo Zhou, Atsushi Wakamiya and Shigehiro Yamaguchi*, *Chem. Sci.* **2014**, 5, 1296–1304. "**Constraint-induced structural deformation of planarized triphenylboranes in the excited state**" (DOI: 10.1039/c3sc52751d)

<Interdisciplinary research between organic chemistry and theoretical chemistry>
Triphenylboranes planarized with three methylene bridges exhibited dual fluorescence bands despite their structural constraint. To elucidate the origin, their excited state dynamics were experimentally and theoretically studied by Stephan Irle and Shigehiro Yamaguchi's groups. The measurements of fluorescence lifetimes and transient absorption spectra indicated that the planarized triphenylboranes adopt two local minimum structures in the lowest-energy excited singlet state. Based on the calculated partial atomic charge on the boron atom, the structural deformation to the bowl-shaped structure results in an increase in the electron density on the boron center. Thus, the enhanced intramolecular charge-transfer character plays a role in this structural deformation. These results imply that structural constraint in a planar fashion is not only a strategy to construct a rigid skeleton, but also a viable mechanism to impart flexibility to the skeleton.

10. Chunxue Yuan, Shohei Saito,* Cristopher Camacho, Tim Kowalczyk, Stephan Irle,* and Shigehiro Yamaguchi*, *Chem. Eur. J.* **2014**, *20*, 2193–2200. "**Hybridization of a flexible cyclooctatetraene core and rigid aceneimide wings for multiluminescent flapping p systems**" (DOI: 10.1002/chem.201303955)

<Interdisciplinary research between organic chemistry and theoretical chemistry>
The hybridization of flexible and rigid π-conjugated frameworks is a potent concept for producing new functional materials. In this article, a series of multifluorescent flapping π systems that combine a flexible cyclooctatetraene (COT) core and rigid aceneimide wings with various π-conjugation lengths has been designed and synthesized by Stephan Irle and Shigehiro Yamaguchi's groups, and their structure/properties relationships have been investigated. The relationship between the packing structures and the fluorescence properties was investigated by preparing a series of hybrid π systems with different sizes of substituents on the imide moieties, which revealed the effect of the twofold π-stacked structure of the V-shaped molecules on the large bathochromic shift in emission.

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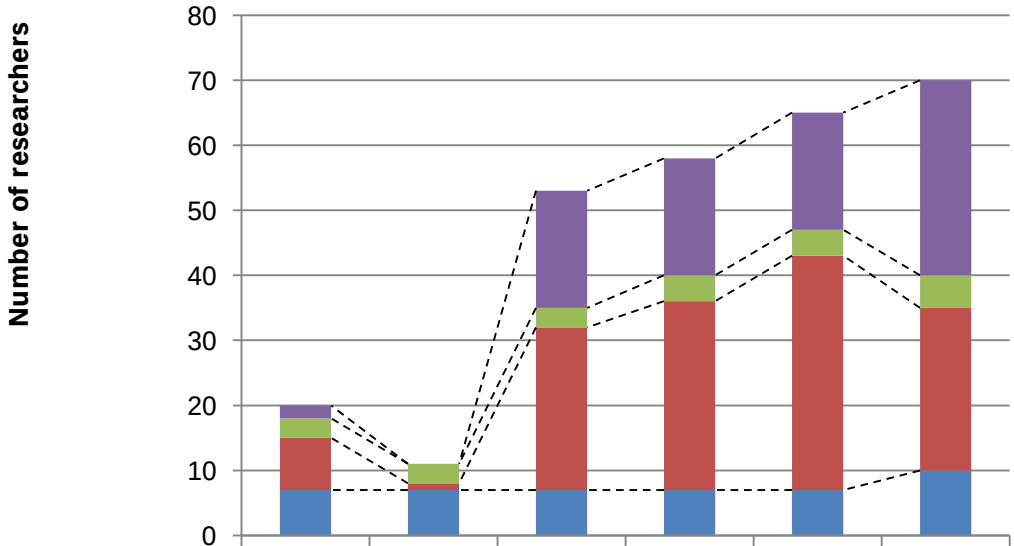
Appendix 4-2. Number of overseas researchers and annual transition

*Make a graph of the transition in the number of overseas researchers since the application.

Annual Transition in the Number of Overseas Researchers



	At beginning	FY2012	FY2013	FY2014	FY2015	Final goal
Researchers from abroad excluding PIs	2	0	18	18	18	30
PIs from abroad	3	3	3	4	4	5
Japanese researchers excluding PIs	8	1	25	29	36	25
Japanese PIs	7	7	7	7	7	10

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Appendix 4-3. Postdoctoral positions through open international solicitations

- In the “number of applications” and “number of selection” columns, put the number and percentage of overseas researchers in the < > brackets.

FY	Number of Applications	Number of Selection
FY2012	0 < 0, 0%>	0 < 0, 0%>
FY2013	141 <138, 97.9%>	16 <15, 93.8%>
FY2014	5 < 4, 80%>	5 < 4, 80%>
FY2015	24 <24, 100%>	9 < 9, 100%>

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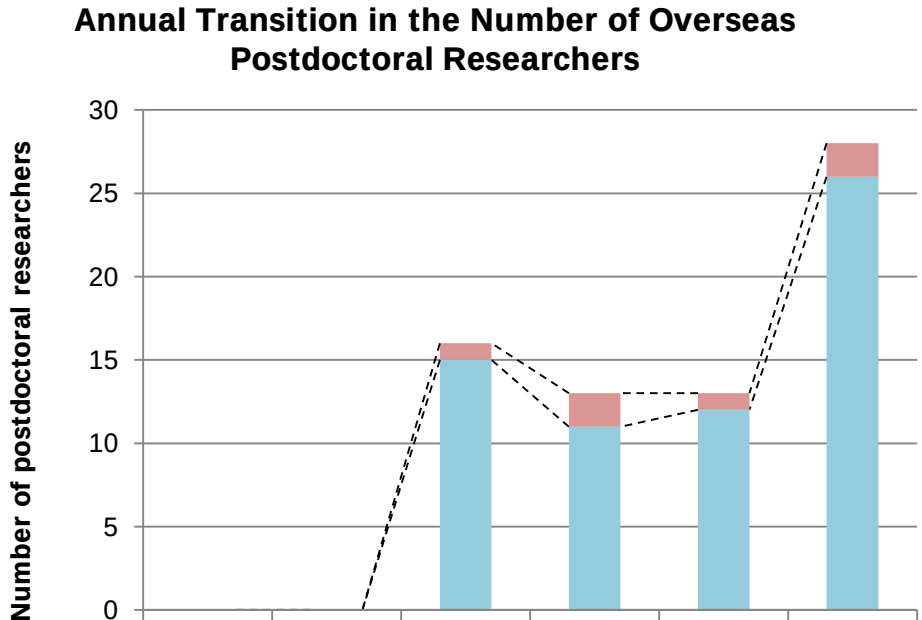
Appendix 4-4. Number of overseas postdoctoral researchers

* Make a graph of the transition in the number of overseas postdoctoral researchers since the project application was submitted.



	At beginning	FY2012	FY2013	FY2014	FY2015	Final goal
Japanese postdoctoral researchers	0	0	1	2	1	2
Overseas postdoctoral researchers	0	0	15	11	12	26

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Appendix 4-5. Status of postdoctoral researchers' employment at institutions

- List each researcher in 1 line. If the list exceeds this form, please add extra pages.

Period of project participation	Previous Affiliation (organization, *country)	Next Affiliation (Position title, organization, *country)	Nationality
4/1/2013 ~2/28/2014	Graduate School of Science, NU, Japan	Designated Assistant Professor, Institute for Advanced Research, NU, Japan	China
4/1/2013 ~4/30/2015	Graduate School of Science, NU, Japan	Assistant Professor, Indian Institute of Science Education and Research, India	India
5/1/2013 ~3/31/2014	Universitat Rovira i Virgili, Spain	Marie Curie Fellow, University of St Andrews, UK	Spain
6/1/2013 ~3/31/2014	RIKEN Advanced Science Institute, Japan	Research Fellow, Swiss Federal Institute of Technology in Zurich, Swiss	French
6/1/2013 ~5/31/2014	IRCBM, COMSATS Institute of Information Technology, Pakistan	Assistant Professor, IRCBM, COMSATS Institute of Information Technology, Pakistan	Pakistan
6/1/2013 ~8/31/2015	Max-Planck-Institutes, Germany	Postdoctoral fellow, Max Planck Institutes, Germany	China
6/1/2013 ~11/30/2015	University of South Florida, USA	Postdoctoral Research Associate, The University of Sydney, Australia	India
6/16/2013 ~1/31/2016	AstraZeneca India Pvt Ltd, India	Designated Assistant Professor, Graduate School of Medicine, NU, Japan	India
7/5/2013 ~7/31/2014	University College Dublin-Centre for Synthesis & Chemical Biology, Ireland	Senior postdoc, Universidad Nacional Autonoma de Mexico, Mexico	Mexico
10/1/2013 ~7/31/2015	Graduate School of Science, NU, Japan	Associate Professor, Nanchang University, China	China
10/1/2013 ~12/31/2015	Indian Institute of Technology, India	Researcher, Anthem Bioscience, Pvt. Ltd., India	India
10/1/2013 ~Present	National Institute for Basic Biology, Japan	-	Japan
10/1/2013 ~Present	Research Center for Materials Science, NU, Japan	-	China
11/1/2013 ~Present	Graduate School of Natural Science and Technology , Okayama University, Japan	-	China

1/1/2014 ~3/31/2014	The University of North Carolina, USA	Postdoctoral Fellow, JSPS, Japan	USA
1/16/2014 ~3/14/2016	Heinrich-Heine-University Dusseldorf, Germany	Associate Consultant, Next Move KK, Japan	Germany
5/1/2014 ~1/31/2015	University of Amsterdam, The Netherlands	CNRS Research Associate, Institut des Sciences Chimiques de Rennes, French	Spain
9/1/2014 ~12/19/2014	Queen's University, Canada	Postdoc Fellow, Queen's University, Canada	Swiss
11/1/2014 ~ 10/31/2015	Queen's University, Canada	-	Canada
11/1/2014 ~11/30/2015	Graduate School of Science, NU, Japan	Designated Associate Professor, Institute of Transformative Bio-Molecules, Japan	Japan
12/16/2014 ~Present	University of Rovira and Virgili, Spain	-	Sweden
4/16/2015 ~Present	University of British Columbia, Canada	-	Canada
4/16/2015 ～Present	University of British Columbia, Canada	-	Canada
5/16/2015 ~Present	University of Jyväskylä, Finland	-	Finland
6/1/2015 ~10/31/2015	Graduate School of Science, NU, Japan	Postdoctoral Fellow, JSPS, Japan	Germany
11/1/2015 ~Present	University College London, UK	-	USA
11/1/2015 ~Present	The University of Hong Kong, China	-	China
12/1/2015 ~3/31/2016	Bangalore University, India	-	India
1/16/2016 ~Present	University of Münster, Germany	-	Bolivia
3/1/2016 ~Present	Indian Institute of Science, India	-	India

* The country in which the organization is physically located.

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Appendix 4-6. Holding International Research Meetings

For each fiscal year, indicate the number of international research conferences or symposiums held and give up to two examples of the most representative ones using the table below.

FY 2012-2013: 2 meetings

Major examples (meeting title and place held)	Number of participants
The 1st International Symposium of Transformative Bio-Molecules (ISTbM-1) Noyori Conference Hall, Nagoya University April 18, 2013	From domestic institutions: 290 From overseas institutions: 10
10th Hirata Award Noyori Conference Hall, Nagoya University February 18, 2014	From domestic institutions: 230 From overseas institutions: 10

FY 2014: 3 meetings

Major examples (meeting title and place held)	Number of participants
The 2nd International Symposium of Transformative Bio-Molecules (ISTbM-2) Noyori Conference Hall, Nagoya University May 12, 2014	From domestic institutions: 288 From overseas institutions: 8
The 20th Nagoya Medal of Organic Chemistry Noyori Conference Hall, Nagoya University October 27, 2014	From domestic institutions: 385 From overseas institutions: 3

FY 2015: 3 meetings

Major examples (meeting title and place held)	Number of participants
The 3rd International Symposium of Transformative Bio-Molecules (ISTbM-3), Hirata Award, Okazaki Award Toyoda Auditorium, Nagoya University May 25-26, 2015	From domestic institutions: 380 From overseas institutions: 20
The 21st Nagoya Medal of Organic Chemistry Toyoda Auditorium, Nagoya University January 22, 2016	From domestic institutions: 415 From overseas institutions: 5

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Appendix 5-1. Host institution's commitment

1. In-kind contributions from host institution

(personnel, laboratory space, etc.)

Laboratory space

Nagoya University (NU) is providing 5,357 m^2 plus an additional 463 m^2 of an old building to be incorporated in ITbM's new building, adding to a total of 5,820 m^2 research space (including 4,166 m^2 provided complimentarily) in addition to the ITbM's new building.

Personnel and salaries

NU has been covering salaries of
1) 7 PIs of NU.
2) 7 designated associate professors who take charge of education in each department to relieve the PIs of this responsibility.
3) 4 administrative staff + 1 URA through assignment from the University's human resource.

Financial support toward construction of ITbM's new building

NU provided the financial support toward construction of ITbM's new building (800 million JPY).

2. System under which the center's director is able to make substantive personnel and budget allocation decisions

Decision making system

NU established the Institute rule, "Nagoya University Institute of Transformative Bio-Molecules Rules", to limit the role of the President of NU only to the appointment of the Director. All matters concerning operation and management of the Center fall under the purview of the Director.
NU also established "Nagoya University Institute of Transformative Bio-Molecules Steering Committee Rules" to organize the system, which enables the Director to exercise strong leadership in the Center concerning important matters such as personnel and execution of the budget.

Decision supporting system

Steering Committee meeting is held once a month to provide advice to the Director about the management of ITbM. Informal PI meetings are also held when necessary to discuss details such as research progress and lab management. Accordingly, the Director makes decisions on the allocation of personnel and facilities by consulting the Administrative Director who handles the budget.

3. Support for the center director in coordinating with other departments at host institution when recruiting researchers, while giving reasonable regard to the educational and research activities of those departments

Employment of 7 associate professors

NU has employed 7 associate professors to carry out educational activities and those of entrance examinations to allow NU PIs to concentrate on their research at ITbM.

Students allocation

All the 7 NU PIs are holding strong ties with their original departments, and undergraduate and graduate students are assigned in the same way before starting ITbM. One overseas PI in biology was assigned as a collaborating researcher in the Graduate School of Science, and a few graduate students have been allocated to the group every year.

4. Revamping host institution's internal systems to allow introducing of new management methods

(e.g., English-language environment, merit-based pay, cross appointment, top-down decision making unfettered by conventional modes of operation)

As denoted in **2**, it was authorized by NU that the Director has the authority to make decisions over appointment of personnel, the Center's budget, and research priorities in addition to other matters as they arise. The Steering Committee authorizes the Director to make final decisions, thus it is the place for discussion and acts as an advisor to the Director.
According to the "Implementation Guidelines for the Special Bonus System for Persons in the Service of Nagoya University Institute of Transformative Bio-Molecules", which is the system to provide special bonus to the Director, the Vice Director, PIs, and the Administrative Director based on their performance and evaluations, the determination of eligible persons and the amount of bonus is left to the discretion of the Director. The Executive Board of NU determines the special bonus of the Director.
NU assigned administrative staff who are eligible in English. Thus, the Administrative Department is composed of personnel with excellent ability, experience in a variety of areas, and a good command of English. All the administrative information is provided in both English and Japanese. The Steering Committee meetings are also conducted in English.

5. Utilities and other infrastructure support provided by host institution.

(facilities, e.g., laboratory space; equipment; land, etc.)

As denoted in **1**, NU is providing ITbM with sufficient space including the original laboratory spaces that the NU PIs have been allocated even after establishment of the new building.
NU is very well equipped with top-level major instruments necessary for ITbM's research. The quality and number of these instruments rivals the best institutions in the world. These instruments can be used by all ITbM members.

NU revised the rule of the use of halls of residence to provide ITbM's foreign researchers to reside, and to extend the possible duration from one to two years.

6. Support for other types of assistance

In order to promote efficient use of intellectual properties and research outcomes from ITbM and other NU institutes, NU conducted the organizational reform of research supporting units to establish the "Department for Academic Research & Industry-Academia-Government Collaboration". ITbM's activities are strongly supported by this department particularly related to collaboration and technology transfer to industries through business matching.

Most tasks to operate the new building have been supported by the Graduate School of Science to reduce the burden of ITbM. The guard system, fire alarm system, door-access control system, security camera system at ITbM are operated through the resources of the Graduate School of Science.

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Appendix 5-2. Female researchers

*Enter the number and percentage of female researchers in the top of each space and the total number of all the researchers in the bottom.

		FY2012	FY2013	FY2014	FY2015	Final goal
Researchers		2, 18 %	10, 19 %	12, 21 %	17, 26 %	14, 20 %
		11	53	58	65	70
	Principal investigators	2, 20 %	2, 20 %	2, 18 %	2, 18 %	3, 20 %
		10	10	11	11	15
	Other researchers	0, 0 %	8, 19 %	10, 21 %	15, 28 %	11, 20 %
		1	43	47	54	55