# World Premier International Research Center Initiative (WPI)
# Executive Summary (For Final Evaluation)

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| Host Institution | Nagoya University | Host Institution Head | Seiichi Matsuo |
| Research Center | Institute of Transformative Bio-Molecules | | |
| Center Director | Kenichiro Itami | Administrative Director | Tsuyoshi Matsumoto |

Instruction: Based on the Center's Progress Report and Progress Plan, prepare this summary within 6 pages.

## A. Progress Report of the WPI Center

### I. Summary

ITbM was launched at Nagoya University (NU) as a unique research institute to develop innovative functional molecules "transformative bio-molecules" that make a marked change in the form and nature of biological science and technology. By taking full advantage of our cutting-edge molecular synthesis expertise and intense interactions with leading plant/animal biology research, ITbM has been conducting 'needs-inspired' basic research and explored new research areas of "plant chemical biology", "chemical chronobiology", and "chemistry-enabled live imaging". Going forward with its mission/goal of developing transformative bio-molecules, ITbM set the plan "ITbM2.0", and started the following challenges in early 2020: "parasitic plants", "chemistry-enabled plant adaptation", "clock diseases", "chemistry-enabled bioimaging", and "nanocarbon chemistry and biology".

**The achievements of 2012.11-2021.3 (papers: 2012.11-2020.12)**

- Journal publications: 1060 peer-reviewed papers (262 papers IF>10; 424 papers IF>7; 67 highly cited papers (top 1%); 9 hot papers (top 0.1%), 380 international collaborative papers
- Awards and honors to faculty members: 169
- Patent applications: 148 (incl. 46 cases co-filed among several PI groups)
- Patent license agreements: 43
- Material transfer agreements: 45
- Collaborative research with industries: 101
- Commercialization of molecules/catalysts: 22
- Spin-off startups/ventures: 3 companies
- Total sum of external research funds: 9.28 billion yen

The synergy of ITbM researchers' high research profile and the new research style at ITbM has facilitated interdisciplinary research at a pace more rapidly than initially expected. ITbM's "Mix Labs" that mixes 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 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.

ITbM has been extending its global network to further advance its interdisciplinary research via extensive collaboration. With the cutting-edge research outcomes, ITbM is now widely recognized as an international research hub of chem-bio research. ITbM is positioned as a flagship research institute in NU, and has been inducing system reforms of NU. In 2018, a new graduate program "Graduate Program of Transformative Chem-Bio Research (GTR)" was established as a MEXT "Doctoral Program for World-leading Innovative & Smart Education (WISE)" having ITbM as its core. The Graduate School of Science makes a system reform and officially allocates PhD students also to ITbM's overseas PI groups from FY2022. ITbM will work proactively in nurturing PhD students who can pioneer new science at the interface of multiple disciplines.

Societal implementation of the ITbM's research outcomes is in progress as represented by the development of molecules to combat parasitic plants *Striga*. ITbM launched a membership discussion forum "ITbM Consortium" in 2017 to provide matching opportunities with industries, which was revamped in 2020 as "ITbM/GTR Consortium" and incorporated a wider range of researchers who engage in the GTR program.

ITbM has now become truly exciting and internationally visible institute where new

interdisciplinary research fields emerge and new molecules are born every day. ITbM's unique "Mix" culture has led researchers from different fields to work together, take risks, think/act differently, thereby finding unique problems and solutions, discovering something new, and providing unique solutions to key global problems. Researchers world-wide have recognized the strength of ITbM. Although since FY2020 several activities have been restricted due to the COVID-19 pandemic, our dream of changing the world with molecules has been clearly bearing fruit. ITbM's challenge continues.

## II. Items

### 1. Overall Image of Your Center

ITbM has gathered top-researchers from the different disciplines including synthetic chemistry, plant biology, animal biology, and theoretical sciences under one roof, who have been carrying out interdisciplinary research through extensive collaboration. In the 9 years, ITbM has grown to a size of 200 people including 66 researchers (13 PIs, 53 other researchers, 30% non-Japanese), 70 support staff, and many PhD students. ITbM has also been proactive to appoint female researchers. Including three female PIs, 20 female researchers are on staff at ITbM, making up 30% of total researchers.

In order to mix the people to promote interdisciplinary research, ITbM installed Mix Labs and Mix Offices, where researchers and students from different fields discuss on a daily basis. This style has significantly promoted bottom-up interdisciplinary projects among young researchers. ITbM also installed "soft" measures to promote interdisciplinary research such as ITbM Research Award, which significantly accelerates collaborations in a bottom-up manner.

Collaboration with partner institutions is also a key to promote interdisciplinary research. ITbM's target ID platform is being developed through collaboration with RIKEN Center for Sustainable Resource Science (CSRS) and Institute of Chemistry (IoC) at Academia Sinica, Taiwan. International collaboration has also contributed to enhance the ITbM's internationalization and international visibility. ITbM has been proactive to organize outreach events and make international press releases, which also resulted in receiving world-wide recognition of ITbM.

### 2. Advancing Research of the Highest Global Level Research Activities

ITbM has been promoting 'needs-inspired' basic research to develop transformative bio-molecules that make a marked change in the form and nature of biological science and technology. Selected achievements are summarized below.

*Striga* and related parasitic plants: The parasitic plant *Striga* has been causing huge damage on crop production in Africa. ITbM has been tackling to provide molecular solutions to this issue, and succeeded in identification of strigolactone receptors and development of *Striga* germinator sphynolactone-7 (SPL7). SPL7 binds to a specific strigolactone receptor selectively, and activated it with a high-affinity to provoke *Striga* germination with potency in the *femtomolar* ($10^{-15}$ molar) range. The field test has been ongoing in Kenya in collaboration with KALRO toward the societal implementation. ITbM has also been tackling the research on other parasitic plants.

Plant reproduction: ITbM has identified a series of new key biomolecules such as LURE, AMOR and CALL1 that control species-specific plant fertilization. Recently the target protein of the LURE has been identified and the structure was elucidated by the crystallographic analysis. The researchers continue their challenges to overcome species barriers. Another topical progress was made on creation of plant chimeras through grafting. Using tobacco that significantly breaks down the barrier to grafting, they have identified a key enzyme that remodels the cell wall. Those discovery are expected to lead to advances in research to improve plant fertilization efficiency.

Stomatal development and functional control: ITbM has developed a series of unique molecules that enhance the number of stomata. The research on stomatal opening/closing mechanism revealed that the stomatal aperture is a limiting factor of photosynthesis and plant growth, and molecules to control stomatal movements have also been developed. The stomatal closing molecules have prevented plant leaves from drying-up and suppress withering when sprayed onto the plants. These research outcomes have gained a significant amount of attention, and have been led to several academia-industry joint research projects.

Biological clock control: A number of potent molecules that can control the animal/plant biological clocks have been discovered. Some of unique animal-clock control molecules are investigated toward application with pharmaceutical companies, based on the identification of the target proteins, structural analysis, and evaluation of biological functions. The researchers also used drug-repurposing approach, and developed molecules that either shorten or lengthen the circadian rhythm in human cells. DHEA (dehydroepiandrosterone) demonstrated notable period-shortening activities, and significantly reduced jet lag symptoms in mice. In the study of seasonal clock, medaka fish was found to show different behavior upon seasonal changes, and the reason was revealed as that the genes encoding photopigments vary dynamically among

seasons. Chemical screening identified 'Celastrol' as a potent molecule that reversed the depressive behavior. Molecular modulation of the plant biological clock also has notable progress. As for the plant clock control, the molecule PHA767491, identified as an animal CDC7/CDK9 inhibitor, was found to regulate multiple gene expression and lengthened the plant circadian period. It may lead to the development of an optimized variety of crops.

New fluorescent molecules for advanced bioimaging: 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. A series of unprecedented molecules that exhibit high responsive property to environment polarity and have discovered near infrared emissive fluoresceins. These super high-performance molecules are commercially available and expected to serve a significant role in leading the bio-imaging field. Indeed, the molecule named as PREX 710 exhibits the high fluorescence longevity and applicable to a single-molecule microscopy under physiological conditions. Recently new fluorescent molecule named Kakshine was also developed, which makes the nuclei of various organisms shine brightly. The Kakshine and its derivatives are highly compatible with STED-FILM and a two-photon microscopy, and applicable to deep imaging of organisms.

Efficient molecular 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. Facile synthesis of peptide/protein performed by Bode-Oishi group also provides alternative approach to bioactive molecules. They applied their KAHA ligation method into a microbial fermentation process to obtain bioactive unnatural peptides. These synthesis technologies have been applied to ITbM's interdisciplinary research and advanced towards developing candidate molecules for medicines and agrochemicals.

Molecular nanocarbons: Chemists have tried to synthesize carbon nanobelts for more than 60 years, but none have succeeded until now. Itami has reported the first organic synthesis of a carbon nanobelt. Carbon nanobelts are expected to serve as a useful template for building carbon nanotubes and open a new field of nanocarbon science. Itami has also developed chemical synthesis of various forms of nanocarbons in a controlled fashion. The simple and powerful synthetic methods generate a range of novel applications of nanocarbons, and indeed ITbM has paved a way to their unprecedented biological applications.

### 3. Feeding Research Outcomes Back into Society

ITbM has strategically created a wide range of networks consisting of domestic/international industries toward societal implementation of the research outcomes. As summarized above, ITbM has filed 148 patent applications, and its 31% have been derived from the interdisciplinary researches between chemistry and biology. Base on the patents, 3 ITbM-based startups have launched. 22 molecules are commercially available as tool reagents for researches, such as novel fluorescent dyes LipiDye and LipiDye II that stain the lipid droplets located in cells with high sensitivity and have widely spread to not only academia but industries including medical, pharmaceutical, agrochemical and cosmetic companies. ITbM concluded the license agreement of SPL7, which induces suicide germination of *Striga* and has decided to commercialize as a reagent for researchers. SPL7 is expected to be utilized as an agrichemical application in Africa and other countries. The achievements have been proactively announced through international media and various social events, which has been significantly promoting ITbM's international visibility.

ITbM has been conducting many collaborative research projects with companies and has concluded 45 MTAs to further promote the societal implementation. To create the opportunities for academia-industry partnership, ITbM organizes a membership discussion forum "ITbM/GTR Consortium", where 'Seeds' and 'Needs' meet each other.

### 4. Generating Fused Disciplines

Under the strong leadership of the Director, all members at ITbM have been working beyond their discipline and developing interdisciplinary research spanning chemistry, plant/animal biology, and theoretical sciences toward making transformative molecules. The success of the interdisciplinary research is represented by the joint publications and patents; 77 papers and 46 patents are based on the interdisciplinary research, and 380 papers have been published by international collaboration.

ITbM set the plan "ITbM2.0" in early 2020, and started the following challenges: "parasitic plants", "chemistry-enabled plant adaptation", "clock diseases", "chemistry-enabled bioimaging", and "nanocarbon chemistry and biology". ITbM's interdisciplinary research has been making significant progress under the "Mix" concept, and the initiatives to promote interdisciplinary research have been effective so far. The ITbM Research Award, established to foster interdisciplinary collaboration among young researchers and students, has been granted to 18

new projects. The ITbM Workshop and Tea break Meeting are also providing opportunities to find new partners and seeds for collaboration. These initiatives are organized by the Administrative Department of ITbM, in which the Research Promotion Division (RPD) and the Strategic Planning Division (SPD) are playing key roles. ITbM's 4 supporting centers (Molecular Structure Center, Live Imaging Center, Chemical Library Center, and Peptide Protein Center) are also making a major contribution to the promotion of ITbM's interdisciplinary research.

**5. Realizing an International Research Environment**

ITbM has 5 world-leading overseas PIs. They have been actively contributing to promote ITbM activities. 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 online meetings or e-mails. They also send a few researchers of his/her institutes to ITbM, although they have been suspended for a while due to the COVID-19 pandemic.

ITbM created a new post of non-Japanese Junior PI, and started the open call in late 2020. 31 applications were received, and the selection process has started in February 2021.

ITbM has been functioning as a global talent pool. ITbM has hired 106 postdocs from over the world, in which 69 (65%) are non-Japanese. Out of the 67 postdocs who left ITbM, 39 found faculty positions in academia in Japan and overseas. Academic promotion of young faculty members is also notable. So far, 10 associate/assistant professors have been promoted to other academic institutions/departments. They have the title of "Affiliated Researcher of ITbM", and continue their collaboration with ITbM. Accordingly, ITbM's network has been widely spreading.

ITbM proactively offers PhD students the opportunities to conduct research abroad. So far 39 PhD students have visited overseas institutions to engage in collaborative research.

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.

ITbM has been hosting annual international symposia (ISTbM) and three international awards (Hirata Award, Tsuneko & Reiji Okazaki Award, Nagoya Medal of Organic Chemistry). In addition, ITbM faculty members have been organized various international symposia/workshops, which have been significantly contributing to increase ITbM's international visibility and extending international network.

**6. Making Organizational Reforms**

NU gave the executive authority to the Center Director to make top-down decisions over the appointments of ITbM's personnel, budget, research priorities, and incentive-based bonuses.

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.

ITbM's high research performance has largely contributed to establish various initiatives of NU, such as being selected as "Designated National University" by MEXT (2018), concluding a basic agreement with RIKEN. NU launched the new graduate program "Graduate Program of Transformative Chem-Bio Research (GTR)" with ITbM as a core. ITbM's Mix Lab will provide a superb place to nurture young researchers who pioneer new science. NU established Nagoya University Institute for Advance Study (NAIAS) to strengthen the world-leading research base for basic research at NU, and ITbM is sustained under this umbrella.

NU has been strongly supporting ITbM by such as (1) covering salaries, (2) provision of space, (3) financial support towards construction of ITbM's building, (4) support towards the operation of the building, and (5) ITbM's priority to the use of hall of residence. NU promised to secure the employment of most of the ITbM's faculty members and several essential staffs after the WPI fund ends, and thus the ITbM's activity is secured.

**7. Others**

In November 2020, Itami et al retracted the paper titled "Living annulative $\pi$-extension polymerization for graphene nanoribbon synthesis" published in Nature 2019. The Itami group noticed that some of the results were unreproducible and the paper includes incorrect data. The group recognized that these issues undermine the group's confidence in the integrity of the study as a whole, and decided to retract the paper. The group also retracted the two related papers published in JACS 2020 and ACS Appl Nano Mater 2019 for the same reason. We regret any confusion and apologize to the scientific community.

ITbM is aware of researchers' responsibility and takes actions to avoid any research misconduct. ITbM has established the own policy in accordance to the guidelines of NU and MEXT.

ITbM also recognizes the importance of communication with the general public widely so

that ITbM always addresses the environmental and safety issues carefully upon development of molecules that modulate biological system in plants and animals. ITbM has set up an Environment and Safety Committee to hold the meeting annually so that researchers at ITbM are constantly aware of these issues when conducting their research.

## B. Progress Plan

### 1. Mid- to Long-term Research Objectives and Strategies Based on the Center's Research Results to Date

The mission of ITbM has been to conduct 'needs-inspired' basic research while developing transformative bio-molecules that make a marked change in the form and nature of biological science and technology. By marrying state-of-the-art synthetic chemistry, catalytic chemistry, plant biology, animal biology, live imaging, and theoretical science, ITbM has advanced new research areas of "plant chemical biology", "chemical chronobiology", and "chemistry-enabled live imaging". This exciting endeavor has resulted in the development of a range of promising bio-functional molecules, many of which have been commercialized, and the discovery of molecular mechanisms of important biological events. An exciting example during the ITbM's first chapter is the development of molecules to potentially combat the parasitic plant *Striga*. Molecules developed at ITbM have entered the exciting phase of being tested in the fields of Kenya starting since 2019.

All of these tour-de-force achievements have led scientists in the world to place ITbM as an enabling institute where new bioactive molecules with targeted properties can be rapidly discovered, designed, and synthesized. Going forwards, our mission/goal of developing transformative bio-molecules will not change, instead we will redefine our focus to advancing societal implementation of the research outcomes and to develop new scientific fields continuously.

Given this context, we will tackle the following challenges in the next 5-10 years. Through these challenges, ITbM will become more visible, and further be recognized as a world-leading research institute.

**(1) Parasitic Plants:** Based on our discovery of significant potential molecules for combatting the parasitic plant *Striga*, ITbM will make efforts to provide molecular solutions to the food security issues, especially focusing on Africa. For this purpose, we have initiated a collaboration with Kenya Agricultural & Livestock Research Organization (KALRO) and the International Center for Research and Education (ICREA) of NU. We are confident that our molecular approach can be used to combat other parasitic plants causing huge damage in other regions. For example, we will apply our knowledge and experience on *Striga* to a devastation caused by another parasitic plant *Orobanche* which infests a wider area including India, the Middle East, European countries and Australia. We will tackle this issue.

Adding to our efforts in parasitic plant science, we will develop brand-new molecules for plants and animals as the next generation of transformative bio-molecules. Plants and animals have their unique but uncovered biological systems consisting of local and systemic cellular communications that are most likely all governed by small molecules. The next-generation molecules will be further designed to specifically control target systems even at the whole organism level. We will particularly focus on **(2) chemistry-enabled plant adaptation** and **(3) clock-disease** as new challenging directions based on what we have achieved so far. We will also continue to work on **(4) chemistry-enabled bioimaging** via developing new fluorescent molecules and contribute to advance biological research.

**(2) Chemistry-enabled plant adaptation:** Plants have inherent stress tolerance systems that enable them to adapt to environmental changes and survive under stressful conditions that are essential functions due to their inability to move. However, recent global climate change exceeds the tolerance of the current abiotic stress response of plants, and they often face to serious situations such as failing to fertilize, failing to develop, and eventual death. If such environmental stress can be overcome by synthetic molecules, food production can be maintained or even increased even in a severe $CO_2$-rich environment, improving food security and combatting climate change. We aim to develop such environmental stress-overcoming molecules to maximize the adaptive power of plants via an interdisciplinary approach.

**(3) Clock-disease:** Disturbances in the circadian system have a profound impact on health, and they have been linked to several pathologies, including obesity, psychiatric disorders, cardiovascular disease, and even cancer. Through extensive chemistry-biology-theory collaboration, ITbM has developed many molecules such as jet-lag reducing molecule and circadian clock-controlling molecules having anti-cancer effect. In the next chapter, we will challenge to develop transformative bio-molecules to understand and regulate the circannual clock to combat global climate and environmental changes. Seasonal human morbidity is observed in heart, cerebrovascular, infectious, and psychiatric diseases. In plants, seasonality is observed in growth,

pollination, pest and pathogen infestation, and flowering. We will uncover the underlying molecular bases of circannual rhythms in plants and animals. Since we have already identified several hit compounds that regulate flowering time in plants and winter depression-like behavior in animals, we will develop transformative bio-molecules that regulate plant and animal adaptation to climate and environmental changes.

**(4) Chemistry-enabled bioimaging:** Bioimaging is one of the indispensable techniques in the current biology. A key to open a new avenue in this technique relies on the development of useful fluorescence dyes. We have developed a series of new fluorescent dyes. Their outstanding photostability enabled acquiring not only 3-D structures of cytoskeletons, but also mitochondrial inner-membrane dynamics in the living cells by conducting the STED imaging. Near-infrared (NIR) fluorescent dyes is the other target molecules in our research, which have several advantages, such as diminishing photo-damage to bio-samples, minimal interference from cell autofluorescence, as well as deep penetration in biological tissues. With these sophisticated dyes in hand, together with state-of-the-art imaging instrumentations, we will make full use of these cutting-edge discoveries to understand and control biological systems, and also to contribute to the advancement of medical diagnosis.

**(5) Nanocarbon chemistry and biology:** In addition to strengthening our enabling platforms to tackle the above-mentioned unanswered scientific questions potentially leading to significant societal impact, we recognize the need for new molecular structures and hence properties to maximize the power of molecules. To this end, we will apply molecular nanocarbons as new molecular entities in biology and explore "nanocarbon biology" as a new scientific field. All the findings will be applied to other projects at ITbM, adding a new dimension in biological science and technology.

## 2. Management System of the Research Organization

We are sure the top-down management system established at the start is indispensable to ITbM to make a quick and flexible decision, and will continue. Irrespective of the independency of the ITbM, we have been building a good relationship with the Faculties/Departments of NU that many of ITbM's researchers are co-affiliated to. PhD students and undergraduate students are continued to be allocated to ITbM PI groups.

We strongly recognize the importance of nurturing the next generation who will lead ITbM in future. We will involve young faculties into the discussion on our long-term plan.

For implementation of the research projects, it is inevitable to strengthen relationships with external organizations. We continue and strengthen our present collaboration.

NU will continue its extensive system reform to become a visible world-class research university. In the plan, ITbM is positioned as a core research center of NU for the future, and is responsible to cooperate with NU and devise various tasks to achieve the goal. We will cooperate with NU and the related departments and research centers to take up the challenges of spreading Mix Lab concept as a good practice to promote interdisciplinary research.

### ・Center's Position within the Host Institution and Measures to Provide It with Resources

To secure the employment of ITbM's faculties and staffs, NU makes an organizational reform in 2019. NU launches "Nagoya University Institute for Advanced Study (NAIAS)", and positions ITbM under this umbrella. Irrespective of the reorganization, the Director of ITbM has the authority to make decisions of ITbM.

ITbM is now indispensable as a core of the new graduate program GTR, which endorses ITbM's continuation. While NU PI groups have been fully allocated PhD/undergraduate students, overseas PI groups have a limited number of PhD students. However, the Graduate School of Science is going to make its system reform, and will officially allocate PhD students to ITbM's overseas PI groups from FY2022. Accordingly, more PhD students will be officially allocated to ITbM.

Toward future development of ITbM, NU promised to make all effort to secure personnel of ITbM. NU have been requesting funding to MEXT to further develop its activities, and was given 4 positions to the present (FY2021). NU continues this request to provide positions to ITbM with highest priority. In addition to this request, 7 more tenure positions were secured in FY2019. NU also promised to provide additional support by all means from FY2022 to secure almost all the ITbM's designated faculty members and the selected postdocs/staff who are essential to run ITbM. NU will also make a full support to collect any funds to sustain ITbM. NU has also committed its full support to collect funds to sustain ITbM. NU will boost the reputation of ITbM to further increase the endowment by all means including through the Nagoya University Foundation and academia-industry partnership.

# World Premier International Research Center Initiative (WPI)
# Progress Report of the WPI Center
# (For Final Evaluation)

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| Host Institution | Nagoya University | Host Institution Head | Seiichi Matsuo |
| Research Center | Institute of Transformative Bio-Molecules | | |
| Center Director | Kenichiro Itami | Administrative Director | Tsuyoshi Matsumoto |

Common Instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2021) situation of your WPI center.
* As a rule, keep the length of your report within the specified number of pages. (The attached forms are not included 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. Overall Image of Your Center (write within 2 pages including this page)

Describe the Center's current identity and overall image.
- List the Principal Investigators in Appendix 2, and enter the number of center personnel in Appendix 3-1, 3-2, diagram the center's management system in Appendix 3-3, draw a campus map in Appendix 3-4, and enter project funding in Appendix 3-5, 3-6.

ITbM was launched at Nagoya University (NU) as a unique research institute to develop innovative functional molecules "transformative bio-molecules" that make a marked change in the form and nature of biological science and technology. By taking full advantage of our cutting-edge molecular synthesis expertise and intense interactions with leading plant/animal biology research, ITbM has been conducting 'needs-inspired' basic research and explored new research areas of "plant chemical biology", "chemical chronobiology", and "chemistry-enabled live imaging". Going forward with its mission/goal of developing transformative bio-molecules, ITbM set the plan "ITbM2.0", and started the following challenges in early 2020: "parasitic plants", "chemistry-enabled plant adaptation", "clock diseases", "chemistry-enabled bioimaging", and "nanocarbon chemistry and biology".

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- Spin-off startups/ventures: 3 companies
- Total sum of external research funds: 9.28 billion yen

ITbM has gathered top-researchers from the different disciplines of synthetic chemistry, plant biology, animal biology, and theoretical sciences under one roof, who have been carrying out interdisciplinary research through extensive collaboration. ITbM started with 10 PIs (7 from NU, 3 from overseas), and later appointed 3 more PIs (1 from NU, 2 from overseas) who were necessary to further advance its research at the time. In order to enable world-class researchers to participate in ITbM as overseas PIs, ITbM introduced the Co-PI system. Through this system, ITbM employs brilliant young researchers as Co-PIs who work full time at ITbM while cooperating with the overseas PIs. This system enables the overseas PIs to carry out research at ITbM with continuity, and has contributed to improving the global visibility of ITbM. Co-PIs were also allocated to NU PIs to enable NU PIs to focus on their research. In the net 8 years since its inception, ITbM has grown to a size of 200 people including 66 researchers (13 PIs, 53 other researchers, 30% non-Japanese), 70 support staff, and a large number of PhD students.

In order to "Mix" ITbM researchers and promote interdisciplinary research, ITbM created Mix Labs and Mix Offices. In these spaces, researchers and students from different fields discuss and communicate about science, education and other administrative matters on a daily basis. This style has significantly promoted bottom-up interdisciplinary projects among young researchers. The ITbM Research Award, established to promote interdisciplinary research proposed by young researchers, further

accelerates collaborations in a bottom-up manner.

These endeavors have resulted in the development of a range of promising bio-functional molecules and the discovery of molecular mechanisms of important biological events. A representative outcome is the discovery/development of molecules to combat the parasitic plant *Striga*, which were developed from a bottom-up collaboration of young researchers initiated at the Mix Lab. Industrial collaboration of ITbM has been developing, as represented by the increasing number of patent licensing and commercialized molecules. ITbM's membership forum "ITbM Consortium" launched in 2018 with 17 companies was revamped in 2020 as "ITbM/GTR Consortium" and incorporated the researchers who engage in the new doctoral program "Graduate Program of Transformative Chem-Bio Research (GTR)". The GTR was established as a MEXT's "Doctoral Program for World-leading Innovative & Smart Education (WISE)" having ITbM as its core (see Section 6-3).

ITbM's extraordinary achievements are also evident in the records of competitive funds, prestigious awards, and invited lectures. In the past 9 years, research funds amounting to 9.28 billion yen have been garnered by our PIs and researchers. Considering the relatively small size and the nature of ITbM's science focusing on basic research, this number is remarkably high for an institute in Japan. Overseas PIs have been constantly obtaining KAKENHI grants and submitting patents and papers from their work at ITbM. In addition to many awards collected by ITbM researchers, 4 PIs have been selected as Highly Cited Researchers (Clarivate Analytics), which represents ITbM's high activity and visibility.

ITbM's research activities are supported by many capable and dedicated staff in ITbM. A key player is the Administrative Department of ITbM, especially the members of the Research Promotion Division (RPD) and the Strategic Planning Division (SPD). The RPD finds inventions and scientific discoveries from each research group at an early stage, and the SPD promotes patent application and societal implementation. The RPD also has staff to provide local support to ITbM's foreign researchers and their families, enabling them to fully concentrate on their research. ITbM's four supporting centers (Molecular Structure Center, Live Imaging Center, Chemical Library Center, and Peptide Protein Center) also make major contributions to ITbM's interdisciplinary research.

ITbM has strategically extended its collaboration network. ITbM has published 380 international joint papers. International collaboration has been considerably enhanced by ITbM's internationalization and international visibility, with these collaborations contributing greatly to interdisciplinary research. ITbM's target ID platform is being developed through collaboration with RIKEN Center for Sustainable Resource Science (CSRS) and Institute of Chemistry (IoC) at Academia Sinica, Taiwan. In 2020, the IoC Itami lab was launched and faculty staff hired.

Nurturing young researchers is a key mission of ITbM and critical for our future development. ITbM financially supports PhD students going abroad and have sent 39 PhD students on overseas exchanges. A notable number of postdoctoral researchers have carried out research at ITbM, and are currently in outstanding academic and industrial positions in Japan and overseas. The ITbM spirit is everywhere and ITbM has been recognized as a key hub in the global talent pool.

ITbM has also been proactive to appoint and foster female researchers. Including three female PIs, 20 female researchers are on staff at ITbM, making up 30% of total researchers as of March 31, 2021. Their remarkable activity is represented by a number of awards such as the Arthur C. Cope Scholar Award (Crudden), Killam Research Fellowship (Crudden), ASPB Award (Torii), Saruhashi Award (Torii), and the JST President Award for a Brilliant Female Researcher (Fukazawa).

ITbM's challenges have contributed to significant system reform at NU as a core research center. NU was recognized for its abilities to develop world-leading education and research activities and was named a "Designated National University", in part because of ITbM's high-profile activities. To achieve the goal, NU launched research supporting programs such as the "WPI-next" program to promote cutting-edge sciences at NU, which referred to ITbM's unique structures such as the Co-PI system. In 2019, NU made an organizational reform to establish "Nagoya University Institutes for Advanced Study (NAIAS)", positioning ITbM under this umbrella to secure the employment of ITbM staff through providing the needed financial support.

ITbM has also influenced the education system of the graduate schools. NU recognizes that ITbM's Mix Lab is one of the best places to nurture young researchers, and has launched the new graduate program GTR as denoted above. In this program, ITbM is positioned as a hub, through which the pioneering spirit of ITbM has been widely spread over many Departments in NU.

ITbM has become a truly exciting and internationally visible institute where new interdisciplinary research fields emerge and new molecules are born every day. Although since FY2020 several activities have been restricted due to the COVID-19 pandemic, our dream of changing the world with molecules is clearly bearing fruit. ITbM's challenge continues.

## 2. Advancing Research of the Highest Global Level (within 15 pages)

### 2-1. Research results to date

Describe issues of a global level that the Center has challenged, and give the results. Select 20 representative results achieved during the period from 2012 through March 2021. Number them [1] to [20] and provide a description of each. Place an asterisk (*) in front of those results that could only have been achieved by a WPI center and explain the reason in the description.

- In Appendix 1-1, list the papers underscoring each research achievement (up to 40 papers) and provide a description of each of their significance. And in Appendix 1-4 list the center's research papers published in 2020.

ITbM has been promoting 'needs-inspired' basic research to develop transformative bio-molecules that make a marked change in the form and nature of biological science and technology. Representative achievements in these 9 year are summarized below.

***[1] Unraveling strigolactone signaling and controlling *Striga* and other parasitic plants**

The parasitic plant *Striga hermonthica* (*Striga*), so-called witchweed, has been causing huge damage to crop production in Africa. Infection of harvests by Striga leads to the loss of $10 billion U.S. dollars' worth of crops from the continent every year. However, genetic intractability of *Striga* stood as a significant barrier to understand Striga in detail and develop *Striga* science.

To overcome the genetic intractability of the *Striga* that had previously interfered with identification of the strigolactone receptors (ShHTLs), ITbM chemists (Itami, Hagihara), biologists (Tsuchiya, Kinoshita), the Molecular Structure Center, the Live Imaging Center and their co-workers designed and developed a fluorescent turn-on probe, Yoshimulactone Green (YLG), which activates strigolactone (SL) signaling and illuminates signal perception by the ShHTLs. Using YLG, they demonstrated that ShHTLs function as SL receptors in *Striga* for the first time. Moreover, live imaging revealed that a dynamic wavelike propagation of SLs' perception wakes up *Striga* seeds (Appendix 1-2 (1): *Science* 2015). Their chemical approach has made *Striga* experimentally accessible to researchers world-wide for analyzing the functions of SL receptors, leading to the discovery of a number of the receptor agonists/antagonists, from ITbM chemical library (Appendix 1-2 (3): *ACS Cent. Sci.* 2018). Using the assay system enabled by YLG, ITbM chemists (Uraguchi, Ooi), biologists (Tsuchiya, Kinoshita), theoretical sciences group (Hijikata, Irle), and the Molecular Structure Center identified a hit molecule (SAM690) by high throughput chemical screening and succeeded in developing of sphynolactone-7 (SPL7) as a *Striga*-selective agonist. They revealed that two functional modules of SPL7 cooperatively acted on strigolactone receptor ShHTL7, and activated it with a high-affinity to provoke *Striga* germination. With potency in the *femtomolar* ($10^{-15}$ molar) range, SPL7 is effective for reducing *Striga* parasitism on a common crop (maize) in Africa without impinging on host strigolactone-related processes, unlike synthetic SL agonist GR24 showing multiple actions in plants and fungi (Appendix 1-2 (2): *Science* 2018). The discovery of SPL7 has motivated all ITbM scientists to tackle the issue of *Striga* through the practical use of SPL7 in Kenyan fields, and SPL7 field experiments began in July 2019 at KALRO Kibos in Kenya.

Due to the considerable impact on the global society and contribution to STI for SDGs of Africa, ITbM's efforts were highlighted in multiple events of the 7th Tokyo International Conference on African Development (TICAD7) held in Yokohama on August 2019; Advisory Panel for the Promotion of Science and Technology Diplomacy highlighted it in "Recommendations towards TICAD7: Achieving an innovation ecosystem together with Africa" as one of the important "science diplomats" of Japan to Africa (https://www.mofa.go.jp/press/release/press4e_002617.html); the TICAD7 official side event organized by MEXT, "Africa-Japan Ministerial Dialogue Meeting on STI for SDGs", invited Directors of ITbM and KALRO to provide a joint presentation as a good practice on Japan-Africa cooperation (https://www.mext.go.jp/en/news/topics/detail/mext_00015.html); the Minister of State for Science and Technology Policy mentioned in his introductory remarks at TICAD7's thematic meeting "STI and Digital Transformation" as a new initiative to contribute STI for SDGs of Africa.

***[2] Identification of a series of molecules that control plant reproduction**

Identification of key plant reproduction molecules is critically important to achieve molecular control of crop production and breeding. The Higashiyama group has been taking two approaches to overcome species barriers: control of species-specific key-and-lock molecules for genome barriers and an increase of fertility of reproductive cells between different species. The group discovered the long sought (nearly 140 years) pollen tube (PT) attractant molecule "LURE" (one of key molecules) as a defensin-like polypeptide secreted from synergid cells (*Nature* 2009). This work provides a major breakthrough not only in the investigation of ligand-receptor interaction but also for the discovery of lock molecules that break species-specific reproductive barriers (Appendix 1-1 (1): *Nature* 2016).

Following the discovery of the LURE receptor, the Higashiyama group identified that an ovular glycochain,

methyl-glucuronosyl arabinogalactan (**A**ctivation **Mo**lecule for **R**esponse-capability, AMOR), induces competency of the PT to respond to ovular attractant LURE peptides in Torenia. With the Itami group, they determined that the terminal disaccharide residue of AMOR was necessary and only the β-isomer of methyl-glucuronosyl galactose (4-Me-GlcA-β-(1/6)-Gal) showed AMOR activity through an extensive structure-activity relationship study (Plant Physiol. 2018). No specific sugar-chain structure of plant extracellular matrix has been identified as a bioactive molecule involved in intercellular communication. This study suggested that the AMOR sugar chain in the ovary renders the PT competent to the chemotropic response prior to final guidance by LURE peptides (Appendix 1-1 (2): *Curr. Biol.* 2016).
The discovery of PT attractant polypeptides (LUREs) and their receptor PRK6 led the Higashiyama group to investigate ligand-receptor interactions atomically. They revealed that the extracellular domain of the leucine-rich repeat receptor kinase (LRR-RK) PRK6 from *Arabidopsis thaliana* directly interacts with AtLURE1 peptides. A C-terminal loop of the LRR domain (AtPRK6LRR) is responsible for the recognition of AtLURE1.2, mediated by a set of residues largely conserved among PRK6 homologs from *Arabidopsis lyrata* and *Capsella rubella*, as supported by in vitro mutagenesis and semi-*in-vivo* PT growth assays with the Tama group (Appendix 1-1 (3): *Nature Commun*. 2017).
The Higashiyama group revealed an interesting phenotype of miss-localization of small GTPase, a biological molecular switch which is also important for tip growth (*Plant Cell Physiol*. 2020; cover of the issue). They also revealed that the removal of an epigenetic modification, H3K27me3, specific in the sperm cell of pollen, leads to gene expression for sperm cell differentiation and chromatin remodeling in preparation for fertilization (*Nature Cell Biol.* 2020). In addition, Higashiyama and Notaguchi have reported that the use of tobacco significantly breaks down the barrier to grafting, and identified a cell wall remodeling enzyme involved in the mechanism with the Live Imaging Center (Appendix 1-2 (4): *Science* 2020). They also demonstrated that the use of microfluidic devices is of significant value to high-throughput grafting studies (*Plant J*. 2020).

***[3] Elucidation of mechanisms involved in early embryogenesis of plants**
In flowering plants, the detailed mechanism of early embryogenesis remains largely unknown despite an immense amount of effort of the scientific community. The Higashiyama group has been tackling this challenge using live-imaging.
Higashiyama and Maruyama discovered that the fusion of the persistent synergid cell and the endosperm selectively inactivate the persistent synergid cell in *Arabidopsis thaliana*. They revealed that the synergid-endosperm fusion causes rapid dilution of a PT attractant in the persistent synergid cell and selective disorganization of the remaining synergid nucleus during the endosperm proliferation, preventing further attraction of multiple PTs after fertilization (Appendix 1-1 (4): *Cell* 2015). Only two other examples of plant cell fusion have been observed so far, and over 110 years have passed since the identification of the two cell fusions, which occurred between two sets of gametes during fertilization. Higashiyama and Ueda successively revealed the dynamics of organelles in early plant embryogenesis. They found that the preexisting alignment of MTs and F-actin in the egg cell is lost in fertilization, and then, MTs organize into a transverse ring defining the zygote subapical region and driving cell outgrowth in the apical direction. On the other hand, F-actin forms an apical cap and longitudinal arrays and is required to position the nucleus to the apical region of the zygote, setting the plane of the first asymmetrical division (Appendix 1-1 (5): *PNAS* 2016). In addition, they revealed that the vacuoles form tubular strands around the apically migrating nucleus, which gradually accumulates at the basal region and fills the space, resulting in an asymmetric distribution in the mature zygote. They also identified that shoot *gravitropism2* (*sgr2*), in which the vacuolar structural change was impaired, failed to form tubular vacuoles and to polarly distribute the vacuole, and revealed in *sgr2* that large vacuoles occupied the apical tip and thus nuclear migration was blocked, resulting in failure to undergo asymmetrical division (Appendix 1-1 (6): *PNAS* 2019).
Furthermore, the Higashiyama group succeeded in the generation of pollen tubes in *Arabidopsis thaliana* whose vegetative nucleus and sperm cells are isolated and sealed by callose plugs in the basal region due to apical transport defects induced by mutations in the WPP domain-interacting tail-anchored proteins (WITs) and sperm cell-specific expression of a dominant mutant of the CALLOSE SYNTHASE 3 protein, and discovered the physiologically "anuclear" mutant pollen tubes maintain the ability to grow and enter ovules (*Nature Commun.* 2021).

***[4] Elucidation of stomatal development mechanism and its molecular control**
Plant stomata, the cellular interface between a plant and the atmosphere, develop according to positional cues, which include a family of secreted peptides called epidermal patterning factors (EPFs). Although stomatal development is considered to play a key role in crop plant productivity and water-use efficiency,

the mechanism of stomatal development at a molecular level remains unclear.
The Torii group has made a number of remarkable discoveries on biomolecules, such as genes, receptors, transcription factors and peptides, involved in controlling the number and density of plant stomata, and leads the field of developmental biology of plant stomata at the molecular level. They identified stomagen peptide (also called EPF-LIKE9) in Arabidopsis, which promotes stomatal development, requires ERECTA (ER)-family receptor kinases and interferes in the inhibition of stomatal development through interaction with Epidermal Patterning Factor 2 (EPF2)–ER complex. They revealed that the stomagen peptide competitively replaces EPF2 binding to ER and induces rapid phosphorylation of downstream signaling components in vivo. Their findings demonstrate how plant receptor agonists/antagonists define inductive/inhibitory cues to fine-tune tissue patterning on the plant epidermis (Appendix 1-1 (7): *Nature* 2015).
Through collaboration with the Tama group of ITbM, the Torii-Uchida group revealed the molecular basis of how two MAOKs, MPK3/6, are recruited to the nucleus to inhibit a master regulatory transcription factor of stomatal development. They found that the bHLH protein SCREAM functions as a scaffold recruiting MPK3/6 to downregulate SPEECHLESS, a transcription factor initiating stomatal cell lineages and SCREAM directly binds with MPK3/6 through an evolutionarily-conserved yet unconventional bipartite motif. Structural analyses of MPK6 unraveled bipartite binding of SCREAM with MPK6 that is distinct from an upstream MAPKK (Appendix 1-2 (5): *Nature Plants* 2019).
The Torii-Uchida group has been exploring small molecules that affect the density and/or patterning of stomata through chemical screening. They succeeded in identifying the first-in-class synthetic molecules enhancing the number of stomata in *Arabidopsis thaliana* with the Itami group and the Chemical Library Center. Some promising lead compounds have further been optimized through structure-activity relationship study by using C–H functionalization reactions at a late stage of the synthesis (Appendix 1-2 (6): *Chem. Commun.* 2017). In addition, some compounds could promote root growth in various plant species such as *Arabidopsis thaliana* as well as edible plants (cucumber, lettuce, etc.). These results have inspired academia-industry collaborations towards the practical use of molecules in the field.

***[5] Control of stomatal opening/closing**
On the other hand, control of stomatal movements (opening/closing) have long been considered to be not only critical not only environmental responses of plant in basic plant science but also an application in future agriculture, such as increasing of biomass (plant growth) and drought tolerance. The Kinoshita group has successively identified major components of blue light-dependent stomatal opening such as blue light-receptor phototropins, protein phosphatase 1, and the plasma membrane $H^+$-ATPase (*Curr. Biol.* 2011, *Plant Physiol.* 2013, *Plant Cell Physiol.* 2015). However, the signaling mechanisms between blue light perception and the $H^+$-ATPase activation have remained largely unknown.
The Kinoshita group demonstrated that the transgenic Arabidopsis plants overexpressing $H^+$-ATPase show enhanced light-induced stomatal opening and photosynthesis, leading to plant growth. They also revealed stomata in the transgenic plants closed normally in response to darkness and abscisic acid. In contrast, the overexpression of the other key components, phototropin or inward-rectifying $K^+$ channels, in guard cells had no effect on these phenotypes. These results demonstrate that stomatal aperture is a limiting factor in photosynthesis and plant growth, and that manipulation of stomatal opening by overexpressing $H^+$-ATPase in guard cells is useful for the promotion of plant growth (Appendix 1-1 (8): *PNAS* 2014).
The Kinoshita group identified a novel positive regulator, **b**lue light-dependent **H**$^+$-ATPase **p**hosphorylation (BHP), for the $H^+$-ATPase activation in the stomatal opening by an elegant combination of chemical screening and reverse genetics. They revealed that BHP is abundantly expressed in the cytosol of guard cells and interacts with BLUS1, a serine/threonine protein kinase that is identified as a positive regulator between the phototropin and the $H^+$-ATPase, both *in vitro* and *in vivo* (*Sci. Rep.* 2017).
Following the achievements as above, the Kinoshita group and the Chemical Library Center have screened more than 30,000 molecules from various chemical libraries, identified compounds that affect stomatal movements (opening or closing), and revealed that SCL1 and SCL2 (**s**tomata **cl**osing compounds) suppressed blue light-induced phosphorylation of plasma membrane $H^+$-ATPase for stomatal opening and had no effect on ABA-dependent negative responses such as inhibition of seed germination. In addition, they demonstrated that spraying the leaves of both of dicot and monocot plants with SCL1 suppressed strongly withering of leaves and confers tolerance to drought stress in plants (Appendix 1-2 (7): *Plant Cell Physiol.* 2018).
Recently, the Kinoshita group demonstrated that overexpression of *Oryza sativa* $H^+$-ATPase 1 (OSA1), a PM $H^+$-ATPase isoform in rice, conferred enhancement of the grain yield in rice. The OSA1-overexpressing rice plants showed enhanced light-induced stomatal opening, photosynthesis, ammonium uptake in roots, and

biomass in hydroponic culture in China. Their findings showed that OSA1 overexpression could contribute to enhance the rice yield with increased both C and N acquisition simultaneously by paddy rice (Appendix 1-1 (9): *Nature Commun* 2021). These results strongly indicated that overexpression of PM $H^+$-ATPase in plants is useful for enhancement of plant growth. As an application of this technology to other plants is highly anticipated, they named these plants as "PUMP" plants (**p**romotion and **u**pregulation of the plasma **m**embrane $H^+$ (**p**roton)-ATPase).
These research outcomes have gained a significant amount of attention, leading to the initiation of several academia-industry joint research projects with agrochemical, chemical, and trading companies by using commercial flowering plants and licensing of the research to agrochemical companies by using commercial cultivar (rice, maize, and rape seed).

***[6] New approach to ligand-receptor pair: delineation of specific auxin response**
The Torii-Uchida group focused on the two plant peptide hormones, CLV3 and CLE25, which belong to the CLE (**Cl**avata3/**E**mbryo Surrounding Region-related) family and have root-shortening activity. On the other hand, CLE41 peptide, which shares a partly similar amino-acid sequence with CLE3/25 and is known as tracheary element differentiation inhibitory factor (TDIF), promotes the stem cell activity in the vascular meristem without affecting root/shoot stem cells. Through systematic swapping of the amino acid sequences of CLV3 and CLE25, they succeeded in creating a novel synthetic bifunctional peptide, KIN, that exhibits vascular-thickening function in addition to the original root-shortening function. Computational studies suggest that the KIN peptide binds to both CLV1 and TDR, receptors for CLV3/CLE25 and TDIF/CLE25, respectively (Appendix 1-2 (8): *Nature Commun.* 2017).
The phytohormone auxin regulates nearly all aspects of plant growth and development. Despite substantial progress in understanding of auxin biology, delineating specific auxin response remains a major challenge. Auxin regulates transcriptional responses via its receptors, TIR1/AFB F-box proteins. Through extensive collaborations with Hagihara (CSRS RIKEN, former Co-PI of Itami group) and the Kinoshita group, the Torii-Uchida group developed an engineered, orthogonal auxin-TIR1 receptor pair, which triggers auxin signaling without affecting endogenous auxin or TIR1/AFBs. A synthetic convex IAA (cvxIAA), designed by docking study of IAA-TIR1 complex, hijacks the downstream auxin signaling *in vivo* both at the transcriptomic level and in specific developmental contexts, only in the presence of a complementary, concave TIR1 (ccvTIR1) receptor (bump-and-hole strategy). Harnessing the cvxIAA-ccvTIR1 system, they provided conclusive evidence for the role of the TIR1-mediated pathway in auxin-induced seedling acid growth (Appendix 1-1 (10): *Nature Chem. Biol.* 2018). In addition, they have identified a super-strong pair of a newly engineered (mutated) TIR1 and a newly developed synthetic convex IAA (pico-cvxIAA), that triggers auxin responses 10,000 times more strongly than the endogenous IAA-TIR1 pair (*Plant Cell Physiol.* 2018). By taking advantage of this technology, they developed a protein-knock down methodology by applying the pico-cvxIAA–ccvTIR1 pair to mammalian cells. In this system, a specific protein which is tagged by a ccvTIR1-interacting degron motif is rapidly degraded upon the treatment of cells with an extremely low concentration of pico-cvxIAA (*Nucleic Acids Res* 2020).

**[7] Mechanistic elucidation of seasonal clock**
Organisms are exposed to seasonal changes in environment, such as photoperiod, temperature, and precipitation. Among them, organisms use changes in photoperiod for seasonal adaptation to maximize their survival. Although this phenomenon attracts tremendous general interest, its underlying molecular mechanism remains unknown. The Yoshimura group identified the photoperiodic center in fish (masu salmon), the saccus vasculosus, which is the sensor of seasonal changes in day length. They revealed that expression of key genes, rhodopsin family genes, regulates seasonal reproduction in coronet cells of the saccus vasculosus of masu salmon. In addition, they demonstrated that an isolated saccus vasculosus has the capacity to respond to photoperiodic signals and its removal abolishes photoperiodic response of the development of gonads (Appendix 1-1 (11): *Nature Commun.* 2013).
In addition, the Yoshimura group revealed that in quail, novel photopigment (OPN5)-positive neurons existing deep inside the brains respond directly to light and regulate seasonal reproduction. Separately, they carried out a siRNA knockdown experiment of OPN5, which in vivo inhibits the secretion of the thyroid-stimulating hormone (TSH), so-called the 'spring hormone' which triggers spring breeding in birds (Appendix 1-1 (12): *Curr. Biol.* 2014). As OPN5 also exists in humans, it will contribute to understanding how mammals regulate their biological clocks. This result may also lead to improvements in animal breeding and provide a deeper understanding of the evolution of eyes and photoreceptors. Subsequently to the discoveries of the photoperiodic center in both fish (masu salmon) and birds (quail), the Yoshimura group revealed that dynamic plasticity in phototransduction regulates seasonal changes in color perception in

medaka fish. They demonstrated the medaka kept in summer conditions are more attracted to computer-generated orange-red-colored medaka (nuptial coloration) than medaka kept in winter conditions, and revealed that the genes encoding photopigments such as opsin and their downstream pathway varies dynamically among seasons and photopigment-null fish showed significant differences from wild type in behavioral analysis and suggested plasticity in color perception is crucial for the emergence of seasonally regulated behaviors (Appendix 1-1 (13): *Nature Commun.* 2017). In addition, they discovered that an uncharacterized long non-coding RNA (lncRNA), so-called LDAIR, is strongly regulated by photoperiod using genome-wide expression analyses in medaka, and that photoperiodic regulation of corticotropin-releasing hormone receptor 2 by LDAIR modulates adaptive behaviors to seasonal environmental changes (Appendix 1-1 (14): *Nature Ecol. Evol.* 2019).

***[8] Precise control animal clock by molecules**

Chronic circadian rhythm disruption due to shift work or frequent travel across time zones leads to jet-lag and an increased risk of diabetes, cardiovascular disease, and cancer. The development of new drugs to treat circadian rhythm-related disorders, however, is costly and hugely time-consuming. The Yoshimura group and Chemical Library Center performed a high-throughput chemical screening of existing drugs for circadian clock modulators in human U2OS cells (so called drug repositioning). They found that approximately 5% of the drugs screened altered the circadian period, including the period-shortening compound dehydroepiandrosterone (DHEA; also known as prasterone). They demonstrated that dietary administration of DHEA to mice accelerated re-entrainment to advanced light–dark (LD) cycles, thereby reducing jet-lag. They also revealed tyrosine kinases, ABL1 and ABL2, and the BCR serine/threonine kinase are involved in regulating circadian period. (Appendix 1-2 (9): *EMBO Mol. Med.* 2018). In addition to the identification of the molecules that regulate the circadian clock in vivo, the Yoshimura group succeeded in the identification of molecules that regulate the seasonal clock. They revealed that whole brain metabolomic analysis of medaka kept in winter conditions revealed seasonal changes in 68 metabolites associated with depression, transcriptome analysis identified 3306 differentially expressed genes including circadian clock genes, and, finally, seasonal changes in the NRF2 pathway regulate winter depression-like behavior. They also performed chemical screening and identified the molecule 'Celastrol', a traditional Chinese medicine, that reversed the depressive behavior through NRF2 antioxidant pathway with the Chemical Library Center (Appendix 1-2 (10): *PNAS* 2020).

Based on the discovery of KL001 that directly targets the core clock protein CRY by the Kay-Hirota group (*Science* 2012), the groups of Yoshimura and Kay-Hirota identified clock-modulating molecules by developing KL001 derivatives (Appendix 1-2 (11): *Angew. Chem. Int. Ed.* 2015) and established the practical design of small-molecule CRY modulators by a computational approach (*ChemMedChem* 2015) through extensive collaboration with synthetic chemistry groups (Itami) and theoretical scientists (Irle). Kay-Hirota group identified GO289 as a new period-lengthening compound from cell-based phenotypic screening of circadian clock modulators. Through affinity-based target deconvolution in cooperation with the Molecular Structure Center, the groups of Kay-Hirota and Itami succeeded in revealing that GO289 is a potent and selective inhibitor of a protein kinase CK2. GO289 exhibited selective inhibition of cancer cell growth that correlated with cellular clock function. X-ray crystal structure of the CK2$\alpha$-GO289 complex revealed the interaction of GO289 with CK2-specific residues and no direct interaction with the hinge region that is highly conserved among kinases. The discovery of GO289 provides a direct link between the circadian clock and cancer regulation, and reveals unique design principles underlying kinase selectivity (Appendix 1-1 (15): *Science Adv.* 2019). Based on longdaysin, a casein kinase I (CKI) inhibitor that strongly lengthens the circadian period, Hirota group and Feringa lab (U. Groningen) in collaboration with Itami and Tama groups have developed photocaged derivatives and achieved light-inducible and quantitative control over the CKI activity accompanied by an accurate regulation of circadian period in cultured human cells and mouse tissues, as well as in living zebrafish (*JACS* 2019). They further enabled reversible regulation of the circadian period by introducing an azobenzene photoswitch into longdaysin (*Nature Commun.* 2021). The Hirota-Kay group in collaboration with Itami and Tama groups, and the Chemical Library Center discovered the first-in-class isoform-selective regulators KL101 and TH301 against CRY1 and CRY2, respectively, from high throughput cell-based phenotypic screening. X-ray crystal structures of CRY1 and CRY2 in complex with KL101 and TH301 revealed very high conservation of compound-interacting residues between CRY1 and CRY2. The C-terminal tail is diverged and is required for selective effects of KL101 and TH301. By using these isoform-selective compounds, they further discovered that both CRY1 and CRY2 enhance differentiation of brown adipocytes in culture, providing a new possibility for treatment of obesity (Appendix 1-1 (16): *Nature Chem. Biol.* 2020). Kay-Hirota group also identified a new CRY1-selective compound, KL201, from cell-based phenotypic screening and determined CRY1-KL201 interaction by X-ray

crystallography. In collaboration with Itami group, they revealed structure activity relationship of KL201 (*Cell Chem. Biol.* 2020). Hirota group in collaboration with Tama group and the Chemical Library Center further discovered the CRY1-selective molecules TH303 and TH129 from cell-based phenotypic screening, and revealed compound-induced conformational change of CRY1 by X-ray crystallography, in which benzophenone group interacted with Phe residue. Together with Itami group and Feringa lab, they developed a photo-responsive TH129 derivative by replacing benzophenone with an azobenzene photoswitch, and achieved reversible regulation of CRY1 function (Appendix 1-2 (12): *JACS* 2021).

***[9] Development of molecules that control biological clock of plants**

Nakamichi (Kinoshita group) and his collaborators have been conducting research in the field of plant chronobiology, and have successively identified key biological molecules and synthetic small molecules that control the biological clock in plants. They revealed that mutations of clock-associated genes in crops are responsible for flowering time modification (*Plant Cell Physiol.* 2015), and that modification of the clock in Arabidopsis is useful to control flowering time, and improve biomass and stress responses (*Plant Cell Physiol.* 2016).

Nakamichi (Kinoshita group) identified, in collaboration with the groups of Itami, Hirota-Kay, and Yanai, and the Chemical Library Center and Molecular Structure Center, that an animal CDC7/CDK9 inhibitor, PHA767491, lengthens the *Arabidopsis* circadian period and this molecule inhibits multiple CKL proteins rather than CDC7/CDK9 homologs by affinity proteomics. They revealed that PHA767491 treatment induced accumulation of CKL4 phosphorylated transcriptional repressors PRR5 and TOC1, accompanied by decreasing expression of PRR5- and TOC1-target genes, and, as a result, lengthened the circadian period in plants (Appendix 1-1 (17): *PNAS* 2019). Based on the discovery, they succeeded in identifying AMI-331, which exhibited about 100 times more potent inhibitory activity than the original compound, and Casein Kinase 1 as one of the target molecules through affinity proteomics analyses through extensive collaboration with Prof. J. Yamaguchi (former Co-PI of Itami group; now of Waseda U.) (Appendix 1-2 (13): *Plant Direct* 2019). In addition, they have been conducting chemical screening and found the other period lengthening molecules. Through the comprehensive gene expression analyses in combination with in vitro and in silico studies (with Fujimoto of the Yanai group), they determined that 3,4-dibromo-7-azaindole (PAC5) inhibits CK1 kinase activity and binds to the ATP binding pocket of CK1 (*Plant Cell Physiol.* 2019).

***[10] Novel characteristic probes applicable to the advanced live imaging**

The development of super-resolution stimulated emission depletion (STED) microscopy represents a major breakthrough in cellular and molecular biology. However, intense laser beams are required for STED microscopy, which give rise to photobleaching of fluorescent probes. The Yamaguchi group has developed the outstanding photostable fluorescent dye C-Naphox (diarylmethylene bridged **na**phtho-**ph**osphole P-**ox**ide) and reported several distinct advantages relative to conventional dyes, such as intense fluorescence emission by the combination of an electron-donating group with an electron-accepting group, high quantum yields even in polar and protic solvents, large Stokes shift arising from an intramolecular charge transfer, and solvent polarity sensitivity from bluish green to reddish orange. They demonstrated that almost all (99.5%) C-Naphox remained intact even after irradiation with a Xe lamp for 12 hours, while the fluorescence intensities of representative STED imaging probes (Alexa Flour 488 and Atto 488) were significantly diminished under the same conditions. In addition, they applied C-Naphox in repeated STED imaging of HeLa cells and recorded 83% of the initial fluorescence intensity persisted even after 50 STED images (Appendix 1-1 (18): *Angew. Chem. Int. Ed.* 2015).

However, C-Naphox still has drawbacks for practical use in bio-imaging, *i.e.*, water insolubility, target selectivity, and polarity-sensitivity fluorescence. The groups of Yamaguchi and Higashiyama, and the Live Imaging Center succeeded in developing a new super-photostable dye, PhoxBright 430 (PB430). PB430 has high solubility in water, is capable of labeling proteins while maintaining high fluorescence quantum yields, also exhibits outstanding resistance to photoirradiation even under STED conditions, and allows continuous acquisition of STED images. Using a PB430-conjugated antibody, they succeeded in creating three-dimensional super-resolution STED images as well as carrying out photostability-based multicolor STED imaging of fluorescently labeled cytoskeletal structures (Appendix 1-1 (19): *JACS* 2017).

The groups of Yamaguchi and Higashiyama, and the Live Imaging Center also developed a highly photostable and water-soluble near-infrared phosphorus-substituted rhodamine, PREX 710 (Appendix 1-1 (20): *Angew. Chem. Int. Ed.* 2018). By the nature of membrane permeability and localization in the mitochondria, they demonstrated that PREX 710 can be used to stain mitochondria in living cells, which allowed long-term and multi-color imaging in the vis-NIR range. Moreover, they showed the high fluorescence longevity of PREX 710 by tracking a dye-labeled biomolecule (IgG, NeutrAvidin) by single-

molecule microscopy under physiological conditions. Furthermore, they achieved deep imaging of blood vessels in mice brain using the bright NIR emitting PREX 710-dextran conjugate.
The Yamaguchi group developed an outstandingly photostable fluorescent dye with a long lifetime, MitoPB Yellow, which enabled the visualization of nano-scale dynamics of mitochondrial cristae in living cells (in collaboration with the Live Imaging Center, RIKEN, and U. Tokyo). By taking advantage of the exceptionally high photostability of MitoPB Yellow, they achieved the first ever monitoring of a rapid inter-cristae mergence in a single mitochondrion, and inner-membrane fusion in the inter-mitochondria interaction was monitored for the first time (Appendix 1-1 (21), *PNAS* 2019). Based on the structure of MitoPB Yellow, they have developed a new small-molecule fluorescent probe LysoPB Yellow which can selectively stain the lysosomal membrane. They demonstrated that LysoPB Yellow displayed excellent retention ability as well as negligible cytotoxicity, and was suitable for application to the observation of living cells for 24 h by long-term time-lapse confocal imaging. They have developed the LAQ1 that shows strong fluorescence only in the hydrophobic lipid droplets (LDs), achieved the recording of the movement of small LDs about 500 nm in size, and visualized lipolysis and lipogenesis in living cells in time-lapse 3D imaging (*ACS Materials Lett.* 2020). In lipid biology, Taki and Yamaguchi developed an environmentally sensitive fluorescent fatty acid (FA), AP-C12, as a practical molecular tool for visualizing fatty acid metabolism in living cells. They revealed that the environmental responsiveness of AP-C12 enables visualization of the distribution of fatty acid metabolites as different colors in the images. Taking advantage of the unique staining ability of AP-C12, they succeeded in detecting various stages of LD-bearing autophagosomes in lipophagy (manuscript in preparation).
The Live Imaging Center, with a researcher from the Itami group, has developed the bright DNA staining dye, Kakshine, that makes the nuclei of various organisms shine brightly. Kakshine and its derivatives, with a pyridocyanine backbone, offer remarkable advantages compared with conventional DNA staining dyes, such as high DNA selectivity, enhanced cell permeability, ability to stain organellar DNA, limited cell toxicity and custom-tailed photophysical properties. In addition, these molecules are also highly compatible with stimulated emission depletion fluorescent lifetime imaging microscopy (STED-FLIM) and a two-photon microscopy, which allowed us to reveal the fine structure of nuclear DNA and mitochondrial DNA at a super-resolution level and to achieve deep imaging of whole plant tissue (Appendix 1-2 (14): *Nature Commun.* 2021).

***[11] Exploration of biological processes shepherded by the advanced live imaging**
Imaging technologies for visualizing and analyzing precise morphology and gene expression patterns are essential for understanding biological processes during development in all organisms. Through chemical screening, Higashiyama and Kurihara developed a clearing method using chemical solutions, "ClearSee®", which enables the deep imaging of plant tissues. ClearSee® rapidly diminishes chlorophyll autofluorescence while maintaining fluorescent protein stability (Appendix 1-1 (22) *Development* 2015). ClearSee® enabled the direct observation of the inside of the body of the plant without causing damage to the plant and made a significant impact in plant biology. However, because there were still some plant species and tissues that could not be made transparent even by ClearSee®, they further improved its composition to prevent oxidation and have developed ClearSeeAlpha, which can be applied to a broader range of plant species and tissues, such as *Arabidopsis* seeds (*Plant Cell Physiol.* 2021).
Using advanced live imaging, the Higashiyama group revealed that the central cell has a weak mechanism for rejecting polyspermy (*Front. Plant Sci.* 2021) and clarified the process of egg cell formation from the megaspore after meiosis (*PLoS Biol.* 2021). In addition, they revealed that mitochondria are distributed at a high density to apical cells (stem cells that produce most of the plant body) during asymmetric division of fertilized eggs (*Quant. Plant Biol.* 2021), the nuclear membrane fusion factor GEX1 starts to express during female gamete differentiation (*Front. Plant Sci.* 2020), intercellular signaling peptides are responsible for the arrangement of ovular primordia (*Curr. Biol.* 2020), and pollen tubes in which all the nuclei have been left behind can be successfully elongated and attracted (*Nat. Commun.* 2021).

***[12] New avenues of catalysis for efficient molecular synthesis**
The development of a general catalytic method for the direct and stereoselective construction of contiguous all-carbon quaternary stereocenters in a single synthetic operation remains a formidable challenge and largely unexplored in design of catalysts and development of chemical synthesis. The Ooi group has developed a catalytic system to establish stereocenters of contiguous quaternary carbons. Specifically, they achieved a highly enantio- and diastereoselective [3+2] annulation reaction 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 (Appendix 1-1 (23): *Nature Chem.* 2013). In addition, the Ooi group established a catalyst-directed pinpoint inversion of diastereo-chemical preference in the 1,6-addition reaction with full control over other selectivities preserved. This rigorous diastereodivergence was enabled by the slight structural adjustment of a chiral iminophosphorane catalyst developed by themselves, providing access to all the stereoisomers with high regio-, distereo- and enantioselectivity. They demonstrated that the utility of this method in the facile stereodivergent preparation of densely functionalized proline derivatives. In addition, they elucidated the origin of the diastereodivergence experimentally and computationally (Appendix 1-1 (24): *Nature Commun.* 2017).
The Ooi group has also developed a strategy for the allylic C–H alkylation of enol silyl ethers and their derivatives, which relies on the combined use of appropriate photoredox and Brønsted base catalysts for the generation of requisite allylic radicals while suppressing undesired desilylation process. With the hybrid catalysis, a series of enol silyl ethers smoothly react with electron-deficient olefins to give the corresponding functionalized enol silyl ethers (Appendix 1-1 (25): *Nature Commun.* 2019). In addition, they have demonstrated that the catalytic C-H alkylation of various nitrogen- or oxygen-containing organic compounds with electron-deficient olefins proceeds smoothly under light irradiation using amidyl radicals generated from zwitterionic triazolium amidates and photoredox catalysts (*ACS Catal.* 2020).
The Suzuki–Miyaura cross-coupling (Nobel Prize in Chemistry, 2010) is one of the most often utilized reactions in the synthesis of pharmaceutical compounds and functional materials to afford a planer biaryl or polyene compounds. However, the creation of carbon-carbon bonds with stereochemistry using the Suzuki-Miyaura reaction has only been demonstrated in the last few years. The Crudden group made significant advances in this approach, in which multiply functionalized chiral cross-coupling partners can be employed in iterative coupling without the use of protecting groups. Through extensive investigation of the reaction system, they identified that the orthogonal reactivity of boron-carbon bonds in different positions in a single molecule permits the chemo- and stereoselective sequential coupling of aromatic and aliphatic molecules, and affords the rapid generation of multiply arylated molecules stereoselectively (Appendix 1-1 (26): *Nature Commun.* 2016). They also developed new chemical transformations of readily available sulfone derivatives through carbon–sulfonyl (C–$SO_2$) bond activation to provide a new class of bio-molecules. They found that the strong electron-withdrawing triflyl group was crucial for the Pd-catalyzed desulfonylative cross-coupling of $\alpha$-fluorinated benzylic sulfones (Appendix 1-1 (27): *Nature Commun.* 2019). During investigation, they discovered unprecedented synthesis of *gem*-difluoroalkenes through the Ramberg–Bäcklund reaction of alkyltriflones promoted by Grignard reagents (*JACS* 2020) and that a tetrazolyl group was an effective substituent for the generation of *tert*-alkyl radicals in the presence of Zn and 1,10-phenanthroline as a reducing agent to construct quaternary centers (*Chem. Sci.* 2021).

**[13] Unprecedented approach to peptide/protein synthesis**
The chemical syntheses of peptides and conjugated proteins are in great demand for understanding biological processes and developing new protein-based therapies. Ordinary solid-phase peptide synthesis can routinely provide peptide fragments up to 40 amino acid residues but is not suited for the preparation of proteins. The Bode group has discovered and developed a bio-mimetic peptide ligation reaction, which is known as the KAHA ligation (*JACS* 2006). They have developed a new method of synthetic fermentation. Microbial fermentation is known to rapidly provide potent molecules as a mixture that can be easily screened based on biological activity, and the active components can then be isolated. They applied their KAHA ligation method into a microbial fermentation process and succeeded in demonstrating that bioactive, unnatural peptides can be grown from a mixture of amino acid building blocks in water. As a proof-of-concept, they identified a hepatitis C virus NS3/4A protease inhibitor among around 6,000 unnatural peptides produced from just 23 amino acid building blocks (Appendix 1-1 (28): *Nature Chem.* 2014).
The Bode group has been developing the KAHA ligation and has synthesized various proteins not accessible by expression or bioengineering approaches. Actually, this ligation has proven to be remarkably robust, but has limitations including the introduction of a non-canonical homoserine residue at the ligation site, the formation of esters as the primary ligation products, and a preference for relatively high concentrations (10–20 mM) and temperatures (50–60 °C). They reported the synthesis of an *N*-terminus-protected oxazetidine as a canonical serine precursor for use in the KAHA ligation and demonstrated that the four-membered oxazetidine can be used for rapid serine-forming ligations with *C*-terminus of peptide. They also revealed this ligation proceeds at lower concentration (100 μM–5 mM) and milder temperatures (20–25 °C). By using the serine precursor, they achieved the synthesis of S100A4, a 12 kDa calcium-binding protein that is not easily accessible by the conventional methods, such as native chemical ligation (NCL) or other amide forming reactions due to its primary sequence and properties (Appendix 1-1 (29): *Nature Chem.* 2015). In addition, the group has been developing monomers for KAHA ligation (*ACIE* 2019, *ACIE* 2019,

*Synthesis* 2019) and has discovered beta-peptides targeting penicillin-binding proteins (*ACS Chem. Biol.* 2019).
The Bode-Oishi group demonstrated the selective formation of Ubc9–SUMO conjugates and the trapping of an E3 ligase (RanBP2) to form the stable, covalently linked SUMO1–Ubc9–RanBP2 ternary complexes with the Hirota-Kay group and Molecular Structure Center. The powerful combination of ligation methods, which minimizes challenges of functional group manipulations, will enable chemical probes based on E2 conjugating enzymes to trap E3 ligases and facilitate the synthesis of other protein classes (Appendix 1-1 (30): *JACS* 2019).

***[14] Development of biology-friendly functional materials**
The formation of organic films on gold employing N-heterocyclic carbenes (NHCs) has been previously shown to be a useful strategy for generating stable organic films. However, NHCs or NHC precursors typically require an inert atmosphere and harsh conditions for their generation and use. The Crudden group has developed a simple direct method to form self-assembled NHC monolayers on gold. Using the bench-stable benzimidazolium hydrogen carbonate as a replacement for conventional air-sensitive NHCs or NHC precursors, NHC films were able to be prepared much more easily in solution or by vapor-phase deposition from the solid state. They applied these materials into surface plasmon resonance (SPR)-type biosensing and revealed that NHC-based films provide specific physicochemical durability, such as thermal stability and stability in extreme pH, versus conventional thiol-based ones (Appendix 1-1 (31): *Nature Commun.* 2016). The advantages over conventional thiol-based gold complex, in addition, led the Crudden-Nambo group to develop the size-controlled synthesis of water-soluble NHC-gold nanoparticles (*Angew. Chem. Int. Ed.* 2017), ultra-stable gold nanoparticles modified with novel multivalent NHC ligands (Appendix 1-2 (15): *JACS* 2018), and NHC-stabilized gold nano-clusters (Appendix 1-1 (32): *Nature Chem.* 2019).

**[15] Synthesis of carbon nanorings, nanobelts and pure nanotubes**
Carbon nanotubes (CNTs) can only be produced as mixtures with regard to diameter and sidewall structure. Given that the electronic properties of CNTs are primarily determined by the sidewall structures, structural uniformity is critically important for CNT-based electronics. Thus, the selective and predictable synthesis of structurally uniform CNTs and ultra-short carbon nanotubes (carbon nanorings and nanobelts) is recognized as one of the greatest challenges in science and technology. The Itami group has made significant progress toward this Holy Grail.
The Itami group achieved the first selective synthesis of carbon nanorings, representing the shortest sidewall segments of armchair CNTs (*Angew. Chem. Int. Ed.* 2009). In 2013, they succeeded in the first diameter-selective synthesis of CNTs using nanorings as templates (Appendix 1-1 (33): *Nature Chem.* 2013). The diameter of the nanoring template, which can be controlled using Itami's method, determines the diameter of the final CNT. A range of carbon nanorings of varying sizes is also commercially available, thus encouraging others to explore the bottom-up synthesis of CNTs and their use in materials science and biology.
The Itami group successively achieved the first synthesis of a carbon nanobelt (CNB) - a long-sought-after ultra-short CNT (Appendix 1-1 (34): *Science* 2017). The synthesis of these highly strained, belt-shaped aromatic compounds had been one of the most difficult problems in chemistry for the last 60 years (even before the discovery of CNTs). This achievement is both an experimental tour de force and a triumph of synthetic chemistry. Itami's carbon nanobelt, which can be synthesized from *p*-xylene (petroleum feedstock), was commercialized in 2018, thereby accelerating the discovery of extraordinary properties, functions, and applications. In 2021, they finally achieved the synthesis of a zigzag carbon nanobelt fully characterized by X-ray crystallography, and revealed its wide energy gap with blue fluorescence properties by photophysical measurements (Appendix 1-1 (35): *Nature Chem.* 2021). With synthetic strategies towards all three types of CNB in hand, the road to the precise synthesis of CNTs can now proceed to the next stage.
Furthermore, the Itami group succeeded in the first experimental measurements of the ultimate tensile strengths of structure-defined and single-walled CNTs, and revealed that the strength depends on the chiral structure of the nanotube, with small-diameter, and near-armchair nanotubes exhibiting the highest tensile strengths (≧70 GPa) (Appendix 1-2 (16): *Nature Commun.* 2019).

**[16] Synthesis of topologically unique, three-dimensional nanocarbons**
The Itami group has also created completely novel, topologically unique nanocarbons. Aside from theoretical studies that predict interesting properties for these types of species, three-dimensionally curved nanocarbons are a virtually unexplored group of materials. In 2013, they accomplished the synthesis of a novel **w**arped **n**ano**g**raphene (WNG) containing both positive and negative curvatures on its π-surface

(Appendix 1-1 (36): *Nature Chem.* 2013). WNG is unique and clearly distinct from any other existing nanocarbon. The negatively curved geometry of WNG engenders a flexible configuration in solution, thereby displaying significant solubility. As WNG is also commercially available, many industries are now using WNG as a key molecule in optoelectronic devices.
The groups of Itami and Higashiyama, and the Live Imaging Center have also synthesized a water-soluble WNG that exhibits green-yellow fluorescence with a long lifetime, good photostability and notably low cytotoxicity to cells (Appendix 1-2 (17): *Angew. Chem. Int. Ed.* 2018). Furthermore, the water-soluble WNG was readily introduced into HeLa cells and induced cell death upon light irradiation, demonstrating its applicability for photodynamic therapy.
Through extensive campaign of the syntheses of structurally unique nanocarbons, the Itami groups achieved the syntheses of all-benzene catenane and trefoil knot, observed their characteristic fluorescence associated with fast energy transfer between two aromatic rings, and confirmed the topological chirality of the all-benzene knot by enantiomer separation and circular dichroism spectroscopy (Appendix 1-1 (37): *Science* 2019). They also achieved the synthesis of negatively curved polyaromatics by annulative coupling to install eight-membered ring through C-H functionalization (*Nature Catal.* 2020).

**[18] Theoretical sciences**
The Tama group has actively been collaborating with the biology groups of Kay-Hirota, Torii, and Higashiyama, to reveal the precise biological mechanism of both animals and plants. Simulations of biomolecular structure and dynamics can reveal the mechanisms of biomolecules functions by complementing the static pictures obtained from X-ray crystallography data. In collaboration with the Kay-Hirota group, the Tama group has shown the critical role of protein dynamics in the function of multiple proteins, involved in circadian rhythm regulation, such as Casein Kinase II and Cryptochromes (Appendix 1-2 (18): *Proteins 2018, eLife 2020, Nature Chem. Biol. 2020*). In addition, computational modeling of biomolecules interactions with small chemical compounds or other biomolecules can provide insights into the specificity and/or design of new partner molecules. Such approaches were particularly helpful in our understanding/design of photoactivable or photo-switchable small molecules (from Itami & Feringa groups) with multiple protein targets involved in circadian rhythm (Kay-Hirota group), a critical step toward controlling the circadian period by light (*JACS* 2019, *JACS* 2021, *Nature Commun.* 2021). Similarly, in collaboration with the groups of Torii and Frommer, such approaches have enabled the characterization, at an atomic level, of critical interactions involved in stomata development in plant leaves (*Nature Plants* 2019).
The Yanai group has also been collaborating actively with the multiple ITbM groups since its launch. The group performed advanced quantum chemical (QC)-based theoretical investigation into photochemical characterization of the dyes involving the thermally activated nonradiative decays; its understanding is key for controlling quantum yield and photo-resistant nature of the dyes. The rate constant of thermally activated nonradiative decay is related to the activation energy in the photoreaction; thus, high-accuracy QC computation of excited-state potential energy surfaces and their transition rates are critical. In collaboration with the Yamaguchi group, they also performed computational QC analysis on a series of diarylboryl and dithienophosphole P-oxide-containing D–A–A-type fluorophores as NIR emissive systems. The measured fluorophores exhibit emission in the near-infrared (NIR) region, while maintaining high fluorescence quantum yields even in polar solvents. Their theoretical calculations successfully detailed the differences among these electron-accepting substituents, revealing the crucial role of the boryl group in lowering the nonradiative decay rate constant by decreasing the non-adiabatic coupling in the internal conversion process (*Chem Sci.* 2021). In addition, the group demonstrated a docking study and molecular dynamics simulation of B-AZ and its potential target molecule CK1$\delta$ with Nakamichi (Kinoshita group, Appendix 1-2 (19): *Plant Cell Physiol.* 2019), and in silico drug discovery of antiviral drugs (with the Ooi group and the Kimura group in Medical School of NU).

**[19] Exploration of biological network in plants**
Sugars, one of the secondary metabolites assimilated from inorganic carbon dioxide through photosynthesis, cross multiple membranes on their way from production sites to storage or use locations in plants. The Frommer group has discovered that specific transport systems, named SWEETs, were responsible for vacuolar uptake and release, for efflux from the cells, and for uptake into the vasculature in combination with transporter biochemistry and live imaging. Recently, they revealed that the sugar transporter SWEETs were hijacked during *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) infection and that Xoo caused bacterial rice blight, one of the most serious rice diseases in Asia and Africa. By constructing an international research team, they elucidated the mechanism of the transcription-activator-like effectors (TALes) of *Xoo*. Utilizing the CRISPR-Cas9-mediated genome editing to introduce mutations in SWEET gene promoters, they have

created rice plants resistant to *Xoo* (Appendix 1-1 (38): *Nature Biotech.* 2019) and provided a new strategy for conferring resistance to bacterial infection (Appendix 1-1 (39): *Nature Biotech.* 2019).
Since the Frommer-Nakamura group launched in ITbM (2016), they have been actively collaborating with the other groups of ITbM. They have successfully implemented a method using SNAP-tag and synthetic fluorescent probes in the area of plant cell imaging in collaboration with the groups of Yamaguchi (ITbM) and Urano (U. Tokyo). Using DRBG-488, a synthetic dye that is impermeable to the plasma membrane, they succeeded in visualizing the endocytosis process of auxin transporters localized at the plasma membrane (Appendix 1-2 (20): *Plant Cell* 2020).

**[20] Development of anti-infectious diseases researches**
Novel drug resistance has been emerging and spreading globally. Strains that express class-B metallo-β-lactamases (IMP-1, NMD-1, and VIM-2) are reported to be particularly able to resist not only β-lactam antibiotics but also most existing anti-microbial drugs. Recently, superbugs that are resistant to all clinically used antibiotics are reported. Development/identification of metallo-β-lactamase is considered urgent and small molecules that inhibit metallo-β-lactamases are expected to be new possibilities for treatment, controlling the spread of infection, and suppressing the global threat of infectious diseases. The Chemical Library Center succeeded in identifying a molecule, G09, that strongly inhibits one of the metallo-β-lactamase, IMP-1, using a chemical from the ITbM chemical library, in collaboration with the Arakawa group (Medical School, NU, AMED-JGRID). In addition, they revealed that G09 tolerated a drug efflux pump (AcrB) and exhibited inhibitory activity against clinically isolated drug resistant bacteria (Appendix 1-1 (40): *mBio* 2020).
The Crudden group demonstrated the first biosensor capable of detecting the measles virus in minutes with no preprocessing steps and at the lower limit of concentrations that can cause infections in primates. The key sensing element is an electrode coated with a self-assembled monolayer containing the measles antibody, immobilized through an N-heterocyclic carbene (NHC). This NHC-based biosensor thus represents an important development for both the rapid detection of the measles virus and as a platform technology for the detection of other biological targets of interest (*ACS Sens.* 2020).

## 2-2. Research environment including facilities and equipment

Describe the degree to which the Center has prepared a research environment appropriate for a world premier international research center, including facilities, equipment and support systems, and describe the functionality of that environment.

**Mix Lab & Mix Office:** The 6-storey ITbM building was completed at the end of FY2014, in a design that reflects the "Mix" concept. The Mix Labs on the second and fourth floors consist of a large Bio Mix Lab and a Chem Mix Lab, which are located next to each other and are accessible through a single door. There are no barriers within the Bio Mix Labs and the Chem Mix Labs. The Mix Office spaces located directly above the Mix Labs are melting pots from different research groups/fields, and the seating arrangement is changed often to facilitate new encounters and promote interdisciplinary research. The building is also equipped with a childcare room for researchers and visiting researchers accompanied by small children. In addition, NU has provided 5,400 $m^2$ of research space for ITbM around the ITbM building, enabling easy access to the provided spaces. The arrangement has provided significant opportunities for ITbM researchers to collaborate with each other and with those of other departments on campus.

**Co-PI system:** ITbM introduced the Co-PI system to enable world-class researchers to participate in ITbM's research activities. To make the overseas PIs' research at ITbM possible, ITbM employed young researchers as Co-PIs who are full time at ITbM and cooperate with the overseas PIs. This system has led to increased attention on ITbM's research results and activities from the international science community, and has contributed to improving the global visibility of ITbM.

**Facilities and equipment:** NU is very well equipped with top-level major instruments necessary for ITbM's research, such as multiconfocal laser microscopes, and mass spectrometers. Many of these are set up at one of ITbM's four supporting centers. The quality and number of these instruments rivals the best institutions in the world.

**Administrative Department and Secretaries:** The Administrative Department is staffed by talented individuals with a good command of English, including one native English speaker, as well as a global outlook and vision. The Research Promotion Division (RPD) and Strategic Planning Division (SPD) in the Department work closely with researchers and support research through international public relations, outreach activities, education, and organization of events. Another important and unique role is to offer seamless support of research by following-up on research progress and constructing strategies and roadmaps to societal implementation. The RPD also has staff tasked with supporting the daily lives

of foreign researchers and their families. The staff provides a wide range of support such as assistance in registration at city council and banks, linguistic support (interpretation and translation) and giving advice on daily life, education and health care. Secretaries allocated to PIs also play important roles in support of researchers and students, especially those coming from/going to abroad. ITbM has recently hired personnel at the Administrative Department to increase funds/donations from various sectors in Japan and overseas.

## 2-3. Competitive and other funding

Describe the results of the Center's researchers to date in securing competitive and other research funding.
・ In Appendix 3-6, describe the transition in acquiring research project funding.

At the start of ITbM, the amount of competitive funding in FY2012 was 528 million yen. In FY2013, it was 1,141 million yen, more than double the amount in FY2012. The amount further increased or was comparable in the following years, and the sum for the 9 years (FY2012-FY2020) amounts to 9.28 billion yen. Major competitive funding successes include JST-ERATO (2 projects), JST-CREST (3 projects), JST-PRESTO (11 projects), Grant-in-Aid for Scientific Research on Innovative Areas (2 project as Area Representative, 1 project for Area manager), JST-ALCA (1 project), AMED (2 Projects), and Grants-in-Aid for Specially Promoted Research (2 projects) among others. In 2020, Y. Sato (Live Imaging Center) joined a project of the Moonshot Research and Development Program (Cabinet Office). A PRESTO researcher in ITbM was selected to the Fusion Oriented Research for disruptive Science and Technology program, and will enter in FY2022.

Overseas PIs have also been successful in obtaining KAKENHI (Grant-in-Aid for Scientific Research), such as Bode (KIBAN A, Scientific Research on Innovative Areas), Crudden (KIBAN B, Scientific Research on Innovative Areas), Torii (KIBAN A, B, Scientific Research on Innovative Areas), Frommer (KIBAN A). In addition, ITbM collected the JSPS Bilateral Program (Joint Research Projects) for FY2015-2016 to strengthen the research collaboration with NSF-CCHF.

Altogether, considering the relatively small number of research groups and the nature of ITbM's science focusing on basic research, this number is amazingly high for an institute in Japan.

## 2-4. State of joint research

Describe the results of joint research conducted with other research organizations both in and outside Japan.

ITbM has strategically extended its collaborating networks with academia and industry to expand its range of joint research activities. ITbM and the **overseas PIs' host institutions** are extensively collaborating, and co-authored papers have been published with ETH-Zürich (Switzerland), Queen's University (Canada), University of Texas at Austin (USA), the University of Southern California (USA), and the Heinrich Heine University Düsseldorf (HHUD, Germany). ITbM has been conducting collaborative research with other organizations as described below.

**NSF Center for Selective C-H Functionalization (CCHF) (USA):** ITbM became a partner of NSF-CCHF, which consists of 23 research groups spread over 15 top institutions in the USA, along with the involvement of some major pharmaceutical and agrochemical companies. ITbM and CCHF exchange graduate students each year, and many collaborative research projects have been conducted, some of which have been published as joint papers in top journals. In 2016, ITbM hosted a joint workshop "2016 International C–H Functionalization Workshop", inviting members of CCHF (7 faculty members, 3 postdoctoral researchers, 12 students, and 1 staff), and IBS (2 faculty members, 4 postdoctoral researchers, and 11 students). The 2nd joint workshop was held in Seoul in July 2019, and the 3rd was held online in August and November 2020.

**Academia Sinica (Taiwan):** ITbM and the Institute of Chemistry (IoC) at Academia Sinica have organized joint workshops in 2016 & 2017 and deepened their collaborative relationship. As a result, Hirota (ITbM) and Prof. Yu-Ju Chen (Director of IoC) initiated a project aimed at target protein identification related to circadian rhythms. Itami will soon became the first Joint Appointment Research Fellow at Academia Sinica and Itami Lab was launched at IoC, operated by a young IoC faculty staff.

**Freiburg University (Germany):** Nagoya University and Freiburg University concluded an MOU for promotion and collaboration, and established a co-funding system for their collaborative research. The proposal entitled "Multicomponent Supramolecular Catalysts for Sustainable Chemical Synthesis" organized by Ooi and Itami of ITbM and Prof. Breit of Freiburg University was selected to the fund in 2015, and collaborative research towards the development of new catalysts has been launched. The groups have exchanged researchers, and a joint symposium "1st International Symposium on Catalysis for Sustainable

Chemical Synthesis" was held at Freiburg University in 2017, inviting 8 world-leading synthetic chemists.

**Ben Feringa Group (University of Groningen, Netherland):** Dr. Ben Feringa (Nobel Prize in Chemistry 2016) is a world-leading chemist in the field of molecular machines and catalysis. To expand the scope of ITbM's biological clock research, ITbM has collaborated with Feringa group. By combining ITbM's clock-modulating molecules and his photo-switching molecules, significant inroads to understanding the photopharmacology of biological clock have been made, and this has already led to the discovery of a photo-switchable, clock-control molecule applicable to reversible circadian period.

**RIKEN Center for Sustainable Resource Science (CSRS) (Japan):** In 2015, both institutes decided to enter a partnership to collaborate in chemistry and plant biology. In 2016, both directors made a joint statement on the combined use of the research support platform and confirmed further promotion of collaboration between ITbM and CSRS. A number of collaborations involving the ITbM Chemical Library Center have started, and hit molecules have been identified in several projects. The joint workshop takes place annually in either Nagoya or Wako/Yokohama. In 2017, RIKEN NP-Depo (Headed by Dr. Hiroyuki Osada) and ITbM Chemical Library Center established the ITbM-CSRS Authentic Library. The Library can be used to validate newly established assay systems. The Library is accessible to researchers inside and outside of Japan to conduct chemical screening.

**Nagoya University Graduate School of Medicine and its WISE program (CIBoG)** : ITbM and GTR have entered a collaboration with the Graduate School of Medicine and its WISE program CIBoG in 2019, and ITbM's collaboration has started to expand toward biomedical sciences. More than 10 collaborations were begun.

By popular request of GTR researchers, GTR and CIBoG started to share classes, and thus ITbM/GTR researchers were able to learn the basics of medical science, which will further advance the interdisciplinary research.

**Collaboration with industries:** ITbM has been involved in a total of 101 collaborative research projects with 45 companies, including 50 in chemistry, 43 in biology, and 8 in theoretical sciences. In the early days of ITbM, the scale of industrial collaboration was small, mainly focusing on fundamental studies. However, as the research achievements of ITbM have become more visible, large collaborative research toward practical applications are increasing.

## 2-5. Appraisal by society and scientific organizations

Describe how society and/or scientific organizations in and outside Japan have recognized the Center's research achievements.

- To substantiate the above evaluation, list the main awards received and invitational/Keynote lectures given by the Center's researchers in Appendix 1-3.

ITbM's researchers are being widely recognized by the international science community as well as by 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 researchers.

The PIs have been designated as "Highly Cited Researchers" by Clarivate Analytics; Itami (2017, 2018, 2019, 2020), Frommer (2017, 2018, 2019, 2020), Kay (2017, 2018), and Higashiyama (2019, 2020). This represents a global standard for high activity and visibility. In 2017, Frommer received the Alexander von Humboldt Professorship and transferred to his present position. Frommer was also awarded the 11th Tsungming Tu Award from Taiwan, the most prestigious academic honor conferred to foreign scholars. Yoshimura became the first Japan-based animal biologist to receive the Van Meter Award, which was established in 1930 by the American Thyroid Association. Itami became the youngest Japanese chemist to receive the Arthur C. Cope Scholar Award from the American Chemical Society in 2015. Crudden awarded a highly competitive Killam Research Fellowship from the Canada Council in recognition of her exceptional career achievements in 2015. Crudden is also a 2019 Arthur C. Cope Scholar. Torii was awarded the Saruhashi Award in 2015, which is granted each year to a female scientist in recognition for their distinguished research in natural sciences. In 2019, Yamaguchi received the Humboldt Research Award, expanding ITbM's research network in Germany. Higashiyama was awarded the 2019 Asahi Prize for 2019, recognized as one of the most authoritative private awards, presented by Japanese newspaper Asahi Shimbun. In FY2020, Ooi has received the Chemical Society of Japan Award.

ITbM PIs have been invited to give lectures at nearly 550 international conferences held worldwide and at over 560 academic meetings, as well as at public workshops, where they have successfully promoted their research along with the activities of ITbM. It is noteworthy that ITbM researchers have recently been invited to the conferences of different disciplines. For instance, Itami was invited as a keynote speaker to "Cold Spring Harbor Asia Conference on Latest Advances in Plant Development & Environmental Responses" (2016), "The Annual Conference of Japan Society for Chronobiology" (2016), and "The Annual Meeting of the Japanese Society of Nephrology" (2019). Taki and Yamaguchi have

recently been invited to many symposia in biology for the medical application of fluorescent molecules such as the Annual Meeting of the Japanese Cancer Association (2019) and the Annual Meeting of the Japanese Society for Neurochemistry (2020).

All ITbM PIs serve on 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. In early 2021, Crudden was appointed Editor-in-Chief of *ACS Catalysis* (American Chemical Society).

In addition to the huge number of awards and honors, societal implementation of ITbM's molecules is influential to the public. In particular, the molecule developed to combat the parasitic plant *Striga* has been widely covered in the public media, and was highlighted at multiple events of the 7th Tokyo International Conference on African Development (TICAD7) held in Yokohama on August 2019 as denoted in Section 2-1[1]; ITbM will be recognized more widely when the molecule is developed as a tool in Kenya and becomes available widely to all the farmers in Africa.

## 3. Feeding Research Outcomes Back into Society **(within 2 pages)**

### 3-1. 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.

Since it was founded in 2012, ITbM has kept developing innovative technologies that meet the needs of society. As a result, between October 2012 and March 2021, 148 patent applications were made including 104 domestic/US applications and 44 PTCs. 46 of these applications have been derived from interdisciplinary research between chemistry and biology. Notably, these were not only in Japan - 88 of patent applications were transferred into national phase in each country. Additionally, a total of 88 licenses or material transfer agreements have been concluded with global companies based on published patents and ITbM technologies.

Based on ITbM patents and technologies, three startups were established. "Gra&Green Inc." established in 2017 aims to innovate the seeds & seedlings industry to impact next-generation food & agriculture by using cutting-edge biotechnology, such as novel "inter-family" grafting technology and its own genome editing tool. "Craftide Co., Ltd.", established in 2018, is focusing on developing research tools for peptide-based drug discovery using cutting-edge peptide synthesis technology. In early 2020, "Phytometrics Inc." started providing advanced machine learning services for AI agriculture and plant science.

ITbM has worked closely together with NU's US technology transfer office (NU Tech) for licensing and collaborative research with overseas companies. At the NU Tech Round Table, technology showcase event in RTP, NC, one of the top ranked biotech hubs in the US, ITbM researchers have presented their technologies to science stakeholders every year since 2016. To date, NU Tech's support has led to 26 agreements in the agrochemical, research reagent and diagnostics fields with partners including major global companies. This includes the commercialization of Dr. Torii's synthetic auxin (cvxIAA) technology.

As a result of technology transfer initiatives, 22 compounds with patents or patents pending were commercialized. In 2020, LiPiDyeII, which added significant value to LiPiDye by restructuring its molecules, was launched by Funakoshi Co., Ltd. As a result, it has been given very high photo-stability functionality to facilitate long observation under strong florescent microscopy. This allows not only for in vitro study, but I also anticipated to find use in in vivo study in neuroscience, for example in observation of sliced brain tissue samples under physiological conditions. The next-gen synthetic auxin, 5-Adamantyl-IAA developed by the Torii group has been developed for super-sensitive and high-specific AID (auxin-inducible degron) systems in animal and plant research. It was modified cvxIAA that previously developed synthetic auxin. 5-Adamantyl-IAA has 1000 times stronger binding affinity to modified TIR1 receptors than native auxin. This lower concentration of auxin can build a low-toxic mammalian cell AID system. 5-Adamantyl-IAA is available from TCI Chemicals Co., LTD and used by both plant and animal cell biologists. GNRs (graphene nanoribbons) concluded collaborative research and the license agreement with Taoka Chemical Co., Ltd. in 2019 are also going forward towards the mass-production and commercialization, whereas the related papers have been retracted (see Section 7). The application development using the GNRs will be accelerated in various fields.

ITbM worked toward enhanced the academia-industry partnership over 7 years. As a result, ITbM succeeded many technology developments and gain research funding through 101 research collaboration with 45 companies.

In 2018, to promote collaboration between academia and industry more, ITbM has launched the ITbM Consortium. On top of this, by incorporating GTR in its framework the consortium became the ITbM/GTR

Consortium in 2020. The benefits of the consortium are the ability to access to the latest technologies from ITbM and GTR for the member companies, as well the ability to obtain needs existing in member companies for ITbM/GTR researchers. ITbM has contributed to social development as well even during the COIVD-19 pandemic. Until last year, the annual ITbM consortium workshop had been held physically. Instead, the virtual consortium workshop has been held twice in 2020. To further fulfill our social commitment more, one of these workshops was held for not only for paid members but also for 15 non-member companies who are interested in ITbM/GTR consortium. Conclusively, one new member that has joined in.

## 3-2. Achievements of Center's outreach activities

* Describe what was accomplished in the center's outreach activities during the period from 2012 through March 2021 and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 5, describe the concrete contents of these outreach activities and media reports or coverage of the activities.

ITbM has strategically created a wide range of networks with not only top scientists but also with journalists, artists, high school teachers/students, and the general public. Based on this network, ITbM has actively organized various outreach activities including scientific symposia/seminars, exhibitions, international press releases, public lectures, science education and so on.

**International press releases**

In 2013, ITbM established an international press release platform in the RPD and has been regularly releasing international press releases on ITbM's interdisciplinary research outcomes, international awards/events and other outreach activities, through international press release services such as EurekAlert!, ResearchSEA and AlphaGalileo in North America, Asia, and Europe, respectively. Through RPS members' writing skills and science visualization, these are released in a way that complex scientific results can be easily understood by the general public as well as those in different fields, and that the excitement of the research can be understood quickly and shared with the readers. To date, ITbM has distributed a large number of press/event releases and press conferences about their research activities and has been covered in various media. A number of ITbM's research news items have been translated in various languages, such as Chinese, Dutch, French, Germany, Indonesian, Korean, Portuguese, Russian, and Spanish. The distribution of press releases and subsequent media coverage are considered to have been a highly effective method for dissemination of ITbM's activities, leading to increased attention from the academic, industrial, public and media sectors. For example, a press release on SCL1, a molecule that closes stomata to improve drought tolerance, developed in collaboration between the Kinoshita group and Chemical Library Center in 2018, received a number of inquiries from both academia and industry within a few days and led to international collaborations with agrochemical companies. ITbM is also working together with its partner institutes, Emory University and RIKEN CSRS, to release joint press releases and strengthen these collaborations.

**Outreach and network**

The RPD has also been involved in various outreach activities, including the largest event: Science Agora. Lab tours and seminars to introduce ITbM have been also held for students, teachers, and the general public from local and overseas high schools, and for other visitors. ITbM's activities are also introduced to the academic community by means of booth exhibitions at international events, including the AAAS Annual Meetings (USA), to the public, Super Science High School Presentations, and various exhibitions to industries. PIs, staff and RPD members are also involved in holding public lectures in high schools and science cafés. ITbM's research activities were presented to over 5,000 high school students over two years (FY2017 and 2018), and the RPD held many outreach events for the general public (over 50 outreach events every year). In 2018, ITbM organized the 7th WPI Science Symposium, entitled "Transformative Science", which collected more than 800 participants including 400 high school students, and shared the excitement of science with all. These events not only are effective for fostering future scientists (high school students) but are effective for the younger generation, *e.g.*, elementary school students, including their parents, to develop a curiosity towards molecules. This led to the establishment of ITbM's "MoleQrious!" project. The final goal of this campaign is to create a society in which molecules are recognized at the same level as common scientific words, such as the "genome".

The 9-year-educational campaign has had a substantial payoff in the form of collaboration with one of the oldest department stores in Japan, Matsuzakaya. This is the first attempt to receive private financial support for management of the event and is considered a good strategy towards sustainable management of the center. In April 2019, ITbM will start a series of ITbM lectures at Chunichi Culture Center in Sakae, the center of Nagoya, to introduce ITbM's cutting-edge science to the general public and show its potential

contribution to society.
The 9-year networking with high schools resulted in joint events including the annual WPI science symposium and Kagaku-zanmai, the largest science event in the Tokai area, an extensive network for University-High School Collaboration, and the involvement of ITbM as a committee member at designated high schools of the MEXT Super Science High School Program.
In FY2020, the RPD has proactively constructed a domestic/ international network, expanded their activities, and held over 30 events even during the COVID-19 pandemic.

## 4. Generating Fused Disciplines (within 3 pages)

### 4-1. State of strategic (or "top-down") undertakings toward creating new interdisciplinary domains

Describe the content of "top-down" measures taken by the Center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields.

Led by the strong initiative of the Director, all members of ITbM have been working beyond their disciplines and developing interdisciplinary research into transformative molecules spanning chemistry, plant/animal biology, and theoretical sciences.

Thanks to the 'Mix' strategy at ITbM, ITbM has succeeded in creating more than 100 interdisciplinary research projects. In 2015, ITbM has defined its three flagship research areas: 'plant chemical biology', 'chemical chronobiology', and 'chemistry-enabled live imaging'. To develop these research areas, ITbM has prepared a unique set of platforms: (i) small-molecule synthesis, (ii) phenotypic assay development, (iii) theoretical design and bio-simulation, (iv) chemical library generation/curation (Chemical Library Center), (v) laser microscopy (Live Imaging Center), (vi) omics and molecular analysis (Molecular Structure Center, see also 3-2), and (vii) peptide and protein synthesis (Peptide/Protein Center). Going forward with its mission/goal of developing transformative bio-molecules, ITbM set the plan "ITbM2.0", and started the following challenges in early 2020: "parasitic plants", "chemistry-enabled plant adaptation", "clock diseases", "chemistry-enabled bioimaging", and "nanocarbon chemistry and biology".

### 4-2. State of "bottom-up" undertakings from the center's researchers toward creating new interdisciplinary domains

Describe the content of "bottom-up" measures taken by the Center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields.

ITbM's Mix concept as described in Section 2-2 has facilitated bottom-up interdisciplinary projects among young researchers. Particularly, Mix Labs and Mix Offices function as places where new unique ideas in research are being generated based on daily communications among researchers from different fields working side-by-side. Other strategic measures listed below also contribute to facilitation of interdisciplinary research in a bottom-up manner.

**ITbM Research 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 to be spent over 2 years. The proposals prepared in English are pre-evaluated, and finally selected through oral presentation in English followed by paper screening, adjudicated by all NU PIs, several overseas PIs, and in some cases, visiting professors with high research profiles. So far, 18 proposals among 30 were selected after careful evaluation, and many proposals have made good progress to mature into ITbM's representative research projects including the *Striga* project. The award also contributes to motivate young researchers and students to apply for external grants, and provides them practice with writing grants and defending their ideas.

**ITbM Workshop** is held annually to share research progress and to provide an opportunity for new collaboration in ITbM. Members who participate in the workshop are those engaged in ITbM research including faculty members, postdoctoral researchers, technical staff, students, and administrative staff. At these workshops, extensive discussions about the details and plans of research are held in one – two days. The workshop functions to highlight and expand the bottom-up collaborations generated during daily discussions around the bench to all ITbM members and encourage further participants. Although the event for 2020 was suspended due to COVID-19, ITbM finally organized the event on-line in March and April 2021, which dispelled the gloomy atmosphere and encouraged many researchers in ITbM.

**ITbM Tea Break Meeting** started in 2015 to promote "Mix" based on casual discussions such as on research progress and Mix Lab/Mix Office management. The meeting has provided an important opportunity to mix researchers, students, technical staff, and administrative staff, to enable network-building among

ITbM's researchers who come from various disciplines and backgrounds. In FY2020, it was held online.

**Research Promotion Division (RPD)** has been playing a critical role as a catalyst to initiate collaboration. RPD staff attend all group meetings to enable collaborations between groups of different research fields. Thus, the RPD can assist in strategic planning at an early stage of the research, including early feedback on research that should be covered under intellectual property and developing industrial collaborations with the help of the SPD (see below). By having a detailed understanding of the science, the RPD is able to carry out effective public relations, science visualization, public outreach, and so on.

**Strategic Planning Division (SPD)** was separated from RPD in 2016 to focus on promotion of societal implementation of the research outcomes, which is also critical for ITbM's sustainability. The SPD is spearheading initiatives to promote collaborative research with industry. The SPD has been building strong ties with the Academic Research & Industry–Academia–Government Collaboration Department of NU, which is enabling them to further promote, expand and strengthen collaborations with industry.

**The four supporting centers** (Molecular Structure Center, Live Imaging Center, Chemical Library Center, and Peptide Protein Center) have also been making remarkable contributions to the promotion of ITbM's interdisciplinary research. To date, ITbM has collaborated with over 1000 users inside and outside of ITbM and has been a part of nearly 100 publications on interdisciplinary research. For example, the Live Imaging Center cooperated on two Grant-in-Aid for Scientific Research on Innovative Areas, and has been elected the most used center in Japan in 2017. In 2020, the center was also invited to a project of the Moonshot Research and Development Program organized by the Cabinet Office of Japan, which will also expand the collaboration network. The Chemical Library Center has distributed around one million compounds for 88 collaborators inside and outside Japan, filing 11 patents, and expanding its activities such as on drug discovery and development, metabolomics, and predictive toxicology. In 2021, the center was awarded the global health R&D Fund and will initiate international collaborative research to identify novel bactericidal drug targets against multi-drug resistant infectious diseases. The Molecular Structure Center plays a key role in identifying target proteins by installing immunoprecipitation, stable isotope labeling of amino acids in cell culture (SILAC), phosphoproteomics, and mass spectrometry (MS) imaging through collaborations with Academia Sinica and RIKEN CSRS. The Peptide/Protein Center is a critical part of ITbM, delivering tailor-made peptides for plant and animal biologists. The center has established a spin-off company "Craftide. Co., Ltd.", in December 2018, to apply the technologies of the center to mid-sized drug development.

## 4-3. Results of research in fused research fields

Describe the Center's record and results by interdisciplinary research activities yielded by the measures described in 4-1 and 4-2.

- In Appendix 1-2, list up to 20 of the Center's main papers on interdisciplinary research that substantiate the above record of results, and describe their content.

The synergy of ITbM researchers' high research profile and the new research style at ITbM has facilitated interdisciplinary research in the three flagship research areas that ITbM has defined. A number of collaborative research projects have been promoted, and joint publications and patent filings by multiple PI groups are constantly increasing in number. So far, 77 papers and 46 patents are based on the interdisciplinary research, and 380 papers have been published by international collaboration. Representative outcomes are denoted below.

**Parasitic Plants**

The progress of the *Striga* project denoted in Section 2-1[1] would never have been achieved without the full Mix of ITbM. Yoshimulactone Green (YLG) was developed by spontaneous collaboration among the ITbM chemists (**Itami** group), biologists (**Kinoshita** group), **Molecular Structure Center**, and **Live Imaging Center** (Appendix 1-2 (1): *Science* 2015). The discovery has accelerated the development of sphynolactone-7 (SPL7) by further collaboration among the ITbM chemists (**Ooi** group), biologists (**Kinoshita** group), **theoretical science** group, and **Molecular Structure Center** (Appendix 1-2 (2): *Science* 2018). These achievements further led to the identification of strigolactone receptor agonists/antagonists in collaboration with the **Chemical Library Center** (Appendix 1-2 (3): *ACS Cent. Sci.* 2018). The discovery of SPL7 has motivated all ITbM scientists to tackle the issue of *Striga* through the practical use of SPL7 in the fields and the field experiments of SPL7 began in July 2020 at KALRO Kibos in Kenya.

**Chemistry-enabled Plant Adaptation**

The **Torii-Uchida** group has recently been exploring small molecules that can control the density and/or patterning of stomata through chemical screening using the ITbM chemical library. They collaborated with the **Itami** group and the **Chemical Library Center**, and identified first-in-class synthetic molecules

that increase the number of stomata and promote root growth in various plant species such as *Arabidopsis thaliana* and edible plants (cucumber, lettuce, etc.) (Appendix 1-2 (6): *Chem. Commun.* 2017).

The **Kinoshita** group and the **Chemical Library Center** succeeded in identifying nine stomatal closing molecules (SCL1–SCL9) that suppress light-induced stomatal opening (Appendix 1-2 (7): *Plant Cell Physiol.* 2018).

The **Torii-Uchida** group developed the novel bifunctional synthetic peptide, KIN, that exhibits dual effects of vascular thickening and root shortening. In collaboration with **computer scientists**, they indicated that the KIN could bind to two receptors, CLV1 and TDR, that regulate these two phenotypes respectively (Appendix 1-2 (8): *Nature Commun.* 2018). Inspired by this success, the groups of **Torii-Uchida**, **Kinoshita**, and **Itami** have engineered an orthogonal auxin-TIR1 receptor pair through a bump-and-hole strategy, which triggers auxin signaling without interfering with endogenous auxin or TIR1/AFBs. Through this study, they provided conclusive evidence for the role of the TIR1-mediated pathway in auxin-induced seedling acid growth (Appendix 1-1 (10): *Nature Chem. Biol.* 2018).

**Clock Diseases**

Through extensive collaborations within ITbM, the groups of **Yoshimura**, **Itami**, **Kay-Hirota**, and **computational sciences**, have demonstrated that transformation of a period-lengthening molecule KL001 resulted in the development of period-shortening derivatives synthesized via catalytic C-H coupling reactions (Appendix 1-2 (11): *Angew. Chem. Int. Ed.* 2015). Further collaborations of the groups of **Kay-Hirota**, **Itami**, **Tama** and **Molecular Structure Center** resulted in identification of the small molecule GO289 as a potent and selective inhibitor of CK2 with outstanding physicochemical properties *in cells* (Appendix 1-1 (15): *Science Adv.* 2019). In addition, the groups of **Hirota-Kay**, **Itami**, **Tama**, and **Chemical Library Center** discovered first-in-class isoform-selective regulators KL101 and TH301 against CRY1 and CRY2, respectively, and demonstrated that both CRY1 and CRY2 enhance differentiation of brown adipocytes in culture, providing a new possibility for treatment of obesity (Appendix 1-1 (16): *Nature Chem. Biol.* 2020).

The **Yoshimura** group and the **Chemical Library Center** succeeded in identifying the period-shortening compound dehydroepiandrosterone (DHEA; also known as prasterone) which accelerated re-entrainment to advanced light–dark (LD) cycles *in vivo*, thereby reducing jet-lag of mice (Appendix 1-2 (9): *EMBO Mol. Med*. 2018) and the molecule 'Celastrol,' a traditional Chinese medicine, that reversed the depressive behavior through NRF2 antioxidant pathway with the Chemical Library Center (Appendix 1-2 (10): *PNAS* 2020).

**Chemistry-enabled Bioimaging**

Collaboration of the groups of **Yamaguchi**, **Higashiyama**, and **Live Imaging Center** has repeatedly discovered unprecedented fluorescent dyes, C-Naphox, PhoxBright 430 (PB430), PREX 710, and MitoPB Yellow (Appendix 1-1 (18)-(21)). These dyes are outstandingly photostable fluorescent dyes with a long lifetime under the intense laser beams required for STED microscopy. Among them is MitoPB Yellow, which enabled the visualization of nano-scale dynamics of mitochondrial cristae in living cells. They achieved the first ever monitoring of a rapid inter-cristae mergence in a single mitochondrion and of inner-membrane fusion in the inter-mitochondria interaction.

The groups of **Itami**, **Higashiyama** and **Live Imaging Center** have cooperatively developed a water-soluble warped nanographene (WNG) and revealed that the WNG has unique properties suited to biological applications. They demonstrated that the water-soluble WNG was readily encaptured into HeLa cells and induced cell death upon light irradiation (Appendix 1-2 (14): *Angew. Chem. Int. Ed.* 2018).

**Nanocarbon Chemistry and Biology**

The **Itami** group achieved syntheses of topologically unique 2D/3D nanocarbons and created a chemical library consisting of structurally diverse and uniform, and atomically precise nanocarbon molecules with the **Chemical Library Center.** This resource motivated biology groups inside/outside of ITbM including industries to explore the as yet uncovered biological functions of nanocarbon molecules in living organisms (with the groups **Yoshimura**, **Kay-Hirota**, **Frommer-Nakamura**, and **Nakamichi-Kinoshita**).

**Target ID platform**

According to the research progress, target protein identification (target ID) became indispensable to elucidate the molecular mechanisms of biological functions and to develop transformative bio-molecules. Thus, ITbM has been developing the target ID platform. The **Molecular Structure Center** plays a central role to proteomics research applicable to identify target proteins and to explore signal transduction by installation of a variety of methods, such as pull-down assay (**Hirota** and **Itami** *et al. Science Adv.* 2019:

**Nakamichi** and **Itami** *et al. PNAS* 2019), co-immunoprecipitation (**Kinoshita** *et al. Sci. Rep.* 2017), phosphoproteomics (**Higashiyama-Ueda** *et al. PNAS* 2016 & 2019), shotgun proteomics for identification of target proteins of GO289 against AML cells, stable isotope labeling of amino acids in cell culture (SILAC) for target ID of natural product picrotoxinin that shortens circadian clock (collaboration of **Ooi** and **Yoshimura**), and mass spectrometry imaging (collaboration of **Crudden-Nambo** and **Yoshimura**). ITbM is also planning to establish a global target identification platform with other institutions, such as the **Institute of Chemistry at Academia Sinica** and **RIKEN CSRS**. ITbM has also started a collaboration with a **bio-informatician** (Dr. Shimamura) from the Division of System Biology in the Medical School of NU to accelerate omics research.

# 5. Realizing an International Research Environment **(within 4 pages)**

## 5-1. International Circulation of Best Brains

### 5-1-1. Center's record of attracting and retaining top-world researchers from abroad

Describe the participation of top-world researchers as PIs and their stays as joint researchers at the Center.

・ In Appendix 3-2, give the number of overseas researchers among all the Center's researchers, and the yearly transition in their numbers. In Appendix 4-2 give the achievements of overseas researchers staying at the center to substantiate this fact.

All of the five world-leading ITbM overseas PIs have been actively involved in various activities of ITbM. They live in Nagoya for 1-2 months per year and attend 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 video conferences or e-mails. They also regularly send young researchers from their own institutes to ITbM.

Frommer, who joined ITbM as the fifth overseas PI in FY2016, is a good example of a world-class researcher who was intrigued by ITbM. While Frommer was first planning to conduct collaborative research with ITbM researchers, he became aware of ITbM's unique research environment and approached us to become a PI.

In 2019, ITbM invited Dr. Ueli Grossniklaus (Professor, University of Zurich) for three months. Dr. Grossniklaus is an eminent plant microbiologist and has been recognized as a Highly Cited Researcher since 2014. During his stay, a win-win relationship was established especially with ITbM's chemists and centers, and several collaborative research projects have been launched with him. This certainly raised ITbM's international profile. He also accepted the position of GTR Advisory Board member, and gave a special lecture online in January 2021, titled "Interdisciplinary PhD Education as a Gateway to Professor Life" in the midst of the COVID-19 pandemic. Under such a situation, the lecture encouraged many young researchers and PhD students, and provided a great opportunity to turn their eyes to the world again.

Although almost all in-person visit from overseas countries have been suspended since early FY 2020 due to COVID-19, ITbM continues its effort to build bonds with overseas researchers to expand research networks.

### 5-1-2. Employment of young researchers at the Center and their job placement after leaving the Center

Describe the Center's employment of young researchers, including postdoctoral researchers, and the positions they acquire after leaving the Center.

・ Enter the following to substantiate the facts provided above:
- In Appendix 4-3, describe the Center's state of international recruitment of postdoctoral researchers, the applications received, and selections made.
- In Appendix 3-2, give the percentage of postdoctoral researchers employed from abroad
- In Appendix 4-4, describe the positions that postdoctoral researchers acquire upon leaving the Center.

Mentoring young researchers is a key to the future development and global standing of ITbM. Since ITbM's launch, a significant number of postdoctoral researchers have carried out research at ITbM, and are now in key positions in academia and industry in Japan and overseas. Thus, ITbM has been a key part of the global talent stream.

ITbM postdoctoral researchers hired through WPI funding are predominantly non-Japanese, although Japanese researchers have also been affiliated as JSPS Research Fellows. By the end of FY2020, 106 postdoctoral researchers have been affiliated to ITbM, of which 69 (65%) are non-Japanese. On average, 25-30 postdoctoral researchers are resident at ITbM every year.

The employment of postdoctoral researchers is on a one-year contract, which can be renewed up to three years. ITbM has been able to recruit these highly trained personnel from various research institutions throughout the world such as UC Berkeley, University of North Carolina, University of Washington, University of Pennsylvania, University of Pittsburgh, Queen's University, University of British Columbia,

University of Toronto, Max Planck Institutes, Free University Berlin, Technical University Berlin, University of Münster, University College London, University of Edinburgh, National University of Singapore, Beijing Institute of Technology, and Academia Sinica. ITbM also accepted PhD students from overseas institutions in cooperation with the Graduate School of Science as their official affiliation.

In addition, ITbM created a new post of non-Japanese Junior PI, and started the open call in late 2020. 31 applications were received, and the selection process started in February 2021.

So far 67 postdoctoral researchers from abroad have left ITbM, of whom 39 found faculty positions in academia in the US, Canada, Germany, France, Poland, UK, Australia, Mexico, China, Taiwan, India, Pakistan, and Japan. Thus, affiliation to ITbM is obviously a successful career path.

Academic promotion of young faculty members is also notable. In FY2013-2018, Dr. Hagihara was recruited as Team Leader of RIKEN CSRS, Dr. Yamaguchi as Professor at Waseda University, Dr. Yokogawa as Associate Professor (PI) at the University of Tokyo, Dr. Hijikata as Associate Professor at Hokkaido University (ICReDD), and Dr. Fukazawa as Professor at Kyoto University (iCeMS). Since FY2019, there have been even more promotions: Dr. Uchida as Professor at Nagoya University, Dr. Ueda as Professor at Tohoku University, Dr. Uraguchi as Professor at Hokkaido University, Dr. Nakamichi as Professor at Nagoya University, and Dr. Murakami as Associate Professor (PI) at Kwansei Gakuin University. Many of them have the title of "Affiliated Researcher of ITbM", and continue their collaboration with ITbM. Accordingly, ITbM's network has widened further.

### 5-1-3. Overseas satellites and other cooperative organizations

- In Appendix 4-1, describe the state of cooperation with overseas satellites and other cooperative organizations. In Appendix 4-5, describe the state of the Center's agreements concluded with these organizations.

Although no satellite institutes are established, ITbM has several international cooperating institutions. In addition to the overseas PIs' host institutions designated from the inception of ITbM, we have strategically expanded our collaboration network with national/international institutions to augment the research activities of ITbM. ITbM has published 380 international joint papers.

**Queen's University (Canada), University of Texas at Austin (USA), ETH Zürich (Switzerland), University of Southern California (USA), and Heinrich Heine University Düsseldorf (HHUD, Germany)** are partners as host institutions of the overseas PIs, and have been collaborating with ITbM in various aspects. In particular, Frommer is a member of CEPLAS, which is a joint initiative of HHUD, University of Cologne (UoC), Max Planck Institute for Plant Breeding Research Cologne (MPIPZ) and Forschungszentrum Jülich (FZJ). CEPLUS is the only plant research center selected as the Cluster of Excellence supported by the German Research Excellence Initiative, and a world-leading institute of plant science. HHUD has communicated a significant interest in collaborating with ITbM, and has concluded research collaboration agreements and tuition-free student exchange in 2018.

**National Science Foundation Center for Selective C-H Functionalization (NSF-CCHF, USA)** and **Institute for Basic Science (IBS, South Korea)** are international partners that have been extensively collaborating in the field of C-H activation chemistry constituting an important area of ITbM's research. CCHF is a virtual institute with 23 world leading 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 carry out research exchanges of 3-6 months between the institutes. The network also expanded to include other related institutes such as the IBS. ITbM organized the 1st workshop at ITbM in 2016, and IBS hosted the 2nd workshop in July 2019 in Korea. The 3rd event was scheduled in US in August 2020, but it was postponed due to the COVID-19 pandemic. Instead, several online symposia were organized by CCHF, and ITbM researchers actively involved and planted new seeds of collaboration.

**RIKEN Center for Sustainable Resource Science (CSRS, Japan)** is an important partner in Japan. CSRS, focusing on plant biology and synthetic chemistry, was established at almost the same time as ITbM. Directors of ITbM and CSRS made a joint statement on the joint use of the research support platform, and confirmed further promotion of collaboration between CSRS and ITbM. The CSRS-ITbM Joint Workshop is an annual event. In 2018, Hagihara (ex Itami group) transferred to the CSRS as Team Leader of the CSRS, which has greatly promoted the collaboration. Several collaborative research projects with CSRS are ongoing.

**Institute of Chemistry (IoC) at Academia Sinica (Taiwan)** is also an international partner of ITbM. Based on research agreements, collaborative research projects are ongoing through the exchange of researchers. Joint workshops were held in 2016 & 2017 and collaborative relationship has been deepened. In 2019, Director Itami became the first Joint Appointment Research Fellow at Academia Sinica and launched the Itami lab at IoC in September 2020, accelerating the collaboration between ITbM and

IoC.

**Kenya Agricultural & Livestock Research Organization (KALRO)** and NU have concluded an MOU for scientific and technical collaboration in research and education in 2019. In this framework, the cooperation of ITbM and KALRO was officially started, and the molecule to combat *Striga* has been tested in the research fields of KALRO in Kenya. The collaboration of KALRO is also essential for ITbM to apply ITbM's bio-functional molecules to adapt plants under the stressful natural conditions in Africa. While the collaborative *Striga* research has been suspended for almost one year due to COVID-19, ITbM researchers have recently been allowed to fly to Kenya with the strong support of NU. We will restart the field tests soon in FY2021.

## 5-2. Center's record of holding international symposia, workshops, research meetings, training meetings and others

- In Appendix 4-6, describe the main international research meetings held by the Center.

ITbM has hosted international symposia (ISTbM) and three international awards (Hirata Award, Tsuneko & Reiji Okazaki Award, Nagoya Medal of Organic Chemistry) annually, which have contributed to increasing ITbM's international visibility. Those events for 2020 were postponed, and will be held online during FY2021.

**ITbM International Symposium on Transformative Bio-Molecules (ISTbM)**

ITbM organizes an international symposium every year in Nagoya by inviting world leading researchers who carry out research in ITbM-related fields, such as organic chemistry, animal/plant biology and theoretical science. To date, 74 speakers have been invited, 21 from organic chemistry, 21 from plant/animal biology, 6 from theoretical sciences, and 26 from ITbM.

**Hirata Award**

The Hirata Award (former name: the Hirata Memorial Lecture) started in 2005 at NU in memory of the great achievements of the late Dr. Yoshimasa Hirata, an Honorary Professor of Nagoya University, and is an international award given to a rising star in the field of organic chemistry. Previous winners of the award are: Drs. Justin Dubois (2004), David R. Liu (2005), Phil S. Baran (2006), Peter H. Seeberger (2007), Scott J. Miller (2008), Jeffrey W. Bode (2009), Jin-Quan Yu (2010), Mohammad Movassaghi (2011), Tobias Ritter (2012), Martin D. Burke (2013), Ashraf Brik (2015), Emily Balskus (2016), David A. Nicewicz (2017), Ruben Martin (2018), and Abigail G. Doyle (2019).

**Tsuneko & Reiji Okazaki Award**

The Tsuneko & Reiji Okazaki Award was established in 2015 by ITbM in memory of the great achievements of Dr. Tsuneko Okazaki, University Professor and the late Dr. Reiji Okazaki, Honorary Professor of NU. Previous winners of the award are: Drs. Feng Zhang (2015), Yukiko Yamashita (2016), Maria Barna (2017), Cyril Zipfel (2018), and Kay M. Tye (2019).

**Nagoya Medal of Organic Chemistry**

The Nagoya Medal Prize was initially proposed by Drs. Hisashi Yamamoto and Ryoji Noyori, and founded in 1995 through the financial support of MSD Life Science Foundation (previously: Banyu Life Science Foundation International). The Nagoya Gold Medal Prize has been awarded every year to an organic chemist who has made significant original contributions to the field in its broadest sense. The Silver Medal, established in 1999, has been presented every year to a front-runner based in Japan whose research has had a major impact on the field of synthetic organic chemistry. Currently ITbM is hosting the Nagoya Medal from 2013 along with Itami as the chair of the Nagoya Medal selection committee.

**CSRS-ITbM Joint Workshop**

ITbM and CSRS 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/Yokohama. In 2015, both institutes decided to enter a partnership to collaborate in chemistry and plant biology. In 2016, both directors made a statement on the joint use of the research support platform and confirmed further promotion of collaboration between ITbM and CSRS.

**The EMBO Workshop "Functional live imaging of plants"**

The EMBO workshop with an experimental course was held for the first time in Japan at ITbM from May 21-30, 2019 (Organizer: Higashiyama). The course features lectures (40% of course time) along with practical sessions and image analysis (60%), and the participants rotated through five practical sessions in the Live Imaging Center of ITbM. In addition to 57 domestic researchers, 51 researchers from 21

overseas countries were also invited, and this proved an excellent opportunity to improve the recognition of ITbM.

**ITbM Seminar**

ITbM has been holding a series of ITbM Seminars inviting researchers from related fields.

**Others**

As part of the collaboration with international partner institutions, the following activities were organized:

- 1st international joint workshop with NSF-CCHF and IBS-KAIST (Nagoya, 2016)
- 1st joint workshop of ITbM and IoC, Academia Sinica (Nagoya, 2016)
- 1st international symposium by ITbM and the University of Freiburg "Multicomponent Supramolecular Catalysts for Sustainable Chemical Synthesis" (Freiburg, Germany, 2017): Ooi served as one of the chairs of the symposium.
- 2nd joint workshop of ITbM and IoC, Academia Sinica (Taipei, Taiwan, 2017)
- 2nd international joint workshop with NSF-CCHF and IBS-KAIST (Daejeon, Korea, 2019)

ITbM researchers have been appointed to organize the following international symposia/workshops:

- International Symposium on Biological Rhythms "Towards understanding the molecular clockwork" (Nagoya, 2016): Yoshimura served as one of the organizers of the symposium.
- The 25th International Congress on Sexual Plant Reproduction (Gifu, 2018): Higashiyama and Ueda served as members of the organizing committee.
- Japan-Taiwan Plant Biology 2019 (Nagoya, 2019): Kinoshita, Nakamura, and Kanaoka served as organizing committee.
- International symposium of Journal of Plant Research (84th Annual Meeting of the Botanical Society of Japan, Nagoya, 2020): Higashiyama served as the secretary general.

The 9th Chemical Protein Synthesis Meeting, scheduled for 2021 in Nagoya (Organizer: Bode), will be postponed due to COVID-19.

## 5-3. System for supporting the research activities of overseas researchers

Describe the Center's preparations to provide an environment conducive for overseas researchers to concentrate on their work, including for example living support in various languages or living support for their families.

To allow the researchers from abroad to settle down in Japan and focus on their research, ITbM has established various support systems. Especially, dedicated staff in ITbM's Administrative Department are responsible for providing local support to **ITbM's foreign researchers and their families** staying in Japan. The main purpose of this role is to offer a comfortable environment to ITbM's researchers, so that they are able to fully concentrate on their research activities. Many foreign researchers who come to work in Japan have difficulties with the language barrier, as almost all the procedures at local government offices and medical centers are carried out in Japanese only. ITbM has assigned a **local support officer** to the RPD, who cooperates with the **administrative staff** and the **secretaries of PI groups** to provide on-scene support to foreign researchers at ward offices, including help with national health insurance and the pension system, as well as assistance in immigration affairs and other matters that may arise in their daily lives.

The Administrative Department has been sending all notices from the university to researchers in both English and Japanese. 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.

In order to provide a better environment for foreign researchers, 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.

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 international schools near NU to accept preschool children of the researchers arriving from overseas. NU also has a nursery on campus, and it accepts the children of foreign researchers from ITbM.

The local support officer has collected information of hospitals with English services in Nagoya to cover major medical departments. To provide advanced support, ITbM signed a contract with International SOS Japan Ltd. in 2016 to provide advanced medical service information 24 hours a day.

In order to provide more useful information, some beneficial services from the International Education & Exchange Center (IEEC) in NU are being shared with ITbM's foreign researchers. The IEEC mainly provides assistance to international students, but in recent years, the IEEC has started expanding their services to support foreign faculty members and postdoctoral fellows as well. Services include: seminars on tax adjustment, orientation for renting an apartment in Japan, health consultations, and information on cultural events such as Japanese flower arranging (Kado) and Origami lessons.

With ITbM's contribution, NU has established the **Dual Career Program**, which provides opportunities for partners/spouses to hold positions in NU on the basis of proper evaluation. This program will largely promote the recruiting of top researchers around the world.

### 5-4. Others

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. For this purpose, ITbM launched the program "Overseas Training of PhD Students", which financially supports PhD students to conduct research at overseas institutions. Annually, 2-4 PhD students have travelled for 3-6 months to various institutions in countries such as the US and Germany. ITbM has also provided various opportunities for faculty members and postdocs to make international networks. Many of them are involved in collaborative research with overseas PI groups. Several researchers have started collaborations with overseas researchers who have visited ITbM. ITbM's annual international symposia described in Section 5-2 have also helped in this regard. ITbM is also utilizing the international programs run by NU, such as "Top Global University Project (MEXT)", "Dispatching Young Researchers Abroad Program at the Graduate School of Science (NU)", and the Core-to-Core Program "Elements Function for Transformative Catalysis and Materials". From 2018, the WISE program GTR supports the PhD students in international collaborations and participation in international symposia. The total number of PhD students who have travelled to overseas institutions amounts to 39 as of the end of FY2019 (suspended during FY2020).

## 6. Making Organizational Reforms (within 3 pages)

### 6-1. Decision–making system in the center

Describe the strong leadership that the director is giving on the Center's operation and its effect, and the division of roles and authority between the Center and its host institution.
- In Appendix 3-3, draw a concrete diagram of the Center's management system.

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

The ITbM Steering Committee is held monthly, which is a place for discussion and provides advice to the Director to make the final decisions. The Committee members include the Trustee of NU (in charge of WPI affairs). The Director operates and manages ITbM in consultation with the Steering Committee.

In addition, the Director and core members of ITbM hold a meeting with the President of NU once a month to discuss any issues related to the management of ITbM.

### 6-2. Arrangement of administrative support staff and effectiveness of support system

Describe the assignment of the Center's administrative support staff who have English language and other specialized skills, effort made in establishing the support system, and the system's effectiveness.

The Administrative Department was organized to provide the environment for ITbM researchers to fully focus on their research projects. Led by the Administrative Director, the Department consists of 3 divisions; Management Division, Research Promotion Division (RPD), and Strategic Planning Division (SPD). The Management Division has 10 staff consisting of Division Head, 4 staff in the General Affairs

Unit and 5 staff in the Accounting Unit. Half of the staff are competent English speakers, and the Department is able to manage all issues requiring English.

The RPD & SPD units have 8 staff including the Division Heads, who are experienced individuals with specialized skills, such as a science designer and a patent attorney. Most of them hold a PhD or a Masters Degree in related fields and are proficient in English. Their high performance strongly supports ITbM's interdisciplinary research in various aspects.

ITbM has 10 secretaries employed to assist NU/overseas PIs and the 4 supporting centers to facilitate smooth communication with the groups via cooperation with the Administrative Department.

### 6-3. System reforms advanced by WPI program and their ripple effects

Concisely itemize the system reforms made to the Center's research operation and administrative organization, and describe their background and results. Describe the ripple effects that these reforms have on the host institution. (If any describe the ripple effects on other institutions.)

Under President Matsuo's vision for Reform, Autonomy and Innovation 2020 (NU MIRAI 2020), NU has been carrying out extensive system reform to become a world-class research university. In the initiative, ITbM is positioned as a core research center of Nagoya University, and thus the basic policy and the measures of system reform have been established to match ITbM's needs. ITbM's measures are fed back to NU through the regular meetings of ITbM core members and the President.

**Named to "Designated National University" by MEXT:** NU was recognized for its abilities to develop world-leading education and research activities and was selected as a "Designated National University" as of March 20, 2018. ITbM's high-profile activities significantly contributed to this designation. NU will make all efforts to become an international leading university and play a leading role in the reform of national universities by actively disseminating the concrete results of their influence and efforts that have contributed to the development of the society and economy.

**"WPI-next" and related programs at NU:** In 2014, NU launched the "WPI-next" program to support world-leading science at NU, which referred to ITbM's unique concepts such as the Co-PI system. This program was reorganized as the "Cutting-edge International Research Units" program, and two more programs, "Research Units Geared toward Young International Researchers" and "Young Researcher Units for the Advancement of New and Undeveloped Fields" were launched in the framework of the Program for Promoting the Enhancement of Research Universities.

**Graduate Program of Transformative Chem-Bio Research (GTR) as MEXT WISE Program (Doctoral Program for World-leading Innovative & Smart Education):** NU recognizes the significance of the "Mix" concept to nurture young researchers. Graduate Program of Transformative Chem-Bio Research (GTR) was selected in 2018 as a MEXT WISE program. In the program, ITbM is positioned as a hub for promoting interdisciplinary research in the field of natural sciences. Through this program, ITbM's Mix concept, which is driven by the "excitement" of research and tackles new interdisciplinary fields, is widely spreading to related departments and also to collaborating research institutes and companies.

**ITbM's Mix concept reflected in design of the CIRFE research building:** The Center for Integrated Future Electronics (CIRFE), established by Professor Hiroshi Amano (2014 Nobel Prize in Physics) with the aim of creating industry-academia-government collaboration, was designed based on the ITbM's Mix Lab and named after ITbM as "CIRFE *Transformative* Electronics Commons (C-TECs)". ITbM's know-how was also provided in their research integration strategy, creating a venue for open innovation that leads the future electronics industry.

**Nagoya University Institute for Advanced Study (NAIAS):** NAIAS was established in October 2019 to strengthen the world-leading research base for basic research at NU. The NAIAS consists of ITbM and Kobayashi-Masukawa Institute for Origin of Particles and the Universe (KMI), and the Institute of Advanced Studies (IAR) that supports the development of new fields of research. In the NAIAS, researchers from multiple fields will work together to develop new research horizons. NAIAS has the integrated department of research promotion, which horizontally develops know-how cultivated in ITbM.

**Conclusion of a Basic Agreement of NU with RIKEN:** NU concluded a basic agreement on June 13, 2017 with RIKEN regarding the promotion of their partnership and cooperation to begin an inter-institutional partnership with the aim to produce world-class, top-level research achievements and innovation. In the past, ITbM and the Graduate School of Bioagricultural Sciences have both collaborated separately with the RIKEN Center for Sustainable Resource Science (CSRS). As other collaborative research is projected between the two institutions, the agreement between the two institutions was considered to be very comprehensive, aiming for cooperation in all fields in which collaboration is possible.

**International Public Relations:** ITbM has shared its expertise and experience on international

public relations to the Academic Research and Industry-Academia-Government Collaboration Department and public relations office of NU. As a result, NU has started to prepare international press releases on research accomplishments for the entire university.

**Information distributed in English:** With respect to the English e-mail distribution by ITbM, NU started to circulate information of grants, funding and other information in both English and Japanese from the end of FY2013.

**Department for "Academic Research & Industry-Academia-Government Collaboration":** In order to promote technology transfer and research outcomes from ITbM and other NU's institutes, NU conducted organizational reform of research supporting units to establish this department in 2015. At the same time, the URA system that started in 2013 was also reviewed extensively with respect to the role of the RPD at ITbM. Through this mutual feedback, ITbM's activities have largely advanced.

## 6-4. Support by Host Institution

The following two items concern the support that the host institution provides the Center. Describe the measures that the host institution has taken to sustain and advance the Center's project. That include those items of support that it committed to at the time of the initial project proposal submittal or in its revised commitment following the project's interim evaluation.

### 6-4-1. Record of host institution support and its effects

- In Appendix 6-1, describe the concrete measures being taken by the host institution.

NU has strongly supported ITbM in many aspects. Representative concrete measures are 1) covering salaries, 2) provision of space, 3) financial support towards construction of ITbM's building, 4) support towards the operation of the building, and 5) ITbM's priority to the use of the residence hall. More details are available in Appendix 6-1.

To secure the employment of ITbM's faculty members and staff, NU has instituted organizational reform in 2019. NU established the "Nagoya University Institute for Advanced Study (NAIAS)", positioned ITbM under this umbrella, and provides support as necessary. NU has also been requesting faculty positions from MEXT to strengthen ITbM's activities since 2018. This request has been gradually approved and 4 positions have been allocated to ITbM during 2018-2021. NU continues the request in the following years to strengthen ITbM activities. In addition, 7 tenure positions were secured in FY2019. NU also promised to provide additional support by all means from FY2022 to secure almost all the ITbM's designated faculty members and the selected postdocs/staff who are essential to run ITbM. NU will also make a full support to collect any funds to sustain ITbM. NU has also committed its full support to collect funds to sustain ITbM. NU will boost the reputation of ITbM to further increase the endowment by all means including through the Nagoya University Foundation and academia-industry partnership.

### 6-4-2. Position of the Center within the host institution's mid-term plan

- To Appendix 6-2, excerpt the places, in the host institution's "Mid-term objectives" and/or "Mid-term plan" that clearly show the positioning of the WPI center within its organization.

Following the launch of ITbM in 2012, NU immediately amended its 2nd phase 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)" including the promotion of ITbM's research in the plan.

In 2015, President Matsuo formulated the vision "NU MIRAI 2020", which states "Through excellence in its education and research, Nagoya University aspires to become one of the world's leading universities", "Research: Inspired by our Nobel laureates, we are committed to the creation and discovery of knowledge through research, … supporting frontier research led by … ITbM for WPI program".

In 2016, the 3rd phase mid-term plan was issued and reorganized in April 2020 due to the establishment of Tokai National Education and Research System composed of NU and Gifu University. ITbM has been included both in education and research; "(TK30-2) … NU will improve its international compatibilities by developing joint degree programs with world class partner universities. NU will provide the education program in the doctoral course integrated with the advanced researches conducted in various NU institutes such as the Institute of Transformative Bio-Molecules (ITbM) to attract capable doctoral candidates." "(TK34-1) NU will promote the world-leading fundamental research and establish an international and original research center engaged in cross-section study, international collaborative study, and comprehensive study by promoting "World Premier International Research Center Initiative"".

In 2018, NU was named a "Designated National University". In the plan, NU has identified four key research areas, in which the first area is "interdisciplinary research in chemistry and biology led by ITbM". The plan clearly states that NU will invest human and financial resources intensively into the key areas,

and following the president's initiative, ITbM is positioned to be a core research center of NU for the foreseeable future.

### 6-5. Others

Describe efforts advanced to foster young researchers (e.g., start-up funding, autonomous research environment) and to enlist female researchers.

・ In Appendix 3-1, 3-2, give the transition in the number and ratio of female researchers.

**Fostering Young Researchers**

The ITbM Research Award is a key way in which ITbM nurtures young researchers. For example, the novel fluorescent probe "Yoshimulactone" arose from the proposal of Masahiko Yoshimura (a PhD student in Itami group at the time) in 2014. This project paved the way to the development of *Striga*'s suicide germinator SPL7.

Personnel exchange between overseas institutes such as NFS-CCHF has occurred every year, except for FY2020. ITbM has sent 39 students to universities in the US and Europe, and accepted 36 students from those countries. ITbM holds the Joint Workshop with NSF-CCHF (USA) and IBS (Korea) on a regular basis as denoted above. In the workshop, postdoctoral researchers and PhD students who met for the first time are requested to form several groups, and each group prepares a research proposal in English within a day. This is a big challenge especially for the Japanese PhD students, but it is an excellent training environment.

On the educational front, to establish a system for students to learn "chemical biology", ITbM has started a lecture series on chemical biology. Three of the PhD students have been awarded the prestigious JSPS "IKUSHI Prize", which is awarded to outstanding PhD students expected to contribute to Japan's future scientific advancement in the presence of the Emperor. In 2018, NU launched the "Graduate Program of Transformative Chem-Bio Research (GTR)", which has ITbM as a hub for promoting interdisciplinary research in the field of natural sciences. In this framework, ITbM proactively engages in the education of PhD students through research activities.

**Appointment and activities of Female Researchers**

At the inception of ITbM, two female PIs (Torii, Crudden) were founding members, and they are leading the world by conducting cutting-edge science. Their remarkable achievements are evident in their collected number of awards (see Section 2-5, Appendix 1-3). One more female PI (Tama) joined ITbM in 2016, and has been promoting various research projects via strengthening of the theoretical platform. While ITbM's excellent female researchers have been promoted, ITbM continued to appoint female researchers. As of the end of FY2020, ITbM has 20 female researchers, which is 30% of all researchers.

ITbM has taken a proactive approach to supporting female researchers. Recently JST launched the "Jun Ashida Award" to foster female researchers, with Torii as the chair. Dr. Yoko Mizuta from the Higashiyama group has recently received JST-PRESTO and A-STEP, and is appointed as a YLC Assistant Professor of NU in 2019. ITbM has 2 JSPS Restart Postdoctoral Fellows to support parental leave for female researchers. ITbM has installed a childcare room in the ITbM building to support the researchers with children.

The activity of female PhD students is also remarkable. For example, Akiko Yagi of the Itami group and Maki Hayashi of the Kinoshita group were awarded the "L'Oreal-UNESCO Award for Women in Science, Japan Encouragement Prize" in 2014 and 2015. Yagi was appointed as Designated Associate Professor of ITbM, while Hayashi was awarded JSPS Research Fellowship for Young Scientists (PD) and appointed at Tohoku University.

As a part GTR, ITbM has organized special lectures to foster female top leaders to raise awareness of gender equality issues. NU has been actively engaged in developing female 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.

## 7. Others

In addition to the above 1.-6. evaluation items, note any of the Center's leading activities, distinctive features or other important points that denote its status as an "internationally visible research center."

**Retraction of papers**

In November 2020, Itami et al retracted the paper titled "Living annulative π-extension polymerization for graphene nanoribbon synthesis" published in Nature 2019. The Itami group noticed that some of the results were unreproducible and the paper includes incorrect data. The group recognized that these issues undermine the group's confidence in the integrity of the study as a whole, and decided to retract the paper. The group also retracted the two related papers for the same reason; "Step-growth annulative π-extension polymerization for synthesis of cove-type graphene nanoribbons" published in JACS 2020, "Graphene nanoribbon dielectric passivation layers for graphene electronics" published in ACS Appl Nano Mater 2019. We regret any confusion and apologize to the scientific community.

**ITbM's policy to prevent research misconduct**

As a world-leading research institute, ITbM is aware of researchers' responsibility and takes actions to avoid any research misconduct. ITbM has established its own policy in accordance with the guidelines of NU and MEXT, including; (i) each research group shall provide education on research misconduct prevention at the beginning of each fiscal year, (ii) each research group shall prepare a concrete action plan according to the policy, and (iii) each PI shall collect all the researchers' signatures to agree to abide by the plan. Thus, all the researchers recognize potential misconduct for each research procedure, and are able to act appropriately to avoid any research misconduct.

**ITbM's 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 from ITbM learn about safety of both chemistry and biology labs/experiments, such as the 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 gas cylinders 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 that ITbM always addresses environmental and safety issues carefully. 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 preparation and improvement of ITbM's safety training course stated above. In addition, ITbM has been actively involved in public outreach events as denoted above and explaining ITbM's concern for safety and environmental issues. In the media, ITbM also weighs in on safety issues when needed.

**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 (2012-2019), Assistant to the President, Professor of Chubu University (2020-)
- Designated Professor, President office of Shizuoka 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 FY 2020 Follow-up (including Site Visit Results)

* Describe the Center's response to results of FY 2020 follow-up. Note: If you have already provided this information, please indicate where in the report.

**Comment 1:** Involvement of overseas PIs.

While overseas PIs have undoubtedly made significant contributions to ITbM's research activities to date, they are now formally employed as visiting professors in ITbM. Tighter engagement of the foreign PIs with ITbM (through cross-appointment, for instance) may be favorable to center's future directions in view of securing their commitment to ITbM, student recruitment/education, and other formal roles played by them in NU.

**<ITbM's response>**

ITbM's overseas PIs have been contributing to ITbM's activity in many aspects. Whereas their contribution to the scientific achievements is obvious, they have been committing to advance ITbM with huge passion in good communications with other PIs and researchers in Nagoya. ITbM's overseas PI position is beneficial for them, which provide them various opportunities to expand their research scope through extensive collaboration with other research areas, and thus, a win-win relationship has been established. ITbM has concluded MOU with their host universities, and the universities are all positive to affiliate them to ITbM. Therefore, our relationship will not change, and they will continuously commit to ITbM's activity.

While a few overseas PI groups have been allocated PhD students of NU, the students' affiliation should have been the ITbM's NU PI groups. However, the Graduate School of Science is going to make its system reform, and will officially allocate PhD students to ITbM's overseas PI groups from FY2022, formally assigning the Co-PIs as supervisors. Accordingly, the ties of overseas PIs and ITbM will be further strengthened.

**Comment 2:** Securing tenure positions for core staff members in Research Centers

Excellent collaboration by the four supporting centers is seen to be instrumental for the remarkably high activity of ITbM in many aspects. For ITbM's long-term sustainability, careful consideration should be given to securing tenure positions for the core staffs in these research centers.

**<ITbM's response>**

ITbM and NU recognize the importance of the four centers, and share the recognition that the centers need to be secured after the completion of the WPI support. The NU President and headquarters confirms the commitment to secure the four center chiefs and several technicians (see Section 6-4-1). ITbM and NU will work together to find all possible ways to ensure that the four centers will continue to hold and advance their activities.

**Comment 3 (from the WPI follow-up report):**

It is also recommended to further improve the researcher gender balance at ITbM.

**<ITbM's response>**

ITbM noticed that improvement of the gender balance is an urgent issue. Whereas the ratio of female researcher is 30% as of March 31, 2021, it still has room to be improved as an international research institute. ITbM hired 3 female researchers as the faculty staff during FY2019-FY2020. We will continue to seek female researchers.

# Appendix 1-1 List of Papers Underscoring Each Research Achievement

* List papers underscoring each research achievement [1] ~ [20] listed in the item 2-1 "Research results to date" of 2. "Advancing Research of the Highest Global Level" (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.
* Place an asterisk (*) in front of those results that could only have been achieved by a WPI center.

The discoveries of Yoshimulactone (*Science* 2015) and SPL7 (*Science* 2018) had a huge and global impact not only on researchers of both academia and industries but also for those who have been involved in food security. It should be strongly emphasized that these astonishing achievements have emerged via a bottom-up collaboration initiated at the Mix Lab between chemists, biologists, and theoretical scientists. We will provide a description of the significance of them in Appendix 1-2.

* "Probing strigolactone receptors in *Striga hermonthica* with fluorescence", Tsuchiya, Y., Yoshimura, M., Sato, Y., Kuwata, K., Toh, S., Holbrook-Smith, D., Zhang, H., McCourt, P., Itami, K., Kinoshita, T., and Hagihara, S. *Science* **349**, 864 (2015).
DOI: 10.1126/science.aab3831

*"A femto-molar range suicide germination stimulant for the parasitic plant *Striga hermonthica*", Uraguchi, D., Kuwata, K., Hijikata, Y., Yamaguchi, R., Imaizumi, H., Sathiyanarayanan, A. M., Rakers, C., Mori, M., Akiyama, K., Irle, S., McCourt, P., Kinoshita, T., Ooi, T., and Tsuchiya, Y. *Science* **362**, 1301 (2018).
DOI: 10.1126/science.aau5445

(1) "Tip-localized receptors control pollen tube growth and LURE sensing in Arabidopsis", Takeuchi, H., and Higashiyama, T. *Nature* **531**, 245 (2016).
DOI: 10.1038/nature17413

The Higashiyama group succeeded in identifying that pollen-specific receptor-like kinase 6 (PRK6) is an essential receptor for sensing of the LURE1 attractant peptide in *Arabidopsis thaliana* under semi-*in-vivo* conditions, and is essential for ovule targeting in the pistil. They revealed PRK6 interacted with pollen-expressed ROPGEFs (**R**ho **o**f **p**lant **g**uanine nucleotide-**e**xchange **f**actors), which are important for pollen tube growth through activation of the signaling switch Rho GTPase ROP1. As a result, they concluded that PRK6 acts as a key membrane receptor for external AtLURE1 attractants, and recruits the core tip-growth machinery, including ROP signaling proteins. This work provides a major breakthrough not only to investigate ligand-receptor interaction but also to discover molecules that break species-specific reproductive barriers.

*(2) "The AMOR arabinogalactan sugar chain induces pollen-tube competency to respond to ovular guidance", Mizukami, A. G., Inatsugi, R., Jiao, J., Kotake, T., Kuwata, K., Ootani, K., Okuda, S., Sankaranarayanan, S., Sato, Y., Maruyama, D., Iwai, H., Garénaux, E., Sato, C., Kitajima, K., Tsumuraya, Y., Mori, H., Yamaguchi, J., Itami, K., Sasaki, N., and Higashiyama, T. *Curr. Biol.* **26**, 1091 (2016).
DOI: 10.1016/j.cub.2016.02.040

Based on a finding that pollen tubes growing through a cut style acquired a response capability in the medium by receiving a sufficient amount of a factor derived from mature ovules of *Torenia fournieri*, the Higashiyama group identified that ovular glycochain, methyl-glucuronosyl arabinogalactan (AMOR), induces competency of the pollen tube to respond to ovular attractant LURE peptides in Torenia. With the Itami group, they further revealed the essential part of the AMOR was proved to be a terminal disaccharide unit and only the b-isomer of methyl-glucuronosyl galactose (4-Me-GlcA-β-(1/6)-Gal) showed AMOR activity via structure-activity relationship study (see also, Jiao *et al. Plant Physiol.* 2018). This is a quite interesting finding because any specific sugar-chain unit of plant extracellular matrix has not been identified as a bioactive molecule.

(3) "Structural basis for receptor recognition of pollen tube attraction peptides", Zhang, X., Liu, W., Nagae, T. T., Takeuchi, H., Zhang, H., Han, Z., Higashiyama, T., and Chai, J. *Nature Commun.* **6**, 1331 (2017).
DOI: 10.1038/s41467-017-01323-8

The Higashiyama group revealed that the extracellular domain of the leucine-rich repeat receptor kinase (LRR-RK) PRK6 from *Arabidopsis thaliana* directly interacts with AtLURE1 peptides. Structural study revealed that a C-terminal loop of the LRR domain (AtPRK6LRR) is responsible for recognition of AtLURE1.2, mediated by a set of residues largely conserved among PRK6 homologs from *Arabidopsis lyrata* and *Capsella rubella*, supported by in vitro mutagenesis and semi-in-vivo pollen tube growth assays. This study provided a strong evidence that PRK6 actually functions as a receptor of the LURE peptides in *A. thaliana* and revealed a unique ligand recognition mechanism of LRR-Rs as well as giving a great potential for a design of small molecule pollen tube attractants to overcome genetic barrier.

*(4) "Rapid elimination of the persistent synergid through a cell fusion mechanism", Maruyama, D., Völz, R., Takeuchi, H., Mori, T., Igawa, T., Kurihara, D., Kawashima, T., Ueda, M., Itoh, M., Umeda, M., Nishikawa, S., Groß-Hardt, R., and Higashiyama, T. *Cell* **161**, 907 (2015).
DOI: 10.1016/j.cell.2015.03.018

The Higashiyama group disclosed by live imaging that two female gametes (the egg and the central cell) coordinately prevent attractions of excess number of pollen tubes known as "polytubey block". They observed in *Arabidopsis thaliana* that the synergid-endosperm fusion causes rapid dilution of pollen tube attractant in the persistent synergid cell and selective disorganization of the synergid nucleus, preventing further attractions of pollen tubes. Simultaneously, the synergid-endosperm cell fusion is induced by fertilization of the central cell, while the egg cell fertilization activates ethylene signaling, an inducer of the synergid nuclear disorganization. In case of unsuccessful fertilization, the persistent synergid cell attracts a second pollen tube to recover the failure of earlier fertilization. Over 110 years have passed since the identification of the two cell fusions in plant, the findings have possibilities to replace the principles that rewrite existing textbooks.

*(5) "Cytoskeleton dynamics control the first asymmetric cell division in Arabidopsis zygote", Kimata, Y., Higaki, T., Kawashima, T., Kurihara, D., Sato, Y., Yamada, T., Hasezawa, S., Berger, F., Higashiyama, T., and Ueda, M. *Proc. Natl. Acad. Sci. USA* **113**, 14157 (2016).
DOI: 10.1073/pnas.1613979113

The zygote divides unequally and the daughter cells inherit different developmental fates. However, the cytological events leading to zygote polarization have remained unknown in flowering plants. Higashiyama and Ueda unveiled the dynamics of the major elements of the cytoskeleton, microtubules (MTs) and actin filaments (F-actins), during the entire process of zygote polarization by using live imaging with Arabidopsis. By combining image analysis and biological experiments using specific inhibitors of the cytoskeleton, they revealed the preexisting alignment of MTs and F-actin in the egg cell is lost in fertilization. Then, they revealed that MTs organize into a transverse ring defining the zygote subapical region and driving cell outgrowth in the apical direction. In addition, they revealed F-actin forms an apical cap and longitudinal arrays, and is required to position the nucleus to the apical region of the zygote, setting the plane of the first asymmetrical division.

*(6) "Polar vacuolar distribution is essential for accurate asymmetric division of Arabidopsis zygotes", Kimata, Y., Kato, T., Higaki, T., Kurihara, D., Yamada, T., Segami, S., Morita, M. T., Maeshima, M., Hasezawa, S., Higashiyama, T., Tasaka, M., and Ueda, M. *Proc. Natl. Acad. Sci. USA* **116**, 2338 (2019).
DOI: 10.1073/pnas.1814160116

Higashiyama and Ueda revealed by live imaging that the vacuoles formed tubular strands around the apically migrating nucleus, which gradually accumulated at the basal region and filled the space, resulting in asymmetric distribution in the mature zygote. They also revealed that mutant *shoot gravitropism2* (*sgr2*), in which the vacuolar structural change was impaired, failed to form tubular vacuoles and to polarly distribute the vacuole. In *sgr2*, they further revealed that large vacuoles occupied the apical tip and thus nuclear migration was blocked, resulting in fail of asymmetrical division. Furthermore, they observed that both tubular vacuole formation and asymmetric vacuolar distribution depended on the longitudinal array of actin filaments. These results provided new insight of vacuole in asymmetric zygote division, in which its dynamics is crucial not only for the polar distribution along actin filaments but also for adequate nuclear positioning.

(7) "Competitive binding of antagonistic peptides fine-tunes stomatal patterning", Lee, J. S., Hnilova, M., Maes, M., Lin, Y. C. L., Putarjunan, A., Han, S. K., Avila, J., and Torii, K. U. *Nature* **522**, 439 (2015).
DOI: 10.1038/nature14561

The Torii group revealed in Arabidopsis that stomagen (also called EPF-LIKE9) peptide, which promotes stomatal development, requires ERECTA (ER)-family receptor kinases and interferes in the inhibition of stomatal development through interaction with epidermal patterning factor 2 (EPF2)–ER complex. They further revealed that the stomagen competitively replaced EPF2 binding to ER and induces rapid phosphorylation of downstream signaling components in vivo. Their findings demonstrated how plant receptor agonists/antagonists define inductive/inhibitory cues to fine-tune tissue patterning on the plant epidermis. As stomatal development is considered to play a key role in crop plant productivity and water-use efficiency, this study is expected to be important for understanding the productivity of plants in both natural and agricultural systems, and give a potential strategy for the control of stomatal development by small molecules.

*(8) "Overexpression of plasma membrane $H^+$-ATPase in guard cells promotes light-induced stomatal opening and enhances plant growth", Wang, T., Noguchi, K., Ono, N., Inoue, S., Terashima, I., and Kinoshita, T. *Proc. Natl. Acad. Sci. USA* **111**, 533 (2014).
DOI: 10.1073/pnas.1305438111

The Kinoshita group revealed that the transgenic Arabidopsis plants overexpressing $H^+$-ATPase using the guard cell promoter GC1 showed enhanced light-induced stomatal opening, photosynthesis, and plant growth. The transgenic plants produced larger and increased numbers of rosette leaves, with greater fresh and dry weights than the wild type. The dry weights of total flowering stems, including seeds, siliques, and flowers, also were greater than those of the wild type. In addition, stomata in the transgenic plants closed normally in response to darkness and abscisic acid. Overexpression of the other key components, phototropin or inward-rectifying $K^+$ channels, in guard cells had no effect on these phenotypes. This research outcome has gained a significant amount of attention, leading to the initiation of several academia-industry joint research and licensing of the research to agrochemical companies by using commercial cultivar (rice, maize, and rape seed).

*(9) "Plasma membrane H+-ATPase overexpression increases rice yield via simultaneous enhancement of nutrient uptake and photosynthesis," Zhang, M., Wang, Y., Chen, X., Xu, F., Ding, M., Ye, W., Kawai, Y., Toda, Y., Hayashi, Y., Suzuki, T., Zeng, H., Xiao, L., Xiao, X., Xu, J., Guo, S., Yan, F., Shen, Q., Xu, G., Kinoshita, T., and Zhu, Y. *Nature Commun.*, 12, 735 (2021).
DOI: 10.1038/s41467-021-20964-4
** Prof. Kinoshita is one of the corresponding authors in this paper.*

The Kinoshita group demonstrated that overexpression of *Oryza sativa* $H^+$-ATPase 1 (OSA1), one of PM $H^+$-ATPase isoform in rice, conferred enhancement of the grain yield in rice in collaboration with the groups of

Zhu (Nanjing Agricultural University) and Wang (Peking University, Former member of the Kinoshita group). The OSA1-overexpressing rice plants showed enhanced light-induced stomatal opening, photosynthesis, ammonium uptake in roots, and biomass in hydroponic culture in China. Their findings showed that OSA1 overexpression could contribute to enhance the rice yield (a 33% increase in grain yield) with increased both C and N acquisition (a 46% increase in nitrogen use efficacy) simultaneously by paddy rice. These results strongly indicated that overexpression of PM $H^+$-ATPase in plants is useful for enhancement of plant growth.

*(10) "Chemical hijacking of auxin signaling with an engineered auxin-TIR1 pair", Uchida, N., Takahashi, K., Iwasaki, R., Yamada, R., Yoshimura, M., Endo, T. A., Kimura, S., Zhang, H., Nomoto, M., Tada, Y., Kinoshita, T., Itami, K., Hagihara S., and Torii, K. U. *Nature Chem. Biol.* **14**, 299 (2018).
DOI: 10.1038/nchembio.2555

The groups of Torii-Uchida, Itami and Kinoshita developed that an engineered, orthogonal auxin-TIR1 receptor pair, which triggers auxin signaling without affecting endogenous auxin or TIR1/AFBs. A synthetic convex IAA (cvxIAA), designed by docking study of IAA-TIR1complex, hijacks the downstream auxin signaling in vivo both at the transcriptomic level and in specific developmental contexts, only in the presence of a complementary, concave TIR1 (ccvTIR1) receptor. Harnessing the cvxIAA-ccvTIR1 system, they provided conclusive evidence for the role of the TIR1-mediated pathway in auxin-induced seedling acid growth. The cvxIAA-ccvTIR1 system serves as a powerful tool for solving outstanding questions in auxin biology and for precise manipulation of auxin-mediated processes as a controllable switch.

(11) "The saccus vasculosus of fish is a sensor of seasonal changes in day length", Nakane, Y., Ikegami, K., Iigo, M., Ono, H., Takeda, K., Takahashi, D., Uesaka, M., Kimijima, M., Hashimoto, R., Arai, N., Suga, T., Kosuge, K., Abe, T., Maeda, R., Senga, T., Amiya, N., Azuma, T., Amano, M., Abe, H., Yamamoto, N., and Yoshimura, T. *Nature Commun.* **4**, 2018 (2013).
DOI: 10.1038/ncomms3108

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. The Yoshimura group identified the photoperiodic center in fish (masu salmon), the saccus vasculosus, which is the sensor of seasonal changes in day length. They revealed that expression of key genes, rhodopsin family genes, regulates seasonal reproduction in coronet cells of the saccus vasculosus of masu salmon. In addition, they demonstrated that an isolated saccus vasculosus has the capacity to respond to photoperiodic signals and its removal abolishes photoperiodic response of the development of gonad.

(12) "Intrinsic photosensitivity of a deep brain photoreceptor", Nakane, Y., Shimmura, T., Abe, H., and Yoshimura, T. *Curr. Biol.* **24**, R596 (2014).
DOI: 10.1016/j.cub.2014.05.038

In most mammals including humans, eyes are the exclusive photoreceptor organs. On the other hand, it has been said that vertebrates apart from mammals sense seasonal changes by receiving light directly inside their brains. The Yoshimura group revealed that in quail, novel photopigment (OPN5)-positive neurons, existing deep inside the brains, respond directly to light and regulate seasonal reproduction. They identified the neurons capable of phototransduction by whole-cell patch-clamp recordings. Separately, they carried out a siRNA knockdown experiment of OPN5 in vivo inhibits the secretion of the thyroid-stimulating hormone (TSH), so-called the 'spring hormone', which triggers breeding in birds. This is the first demonstration of the intrinsic photosensitivity of deep brain neurons in birds, may also lead to improvements in animal breeding, and provides a deeper understanding of the evolution of eyes and photoreceptors.

(13) "Dynamic plasticity in phototransduction regulates seasonal changes in color perception", Shimmura, T., Nakayama, T., Shinomiya, A., Fukamachi, S., Yasugi, M., Watanabe, E., Shimo, T., Senga, T., Nishimura, T., Tanaka, M., Kamei, Y., Naruse, K., and Yoshimura, T. *Nature Commun.* **8**, 412 (2017).
DOI: 10.1038/s41467-017-00432-8

Subsequently to the discovery of the photoperiodic center in fish and birds, the Yoshimura group revealed dynamic plasticity in phototransduction regulates seasonal changes in color perception in medaka fish. They demonstrated that medaka are active and exhibit clear phototaxis in summer conditions, but remain at the bottom of the tank and fail to exhibit phototaxis in winter ones. In addition, they demonstrated the medaka kept in summer conditions are more attracted to computer-generated orange-red-colored medaka (nuptial coloration) than medaka kept in winter conditions. Then, they revealed that the genes encoding photopigments such as opsin and their downstream pathway varies dynamically among seasons. In addition, they demonstrated photopigment-null fish showed significant differences from wild type in behavioral analysis and suggested plasticity in color perception is crucial for the emergence of seasonally regulated behaviors.

(14) "Seasonal regulation of the lncRNA *LDAIR* modulates self-protective behaviours during the breeding season", Nakayama, T., Shimmura, T., Shinomiya, A., Okimura, K., Takehana, Y., Furukawa, Y., Shimo, T., Senga, T., Nakatsukasa, M., Nishimura, T., Tanaka, M., Okubo, K., Kamei, Y., Naruse, K., and Yoshimura T. *Nature Ecol. Evol.*, **3**, 845 (2019).
DOI: 10.1038/s41559-019-0866-6

To cope with seasonal environmental changes, animals adapt their physiology and behaviour in response to photoperiod. However, the molecular mechanisms underlying these adaptive changes are not completely understood. By using genome-wide expression analysis, the Yoshimura group discovered that an uncharacterized long noncoding RNA (lncRNA), *LDAIR*, is strongly regulated by photoperiod in Japanese medaka fish (*Oryzias latipes*). They showed that numerous transcripts and signaling pathways are activated during the transition from short- to long-day conditions; however, *LDAIR* is one of the first genes to be induced and its expression shows a robust daily rhythm under long-day conditions. They revealed the *LDAIR* locus regulates a gene neighbourhood, including *corticotropin releasing hormone receptor 2*, which is involved in the stress response and *LDAIR* affects self-protective behaviours under long-day conditions, through analyses of transcriptome analysis and behavior of *LDAIR*knockout fish, respectively.

*(15) "Cell-based screen identifies a new potent and highly selective CK2 inhibitor for modulation of circadian rhythms and cancer cell growth", Oshima, T., Niwa, Y., Kuwata, K., Srivastava, A., Hyoda, T., Tsuchiya, Y., Kumagai, M., Tsuyuguchi, M., Tamaru, T., Sugiyama, A., Ono, N., Zolboot, N., Aikawa, Y., Oishi, S., Nonami, A., Arai, F., Hagihara, S., Yamaguchi, J., Tama, F., Kunisaki, Y., Yagita, K., Ikeda, M., Kinoshita, T., Kay, S. A., Itami, K., and Hirota, T. *Sci. Adv.* **5**, eaau9060 (2019).
DOI: 10.1126/sciadv.aau9060

The groups of Kay-Hirota and Itami succeeded in identifying GO289 as a lead compound, which strongly lengthened circadian period, and is a potent and selective inhibitor of CK2 with outstanding physicochemical properties. They also identified multiple phosphorylation sites inhibited by GO289 on clock proteins, including PER2 with the help of the Molecular Structure Center and Tama group. In addition, they demonstrated that GO289 exhibited selective inhibition of cancer cell growth. They further revealed the interactions between GO289 and CK2-specific residues by X-ray crystal structure of the CK2$\alpha$-GO289 complex, and revealed that GO289 does not interact with the hinge region of CK2 that is highly conserved among kinases. The discovery of well-defined GO289 provides a direct link between the circadian clock and cancer regulation, and reveals some unique design principles underlying kinase selectivity.

*(16) "Isoform-selective regulation of mammalian cryptochromes", Miller, S., Son, Y. L., Aikawa, Y., Makino, E., Nagai, Y., Srivastava, A., Oshima, T., Sugiyama, A., Hara, A., Abe, K., Hirata, K., Oishi, S., Hagihara, S., Sato, A., Tama, F., Itami, K., Kay, S. A., Hatori, M., and Hirota, T. *Nature Chem. Biol.*, **16**, 676 (2020).
DOI: 10.1038/s41589-020-0505-1

The Hirota-Kay group in collaboration with Itami and Tama groups, and Chemical Library Center discovered first-in-class isoform-selective regulators KL101 and TH301 against CRY1 and CRY2, respectively, from high throughput cell-based phenotypic screening. Using X-ray crystal structures of CRY1 and CRY2 in complex with KL101 and TH301, they revealed very high conservation of compound-interacting residues between CRY1 and CRY2, and a unique mechanism underlying compounds' selectivity in which the disordered C-terminal region outside the pocket was required for the differential effects of KL101 and TH301 against CRY isoforms. By using these isoform-selective compounds, they further discovered that both CRY1 and CRY2 enhance differentiation of brown adipocytes in culture, providing a new possibility for treatment of obesity.

*****(17) "Casein kinase 1 family regulates PRR5 and TOC1 in the Arabidopsis circadian clock", Uehara, T. N., Mizutani, Y., Kuwata, K., Hirota, T., Sato, A., Mizoi, J., Takao, S., Matsuo, H., Suzuki, T., Ito, S., Saito, A. N., Ohkawa, T. N., Shinozaki, K. Y., Yoshimura, T., Kay, S. A., Itami, K., Kinoshita, T., Yamaguchi, J., and Nakamichi, N. *Proc. Natl. Acad. Sci. USA,* **116**, 11528 (2019).
DOI: 10.1073/pnas.1903357116

Nakamichi (Kinoshita group) identified that an animal CDC7/CDK9 inhibitor, PHA767491, lengthens the *Arabidopsis* circadian period and this molecule inhibits multiple CKL proteins rather than CDC7/CDK9 homologs by affinity proteomics in collaboration with the groups of Itami, Hirota-Kay, and Yanai, and the Chemical Library Center and Molecular Structure Center. They revealed that PHA767491 treatment induced accumulation of CKL4 phosphorylated transcriptional repressors PRR5 and TOC1, accompanied by decreasing expression of PRR5- and TOC1-target genes, and, as a result, lengthened the circadian period in plants

*(18) "A Phosphole Oxide Based Fluorescent Dye with Exceptional Resistance to Photobleaching: A Practical Tool for Continuous Imaging in STED Microscopy", Wang, C., Fukazawa, A., Taki, M., Sato, Y., Higashiyama, T., and Yamaguchi, S. *Angew. Chem. Int. Ed.* **54**, 15213 (2015).
DOI: 10.1002/anie.201507939

The Yamaguchi group has developed the outstanding photostable fluorescent dye C-Naphox (diaryl-methylene bridged **na**phtho**ph**osphole P-**ox**ide) and reported several distinct advantages relative to conventional probes, such as intense fluorescence emission by the combination of an electron-donating group (diphenylamino moiety) with an electron-accepting group (the core structure of C-Naphox), high quantum yields, large Stokes shift, and solvent polarity sensitivity (environment-responsiveness) in collaboration with the Higashiyama group and the Line Imaging Center. They demonstrated that almost all (99.5%) of C-Naphox remained intact even after irradiation with a Xe lamp for 12 hours although representative STED imaging probes significantly diminished their fluorescence intensities under the same conditions. In addition, they applied C-Naphox into repeated STED imaging of HeLa cells and recorded 83% of the initial fluorescence intensity of C-Naphox persisted even after recording 50 STED images.

*(19) "Super-Photostable Phosphole-Based Dye for Multiple-Acquisition Stimulated Emission Depletion Imaging", Wang, C., Taki, M., Sato, Y., Fukazawa, A., Higashiyama, T., and Yamaguchi, S. *J. Am. Chem. Soc.* **139**, 10374 (2017).
DOI: 10.1021/jacs.7b04418

C-Naphox still has drawbacks for practical use in bio-imaging, i.e. water insolubility, target selectivity, and

polarity-sensitivity fluorescence. The groups of Yamaguchi and Higashiyama, and the Live Imaging Center succeeded in developing a new super-photostable dye, PhoxBright 430 (PB430). They revealed that PB430 also has high solubility in water, and is capable of labeling proteins with maintaining high fluorescence quantum yields. This dye also exhibits outstanding resistance to photoirradiation even under the STED conditions and allows continuous acquisition of STED images. Indeed, using a PB430-conjugated antibody, they succeed in creating a 3-D reconstruction of super-resolution STED images as well as photostability-based multicolor STED imaging of fluorescently labeled cytoskeletal structures.

*(20) "A Highly Photostable Near-Infrared Labeling Agent Based on a Phospha-rhodamine for Long-Term and Deep Imaging", Grzybowski, M., Taki, M., Senda, K., Sato, Y., Ariyoshi, T., Okada, Y., Kawakami, K., Imamura, T., and Yamaguchi, S. *Angew. Chem. Int. Ed.* **57**, 10137 (2018).
DOI: 10.1002/anie.201804731

The Yamaguchi group and the Live Imaging Center also developed a highly photostable and water-soluble near-infrared phosphorus-substituted rhodamine, PREX 710. By the nature of membrane permeability and localization in the mitochondoria, they demonstrated that PREX 710 can be used to stain mitochondria in living cells, which allowed long-term and multi-color imaging in the vis-NIR range. Moreover, they showed the high fluorescence longevity of PREX 710 by tracking a dye-labeled biomolecule (IgG, NeutrAvidin) by single-molecule microscopy under physiological conditions. Furthermore, they achieved deep imaging of blood vessels in mice brain using the bright NIR emitting PREX 710-dextran conjugate.

*(21) "A photostable fluorescent marker for the superresolution live imaging of the dynamic structure of the mitochondrial cristae", Wang, C., Taki, M., Sato, Y., Tamura, Y., Yaginuma, H., Okada, Y., and Yamaguchi, S. *Proc. Natl. Acad. Sci. USA*, **116**, 15817 (2019).
DOI: 10.1073/pnas.1905924116

The Yamaguchi group developed an outstandingly photostable fluorescent dye with a long lifetime, MitoPB Yellow, which enabled the visualization of nano-scale dynamics of mitochondrial cristae in living cells (with the Live Imaging Center, RIKEN, and WPI-IRCN of U. Tokyo). By taking advantage of the exceptionally high photochemical prperties of MitoPB Yellow, they achieved the first ever monitoring of a rapid inter-cristae mergence in a single mitochondrion and the inner-membrane fusion in the inter-mitochondria interaction was monitored for the first time. The MitoPB Yelow gives information on the dynamic ultrastructures such as the intermembrane fusion in different mitochondria as well as the intercristae mergence in a single mitochondrion during the apoptosis-like mitochondrial swelling process.

*(22) "ClearSee: a rapid optical clearing reagent for whole-plant fluorescence imaging", Kurihara, D., Mizuta, Y., Sato, Y., and Higashiyama, T. *Development* **142**, 4168 (2015).
DOI: doi:10.1242/dev.127613

The Higashiyama group and Live Imaging Center developed a clearing method using chemical solutions, ClearSee, for deep imaging of morphology and gene expression in plant tissues. ClearSee rapidly diminishes chlorophyll autofluorescence while maintaining fluorescent protein stability. They demonstrated whole-organ and whole-plant imaging in both confocal and two-photon excitation microscopy by using ClearSee-treated samples. In addition, they showed that ClearSee is applicable to multicolor imaging of fluorescent proteins to allow structural analysis of multiple gene expression. ClearSee is expected to be useful not only for deep imaging in conjunction with genetic markers and for plant species not amenable to transgenic approaches but also for whole imaging for intact morphology, and accelerate the discovery of new phenomena in plant biological research.

(23) "Ligand-enabled multiple absolute stereocontrol in metal-catalysed cycloaddition for construction of contiguous all-carbon quaternary stereocentres", Ohmatsu, K., Imagawa, N., and Ooi, T. *Nature Chem.* **6**, 47 (2013).
DOI: 10.1038/NCHEM.1796

The development of a general catalytic method for the stereoselective construction of contiguous all-carbon quaternary stereocenters in a single synthetic operation remains a formidable challenge. The Ooi group has developed a catalytic system to establish stereocenters of contiguous quaternary carbons with a high enantio- and diastereoselective [3+2] annulation reaction. This reaction is catalyzed by a palladium complex bearing a novel phosphine ligand and a chiral ammonium salt, which enables the single-step construction of three contiguous stereocenters, including vicinal all-carbon quaternary stereocenters. 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 pyrrolidines.

(24) "Complete diastereodivergence in asymmetric 1,6-addition reactions enabled by minimal modification of a chiral catalyst", Uraguchi, D., Yoshioka, K., and Ooi, T. *Nature Commun*. **8**, 14793 (2017).
DOI: 10.1038/ncomms14793

The development of a catalytic process capable of producing each and all of those stereoisomers from the same starting materials (diastereodivergent catalysis) poses a formidable challenge. The Ooi group established a catalyst-directed pinpoint inversion of diastereochemical preference in the 1,6-addition of azlactones to δ-aryl dienyl carbonyl compounds with full control over other selectivities preserved. This rigorous diastereodivergence was enabled by the slight structural adjustment of a chiral iminophosphorane catalyst developed by themselves, providing access to all the stereoisomers with high regio-, distereo- and enantioselectivity. They demonstrated the utility of this method in the facile stereodivergent preparation of densely functionalized proline derivatives. In addition, they elucidated experimentally and computationally the origin of the diastereodivergence.

(25) "Direct allylic C–H alkylation of enol silyl ethers enabled by photoredox–Brønsted base hybrid catalysis", Ohmatsu, K., Nakashima, T., Sato, M., and Ooi, T. *Nature Commun.* **10**, 2706 (2019).
DOI: 10.1038/s41467-019-10641-y

Enol silyl ethers, versatile enolate equivalents, are known to undergo one-electron oxidation to generate the radical cations that spontaneously form electrophilic α-carbonyl radicals via elimination of the silyl groups. The Ooi group has developed a strategy for the allylic C–H alkylation of enol silyl ethers, which relies on the combined use of appropriate photoredox and Brønsted base catalysts for the generation of requisite allylic radicals while suppressing undesired desilylation process. With the hybrid catalysis, a series of enol silyl ethers smoothly react with electron-deficient olefins to give the corresponding functionalized enol silyl ethers. This operationally simple protocol, in concert with the ready availability of enol silyl ethers and their conventional polar reactivity, provides rapid and reliable access to an array of complex carbonyl compounds and will find widespread use among practitioners of organic synthesis.

(26) "Iterative protecting group-free cross-coupling leading to chiral multiply arylated structures", Crudden, C. M., Ziebenhaus, C., Rygus, J. P. G., Ghozati, K., Unsworth, P. J., Nambo, M., Voth, S., Hutchinson, M., Laberge, V. S., Maekawa Y., and Imao, D. *Nature Commun.* **7**, 11065 (2016).
DOI: 10.1038/ncomms11065

The Crudden group made significant advance in cross-coupling chemistry, in which multiply functionalized

chiral cross-coupling partners can be employed in iterative coupling without the use of protecting groups. Through extensive investigation on the reaction conditions, they identified that the orthogonal reactivity of boron-carbon bonds in different positions in a single molecule permits the chemoselective, sequential coupling of aromatic, aliphatic and stereochemistry-bearing B–C bonds. This method permits the rapid generation of multiply arylated, chiral organic molecules with control of stereochemistry, without the need for protection/deprotection sequences. The approach is expected to be the preparation of chiral enantioenriched compounds, which are likely to provide interesting lead compounds for pharmaceutical and medicinal applications, by escaping from 'flatland'.

*(27) "Modular synthesis of α-fluorinated arylmethanes via desulfonylative cross-coupling", Nambo, M., Yim, J. C. H., Freitas, L. B. O., Tahara, Y., Ariki, Z. T., Maekawa, Y., Yokogawa, D., and Crudden, C. M. *Nature Commun.* **10**, 4528 (2019).
DOI: 10.1038/s41467-019-11758-w

α-Fluoromethylarenes are common substructures in pharmaceuticals and agrochemicals, with the introduction of fluorine often resulting in improved biological activity and stability. Despite recent progress, synthetic routes to α-fluorinated diarylmethanes are still rare. They developed the Pd-catalyzed Suzuki-Miyaura cross-coupling of α-fluorinated benzylic triflones with arylboronic acids affording structurally diverse α-fluorinated diarylmethanes through carbon–sulfonyl ($C–SO_2$) bond activation to provide medicinally important fluoromethyl- and difluoromethylarenes in good yields. The ability to convert aromatic methyl groups to reactive sulfones is particularly exciting for late-stage functionalization approaches to the synthesis of fluorinated analogs of biomolecules. These reactions not only provide facile access to α-fluorinated arylmethanes from stable and readily available reagents, but also open up avenues for the development of unexplored fluorinated molecules.

(28) "Synthetic fermentation of bioactive non-ribosomal peptides without organisms, enzymes or reagents", Huang, Y. L., and Bode, J. W. *Nature Chem*. **6**, 877 (2014).
DOI: 10.1038/NCHEM.2048

Microbial fermentation can rapidly provide potent molecules as a mixture that can be easily screened based on biological activity, and then the active components can be isolated. Its success in drug discovery has inspired extensive efforts to modulate and control the products. The Bode group has discovered and developed a bio-mimetic peptide ligation reaction, known as the KAHA ligation (JACS. 2006). This reaction proceeds without additional organisms, enzymes, and reagents, and can be used to synthesize a number of peptides/proteins in water. They applied this KAHA ligation into a microbial fermentation process, named "synthetic fermentation", and succeeded in demonstrating that bioactive, unnatural peptides can be grown from a mixture of amino acid building blocks in water. As a proof-of-concept, they identified a hepatitis C virus NS3/4A protease inhibitor (IC50 = 1.0 μM) among c.a. 6,000 unnatural peptides produced from just 23 amino acid building blocks.

(29) "An oxazetidine amino acid for chemical protein synthesis by rapid, serine-forming ligations", Pusterla, I., and Bode, J. W. *Nature Chem.* **7**, 668 (2015).
DOI: 10.1038/NCHEM.2282

The KAHA ligation, developed by the Bode group, has proven to be remarkably robust, but has limitations including the introduction of a non-canonical homoserine residue at the ligation site, and a preference for relatively high concentrations (10-20 mM) and temperatures (50-60 °C). They reported the synthesis of an N-terminus protected oxazetidine as a canonical serine precursor for use in the KAHA ligation and demonstrated, when incorporated at the N-terminus of a peptide segment, that the four-membered

oxazitidine can be used for rapid serine-forming ligations with C-terminus of peptide. In addition, they demonstrated this ligation operates at lower concentration (100 μM-5 mM) and milder temperatures (20-25 °C). The utility of the reaction was demonstrated by the synthesis of S100A4, a 12 kDa calcium-binding protein that is not easily accessible by the conventional methods, such as native chemical ligation (NCL) or other amide forming reactions.

*(30) "Chemical Synthesis of Atomically Tailored SUMO E2 Conjugating Enzymes for the Formation of Covalently Linked SUMO−E2−E3 Ligase Ternary Complexes", Zhang, Y., Hirota, T., Kuwata, K., Oishi, S., Gramani, S. G., and Bode, J. W. *J. Am. Chem. Soc.* **141**, 14742 (2019).
DOI: 10.1021/jacs.9b06820

The Bode-Oishi group achieved the synthesis of atomically tailored variants of the SUMO conjugating enzyme Ubc9, and demonstrated that the selective formation of Ubc9–SUMO conjugates and the trapping of an E3 ligase (RanBP2) to form the stable, covalently linked SUMO1–Ubc9–RanBP2 ternary complexes with the Hirota-Kay group and Molecular Structure Center. This strategy should be applicable to the synthesis of other E2−Ub/Ubl conjugates, as most E2 ligases are <200 residues and have a conserved catalytic Cys that could be simply replaced to Dap (2,3-diaminopropionic acid) by chemical synthesis. Having now established an effective route, confirmed that the Ubc9−SUMO conjugate can be readily formed under endogenous SUMOylation conditions, and demonstrated selective trapping of an E3 ligase with an appropriately placed photoaffinity tag, we will pursue the identification of new E3 ligases. The powerful combination of ligation methods including KAHA ligation the Bode group discovered and developed will enable chemical probes based on E2 conjugating enzymes to trap E3 ligases and facilitate the synthesis of other protein classes

(31) "Simple direct formation of self-assembled N-heterocyclic carbene monolayers on gold and their application in biosensing", Crudden, C. M., Horton, J. H., Narouz, M. R., Li, Z., Smith, C. A., Munro, K., Baddeley, C. J., Larrea, C. R., Drevniok, B., Thanabalasingam, B., McLean, A. B., Zenkina, O. V., Ebralidze, I. I., She, Z., Kraatz, H. B., Mosey, N. J., Saunders, L. N., and Yagi, A. *Nature Commun.* **7**. 12654 (2016).
DOI: 10.1038/ncomms12654

The formation of organic films on gold employing ***N*-h**eterocyclic **c**arbenes (NHCs) has been previously shown to be a useful strategy for generating stable organic films. However, NHCs or NHC precursors typically require inert atmosphere and harsh conditions for their generation and use. The Crudden group has developed a simple direct method to form self-assembled NHC monolayers on gold. Using the bench-stable benzimidzolium hydrogen carbonate as a replacement for conventional air-sensitive NHCs or NHC precursors, NHC films were able to be prepared much more easily in solution or by vapor-phase deposition from the solid state. They applied these materials into surface plasmon resonance (SPR)-type biosensing and revealed that NHC-based films provide specific physicochemical durability, such as thermal stability and stability in extreme pH, versus conventional thiol-based ones.

*(32) "*N*-Heterocyclic carbene-functionalized magic-number gold nanoclusters" Narouz, M. R., Osten, K. M., Unsworth, P. J., Man, R. W. Y., Salorinne, K., Takano, S., Tomiharam R., Kaappa, S., Malola, S., Dinh, C. T., Padmos, J. D., Ayoo, K., Garrett, P. J., Nambo, M., Horton, J. H., Sargent, E. H., Häkkinen, H., Tsukuda, T., and Crudden, C. M. *Nature Chem.* **11**, 419 (2019).
DOI: 10.1038/s41557-019-0246-5

Magic-number gold nanoclusters are atomically precise nanomaterials that have enabled unprecedented insight into structure–property relationships in nanoscience. Thiolates are the most common ligand, binding to the cluster via a staple motif in which only central gold atoms are in the metallic state. The lack of other strongly bound ligands for nanoclusters with different binding modes has been a significant limitation in the

field. The Crudden group reported a previously unknown ligand for gold(0) nanoclusters, *N*-heterocyclic carbenes (NHCs), which feature a robust metal–carbon single bond and impart high stability to the corresponding gold cluster. They demonstrated that the addition of a single NHC to gold nanoclusters resulted in significantly improved stability and catalytic properties in the electrocatalytic reduction of CO2, and revealed the performance of these clusters in electrocatalytic CO2 reduction correlated with cluster stability, with the most stable cluster having the *highest* Faradaic efficiency, catalytic activity and current density.

(33) "Initiation of carbon nanotube growth by well-defined carbon nanorings", Omachi, H., Nakayama, T., Takahashi, E., Segawa, Y., and Itami, K. *Nature Chem*. **5**, 572 (2013).
DOI: 10.1038/NCHEM.1655

Currently, carbon nanotubes (CNTs) can only be produced as mixtures with regard to diameter and sidewall structure. Given that the electronic properties of CNTs are primarily determined by the sidewall structures, structural uniformity is critically important for CNT-based electronics and biology. The Itami group succeeded in the first diameter-selective synthesis of CNTs using carbon nanorings as templates. This method is extremely simple; it only involves reacting ethanol (as a carbon source) at 500 °C with carbon nanorings coated onto a sapphire substrate. The diameter of the nanoring template, which can be controlled using Itami's method, determines the diameter of the final CNT. A range of carbon nanorings of varying sizes is also commercially available, thus encouraging others to explore the bottom-up synthesis of CNTs.

(34) "Synthesis of a Carbon Nanobelt", Povie, G., Segawa, Y., Nishihara, T., Miyauchi, Y., and Itami, K. *Science* **356**, 172 (2017).
DOI: 10.1126/science.aam8158

The Itami group achieved the first synthesis of a carbon nanobelt - a long-sought-after ultra-short CNT. The synthesis of these highly strained, belt-shaped aromatic compounds had been one of the most difficult problems in chemistry for the last 60 years (even before the discovery of CNTs). Itami synthesized the carbon nanobelt through iterative Wittig reactions followed by a nickel-mediated aryl-aryl coupling reaction. The cylindrical shape of its belt structure was confirmed by X-ray crystallography, and its fundamental optoelectronic properties were elucidated by ultraviolet-visible absorption, fluorescence, and Raman spectroscopic studies. This achievement is both an experimental tour de force and a triumph of synthetic chemistry. Itami's carbon nanobelt, which can be synthesized from *p*-xylene (petroleum feedstock), was commercialized in 2018, thereby accelerating the discovery of extraordinary properties, functions, and applications.

(35) "Synthesis of a zigzag carbon nanobelt", Cheung, K. Y., Watanabe, K., Segawa, Y., and Itami, K. *Nature Chem.* **13**, 255 (2021).
DOI: 10.1038/s41557-020-00627-5

The structure-selective precise synthesis of carbon nanotubes (CNTs) has been long sought in materials science. The aromatic molecules corresponding to segment structures of CNTs, that is, carbon nanobelts (CNBs), are of interest as templates for CNT growth. Among the three types of CNB (armchair, chiral and zigzag CNBs), zigzag CNBs have been considered the most difficult type to synthesize.
The Itami group achieved the synthesis, isolation and structural characterization of a zigzag CNB. As predicted by theoretical calculations, they showed this CNB was isolated as a stable compound. In addition, they characterized the structure of the zigzag CNB by X-ray crystallography and found its wide energy gap with blue fluorescence properties by photophysical measurements. With synthetic strategies towards all three types of CNB in hand, the road to the precise synthesis of CNTs can now proceed to the next stage.

(36) "A grossly warped nanographene and the consequences of multiple odd-membered-ring defects", Kawasumi, K., Zhang, Q., Segawa, Y., Scott, L. T., and Itami, K. *Nature Chem*. **5**, 739 (2013).
DOI: 10.1038/NCHEM.1704

The Itami group has also created completely novel, topologically unique nanocarbons. Aside from theoretical studies that predict interesting properties for these types of species, three-dimensionally curved nanocarbons are a virtually unexplored group of materials. They accomplished the synthesis of a novel warped nanographene (WNG) containing both positive and negative curvatures on its π-surface. A WNG ($C_{80}H_{30}$) that incorporates five 7-membered rings and one 5-membered ring embedded in a hexagonal lattice has been synthesized by stepwise chemical methods using Itami's original C-H activation catalyst. Its grossly warped structure is revealed by single crystal X-ray crystallography. WNG is unique and clearly distinct from any other existing nanocarbon. As WNG is also commercially available, many academic research groups and industries are now using WNG as a key molecule in optoelectronic devices and biology.

*(37) "Topological molecular nanocarbons: All-benzene catenane and trefoil knot", Segawa, Y., Kuwayama, M., Hijikata, Y., Fushimi, M., Nishihara, T., Pirillo, J., Shirasaki, J., Kubota, N., and Itami, K. *Science* **365**, 272 (2019).
DOI: 10.1126/science.aav5021

Through extensive campaign of the syntheses of structurally unique nanocarbons, the Itami groups achieved the syntheses of all-benzene catenane and trefoil knot consisting solely of para-connected benzene rings. They observed their characteristic fluorescence associated with fast energy transfer between two aromatic rings, confirmed the topological chirality of the all-benzene knot by enantiomer separation and circular dichroism spectroscopy, revealed all-benzene knot has rapid vortex-like motion in solution even at –95°C. In collaboration with Dr. Hijikata (WPI-ICReDD, former Co-PI of the Irle group), this interesting dynamic behavior of the knot was theoretically predicted and could stimulate deeper understanding and applications of these previously untapped classes of topological molecular nanocarbons.

(38) "Broad-spectrum resistance to bacterial blight in rice using genome editing", Oliva, R., Ji, C., Atienza-Grande, G., Huguet-Tapia, J. C., Perez-Quintero, A., Li, T., Eom, J. S., Li, C., Nguyen, H., Liu, B., Auguy, F., Scillano, C., Luu, V. T., Dossa, G. S., Cunnac, S., Schmidt, S. M., Slamet-Loedin, I. H., Cruz, C. V., Szurek, B., Frommer, W. B., White, F. F., and Yang, B. *Nature Biotechnol.* **37**, 1344 (2019).
DOI: 10.1038/s41587-019-0267-z
** Prof. Frommer is one of the corresponding authors in the paper.*

Rice bacterial blight is a deadly disease that has been widely spread in Asia and Africa. The pathogen, *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), secretes one or more of six known transcription-activator-like effectors (TALes) that bind specific promoter sequences and induce, at minimum, one of the three host sucrose transporter genes *SWEET11*, *SWEET13* and *SWEET14*, the expression of which is required for disease susceptibility. The Frommer group used CRISPR–Cas9-mediated genome editing to introduce mutations in all three *SWEET* gene promoters, performed sequence analyses of TALe genes in *Xoo* strains, and revealed multiple TALe variants for *SWEET13* and *14* alleles. They created a total of five promoter mutations simultaneously introduced into the rice line Kitaake and the elite mega varieties IR64 and Ciherang-Sub1. They demonstrated genome-edited *SWEET* promoters endow rice lines with robustness and broad-spectrum bactericidal resistance in the paddy field.

(39) "Diagnostic kit for rice blight resistance", Eom, J. S., Luo, D., Atienza-Grande, G., Yang, J., Ji, C., Luu, V. T., Huguet-Tapia, J. C., Char, S. N., Liu, B., Nguyen, H., Schmist, S. M., Szurek, B., Cruz, C. V., White, F.

F., Oliva, R., Yang, B., and Frommer, W. B. *Nature Biotechnol.* **37**, 1372 (2019).
DOI: 10.1038/ s41587-019-0268-y

The TALes, key regulators of the rice bacterial blight, bind to effector-binding elements (EBEs) in *SWEET* gene promoters and induce *SWEET* genes. EBE variants that cannot be recognized by TALes abrogate induction, causing resistance. The Frommer group succeeded in developing a diagnostic kit to enable analysis of bacterial blight in the field and identification of suitable resistant lines. Specifically, they include a *SWEET* promoter database, RT–PCR primers for detecting *SWEET* induction, engineered reporter rice lines to visualize SWEET protein accumulation and knock-out rice lines to identify virulence mechanisms in bacterial isolates. They also developed CRISPR–Cas9 genome-edited Kitaake rice to evaluate the efficacy of EBE mutations in resistance, software to predict the optimal resistance gene set for a specific region, and two resistant 'mega' rice lines that are most likely to resist rice blight. This diagnostic kit to enable breeders, crop management teams and farmers to reduce the effect of bacterial blight on rice yields worldwide.

*(40) "Sulfamoyl Heteroarylcarboxylic Acids as Promising Metallo-b-Lactamase Inhibitors for Controlling Bacterial Carbapenem Resistance", Wachino, J., Jin, W., Kimura, K., Kurosaki, H., Sato, A., and Arakawa, Y. *mBio* 11, e03144 (2020).
DOI: 10.1128/mBio .03144-19
Strains that express class-B metallo-b-lactamases (MBLs) are reported to be able to resist not only b-lactam antibiotics but also most existing anti-microbial drugs. Development/identification of metallo-b-lactamase is considered the urgent need and small molecules that inhibit metallo-b-lactamases are expected to be new possibilities for treatment, control the spread infection of them, and suppress global threat of infectious diseases. The Chemical Library Center succeeded in identifying a molecule, SHCs, that can competitively inhibit the globally spreading and clinically relevant MBLs (IMP-1, NMD-1, and VIM-2). They demonstrated that the addition of SHCs restored meropenem efficacy against MBL-producing *Enterobacteriaceae* to satisfactory clinical levels and combination therapy successfully cured mice infected with MBLs producing *E. coli* and clinically isolated *Klebsiella pneumoniae*. They revealed the mode of action of SHCs against MBLs by X-ray crystallographic analyses, low toxicity of SHCs in cell lines and mice, and high metabolic stability.

# Appendix 1-2 List of Papers of Representative of Interdisciplinary Research Activities

* List **up to 20 papers** 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) "Probing strigolactone receptors in *Striga hermonthica* with fluorescence", Tsuchiya, Y., Yoshimura, M., Sato Y., Kuwata, K., Toh, S., Holbrook-Smith, D., Zhang, H., McCourt, P., Itami, K., Kinoshita, T., and Hagihara, S. *Science* **349**, 864 (2015).
DOI: 10.1126/science.aab3831.Yoshimulactone

A molecular approach has been used to identify the protein responsible for germination of *Striga* seeds by green fluorescence. *Striga*, a parasitic plant known as witchweed, has seriously affected millions of hectares of the 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 understood up to now. In a new study reported in *Science*, ITbM chemists (**Itami group**) and biologist (**Kinoshita group**) and their team have come together to develop a fluorescent molecule "Yoshimulactone" Green (YLG) 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.

(2) "A femto-molar range suicide germination stimulant for the parasitic plant *Striga hermonthica*", Uraguchi, D., Kuwata, K., Hijikata, Y., Yamaguchi, R., Imaizumi, H., Sathiyanarayanan, A. M., Rakers, C., Mori, M., Akiyama, K., Irle, S., McCourt, P., Kinoshita, T., Ooi, T., and Tsuchiya, Y. *Science* **362**, 1301 (2018).
DOI: 10.1126/science.aau5445

ITbM chemists (**Ooi group**), biologist (**Kinoshita group**), theoretical sciences group (**Irle group**), and the **Molecular Structure Center** have also developed *Striga* germinator sphynolactone-7 (SPL7). SPL7 has two functional modules, which cooperatively acted on the specific strigolactone receptor, and activated it with a high-affinity to provoke *Striga* germination with potency in the *femtomolar* ($10^{-15}$ molar) range. The SPL7 is effective for reducing *Striga* parasitism on practical crop (maize) without impinging on host strigolactone-related processes even though synthetic SL agonist GR24 showed multiple actions to plant because of pan-agonist of ShHTLs. The discovery of SPL7 gets all ITbM scientists motivated to tackle the issue of *Striga* by practical use of SPL7 in near future in the field of Kenya, Africa.

(3) "Discovery of shoot branching regulator targeting strigolactone receptor DWARF14", Yoshimura, M., Sato, A., Kuwata, K., Inukai, Y., Kinoshita, T., Itami, K., Tsuchiya, Y., and Hagihara, S. *ACS Cent. Sci.* **4**, 230 (2018).
DOI: 10.1021/acscentsci.7b00554

DWARF14 (D14) is a strigolactone receptor that plays a central role in suppression of shoot branching, and hence is a potential target to increase crop productions and biomass. The groups of **Itami** and **Kinoshita**, and the **Chemical Library Center** succeeded in identifying SL receptor agonists/antagonists from ITbM chemical library by using the Yoshimulactone, and among them, they revealed that a novel small molecule DL1 acts as a potent antagonist of D14-type strigolactone receptors They revealed that DL1 competes with endogenous strigolactones, thereby increasing the number of shoot branching in a model plant Arabidopsis as well as in rice. Thus, DL1 is expected to be useful not only as a tool to understand the biological roles of D14 receptors in plant growth and development, but also as a potent agrochemical to improve the crop yield.

(4) "Cell-cell adhesion in plant grafting is facilitated by b-1,4-glucanases", Notaguchi, M., Kurotani, K., Sato, Y., Tabata, R., Kawakatsu, Y., Okayasu, K., Sawai, Y., Okada, R., Asahina, M., Ichihashi, Y., Shirasu, K., Suzuki, T., Niwa, M., and Higashiyama, T. *Science* **369**, 698 (2020).
DOI: 10.1126/science.abc3710

Plant grafting is conducted for fruit and vegetable propagation, whereby a piece of living tissue is attached to another through cell-cell adhesion. However, graft compatibility limits combinations to closely related species, and the mechanism is poorly understood. **Notaguchi** and **Higashiyama** found that Nicotiana is capable of graft adhesion with a diverse range of angiosperms with the **Live Imaging Center**. Comparative transcriptomic analyses on graft combinations indicated that a subclade of b-1,4-glucanases secreted into the extracellular region facilitates cell wall reconstruction near the graft interface. Grafting was promoted by overexpression of the b-1,4-glucanase. Using Nicotiana stem as an intercision, they produced tomato fruits on rootstocks from other plant families. These findings demonstrate that the process of cell-cell adhesion is a potential target to enhance plant grafting techniques.

(5) "Bipartite anchoring of SCREAM enforces stomatal initiation by coupling MAP kinases to SPEECHLESS", Putarjunan, A., Ruble, J., Srivastava, A., Zhao, C., Rychel, A. L., Hofstetter, A. K., Tang, X., Zhu, J. K., Tama, F., Zheng, N., and Torii, K. U. *Nature Plants* **5**, 742 (2019).
DOI: 10.1038/s41477-019-0440-x

**The groups of Torii-Uchida** and **Tama** revealed that the basic helix-loop-helix protein SCREAM that recruits MPK3/6 to downregulate SPEECHLESS, a transcription factor that initiates stomatal cell lineages. They identified SCREAM directly binds to MPK3/6 through an evolutionarily conserved, yet unconventional, bipartite motif and mutations in this motif abrogate association, phosphorylation and degradation of SCREAM, unmask hidden non-redundancies between MPK3 and MPK6, and result in uncontrolled stomatal differentiation. Structural analyses of MPK6 showed bipartite binding of SCREAM to MPK6 that is distinct from an upstream MAPKK. Their findings elucidate, at the atomic resolution, the mechanism that directly links extrinsic signals to transcriptional reprogramming during the establishment of stomatal cell fate, and highlight a unique substrate-binding mode adopted by plant MAPKs.

(6) "Discovery of synthetic small molecules that enhance the number of stomata: C-H functionalization chemistry for plant biology", Ziadi, A., Uchida, N., Kato, H., Hisamatsu, R., Sato, A., Hagihara, S., Itami, K., and Torii, K. U. *Chem. Commun.* **53**, 9632 (2017).
DOI: 10.1039/c7cc04526c

The **Torii-Uchida group** has explored small molecules that enhanced the density and/or patterning of stomata through chemical screening. They succeeded in identifying the first-in-class synthetic molecules enhancing the number of stomata in *Arabidopsis thaliana* with the **Itami group** and the **Chemical library Center**. Several promising lead compounds have further been optimized through structure-activity relationship study of hit compounds by using C–H functionalization reactions at late stage of the synthesis. In addition, some compounds could promote root growth in various plant species such as *Arabidopsis thaliana* as well as edible plants (cucumber, lettuce, etc.). These results motivated them to initiate not only stomatal (chemical) biology as basic research but also develop academia-industry collaboration towards practical use of molecules in the field.

(7) "Identification and characterization of compounds that affect stomatal movements", Toh, S., Inoue, S., Toda, Y., Yuki, T., Suzuki, K., Hamamoto, S., Fukatsu, K., Aoki, S., Uchida, M., Asai, E., Uozumi, N., Sato, A., and Kinoshita, T. *Plant Cell Physiol.* **59**, 1568 (2018).
DOI:10.1093/pcp/pcy061

The **Kinoshita group** and **Chemical Library Center** have been screened more than 30,000 molecules from various chemical libraries to identify compounds that affect stomatal movements (opening/closing) in *Commelina benghalensis* and characterized the underlying their molecular mechanisms. They further revealed that the **s**tomatal **cl**osing compounds (SCLs) suppressed blue light-induced phosphorylation of PM $H^+$-ATPase for stomatal opening and had no negative effect on ABA-dependent responses including seed germination and expression of ABA-induced genes. In addition, they demonstrated that SCLs prevented plant leaves from drying-up and suppress withering when sprayed onto the plants (both of dicot (Chinese cabbage and rose) and monocot (oat) plants).

(8) "Cryptic bioactivity capacitated by synthetic hybrid plant peptides", Hirakawa, Y., Shinohara, H., Welke, K., Irle, S., Matsubayashi, Y., Torii, K. U., and Uchida, N. *Nat. Commun.* **8**, 14318 (2016). DOI: 10.1038/ncomms14318

The groups of **Torii-Uchida** and **computational sciences group (Irle)** focused on the two plant peptide hormones, CLV3 and CLE25, which have root shortening activity. On the other hand, amino acid sequence homolog CLE41 peptide promotes the stem cell activity in the vascular meristem without affecting root / shoot stem cells. Through systematic swapping the amino acid sequences of CLV3 and CLE25, they succeeded in creating a novel synthetic bifunctional peptide, KIN, that exhibits vascular-thickening function as well as the original root-shortening function. They also exhibited computationally that KIN peptide binds to both CLV1 and TDR, receptors for CLV3/CLE25 and TDIF/CLE25, respectively. This result indicated that it could be possible to create novel synthetic plant peptide hormones even if the structural basis of the specificity between ligands and receptor has not been fully understood.

(9) "Identification of circadian clock modulators from existing drugs", Tamai, T. K., Nakane, Y., Ota, W., Kobayashi, A., Ishiguro, M., Kadofusa, N., Ikegami, K., Yagita, K., Shigeyoshi, Y., Sudo, M., Nishiwaki-Ohkawa, T., Sato, A., and Yoshimura, T. *EMBO Mol. Med.* **10**, e8724 (2018) DOI 10**.**15252/emmm.201708724

Using drug-repurposing approach, the **Yoshimura group** and the **Chemical Library Center** performed a high-throughput chemical screening of existing drugs and have identified circadian clock modulators in human U2OS cells (drug repositioning). They identified that approximately 5% of the drugs screened altered circadian period, including the period-shortening compound dehydroepiandrosterone (DHEA; also known as prasterone). They demonstrated that dietary administration of DHEA to mice accelerates re-entrainment to advanced light–dark (LD) cycles, thereby reducing jet-lag. Their drug screening also revealed the involvement of tyrosine kinases, ABL1 and ABL2, and the BCR serine/threonine kinase in regulating circadian period. They concluded that drug repositioning is a useful approach to identify new circadian clock modulators and potential therapies for circadian disorders.

(10) "Seasonal changes in NRF2 antioxidant pathway regulates winter depression-like behavior", Nakayama, T., Okimura, K., Shen, J., Guh, Y. J., Tamai, K., Shimada, A., Minou, S., Okushi, Y., Shimmura, T., Furukawa, Y., Kadofusa, N., Sato, A., Nishimura, T., Tanaka, M., Nakayama, K., Shiina, N., Yamamoto, N., Loudon, A. S., Ohkawa, T. N., Shinomiya, A., Nabeshima, T., Nakane, Y., and Yoshimura, T. *Proc. Natl. Acad. Sci. USA* **117**, 9594 (2020). DOI: 10.1073/pnas.2000278117

The **Yoshimura group** succeeded in the identification of molecule that regulate seasonal clock. They revealed that whole brain metabolomic analysis of medaka kept in winter conditions revealed seasonal changes in 68 metabolites associated with depression, transcriptome analysis identified 3306 differentially expressed genes including circadian clock genes, and, finally, seasonal changes in the NRF2 pathway regulate winter depression-like behavior. They also performed chemical screening and identified the molecule 'Celastrol,' a traditional Chinese medicine, that reversed the depressive behavior through NRF2 antioxidant pathway with the **Chemical Library Center**.

(11) "C-H activation generates period-shortening molecules that target cryptochrome in the mammalian circadian clock", Oshima, T., Yamanaka, I., Kumar, A., Yamaguchi, J., Ohkawa, T. N., Muto, K., Kawamura, R., Hirota, T., Yagita, K., Irle, S., Kay, S. A., Yoshimura, T., and Itami, K. *Angew. Chem. Int. Ed.* **54**, 7193 (2015). DOI: 10.1002/anie.201502942

Inspired by the discovery of KL001 (Hirota, Kay *et al.*, *Science* 2012), the **groups of Itami**, **Yoshimura**, and **theoretical sciences** identified clock-modulating molecules by cell-based phenotypic chemical screening. By using cutting-edge C**-**H activation chemistry, Itami G constructed a focused library of KL001 derivatives, and succeeded in uncovering the critical sites on KL001 derivatives that induce a rhythm-changing activity and rhythm-lengthening/shortening selectivity

towards the cryptochrome (CRY)-mediated circadian clock regulation. Through structure-activity relationship study, they further succeeded in identifying the first period-shortening molecules that target CRY among library compounds. These compounds are expected to provide a tool to investigate the regulatory mechanism of CRY in the circadian timekeeping mechanism.

(12) "Photopharmacological Manipulation of Mammalian CRY1 for Regulation of the Circadian Clock", Kolarski, D, Miller, S., Oshima, T., Nagai, Y., Aoki, Y., Kobauri, P., Srivastava, A., Sugiyama, A., Amaike, K., Sato, A., Tama, F., Szymanski, W., Feringa, B. L., Itami, K., and Hirota, T. *J. Am. Chem. Soc.* **143**, 2078 (2021).
DOI: 10.1021/jacs.0c12280

The **Hirota group** in collaboration with **Tama group** and **Chemical Library Center** discovered CRY1-selective molecules TH303 and TH129 from cell-based phenotypic screening, and revealed compound-induced conformational change of CRY1 by X-ray crystallography. Based on these discoveries, together with **Itami** group and Feringa lab (University of Groningen, The Netherlands), they identified benzophenone derivatives (photo-responsive TH129 derivatives) that lengthened the circadian period and revealed these compounds selectively interacted with the CRY1 photolyase homology region, resulting in activation of CRY1 but not CRY2. By replacing benzophenone with azobenzene photoswitch, they achieved reversible regulation of CRY1 function.

(13) "Structure–function study of a novel inhibitor of the casein kinase 1 family in Arabidopsis thaliana", Saito, A. N., Matsuo, H., Kuwata, K., Ono, A., Kinoshita, T., Yamaguchi, J., and Nakamichi, N. *Plant Direct.* **3**, 1 (2019).
DOI: 10.1002/pld3.172

Inspired by the discovery PHA-767491 (PNAS 2019, Appendix 1-1 (17)), **Nakamichi of Kinoshita group**, together with the **Molecular Structure Center** and **Chemical Library Center,** and Yamaguchi group (Waseda Univ.) performed a structure–activity relationship study of analogues of the CK1 inhibitor PHA767491. As a result, they succeeded in identifying lead compounds (AMI-212 and AMI-331) which showed 100-fold more potent than the parent molecule. Affinity proteomics using an AMI-331 probe showed that the targets of AMI-331 inhibition are mostly CK1 kinases. As such, AMI-331 is a potent and selective CK1 inhibitor that shows promise in the research of CK1 in plants.

(14) "*N*-Aryl pyrido cyanine derivatives are nuclear and organelle DNA markers for two-photon and super-resolution imaging", Uno, K., Sugimoto, N., and Sato, Y. *Nature Commun.* 2021 (accepted).

The **Live Imaging Center** has developed the bright DNA staining dye, Kakshine, that makes the nuclei of various organisms shine brightly, with a researcher from the **Itami group**. Kakshine and its derivatives, with a pyrido cyanine backbone, offer remarkable advantages compared with conventional DNA staining dye, such as high DNA selectivity, enhanced cell permeability, ability to staining organellar DNA, limited cell toxicity and custom-tailed photophysical properties. In addition, these molecules are also highly compatible with a stimulated emission depletion fluorescent lifetime imaging microscopy (STED-FLIM) and a two-photon microscopy, which allowed us to reveal fine structure of nuclear DNA and mitochondrial DNA at super-resolution level and to achieve deep imaging in whole plant tissue.

(15) "Ultrastable Gold Nanoparticles Modified by Bidentate N-Heterocyclic Carbene Ligands", Man, R. W. Y., Li, C. H., LacLean, M. W. A., Zenkina, O. V., Zamora, M. T., Saunders, L. N., Rousine-Webb, A., Nambo, M., and Crudden, C. M. *J. Am. Chem. Soc.* **140**, 1576 (2018).
DOI: 10.1021/jacs.7b08516

The **Crudden group** achieved the syntheses of gold nanoparticles (Au NPs) stabilized by bidentate *N*-heterocyclic (NHC) ligands. They investigated different synthetic routes, top-down and bottom-up approaches, to the NPs, and performed the first detailed analysis of NP's preparation methods, NHC alkylation, and multidenticity on NHC-protected Au NPs. Through structure-property

relationship study, they revealed that the presence of an alkyl linker on the ligands and the use of bidentate NHC ligands enhanced the stability of the NPs. On the other hand, by using top-down approaches that employ ligand exchange to introduce the NHC, they revealed bidentate NHC-protected NPs displayed unprecedented stability to external thiol, which has been an unsolved problem to date with all nanoparticles.

(16) "Strength of carbon nanotubes depends on their chemical structures", Takakura, A., Beppu, K., Nishihara, T., Fukui, A., Kozeki, T., Namazu, T., Miyauchi, Y., and Itami, K. *Nature Commun.* **10**, 3040 (2019).
DOI: 10.1038/s41467-019-10959-7

Single-walled carbon nanotubes (SWCNTs) theoretically possess ultimate intrinsic tensile strengths in the 100–200GPa range, among the highest in existing materials. However, all of the experimentally reported values are considerably lower and exhibit a considerable degree of scatter, with the lack of structural information inhibiting constraints on their associated mechanisms.
The **Itami group** succeeded in the first experimental measurements of the ultimate tensile strengths of individual structure-defined, SWCNTs. The strength depends on the chiral structure of the nanotube, with small-diameter, near-armchair nanotubes exhibiting the highest tensile strengths. This observed structural dependence is comprehensively understood via the intrinsic structure-dependent inter-atomic stress, with its concentration at structural defects inevitably existing in real nanotubes. These findings highlight the target nanotube structures that should be synthesized when attempting to fabricate the strongest materials.

(17) "A water-soluble warped nanographene: synthesis and applications for photoinduced cell death", Lin, H. A., Sato, Y., Segawa, Y., Nishihara, T., Sugimoto, N., Scott, L. T., Higashiyama, T., and Itami, K. *Angew. Chem. Int. Ed.* **57**, 2874 (2018)
DOI: 10.1002/anie.201713387

The biological applications of nanographenes, such as bioimaging, cancer therapies and drug delivery, provide significant opportunities for breakthroughs in the field. However, the intrinsic aggregation behavior and low solubility of nanographenes, which stem from their flat structures, hamper their development for biological applications. The **Itami group** has synthesized a water-soluble warped nanographene (WNG) by sequential regioselective C-H borylation and cross-coupling. A water-soluble WNG exhibits green-yellow fluorescence with a long lifetime, good photostability and notably low cytotoxicity to cells. With the **Live Imaging Center**, they revealed that the water-soluble WNG was readily introduced into HeLa cells and induced cell death upon light irradiation, demonstrating the applicability for photodynamic therapy.

(18) "Conformational dynamics of human protein kinase CK2a and its effect on function and inhibition", Srivastava, A., Hirota, T., Irle, S., and Tama, F. *Proteins*, **86**, 344 (2018).
DOI: 10.1002/prot.25444

In collaboration with the **groups of the Hirota-Kay and Irle**, the **Tama group** explored the nature of conformational flexibility of the circadian rhythms-related enzyme (CK2a) by using analysis of multiple crystal structures and long timescale molecular dynamics simulations, and found that the enzyme shows considerably higher flexibility in the solution as compared to that observed in crystal structure ensemble. They observed that multiple conformations of hinge region were located near the active site and these multiple conformations, the most populated conformational state was inadequately represented in the crystal structure ensemble. The results presented in this work provide novel insight into the conformational heterogeneity of the catalytic subunit of the CK2 and underline the importance of dynamics of enzyme in the solution state.

(19) "3,4-Dibromo-7-Azaindole Modulates Arabidopsis Circadian Clock by Inhibiting Casein Kinase 1 Activity", Ono, A., Sato, A., Fujimoto, K. J., Matsuo, H., Yanai, T., Kinoshita, T., and Nakamichi, N. *Plant Cell Physiol.* **60**, 2360 (2019).
DOI: 10.1093/pcp/pcz183

**Nakamichi of the Kinoshita group** found that small molecule 3,4-dibromo-7-azaindole (B-AZ), which biological activities have not previously been reported, lengthened the circadian period of *Arabidopsis thaliana* (Arabidopsis) in collaboration with the **Yanai group** and **Chemical Library Center**. Biological studies (comprehensive gene expression analyses) revealed that B-AZ inhibited Casein Kinase1 family (CK1) that phosphorylates PRR5 and TOC1 for targeted degradation. Simultaneously, a docking study and molecular dynamics simulation suggested that B-AZ interacts with the ATP-binding pocket of human CK1 delta, whose amino acid sequences are highly similar to those of Arabidopsis CK1 (with **Fujimoto** of the Yanai group). From the above, they determined that B-AZ inhibits CK1 activity, binds to the ATP binding pocket of CK1 and, as a result, lengthen circadian clock via accumulation of PRR5 and TOC1.

(20) "Covalent Self-Labeling of Tagged Proteins with Chemical Fluorescent Dyes in BY-2 Cells and Arabidopsis Seedlings", Iwatate, R. J., Yoshinari, A., Yagi, N., Grzybowski, M., Ogasawara, H., Kamiya, M., Komatsu, T., Taki, M., Yamaguchi, S., Frommer, W. B., and Nakamura, M. *Plant Cell* **32**, 3081 (2020).
DOI: 10.1105/tpc.20.00439

Covalent, targeted labeling, such as with a SNAP-tag, uses synthetic dyes to label specific proteins in vivo for studying biological processes such as endocytosis. Despite its potential, such chemical tagging has not been used effectively in plants. Cell wall and membrane permeability of the available synthetic dye have been pointed out as one of the major drawbacks. The **Frommer-Nakamura group** tested structurally and physico-chemical property diverse 31 synthetic dyes to investigate cellular uptake into BY-2 cells and identified three permeable ones in collaboration with the **Yamaguchi group**. Successful SNAP-tagging was verified by live cell imaging and visualization of microtubule arrays in interphase and during mitosis in Arabidopsis seedlings. Fluorescence activation-coupled protein labeling with DRBG-488 was used to observe the auxin transporter PIN2 endocytosis and delivery to the vacuole as well as preferential delivery of newly synthesized PIN2 to the actively forming cell plate during mitosis.

# Appendix 1-3
# Major Awards, Invited Lectures, Plenary Addresses (etc.) (within 2 pages)

*Prepare the information below during the period from the start of the center through March 2021.

## 1. Major Awards

*List main internationally-acclaimed awards received/unofficially announced in order from the most recent.
*For each, write the recipient's name, the name of award, and the date issued.
In case of multiple recipients, underline those affiliated with the center.

| Date | Recipient's name | Name of award |
|---|---|---|
| Mar. 1, 2021 | Takashi Ooi | Chemical Society of Japan Award |
| Jan. 5, 2021 | Kohsuke Ohmatsu,<br>Kei Murakami | Thieme Chemistry Journals Award 2021 |
| Dec. 03, 2020 | Masakazu Nambo | 39th Incentive Award, The Society of Synthetic Organic Chemistry |
| Nov. 18, 2020<br>(Announcement) | Kenichiro Itami, Wolf Frommer,<br>Tetsuya Higashiyama | 2020 Highly Cited Researchers |
| Sep. 11, 2020 | Cathleen Crudden | Fellow of the Royal Society of Canada |
| Aug. 2020 | Takashi Yoshimura | Aschoff and Honma Prize for Biological Rhythm Research, Aschoff and Honma Memorial Foundation, Japan |
| Jun. 2020 | Steve Kay | Director's award for research, Society for Research on Biological Rhythms, US |
| Feb. 1, 2020 | Kohsuke Ohmatsu | Lectureship Award MBLA 2020, Japan |
| Jan. 7, 2020 | Kei Murakami | 69th Distinguished Young Chemists Award, The Chemical Society of Japan |
| Jan. 01, 2020 | Tetsuya Higashiyama | Asahi Award, Asahi Shimbun, Japan |
| Nov. 19, 2019<br>(Announcement) | Kenichiro Itami, Wolf Frommer,<br>Tetsuya Higashiyama | 2019 Highly Cited Researchers |
| Sep. 16, 2019 | Live Imaging Center (Yoshikatsu Sato) | 16th the Botanical Society Japan Special Prize |
| Aug. 26, 2019 | Takashi Yoshimura | Axelrod lectureship award, European Biological Rhythms Society |
| May 6, 2019 | Keiko Torii | Walter E and Helen Parke Loomis Lecture, Iowa State University |
| Apr. 16, 2019 | Steve Kay | Fellow of the Royal Society |
| Apr. 2, 2019 | Cathleen Crudden | 2019 Arthur C. Cope Scholar Award, American Chem. Soc. |
| Mar. 26, 2019 | Shigehiro Yamaguchi | Humboldt Research Award, Germany |
| Mar. 25, 2019 | Tetsuya Higashiyama | BBB Awards for Excellence to Authors |
| Dec. 7, 2018 | Kenichiro Itami | The Netherlands Scholar Award for Supramolecular Chemistry |
| Nov. 27, 2018<br>(Announcement) | Kenichiro Itami, Wolf Frommer,<br>Steve Kay | 2018 Highly Cited Researchers |
| Sep. 15, 2018 | Tetsuya Higashiyama | 15th Academic Award of The Botanical Society of Japan |
| Aug. 27, 2018<br>Sep. 15, 2015<br>Sep. 17, 2013 | Jeffery Bode (2018)<br>Shigehiro Yamaguchi (2015)<br>Kenichiro Itami (2013) | Mukaiyama Award, Japan |
| May 31, 2018<br>May 31, 2017 | Tetsuya Higashiyama (2018)<br>Kenichiro Itami (2017) | Chunichi Cultural Award, Chunichi Shimbun, Japan |
| May 23, 2018 | Cathleen Crudden | 2018 IPMI Carol Tyler Award |
| May 8, 2018 | Wolf Frommer | Tsungming Tu Award, Taiwan |
| Apr. 25, 2018 | Kenichiro Itami | Guthikonda Lectureship in Organic Chemistry 2018, US |
| Feb. 7, 2018<br>Feb. 10, 2013<br>Feb. 4, 2012 | Takeshi Yanai (2018)<br>Kenichiro Itami (2013)<br>Shigehiro Yamaguchi (2012) | The JSPS Award, Japan |
| Feb. 2, 2018<br>Feb. 4, 2015<br>Feb. 4, 2014 | Tetsuya Higashiyama (2018)<br>Keiko Torii (2015)<br>Takashi Ooi (2013) | Inoue Prize for Science, Japan |
| Jan. 15, 2018 | Takashi Ooi | The Society of Synthetic Organic Chemistry Award, Japan |
| May 19, 2017 | Tetsuya Higashiyama | Kihara Foundation Award, Japan |
| Apr. 20, 2017<br>Apr. 17, 2014 | Kenichiro Itami (2017)<br>Tetsuya Higashiyama (2014) | Yomiuri Techno Forum Gold Medal Prize, Yomiuri Shimbun, Japan |
| Oct. 31, 2016 | Kenichiro Itami | The Holger Erdtman Lecture, KTH, Sweden |
| Sep. 23, 2016 | Kenichiro Itami | The Nagase Prize, Japan |

| | | |
|---|---|---|
| Sep. 1, 2016 | Steve Kay | Funding Award: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases |
| Jul. 15, 2016 | Keiko Torii | Distinguished Lecture, Institute of Plant Molecular Biology, Academia Sinica, Taipei |
| Apr. 22, 2016 | Shigehiro Yamaguchi | Nagase Foundation Award |
| Mar. 26, 2016 | Shigehiro Yamaguchi | 33rd Academic Award, Chemical Society of Japan |
| Oct. 19, 2015 | Takashi Yoshimura | 2015 Van Meter Award, American Thyroid Association |
| Jun. 26, 2015 | Keiko Torii | ASPB Fellow Award, American Society of Plant Biologists |
| May 23, 2015 | Keiko Torii | 35th Saruhashi Award |
| Dec. 25, 2014 | Kenichiro Itami | Swiss Chemical Society Lectureship Award |
| Dec. 19, 2014 | Tetsuya Higashiyama | NISTEP Award |
| Aug. 12, 2014 | Kenichiro Itami | Arthur C. Cope Scholar Award, American Chemical Society |
| Aug. 20-23, 2013 | Kenichiro Itami | Asian Rising Star Award |

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

*List up to 20 main presentations in order from most recent.
*For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

| Date(s) | Lecturer/ Presenter's name | Presentation title | Conference name |
|---|---|---|---|
| Nov. 29, 2020 | Takashi Yoshimura | Seasonal clock: Towards the understanding of human seasonal clocks. | The 12th Sleep Respiration Forum online from Barcelona (plenary lecture, Online) |
| Jan.22-24, 2020 | Keiko Torii | Harnessing synthetic chemistry to dissect plant hormone signaling and Development. | 2020 International Symposium on Chemical Biology, Geneve, Switzerland |
| Jan. 19-30, 2020 | Florence Tama | Flexible fitting methods and applications. | EMBO workshop, CEM3DIP 2020: Single particle cryoEM of macromolecular-assemblies and cellular tomography, Kolkota, India |
| Aug. 26, 2019 | Takashi Yoshimura | Molecular basis of seasonal changes in behavior. | *XVI Congress of the European Biological Rhythms Society*, Lyon, France |
| Jul. 15, 2019 | Kenichiro Itami | Making new forms of nanocarbons. | The 20th European Symposium in Organic Chemstry (ESOC), Vienna, Austria |
| Jul. 9, 2019 | Toshinori Kinoshita | Regulation of light-induced stomatal opening and plasma membrane H+-ATPase. | The 18th International Workshop on Plant Membrane Biology, University of Glasgow, UK |
| Jun. 2-7, 2019. | Shigehiro Yamaguchi | Main Group-Containing pi-Electron Materials with Structural Constraint. | 14th International Symposium on Functional pi-Electron Systems (Fpi14), Berlin, Germany |
| Nov. 18, 2018 | Wolf Frommer | In vivo biochemistry with sensors for signaling molecules and transporters. | International Meeting on Optical Biosensors in memory of Roger Y. Tsien on the 10th year anniversary of his Nobel prize: Ghent, Belgium |
| Sep. 24, 2018 | Keiko Torii | Making a pore: signaling and transcription factor control of stomatal differentiation. | Plenary Lecture: Annals of Botany Lecture, COMBIO 2018, Sydney, Australia |
| Jun. 29, 2018 | Tetsuya Higashiyama | Cruising inside flowers: from cellular dynamics to key signaling molecules. | Keynote speaker: International Conference on Arabidopsis Research ICAR 2018, Turku, Finland |
| Jan. 24, 2018 | Kenichiro Itami | Exploring Molecular Nanocarbon Science. | Prof. Bäckvall 70th Anniversary Symposium, The Royal Swedish Academy of Sciences |
| Jun. 26-29, 2017 | Shigehiro Yamaguchi | Main Group Strategy for Functional pi-Electron Materials. | Gordon Research Conference 2017, Physical Organic Chemistry Symposium, Holderness, USA |
| Jun. 26, 2017 | Kenichiro Itami | Creation of molecular nanocarbons by metal catalysis. | 19th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS19), Jeju, Korea |
| Jun. 9, 2017 | Takashi Yoshimura | Understanding the molecular basis of vertebrate seasonal adaptation. | 18th International Congress of Comparative Endocrinology, Lake Louise, Canada |
| Sep. 2-3, 2016 | Steve Kay | Circadian Rhythm Networks in Health and Disease. | Nobel Prize Laureate Summit, Chengdu, China |
| Aug. 25, 2016 | Takashi Yoshimura | Universality and diversity in the photoperiodic signal transduction in vertebrates. | Plenary Lecture: 28th Conference of European Comparative Endocrinologists Leuven, Belgium |
| Jul. 20-25, 2014 | Keiko Torii | Receptor Kinase Specificity and Integration in Stomatal Patterning. | Gordon Research Conference, Plant Development, Holderness, NH, USA |

# Appendix 1-4 2020 List of Center's Research Results

## Refereed Papers

- List only the Center's papers published in 2020. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.
   A. WPI papers
      List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state "WPI" and the name of the WPI center (WPI-center name)). (Not including papers in which the names of persons affiliated with the WPI program are contained only in acknowledgements.)
   B. WPI-related papers
      List papers related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (Including papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

      Note: On 14 December 2011, the Basic Research Promotion Division in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. From 2012, the authors' affiliations must be clearly noted.

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

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

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

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

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

### A. WPI papers (Jan 1, 2020 – Dec 31, 2020)

1. Original Articles

(1) Bose, Moumita; Li, Zilong; Matsumoto, Tsuyoshi; Tatsumi, Kazuyuki, Inorg. Chem., 2020, 59, 968-971. "A Dithiolato and Hydrido Bridged (CO/CN)Fe-Ni Complex with Unprotected CN: A Model for the [Ni-R] State of the [Ni-Fe] Hydrogenase Active Site" (DOI: 10.1021/acs.inorgchem.9b03082).

(2) Minh-Hai Nguyen; Thi-Nguyet Nguyen; Danh-Quang Do; Hung-Huy Nguyen; Quan-Manh Phung; Thirumalaivasan, Natesan; Wu, Shu-Pao; Thi-Hien Dinh, Inorg. Chem. Commun., 2020, 115, 107882. "A highly selective fluorescent anthracene-based chemosensor for imaging Zn2+ in living cells and zebrafish" (DOI: 10.1016/j.inoche.2020.107882).

(3) Chen, Wei Wei; Takahash, Nozomu; Hirata, Yoshito; Ronald, James; Porco, Silvana; Davis, Seth J.; Nusinow, Dmitri A.; Kay, Steve A.; Mas, Paloma, Nat. Plants, 2020, 6, 416+. "A mobile ELF4 delivers circadian temperature information from shoots to roots" (DOI: 10.1038/s41477-020-0634-2), *Highly Cited Paper.*

(4) Saitow, Masaaki; Yanai, Takeshi, J. Chem. Phys., 2020, 152, 114111. "A multireference coupled-electron pair approximation combined with complete-active space perturbation theory in local pair-natural orbital framework" (DOI: 10.1063/1.5142622).

(5) Borgo, Christian; D'Amore, Claudio; Cesaro, Luca; Itami, Kenichiro; Hirota, Tsuyoshi; Salvi, Mauro; Pinna, Lorenzo A., Biochem. Biophys. Res. Commun., 2020, 531, 409-415. "A N-terminally deleted form

of the CK2 alpha' catalytic subunit is sufficient to support cell viability" (DOI: 10.1016/j.bbrc.2020.07.112).

(6) Suzuki, Naoya; Wakioka, Masayuki; Ozawa, Fumiyuki; Yamaguchi, Shigehiro, Asian J. Org. Chem., 2020, 9, 1326-1332. "A Near-Infrared Emissive pi-Conjugated Polymer Consisting of an Excited-State Intramolecular Proton Transfer Unit" (DOI: 10.1002/ajoc.202000234).

(7) Antunez-Sanchez, Javier; Naish, Matthew; Ramirez-Prado, Juan Sebastian; Ohno, Sho; Huang, Ying; Dawson, Alexander; Opassathian, Korawit; Manza-Mianza, Deborah; Ariel, Federico; Raynaud, Cecile; Wibowo, Anjar; Daron, Josquin; Ueda, Minako; Latrasse, David; Slotkin, R. Keith; Weigel, Detlef; Benhamed, Moussa; Gutierrez-Marcos, Jose, eLife, 2020, 9, e58533. "A new role for histone demethylases in the maintenance of plant genome integrity" (DOI: 10.7554/eLife.58533).

(8) Li, Yuanming; Segawa, Yasutomo; Yagi, Akiko; Itami, Kenichiro, J. Am. Chem. Soc., 2020, 142, 12850-12856. "A Nonalternant Aromatic Belt: Methylene-Bridged [6]Cycloparaphenylene Synthesized from Pillar[6]arene" (DOI: 10.1021/jacs.0c06007).

(9) Kawamoto, Nozomi; Del Carpio, Dunia Pino; Hofmann, Alexander; Mizuta, Yoko; Kurihara, Daisuke; Higashiyama, Tetsuya; Uchida, Naoyuki; Torii, Keiko U.; Colombo, Lucia; Groth, Georg; Simon, Ruediger, Curr. Biol., 2020, 30, 4352+. "A Peptide Pair Coordinates Regular Ovule Initiation Patterns with Seed Number and Fruit Size" (DOI: 10.1016/j.cub.2020.08.050).

(10) Yano, Yuuta; Mitoma, Nobuhiko; Ito, Hideto; Itami, Kenichiro, J. Org. Chem., 2020, 85, 4-33. "A Quest for Structurally Uniform Graphene Nanoribbons: Synthesis, Properties, and Applications" (DOI: 10.1021/acs.joc.9b02814), *Highly Cited Paper*.

(11) Uraguchi, Daisuke; Ueoka, Fumito; Tanaka, Naoya; Kizu, Tomohito; Takahashi, Wakana; Ooi, Takashi, Angew. Chem.-Int. Edit., 2020, 59, 11456-11461. "A Structurally Robust Chiral Borate Ion: Molecular Design, Synthesis, and Asymmetric Catalysis" (DOI: 10.1002/anie.202001637).

(12) Nishimura, Kohei; Yamada, Ryotaro; Hagihara, Shinya; Iwasaki, Rie; Uchida, Naoyuki; Kamura, Takumi; Takahashi, Koji; Torii, Keiko U.; Fukagawa, Tatsuo, Nucleic Acids Res., 2020, 48, e108. "A super-sensitive auxin-inducible degron system with an engineered auxin-TIR1 pair" (DOI: 10.1093/nar/gkaa748).

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(151) Miyatake, Koji; Saito, Takeo; Nunome, Tsukasa; Yamaguchi, Hirotaka; Negoro, Satomi; Ohyama, Akio; Wu, Jianzhong; Katayose, Yuichi; Fukuoka, Hiroyuki, Breed. Sci., 2020, 70, 438-448. "Fine mapping of a major locus representing the lack of prickles in eggplant revealed the availability of a 0.5-kb insertion/deletion for marker-assisted selection" (DOI: 10.1270/jsbbs.20004).

2. Review Articles

(152) Sanchez, Sabrina E.; Rugnone, Matias L.; Kay, Steve A., Mol. Plant., 2020, 13, 363-385. "Light Perception: A Matter of Time" (DOI: 10.1016/j.molp.2020.02.006).

(153) Wu, Dino; Taguchi, Jumpei; Tanriver, Matthias; Bode, Jeffrey W., Angew. Chem.-Int. Edit., 2020, 59, 16847-16858. "Synthesis of Acylboron Compounds" (DOI: 10.1002/anie.202005050).

3. Proceedings

N/A

4. Other English Articles

(154) Putarjunan, Aarthi; Torii, Keiko U., Mol. Plant., 2020, 13, 536-538. "Heat Shocking the Jedi Master: HSP90's Role in Regulating Stomatal Cell Fate" (DOI: 10.1016/j.molp.2020.03.001).

(155) Schmidt, Sarah M.; Belisle, Melinda; Frommer, Wolf B., EMBO Rep., 2020, 21, e50680. "The evolving landscape around genome editing in agriculture Many countries have exempted or move to exempt forms of genome editing from GMO regulation of crop plants" (DOI: 10.15252/embr.202050680).

(156) Pick, Joel L.; Hatakeyama, Masaomi; Ihle, Kate E.; Gasparini, Julien; Haussy, Claudy; Ishishita, Satoshi; Matsuda, Yoichi; Yoshimura, Takashi; Kanaoka, Masahiro M.; Shimizu-Inatsugi, Rie; Shimizu, Kentaro K.; Tschirren, Barbara, Evol. Lett., 2020, 4, 200-211. "Artificial selection reveals the role of transcriptional constraints in the maintenance of life history variation" (DOI: 10.1002/evl3.166).

# Appendix 2　FY 2020 List of Principal Investigators

NOTE:

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

*In the case of researcher(s) not listed in the latest report, attach a "Biographical Sketch of a New Principal Investigator"(Appendix 2a).

*Enter the host institution name and the center name in the footer.

| | <Results at the end of FY2020> | | | | | Principal Investigators Total: 13 |
|---|---|---|---|---|---|---|
| Name | Age | Affiliation (Position title, department, organization) | Academic degree, Specialty | Effort (%)* | Starting date of project participation | Status of project participation (Describe in concrete terms) | Contributions by PIs from overseas research institutions |
| Kenichiro ITAMI | 49 | Director, Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr.Eng<br>Specialties: Organic Synthesis, Catalysis, Pharmaceuti-cal Science, Nanocarbon Chemistry | 80 | from the beginning | usually stays at the center | |
| Tetsuya HIGASHIYAMA | 49 | Vice-Director, Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr.Sci<br>Specialties: Live Cell Biology, Plant Reproduction, Bio-active molecules, Peptides | 90 | from the beginning | usually stays at the center | |
| Jeffrey W. BODE | 47 | Professor of Organic Chemistry<br>Department of Chemistry and Applied Biosciences, ETH Zürich, Switzerland | Doctoral of Natural Science<br>Specialties: Organic Synthesis, Peptide and Protein Chemistry, Catalysis, Ligation and Bioconjugati-on reactions | 21 | from the beginning | Connected 24 hours through iPad to the center.<br>Holds on-line group meeting once a week.<br>Joins PI meeting online. | |
| Cathleen M. CRUDDEN | 54 | Professor<br>Department of Chemistry, Queen's University, Canada | Ph.D<br>Specialities: Catalysis, Organic Synthesis, Materials Chemistry, Chirality | 21 | from the beginning | Holds Skype group meeting once a week.<br>Joins PI meeting online. | |
| Toshinori KINOSHITA | 52 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr.Sci<br>Specialities: Plant Molecular Physiology | 90 | from the beginning | usually stays at the center | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Takashi OOI | 55 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Engineering<br>Specialties: Organic Synthesis, Catalysis, Molecular Recognition | 90 | from the beginning | usually stays at the center | |
| Keiko TORII | 55 | Professor<br>College of Natural Sciences<br>The University of Texas at Austin<br>Investigator<br>Howard Hughes Medical Institute | Ph.D.<br>Specialties: Plant Development, Signal Transduction, Stem Cell Maintenance/Differentiati-on in Plants | 21 | from the beginning | Holds on-line plant biology meeting "Mixplant meeting" once a week.<br>Joins PI meeting online. | |
| Shigehiro YAMAGUCHI | 52 | Vice-Director, Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Engineering<br>Specialties: Main Group Chemistry, Physical Organic Chemistry | 90 | from the beginning | usually stays at the center | |
| Takashi YOSHIMURA | 51 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Agriculture<br>Specialties: Animal Physiology, Systems Biology, Neuroendoc-rinology | 70 | from the beginning | usually stays at the center | |
| Steve A. Kay | 61 | University and Provost Professor of Neurology, Biomedical Engineering and Biological Sciences, Director of Convergent Bioscience<br>Co-Director of the USC Norris Center for Cancer Drug Development,<br>Keck School of Medicine, University of Southern California | Ph.D.<br>Specialties: Chronobiology, Genetics, Biochemistry, Systems Biology | 21 | from April 1st 2014 | Holds on-line meeting on an as-needed basis.<br>Joins PI meeting online. | |
| Florence Tama | 46 | Professor<br>Institute of Transformative Bio-Molecules / Department of Physics, Graduate School of Science, Nagoya University | Ph.D<br>Specialties: Computational Biophysics | 50 | from April 1st 2016 | usually stays at the center | |
| Wolf B. Frommer | 63 | Professor, Heinrich Heine University Düsseldorf and Max Planck Institute for Breeding Research | Dr. rer. nat.<br>Specialties: Biology | 21 | from October 16th 2016 | Holds on-line group meeting once a week.<br>Joins PI meeting online. | |
| Takeshi Yanai | 46 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr.Eng<br>Specialties: Theoretical Chemistry, Computatoinal Quantum Chemistry | 90 | from April 1st 2018 | usually stays at the center | |

*Percentage of time that the principal investigator devotes to his/her work for the center vis-à-vis his/her total working hours.

**Principal investigators unable to participate in project in FY 2020**

| Name | Affiliation (Position title, department, organization) | Starting date of project participation | Reasons | Measures taken |
|---|---|---|---|---|
| N/A | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

# Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

**Name (Age)**

N/A

**Affiliation and position** (Position title, department, organization, etc.)

**Academic degree and specialty**

**Effort** **%**

* Percentage of time that the principal investigator will devote to working for the center vis-à-vis his/her total working hours.

**Research and education history**

**Achievements and highlights of past research activities**

**Achievements**

**(1) International influence** * Describe the kind of attributes listed below.

a) Recipient of international awards

b) Member of a scholarly academy in a major country

c) Guest speaker or chair of related international conference and/or director or honorary chairman of a major international academic society in the subject field

d) Editor of an international academic journal

e) Peer reviewer for an overseas competitive research program (etc.)

**(2) Receipt of major large-scale competitive funds (over the past 5 years)**

**(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)**

**(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)**

# Appendix 3-1 FY 2020 Records of Center Activities

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

### 1-1. Number of researchers and other center staffs

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

**a) Principal Investigators**

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

(number of persons)

| | At the beginning of project | At the end of FY 2020 | Final goal (March, 2022) |
|---|---|---|---|
| Researchers from within the host institution | 7 | 8 | 8 |
| Researchers invited from abroad | 3 | 5 | 5 |
| Researchers invited from other Japanese institutions | 0 | 0 | 0 |
| Total principal investigators | 10 | 13 | 13 |

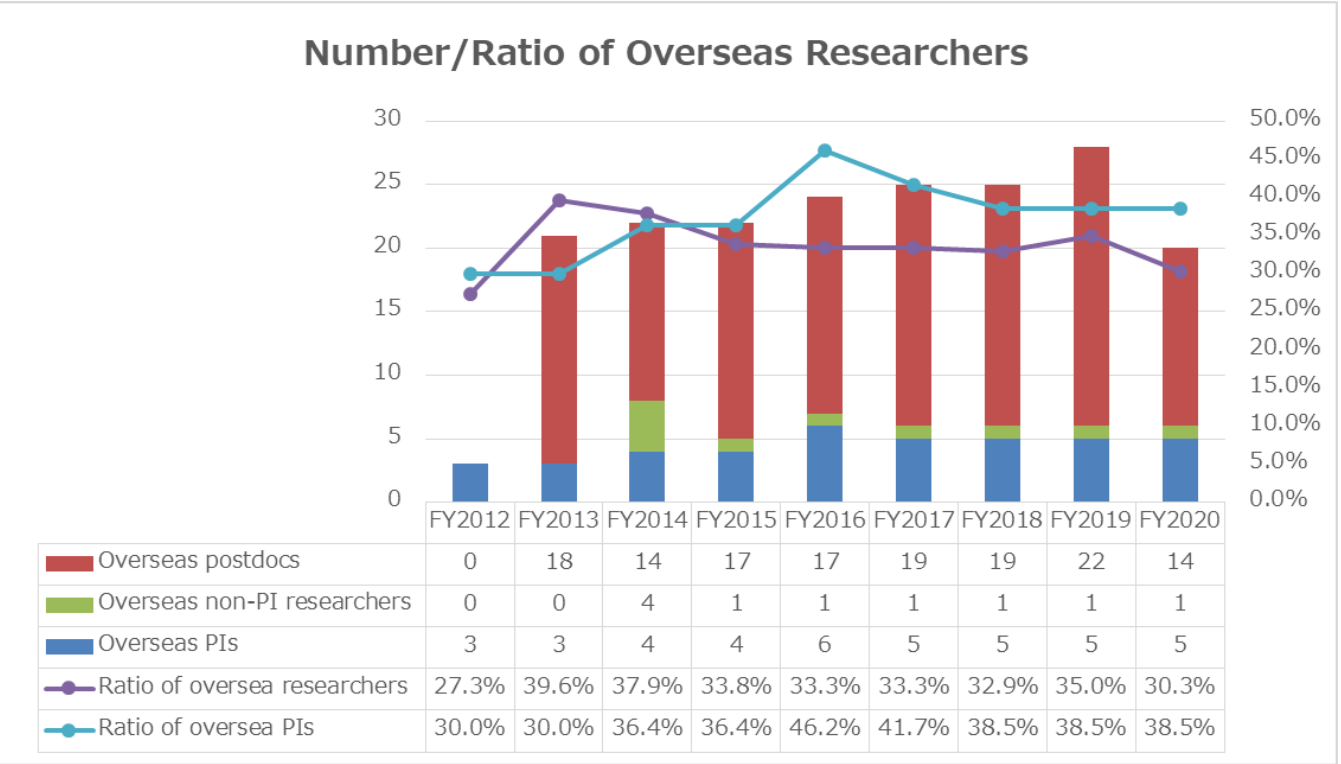
**b) Total members**

| | At the beginning of project | | At the end of FY 2020 | | Final goal (March, 2022) | |
|---|---|---|---|---|---|---|
| | Number of persons | % | Number of persons | % | Number of persons | % |
| Researchers | 20 | | 66 | | 80 | |
| Overseas researchers | 5 | 25 | 20 | 30 | 27 | 34 |
| Female researchers | 4 | 20 | 20 | 30 | 20 | 25 |
| Principal investigators | 10 | | 13 | | 13 | |
| Overseas PIs | 3 | 30 | 5 | 38 | 6 | 46 |
| Female PIs | 2 | 20 | 3 | 23 | 3 | 23 |
| Other researchers | 8 | | 30 | | 35 | |
| Overseas researchers | 0 | 0 | 1 | 3 | 1 | 3 |
| Female researchers | 1 | 13 | 8 | 27 | 9 | 26 |
| Postdocs | 2 | | 23 | | 32 | |
| Overseas postdocs | 2 | 100 | 14 | 61 | 20 | 63 |
| Female postdocs | 1 | 50 | 9 | 39 | 8 | 25 |
| Research support staffs | 10 | | 59 | | 50 | |
| Administrative staffs | 10 | | 11 | | 12 | |
| Total number of people who form the "core" of the research center | 40 | | 136 | | 142 | |

# Appendix 3-2　Annual Transition in the Number of Center Personnel

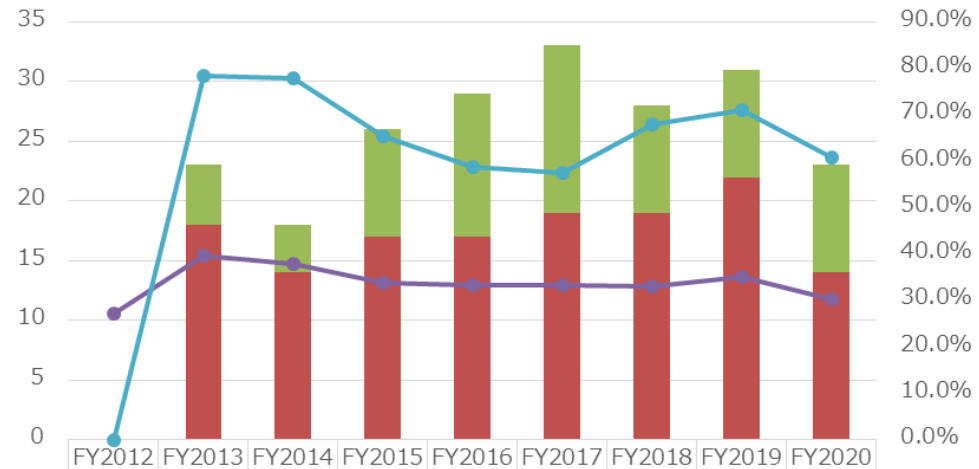
*Make a graph of the annual transition in the number of center personnel since the start of project.


| | At beginning | FY2012 | FY2013 | FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 | Final goal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PI : Researchers from within host institution | 7 | 7 | 7 | 7 | 7 | 8 | 7 | 8 | 8 | 8 | 8 |
| PI : Researchers invited from abroad | 3 | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| PI : Researchers invited from other Japanese institutions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other researchers (incl. postdocs) | 10 | 1 | 43 | 47 | 54 | 59 | 63 | 63 | 67 | 53 | 67 |
| Research support staffs | 10 | 3 | 19 | 27 | 34 | 47 | 47 | 51 | 59 | 59 | 50 |
| Administrative staffs | 10 | 9 | 11 | 11 | 12 | 13 | 13 | 11 | 12 | 11 | 12 |



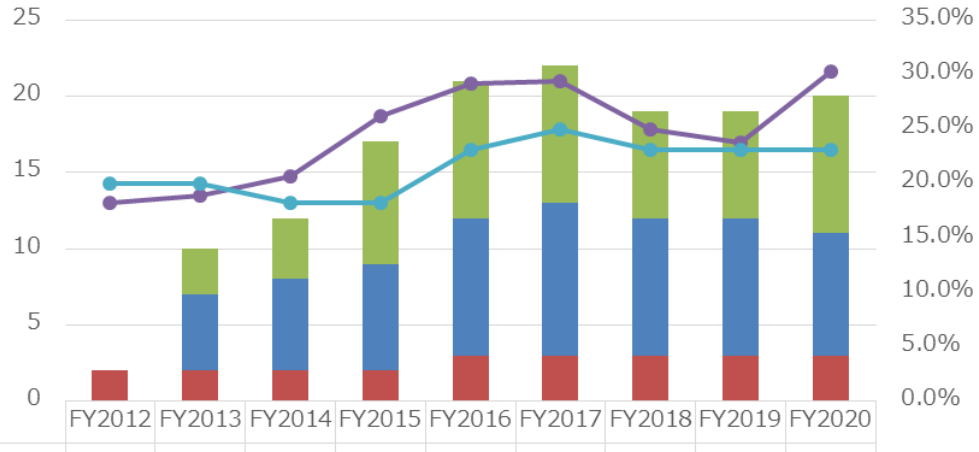

| | FY2012 | FY2013 | FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 |
|---|---|---|---|---|---|---|---|---|---|
| Overseas postdocs | 0 | 18 | 14 | 17 | 17 | 19 | 19 | 22 | 14 |
| Overseas non-PI researchers | 0 | 0 | 4 | 1 | 1 | 1 | 1 | 1 | 1 |
| Overseas PIs | 3 | 3 | 4 | 4 | 6 | 5 | 5 | 5 | 5 |
| Ratio of oversea researchers | 27.3% | 39.6% | 37.9% | 33.8% | 33.3% | 33.3% | 32.9% | 35.0% | 30.3% |
| Ratio of oversea PIs | 30.0% | 30.0% | 36.4% | 36.4% | 46.2% | 41.7% | 38.5% | 38.5% | 38.5% |

## Number/Ratio of Overseas Postdoc




| | FY2012 | FY2013 | FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 |
|---|---|---|---|---|---|---|---|---|---|
| Japanese postdocs | 0 | 5 | 4 | 9 | 12 | 14 | 9 | 9 | 9 |
| Overseas postdocs | 0 | 18 | 14 | 17 | 17 | 19 | 19 | 22 | 14 |
| Ratio of oversea researchers | 27.3% | 39.6% | 37.9% | 33.8% | 33.3% | 33.3% | 32.9% | 35.0% | 30.3% |
| Ratio of overseas postdocs | 0.0% | 78.3% | 77.8% | 65.4% | 58.6% | 57.6% | 67.9% | 71.0% | 60.9% |

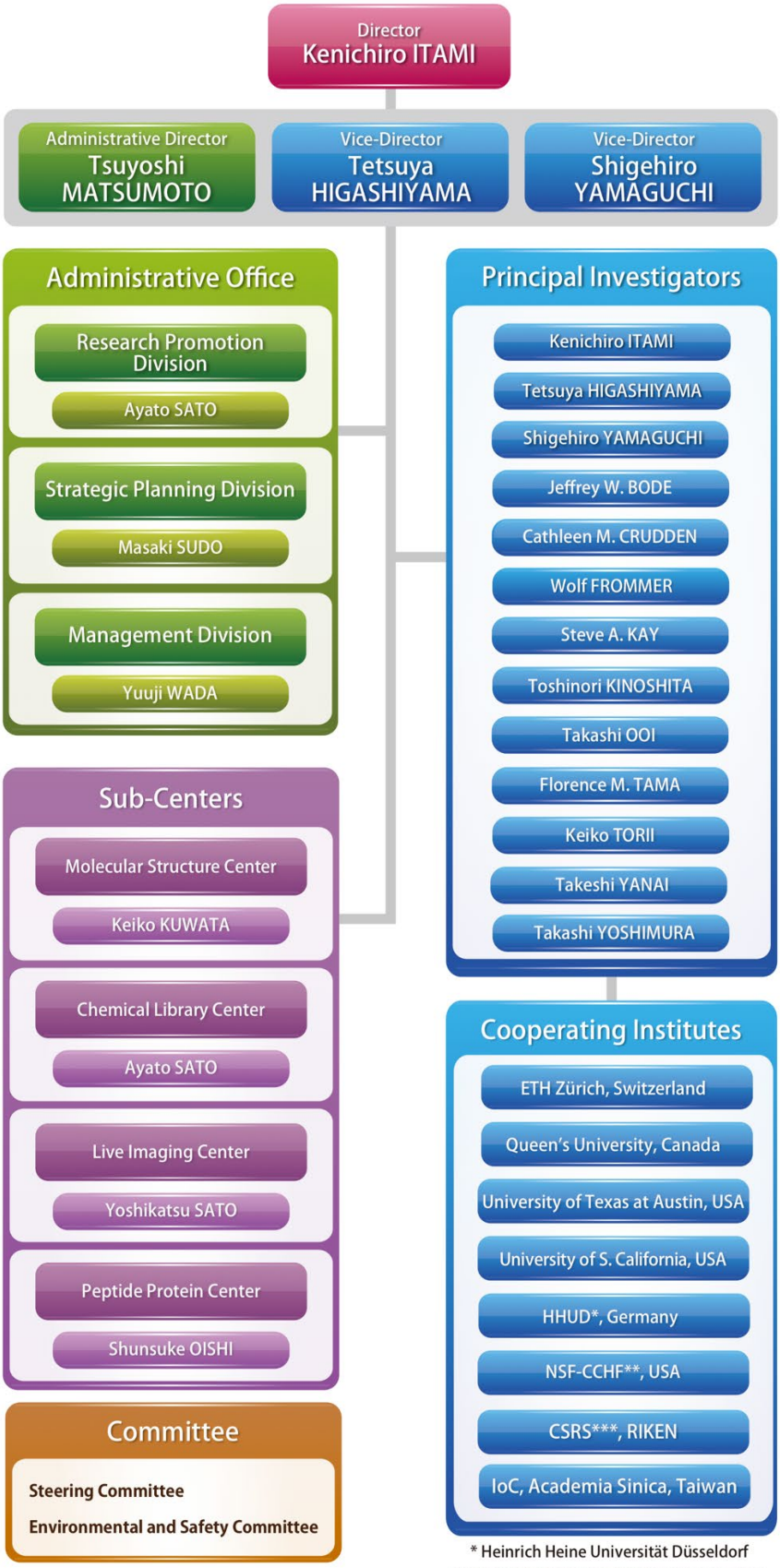
## Number/Ratio of Female Researchers




| | FY2012 | FY2013 | FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 |
|---|---|---|---|---|---|---|---|---|---|
| Female postdocs | 0 | 3 | 4 | 8 | 9 | 9 | 7 | 7 | 9 |
| Female non-PI researchers | 0 | 5 | 6 | 7 | 9 | 10 | 9 | 9 | 8 |
| Female PIs | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 |
| Ratio of female researchers | 18.2% | 18.9% | 20.7% | 26.2% | 29.2% | 29.3% | 25.0% | 23.8% | 30.3% |
| Ratio of female PIs | 20.0% | 20.0% | 18.2% | 18.2% | 23.1% | 25.0% | 23.1% | 23.1% | 23.1% |

# Appendix 3-3 Diagram of Management System

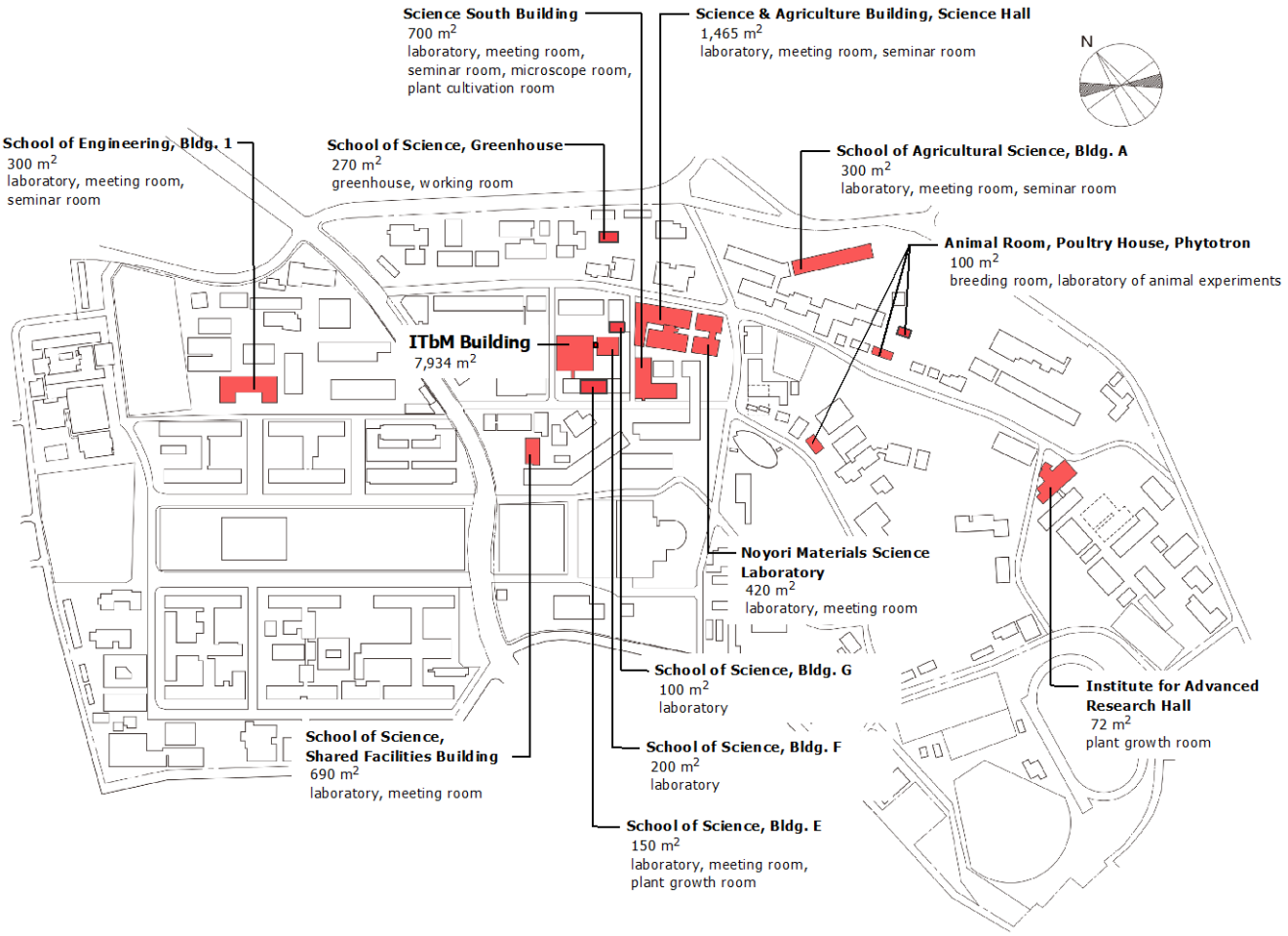
- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such as the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




* Heinrich Heine Universität Düsseldorf
** Center for Selective C-H Functionalization
*** Center for Sustainable Resource Science
**** Center for Sustainable Resource Science

# Appendix 3-4 Campus Map

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



# Appendix 3-5 Project Expenditures in FY2020

## 1) Overall project funding

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

(Million yens)

| Cost items | Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.) | Total costs | Amount covered by WPI funding |
|---|---|---|---|
| Personnel | Center director and administrative director | 32 | 17 |
| | Principal investigators (no. of persons):12 | 105 | 16 |
| | Other researchers (no. of persons):49 | 263 | 194 |
| | Research support staffs (no. of persons):29 | 64 | 61 |
| | Administrative staffs (no. of persons):23 | 93 | 65 |
| | Subtotal | 557 | 353 |
| Project activities | Cost of dispatching scientists (no. of persons):2 | 8 | 8 |
| | Research startup cost (no. of persons):3 | 4 | 4 |
| | Rental fees for facilities | 23 | 3 |
| | Cost of consumables | 45 | 44 |
| | Cost of utilities | 51 | 51 |
| | Other costs | 117 | 110 |
| | | | |
| | Subtotal | 248 | 220 |
| Travel | Domestic travel costs | 1 | 0 |
| | Overseas travel costs | 0 | 0 |
| | Travel and accommodations cost for invited scientists<br>(no. of domestic scientists):3<br>(no. of overseas scientists):0 | 1 | 1 |
| | Travel cost for scientists on transfer<br>(no. of domestic scientists):2<br>(no. of overseas scientists):3 | 1 | 1 |
| | Subtotal | 3 | 2 |
| Equipment | Depreciation of buildings | 36 | 7 |
| | Depreciation of equipment | 70 | 25 |
| | Subtotal | 106 | 32 |
| Research projects (Detail items must be fixed) | Project supported by other government subsidies, etc. *1 | 158 | |
| | KAKENHI | 430 | |
| | Commissioned research projects, etc. | 127 | |
| | Joint research projects | 18 | |
| | Ohers (donations, etc.) | 34 | |
| | Subtotal | 767 | 0 |
| Total | | 1681 | 607 |

Costs (Million yens)

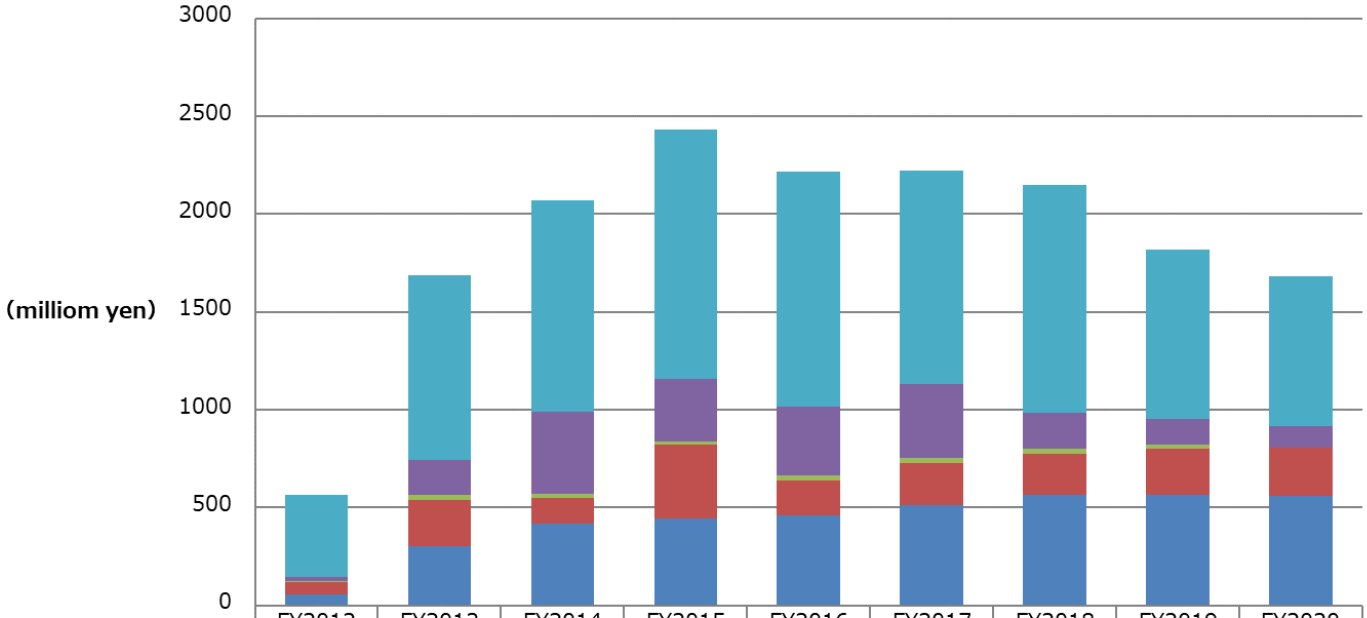
| | |
|---|---|
| **WPI grant in FY 2020** | 659 |
| Costs of establishing and maintaining facilities | 0 |
| Costs of equipment procured | 81 |
| Live cell imaging system | 15 |
| Nuclear magnetic resonance apparatus | 14 |
| Circular Dichroism spectrometer | 12 |
| All-in-one fluorescence microscope | 9 |
| Others | 31 |

*1. Funding sources that include government subsidies (including Enhancements promotion expenses (機能強化促進経費), National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc.), indirect funding, and allocations from the university's own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by KAKENHI or under commissioned research projects or joint research projects, the amounts should be entered in the "Research projects" block.

# Appendix 3-6　Annual Transition in the Amounts of Project Funding

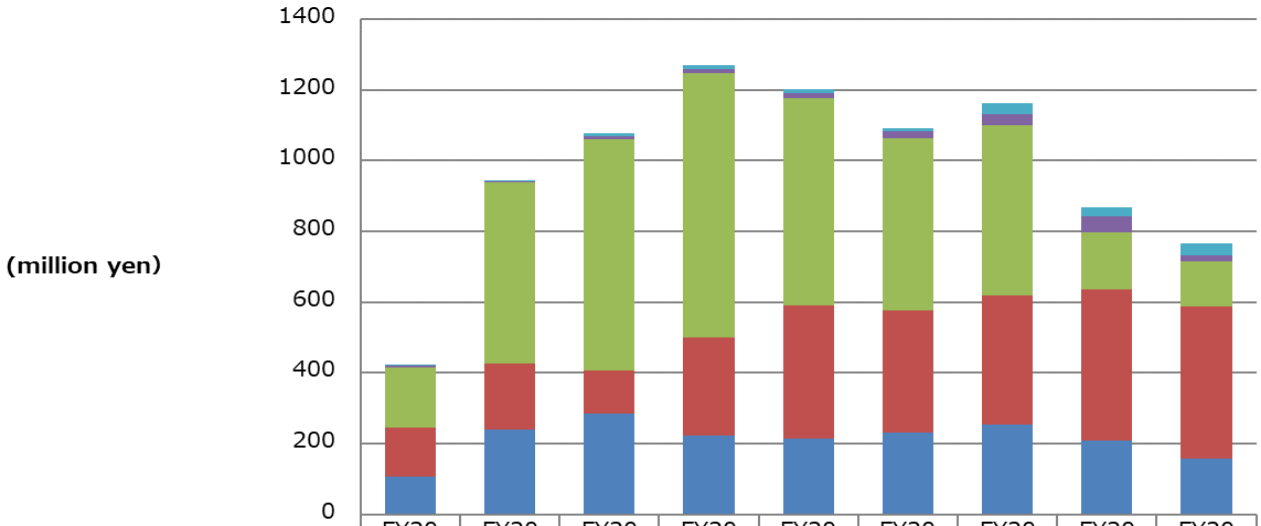
*Make a graph of the transition in the number of overall project funding.

## Transition of Project Expenditures




| | FY2012 | FY2013 | FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 |
|---|---|---|---|---|---|---|---|---|---|
| Research Projects | 421 | 946 | 1078 | 1271 | 1203 | 1093 | 1163 | 869 | 767 |
| Equipment | 22 | 180 | 423 | 322 | 348 | 376 | 186 | 127 | 106 |
| Travel | 4 | 25 | 18 | 17 | 25 | 26 | 26 | 23 | 3 |
| Project Activities | 65 | 236 | 130 | 375 | 183 | 216 | 208 | 235 | 248 |
| Personnel | 53 | 301 | 419 | 445 | 457 | 511 | 565 | 565 | 557 |

## Transition of Research Project Expenditures




| | FY2012 | FY2013 | FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 |
|---|---|---|---|---|---|---|---|---|---|
| Ohers (donations, etc.) | 1 | 3 | 9 | 12 | 11 | 9 | 32 | 26 | 34 |
| Joint research projects | 4 | 3 | 8 | 11 | 14 | 21 | 32 | 46 | 18 |
| Commissioned research projects, etc. | 170 | 512 | 654 | 748 | 586 | 486 | 481 | 161 | 127 |
| KAKENHI | 138 | 187 | 122 | 276 | 377 | 347 | 365 | 426 | 430 |
| Project supported by other government subsidies, etc. *1 | 108 | 241 | 285 | 224 | 215 | 230 | 253 | 210 | 158 |

*1 Definition is as shown in Appendix 3-5 (Project Expenditures)

# Appendix 4-1 FY 2020 Status of Collaboration with Overseas Satellites

- If satellite and partner institutions have been established, fill in required items of the form below.

## 1. Satellites and partner institutions

- List the satellite and partner institutions in the table below (including the domestic satellite institutes).
- Indicate newly added and deleted institutions in the "Notes" column.

### <Satellite institutions>

| Institution name | Principal Investigator(s), if any | Notes |
|---|---|---|
| N/A | N/A | |
| | | |
| | | |
| | | |

### < Partner institutions>

| Institution name | Principal Investigator(s), if any | Notes |
|---|---|---|
| ETH Zurich | Jeffrey W. BODE | |
| Queen's University | Cathleen M. CRUDDEN | |
| University of Texas at Austin | Keiko TORII | |
| University of Southern California | Steve A. KAY | |
| Heinrich Heine University Düsseldorf | Wolf B. FROMMER | |
| NSF Center for Selective C-H Functionalization | N/A | |
| Institute for Basic Science | N/A | |
| RIKEN Center for Sustainable Resource Science (CSRS) | N/A | |
| Institute of Chemistry (IoC), Academia Sinica | N/A | |
| Kenya Agricultural & Livestock Research Organization (KALRO) | N/A | |

- If overseas satellite institutions have been established, fill in required items on the form below. If overseas satellite institutions have not been established, it is not necessary to complete the form.

## 2. Coauthored Papers

- List the refereed papers published in FY 2020 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1-4. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1-4 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2021 and not described in Appendix 1-4.

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

1) N/A
2) N/A
3) N/A
4) N/A

### Overseas Satellite 2 **Name** (Total: OO papers)

1) N/A
2) N/A
3) N/A
4) N/A

## 3. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2020. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

### Overseas Satellite 1:

<To satellite>

| | Under 1 week | From 1 week to 1 month | From 1 month to 3 months | 3 months or longer | Total |
|---|---|---|---|---|---|
| FY2020 | N/A | N/A | N/A | N/A | N/A |
| | | | | | |

<From satellite>

| | Under 1 week | From 1 week to 1 month | From 1 month to 3 months | 3 months or longer | Total |
|---|---|---|---|---|---|
| FY2020 | N/A | N/A | N/A | N/A | N/A |
| | | | | | |

### Overseas Satellite 2:

<To satellite>

| | Under 1 week | From 1 week to 1 month | From 1 month to 3 months | 3 months or longer | Total |
|---|---|---|---|---|---|
| FY2020 | N/A | N/A | N/A | N/A | N/A |
| | | | | | |

<From satellite>

| | Under 1 week | From 1 week to 1 month | From 1 month to 3 months | 3 months or longer | Total |
|---|---|---|---|---|---|
| FY2020 | N/A | N/A | N/A | N/A | N/A |
| | | | | | |

## Appendix 4-2　FY 2020 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.
* Enter the host institution name and the center name in the footer.

**Total:　0**

| | Name | Age | Affiliation | | Academic degree, specialty | Record of research activities (Awards record, etc.) | Time, duration | Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium) |
|---|---|---|---|---|---|---|---|---|
| | | | Position title, department, organization | Country | | | | |
| 1 | N/A | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |

# Appendix4-3 Postdoctoral Positions through Open International Solicitations

* In the column of number of applications and number of selection, put the total number (upper), the number and percentage of overseas researchers in the < > brackets (lower).

| Fiscal year | number of applications | number of selection |
|---|---|---|
| **FY 2012** | 0<br>< 0, 0%> | 0<br>< 0, 0%> |
| **FY 2013** | 141<br>< 138, 98%> | 16<br>< 15, 94%> |
| **FY 2014** | 5<br>< 4, 80%> | 5<br>< 4, 80%> |
| **FY 2015** | 24<br>< 24, 100%> | 9<br>< 9, 100%> |
| **FY 2016** | 7<br>< 5, 71%> | 7<br>< 5, 71%> |
| **FY 2017** | 18<br>< 10, 56%> | 13<br>< 10, 77%> |
| **FY 2018** | 11<br>< 8, 73%> | 8<br>< 8, 100%> |
| **FY 2019** | 35<br>< 20, 57%> | 5<br>< 2, 40%> |
| **FY 2020** | 8<br>< 5, 62%> | 3<br>< 1, 33%> |

Nagoya University

Institute of Transformative Bio-Molecules

# Appendix 4-4 Status of Employment of Postdoctoral Researchers

Enter the information below during the period from the start of the center through the end of FY 2020.

- For each person, fill in the spaces to the right. More spaces may be added.
- Leave "Position as of April 2021" blank if unknown.
- Enter the host institution name and the center name in the footer.

### Japanese Postdocs

| Employment period | Position before employed at WPI center | | Next position after WPI center | | Position as of April 2021* | |
|---|---|---|---|---|---|---|
| | Position title, organization | Country where the organization is located | Position title, organization | Country where the organization is located | Position title, organization | Country where the organization is located |
| 2013/4/1-<br>2014/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Yokohama City University | Japan | Assistant Professor,<br>Yokohama City University | Japan |
| 2013/4/1-<br>2014/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Okayama University | Japan | (Private Company) | Japan |
| 2013/4/1-<br>2019/5/31 | Research Fellow,<br>Nagoya University | Japan | Postdoc, University of<br>Geneva | Switzerland | Assistant Professor,<br>The University of Tokyo | Japan |
| 2013/4/1-<br>2013/11/30 | Research Fellow,<br>Nagoya University | Japan | Designated Associate<br>Professor, Nagoya<br>University | Japan | Associate Professor,<br>Kwansei Gakuin University | Japan |
| 2014/4/1-<br>2017/3/31 | HFSP Postdoc,<br>Monash University | Australia | Research Fellow, Gakushuin<br>University | Japan | | |
| 2015/4/1-<br>2018/3/31 | Technical Assistant, Nagoya<br>University | Japan | Suntory Flowers Ltd. | Japan | Technical Assistant, Nagoya<br>University | Japan |
| 2015/4/1-<br>2017/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Chuo University | Japan | Assistant Professor,<br>Chuo University | Japan |
| 2015/4/1-<br>2018/3/31 | Research Fellow,<br>Kyushu University | Japan | Research Fellow,<br>Nagoya University | Japan | Research Fellow,<br>The University of Tokyo | Japan |
| 2015/4/1-<br>2019/3/31 | Research Fellow,<br>The University of Tokyo | Japan | Assistant Professor,<br>Ritsumeikan University | Japan | Assistant Professor,<br>Ritsumeikan University | Japan |

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|---|---|---|---|---|---|---|
| 2015/4/1-<br>2016/3/31 | Research Fellow,<br>Nagoya University | Japan | | | | |
| 2015/10/1-<br>2016/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Waseda University | Japan | Lecturer,<br>Waseda University | Japan |
| 2016/2/1-<br>2016/3/31 | Research Fellow,<br>Kyoto University | Japan | Assistant Professor,<br>Nagoya University | Japan | Assistant Professor,<br>Nagoya University | Japan |
| 2016/4/1-<br>2019/3/31 | Research Fellow, Technical University of Munich | Germany | Assistant Professor,<br>National Institute for Basic Biology | Japan | Assistant Professor,<br>National Institute for Basic Biology | Japan |
| 2016/4/1-<br>2017/6/18 | Doctoral Student,<br>Kyoto University | Japan | Assistant Professor, Kochi University of Technology | Japan | Assistant Professor,<br>Osaka University | Japan |
| 2017/1/1-<br>2020/10/31 | Associate Specialist, Chinese Academy of Sciences (PSC) | 中国 | Researcher, The National Institute of Advanced Industrial Science and Technology | Japan | Researcher, The National Institute of Advanced Industrial Science and Technology | Japan |
| 2017/2/1-<br>2017/3/31 | Research Fellow,<br>Nagoya University | Japan | | | Program-Specific Research Associate,<br>Kyoto University | Japan |
| 2017/4/1-<br>2018/10/31 | Research Fellow,<br>Nagoya University | Japan | Air Liquide Laboratories | Japan | AGC Inc. | Japan |
| 2018/4/1-<br>2021/3/31 | Research Fellow,<br>Nagoya University | Japan | Researcher, ETH Zurich | Switzerland | Researcher, ETH Zurich | Switzerland |
| 2018/4/1-<br>2018/6/30 | Doctoral Student,<br>Kyoto University | Japan | Assistant Professor,<br>The University of Tokyo | Japan | Designated Assistant Professor,<br>The University of Tokyo | Japan |
| 2018/4/1-<br>2019/3/31 | Doctoral Student, Tokyo Institute of Technology | Japan | Assistant Professor,<br>Kyushu University | Japan | Assistant Professor,<br>Kyushu University | Japan |
| 2013/9/1-<br>2017/6/15 | Student, California State University | USA | - | | | |

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|---|---|---|---|---|---|---|
| 2013/10/1-<br>2017/2/28 | Doctoral Student, National Institute for Basic Biology | Japan | Designated Assistant Professor, Yokohama City University | Japan | | |
| 2014/11/1-<br>Present | Research Fellow, University of Toronto | Canada | Designated Associate Professor, Nagoya University | Japan | Designated Professor, Nagoya University | Japan |
| 2016/4/1-<br>Present | Research Fellow,<br>Chubu University | Japan | (Currently at ITbM) | | (Currently at ITbM) | |
| 2016/4/1-<br>2019/3/31 | Doctoral Student,<br>Kyoto University | Japan | NUProtein Co., Ltd. | Japan | - | |
| 2016/12/1-<br>2019/9/30 | Post-doctoral Position, Nara Institute of Science and Technology | Japan | - | | | |
| 2017/9/1-<br>Present | Research Fellow, Osaka Prefecture University | Japan | (Currently at ITbM) | | (Currently at ITbM) | |
| 2017/12/1-<br>Present | Research Fellow, Tokyo University of Science | Japan | (Currently at ITbM) | | (Currently at ITbM) | |
| 2018/3/1-<br>2018/4/30 | Doctoral Student,<br>Nagoya University | Japan | Postodoctoral Researcher, ETH-Zürich | Switzerland | Program-Specific Assistant Professor, Kyoto University | Japan |
| 2019/4/1-<br>2019/4/30 | Designated Assistant Professor, National Institute for Basic Biology | Japan | Designated Assistant Professor, National Institute for Basic Biology | Japan | Designated Assistant Professor, Exploratory Research Center on Life and Living Systems | Japan |
| 2019/4/1-<br>2019/6/30 | Technical Assistant, Nagoya University | Japan | Research Fellow,<br>Nagoya University | Japan | (Currently at ITbM) | |
| 2021/1/1-<br>Present | Research Fellow,<br>Nagoya University | Japan | (Currently at ITbM) | | | |
| 2019/8/1-<br>Present | Research Fellow,<br>Hokkaido University | Japan | (Currently at ITbM) | | (Currently at ITbM) | |

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|---|---|---|---|---|---|---|
| 2020/4/1-<br>2020/ 9 /30 | Research Fellow,<br>Nagoya University | Japan | Research Fellow,<br>Nagoya University | Japan | Research Fellow,<br>Nagoya University | Japan |
| 2020/5/1-<br>2020/9/30 | Research Fellow,<br>Nagoya University | Japan | Researcher, Heinrich-Heine-Universität Düsseldorf | Germany | Researcher, Heinrich-Heine-Universität Düsseldorf | Germany |
| 2020/6/1-<br>Present | Research Associate, National Institute for Basic Biology | Japan | (Currently at ITbM) | | (Currently at ITbM) | |
| 2020/10/1-<br>Present | Researcher, Kyoto Sangyo University | Japan | (Currently at ITbM) | | (Currently at ITbM) | |
| 2020/10/1-<br>Present | NPO Hitomaki | Japan | (Currently at ITbM) | | (Currently at ITbM) | |
| 2009/4/1-<br>2013/5/31 | Doctoral Course, Azabu University | Japan | Designated Assistant Professor, National Institute for Basic Biology | Japan | Associate Professor, Tokyo University of Agriculture and Technology | Japan |
| 2015/4/1-<br>2018/12/31 | Research Fellow,<br>Nagoya University | Japan | Researcher, Institute of Physical and Chemical Research | Japan | Researcher, Institute of Physical and Chemical Research | Japan |
| 2015/4/1-<br>2020/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor, Nagoya University | Japan | Assistant Professor, Nagoya University | Japan |
| 2015/4/1-<br>2018/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Yokohama City University | Japan | (Private Company) | Japan |
| 2016/6/1-<br>2017/11/30 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Hokkaido University | Japan | Assistant Professor,<br>Hokkaido University | Japan |
| 2016/4/1-<br>2019/3/31 | Research Fellow,<br>Nagoya University | Japan | Program-Specific Assistant Professor, Kyoto University | Japan | Program-Specific Assistant Professor, Kyoto University | Japan |
| 2014/4/1-<br>2015/12/31 | Research Fellow,<br>Nagoya University | Japan | Associate Professor,<br>University of Science and Technology of China | China | Assistant Professor,<br>Tohoku University | Japan |
| 2014/10/1-<br>2018/5/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor, Nagoya University | Japan | Assistant Professor, Nagoya University | Japan |

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|---|---|---|---|---|---|---|
| 2013/5/1-<br>2014/3/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor, Gifu Pharmaceutical University | Japan | Assistant Professor, Gifu Pharmaceutical University | Japan |
| 2014/4/1-<br>2015/3/31 | Postdoctral Fellow,<br>Technische Universität Berlin | Germany | Researcher, National Institute for Materials Science | Japan | Researcher, National Institute for Materials Science | Japan |
| 2013/9/1-<br>2015/3/31 | Doctoral Student,<br>Nagoya University | Japan | Research Fellow, The University of Tokyo | Japan | Idemitsu Kosan Co., Ltd. | Japan |
| 2013/4/1-<br>2015/10/31 | Doctoral Student,<br>Osaka University | Japan | Research Fellow, Osaka Unversity | Japan | Assistant Professor,<br>Kyoto University | Japan |
| 2017/4/1-<br>2018/3/31 | Doctoral Student,<br>Kyoto University | Japan | Assistant Professor,<br>Kyoto University | Japan | Assistant Professor,<br>Kyoto University | Japan |
| 2019/4/1-<br>2019/12/31 | Doctoral Student,<br>Nagoya University | Japan | Researcher, Emory University | USA | Researcher, Emory University | USA |
| 2015/4/1-<br>2016/3/31 | Doctoral Student,<br>Nagoya University | Japan | Mitsubishi Chemical Corporation | Japan | Mitsubishi Chemical Corporation | Japan |
| 2017/4/1-<br>Present | Tokai Medical Products, Inc | Japan | Research Fellow,<br>Nagoya University | Japan | Designated Assistant Professor, Nagoya University | Japan |
| 2015/4/1-<br>2018/3/31 | Researcher,  University of Toronto | Japan | Assistant Professor (Non-tenured), Meiji University | Japan | Assistant Professor, Meijo University | Japan |
| 2015/4/1-<br>2016/6/30 | Research Fellow,<br>Kyushu University | Japan | Assistant Project Scientist, University of California, San Diego | USA | Assistant Project Scientist, University of California, San Diego | USA |

**Overseas Postdocs**

| Employment period | Position before employed at WPI center | | Next position after WPI center | | Position as of April 2021* | | Nationality |
|---|---|---|---|---|---|---|---|
| | Position title, organization | Country where the organization is located | Position title, organization | Country where the organization is located | Position title, organization | Country where the organization is located | |

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| 2013/4/1-<br>2013/11/14 | Research Fellow,<br>Nagoya University | Japan | Research Fellow,<br>Nagoya University | Japan | Associate Professor,<br>National University of Kaohsiung | Taiwan | Taiwanese |
| 2013/4/1-<br>2014/4/7 | Research Fellow,<br>Nagoya University | Japan | Doctoral Student,<br>Massachusetts Institute of Technology | USA | Associate Professor,<br>Western Washington University | USA | USA |
| 2014/1/1-<br>2016/2/29 | Doctoral Student, University of North Carolina | USA | Amgen Inc. | USA | Researcher, Amgen Inc.,<br>Process Development | USA | USA |
| 2015/11/1-<br>2019/9/30 | Doctoral Student,<br>University of Hong Kong | Hong Kong | Associate professor, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University | China | Associate professor, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University | China | Chinese |
| 2017/4/1-<br>2019/2/16 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Shanghai Jiao Tong University | China | Assistant Professor,<br>Shanghai Jiao Tong University | China | Chinese |
| 2017/10/15-<br>Present | Assistant, Polish Academy of Sciences | Poland | Senior Scientist, Polish Academy of Sciences | Poland | Senior Scientist, Polish Academy of Sciences | Poland | Polish |
| 2018/11/1-<br>Present | Postdoc,<br>Stockholm University | Sweden | (Currently at ITbM) | | (Currently at ITbM) | | Spanish |
| 2013/4/1-<br>2015/4/30 | Doctoral Student,<br>Nagoya University | Japan | Assistant Professor, Indian Institute of Science Education and Research | India | Assistant Professor, Indian Institute of Science Education and Research | India | Indian |
| 2013/4/1-<br>2019/3/31 | Research Fellow,<br>The University of Tokyo | Japan | Professor, Peking University | China | Professor, Peking University | China | Chinese |
| 2013/6/16-<br>2016/1/31 | AstraZeneca India Pvt Ltd | India | Designated Assistant Professor,<br>Nagoya University | Japan | Schrödinger, Inc. | Germany | Indian |
| 2013/6/1-<br>2014/3/31 | Researcher, Institute of Physical and Chemical Research | Japan | Reserch Fellow,<br>ETH Zürich | Switzerland | Scientist, Sygnature Discovery | UK | French |

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|---|---|---|---|---|---|---|---|
| 2013/6/1-<br>2014/5/31 | Assistant Professor, COMSATS Institute of Information and Technology | Pakistan | Assistant Professor, COMSATS Institute of Information and Technology | Pakistan | Associate Professor, COMSATS Institute of Information and Technology | Pakistan | Pakistani |
| 2013/6/1-<br>2015/11/30 | Doctoral Student, University of South Florida | USA | Postdoctoral Research Associate, The University of Sydney | Australia | Postdoctoral Research Associate, The University of Sydney | Australia | Indian |
| 2013/6/1-<br>2015/8/31 | Post-Doc Research Fellow, Max-Planck-Institut | Germany | Post-Doc Research Fellow, Max-Planck-Institut | Germany | Professor, South China University of Technology | China | Chinese |
| 2013/7/5-<br>2014/7/31 | Doctoral Student, University College Dublin (CSCB) | Ireland | Research Fellow, National Autonomous University of Mexico (UNAM) | Mexico | Senior Researcher, Universidad Autónoma Chapingo | Mexico | Mexican |
| 2013/10/1-<br>2015/12/31 | Doctoral Student, Indian Institute of Technology Madras | India | - | | Anthem Bioscience, Pvt. Ltd. | India | Indian |
| 2013/10/1-<br>2015/7/31 | Student, Nagoya University | Japan | Associate Professor, Nanchang University | China | Associate Professor, Nanchang University | China | Chinese |
| 2013/11/1-<br>2016/8/31 | Postdoc Research Fellow, Okayama University | Japan | Lecturer, Xi'an Jiaotong University | China | Associate Professor, Xi'an Jiaotong University | China | Chinese |
| 2014/1/16-<br>2016/3/14 | Research Assistant, Heinrich-Heine-Universität Düsseldorf | Germany | Next Move KK | Japan | | | German |
| 2014/5/1-<br>2015/1/31 | Postdoc, University of Amsterdam | Netherlands | Research Associate, Institut des Sciences Chimiques de Rennes CNRS | France | Senior Researcher, Institut des Sciences Chimiques de Rennes CNRS | France | Spanish |
| 2014/9/1-<br>2014/12/19 | Postdoctoral Fellow, Queen's University | Canada | Postdoctoral Fellow, Queen's University | Canada | Researcher, Private Corporation | Canada | Swiss |
| 2014/12/16-<br>2017/6/30 | Doctoral Student, University Rovira I Virgili | Spain | Designated Assistant Professor, Nagoya University | Japan | (Private Company) | | Swedish |
| 2015/4/16-<br>2020/5/6 | Doctoral Student, University of British Columbia | Canada | Air Liquide | Japan | Air Liquide | Japan | Canadian |

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|---|---|---|---|---|---|---|---|
| 2015/4/16-<br>Present | Doctoral Student, University of British Columbia | Canada | (Currently at ITbM) | | (Currently at ITbM) | | Canadian |
| 2015/5/16-<br>2017/5/15 | Post-doctoral Research Scientist, University of Jyväskylä | Finland | Neste Corporation Inc. | Finland | Neste Corporation Inc. | Finland | Finnish |
| 2015/6/1-<br>2017/4/30 | Postdoctoral Research Fellow, Karlsruhe Institute of Technology | Germany | Schrödinger, Inc. | Germany | Schrödinger, Inc. | Germany | German |
| 2016/3/1-<br>2017/8/31 | Doctoral Student, The Indian Institute of Science | India | Scientist, Central Drug Research Institute | India | Scientist, Central Drug Research Institute | India | Indian |
| 2016/4/1-<br>2020/12/28 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor, Indian Institutes of Technology Gandhinagar | India | Assistant Professor, Indian Institutes of Technology Gandhinagar | India | Indian |
| 2016/5/16-<br>2016/12/31 | Doctoral Student,<br>ETH Zürich | Switzerland | - | | Siegfried AG | Switzerland | Swiss |
| 2016/10/1-<br>2017/10/31 | Research Fellow, Free University of Berlin | Germany | Program-Specific Lecturer, Kyoto University | Japan | Senior Scientist, Merck Healthcare KGaA | Germany | German |
| 2017/1/1-<br>2017/12/31 | Research Fellow, University of Washington | USA | Assistant Professor, Central Drug Research Institute | India | Assistant Professor, Central Drug Research Institute | India | Indian |
| 2017/1/1-<br>2019/10/31 | Research Fellow, Indian Institute of Technology Tirupati | India | Research Associate, University of Cambridge | UK | Research Associate, University of Cambridge | UK | Indian |
| 2017/1/16-<br>2018/8/31 | Doctoral Student, The University of Manchester | UK | Lecturer, The University of Manchester | UK | Research Associate, Kyoto University | Japan | UK |
| 2017/6/1-<br>2020/7/31 | Postdoctoral Fellow,<br>Academia Sinica | Taiwan | Postdoctoral Fellow,<br>Academia Sinica | Taiwan | Postdoctoral Fellow,<br>Academia Sinica | Taiwan | Taiwanese |
| 2017/6/1-<br>2020/3/31 | Doctoral Student, University of Münster | Germany | Designated Professor,<br>Fuzhou University | China | Designated Professor,<br>Fuzhou University | China | Chinese |
| 2017/8/1-<br>2020/11/30 | Doctoral Student,<br>University of Edinburgh | UK | Guangzhou University of Chinese Medicine・Xinglin Young Scholar | China | Guangzhou University of Chinese Medicine・Xinglin Young Scholar | China | Chinese |

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|---|---|---|---|---|---|---|---|
| 2017/8/1-<br>2020/12/31 | Research Associate,<br>Indian Institute of Technology Madras | India | INSPIRE Researcher, Indian Institute of Technology Tirupati | India | INSPIRE Researcher, Indian Institute of Technology Tirupati | India | Indian |
| 2017/8/1-<br>2019/2/28 | Doctoral Student,<br>University of Calabria | Italy | Postdoctoral Researcher,<br>Hokkaido University | Japan | Designated Assistant Professor,<br>Hokkaido University | Japan | Italian |
| 2017/9/1-<br>2019/3/31 | Postdoc,<br>ENS Paris-Saclay | France | - | | Researcher,<br>Institut Curie | France | Hungarian |
| 2015/8/1-<br>2018/8/31 | Research Fellow,<br>Polish Academy of Sciences | Poland | Research Fellow,<br>Polish Academy of Sciences | Poland | Assistant Professor,<br>Polish Academy of Sciences | Poland | Polish |
| 2017/11/1-<br>Present | Doctoral Student,<br>Sun Yat-sen University | China | Associate Professor, Sun Yat-sen University | China | Associate Professor, Sun Yat-sen University | China | Chinese |
| 2017/11/16-<br>2021/3/31 | Postdoctoral Fellow,<br>University of Toronto | Canada | Research scientist,<br>FPInnovations | Canada | Research scientist,<br>FPInnovations | Canada | Canadian |
| 2015/11/18-<br>2018/1/31 | Doctoral Student,<br>University of Calgary | Canada | Post-doctoral -Researcher,<br>Cold Spring Harbor Laboratory | USA | Research Fellow, Purdue University | USA | Indian |
| 2018/4/1-<br>2018/12/31 | Researcher,<br>Institute for Molecular Science | Japan | Associate Professor,<br>Sun Yat-sen University | China | Associate Professor,<br>Sun Yat-sen University | China | Chinese |
| 2018/10/1-<br>2020/7/31 | Student, University of California | USA | Doctoral Student, The Scripps Research Institute | USA | Doctoral Student, The Scripps Research Institute | USA | Swiss |
| 2018/10/1-<br>2019/8/31 | Doctoral Student,<br>National University of Singapore | Singapore | Lecturer, YuLin College | China | Research Fellow, Inner Mongolia University | China | Chinese |
| 2019/1/1-<br>Present | Postdoctoral Scientist,<br>High Energy Accelerator Research Organization | Japan | (Currently at ITbM) | | (Currently at ITbM) | | UK |
| 2019/1/16-<br>2020/9/30 | Postdoctoral Researcher,<br>KU Leuven | Belgium | Associate Professor,<br>Nagoya University | Japan | Associate Professor,<br>Nagoya University | Japan | Vietnamese |

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|---|---|---|---|---|---|---|---|
| 2019/4/1-<br>2019/9/30 | Research Fellow,<br>Nagoya University | Japan | - | | | | USA |
| 2019/8/1-<br>Present | Student, UNIVERSITY OF MADRAS | India | (Currently at ITbM) | | (Currently at ITbM) | | Indian |
| 2019/10/1-<br>Present | Beijing Institute of Technology | China | (Currently at ITbM) | | (Currently at ITbM) | | Chinese |
| 2019/10/1-<br>Present | University of Pennsylvania | | (Currently at ITbM) | | (Currently at ITbM) | | German |
| 2019/12/1-<br>Present | Technische Universität Berlin,<br>Institute of Chemistry | Germany | (Currently at ITbM) | | (Currently at ITbM) | | Chinese |
| 2020/1/16-<br>Present | Q26(Private Company) | UK | (Currently at ITbM) | | (Currently at ITbM) | | UK |
| 2020/1/16-<br>Present | Humbodlt Research Fellowship,<br>TU Berlin | Germany | (Currently at ITbM) | | (Currently at ITbM) | | Chinese |
| 2020/11/1-<br>Present | Osaka University | Japan | (Currently at ITbM) | | (Currently at ITbM) | | Indian |
| 2020/11/1-<br>Present | University of Pittsburgh | USA | (Currently at ITbM) | | (Currently at ITbM) | | Singaporean |
| 2020/12/1-<br>Present | University of Hyderabad | India | (Currently at ITbM) | | (Currently at ITbM) | | Indian |
| 2014/4/1-<br>2019/3/30 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Shanghai University | China | Assistant Professor,<br>Shanghai University | China | Chinese |
| 2016/4/1-<br>2019/2/28 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor, Nanjing University | China | Assistant Professor, Nanjing University | China | Chinese |
| 2014/4/1-<br>2016/9/30 | Research Fellow,<br>Nagoya University | Japan | Associate Professor,<br>Jiangnan University | China | Associate Professor,<br>Jiangnan University | China | Chinese |
| 2014/8/1-<br>2016/7/31 | Research Fellow,<br>Nagoya University | Japan | Assistant Professor,<br>Huazhong University of Science and Technology | China | Assistant Professor,<br>Huazhong University of Science and Technology | China | Chinese |
| 2013/10/1-<br>2017/8/31 | Research Fellow,<br>Nagoya University | Japan | Research Fellow,<br>Nagoya University | Japan | Professor, Jilin University | China | Chinese |

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|---|---|---|---|---|---|---|---|
| 2019/4/1-<br>2021/2/28 | Research Fellow, Nanjing Agricultural University | China | Assistant Professor, Foshan University | China | Assistant Professor, Foshan University | China | Chinese |

# Appendix4-5 List of the Cooperative Research Agreements with Overseas Institutions

*Prepare the information below during the period from the beginning of the Center through March 2021.

1. Name of an Agreement : Memorandum of Understanding
   Dates of an Agreement : April 1, 2013
   Counterpart of an Agreement : Queen's University
   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. Name of an Agreement : Memorandum of Understanding
   Dates of an Agreement : September 1, 2013
   Counterpart of an Agreement : ETH Zurich
   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.
3. Name of an Agreement : The Memorandum of Understanding on the promotion and collaborations
   Dates of an Agreement : March 18, 2014
   Counterpart of an Agreement : Albert-Ludwigs-Universität Freiburg
   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.
4. Name of an Agreement : Memorandum of Understanding on collaboration and cooperation
   Dates of an Agreement : January 7, 2015
   Counterpart of an Agreement : The RIKEN Center for Sustainable Resource Science (CSRS)
   Summary of an Agreement : This MOU is to promote researches in biology, chemistry, and their interdisciplinary fields under collaboration and cooperation.
5. Name of an Agreement : Memorandum of Understanding on Joint Workshop
   Dates of an Agreement : January 7, 2015
   Counterpart of an Agreement : The RIKEN Center for Sustainable Resource Science (CSRS)
   Summary of an Agreement : The MOU is to hold Joint-Workshop under non-disclosure agreement.
6. Name of an Agreement: Memorandum of Understanding
   Dates of an Agreement : April 1, 2017
   Counterpart of an Agreement : Heinrich Heine University Düesseldorf
   Summary of an Agreement : The MOU is to affiliate Dr. Wolf B. Frommer (Heinrich Heine University Düesseldorf) 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.
7. Name of an Agreement: Agreement for Academic Exchange and Cooperation
   Dates of an Agreement: Sep. 7, 2017
   Counterpart of an Agreement: Institute of Chemistry, Academia Sinica
   Summary of an Agreement: The agreement is to develop academic exchange and cooperation in education and research between two institutes, including exchange of students and faculty, exchange of scientific materials, publications and information, and joint research and other activities within the range of interest of both Institutes.
8. Name of an Agreement: Agreement for Academic Exchange and Cooperation
   Dates of an Agreement: May 18, 2018
   Counterpart of an Agreement: Faculty of Mathematics and Natural Sciences, Heinrich Heine University Düesseldorf
   Summary of an Agreement: The agreement is to develop academic exchange and cooperation in education and research between two institutes, including exchange of students and faculty, exchange of scientific materials, publications and information, and joint research and other activities within the range of interest of both Universities.

9. Name of an Agreement : Memorandum of Understanding
   Dates of an Agreement : September 1, 2019
   Counterpart of an Agreement : University of Texas at Austin and Howard Hughes Medical Institute
   Summary of an Agreement : The MOU is to affiliate Dr. Keiko Torii (University of Texas at Austin, 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.

10. Name of an Agreement : Memorandum of Understanding
    Dates of an Agreement : October 1, 2020
    Counterpart of an Agreement : Institute of Chemistry, Academia Sinica
    Summary of an Agreement : The MOU is to affiliate Dr. Kenichiro Itami to Academia Sinica with the position of Joint Appointment Research Fellow of Institute of Chemistry to be engaged in collaborative research at Academia Sinica. The MOU includes relationship, commitment, MTA, IP, publications and so on.

# Appendix4-6 Holding International Research Meetings

* Indicate up to twenty of most representative international research conferences or symposiums held from the start of the center through March 2021 and give the number of participants using the table below.

| Date | Meeting title and Place held | Number of participants |
|---|---|---|
| Sep. 19 - 21, 2020 | The 84th Annual Meeting of the Botanical Society of Japan, Online | From domestic institutions:1500<br>From overseas institutions: 200 |
| Dec. 13, 2019 | The 7th International Symposium of Transformative Bio-Molecules (ISTbM-7), 15th Hirata Award, 5th Okazaki Award<br>Sakata and Hirata Hall, Nagoya University | From domestic institutions: 275<br>From overseas institutions: 30 |
| May 21-30, 2019 | EMBO Practical Course "Functional live imaging of plants", ITbM, Nagoya University | From domestic institutions: 57<br>From overseas institutions: 51 |
| July 20, 2019 | ITbM-GTR Pre-ISNA Symposium "Toward advanced functions from new pi-skeletons", Noyori Conference Hall, Nagoya University | From domestic institutions: 220<br>From overseas institutions: 30 |
| Feb. 28, 2019 | The 24th Nagoya Medal of Organic Chemistry, Nagoya | From domestic institutions:320<br>From overseas institutions: 5 |
| Oct. 4-5, 2018 | The 6th International Symposium on Transformative Bio-Molecules (ISTbN-6), Hirata Award, Okazaki Award, Nagoya | From domestic institutions: 400<br>From overseas institutions: 15 |
| June 11-16, 2018 | The 25th International Congress on Sexual Plant Reproduction, Gifu | From domestic institutions: 50<br>From overseas institutions: 75 |
| Dec. 22, 2017 | The 23rd Nagoya Medal of Organic Chemistry, Nagoya | From domestic institutions: 370<br>From overseas institutions: 5 |
| Nov. 20-21, 2017 | The 5th International Symposium on Transformative Bio-Molecules (ISTbN-5), Hirata Award, Okazaki Award, Nagoya | From domestic institutions: 383<br>From overseas institutions: 15 |
| Sep. 25-26, 2017 | 1st international symposium by ITbM and the University of Freiburg "Multicomponent Supramolecular Catalysts for Sustainable Chemical Synthesis", Freiburg, Germany | From domestic institutions: 20<br>From overseas institutions: 100 |
| July 13-14, 2017 | 2017 IoC-IPMB-ITbM Joint Workshop on New Frontiers by Fusing Chemistry and Biology, Taipei, Taiwan | From domestic institutions: 30<br>From overseas institutions: 60 |
| Nov. 16-17, 2016 | 2016 ITbM-IoC Joint Workshop on Biomolecules and Materials, Nagoya | From domestic institutions: 50<br>From overseas institutions: 20 |
| Nov. 11, 2016 | International Symposium on Biological Rhythms "Towards understanding the molecular clockwork", Nagoya | From domestic institutions: 200<br>From overseas institutions: 30 |
| June 16-17, 2016 | 2016 ITbM-CCHF-IBS International C-H Functionalization Workshop, Nagoya | From domestic institutions: 40<br>From overseas institutions: 60 |

# Appendix 5 List of Media Coverage of Projects Carried out between FY 2012 – 2020

* Select main items of press releases, media coverage, and reports for FY 2012-2020 (especially by overseas media)

## 1) Japan

| No. | Date | Type of the media (e.g., newspaper, magazine, television) | Description |
|---|---|---|---|
| 1 | Feb. 3-Mar. 31, 2021 | Newspapers (7), Websites (27) | Research on ”Plasma membrane H+-ATPase overexpression increases rice yield via simultaneous enhancement of nutrient uptake and photosynthesis”, published in Nature Communications. Featured in: Chunichi Shimbun, Nikkei Shimbun, Kagaku Shimbun, Nikkan Kogyo, Gifu Shimbun, Mainichi Shimbun, Nippon Nougyou Shimbun.<br>Toshinori Kinoshita (PI) |
| 2 | May. 22-Jun. 20, 2020 | Newspapers(2), Magagine(1), Websites (2) | esearch on "Training instance segmentation neural network with synthetic datasets for crop seed phenotyping" published in Nature Communications Biology. Featured in: Kagaku Shimbun, Nikkan Kogyo, Kodomo no kagaku.<br>Yosuke Toda (Assistant Professor, Kinoshita G) and Toshinori Kinoshita (PI) |
| 3 | Apr. 8-May. 24, 2020 | Newspapers(3), Websites (32) | Research on regulation of winter depression-like behavior in medaka behavior, published in PNAS. Featured in: Chunichi Shimbun, Nikkei Shimbun, Mainichi Shimbun.<br>Takashi Yoshimura (PI) |
| 4 | May 14, 2019 | Newspaper(1), Websites (3) | Research on plant circadian clock, published in Proceeding of the National Academy of Sciences. Featured in: Chunichi Shimbun, Fukui Shimbun Online, Nikkei BioTec Online, CNET Japan, etc.<br>Norihito Nakamichi (Associate Professor, Kinoshita G) and Toshinori Kinoshita (PI) |
| 5 | Jul. 19, 2019 | Newspaper(1), Websites (4) | Research on Strength of carbon nanotubes depending on their chemical structures, published in Nature Communications. Featured in: Kagaku Shimbun, Nikkei Shimbun web, Fabcross for engineer web, B to B platform web, University Journal online etc.<br>Kenichiro Itami (Center Director) |
| 6 | Aug. 29, 2019 | Newspaper | Kenichiro Itami 's presentation about the research of a molecule to eradicate African parasitic plants "Striga" on TICAD7. Featured in: Yomiuri Shimbun.<br>Kenichiro Itami (Center Director) |
| 7 | Dec. 4 2019- Jan. 30, 2020 | Newspapers (9), Websites (6) | Tetsuya Higashiyama was awarded the Asahi Award and special interview. Featured in: Yamagata Shimbun, Asahi Shimbun, Chubu keizai Simbun, Yamagata News online, etc.<br>Tetsuya Higashiyama (PI) |

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|---|---|---|---|
| 8 | Nov. 19, 2019-<br>Mar. 23, 2020 | Newspapers (2), Websites(2),TV (1) | Yuichiro Tsuchiya's special research review on eradicattion of African parasitic plants "Striga".<br>Featured in: Mainichi Shimbun, Mainichi Shimbun online, Chukyo TV, Asahi Shimbun, etc.<br>Yuichiro Tsuchiya (Associate Professor, Kinoshita G) |
| 9 | Feb. 2 - 7, 2019 | Newspaper (2) | Research on "Cell-based screen identifies a new potent and highly selective CK2 inhibitor for modulation of circadian rhythms and cancer cell growth", published online in Science Advances, was featured in Kagaku Shimbun & Nikkei Shimbun.<br>Tsuyoshi Hirota (Associate Professor, Co-PI, Kay-Hirota G) and Kenichiro Itami (Center Director) |
| 10 | Nov. 5 - 9, 2018 | Newspaper (5) | Series Articles "Let's know more about plants" were published in Nikkei Shimbun.<br>Keiko Torii (PI) |
| 11 | Oct. 18, 2018 | Newspaper (1), TV (1) | Joint research on tidal power between Toyota Boshoku and ITbM was featured in Mainichi Shimbun & Tokai TV.<br>Kenichiro Itami (Center Director) |
| 12 | May 31 - Jun. 1, 2018 | Newspaper (3) | Tetsuya Higashiyama's Chunichi Cultural Award was featured in Chunichi Shimbun & Chunichi Shunju.<br>Tetsuya Higashiyama (PI) |
| 13 | Oct. 1 2017 | Magazine (1) | Kenichiro Itami's Interview was featured in Technologist's Magazine.<br>Kenichiro Itami (Center Director) |
| 14 | Jun. 1 - Sep. 26, 2017 | TV (1) | Takashi Yoshimura (animal biology), Kenichiro Itami (synthetic chemistry), Tetsuya Higashiyama's (plant biology) research was featured in a TV program series: Kagaku Michiru.<br>Takashi Yoshimura (PI), Kenichiro Itami (Center Director) and Tetsuya Higashiyama (PI) |
| 15 | May 3 - Jun. 1, 2017 | Newspaper (1) | Kenichiro Itami's Chunichi Cultural Award was featured in Chunichi Shimbun.<br>Kenichiro Itami (Center Director) |
| 16 | Mar. 30, 2016 | Web (1) | Research highlight on nanocarbons, published in Nature Review Materials, was featured in Nature Japan.<br>Kenichiro Itami (Center Director) |
| 17 | Mar. 22, 2016 | Web (1) | Research highlight on aromatic rings, published in JACS, was featured in Chemistry World (RSC).<br>Kenichiro Itami (Center Director) |
| 18 | Jul. 10, 2015 | Newspaper (7), Website (10) | Research on plant reproduction, published in Developmental Cell, was featured in Chunichi Shimbun, Asahi Shimbun, Yomiuri Shimbun, Mainichi Shimbun, Nikkei Sangyo, Nikkan Kogyo Shimbun, Yahoo, Jiji, WSJ, Nikon, etc.<br>Tetsuya Higashiyama (PI) |



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|---|---|---|---|
| 19 | Jul. 10, 2015 | Magazine/Web(1) | Keiko Torii's comments on women in science were appeared in Science.<br>Keiko Torii (PI) |

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|---|---|---|---|
| 20 | May 26,2015 | Newspaper (3), Web (4), TV (1) | Construction of ITbM's new building was featured in Asahi Shimbun, Yomiuri Shimbun, Chunichi Shimbun, Nikkan Kogyo, CBC News, etc. |
| 21 | Dec. 21, 2014 | TV (1) | TV program focusing on ITbM's Mix Labs and Cutting Edge Research in Science was featured in NHK BS1 "Chikyu (Earth) Agora" (50 min). |
| 22 | Oct. 9 - Oct. 20, 2014 | Web (26) | Research on Mechanistic Studies of Nickel Catalysis published in JACS (Release Title: "Chemists uncover new role of a key base in organic synthesis" by Emory University) was featured in EurekAlert!, Phys.org, Science Codex, Science Newsline, etc.<br>Kenichiro Itami (Center Director) |
| 23 | Mar. 31 - Apr. 18, 2014 | Web (52) | Research on "Carbon nanotubes grow in combustion flames" was featured in Phys.org, Science Daily, JST Science Portal, MyNavi News, etc.<br>Stephan Irle (PI) |
| 24 | Nov. 25 - Dec. 6, 2013 | Newspaper (3), TV (1) | Research on "Highly challenging construction of contiguous all-carbon quaternary stereocenters" was featured in Chunichi Shimbun, Nikkei Sangyo, Kagaku Shimbun & CBC.<br>Kohsuke Ohmatsu (Lecturer) and Takashi Ooi (PI) |
| 25 | Jul. 15, 2013 - Feb. 15, 2014 | Web (4), Magazine (1) | Research on a new form of carbon: Grossly warped "nanographene" was featured in MyNavi news, Phys.org, Chemistry World, Cutting Edge Chemistry 2013 & Newton.<br>Kenichiro Itami (Center Director) |
| 26 | Jul. 1 - 3, 2013 | Newspapers (6), Web (3), Magazine (1) | Research on the regulatory mechanism of fish seasonal responses was featured in Chunichi Shimbun, Asahi Shimbun, Nikkei Shimbun, Mainichi Shimbun, Yomiuri Shimbun, Mittwoch, Yahoo news, jijicom, CBC & milsil. This result was also highlighted in Switzerland.<br>Takashi Yoshimura (PI) |
| 27 | Mar. 27, 2013 | Newspaper (3), Web (3) | Itami's diameter selective synthesis was highlighted in Nature Nanotechnology.<br>Itami's research results received favorable coverage in the mass media with titles such as 'Templates ring up uniform nanotubes' and 'Grown from a ring'. It was featured in Nature Nanotech- nology, Chunichi Shimbun, Yomiuri Shimbun, Tokyo Shimbun, Nikkan Kogyo web, Nanotech Japan Chemistry world (Royal Society of Chemistry).<br>Kenichiro Itami (Center Director) |
| 28 | Mar. 18 - 22, 2013 | Web (2), Newspaper (3) | Research on "How a Rooster Knows to Crow at Dawn, Elucidation how the timing of rooster crowing is determined by circadian clock" was featured in National Geographic News, Chunichi Shimbun, Nikkei Shimbun, Asahi Shimbun & NHK web.<br>Takashi Yoshimura (PI) |



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|---|---|---|---|
| 29 | Feb. 1, 2013 | Magazine (1) | Kenichiro Itami was elected the 108 most talented people by mainstream media and intellectuals, which was featured in Bungei Shunju (politics and economics).<br>Kenichiro Itami (Center Director) |

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|---|---|---|---|
| 30 | Dec. 19, 2012-<br>Jan. 22, 2013 | Newspaper (4) | Research on "Elucidation of the mechanism that pollen tube discriminates conspecific species by pollen tube attractants" was featured in Chunichi Shimbun, Mainichi Shimbun, Kagaku Shimbun & Tokyo Shimbun.<br>Tetsuya Higashiyama (PI) |

**2) Overseas**

| No. | Date | Type of the media<br>(e.g., newspaper, magazine, | Description |
|---|---|---|---|
| 1 | Jan. 25, 2021 | Websites (Internationa:2l) | Research on circadian clock published in the Journal of the American Chemical Society. Featured in: Phys.org, News-Medical.<br>Tsuyoshi Hirota (Associate Professor, Co-PI, Kay-Hirota G) |
| 2 | Apr. 13, 2020 | Websites (International:1) | Research on circadian clock published in Nature Chemical Biology. Featured in: Neuroscience News .com.<br>Tsuyoshi Hirota (Associate Professor, Co-PI, Kay-Hirota G) |
| 3 | Apr. 1-9, 2020 | Websites (International:1) | Research on "Discovery of a drug to rescue winter depression-like behavior" published in PNAS. Featured in: Neuroscience News. com.<br>Takashi Yoshimura (PI) |
| 4 | Oct. 10, 2019 | Websites (International:3) | Research on circadian clock published in Journal of the American Chemical Society. Featured in: OPTRONICS online, ScienceDaily, Neuroscience News .com, etc.<br>Tsuyoshi Hirota (Associate Professor, Co-PI, Kay-Hirota G) |
| 5 | Aug. 16, 2019 | Newspaper, Websites<br>(International:3/Domestic:1) | Research on A photostable fluorescent marker for the super-resolution live imaging of the dynamic structure of the mitochondrial cristae, published in Proceeding of the National Academy of Sciences. Featured in: Nikkei Sangyo Shimbun, Nikkei Shimbun web, Nihon no Kenkyu .com, Tech ii.com, etc.<br>Shigehiro Yamaguchi (PI) |
| 6 | Jul. 20-Aug. 2,<br>2019 | Newspapers, Websites<br>(International:1/Domestic:3) | Research on Topological molecular nanocarbons:, published in Science. Featured in: Chunichi Shimbun, Kagaku Shimbun, Nikkan Kogyo Shimbun, ScienceDaily, etc.<br>Yasutomo Segawa and Kenichiro Itami (Center Director) |



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|---|---|---|---|
| 7 | Dec. 14 -17, 2018 | Newspaper (5), Web (International: 6/Domestic: 9), Magazine (Domestic:1/International:1) | Research on "Sphynx molecule to rescue African farmers from witchweed", published in Science, was featured in Chunichi Shimbun, Asahi Shimbun, Nikkei Shimbun, Toyo Keizai, Monthly Chemistry magazine, FNN News, CBC TV, NHK, Nagoya TV, Fuji TV, Chemistry World, Science Magazine, etc.<br>Yuichiro Tsuchiya (Associate Professor, Kinoshita G) |

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|---|---|---|---|
| 8 | Apr. 18- May 24, 2018 | Web(International:15/Domestic:5), TV (2) | Research on "Identification of circadian clock modulators from existing drugs", published online in EMBO Molecular Medicine, was featured in AlphaGalileo JP, EurekAlert! JP, ReserchSEA, Health Medicine Network, Science Newsline, NHK, etc.<br>Takashi Yoshimura (PI) |
| 9 | Apr. 9-30, 2018 | Newspaper (3), Web (International:12/Domestic: 12), TV (1) | Research on "Identification and Characterization of Compounds that Affect Stomatal Movements", published online in Plant & Cell Physiology, was featured in Chunichi Shimbun, Nikkei Shimbun, Nikkan Kogyo Shimbun, NHK, etc.<br>Toshinori Kinoshita (PI) |
| 10 | Jan. 26 - Feb. 8, 2018 | Newspaper (5), Web (International: 13/Domestic: 10) | Research on "Zipping-up" rings to make nanographenes, published in Science, was featured in Chunichi Shimbun, Asahi Shimbun, Nikkei Shimbun, Nikkan Kogyo Shimbun, Kagaku Shimbun, C&EN News, etc.<br>Kenichiro Itami (Center Director) |
| 11 | Sep. 4 - Nov. 3, 2017 | Newspape (5), Web (1), TV (1), Magazine (International:1/Domestic:1) | Research on the color perception of Medaka fish, published in Nature Communications, was featured in Chunichi Shimbun, Asahi Shimbun, Yomiuri Shimbun, Nikkan Kogyo Shimbun, Nikkei Shimbun, NHK, Newton magazine, Science Daily & Science Magazine.<br>Takashi Yoshimura (PI) |
| 12 | 1-May-17 | Magazine (International:1) | Research on ClearSee, a reagent to see inside plants, published in Development. was featured in National Geographic.<br>Tetsuya Higashiyama (PI) |
| 13 | Jan. 26 - Feb. 19, 2017 | Newspaper (5), Web (International:4/Domestic:1) | Research on nanographene synthesis, published in Science, was featured in Chunichi Shimbun, Asahi Shimbun, Kagaku Shimbun, Nikkan Kogyo Shimbun, Nikkei Shimbun, NHK News, C&EN News, Science Daily, Phys.org, Materials Today.<br>Kenichiro Itami (Center Director) |
| 14 | Apr. 14 - Dec. 17, 2017 | Newspaper(6), TV(5), Magazine (International:2/Domestic:1) | Research on the synthesis of a carbon nanobelt, published in Science, was featured in Chunichi Shimbun, Asahi Shimbun, Mainichi Shimbun, Yomiuri Shimbun, Nikkei Shimbun, Toyo Keizai, Monthly Chemistry magazine, FNN News, CBC TV, NHK, Nagoya TV, Fuji TV, Chemistry World & Science Magazine.<br>Kenichiro Itami (Center Director) |





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| 15 | Nov 22 - Dec 19, 2016 | Newspaper (4), Web (International: 15/Domestic: 13) | Research on plant cell division, published in PNAS, was featured in Asahi Shimbun, Chunichi Shimbun, Nikkei Sangyo, Mainichi Shimbun, Kyodo News, Global Plant Council.<br>Minako Ueda (Lecturer) and Tetsuya Higashiyama (PI) |
| 16 | Nov 21 - Dec 12, 2016 | Newspaper (1), Web (International: 52/Domestic: 2), Magazine (1) | Research on genetic engineering, published in Plant and Cell Physiology, was featured in Nikkei Sangyo Shimbun, Nikkei Biotech, Chinese Media, etc.<br>Tetsuya Higashiyama (PI) |

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|---|---|---|---|
| 17 | Sep. 2 - 29, 2016 | Newspaper (3), Web (International: 21/Domestic: 50), Magazine (1) | Research on the zig-zag of leaves, published in Current Biology was featured in Chunichi Shimbun, Nikkei Shimbun, Kagaku Shimbun, Kodomono Kagaku magazine, Kyodo News, Indian Media, etc.<br>Toshiaki Tameshige (Postdoc) , Naoyuki Uchida (Associate Professor, Co-PI) and Keiko Torii (PI) |
| 18 | May 23 - Nov. 12, 2016 | Web (International: 70) | Research on the biological rhythm, published in Angewandte Chemie, was featured in Huffington Post, MSN, Fox News, UK, Canadian, Indian and Dutch Media.<br>Kenichiro Itami (Center Director) and Takashi Yoshimura (PI) |
| 19 | Apr. 8 - Jun. 9, 2016 | Newspaper (4), Web (International: 34/Domestic: 21) | Research on "the discovery of AMOR, a sugar chain molecule that increases the fertilization efficiency in plants", published in Current Biology, was featured in Asahi Shimbun, Chunichi Shimbun, Kagaku Shimbun, Nikkei Shimbun, Kyodo News, JST Science Portal, Chinese Media, etc.<br>Tetsuya Higashiyama (PI) |
| 20 | Aug. 8 - 30, 2016 | Newspaper (3), Web (International: 40/Domestic: 25) | Research on the synthesis of organic nanotubes, published in JACS was featured in Nikkei Sangyo Shimbun, Chunichi Shimbun, Kagaku Shimbun, Yahoo News, Mynavi News, Brazilian, Russian, Chinese, Spanish Media, etc.<br>Kenichiro Itami (Center Director) |
| 21 | Mar. 23, 2016 | Web (International: 19/Domestic: 3) | Research on the plant circadian clock, published in the Plant Cell, was featured in Alpha Galileo JP, EurekAlert! JP, etc.<br>Norihito Nakamichi (Associate Professor, Kinoshita G) |
| 22 | Mar. 10, 2016 | Newspaper (2), Web (International: 32/Domestic: 3), TV (1), Radio (1) | Research on plant fertilization, published in Nature, was featured in Science Daily, Global Plant Council, Chunichi, Kagaku Shimbun, Nature News & Views, NHK News, NHK Radio.<br>Tetsuya Higashiyama (PI) |





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| 23 | Aug. 21- Sep. 28, 2015 | Newspaper (5), Web (International: 34/Domestic: 7) | Interdisciplinary research on "the development of a molecule to probe the growth of parasitic plants", published in Science, was featured in Chunichi Shimbun, Nikkei Sangyo Shimbun, Kagaku Shimbun, Yomiuri Shimbun, Science Daily, Nature Chemical Biology, Science.<br>Shinya Hagihara (Associate Professor, Itami G), Yuichiro Tsuchiya (Associate Professor, Kinoshita G) |
| 24 | May 9 - Jun. 19, 2015 | Newspaper (1); Web (International: 53/Domestic: 7); Magazine (2) | Interdisciplinary research on "molecules that can change the circadian rhythm", published in Angewandte Chemie, was featured in Chunichi Shimbun, Science Daily, Chemisch2Weekblad (Dutch), Social News (Spanish), Yahoo, Chemistry, etc.<br>Kenichiro Itami (Center Director), Takashi Yoshimura (PI), Stephan Irle (PI) and Steve A. Kay (PI) |
| 25 | Feb. 27, 2015 | Magazine (1) | Takashi Yoshimura, Stephan Irle and Jeffrey Bode's research was highlighted in Asia Research News 2015, the online and paper-based magazine focusing on Asian research.<br>Takashi Yoshimura (PI), Stephan Irle (PI) and Jeffrey Bode (PI) |

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|---|---|---|---|
| 26 | Jul. 7 - 24, 2014 | Web (International: 62/ Domestic: 9), Magazine (1) | Research on Internal Brain Receptors of Birds published in Current Biology (Release Title: "Shining light on the 100-year mystery of birds sensing spring for offspring") was featured in incl. Yahoo News and 19 Indian websites.<br>Takashi Yoshimura (PI) |
| 27 | May 27 - Jul. 25, 2014 | Newspaper (2), Web (International: 39/Domestic: 2), TV (International: 1), Magazine (1) | Research on Nickel Catalysis published in Angewandte Chemie International Edition (Release Title: "A novel "Kabuto-like" nickel catalyst forms bioactive frameworks from low-cost phenol derivatives") was featured in incl. BBC.<br>Kenichiro Itami (Center Director) |
| 28 | Apr. 1- 18, 2014 | Magazine (1);<br>Web (International: 45/Domestic: 8) | Research on Carbon Nanotubes published in Carbon (Release Title: "Carbon nanotubes grow in combustion flames") was featured in incl. Science Daily, Phys.org, Chem Europe.<br>Kenichiro Itami (Center Director) |
| 29 | Dec. 24, 2013 - Apr. 2, 2014 | Newspaper (4), Web (85), Magazine (1), TV (1) | Research on "Enhanced plant growth through promotion of stomatal opening" was featured in Asahi Shimbun, Shinano Mainichi Shimbun, Mainichi Shimbun, Kagaku Shimbun, Asahi, Chunichi, Nikkei, Phys.org, Science Daily, International Daily News, milsil, JST Science Channel, etc.<br>Toshinori Kinoshita (PI) |

# Appendix6-1 Host Institution's Commitment (Fund, Personnel)

## 1. Contributions from host institution

### (1) Fund, Personnel

* Regarding "Fund" entry, describe with reference to the items in the Progress Report (Jisseki-hokoku-sho) based on Article 12 of the Grant Guidelines (Kofu-yoko).
* Don't include competitive funding obtained by researchers (used as research project funding)

| (FY 2012-2020) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **<Fund>** | **108** | | | | | | | | **(million yen)** |
| **Fiscal Year** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** |
| Personnel | 44 | 129 | 152 | 158 | 157 | 163 | 178 | 187 | 204 |
| Faculty members | 31 | 101 | 110 | 111 | 120 | 118 | 128 | 137 | 153 |
| Full-time | 31 | 78 | 81 | 85 | 94 | 85 | 96 | 102 | 103 |
| Concurrent | 0 | 23 | 29 | 26 | 26 | 33 | 32 | 35 | 50 |
| Postdocs | | | 13 | 13 | 6 | 13 | 19 | 20 | 17 |
| RA etc. | | | | | | | | | |
| Research support staffs | 3 | 3 | 3 | 3 | 1 | 2 | 3 | 3 | 6 |
| Administrative staffs | 10 | 25 | 26 | 31 | 30 | 30 | 28 | 27 | 28 |
| Full-time | 10 | 25 | 26 | 31 | 30 | 30 | 28 | 27 | 28 |
| Concurrent | | | | | | | | | |
| Project activities | 22 | 19 | 22 | 173 | 22 | 22 | 31 | 30 | 28 |
| Travel | | | | | 1 | | 1 | 2 | 1 |
| Equipment | 1 | | 2801 | | 1 | | | | |
| Research projects | | | | | | | | | |
| Total | 67 | 148 | 2975 | 331 | 181 | 185 | 210 | 219 | 233 |
| **<Personnel>** | **152** | | | | | | | | **(person)** |
| **Fiscal Year** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** |
| Personnel | 18 | 18 | 21 | 20 | 21 | 21 | 23 | 24 | 26 |
| Faculty members | 13 | 13 | 14 | 13 | 15 | 14 | 15 | 16 | 17 |
| Full-time | 6 | 6 | 7 | 7 | 8 | 7 | 8 | 8 | 8 |
| Concurrent | 7 | 7 | 7 | 6 | 7 | 7 | 7 | 8 | 9 |
| Postdocs | | | 2 | 2 | 1 | 2 | 3 | 3 | 3 |
| RA etc. | | | | | | | | | |
| Research support staffs | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| Administrative staffs | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Full-time | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Concurrent | | | | | | | | | |

# Appendix6-1 Host Institution's Commitment

## 1. Contributions from host institution

### (2) Provision of land and/or building(s), lab 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 research 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 research building.

**Personnel**
NU has been covering salaries of
1) 8 PIs of NU.
2) 7 designated associate professors who take charge of education in each department to relieve the PIs of this responsibility. In FY2020, the 7 positions were officially secured by the President-Management Point System and allocated to ITbM as tenure positions.
3) 4 administrative staff + 1 URA through assignment from the University's human resource.

As of April 2021, 4 more positions were also allocated to ITbM through the NU's request to MEXT with the highest priority to strengthen ITbM's activity. According to the ITbM's plan, NU also confirms to provide additional support by all means since FY2022 to secure almost all the ITbM's designated faculty members and the selected postdocs/staff who are essential to run ITbM.

**Construction of ITbM's building**
NU provided the financial support toward construction of ITbM's building constructed in late FY2015.

## 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**
As noted above, 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.

**Student allocation**
All the 8 NU PIs are holding strong ties with their original departments, and undergraduate and graduate students are assigned in the same way before starting ITbM. Three overseas PIs in biology were assigned as a collaborating researcher in the Graduate School of Science, and a few PhD students have been allocated to the groups every year. In FY2022, Graduate School of Science is

going to make its system reform, and will officially allocate PhD students to ITbM's overseas PI groups from FY2022.

## 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 the 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

(*In addition to those listed in the item 1. "Contributions from host institution")

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.

# Appendix6-2 The Host Institution's Mid-term Plan

* Excerpt the places in the host institution's "Mid-term objectives" and/or "Mid-term plan" that clearly show the positioning of the WPI center within its organization.

## Medium-term Goal and Plan of National University Corporation Nagoya University

### Phase Two (April 1, 2010 – March 31, 2016)

- Goal regarding research; Goal regarding research level and results and implementation system
  - Proceed with international-level research based on the Nagoya University Research Plan (M4)

- Actions to be taken to achieve goals regarding research; Actions to be taken to achieve goals regarding research level and results and implementation system
  - 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)" (K10)

### Phase Three (April 1, 2016 – March 31, 2022)

- Goal regarding education; Goal regarding education content and results
  - We will provide high quality education focusing on internationally accepted level to develop global-scale human resources with logical thought and imagination (TM30)
- Goal regarding research; Goal regarding research level and results and implementation system
  - To produce the intellectuals as the comprehensive university that conducts world-leading researches (TM34)

- Actions to be taken to achieve goals regarding education; Actions to be taken to achieve goals regarding education content and results
  - Based on the designated national university concept, based on admissions, curriculi, and diploma policies for education courses in the graduate school, NU will further improve education content by promoting international standardization (e.g. using syllabus written in both Japanese and English and developing the course numbering system), expanding common courses, developing and implementing the personnel training program in cooperation between the industry and universities, leading education and research across specialized fields and providing transferable skills training. NU will improve its international compatibilities by developing joint degree programs with world class partner universities. NU will provide the education program in the doctoral course integrated with the advanced researches conducted in various NU institutes such as the Institute of Transformative Bio-Molecules (ITbM) to attract capable doctoral candidates ((TK30-②)).
- Actions to be taken to achieve goals regarding research; Actions to be taken to achieve goals regarding research level and results and implementation system
  - Based on the designated national university concept, NU will promote the world-leading fundamental research and establish an international and original research center engaged in cross-section study, international collaborative study, and comprehensive study by promoting "World Premier International Research Center Initiative," "Center of Innovation (COI) Program," and "The Program for Promoting the Enhancement of Research Universities" (TK34-①).

# World Premier International Research Center Initiative (WPI)
# Progress Plan (For Final Evaluation)

| | | | |
|---|---|---|---|
| Host Institution | Nagoya University | Host Institution Head | Seiichi Matsuo |
| Research Center | Institute of Transformative Bio-Molecules | | |
| Center Director | Kenichiro Itami | Administrative Director | Tsuyoshi Matsumoto |

* Write your report **within 6 pages**.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

## 1. Mid- to Long-term Research Objectives and Strategies Based on the Center's Results during Funded Period

Describe new challenges in the Center's research objectives and plans after the funding period ends. If major adjustments will be made in the Center's operation, such as newly set research themes/objectives or a change in the director, describe the strategic background to the adjustments.

The mission of ITbM has been to conduct 'needs-inspired' basic research while developing transformative bio-molecules that make a marked change in the form and nature of biological science and technology. By marrying state-of-the-art synthetic chemistry, catalytic chemistry, plant biology, animal biology, live imaging, and theoretical science, ITbM has advanced new research areas of "plant chemical biology", "chemical chronobiology", and "chemistry-enabled live imaging". This exciting endeavor has resulted in the development of a range of promising bio-functional molecules, many of which have been commercialized, and the discovery of molecular mechanisms of important biological events. The most exciting example during the ITbM's first chapter is the development of molecules to potentially combat the parasitic plant *Striga*. Molecules developed at ITbM have entered the exciting phase of being tested in the fields of Africa starting since 2019.

All of these tour-de-force achievements have led scientists in the world to place ITbM as an enabling institute where new bioactive molecules with targeted properties can be rapidly discovered, designed, and synthesized. Going forwards, our mission/goal of developing transformative bio-molecules will not change, instead we will redefine our focus with particular attention to advancing societal implementation of the research outcomes and to develop new scientific fields continuously.

Given this context, we will tackle the following challenges in the next 5-10 years. Through these challenges, ITbM will become more visible, and further be recognized as a world-leading research institute.

### (1) Parasitic Plants

The parasitic plant *Striga hermonthica* (*Striga*), so-called witchweed, has been causing huge damage on crop production in Africa. Infection of harvests by Striga leads to the loss of $10 billion U.S. dollars' worth of crops from the continent every year. However, genetic intractability of *Striga* stood as a significant barrier to understand Striga in detail and develop *Striga* science. ITbM developed SPL7 to control infestation of the *Striga*. The SPL7 is expected to be the long-awaited technology to pursue future food security in the African continent.

Based on our discovery, ITbM will make efforts to provide molecular solutions to the food security issues, especially focusing on Africa because of its importance and urgency. We have initiated collaboration with Kenya Agricultural & Livestock Research Organization (KALRO) and the International Center for Research and Education (ICREA) of NU.

We have organized the "*Striga* team" headed by the Center Director, and paved the way toward combating *Striga* by the development of a small molecule SPL7 (or super strigolactone) that can induce suicide germination of *Striga* seeds in the amazingly low concentration of a femtomolar ($10^{-15}$ molar) range. The Director of KALRO promised to provide his full support in the use of SLP7 against *Striga*. Through the extensive collaboration with KALRO, we started to field-test our molecule and plan to work with the government of Kenya to make it available to all Kenyan farmers.

We are confident that our molecular approach can contribute to the fight against other parasitic plants that are causing huge damage to other crops. We plan to tackle this issue in the second chapter of ITbM.

Adding to our efforts in parasitic plant science, we will develop brand-new molecules for plants and

animals as the next generation of transformative bio-molecules. Plants and animals have their unique but uncovered biological systems consisting of local and systemic cellular communications that are most likely all governed by small molecules. The next-generation molecules will be further designed to specifically control target systems even at the whole organism level. We will particularly focus on **(2) chemistry-enabled plant adaptation** and **(3) clock-disease** as new challenging directions based on what we have achieved so far. We will also continue to work on **(4) chemistry-enabled bioimaging** via developing new fluorescent molecules and advance biological research.

**(2) Chemistry-enabled plant adaptation**

Plants have inherent stress tolerance systems that enable them to adapt to environmental changes and survive under stressful conditions that are essential functions due to their inability to move. However, recent global climate change exceeds the tolerance of the current abiotic stress response of plants, and they often face to serious situations such as failing to fertilize, failing to develop, and eventual death. If such environmental stress can be overcome by synthetic molecules, food production can be maintained or even increased even in a severe $CO_2$-rich environment, improving food security and combatting climate change. We aim to develop such environmental stress-overcoming molecules to maximize the adaptive power of plants via an interdisciplinary approach.

ITbM has developed small molecules that enable stomatal control through an extensive mechanistic investigation and a screening of the chemical libraries. Accordingly, a series of molecules that have enhanced the number of stomata in *Arabidopsis thaliana* have been developed. The stomatal opening/closing mechanism was also investigated, which reveals that the stomatal aperture is a limiting factor of photosynthesis and plant growth. Several molecules that can control stomatal movements have also developed, which include those accelerate stomatal opening/closure and restrict stomatal dynamics reversibly. The stomatal closing molecules have prevented plant leaves from drying-up and suppress withering when sprayed onto the plants.

Having defined new interdisciplinary research areas "plant chemical biology" and "chemistry-enabled live imaging", ITbM has been developing a series of bio-functional molecules that promote functions of plant in various aspects along with fluorescent molecules that visualize the dynamics of various bio-molecules including non-proteinaceous ones. For instance, novel molecules that control plant growth and differentiation based on direct chemical transformation of plant hormones have been developed (*e.g.*, auxin and brassinosteroid derivatives, fairy chemicals, and peptide hormones). Some of them show huge potential to enable plants to overcome severe environments such as high or low temperatures experienced during the reproductive phase. A lead molecule that increases the size of whole plants has been discovered. To test such a number of potentially game-changing molecules that control many plant functions in environmentally challenged fields, we will collaborate with KALRO to bring our molecules to the next stage.

We also recognize that a precise understanding of the distribution and activity of our bioactive target molecules is critically important in order to regulate specific targets with pinpoint accuracy. We have already succeeded in making this happen through the preparation of specially designed bump-and-hole auxin derivatives, which is applicable to design plant genes for chemistry-enabled plant adaptation.

**(3) Clock-disease**

The circadian clock is an approximately 24 h cell-autonomous biological clock inherent to all living organisms. The circadian clock regulates virtually all physiological processes including sleep-wake cycles, hormone release, and metabolism. Disturbances in the circadian system have a profound impact on health, and they have been linked to several pathologies, including obesity, psychiatric disorders, cardiovascular disease, and even cancer. ITbM has defined "chemical chronobiology" as a flagship area, and, through an extensive chemistry-biology-theory collaboration, we have developed many molecules such as a jet-lag reducing molecule and circadian clock-controlling molecules having anti-cancer effects.

The rhythm of life on earth is also shaped by seasons. Plants and animals have an approximately 1 year 'circannual clock' and show profound annual cycles in morphology, behavior and health such as flowering, hibernation, immune function and winter depression. The disruption of annual rhythms under global climate change is having dramatic consequences for ecosystems, agriculture and health. Although both 'mitigation' (*i.e.*, reducing greenhouse gases emissions) and 'adaptation' (*i.e.*, increasing nature's resilience to climate change negative impact) are important, adaptation to climate change in agriculture, health and ecosystems by understanding and utilizing the organisms' seasonal adaptation strategies are urgently needed. However, the underlying mechanism by which the circannual clock operates remains

totally unknown in any organisms.

Since the launch of ITbM, we have established molecular solutions to understand and regulate the circadian clock. Based on the knowledge and experience gained in this area, we will challenge the development of transformative bio-molecules to understand and regulate the circannual clock to combat global climate and environmental changes. Seasonal human morbidity is observed in heart, cerebrovascular, infectious, and psychiatric diseases. In plants, seasonality is observed in growth, pollination, pest and pathogen infestation, and flowering. We will uncover the underlying molecular bases of circannual rhythms in plants and animals. We will also discover biomarkers and drug targets involved in seasonally regulated diseases. Since we have already identified several hit compounds that regulate flowering time in plants and winter depression-like behavior in animals, we will develop transformative bio-molecules that regulate plant and animal adaptation to climate and environmental changes.

**(4) Chemistry-enabled bioimaging**

Bioimaging is one of the indispensable techniques in the current biology. A key to open a new avenue in this technique relies on the development of useful fluorescence dyes. One of the most serious obstacles in the current fluorescence imaging is rapid photobleaching of dyes. This issue is more serious in super-resolution imaging, such as STED (stimulated emission depletion) microscopy. In this regard, we have developed a series of new fluorescent dyes consisted of rigid π-skeletons embedding a phosphine oxide (P=O) moiety, named as "PhoxBright". Their outstanding photostability enabled acquiring not only 3-D structures of cytoskeletons, but also mitochondrial inner-membrane dynamics in the living cells by conducting the STED imaging. Near-infrared (NIR) fluorescent dyes is the other target molecules in our research, which have several advantages, such as diminishing photo-damage to bio-samples, minimal interference from cell autofluorescence, as well as deep penetration in biological tissues. We have developed novel NIR dyes by embedding a P=O moiety to xanthene skeletons. PREX 710, a P=O-containing rhodamine, shows outstanding practical utility in a range of applications, including single molecule imaging, multi-color imaging, and deep-tissue imaging. With these sophisticated dyes in hand, together with state-of-the-art imaging instrumentations, we will make full use of these cutting-edge discoveries to understand and control biological systems, and also to contribute to the advancement of medical diagnosis.

In addition to strengthening our enabling platforms to tackle the above-mentioned unanswered scientific questions potentially leading to a big project with equally big societal impact, we recognize the need for new molecular structures and hence properties to maximize the power of molecules. To this end, we will apply molecular nanocarbons as new molecular entities in biology and explore "nanocarbon biology" as a new scientific field. All the findings will be applied to other projects at ITbM, adding a new dimension in biological science and technology.

**(5) Nanocarbon chemistry and biology**

During the last 10 years, Director Itami has opened up a new research field of molecular nanocarbon science by creating a range of structurally uniform and new forms of nanocarbons by bottom-up chemical synthesis. Itami has enabled access to previously inaccessible nanocarbon materials such as carbon nanobelts, nanorings, and warped nanographenes, with atom-by-atom precision. While their inherent physico-chemical properties have been investigated in view of potential applications in materials science, their applications in biology have barely been examined. We will explore these in the next phase of ITbM, along with collaborations with other institutions and companies. We have already found that a saddle-shaped warped nanographene can be incorporated into cells (with almost no cytotoxicity), where it evokes photo-induced cell death.

## 2. Management System of the Research Organization

### 2-1. Describe the Center's Research Organizational Management System that will Execute the Research Strategy and Plan Described above.

- In Appendix 1-1, list the PIs who will ensure that the Center's project is sustained and advanced after the funding period ends.
- In Appendix 1-2, enter the number of Center personnel (researchers, research-support staff, and administrative staff) in FY 2022.
- In Appendix 2, diagram the Center's organizational management system.

We have established a top-down management system at the start, and the Center Director has the authority to make final decisions over all matters concerning the operation and management of ITbM, such as the appointment of personnel, the Center's budget use and research priorities. This system has been

practically realized because of high levels of mutual trust among all the researchers in ITbM. This approach has enabled ITbM to respond to changes with agility, and to make quick and flexible decisions, without cumbersome bureaucracies. Based on its success thus far, this method will continue to be implemented.

Despite the unique independence of ITbM, ITbM's Director and core members have been holding regular meetings with the President once a month to discuss issues related to the future plan of ITbM and NU. We have also been highly successful at building good relationships with the faculties/departments of NU to which many of ITbM's researchers are co-affiliated. These relationships are critically important for ITbM to secure its management and to boost research.

While PhD students and undergraduate students have been allocated to NU PI groups and several overseas PI groups, the Graduate School of Science will make a system reform to officially allocate more PhD students especially to ITbM's overseas PI groups from FY2022. We will continue the communications and further strengthen ties with other faculties and departments of NU.

We strongly recognize the importance of nurturing the next generation of scientists who will lead ITbM in the future. As Higashiyama (Vice Director of ITbM) is planning to step down concurrent with his move to the University of Tokyo in 2022, we will involve young faculty members in the discussion on our long-term plan. We decided to hire a non-Japanese junior PI, and started the selection process in February 2021. This will also enhance ITbM's internationalization.

We believe the strong relationships between ITbM and external organizations are also quite important. We will continue and strengthen our present collaborations with the institutions of overseas PIs, in addition to NSF-CCHF (US), RIKEN CSRS (Japan), Academia Sinica (Taiwan), and KALRO (Kenya).

## 2-2. Initiatives and Plans that will Impel System Reforms

Describe the Center's action plan that embodies the basic policies of the University Reform Plan, and the Center's plan and strategies that lead to host institution reforms either directly or via ripple effects (also to other institutions, if applicable). Describe also the Center's strategies for fostering and securing the next generation of researchers (e.g., introduction of tenure tracks), and the system reform for enhancing the Center's organizational management, such as the implementation/verification PDCA system.

NU was selected as a "Designated National University" as of March 2018 because of its abilities to develop world-leading education and research activities. Based on President Matsuo's Initiatives for Reform, Autonomy and Innovation 2020 (NU MIRAI 2020), NU will continue its extensive system reform to become a visible world-class research university. In the plan, ITbM is positioned as a core research center of NU for the future, and is responsible to cooperate with NU and devise various tasks to achieve the goal. We will take up the challenges of:

**Spreading Mix Lab concept as an effective practice to promote multidisciplinary research:** The ITbM Mix Lab concept is being widely recognized at many institutions inside and outside of NU because of its high success in encouraging unexplored interdisciplinary research. A notable influence is evident in the Amano research center (CIRFE) of NU. This institute designed a new research building "CIRFE Transformative Electronics Commons (C-TECs)" in 2019, which has "transformative" in the name and was designed in reference to ITbM's Mix Lab & Mix Office. ITbM and CIRFE have been sharing good practices, and will continue our effort to develop better forms to make multidisciplinary cutting-edge science. We will also communicate with other departments and spread our Mix Lab concept.

**Developing a new graduate program with ITbM at the core:** NU recognizes the significance of the Mix Lab concept and plans to extensively involve ITbM in the evolution of graduate schools. NU and ITbM have put together a proposal for a program entitled "Graduate Program of Transformative Chem-Bio Research (GTR)", as an application to the *Doctoral Program for World-leading Innovative & Smart Education (WISE Program)* of MEXT, and was successfully selected in late 2018. In GTR, ITbM is positioned as a hub for promoting interdisciplinary research in the field of natural sciences, and the designated faculty members of ITbM will be engaged in the education of PhD students through supervising collaborative research. An important aspect of this program is its ripple effect. Through discussions to prepare the concrete plan, the ITbM spirit of Mix was widely shared among the cooperating institutes and firms, spreading to the researchers on site. The GTR installed three Mix Labs so far to ensure the success of the program. On the other hand, we also recognize that barriers still exist in organizational structures in NU. We will continue to work with NU headquarters and the related departments to improve graduate education at NU.

**Establishing effective public relations system in NU:** In cooperation with other WPI institutes, ITbM has been engaged in various public relations and outreach activities. By sharing the expertise and experience of ITbM, NU now has a system to send out international press releases highlighting research accomplishments of the entire university. ITbM will further cooperate with NU to establish more efficient

public relations system and organize outreach activities as a whole. It is also notable that ITbM has established strong ties with high schools particularly in the Tokai area. Many of the researchers at ITbM have given lectures at high schools through this program. As a result, our cutting-edge science attracts many high school students, and more importantly, many high school teachers. The WPI Science Symposium in 2018 organized by ITbM was a focal point for these interactions. We will share this experience with NU to continue improving our strategy to attract and encourage top students.

## 3. Center's Position within Host Institution and Measures to Provide It with Resources

Describe the Center's future plans with regard to the following points after the funding period ends.

### 3-1. From a Mid- to Long-term Perspective, the Position of the Center within the Organization of the Host Institution

Describe where the Center will be placed within the host institution's overall organizational strategy under the leadership of the institution's head.

- In Appendix 3, diagram the Center's position within the organization of the host institution, and describe that positioning using excerpts from the institution's mid- to long-term plan. If the plan has not been established yet, describe the consideration being given to the Center's positioning.

As mentioned above, ITbM is positioned as a flagship research institute in President Matsuo's initiative NUMIRAI 2020 and the University's "Designated National University" concept. To secure the employment of ITbM's faculty member and staff, NU has decided to make a significant organizational reform in 2019. As noted above, NU launched the Nagoya University Institute for Advanced Study (NAIAS), with ITbM positioned under this umbrella. Even under this new structure, the Director of ITbM retains the authority to make decisions regarding ITbM.

NU and ITbM have undertaken this reorganization, conscious of maintaining the good relationships already established between ITbM with other departments/faculties at NU. Eight NU PIs will continue their cooperation with their original faculties, and the undergraduate/graduate students are allocated. While students were not allocated to the overseas PI groups at the beginning, it is now possible for this to happen and some overseas PIs are currently supervising students.

ITbM is now indispensable as a core of the new graduate program GTR, which endorses ITbM's continuation. Through this program, ITbM will further be able to increase the number of PhD students trained.

ITbM has two research supporting divisions: the research promotion division (RPD) and the strategic planning division (SPD). Their members are making strong ties with the Academic Research & Industry-Academia-Government Collaboration Department and other institutes in NU.

### 3-2. Host Institution's Action Plan for Sustaining and Advancing the Center as a World Premier International Research Center (e.g., Positioning, Financial Resources)

- In Appendix4, describe the host institution's resource allocation plans for the Center, including the allocation of posts (in both its research and administrative divisions).

NU has promised that NU cooperates with ITbM and support it toward future development as a flagship research institute of NU. ITbM has now become an indispensable entity at NU, and is supported in the new framework as noted above. At its inception, ITbM had eight PI positions transferred to it from NU. In 2019, 7 more faculty positions for ITbM were officially secured by the President-Management Point System and allocated to ITbM as tenure positions.

As of April 2021, 4 more positions were also allocated to ITbM through the NU's request to MEXT with the highest priority to strengthen ITbM's activity. According to the ITbM's plan, NU also confirms to provide additional support by all means from FY2022 to secure almost all the ITbM's designated faculty members and the selected postdocs/staff who are essential to run ITbM, as denoted in the host institution's commitment (Appendix 6-1).

With regards to research space, NU continues to support ITbM, and will provide additional space according to ITbM's needs as their highest priority.

NU has also committed its full support to collect funds to sustain ITbM. NU will boost the reputation of ITbM to further increase the endowment by all means including through the Nagoya University Foundation and academia-industry partnership.

# Appendix 1 List of Principal Investigators (for Progress Plan)

* If the number of principal investigators exceeds 10, add rows as appropriate.
* Give age as of 1 April 2022
* For investigators who cannot participate in the center project from FY 2022, indicate the time that their participation will start in the "Notes" column.
* Enter the host institution name and the center name in the footer.

| | Name | Age | Current affiliation (position title, organization, department) | Academic degree and current specialties | Effort(%)* | Notes (Enter "new" or "ongoing") |
|---|---|---|---|---|---|---|
| 1 | Kenichiro ITAMI* | 50 | Director, Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr.Eng<br>Specialties: Organic Synthesis, Catalysis, Pharmaceuti-cal Science, Nanocarbon Chemistry | 80 | ongoing |
| 2 | Jeffrey W. BODE* | 48 | Professor of Organic Chemistry<br>Department of Chemistry and Applied Biosciences, ETH Zürich, Switzerland | Doctoral of Natural Science<br>Specialties: Organic Synthesis, Peptide and Protein Chemistry, Catalysis, Ligation and Bioconjugati-on reactions | 21 | ongoing |
| 3 | Cathleen M. CRUDDEN* | 55 | Professor<br>Department of Chemistry, Queen's University, Canada | Ph.D<br>Specialities: Catalysis, Organic Synthesis, Materials Chemistry, Chirality | 21 | ongoing |
| 4 | Toshinori KINOSHITA* | 53 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr.Sci<br>Specialities: Plant Molecular Physiology | 70 | ongoing |
| 5 | Takashi OOI* | 56 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Engineering<br>Specialties: Organic Synthesis, Catalysis, Molecular Recognition | 70 | ongoing |
| 6 | Keiko TORII* | 56 | Professor<br>College of Natural Sciences<br>The University of Texas at Austin<br>Investigator<br>Howard Hughes Medical Institute | Ph.D.<br>Specialties: Plant Development, Signal Transduction, Stem Cell Maintenance/Differentiati-on in Plants | 21 | ongoing |
| 7 | Shigehiro YAMAGUCHI* | 53 | Vice-Director, Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Engineering<br>Specialties: Main Group Chemistry, Physical Organic Chemistry | 70 | ongoing |
| 8 | Takashi YOSHIMURA* | 52 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Agriculture<br>Specialties: Animal Physiology, Systems Biology, Neuroendoc-rinology | 70 | ongoing |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | Steve A. Kay* | 62 | University and Provost Professor of Neurology, Biomedical Engineering and Biological Sciences, Director of Convergent Bioscience<br>Co-Director of the USC Norris Center for Cancer Drug Development,<br>Keck School of Medicine, University of Southern California | Ph.D.<br>Specialties: Chronobiology, Genetics, Biochemistry, Systems Biology | 10 | ongoing |
| 10 | Florence Tama* | 47 | Professor<br>Institute of Transformative Bio-Molecules / Department of Physics, Graduate School of Science,<br>Nagoya University | Ph.D<br>Specialties: Computational Biophysics | 50 | ongoing |
| 11 | Wolf B. Frommer* | 64 | Professor, Heinrich Heine University Düsseldorf and Max Planck Institute for Breeding Research | Dr. rer. nat.<br>Specialties: Biology | 21 | ongoing |
| 12 | Takeshi Yanai* | 47 | Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | "Dr.Eng<br>Specialties: Theoretical Chemistry, Computatoinal Quantum Chemistry" | 70 | ongoing |
| 13 | Yuichiro Tsuchiya* | 47 | Designated Professor<br>Institute of Transformative Bio-Molecules, Nagoya University | Dr. Agriculture<br>Specialties: Plant Genetics and Chemical Biology | 70 | new |

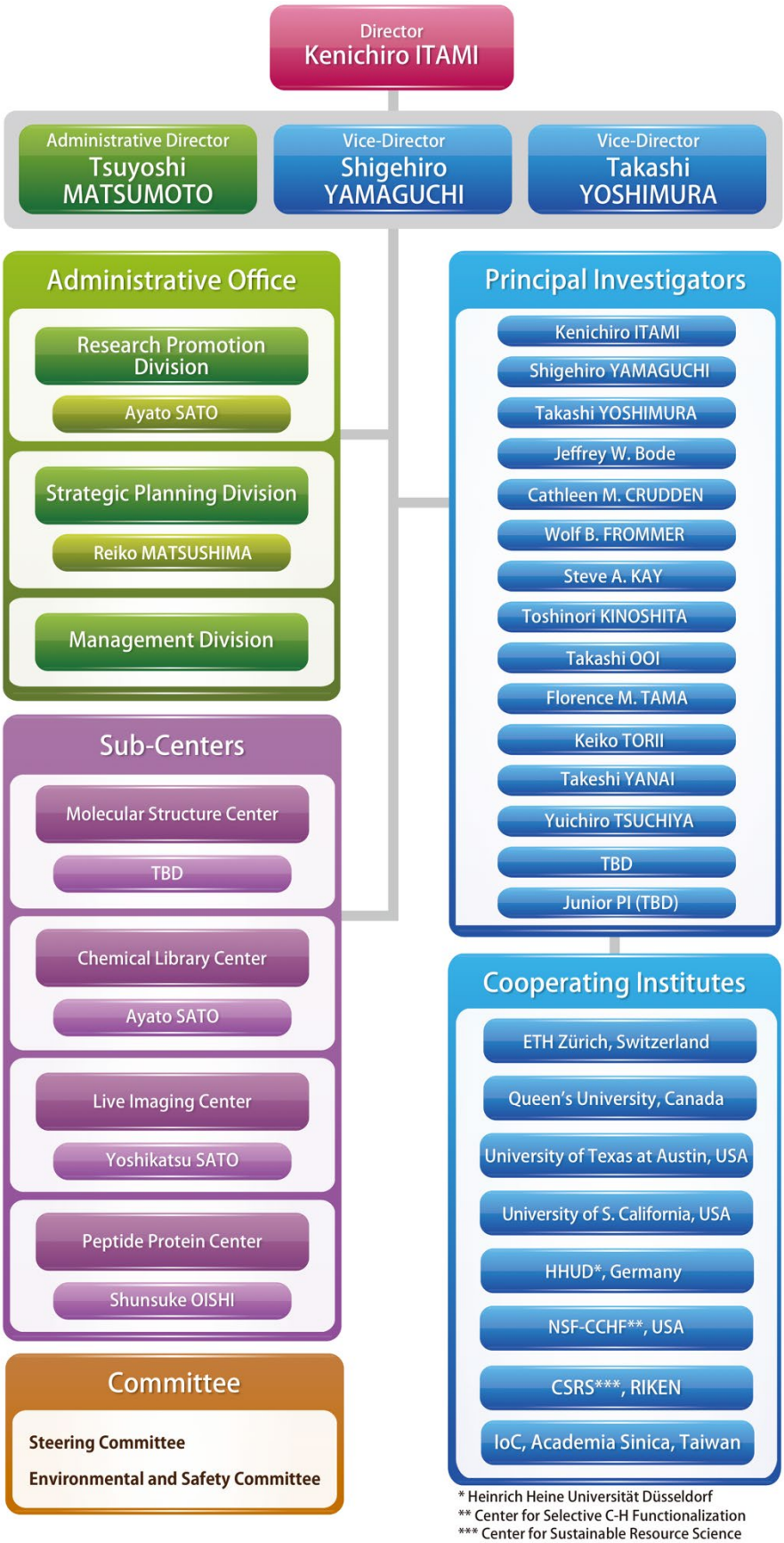
*Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

# Number of Center Personnel

| | | | FY2022 | |
|---|---|---|---|---|
| | | | Number of persons | % |
| Researchers | | | 61 | |
| | Overseas researchers | | 18 | 30 |
| | Female researchers | | 19 | 31 |
| | Principal investigators (PIs) | | 13 | |
| | | Overseas PIs | 5 | 38 |
| | | Female PIs | 3 | 23 |
| | Other researchers | | 28 | |
| | | Overseas researchers | 3 | 11 |
| | | Female researchers | 8 | 29 |
| | Postdocs | | 20 | |
| | | Overseas Postdocs | 10 | 50 |
| | | Female Postdocs | 8 | 40 |
| Research support staffs | | | 50 | |
| Administrative staffs | | | 7 | |
| TOTAL | | | 118 | |

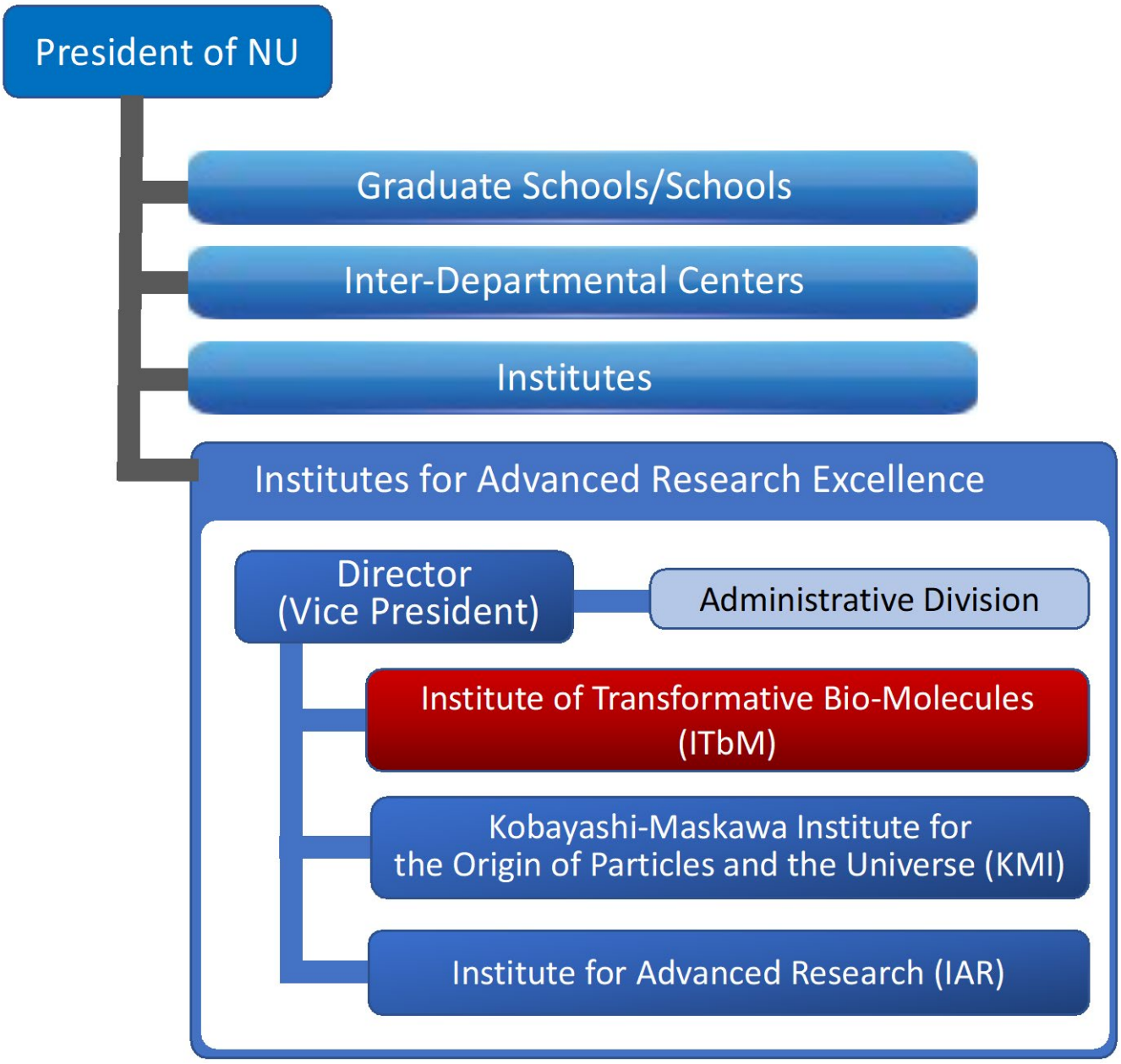
# Appendix 2 Diagram of Center Management System

- Diagram management system after the funding period ends in an easily understood manner.
- If you are planning to change your organization management system and/or its position within the host institution in or after FY 2022 compared to their description in Appendix 3-1 of Activities report, show the changes in the diagram. Especially describe any important changes being planned in such as the center director, administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research).



## Appendix 3 Position of the Center within Host Institution

* Diagram the Center's position within the organization of the host institution, and describe that positioning using excerpts from the institution's mid- to long-term plan. If the plan has not been established yet, describe the consideration being given to the Center's positioning.



# Appendix 4. Resource Allocation Plan for Sustaining and Advancing the WPI Center

| **Annual Plans (FY 2022 – FY 2026)** | | | | | |
|---|---|---|---|---|---|
| **<Fund >** | | | | | **(million Yen)** |
| **Fiscal Year** | **2022** | **2023** | **2024** | **2025** | **2026** |
| - Funding from host institution | **510** | **510** | **510** | **510** | **510** |
| (details) | | | | | |
| Personnel | **431** | **431** | **431** | **431** | **431** |
| Project activities | **78** | **78** | **78** | **78** | **78** |
| Travel | **1** | **1** | **1** | **1** | **1** |
| Equipment | | | | | |
| Other research projects | | | | | |
| Costs of Satellites | | | | | |
| - Funding from external sources | **1190** | **1200** | **1200** | **1200** | **1200** |
| Total | **1700** | **1710** | **1710** | **1710** | **1710** |
| **<Personnel> **** | | | | | **(person)** |
| **Fiscal Year** | **2022** | **2023** | **2024** | **2025** | **2026** |
| Total number of Personnel | **118 (61)** | **118 (61)** | **118 (61)** | **118 (61)** | **118 (61)** |
| - PIs | **13 (13)** | **13 (13)** | **13 (13)** | **13 (13)** | **13 (13)** |
| Full-time | **8 (8)** | **8 (8)** | **8 (8)** | **8 (8)** | **8 (8)** |
| Concurrent | **5 (5)** | **5 (5)** | **5 (5)** | **5 (5)** | **5 (5)** |
| - Other researchers | **28 (28)** | **28 (28)** | **28 (28)** | **28 (28)** | **28 (28)** |
| - Postdocs | **20 (6)** | **20 (6)** | **20 (6)** | **20 (6)** | **20 (6)** |
| - Research support staffs | **50 (9)** | **50 (9)** | **50 (9)** | **50 (9)** | **50 (9)** |
| RAs etc. | **0 (0)** | **0 (0)** | **0 (0)** | **0 (0)** | **0 (0)** |
| - Administrative staffs | **7 (5)** | **7 (5)** | **7 (5)** | **7 (5)** | **7 (5)** |

- Use yen (¥) when writing monetary amounts. If an exchange rate is used to calculate the yen amount, give the rate.
- When entering amounts, round down numbers to the first decimal.
- When funding is stated in a range between two amounts, explain the reason for the lower and upper amounts and fluctuations between them.

** When the host institution covers the expense, enter the amount in parentheses.

< Measures to be implemented from FY 2022>

– Strategy and action plan for allocating personnel (posts) , space, and others measures required for the Centers' Progress.

ITbM is positioned as a flagship research institute in President Matsuo's initiative NU MIRAI 2020 and the University's "Designated National University" concept. To secure the employment of ITbM's faculty member and staff, NU launched the Nagoya University Institute for Advanced Study (NAIAS) in 2019, and ITbM is positioned under this umbrella. Even under this new structure, the Director of ITbM retains the authority to make decisions regarding ITbM.

**Personnel**

NU has been covering the following personnel, which is continued.

・8 PIs of NU (96 million JPY as of FY2021).
・7 designated associate professors who take charge of education in each department to relieve the PIs of this responsibility. In FY2020, the 7 positions were officially secured by the President-Management Point System and allocated to ITbM as tenure positions (77 million JPY).
・4 administrative staff + 1 URA (35 million JPY).

As of April 2021, 4 more positions (50 million JPY) were also allocated to ITbM through the NU's request to MEXT with the highest priority to strengthen ITbM's activity. According to the ITbM's plan, NU also confirms to provide additional 160 million JPY by all means since FY2022 to secure almost all

the ITbM's designated faculty members and the selected postdocs/staff who are essential to run ITbM.

**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 research 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 research building. This support is continued.

**Students allocation**

All the 8 NU PIs are holding strong ties with their original departments, and undergraduate and graduate students are assigned in the same way before starting ITbM. Three overseas PIs in biology were assigned as a collaborating researcher in the Graduate School of Science, and a few PhD students have been allocated to the groups every year. In FY2022, Graduate School of Science is going to make its system reform, and will officially allocate PhD students also to ITbM's overseas PI groups from FY2022 by assigning the Co-PIs as supervisors.