FY 2014 WPI Project Progress Report
World Premier International Research Center Initiative (WPI)

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

* Prepare this report based on the current (31 March 2015) situation of the WPI Center.
* Amounts of money are to be noted in yen in this report. When necessary to convert other currencies into yen, please give the exchange rate used.

Summary of center project progress

Since the launch of the center in December 2012, all members at the Institute of Transformative Bio-Molecules (ITbM) continue to work under the slogan, "changing the world with molecules" to develop molecules to "understand", "see" and "regulate" biological systems, and establish a "world top-level research center". During 2014, ITbM has published over 100 papers in peer-reviewed journals, filed for 12 patents, received 13 awards and obtained a total of 1,290 million yen funding for research.

1. Strengthening of ITbM's research system was achieved by reforming the center's organization. ITbM initially consisted of seven PIs from Nagoya University (NU) and three overseas PIs. Following advances in the center's research, NU's PI, Shigehiro Yamaguchi was appointed as the second Vice-Director to work along with Center Director Kenichiro Itami and Vice-Director Tetsuya Higashiyama, in order to enhance the integration between biology and chemistry. To expand the research on animal/plant biology, Steve Kay of the University of Southern California, a world leader in biological clock research was assigned as an overseas PI, along with employment of a Co-PI to work at NU. A theoretical chemist was also employed as an assistant professor in Stephan Irle's group. In addition, postdoctoral researchers, technicians and secretaries were hired to promote and support ITbM's research. An intellectual properties (IP) manager joined the Research Promotion Division to strategically manage ITbM's research activities.

2. Promotion of interdisciplinary research is ongoing in Mix-Labs, where synthetic chemists, animal/plant biologists and theoretical scientists work side by side in the lab. The ITbM Research Award contributes to accelerating interdisciplinary research. A number of new interdisciplinary research projects are being initiated in a bottom-up style, with more research outcomes being generated than initially expected.

3. Construction of ITbM's new building was finished at the end of March 2015, and directly reflects the Mix-Lab concept, where new interdisciplinary research is initiated by removing the barriers between research fields/groups and integrating people, ideas, equipment and research. The new six-floor building has a total floor space of 7,934 m^2, and contains Mix-Labs where large biology and chemistry labs are accessible by a single door, and Mix-Offices where scientists from different disciplines work in the same space.

4. Collaboration with partner institutes and fostering young researchers is also a key mission of the center. Programs to exchange faculty and graduate students have officially started with partner institutes, including the NSF CCHF (USA), which has already led to joint publications of research results. A joint research agreement was signed with RIKEN CSRS, and a joint workshop was held in January 2015 to exchange ideas. These collaborations are expected to accelerate research, foster young researchers, and increase the overall visibility of ITbM.

5. ITbM's international symposium (ISTbM-2) was held in May 2014. In addition, ITbM organized an international award in organic chemistry, the 20th Nagoya Medal Seminar in October 2014.

6. The Research Promotion Division works closely with ITbM's researchers and supports ITbM's research through international public relations, outreach activities, education and organization of events. ITbM's researchers and research have been covered over 500 times in international and domestic media. Led by the new IP manager, new business opportunities are being realized from ITbM's research outcomes. Local daily support continues to be provided for foreign researchers.

1. Summary of center project

<Plan at start of project>

Our goal is to develop innovative functional molecules that make a marked change in the form and nature of biological science and technology by taking full advantage of the cutting-edge molecular synthesis expertise of our chemistry PIs and intense interactions with our leading plant/animal biology PIs. Through this interaction, which is fundamental to the Center, transformative bio-molecules will be synthesized that can (1) **enhance biotic productivity and quality** and (2) **realize innovative bio-imaging**. To ensure the advancement of these projects, we will (3) **develop catalysts that enable incredibly efficient synthesis and molecule activation on demand**. The ultimate goal is to have a positive impact on global issues such as food production. Our team of PIs is an innovative mix of chemists and biologists from Japan and abroad. A Co-PI system, and an efficient administration with an English focus will ensure that international members will have significant involvement in the project.

The Center will start with 10 PIs, including 3 foreign researchers, and one Administrative Director. These founding members will then hire post-doctoral researchers, research assistants, administrative staff, and secretaries.

The seven world-class PIs selected from Nagoya University all have proven abilities to make major contributions to the objectives of this Center and the flexibility to integrate the accumulated wisdom of diverse disciplines. The large proportion of talented young PIs will help ensure the long-term vitality of the WPI Center and mentoring of the next-generation of researchers in this field.

PIs from overseas cooperating institutes include eminent chemists and biologists from around the world. These PIs will have double affiliation with Nagoya University and their home institutions, and they will actively transmit information and provide significant opportunities for other foreign researchers to participate in the Center. Their present host institutions will be designated as Cooperating Institutes, which are

<Results/progress/alternations from plan at start of project >

Since the official launch of the center two years ago, establishment of the center and interdisciplinary research undergoing at ITbM are making steady progress. The two Mix-Labs, which were implemented to promote interdisciplinary research, have led to successful integration of synthetic chemists, plant/animal biologists, and theoretical scientists. The 'mixing' effect has led to a number of pronounced results. Many of the research projects proposed in FY2013, regarding the creation of bio-functional molecules, have resulted in the discovery of seed molecules for transformative bio-molecules. Based on these research outcomes, a number of patents have been filed for and joint publications between different PI groups have already been published (details on research results are stated in Section 3. Research objectives). Stated below is a summary of this year's main progress for the center.

Organization/Personnel Organization

Administrative Department

There has been no major change in the organization of the Administrative Department since its establishment in FY2013. Led by the Administrative Director, the Administrative Department consists of the Management Division (General Affairs Unit and Accounting Unit) and the Research Promotion Division. More than 50% of the Management Division consists of personnel competent in English who are capable of communicating to foreign researchers regarding administrative affairs. Most of the members in the Research Promotion Division are fluent in English and hold PhD degrees in science. A science designer also plays a role in carrying out effective outreach activities. The Administrative Department effectively manages international symposia/seminars and prepares the official documents in both English and Japanese for the center. In addition, during FY2014, an experienced intellectual properties (IP) manager, with a Masters degree in chemistry was employed as a lecturer at the Research Promotion Division. The IP manager works with Nagoya University's IP office to file for patents and strategically exploit ITbM's research outcomes for industrial applications.

regarded as major gateways to our Center.

We consider this double affiliation strategy to be a considerable strength of our proposal, even if double-affiliated PIs will not be physically present full time at the Center. To ensure close contact and continuity in research, we will support the hiring of Co-PIs. Co-PIs will be based at the Center in Nagoya, but chosen and guided by double-affiliated PIs. Co-PIs will be considered for promotion to full PI status when their research potential is realized.

An International Advisory & Review Board has already been assembled, which will support our research.

The Center will establish an effective and efficient administration staffed by talented individuals with a good command of English, as well as a global outlook and vision. In addition, resources will be allocated to hire a substantial number of technical staff in order to minimize the extra demands on the time of researchers, freeing them to concentrate on their core research activities.

Appointment of the Second Vice-Director

To support the work of the Center Director along with the Vice-Director, Shigehiro Yamaguchi was appointed as the second Vice-Director in April 2014. With the assignment of two Vice-Directors, each specializing in biology or chemistry, interdisciplinary research at the center is expected to advance even further.

Appointment of the Fourth Overseas PI

Steve Kay of the University of Southern California (USA) has been appointed as an overseas PI to join ITbM in April 2014. Kay is one of the world leaders in biological clock research and is currently screening molecules to control the circadian clock of mammals. Tsuyoshi Hirota was also employed as an associate professor and Co-PI to work with Kay at Nagoya University.

Employment of Faculty

In order to meet the growing demand for theoretical chemistry required to accelerate ITbM's research, an assistant professor was employed at Stephan Irle's group. Secretaries, postdoctoral researchers and technicians were also appointed accordingly to each PI.

Promotion of Researchers

In FY2014, three researchers were promoted to international research institutions: senior postdoctoral fellow (Mexico), associate researcher (France), and assistant professor (Pakistan). Three researchers were also promoted as assistant professors (two in the Young Leader Cultivation Program) within Nagoya University.

Operation of Committees

A Steering Committee was organized and are gathered once a month to discuss and evaluate ITbM's research plans, management, personnel, budget and other important issues related to ITbM's overall operation. In addition, PI meetings are held twice a month to share information regarding the management of the center amongst all the PIs and the Administrative Department.

As ITbM is involved in creating new compounds that have action on animals and plants as well as generation of new species, the Environment

and Safety Committee was established to evaluate and guarantee that ITbM's research activities comply with the laws and regulations governing these activities, and also provide relevant advice. The second committee meeting was held in January 2015.

Partner Institutes

In addition to the host institutes of the overseas PIs, which include Queen's University (Canada), University of Washington (USA) and ETH Zürich (Switzerland), partnerships and research have started with the National Science Foundation's Center for Selective C-H Functionalization (NSF CCHF, USA), Freiburg University (Germany), and the RIKEN Center of Sustainable Resource Science (CSRS, Japan). Faculty and student exchange has also started between ITbM and CCHF. In FY2014, ITbM has sent a total of four researchers to CCHF (Scripps Institute, CalTech, Emory University) and has accepted one faculty for an intensive lecture course (Scripps Institute) as well as three researchers (Emory University, Georgia Institute of Technology). NSF has already accepted fund applications from CCHF to send faculty/students to ITbM.

Enforcement of ITbM Research Awards

Established in FY2013 to promote interdisciplinary research proposed by young researchers, calls for the ITbM Research Award have been continued in FY2014. Selected proposals for interdisciplinary research from applicants led by researchers at ITbM other than the PIs will each be awarded 2 million yen over 2 years.

Construction of ITbM's New Building

Designed at the end of FY2012, the new building for ITbM was completed at the end of FY2014. The total floor area of the new six-floor building is 7,934 m^2 and is designed to incorporate the "Mix-Lab" concept to promote interdisciplinary research.

International Symposia

The 2nd International Symposium on Transformative Bio-Molecules (ISTbM-2) was held in May 2014. In October 2014, the 20th Nagoya Medal Seminar, an international award in organic chemistry was organized and co-sponsored by ITbM.

	Presentation of Research Results In 2014, 104 papers were published in peer-reviewed journals (44 papers published in journals with an Impact Factor (2013) > 7, 19 papers published in journals with an Impact Factor (2013) > 10, and 7 Highly Cited Papers). From January to April 2015, 41 papers are already published in peer-reviewed journals. A total of 12 patent applications were filed in FY2014. Through press conferences, distribution of press releases, and networking, ITbM has been covered over 500 times in a range of national and international media, including newspapers, TV, magazines, journals and internet sites. PIs have presented their research in a total of 86 invited lectures at international symposia and a total of 13 international awards and honors have been granted to researchers at ITbM. **Research Grants** In FY2014, the total amount of research grants obtained by Nagoya University's PIs and researchers was 1,290 million yen. From signing MOUs with the partner institutes where the overseas PIs are affiliated to, the overseas PIs became eligible to apply for the Kakenhi grant in Japan. The overseas PIs and their Co-PIs have successfully obtained Kakenhi grants during FY2014.

2. Research fields

<Plan at start of project >	<Results/progress/alternations from plan at start of project >
Target research field: **Molecule-Activation Chemistry* for Advanced Systems Biology**** (This is an area in which Nagoya University has significant international competitive advantages: synthetic chemistry, molecular catalysis, systems biology, plant science, peptide science, live-cell imaging.) The interface of chemistry and molecular biology has already resulted in important new research fields of significant scientific impact, such as chemical biology and medicinal chemistry. We plan to bring this to a new level by exploiting newly developed molecule-activation chemistry partnered with fundamental biological systems of plants and animals. This research endeavor will have significant impacts in the closely related fields of chemical biology and medicinal chemistry, but most importantly,	Target research field: **Molecule-Activation Chemistry for Advanced Systems Biology** (This is an area in which Nagoya University has significant international competitive advantages: synthetic chemistry, molecular catalysis, functional molecular science, systems biology, plant science, plant genetics, plant developmental biology, animal physiology, protein science, live-cell imaging.) The target research field of ITbM has not changed since the start of the project. Steve Kay of the University of Southern California (USA) joined ITbM as an overseas PI in order to accelerate the interdisciplinary research between animal physiology and synthetic chemistry. In addition, Tsuyoshi Hirota, a circadian clock scientist with extensive experience in chemical biology, also joined ITbM as a Co-PI and an associate professor

on areas that are of urgent global importance including world food production, medical care, and bioenergy. *__Molecule-Activation Chemistry__: The synthetic chemistry that enables the activation and direct transformation of stable molecules into target structures. This methodology can rapidly convert biologically active "lead" molecules into more selective and active derivatives. **__Systems Biology__: The biology to unveil the pivotal mechanism of how organisms function as a system. The discovery of key molecules operating biological systems at an individual organism level is crucial.	in Kay's group. Hirota's invaluable research experience in the USA contributes to the creation of an international environment at ITbM. Yuh Hijikata, a theoretical chemist was also employed as an assistant professor in Irle's group to connect biology and chemistry. His experience in bio-simulation is expected to contribute to elucidating biological phenomena occurring in plants and animals. Furthermore, Daisuke Maruyama (Higashiyama group) and Yin Wang (Kinoshita group) also joined ITbM as assistant professors of Nagoya University's Young Leader Cultivation (YLC) Program. Both members have their own research project, contributing to the promotion of research in plant developmental biology and plant physiology, respectively. Kei Murakami was promoted from a postdoctoral researcher to an assistant professor at Itami's group. Murakami's role involves carrying out interdisciplinary research with biologists through the promotion of ITbM's synthetic platform using molecular catalysts (C-H activation, catalytic chemistry). Employment of personnel as stated above has led to acceleration of ITbM's research target on **Molecule-Activation Chemistry for Advanced Systems Biology**. Currently, over 30 prototypic transformative bio-molecules have been identified at ITbM. Future perspectives involve increasing the strengths of each group's research on molecular activation chemistry and systems biology towards the establishment of animal/plant molecular chemistry as a new interdisciplinary field of research, and the creation of transformative bio-molecules. This is envisaged to be the key to solving significant social issues related to the environment, food production, medical technology and bio-energy.

3. Research objectives

< Plan at start of project > Based on our vision of employing Molecule-Activation Chemistry for Advanced Systems Biology, we propose the following research consisting of three major objectives.	<Results/progress/alternations from plan at start of project > In order to further promote and accelerate the interdisciplinary research between chemistry and biology, ITbM set the following research objectives, I) Control of biological systems II) Visualization of biological systems III) Synthesis of new bio-functional molecules

I) Control of Biological Systems

(a) Molecules that dramatically enhance plant growth
(b) Molecules that improve animal reproduction innovatively
(c) Molecules that overcome the genome barrier to produce novel crops

II) Visualization of Biological Systems

(a) Targeting plant fertilization, embryogenesis, and animal season sensing
(b) Highly efficient, full-color fluorescent molecules
(c) Specific conjugation technologies for peptide labeling

III) Synthesis of New Bio-Functional Molecules

(a) Catalysts activating C-H bonds for direct transformations of bio-molecules
(b) Catalysts acting without heavy metals
(c) Catalysts for protein ligation

Research objective (I) aims to precisely control biological systems. We will utilize all the outcomes obtained in this Center to accomplish this objective. Research objective (II) aims to visualize biological systems at will. The outcome of this research objective (II) has significant impact on a wide range of life science-related fields. At the same time, it accelerates research objective (I). In research objective (III), we will develop small-molecule catalysts for achieving ideal chemical synthesis. This is the core of this Center and provides viable methods for realizing both objectives (I) and (II). In addition to these, feedback from objectives (I) and (II) further promote the development of catalysts in objective (III). Thus, the three major research targets are closely integrated. Importantly, progress in these three major fields will together result in the development of transformative bio-molecules.

To achieve the objectives listed above, in FY2014, ITbM's research projects were categorized into three types: research/technological platforms, core projects, and seed projects.

ITbM's strengths in research and technology were initially categorized according to the following six platforms:

1. Small molecule synthesis (reaction and catalyst library): Itami, Yamaguchi, Ooi, Crudden
2. Peptide and protein syntheses: Bode
3. Chemical library and high-throughput screening technology: Chemical Library Center
4. Phenotypic assay development (*in vitro*, cell, tissue, and whole-organism): Higashiyama, Kinoshita, Yoshimura, Torii, Kay
5. Imaging and sensing technology (live imaging and fluorophore library): Live Imaging Center,
6. Theoretical calculations and analytical methods (computational chemistry and MS, NMR, and X-ray): Irle, Molecular Structure Center

The activities of the three research centers (platforms 3, 5 and 6) were integrated to form a strong collaborative research network. Instead of the conventional approach where researchers approach each center separately, the centers are integrated with the research projects. This creates a smooth flow for chemical biology research, thus accelerating the process for discovering molecules, identifying target molecules, and visualizing the localization of molecules and signal transduction. The resources of the research centers are shared and are available to all the researchers at ITbM, thus promoting the interdisciplinary research between biology and chemistry.

Prototypes for transformative bio-molecules are categorized as core projects and seed projects, according to their stage of development.
For the molecules currently under development, the following four research themes were selected as the core projects.

1. Controlling plant reproduction by molecules: Itami, Higashiyama, Bode, Live Imaging Center, Molecular Structure Center, Chemical Library Center
2. Development of molecular tools to combat Striga: Itami, Kinoshita, Ooi, Live Imaging Center, Molecular Structure Center, Chemical

Library Center
3. Controlling and elucidating the mechanism of circadian rhythms by molecules: Itami, Yoshimura, Kay, Bode, Molecular Structure Center, Chemical Library Center
4. Development of molecules for innovative imaging and sensing: Higashiyama, Yamaguchi, Irle, Torii, Crudden, Itami, Live Imaging Center

Identification of the core projects has led to acceleration of ITbM's research, resulting in journal publications on innovative imaging molecules (core projects 2-4). A long-lasting fluorescent molecule with improved properties is scheduled for publication. In addition, reports on molecular tools to combat Striga (core project 2) and molecules altering the circadian rhythm (core project 3), are also being submitted for publication.

With a potential to open up new fields, the following six types of molecules were selected as the seed projects.
1. Molecules controlling plant growth: Itami, Kinoshita, Torii, Bode, Chemical Library Center
2. Molecules increasing the number of stomata: Torii, Itami, Chemical Library Center
3. Molecules that mimic thyroid hormones: Yoshimura, Crudden, Irle
4. Molecules that alter the circadian rhythm in plants: Kinoshita, Itami, Chemical Library Center
5. Molecules that modify cell division: Higashiyama, Molecular Structure Center, Chemical Library Center
6. Miniaturized fluorescent proteins: Itami, Irle, Live Imaging Center

Reorganization of ITbM's research projects by defining the core and seed projects has led to acceleration of ITbM's research target on **Molecule-Activation Chemistry for Advanced Systems Biology**.
By systematizing ITbM's interdisciplinary research (core and seed projects) and research/technological platforms as above, both the ongoing research at each PI's group and the interdisciplinary research between biology and chemistry at ITbM have made profound progress during FY2014. Major research accomplishments are described below.

Ongoing research in each group

Itami's group has developed a number of unique and efficient catalysts for C-H activation/coupling reactions making arene-assembled molecules from unfunctionalized precursors. With these catalysts, Itami and his coworkers have succeeded to synthesize natural products (lamellarins C and I, and dictyodendrins A and F), pharmaceutically relevant molecules (histone deacetylases inhibitor and CCR2/5 antagonists), and nanocarbons (hexaarylbenzenes, pyrene- and thiophene-containing CPPs, along with other molecules). With their synthesis-oriented methodology, Itami and his group have synthesized unique molecules and have succeeded in discovering novel biologically active compounds through the extensive collaboration with other groups at ITbM (Kinoshita, Higashiyama, Torii, Yoshimura, and Kay).

Higashiyama's group has been focusing on hybrid breeding, which has led to the production and increase in yield of various crops. His group has developed various molecules and technologies for innovative bio-imaging, especially focusing on live-cell imaging of plant fertilization and plant embryogenesis. With their continuous biological investigation and efforts in plant biology, Higashiyama and his colleagues have developed a non-transgenic method to control gene expression of male pollen tube cell by using antisense oligomers, various microfluidic devices to control plant reproduction, and a live imaging method to visualize calcium signaling in plant fertilization during FY2014. Furthermore, Higashiyama discovered several candidate molecules, which can mimic the pollen tube attractant, control cell division, or modulate cell polarization.

Yamaguchi's group has succeeded in synthesizing novel fluorescent molecules during FY2014. For one of their molecules, he proposed an original concept, the "functional strap strategy" of ESIPT (excited-state intramolecular proton transfer) system. He found that the molecule synthesized based on the concept contradicts with the majority of the conventional ESIPT system, especially in the range of the visible region. This result suggested that various applications could be exerted in aqueous medium, such as bio-imaging or sensory materials. With these molecules, Yamaguchi initiated the collaboration with the live-imaging team and succeeded in the first publication arising from collaboration of the groups at ITbM (Higashiyama, Irle, Live Imaging Center).

Ooi's group has developed a number of unique and efficient organocatalysts (chiral iminophosphoranes, ammonium betaines) and chiral transition metal catalysts for the construction of continuous asymmetric centers in molecules. They succeeded in synthesizing various types of amino acids including their precursors and α-quaternary amino acids. Ooi's catalysts have a potential to lead to collaborative projects with Bode's group in protein chemistry. Ooi and his group have synthesized unique molecules and have succeeded in discovering novel biologically active compounds through the extensive collaboration with the groups of Kinoshita and Kay-Hirota.

Kinoshita's group has conducted biological studies on the signaling pathways of stomata opening/closing in plants. In FY2014, they succeeded to show that chlorophyll synthesis enzymes, Mg-chelatase complex and CHLM, specifically affect ABA signaling in the control of stomatal aperture and have no effect on ABA-induced gene expression (*J. Plant Res.*). His group also demonstrated that SOC1 is involved in the regulation of stomatal opening via transcriptional regulation of several genes, such as BLUS1 and the plasma membrane H^+-ATPase in guard cells in stomatal movement (*Plant Cell Physiol.*). Furthermore, his group initiated collaborative research with the chemistry teams at ITbM (Itami, Ooi and Chemical Library Center).

Yoshimura's group has led the field of animal circadian rhythms including seasonal sensing. In FY2014, they reported that CSF-containing neurons in the paraventricular organ played a key role to their physiological significance, *i.e.*, the regulation of seasonal reproduction (*Curr. Biol.*). They also discovered tissue-specific glycosylation of the thyroid-stimulating hormone (TSH), known as a springtime hormone, prevented functional crosstalk between signaling molecules in the body (*Cell Rep.*, with the Molecular Structure Center). With their accumulated knowledge on animal biology, they are now trying to control these phenomena with synthetic small molecules in collaboration with ITbM's synthetic chemistry groups (Crudden, Itami, and Ooi).

Crudden's group has synthesized self assembled N-heterocyclic carbene (NHC) monolayers on gold and found that sterically unencumbered

carbenes form well aligned monolayers, which are significantly more stable than the state-of-the-art sulfur-based films (high temperature, refluxing organic solvent, boiling acid, base and oxidation with dilute hydrogen peroxide). This initial work has spawned 18 different collaborations in Canada, Japan, Finland, France, the US and Scotland, covering areas as diverse as bio-sensing to protection of light weight alloys for automotive coatings. They have also developed borenium ions as catalysts for the activation of non-polar bonds for new types of catalytic transformations. Palladium-catalyzed sequential arylation reactions developed by the Crudden group have provided a characteristic library of triarylmethane, triarylacetonitrile, and tetraarylmethane. With these molecules, Crudden's group is now collaborating with the biology and theoretical chemistry groups at ITbM (Higashiyama, Yoshimura, and Irle).

Torii's group has discovered a family of secreted peptides and their corresponding receptors regulating the developmental program in plants. They have conducted research to elucidate the functions of ligand-receptor pairs in plant development, with a specific focus on EPF-peptides and ERECTA-family receptors through developmental genetics. In FY2014, they have characterized and elucidated EPF/EPFL-peptides, an auxin response of EPFL expression and its receptor's expression, and identification of the downstream signal transduction of EPFL-ERECTA. They are also identifying several candidates of synthetic small molecules that affect the development of stomata, *e.g.*, modulating the number of stomata (Itami, Molecular Structure Center, Chemical Library Center).

Bode's group has synthesized a ferric heme protein nitrophorin 4 (NP4) and an unagi fluorescent protein (UnaG) using the KAHA ligation reaction, which was developed by their group. In collaboration with the biologists at ITbM, they have also synthesized a number of peptides and proteins for further biological investigations. In order to provide peptides and/or proteins, they have established a peptide/protein synthetic platform and are able to supply >30 simple peptides on a 1–20 mg scale and a few cyclic peptides to ITbM's biology groups.

Kay's group was established in ITbM at the beginning of FY2014. Tsuyoshi Hirota joined ITbM as a Co-PI in the group and set up a new

laboratory to start their own research on "animal chronobiology." They have already identified hit compounds that modulate the circadian clock using cell-based high-throughput chemical screening through the collaboration with Itami and Ooi's groups (one publication is submitted and a second publication is being preparation).

Irle's group has developed theoretical chemistry tools such as replica exchange umbrella sampling (REUS) molecular dynamics (MD) simulations, density-functional tight-binding (DFTB) method, and the reference interaction site model. In particular, the Fragment Molecular Orbital (FMO)-based DFTB allows fully quantum chemical MD simulations of artificial protein folding and ligand-protein interactions. They applied these methods as a theoretical chemistry platform in collaboration with experimental scientists at ITbM and other theoretical bio-simulation groups around the world (Yamaguchi, Crudden, Yoshimura, Itami, Kay).

Core projects

1. Controlling plant reproduction by molecules

Team: Higashiyama, Itami, Bode, Live Imaging Center, Molecular Structure Center, Chemical Library Center

Platform: Small-molecule synthesis, Peptide-protein synthesis, Chemical library screening, Imaging and sensing technology, Analytical science

Hybrid plants, *e.g.* oilseed rape, have sometimes led to huge benefits to the society far beyond our expectation. Understanding molecular mechanisms of plant reproduction should be essential for not only basic science but also for manufacturing crossbreeding crops in the future. Through the discovery of the pollen tube attractant LURE protein, Higashiyama played a central role in the field of plant reproduction. During FY2014, in addition to the LURE protein, key molecules, including AMOR disaccharide, and several synthetic molecules from ITbM's chemical library have been discovered, and investigation on these molecules has led to notable advances in the plant reproduction project.

LURE1 protein

Bode and Oishi succeeded to synthesize TcLURE1 (from *Torenia concolor*), TfLURE1 (from *Torenia foulnieri*), and chimeric proteins of the two LURE1 proteins, stated above. Immediately after the synthesis, Higashiyama and

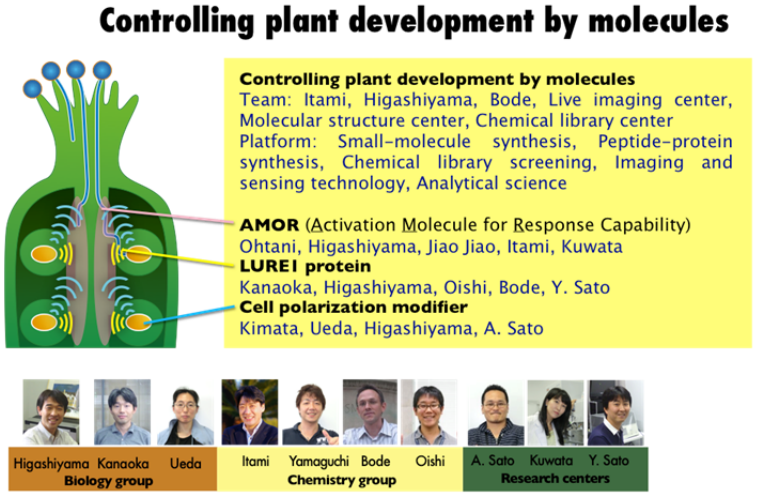
Kanaoka showed that the partial structure of LURE1 may be essential for the species specificity in the pollen tube guidance of *Torenia*.

AMOR (Activation Molecule for Response Capability)

Higashiyama and his colleagues have discovered AMOR disaccharide as a key inducer to increase fertility efficiency during pollen tube guidance. Itami's group has synthesized AMOR and its derivatives, and performed SAR studies to understand how AMOR acts in the process. They are now synthesizing probe molecules to identify target molecules in plants.

Cell polarization modifier

Ueda and Higashiyama have focused on cell polarization to elucidate the molecular mechanism of plant morphology. During FY2014, in collaboration with the Live Imaging Center, they revealed that various polarization events occur simultaneously during zygote polarization, and some of them regulate each other (to be submitted for publication). In addition, they have discovered several compounds, which efficiently inhibit zygotic cell division (Chemical Library Center). Identification of the target proteins for cell division with the molecule that they have discovered is currently ongoing (Molecular Structure Center).



2. Development of molecular tools to combat *Striga*

Team: Kinoshita, Itami, Ooi, Live Imaging Center, Molecular Structure Center, Chemical Library Center

Platform: Small-molecule synthesis, Chemical library and high throughput screening, Imaging and sensing technology, Analytical platform

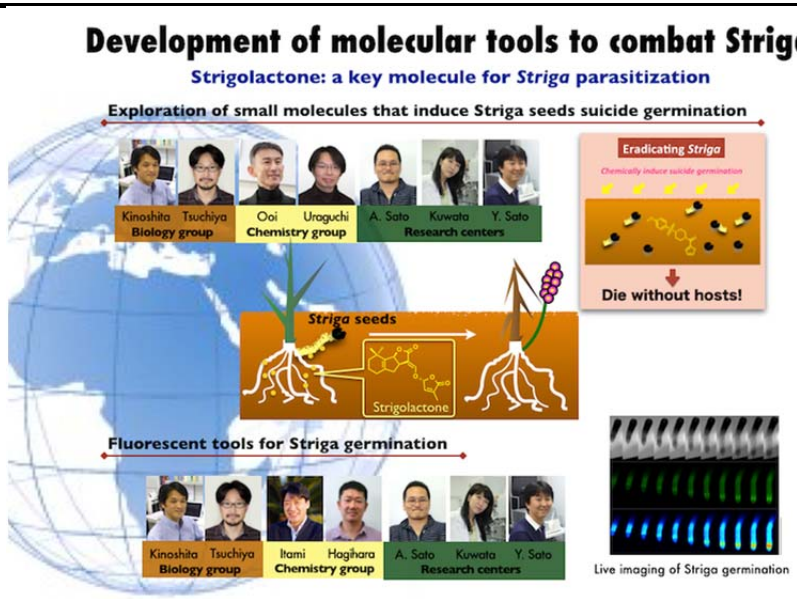
Damages caused by a parasitic plant *Striga hermonthica* comprise the largest impediment to securing food in Africa, which has led to the loss of 10 billion US dollars worth of crops from the continent every year. To solve the *Striga* problem in Africa, ITbM has been developing intensive collaborations and has made significant progress on understanding the *Striga* problems as described below.

Fluorescent tools for *Striga* germination
(2nd ITbM Research Award)

Although strigolactone (SL) has been identified as the inducer of *Striga* germination and understanding on the mechanisms of these molecules is proceeding, the molecular identity of the SL receptor in *Striga* still remains unknown by conventional genetics. To overcome this stagnant situation, Hagihara (Itami group) and Tsuchiya (Kinoshita group) have developed a novel fluorescence turn-on probe, named Yoshimulactone Green (YLG), which enabled rapid identification, characterization, and visualization of SL receptors in *Striga*. As a result, they identified 12 members of SL receptors in parasitic plants, of which YLG dissected an extended 10-membered gene cluster (*ShHTL2-11*) including functional SL receptors in *Striga*. Moreover, the fluorescence turn-on functionality of improved probe YLGW enabled tracking of the signal perception by SL receptors. Live-imaging experiments revealed a wave-like propagation of perception that wakes up *Striga* seeds (Live Imaging Center). Overall, these results open an avenue to access not only SL receptors and regulatory dynamics of SL signal transduction in *Striga*, but also towards the discovery of candidates for transformative bio-molecules that will potentially provide a powerful solution to the *Striga* problem (Chemical Library Center).

Exploration of small molecules that induce suicide germination

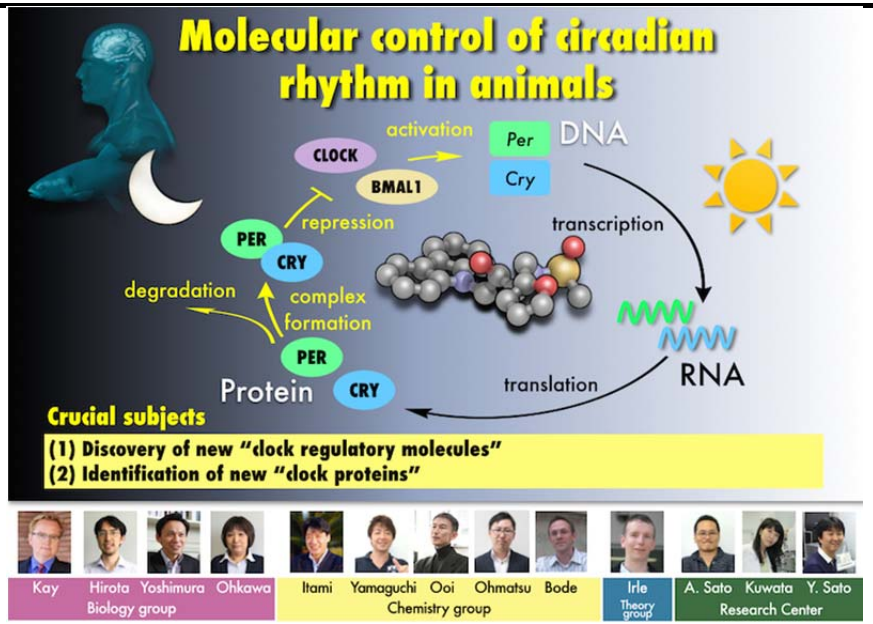
Ooi's group (Narayanan and Uraguchi) has designed and synthesized small molecules that can induce complete germination of *Striga* in the absence of a host. Based on intensive structure-activity relationship studies (approximately 100 compounds) with Tsuchiya, they have found some candidates that showed higher germination activity than strigolactone and possess selective activity on SL receptors (Kinoshita, Live Imaging Center).



3. Controlling and elucidating the mechanism of circadian rhythms by molecules

Team: Yoshimura, Kay, Itami, Ooi, Irle, Bode, Live Imaging Center, Molecular Structure Center, Chemical Library Center
Platform: Small-molecule synthesis, Peptide/protein syntheses, Catalysis library, Chemical library screening, Analytical science

By applying C-H coupling, the groups of Itami and Yoshimura have developed new derivatives of KL001 that was originally discovered by the Hirota-Kay group. Surprisingly, several derivatives showed a period-shortening effect by a simple substitution modification (accepted in *Angew. Chem. Int. Ed.*). The Hirota-Kay group has identified a more potent KL001 derivative and collaborated with the Irle group for QSAR study (to be submitted for publication). The Hirota-Kay group has also identified two new period-lengthening compounds and started collaboration with the groups of Itami and Ooi for characterization.

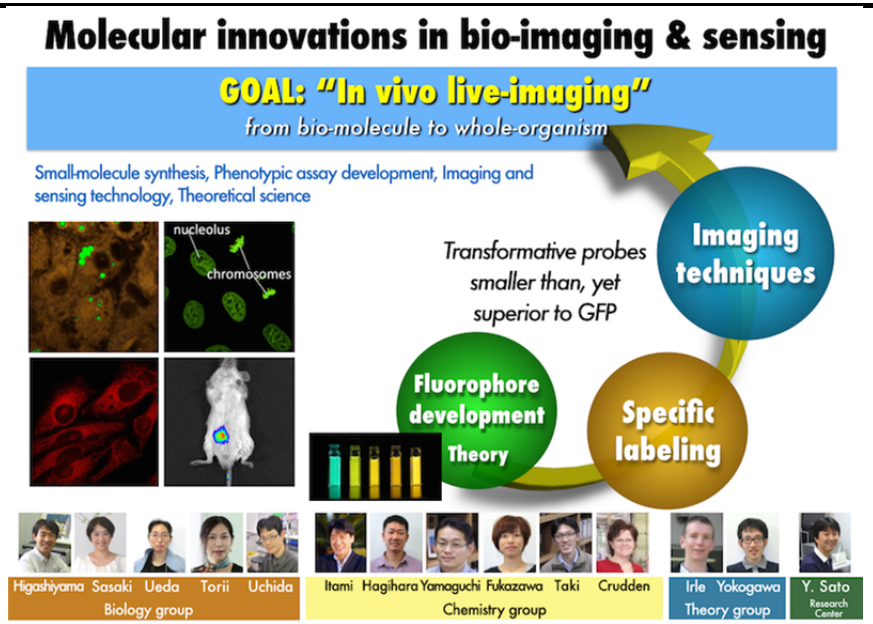


4. Molecular innovations in bio-imaging and sensing

Team: Yamaguchi, Higashiyama, Irle, Torii, Crudden, Itami, Live Imaging Center

Platform: Small-molecule synthesis, Phenotypic assay development, Imaging and sensing technology, Theoretical science

A number of promising fluorescent molecules have been developed for optoelectronic applications such as organic light emitting diodes (OLEDs), and for biological applications such as fluorescent probes. In FY2014, Yamaguchi has started to apply the fluorescent molecules that he and his colleagues have designed for biological research.



Environment polarity-sensitive fluorescent probe

Yamaguchi and Wang have succeeded to synthesize a phosphole *P*-oxide fluorescent molecule, and showed that the molecule possessed superior chemico-physical properties (high quantum yields even in polar and protic solvents, and higher brightness and photostability than some representative dyes, such as BODIPY, fluorescein, and prodan) and biological advantage (low cytotoxicity) through extensive collaboration with Higashiyama and the Live Imaging Center. Utilizing the advantages of these compounds, they succeeded to stain adipocytes selectively in the cell and distinguish the cellular environment by emission colors (*Angew. Chem. Int. Ed*).

Seed projects

1. Molecules controlling plant growth

Team: Itami, Kinoshita, Chemical Library Center

Platform: Small-molecule synthesis, Phenotypic assay development, Chemical library screening and high through assay

Auxin mimic
Itami and Hagihara have synthesized a number of new auxin derivatives with their unique catalysts for C-H activation/coupling reactions. They have found a novel and selective agonist, and also found that this molecule targets unknown auxin receptors that activate H^+-ATPase thorough phosphorylation, which were discovered by Kinoshita's group.

Stomata opening/closing modulator
Kinoshita and Toda have performed chemical screening (approximately 10,000 compounds), and found several small molecules that induce stomatal opening in the dark or inhibit light-induced stomatal opening (Chemical Library Center). Furthermore, they found that some of the molecules suppress blue light-induced phosphorylation of the plasma membrane H^+-ATPase and stomatal opening, and a novel protein kinase is involved in the signaling pathway between phototropin and the H^+-ATPase.

2. Molecules increasing the number of stomata
Team: Torii, Itami, Uchida, Molecular Structure Center, Chemical Library Center
Platform: Small-molecule synthesis, Catalysis library, Chemical library screening and high throughput screening, Analytical science

Torii and Uchida have discovered novel molecules that influence stomata density and patterning (Itami, Chemical Library Center). Their most promising hit compound increases the numbers of stomata and also confers stomatal clustering. They also found that this compound may influence the transduction pathways mediated by the ERECTA-family receptor kinases and downstream MAP kinase cascade. They are currently performing a proteomics-based approach to identify target proteins.

3. Molecules that mimic thyroid hormones
Team: Yoshimura, Crudden, Irle, Molecular Structure Center
Platform: Small-molecule synthesis, Phenotypic assay development (whole-organism), Theoretical science

THR-β specific analogues are expected to overcome the obesity, type 2

diabetes and atherosclerosis. Nambo and Crudden have synthesized THR-β selective analogues with the help of computational design (Irle and Kumar), and revealed that one of the synthetic analogues showed potent activity to reduce the body weight of mouse.

4. Molecules that alter the circadian rhythm in plants
(1st ITbM Research Award)
Team: Nakamichi, J. Yamaguchi, Ohmatsu, Molecular Structure Center, Chemical Library Center,
Platform: Small-molecule synthesis, Chemical library and high throughput screening, Phenotypic assay development, Analytical science

Nakamichi (Kinoshita group) discovered the period affecting compound-1 (PAC1) as a period lengthening molecule through chemical library screening. In collaboration with J. Yamaguchi (Itami group) and Ohmatsu (Ooi group), they developed PACs through focused structure-activity relationship studies of the compound. Surprisingly, they found that one PAC1 analogue showed period shortening activity. Research on target identification, and biological details of PAC1 and its analogue (period shortening) are now ongoing by two distinct approaches, the chemical biology approach (*e.g.*, agarose beads) and the biological approach (genetic screening of mutants insensitive to PAC1)

5. Molecules that modify cell division
(1st ITbM Research Award)
Team: Nambo, Ohkawa, Ueda, Kuwata, Kurihara
Platform: Small-molecule synthesis, Phenotypic assay development, Imaging and sensing technology, Theoretical and analytical platform

With the palladium-catalyzed sequential arylation reaction developed by the Crudden group, Nambo created a characteristic library of over 100 triarylmethane, triarylacetonitrile, and tetraarylmethane derivatives.

4. Management

<Plan at start of project >	<Results/progress/alternations from plan at start of project >
1) Composition of administrative staff i) The Administrative Director manages six units of administration: 1) general affairs unit, 2) accounting unit, 3) international promotion unit, 4) research administration unit, 5) public relations unit, and 6) environmental affairs unit, with the support of Associate Administrative Directors. ii) Two Associate Administrative Directors will be appointed. One is for internal affairs (to manage the general affairs unit and the accounting unit) and the other is for external relations (to manage the international promotion unit, the research administration unit, the public relations unit, and the environmental affairs unit). iii) Beneath the Administrative Director and the Associate Administrative Directors, a total of 18 experts will be involved in 6 units: 4 in the general affairs unit, 3 in the accounting unit, 3 in the public relations unit, 3 in the research administration unit (including 2 PhDs to support foreign PIs in their applications for Japanese domestic research grants), 3 in the international promotion unit (including 2 PhDs), and 2 in the environmental affairs unit. Each unit will have 1 unit chief. iv) A total of 15 bilingual laboratory secretaries will be assigned to assist the PIs. These secretaries will assist with paper work and matters regarding foreign researchers and students.	1) Composition of administrative staff Led by the Administrative Director, the Administrative Department has a well-established structure consisting of the following two divisions, with two Associate Administrative Directors (the Head of Management and the Head of Research Promotion) to assist the work of the Administrative Director. **Management Division** Led by the Head of Management, the Management Division consists of the General Affairs Unit (four staff) and the Accounting Unit (five staff). The nine staff in the Management Division consists of four full-time administrative staff from the university (including two competent English speakers), four contract employees (including three competent English speakers) and one part-time employee. **Research Promotion Division** Led by the Head of Research Promotion (Lecturer, PhD in synthetic chemistry and chemical biology), the Research Promotion Division consists of an Assistant Professor (PhD in organometallic chemistry), a science designer (degree in plant biology), a URA (University Research Administrator, PhD in bioinorganic chemistry holding a concurrent post) to conduct international promotion of research, research administration, public relations, outreach activities, along with event management and a contract employee (degree in plant biology) to support the daily living of non-Japanese researchers in the center. During FY2014, a patent attorney has been assigned to the Research Promotion Division as a lecturer to engage in intellectual properties management at ITbM. Two secretaries were additionally employed in FY2014 to support a Nagoya University PI and the new overseas PI, which added up to a total of eight secretaries (six for Nagoya University PIs and two for overseas PIs), with six of the secretaries having a good fluency in English.

2) Decision-making system

The Center Director will have the authority to make final decisions over the appointment of personnel, the Center budget and research priorities in addition to other matters as they arise.
The Center Director needs to maintain good communications with the Administrative Directors and the PIs in the Center. To this end, we envisage establishing the following councils and committees. In order to ensure sufficient time for the scientific goals of the Center, **the number of meetings will be kept to a minimum.**

i) **Joint Management Council**
Mission: To discuss and to propose issues of fundamental importance to the Center
Members: The Center Director, the Vice Center Director, the Administrative Director, the Associate Administrative Directors, the President of Nagoya University, the Director-General of Nagoya University, any member of the International Advisory and Review Board, and/or the representatives of Cooperating Institutes may also be invited to join the Council Meeting.

ii) **Research Council**
Mission: To discuss important issues regarding research projects and other matters
Members: The Center Director, the Vice Center Director, the Administrative Director, the Associate Administrative Directors, and PIs at Nagoya University.

iii) **Personnel Committee**
Mission: To make the final short list of candidates for new positions
Members: The Center Director, the Vice Center Director, the Administrative Director, the Associate Administrative Directors, and 2 members appointed by the Center Director and selected from the PIs

iv) **Budget Committee**
Mission: To design a budgetary plan
Members: The Center Director, the Vice Center Director, the

2) Decision-making system

To support the work of the Center Director along with the Vice-Director, Shigehiro Yamaguchi was appointed as a second Vice-Director in FY2014 for further promotion of interdisciplinary research and risk management at the center.

Steering Committee
The Steering Committee, which integrates the Councils and Committees listed in ii) - iv) on the left, has been held once a month to discuss and consider important matters of the center, including research plans, operation and management, personnel affairs and the budget.
The Steering Committee is a place for discussion and provides advice for the Center Director to make the final decisions. The Center Director operates and manages the Center in consultation with the Steering Committee.
In FY2014, the Director of the Research Cooperation Department and the Manager of the Research Support Division from Nagoya University Headquarters were included as observers of the Steering Committee to further strengthen the cooperation with the university headquarters and seek advice when needed.

Committee Members:
Center Director, Vice-Center Directors, Administrative Director, Head of Research Promotion, Five Nagoya University PIs, Trustee (in charge of WPI affairs)
Observers:
Four Co-PIs, Three Sub-Center Chief Coordinators

PI Meetings
Regular PI meetings to discuss research and major matters among all PIs are held on a regular basis. Overseas PIs also participate in all PI meetings through the TV conference system. The PI meeting involves discussions on matters related to the management of the center, along with the progress of interdisciplinary research with the Co-PIs. PI meetings play an indispensable role to discuss and determine the direction of the interdisciplinary research for the center.

Administrative Director, the Associate Administrative Directors, and 2 members appointed by the Center Director selected from the PIs v) **Internal Evaluation Committee** *Mission*: To evaluate research activity within the Center and the Cooperating Institutes, and to prepare reports to the External Evaluation Committee *Members*: The Center Director, the Vice Center Director, the Administrative Director, the Associate Administrative Directors, and 2 members appointed by the Center Director selected from the PIs	**Environmental and Safety Committee** As the center 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 Center Director. Members: One Nagoya University PI - Toshinori Kinoshita, Director of Center for Gene Research, Nagoya University One Internal Expert within Nagoya University - Professor of Jurisprudence, Graduate School of Law Four External Experts outside Nagoya University - Trustee/Vice-President of Okayama University - Senior Research Administrator, Strategic Program Support Unit, Okayama University - Head of Natural Environment Division, Department of the Environment, Aichi Prefecture - Senior Councilor, Life & Bio Plaza 21 (NPO) **Other Committees** Regarding the Joint Management Council listed as i) in the left column, the Executive Board of Nagoya University will assume the role of the Council for the time being, depending on the subject to be discussed. As many of ITbM's researchers are associated with the Graduate School of Science, members of ITbM will attend the following three meetings to exchange information: the chief meeting of the Graduate School of Science, the construction meeting and the safety and health meeting.

3) Allocation of authority between center director and host institution **The Center Director** The Center Director will have the authority to make the final decisions over the appointments of personnel, the Center budget, and research priorities in addition to other matters as they arise. To enable this, Nagoya University has taken the significant step of revising its rules in order to give executive authority to the director to make top-down decisions. Nagoya University will also reform its regulations to allow the Center the prerogative to establish its own system for pay structures, employment periods, and other preferential treatment such as the conferment of appropriate titles for its members including project managers and guest researchers. **Host Institution (Nagoya University)** The host institution has the authority and responsibility to allocate some part of the University budget for appropriate financial support of the Center. The host institution has the authority to inspect the management of the Center, and to audit the Center accounts.	3) Allocation of authority between center director and host institution As determined at the time of establishment, the Institute Rules restrict the role of the President of Nagoya University only to the appointment of the Center Director. All matters concerning the operation and management of the center fall under the purview of the Center 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 provides special bonuses to the Center Director, the Vice-Center Directors, PIs, and the Administrative Director based on their performance and evaluations, the selection of eligible persons and the bonus amount is left to the discretion of the Center Director. On the other hand, the Executive Board of Nagoya University determines the bonus amount of the Center Director. The Administration Bureau of the University allocates the budget of the center, and the center has authority independent from other Schools of the Nagoya University in the execution of its budget. However, the budget of the center is subject to internal and external audits as is the case with other budgets within the university.

5. Researchers and center staffs

i) "Core" to be established within host institution

Principal investigators

	At beginning	Final goal (Date: March, 2017)	Results at end of FY 2014	Results at end of April 2015
Researchers from within host institution	7	7	7	7
Foreign researchers invited from abroad	3	5	4	4
Researchers invited from other Japanese institutions	0	3	0	0
Total principal investigators	10	15	11	11

All members

- In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [ ] brackets.
- In the "Administrative staffs" column, put the number and percentage of bilingual staffs in the ( ) brackets.

	At beginning	Final goal (Date: March, 2017)	Results at end of FY 2014	Results at end of April 2015
Researchers	20 < 5, 25% > [4, 20%]	70 < 35, 50% > [14, 20%]	58 < 22, 38% > [12, 21%]	66 < 24, 36 % > [16, 24%]
Principal investigators	10 < 3, 30% > [2, 20%]	15 < 5, 33% > [3, 20%]	11 < 4, 36% > [2, 18%]	11 < 4, 36% > [2, 18%]
Other researchers	10 < 2, 20% > [2, 20%]	55 < 30, 55% > [11, 20%]	47 < 18,38 % > [10, 21%]	55 < 20, 36 % > [14, 25%]
Research support staff	10	40	27	28
Administrative staff	10	20	11 (6, 55%)	11 (5, 45%)
Total	40	130	96	105

ii) Satellites <Plan at start of project > Satellite institutes are NOT applicable.	<Results/progress/alternations from plan at start of project> As planned at the start of the project, satellite institutes are NOT established.
iii) Partner institutions < Plan at start of project > Institution (1): Queen's University, Canada Institution (2): University of Washington, USA Institution (3): ETH Zürich, Switzerland	<Results/progress/alternations from plan at start of project> In addition to the three institutes stated on the left, ITbM has started partnerships with the following institutes: National Science Foundation (NSF) Center for Selective C-H Functionalization (CCHF, USA), Freiburg University (Germany), RIKEN Center for Sustainable Resource Science (CSRS, Japan). Institution (1): Queen's University, Canada - Role Queen's University collaborates with ITbM as a host institution affiliated with Cathleen Crudden, an overseas PI, who is carrying out research to develop transformative bio-molecules through her research on novel molecular transformation catalysis. - Personnel composition and structure Prof. Cathleen Crudden (Double affiliation with ITbM and Queen's University) - Collaborative framework In FY2014, one Co-PI (Assistant Professor Masakazu Nambo), three postdoctoral researchers, and one technician conduct research in close collaboration with Crudden at Nagoya University. Institution (2): University of Washington, USA - Role The University of Washington collaborates with ITbM as a host institution affiliated with Keiko Torii, an overseas PI, who is carrying out research to define key molecules for plant growth and to promote plant growth research using synthetic molecules. - Personnel composition and structure Prof. Keiko Torii (Double affiliation with ITbM and the University of Washington)

	- Collaborative framework In FY2014, one Co-PI (Associate Professor Naoyuki Uchida), three postdoctoral researchers, and two technicians conduct research in close collaboration with Torii at Nagoya University. <u>Institution (3)</u>: ETH Zürich, Switzerland - Role ETH Zürich collaborates with ITbM as a host institution affiliated with Jeffrey Bode, an overseas PI, who is carrying out research to develop transformative bio-molecules using his novel method for polypeptide synthesis. - Personnel composition and structure Prof. Jeffrey Bode (Double affiliation with ITbM and ETH Zürich) - Collaborative framework In FY2014, one Co-PI (Assistant Professor Shunsuke Oishi), two postdoctoral researchers, and one technician conduct research in close collaboration with Bode at Nagoya University. Learning from ETH Zürich, a "clone lab", with the exact same equipment and analytical devices as the labs in ETH Zürich are installed in the Mix-Lab at Nagoya University, and increases the efficiency of research. <u>Institution (4)</u>: The Center for Selective C-H Functionalization (CCHF, National Science Foundation (NSF) Center, USA) - Role C-H activation chemistry constitutes an important area of ITbM's research, and collaboration with CCHF is ongoing to promote the research, internationalization and visibility of ITbM. Around four to five researchers/year (duration: three months) are being exchanged between the institutes, which will foster young scientists. - Personnel composition and structure The following top leading 23 PIs and their research groups working in the field of C-H activation chemistry in 14 universities/institutes across the USA are members of CCHF partnered with ITbM: Emory University (Huw Davies, Simon Blakey, Cora MacBeth, Djamaladdin Musaev, Andy Borovik), University of Washington (Christine Luscombe), University of

California, Berkeley (Richmond Sarpong), Stanford University (Justin DuBois, Richard Zare), University of California, Irvine (Brian Stoltz), University of California, Los Angeles (Ken Houk), The Scripps Research Institute (Donna Blackmond, Jin-Quan Yu), University of Utah (Matthew Sigman), University of Wisconsin at Madison (John Berry), University of Chicago (Jared Lewis), University of Michigan, Ann-Arbor (John Montgomery, David Sherman), Massachusetts Institute of Technology (Mohammad Movassaghi), Princeton University (Erik Sorensen), Georgia Institute of Technology (Stefan France, Christopher Jones, Seth Marder)

- Collaborative framework

Collaborative research is conducted between CCHF and ITbM through mutual exchange of researchers with each other's center. In order to send researchers to ITbM, CCHF makes a joint application with ITbM to the NSF to secure funds. On the other hand, ITbM sends researchers abroad through WPI funds. During FY2014, ITbM has sent four researchers to CCHF (Scripps Institute (2), CalTech (1), and Emory University (1)) and has accepted three researchers from CCHF (Emory University (2) and Georgia Institute of Technology (1)) and one faculty (Scripps Institute). CCHF is also collaborating with KAIST (Korea Advanced Institute of Science and Technology), and is connected with ITbM through TV conferences. These online conferences enable sharing of joint research achievements on a regular basis.

Institution (5): Freiburg University, Germany

- Role

ITbM has collaborated with Freiburg University, which is Europe's main center for research in biochemistry. Through interaction and collaborative research with Freiburg University, ITbM aims to promote its research and internationalization.

- Personnel composition and structure

Gunther Neuhaus (Vice-President and Vice Rector for Research, Freiburg University), Freiburg University's researchers working in natural sciences including Professors Hermann Grabert, Ralf Reski and Thomas Laux.

	- Collaborative framework Nagoya University's European Center is established in Freiburg and strong collaborative relationships already exist with Freiburg University. In addition, Vice-Director Tetsuya Higashiyama and Minako Ueda (ITbM Lecturer) have started collaborative research in plant biology with Freiburg University. ITbM's PI Takashi Ooi has already published papers with Freiburg University in the area of synthetic chemistry. Based on these achievements, ITbM will conduct further collaborative research in biochemistry and chemistry with Freiburg University. Tetsuya Higashiyama, Minako Ueda, Shinya Hagihara, Masayasu Taki and the Administrative Director, Tsuyoshi Matsumoto visited Freiburg University in June 2014 to participate in a joint symposium and initiate collaborative research. In November 2014, the Administrative Director and the Board of Nagoya University have visited Freiburg University to consider concluding an agreement between the institutes. <u>Institution (6)</u>: RIKEN Center for Sustainable Resource Science (CSRS), Japan - Role Based on the following three keywords, "plant science", "chemical biology" and "chemistry" that are common to both centers, ITbM and CSRS will interact effectively to generate new interdisciplinary research. - Personnel composition and structure Prof. Kazuo Shinozaki (CSRS Center Director) and researchers of CSRS - Collaborative framework As of January 2015, ITbM entered a joint research collaboration agreement with CSRS. Both institutes have agreed to share their techniques and resources in order to collaborate effectively. To mark the collaboration agreement between ITbM and CSRS, the "1st CSRS-ITbM Joint Workshop" was held at Nagoya University in January 2015.

6. Summary of center's research environment

< Plan at start of project >

1) Environment in which researchers can devote themselves to their research

Mix-Lab System

To realize truly cross-disciplinary research projects and to nurture the next generation researchers of this field, we will create special laboratories we refer to as **"Mix-Labs"**. Rather than doing research in a small laboratory consisting of one research group, we will ask young researchers of different fields to work together in a large laboratory (**Mix-Lab**). We strongly believe that this working style will not only accelerate the mixing/merging of people, ideas, equipment, and research, but also help nurture a new generation unrestricted by the bounds of traditional disciplines.

An efficient administration run by talented staff will be introduced to free PIs from administrative duties.

Co-supervising system

To reinforce the value of the Mix-Lab concept, all postdoctoral researchers will be supervised by two PIs from different fields for accelerating collaboration and nurturing the next generation of cutting-edge research, unrestricted by the bounds of traditional disciplines.

In order to recruit excellent PIs and Co-PIs, we will provide the following: (a) a team that is responsible for supporting their applications for competitive domestic (Japanese) research funds; (b) opportunities for partners/spouses to hold positions in the University on the basis of proper evaluation (Dual Career Support); and (c) adequate information on education opportunities for the children of foreign PIs who may join them during their time at Nagoya. Through these mechanisms, we expect foreign PIs to spend significant amounts of time at Nagoya.

We will locate the world's most advanced equipment and facilities in a single space at Nagoya University, staffed with expert equipment managers such that it is fully accessible for promoting research, international collaboration, and discovery. A substantial body of postdoctoral researchers and technical assistants will be hired to ensure

<Results/progress/alternations from plan at start of project>

1) Environment in which researchers can devote themselves to their research

Mix-Lab System

Through the establishment of "Mix-Labs", ITbM continues its challenge to achieve extensive mixing of different disciplines. This approach is different from conventional collaborative research and joint seminars in the sense that chemists, biologists and theoreticians share the same office space and work side by side in the labs. Through daily discussions ranging from simple practical questions to sophisticated research hypotheses, innovative ideas that arise from young researchers enable the propagation of new research fields. As a result of these endeavors, many interdisciplinary research projects to create new bio-functional molecules have been established among various combinations of PIs and their group members, *e.g.* Itami-Kinoshita, Higashiyama-Bode, Kinoshita-Ooi, Crudden-Yoshimura-Irle, Ooi-Kay, Yamaguchi-Higashiyama-Irle, Torii-Bode, and Yoshimura-Itami-Kay-Irle. In FY2014, many of these new research projects have been initiated to develop novel molecules to "understand", "see", and "regulate" living organisms.

In order to realize new areas of research and to induce further mixing, the Research Promotion Division attends all seminars at ITbM to comprehend and have a wide perspective of ITbM's research. The Research Promotion Division perceives unpublished data and shares the information with other groups at ITbM to promote interdisciplinary research. Researchers at ITbM also attend group seminars of other PIs to share and exchange ideas. Some of the informal meetings held by young researchers have evolved into regular seminars, involving many researchers including students from different research groups. For example, the "Mix-Plant" seminar, which mainly consisted of plant biologists, now involves chief coordinators of the three research centers with the growing need for their expertise (see below). This enables the chief coordinators to understand the latest research in the plant field and suggest necessary methods accordingly. This Mix-lab concept, where daily discussions lead to initiation of new research and opens doors towards new interdisciplinary research is expected to continue in ITbM's new building.

smooth operation of analytical instruments etc. In order to reduce the educational and administrative burden of PIs, the University will furnish the original faculty of PIs with additional staff (a total of 7 associate professors). A total of 15 bilingual secretaries will be assigned to the PIs in 2013 to help the Investigators cope with their paper work and any matters regarding foreign researchers and students in the groups.	In order to promote interdisciplinary research, the ITbM Research Award was established in FY2013. This provides an opportunity for young faculty members, postdoctoral researchers and students to write research proposals and obtain funding for their research. In addition to the four research proposals selected in FY2013, two new proposals have been selected in FY2014. **Establishment of 3 Research Centers** Since the launch of ITbM, three research centers, the Live Imaging Center, the Molecular Structure Center, and the Chemical Library Center have been established, and have started their own support inside and outside of ITbM. In FY2014, the three research centers formed a new triangle organization, so-called the "Three Centers Mix", to improve the overall efficiency of research in chemistry and biology along with interdisciplinary research. By incorporating the researchers inside the triangular network, the three centers and the researchers are able to share information, discuss extensively, and work together as a team from the start of the research project. Through strengthening this research structure of the three research centers, a new style of chemical biology research is expected to be established in the near future. **Strengthening the activity of the Research Promotion Division** The Research Promotion Division supports ITbM's research through organizing symposia/seminars, international public relations, outreach activities, building networks and providing training to researchers as well as daily support to foreign researchers and their families. In FY2012, the Research Promotion Division consisted of a head, a chief and a university research administrator (concurrent post, supporting the application of external grants). In FY2013, an additional three personnel, a science designer, an administrative assistant and an international public relations officer were employed at the Research Promotion Division to support ITbM's activities. During FY2014, an intellectual properties manager was employed. The Research Promotion Division led by Ayato Sato, now consists of Ayako Miyazaki, Reiko Matsushima, Haruko Hirukawa, Hanae Tsuchiya and Mayumi Watanabe, many having experience abroad with the ability to communicate in both English and Japanese.

The Research Promotion Division focuses on the following activities

(1) Science Design

ITbM's presence continues to be promoted through visual tools, such as posters, websites, journal cover images, booklets, presentation slides, videos and promotional items. This has led to effective communication of ITbM's research, especially during outreach events. Most of the artwork, such as posters, information boards, and abstract booklets used in symposia and events are designed within the Research Promotion Division, thus creating a uniform image of ITbM. Some of the scientific images created at ITbM were selected as journal covers (front cover: 2, inside cover: 3, back cover: 1 in FY2014).

ITbM was also involved in Nagoya University's international project through science design.

EurekAlert!

Alpha Galileo

Asia Research News Magazine 2015

Graphical Abstract for Angewandte Chemie

(2) International Public Relations

ITbM's research activities are promoted both nationally and internationally through dissemination of research outcomes in both Japanese and English by means of press conferences and press releases. ITbM works closely with Nagoya University's Public Relations Office and has released over ten press releases during FY2014, resulting in good media coverage in national newspapers, websites and magazines. Distribution of press releases by international press release services (EurekAlert!, ResearchSEA and Alpha Galileo) has also led to broad media coverage in major science websites around the world, including in non-English websites, such as Chinese, Spanish, Hebrew, Hungarian and Dutch. The press releases are usually associated with images to make the research understandable and accessible to a broad audience. Joint press releases for collaborative research are also being prepared by working with ITbM's partner institutes, Emory University (CCHF) and RIKEN CSRS. As a result of these endeavors, ITbM has been covered approximately 500 times locally and globally in various media during FY2014. This is considered to contribute to increasing the global visibility of ITbM, Nagoya University and the WPI program.

ITbM's website and social media is also managed simultaneously in both English and Japanese to spread news to a wide audience on a

timely basis.
Exhibiting at the International Symposium on Homogeneous Catalysis, ISHC XIX, held at Ottawa (Canada) has led to building a network with Thieme's editors, who created a three-page feature of ITbM in their Synfacts magazine.
Yoshimura, Bode, and Irle's research has also been featured in the annual science magazine, Asia Research News 2015 published by ResearchSEA, distributed at international conferences and to various research institutes around the world.
ITbM will continue to communicate its research to the public and find new ways to perform effective science communication and enhance public engagement.

(3) Local Support to Foreign Researchers

ITbM supports the daily lives of foreign researchers and their families, by assistance in immigration, accommodation, registrations at city council and banks, accompaniment to hospitals, supporting pregnant mothers for childbirth, along with providing advice for daily life in Japan. With the increase in the number of foreign researchers, researchers are encouraged to communicate and help each other. Educational support is also provided to foreign children, such as providing assistance to enter local public schools in Nagoya. Although internationalization in Nagoya has been ongoing, much of the support has been in Chinese, Korean, Portuguese, and Filipino with limited correspondence in English. Therefore, ITbM established a network with Nagoya University and Nanzan University to provide linguistic support in English and Japanese for young foreign children. Liaisons with Nagoya city and Aichi prefecture's Board of Education are also ongoing to help the children of foreign researchers to attend local schools.

(4) Intellectual Properties

During FY2014, ITbM employed a full-time person at the Research Promotion Division to engage in intellectual properties and to devise patent strategies for sustainable management of the center.
As a result of having an intellectual properties manager on site, the process for filing patent became more systematic and there were 12 patent applications with an increase of applications in biological fields,

along with some technological transfers during FY2014.

(5) Event Management

In FY2014, two international symposia, the 2nd International Symposium on Transformative Bio-Molecules (ISTbM-2) and the "Nagoya Medal of Organic Chemistry 2014" and one workshop, the "1st CSRS-ITbM Joint Workshop" were organized and held by ITbM. ISTbM-2 and the joint workshop were organized with the Management Division, and the Nagoya Medal was organized with the strong support from the Banyu Life Science Foundation International. Preparation for the 3rd International Symposium on Transformative Bio-Molecules (ISTbM-3), along with the "11th Hirata Award" and the "1st Tsuneko and Reiji Okazaki Award", which will be held simultaneously in May 2015, is currently ongoing.

(6) Outreach Activities

Various outreach activities are being carried out, including science experiment demonstrations at high schools (Konko, Sendai Daiichi, Ichinomiya, Kikuzato, and Nanzan High School) and at the Science Agora (Miraikan, Tokyo). The Research Promotion Division has created a broad network of high schools in the Tokai area (Aichi, Mie, Gifu, Shizuoka, and Nagano prefectures). In addition, upon the opportunity to supervise students of the Sendai Daiichi High School to prepare for their research presentation at the WPI Joint Symposium (December 2013), the Research Promotion Division has spread their activity to contribute to the high school education in the Tohoku area of Japan.

Lab tours and lectures to introduce ITbM are also held to students and teachers from local and overseas high schools (Bard, Eleanor Roosevelt (USA), Sendai, Kikuzato, Sugiyama (Japan) High Schools) as well as for visitors from abroad including the Minister of education, culture and science from Mongolia.

ITbM's activities are also introduced to the public by means of booth exhibitions at international events, including the International Symposium on Homogeneous Catalysis (Ottawa, Canada) and the AAAS Annual Meeting 2015 (San Jose, USA). ITbM also participated in the Super Science High School Presentation (Yokohama) and the WPI Joint Symposium (Tokyo).

ITbM also cooperated with NHK to create a one-hour TV program, 'Chikyu (Earth) Agora', featuring ITbM's activities.

(7) Education

As ITbM is specific in having Mix-Labs, which integrates chemistry and biology, individual safety and health training is provided to new researchers joining ITbM. This training has been officially approved by Nagoya University this year.

Employment of Faculty Members

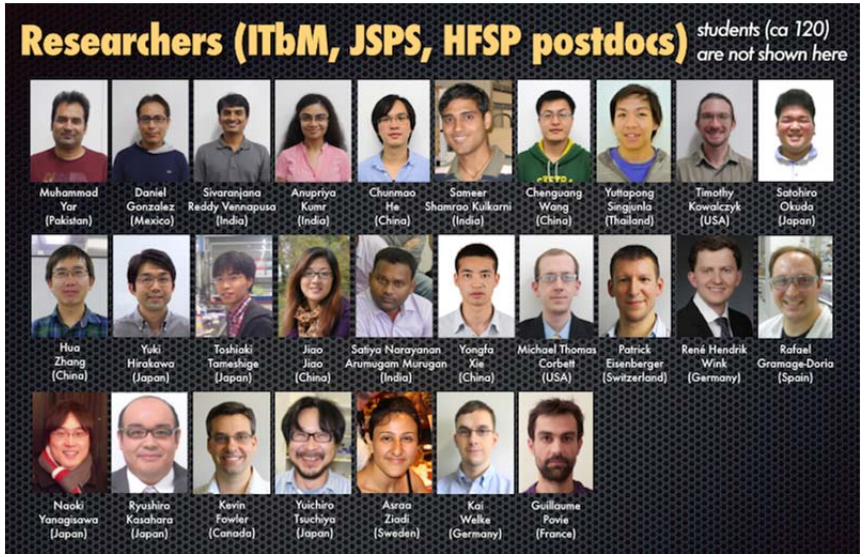
In order to enable Nagoya University's seven PIs to focus on their research, Nagoya University provided permission to employ seven associate professors and lecturers to provide lectures and handle educational affairs in the place of the PIs. Recruitment started from FY2012. Three faculty members were employed in April 2013 and the remaining four faculty members were employed during FY2013.
In addition, four Co-PIs to work with overseas PIs were employed in February 2012 (1), April 2013 (2) and March 2014 (1).
In order to meet the increasing need for a theoretical chemist to enhance ITbM's research, an assistant professor was employed in Stephan Irle's group.

Employment of Technicians and Secretaries

Each PI is able to employ one technician to operate the analytical

	equipment in the labs. Technicians are also employed at the sub-centers to support their work. A total of six technicians were employed in FY2013 and nine technicians were employed in FY2014. In addition, five secretaries with good fluency in English were employed in April 2013 and one secretary with good English competence was employed in July 2013 to assist the three overseas PIs. Two English competent secretaries were additionally employed in FY2014, one to support one Nagoya University and another to support the new overseas PI, Steve Kay's group along with the three sub-centers.
2) Startup research funding We will provide each of the new researchers with research space and start-up funds with an average value of $125,000 USD. If necessary, the start-up money will be increased for top-caliber researchers by using a discretionary budget allocated to the Center Director. We will furnish the new researchers with full access to instruments in the Center. Except for the start-up funds, all of the following costs are covered by our Center: lab spaces fee, utility costs including electricity and water fees, employment costs of two postdoctoral researches, one secretary, and one technical staff.	2) Startup research funding Continuing from last year, communal equipment to conduct Mix-Lab's interdisciplinary research were purchased and installed. A high performance computer was purchased in the server room to conduct theoretical calculations, and the set up for all the servers was completed during FY2014. In addition, large equipment was purchased for the three sub-centers (refer to Section 12). As the three overseas PIs, Crudden, Bode and Torii, ITbM were initially not eligible to apply for research grants within Japan, research funds were provided to the overseas PI's groups. Fortunately, Crudden and Torii were successful in obtaining the Kakenhi grants in FY2014, so the distribution of research funds was reduced for these two groups accordingly. The ITbM Research Award, set up in FY2013 to promote the research activities by young researchers has been awarded to two interdisciplinary research projects in FY2014. The successful research proposals were awarded 2 million yen for over 2 years.
3) Postdoctoral positions through open international solicitations We will engage in high-profile recruitment campaigns to attract highly qualified postdoctoral researchers using web sites with global appeal describing the current efforts of the Center, University, and Nagoya City for internationalization. We will keep channels open to world premier chemists and biologists, and solicit their recommendations for suitable candidates as postdoctoral researchers.	3) Postdoctoral positions through open international solicitations Open recruitment for postdoctoral researchers is being announced on the ITbM website in Japanese and English. The position consists of a one-year contract, with a possible renewal for up to three years, and applications forms are required to be completed in English. Positions are also announced on international websites including Nagoya University, PI's websites, as well as the careers websites of Science, Nature and JREC-IN. Through additional networking with prestigious chemists and biochemists around the world, 5 postdoctoral researchers were recruited in FY2014,

adding up to a total of 13 postdoctoral researchers present at the center. In addition, other researchers, including 6 JSPS postdoctoral researchers, 1 JST PRESTO researcher and 1 postdoctoral researcher from the Swiss National Science Foundation (SNSF) are also affiliated to ITbM and carry out research at the center. ITbM will continue its recruitment to secure talented researchers.



4) Administrative personnel who can facilitate the use of English in the work process

The research groups of the PIs are international in outlook, and have excellent track records in inviting foreign researchers as visiting professors, postdoctoral researchers, and exchange students. English is routinely used in their research groups.
Not only our WPI Center but also all of Nagoya University is internationalized as Nagoya University has started the Global 30 International program to accept foreign undergraduate and graduate students (all of classes and experimental courses are taught in English). The G30 students are also in the laboratory of the PIs.
The Administrative Director is fluent in English, and the projected administrative staff will also have high English skills.

4) Administrative personnel who can facilitate the use of English in the work process

Personnel who are fluent in English and with thorough experience in handling administrative affairs were employed in the General Affairs and Accounting Unit of the Management Division. In addition to their usual work related to administration, the Management Division is actively involved in preparing ITbM's international symposia, such as performing the MC and handling the registration. ITbM regularly sends notices from the university to ITbM researchers in both English and Japanese. This initially included grants and funding information. Subsequently, Nagoya University realized the importance of this endeavor from ITbM, and the university administration office took over this process and started to send grants and funding information in both languages from the end of FY2013.

5) Rigorous system for evaluating research and system of merit-based compensation A rigorous evaluation of researchers will be made by an external evaluation committee, with the assistance of the International Advisory and Review Board. The annual salary of researchers hired from outside the host institute will be adjusted based on the evaluation. There will also be a merit-based fringe benefit system for internal hires.	5) Rigorous system for evaluating research and system of merit-based compensation Special bonuses are provided to the Center Director, the Vice-Director, Nagoya University PIs and the Administrative Director based on their performance and evaluations. They receive full bonuses during the starting period of the project and the amount will vary according to their evaluation in FY2013, from FY2014 onwards. All ITbM researchers are required to submit an activity report regarding their research activity in March. For the PIs, the evaluation committee will reflect the results of the Site Visit report to the special bonuses. As for other faculty and postdoctoral researchers, each PI will conduct the first evaluation, followed by a secondary evaluation by the Center Director, and the results will be reflected in their salary upon renewal of their contract.
6) Equipment and facilities, including laboratory space, appropriate to a top world-level research center **Nagoya University will provide 6,000 m^2 of research space for the Center.** The Science and Agricultural Building and Science South Building are regarded as the premier global facilities, and 3,000 m^2 of the building space will be allocated to the WPI Research Center. These two buildings, which are directly connected, were built in 2011 to accelerate the collaboration of science and agriculture research within Nagoya University. A brand-new live-cell imaging center space of 300 m^2, which was originally part of our G-COE program and will be further developed by our WPI program, is also in the Science South building. A teatime room of 70 m^2 will also be placed in the Science and Agricultural Building to facilitate communication among members of our WPI Center. Nagoya University will provide additional laboratory space of 1,500 m^2 by the end of FY2012, and the other 1,500 m^2 as soon as possible As also noted in the host institution's commitment, Nagoya University will draw up a plan of further allocation of space and a new building for	6) Equipment and facilities, including laboratory space, appropriate to a top world-level research center Nagoya University has provided 5,165 m^2 of research space for the center, which contains 2,165 m^2 of new space on top of the existing 3,000 m^2 of space designated to Nagoya University PIs. In order to install new equipment, an additional 58 m^2 was allocated to the center in FY2013. Upon appointment of Steve Kay of the University of Southern California (USA) as an overseas PI from FY2014, an additional 134 m^2 of new space was allocated to accommodate his research group. A total of 5,357 m^2 of research space was provided to ITbM from Nagoya University during FY2014. The new building for ITbM was completed at the end of FY2014. The total area of the new six-floor building is 7,934 m^2 and has a unique structure where a pre-existing building (floor area 463 m^2) is incorporated within the new building. In addition, the university provided the area from the pre-existing building. The new building is designed to reflect the "Mix-Lab" concept. The second and fourth floors consist of large biology and chemistry labs and the third and fifth floors consist of the office space for

gathering not only activities of the WPI Center but also other organizations relating to the field of our WPI Center. Nagoya University will provide financial support for maintaining the research environment at a world-class level including the enforcement of appropriate safety measures. Nagoya University is very well equipped with top-level major instruments necessary for our WPI research. The quality and number of these instruments rivals the best institutions in the world. The following lists representative instruments that can be used by our WPI research team.	the researchers. The first floor contains the administrative office and the lecture room. On the top (sixth) floor are the Live Imaging Center, Chemical Library Center, and greenhouses. Both 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, along with the Mix Office spaces located directly above. This removes the conventional barriers between research groups, thus creating huge Mix Labs and Mix Offices to promote interdisciplinary research. The new building is also equipped with a childcare room for researchers and visiting researchers accompanied by small children.
7) International research conferences or symposiums held regularly to bring world's leading researchers together	7) International research conferences or symposiums held regularly to bring world's leading researchers together
A large-scale international research conference will be organized each year, primarily at Nagoya University. A limited number of international workshops of a small-to-medium size will be organized each year. For the first year of the Center, the 1st international research conference is scheduled at the end of FY2012 in March 2013. In Japanese universities, such international meetings are usually managed mainly by researchers, including administrative matters. However in our WPI Center, the Administrative Office directed by the Administrative Director and Associate Administrative Directors will manage meetings according to the decision of the subject, candidates of invited speakers, and schedule of each meeting by PIs, in order to avoid further encroachment on researcher's time.	The second international symposium of ITbM (2nd International Symposium on Transformative Bio-Molecules, ISTbM-2) was organized by the Administrative Department and was held at Nagoya University in May 2014. Lectures were delivered by five young researchers at ITbM (Daisuke Yokogawa, Naoyuki Uchida, Norihito Nakamichi, Tsuyoshi Hirota, Kohsuke Ohmatsu) along with five invited speakers (Robert E. Campbell (University of Alberta), David C. Nelson (University of Georgia), David J. Craik (University of Queensland), Sukbok Chang (KAIST, ITbM's partner institute) and Hisashi Yamamoto (University of Chicago/Chubu University)), who are all world-class international researchers working in a range of fields such as life science systems, plant biology, biochemistry, and catalytic/synthetic chemistry, which are all fields strongly related to ITbM's research. The symposium ended in great success with about 300 participants.

ISTbM-2 (May 2014)
(~300 attendees)

As of FY2014, Center Director Kenichiro Itami was selected as the Chairman of the Nagoya Medal of Organic Chemistry. The Nagoya Medal Award was initially proposed by Hisashi Yamamoto (University of Chicago/Chubu University) and Nobel Laureate Ryoji Noyori (Nagoya University), and was founded in 1995 by President Noyori through the financial support of the Banyu Life Science Foundation International. ITbM organized this 20th anniversary event with the Banyu Foundation in October 2014 at Nagoya University, inviting John F. Hartwig (University of California, Berkeley) and Itaru Hamachi (Kyoto University) as the award winners. The symposium ended in great success with about 400 participants including the founders, Hisashi Yamamoto and Ryoji Noyori.

Nagoya Medal of Organic Chemistry 2014 (October 2014)
(~400 attendees)

In January 2015, ITbM officially signed a joint agreement with the RIKEN Center for Sustainable Resource Science (CSRS) led by Center Director

Kazuo Shinozaki. To celebrate the joint agreement between CSRS and ITbM, "The 1st CSRS-ITbM Joint Workshop" was held at Nagoya University in January 2015. RIKEN CSRS Center Director Kazuo Shinozaki and Nagoya University ITbM Center Director Kenichiro Itami gave their addresses at the start of the workshop, covering the missions and goals for each center. This was followed by plenary lectures from the Vice-Center Directors, Hiroyuki Osada of CSRS who spoke about his ventures on chemical biology, and Shigehiro Yamaguchi of ITbM who presented his research on the development of fluorescent molecules for bio-imaging. Oral presentations by 8 other researchers and over 60 poster presentations from both centers were shared amongst 250 people, and were extremely effective in discussing about each other's research and finding new areas for interdisciplinary collaboration. A joint press release, regarding the research collaboration was prepared and distributed from both centers.

The 1st CSRS-ITbM Joint Workshop (January 2015)
(~200 attendees)

8) Other measures, if any

As our foreign PIs are truly world-leading scientists, we are confident that they can maintain their excellent funding profiles in the future. However, there are special challenges to carrying out research in Japan for foreign PIs, in particular access to information only in Japanese,

8) Other measures, if any

(1) Conclude Memorandum of Understanding (MOU) with partner institutions
In FY2013, MOUs with the institutions affiliated with the three overseas PIs, Cathleen Crudden (Queen's University, Canada), Jeffrey

when they seek competitive funding in Japan. We wish to strongly encourage PIs and Co-PIs to become actively involved in the procurement of external funding from Japanese sources, therefore, the Center will provide **a support team**, which will collect Japanese information and translate application documents (Japanese to English and English to Japanese). The team in the research administration unit includes two PhD administrators from chemistry and biology fields.

To facilitate both domestic and international research collaboration by our foreign PIs, the Center and Nagoya University will establish a more efficient and flexible administrative structure to process travel expenses and acceptance of outside researchers.
The Center and Nagoya University will provide opportunities for partners/spouses to hold positions in the University on the basis of proper evaluation (Dual Career Support).

Nagoya University will give priority to the principal and collaborative researchers in assigning university accommodations. In addition, the WPI Center will collect and provide information on international education opportunities, which are increasingly developed in Nagoya City, for the children of overseas researchers.

Nagoya University established a nursery in its campus (as a part of the program to support female employees and researchers), and it will accept the children of foreign researchers at the Center.

Nagoya University is very well equipped with top-level major instruments necessary for our WPI research. The quality and number of these instruments rivals the best institutions in the world. We will hire some expert operators and computer programmers for these facilities, which includes 5 postdoctoral researchers. They will strongly support the leading-edge research by the foreign PIs and other researchers.

Nagoya University has grasped the opportunity offered by being selected to host numerous Global-Centers of Excellence and the Global-30 program both to accelerate globalization of its campus and to promote high-level international research. In addition, we have implemented the mid- and long-term mutual exchange of doctoral students and young

Bode (ETH Zürich, Switzerland) and Keiko Torii (Howard Hughes Medical Institute / University of Washington, USA) were concluded with Nagoya University to appoint the overseas PIs as part time lecturers and grant visiting professorship at Nagoya University. In FY2014, the MOUs for Crudden and Torii were renewed under the same conditions. The MOU was modified for Bode to become an inviting faculty at Nagoya University.
Following the conclusion of the MOU with ETH Zürich and the Howard Hughes Medical Institute / University of Washington partner institutions regarding intellectual properties in FY2013, the MOU for intellectual properties was also signed with Queen's University in FY2014. ITbM has exchanged MOUs with the NSF Center for Selective C-H Functionalization and further negotiations are currently undergoing.

(2) Arrangements for overseas PIs to apply for external grants from FY2014
As the MOUs with the overseas PIs partner institutes were concluded by appointing the three overseas PIs as visiting professors, they became eligible to apply for grant applications in Japan. With the support from the Co-PIs and the Administrative Department, the overseas PIs submitted application forms for the Kakenhi Grants-in-Aid for Scientific Research for FY2014. For FY2014, two projects were selected for Scientific Research B and one project was selected for Scientific Research on Innovative Areas. In addition to the Kakenhi grants, ITbM is collaborating with Nagoya University's URA to collect information and support the application for other research grants and supporting funds.

(3) Setting up the environment to accommodate overseas PIs, foreign researchers, and researchers with children at Nagoya University
Appointment of the three overseas PIs as visiting professors of Nagoya University grants them the authority to stay at Nagoya University's accommodation facilities during their time at ITbM.
ITbM has also negotiated with the international schools near Nagoya University to allow the short time entry for a child of an overseas PI. As a result of liaison, local public schools now accept the entry of international children from abroad.

faculty members, as exemplified by the very successful "International Research Training Group (IRTG)" Program with the University of Münster (FY2005-2011). This program was followed by another Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation, "Innovative Molecular Catalysis and Novel Functional Materials" (FY2011-2014). The Center will take full advantage of these nternational programs to ensure active international research activities.	Arrangements have been made with Nagoya University so that foreign researchers can use the university's accommodation facilities, and university rules have been revised so that they can stay in the accommodation facilities for up to two years (initially one year before changing the regulations). Since the number of university facilities able to accommodate foreign researchers is still limited, the Head of Management has been attending working groups within the university to increase the number of these facilities. (4) Promotion of ITbM's international research activities utilizing Nagoya University's international programs: ITbM utilizes the international programs run by Nagoya University, such the Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation, Program of Leading Graduate Schools, Program for Promoting the Enhancement of Research Universities and the Top Global University Project, to promote international collaborative research. By continuing to build networks through exchange programs, ITbM will work to improve the international visibility of ITbM, Nagoya University and the WPI. (5) Scientific outreach activities by PIs and researchers ITbM's PIs and the Research Promotion Division conduct lectures at high schools as part of ITbM's outreach activities. As a result of these activities and media coverage in newspapers, many of the newly enrolled students were already aware of the word "transformative" and the presence of Center Director Itami, which indicates the growing visibility of the center. ITbM's PIs have received many lecture invitations from high schools in the Tokai region of Japan. ITbM puts strong emphasis on being actively involved in public lectures to nurture the next generation of young scientists and increase the visibility of ITbM. During FY2014, Itami, Yoshimura, Yamaguchi and Higashiyama have presented public lectures at high schools. In addition, postdoctoral researchers have also been involved in outreach activities. Michael Corbett (Ooi group) has given a lecture at Funabashi High School (Chiba) as part of the JSPS program and Réne Wink (Torii group) participated in the WPI Joint Symposium to share his research to high school students.

7. Criteria and methods used to evaluate center's global standing

< Plan at start of project >

The global standing of the Center depends firstly on the performance of the individual researchers, and we will use a set of quantitative metrics combined with more qualitative methods to assess the performance of individual researchers and their contributions to the Center. We consider there are three aspects important to the global standing of the WPI: 1) **research quality and impact**, 2) **breakthrough from the interdisciplinary research activities**, and 3) **human resources development**.

1) Publishing our work in top journals is absolutely required. The number of papers published in top journals will be counted for evaluation. A selection of such data for our PIs clearly indicates we have a group of outstanding individuals that together will give our Center a very high global profile.

Highly cited work is clearly an indication of high quality research and a significant impact. Citations can be quantified by bibliometrics such as total citations, citations per paper, and h-index.

Total number of papers cited more than 80 times (10 PIs): 86

These types of bibliometrics will be gathered for the researchers and used in evaluation throughout the life of the Center. Two more important indicators of research quality and impact are success in obtaining external funding and the number of invited lectures at international conferences and these will also be monitored.

Total number of keynote/plenary/invited lectures by 10 PIs in the last 4 years: >500

With the concentration of research talent and resources at the Center, on the longer term we envisage some of our members being rewarded with significant international prizes in the fields related to the mission of this Center. The number of such prizes will be a good indication of the Center's impact on the wider scientific community. Honors and prestigious positions will also be monitored for the same reason.

<Current assessment>

1) Research quality and impact

The Research Promotion Division uses Thomson Reuter's EndNote and Web of Science to monitor and manage the research publications of the center. During the calendar year of 2014, 104 papers (original articles and reviews) were published in peer-reviewed journals. As of April 2015, 41 papers are already published in peer-reviewed journals.

From January 1st to December 31st, 2014:

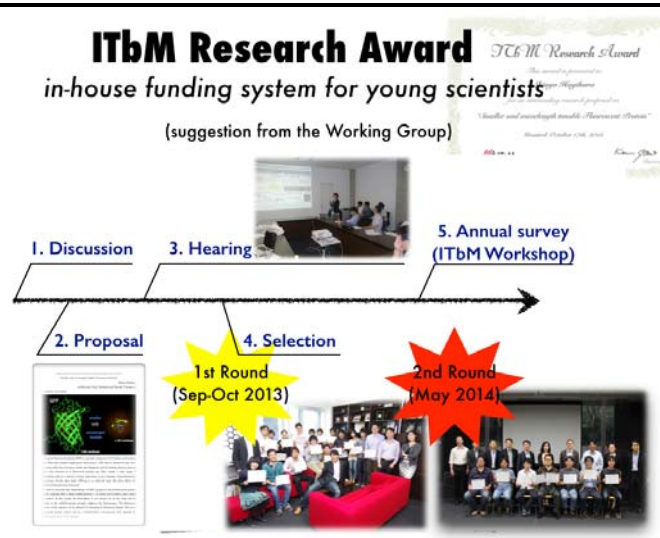
Number of papers: 104, with 44 papers published in journals with an Impact Factor (2013) > 7 and 19 papers published in journals with an Impact Factor (2013) > 10. In 2014, 7 papers were identified as Highly Cited Papers (Thomson Reuters). This includes papers categorized as WPI and WPI-related.

Plenary and invited lectures at international symposia: 86

Awards and Honors: 13

- Kenichiro Itami (Center Director): Nankai University Lectureship Award, Swiss Chemical Society Lectureship Award, ACS American Chemical Society Arthur C. Cope Scholar Award
- Tetsuya Higashiyama (Vice-Director): Yomiuri Techno Forum Gold Medal Prize, NISTEP Award 2014, President of International Association of Plant Reproduction Research (2014-)
- Shigehiro Yamaguchi (Vice-Director): Mukaiyama Award

	・ Cathleen Crudden (PI): Fellowship in the Chemical Institute of Canada (FCIC) ・ Takashi Ooi (PI): Fellow of the Royal Society of Chemistry ・ Keiko Torii (PI): 31st Inoue Prize of Science, ADVANCE Distinguished Lectureship at Kansas State University (NSF funded lectureship for Women Scientists in Leadership) ・ Norihito Nakamichi (Associate Professor): 38th Naito Conference Poster Prize ・ Kei Murakami (Collaborating Researcher, Assistant Professor): Takeda Research Prize, The Society of Synthetic Organic Chemistry **Patent applications:** 12 (10 domestic, 2 international (PCT))
2) Breakthroughs from the interdisciplinary research activities will be monitored and evaluated by number of joint papers by PIs from chemistry and biology fields. Grants and patents resulting from collaboration of PIs from chemistry and biology fields will be also monitored. We have already begun some interdisciplinary collaborations, which are expected to be published in the initial phase of our WPI program.	2) Breakthroughs from the interdisciplinary research activities Two special laboratories called "Mix-Labs" were established in the existing buildings to achieve the 'mixing' of chemists, biologists and theoreticians. The ITbM Research Award was established to promote ITbM's interdisciplinary research and to enable young researchers to independently conduct their own research. For each research project, 2 million yen over 2 years was awarded. The following four projects are currently in progress at ITbM. In FY2013, the four selected research projects led by the young researchers were as follows. ・ Synthetic compounds that alter plant circadian clock and flowering time ・ Discovery of new molecules that control the cell cycle: understanding the mechanism of animal and plant ・ Comprehensive analysis and isolation of unidentified receptors by rationally designed CLE peptides ・ Smaller and wavelength tunable fluorescent proteins In FY2014, two more research projects were selected to accelerate the research between chemistry and biology. ・ Investigating cooperative effects of multiple signaling molecules in pollen tube guidance ・ Fluorogenic probes for strigolactone receptors



The collaborative research projects launched in FY2014 are as follows:

- Controlling plant reproduction by molecules
  - Chemical synthesis of pollen tube attracting LURE peptide: Higashiyama, Bode
  - Identification of pollen tube attracting active molecule, AMOR: Higashiyama, Itami, Molecular Structure Center
  - Small molecules that modulate pollen tube behavior and early embryogenesis: Higashiyama, Chemical Library Center, Live Imaging Center
- Development of molecular tools to combat *Striga*
  - Development of fluorescent molecules that recognize strigolactone receptors: Itami, Kinoshita and 3 research centers
  - Development of new compounds that possess strigolactone activity: Ooi, Kinoshita
- Controlling and elucidating the mechanism of circadian rhythms by molecules: Itami, Yoshimura, Irle, Kay, Molecular Structure Center, Chemical Library Center
- Development of molecules for innovative imaging and sensing
  - Development of fluorescent dyes to elucidate mitochondrial DNA partition mechanism: Higashiyama, Itami, Live Imaging Center
  - Development of fluorescent probes as environment polarity sensors: Yamaguchi, Higashiyama, Irle, Live Imaging Center

	● Molecules controlling plant growth
	  • Discovery of synthetic plant hormones that display unprecedented plant growth expression: Itami, Kinoshita
	  • Molecules that modulate stomata opening/closing: Kinoshita, Chemical Library Center
	● Molecules increasing the number of stomata: Torii, Itami, Chemical Library Center
	● Molecules that mimic thyroid hormones: Yoshimura, Crudden, Irle
	● Molecules that alter the circadian rhythm in plants: Kinoshita, Itami, Chemical Library Center
	● Molecules that modify cell division: Crudden, Higashiyama, Yoshimura, Molecular Structure Center
	● Miniaturized fluorescent proteins: Itami, Kinoshita, Irle
	
	Since the selection of the center as a WPI program, ITbM's research groups have been publishing their high impact research in many prestigious journals (over 200 papers since the launch of the center, including 15 papers in Nature-related journals and 2 in the Proceedings of the National Academy of Sciences). In addition, these research outcomes have been covered approximately 500 times in a range of national and international media including newspapers, TV, magazines, journals and internet sites during FY2014.
	
	The projects stated above including ITbM award research have officially started from April 2013. Some of the research has already been published in peer-reviewed journals and have been filed for patents (*e.g.* Itami, Yamaguchi, Kinoshita, Nambo-Crudden)

3) The development of human resources is key to the future development and global standing of the Center. To evaluate our progress, we will use indicators such as the career paths and academic success of former researchers of the Center and the flow of visitors to and from other international institutions. Six Japanese PIs from Nagoya University have been involved in many international exchange programs and already have good track records of exchanging researchers. In the last three years alone, they have welcomed ***75*** foreign visitors and arranged for ***85*** students and researchers to be sent abroad. The number of student awards garnered will be also monitored as an	3) Development of human resources In FY2014, ITbM has sent a total of four researchers abroad (Scripps Institute, CalTech, Emory University, USA) and has accepted a total of seven researchers from its international partner institutes (Queen's University, Canada; Emory University, Georgia Institute of Technology, USA; ETH-Zürich, Switzerland). ITbM will continue to carry out international exchange of approximately 10 researchers/year with its partner institutes.

important evidence of nurturing the next-generation. For example, the prospective Center Director Itami has produced a number of talented young chemists who have been recognized in the community. Our focus on quantitative measurements of achievements reflects a worldwide trend in the evaluation of research. However, we are also aware that some aspects of research cannot be easily quantified. The importance of truly original contributions may not be recognized immediately and citation numbers may not directly reflect the quality of research. In using research metrics to assess the performance of individual researchers, it is important to take into account their age and career stage. In addition, because our Center will consist of researchers from diverse fields, we will also be conscious of the ways in which these metrics may be influenced by different research styles and conventions in different fields. We will, therefore, establish an Internal Evaluation Committee consisting of directors, PIs and administrative directors to evaluate research activity within the Center. These results will be used together with the recommendations of the International Advisory and Review Board to carry out a rigorous evaluation of the Center and PIs by an external evaluation committee.	The career path for researchers is also assumed as a measure for human resource development of the center. In FY2014, three researchers were promoted to international research institutions: Senior Postdoctoral Fellow (Mexico), Associate Researcher (France), and Assistant Professor (Pakistan), and three researchers were promoted as assistant professors (2 YLC) within Nagoya University. PIs of the ITbM have been invited as speakers in many international institutes and ITbM has invited 48 overseas lecturers to the center in FY2014.

8. Securing competitive research funding

<Plan at start of project >

Prospects for securing resources for each fiscal year (full-year basis)

- Salaries of PIs who hold posts at Nagoya University,
  Administrative staff and new hired additional researchers
  1.4 million USD / year

- Partial support to the costs of utility, maintenance and renovation of laboratory and office space, provided by Nagoya University
  0.8 million USD / year

- Competitive funding based on the past record by PIs
  7.7 million USD / year
(the average of FY 2007-2011)

Sum: 9.9 million USD / year

* At least the following amount of Japanese grants has been already acquired by PIs: the total amount of **5.5 million** USD / year for the first (FY 2012) and the second (FY 2013) years, and the total amount of **4.0 million** USD / year for the third (FY 2014) and the fourth (FY 2015) years.

<Results/progress/alternations from plan at start of project>

Nagoya University covers the salaries for Nagoya University's seven PIs, four administrative staff and seven faculty members associated to Nagoya University's PIs. The university provides financial aid to cover partial costs for utilities, maintenance and renovation of the building, which follows the initial plan and brings about good progress in building the research center.

Competitive funding acquired by Nagoya University's PIs in FY2014

Sum: 1,290 million yen (increase of 13% compared to FY2013)

Breakdown of competitive funding obtained in FY2014
(1 USD = 80 JPY at the start of the program)

- ERATO (2; Itami, Higashiyama): 819 million yen
- CREST (2; Yamaguchi, Ooi): 205 million yen
- PRESTO (2; Kasahara, Hirota): 47 million yen
- ALCA (1; Kinoshita): 29 million yen
- Grant-in-Aid for Specially Promoted Research (1; Yoshimura): 67 million yen

The center will continue to acquire new competitive funding in FY2015 onwards.

9. Other important measures taken to create a world premier international research center

<Plan at start of project >	<Results/progress/alternations from plan at start of project>
Nagoya University has recently launched the Graduate School of Pharmaceutical Science in cooperation with Graduate Schools of Science, Bioagricultural Sciences, Engineering, and Medicine. The central area of Japan, represented by Nagoya City, is very famous as the industrial center of Japan. The establishment of the Graduate School of Pharmaceutical Science in Nagoya University was based on strong demand from industrial community. The achievements of our WPI Center will be directly applied through the activities of Nagoya University and Nagoya City. Thus profound ripple effects are expected not only in Nagoya University but also in other research institutions in central Japan. To establish a truly top world-level research center, the commitment of the host institution is essential. In particular, setting up an efficient and effective administration is crucial. The benefits to the research goals of the Center through assisting the researchers to concentrate on their core research activities cannot be overestimated. In addition, appointing talented individuals, who are capable of handling administration with a global view, is also an essential ingredient to establishing a truly world premier research center. The word "transformative" implies that our molecules will also make a marked change in human society. Thus another important measure is how novel products based on our molecules and resultant new plant species developed by overcoming reproductive barriers are spread and recognized by the general public.	As stated in the previous sections, the Administrative Department consists of experienced staff with good correspondence in both English and Japanese, who prepare meeting documents and grant information in both English and Japanese and also served as MCs at international symposia. Their ability to communicate effectively with foreign researchers has enabled ITbM to function smoothly as an international center. Led by the Administrative Director, the Administrative Department is composed by the Management Division and Research Promotion Division, which work collaboratively and provide full support for the research activities at ITbM. The transformative molecules generated by ITbM's research will be communicated and announced through research publications, press releases and at meetings/conferences. Upon signing non-disclosure and joint research agreements, the molecules developed at ITbM are distributed to research institutes and industries, in order to extend their application and become molecules that can potentially change the society in a positive manner. Improving the international visibility of ITbM's research is of high significance to become established as an international research center. As ITbM's research consists of developing molecules that change the biological systems of plants and animals, it is considered extremely important for the contents of the research to be communicated precisely. It is equally important for the public to correctly understand the environmental and safety issues associated with ITbM's research. ITbM has set up an Environment and Safety Committee so that researchers at ITbM are constantly aware of these issues when conducting their research and can inform the general public accordingly. ITbM is actively involved in public outreach events, and has set up an exhibition booth and experimental corner for public engagement at the Science Agora, which is an annual science event held at Miraikan in Tokyo. ITbM's media coverage is increasing, and upon being featured in Japan national TV program, NHK "Chikyu (Earth) Agora" (broadcasted in December 2014), ITbM emphasized the significance on the safety of the new seed molecules and compounds synthesized at ITbM.

10. Host institution's commitment

<Plan at start of project > -Provision in host institution's mid-to-long-term plan	<Results/progress/alternations from plan at start of project> -Provision in host institution's mid-to-long-term plan
Nagoya University promotes its research activities based on our *Midterm Objectives*, which include establishing world-leading research centers. In addition, the manifesto of the incumbent President—also known as the "*Hamaguchi Plan*"—identifies the strong promotion of world-class research and the globalization of NU as top priorities. This proposal for *the ITbM* (hereinafter referred to as *"the Center"*) coincides wholly with the current conception of NU. If this proposal is adopted, NU will amend its *Midterm Plans* and *Research Promotion and Strategy Plans* to specify the WPI and the Center, and fully commit to providing support for the Center based on clear objectives.	Nagoya University has amended its mid-term plans by adding the following statement "Establishment of core research centers by promoting the projects including the World Premier International Research Initiative and the International Science Innovation Center Development Project (COI)" and includes promotion of ITbM's research in the FY2014 plan. In addition, the Hamaguchi Plan of Nagoya University specifies that "Establishment of the World Premier International Research Initiative (WPI) – Institute of Transformative Bio-Molecules" for the promotion of world class research.
-Concrete Measures (1) Competitive grants obtained by researchers participating in the project and in-kind contributions, etc.	-Concrete Measures (1) Competitive grants obtained by researchers participating in the project and in-kind contributions, etc.
i) NU endorses the fully committed financial support for the Center that is larger than the support from WPI.	Nagoya University covers the salaries of Nagoya University's seven PIs, seven associate professors/lecturers and four administrative officers. The university continues to provide 5,357 m^2 plus an additional 463 m^2 of an old building to be incorporated in ITbM's new building, adding to a total of 5,820 m^2 research space for the center.
ii) NU will continue to cover the equivalent amount of the salaries of those researchers at the Center who already hold posts at NU, and will provide 6,000 m^2 of the research space for the Center. Additional space will be given according to the progress of the research.	The total amount of competitive funding for FY2014 was approximately 1,290 million yen, including the funding from Center Director Kenichiro Itami's JST ERATO project that commenced in FY2013. In addition, the overseas PIs have gained Kakenhi grants in FY2014, thus securing sufficient funds for research.
iii) The total sum of competitive funding for those researchers at the Center who already hold posts at NU is $5.9 million (in FY2012), and receipt of competitive funding at an equal or greater level is promised from FY2013 onwards.	During FY2013, the Administrative Department has assigned ten administrative staff (four staff from Nagoya University) to the Management Division (General Affairs and Accounting units), which includes staff competent in English. The Research Promotion Division consists of five members who can correspond in English, including one
iv) To help with the establishment and smooth operation of the Center, NU will assign 4 staff to the center and cover their salaries as well as employing new bilingual staff.	

	Nagoya University URA (joint affiliation), a science designer and an intellectual properties manager.
(2) System under which the center's director is able to make substantive personnel and budget allocation decisions	(2) System under which the center's director is able to make substantive personnel and budget allocation decisions
i) NU will reorganize the Institute of Advanced Research, which is established as an institute independent from the other departments and research centers, and will place the Center as part of the Institute.	Nagoya University has established the center based on the basic philosophy of the Institute for Advanced Research of Nagoya University, which is "promotion of the world's most advanced project research". Nagoya University has authorized the Center Director to manage and make decisions on important matters of the center.
ii) NU will support the Center Director in his leadership and give full mandate for his decisions on important matters such as personnel and the execution of the Center's budget.	In addition, Nagoya University has established rules for the center such as Steering Committee Rules, which enables the Center Director to exercise strong leadership in the center concerning important matters such as personnel and execution of the budget (details in Section 4. Management), while authorizing the Administrative Director to make decisions accordingly for the Center Director to be exempt from excessive work.
iii) In addition, the Vice Director and Administrative Director will make decisions depending on the matter, to avoid placing an excess burden on the Center Director and enable the progress of daily work at the Center.	
(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	(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
i) NU will assign 7 associate professors, who will mainly take charge of education in each department to relieve the PIs of this responsibility, and to maintain high-level education.	・ Nagoya University has employed seven associate professors/lectures to carry out educational activities in place of Nagoya University's seven PIs. ・ To support the progress of the center, a second Vice-Director Shigehiro Yamaguchi has been appointed in April 2014 to lead the chemistry field of research alongside Vice-Director Higashiyama who leads the biology field.
ii) NU will give priority to female researchers at the Center to enable their children to enter the nursery school operated by NU.	・ Children of female researchers are granted the opportunity to apply for entry to international schools outside the university.
iii) NU will support foreign researchers at the Center in their daily life and the education of their children, making full use of facilities and knowledge base which has been obtained through the operation of international projects such as the "Global 30 Internationalization Program (G30)" and "CAMPUS Asia Support for the Formation of a Core Center", and so on.	・ The Research Promotion Division has assigned staff to provide support to foreign researchers and their families during their stay at ITbM.

iv) NU will provide opportunities for partners/spouses of foreign PIs to hold positions in NU on the basis of proper evaluation (Dual Career Support).	
(4) Revamping host institution's internal systems to allow introducing of new management methods (e.g., English-language environment, merit-based pay, top-down decision making) unfettered by conventional modes of operation	(4) Revamping host institution's internal systems to allow introducing of new management methods (e.g., English-language environment, merit-based pay, top-down decision making) unfettered by conventional modes of operation
i) NU will give full mandate to the Center Director for a flexible management system by implementing the Center as a "Special Research Zone", and by introducing ground breaking working rules and salary system which give the researchers and staff extra allowance to encourage their activities.	· Nagoya University has established "Implementation Guidelines for the Special Bonus for Persons in the Service of Nagoya University Institute of Transformative Bio-Molecules" in FY2012, which is the system to provide special bonuses to the Center Director, Vice-Director, Nagoya University PIs and the Administrative Director based on their performance and evaluations.
ii) NU will gradually implement the Center's trial across the entire university in order to give other researchers and staff incentives to apply.	· All members of the Research Promotion Division and more than half of the Management Division are competent in English. The Management Division translates notifications on administrative affairs in English. This is considered a highly technical skill, which is reflected in the relatively high salaries of the contract employees. · As grants and funding information from the university were initially provided in Japanese, these were translated into English by the ITbM administrative office. The host institution realized the importance of these endeavors and subsequently, the university administration decided to take over this activity and started to distribute grants and funding information in both English and Japanese from the end of FY2013. · Nagoya University's Institute for Advanced Research and COI programs are following the footsteps of ITbM and have started to incorporate ITbM's system and activities in their programs, such as employment of foreign researchers, Co-PI system, and incentive-based salary systems.
(5) Accommodation of center's requirements for infrastructural support (facilities, e.g., laboratory space; equipment; land, etc.)	(5) Accommodation of center's requirements for infrastructural support (facilities, *e.g.*, laboratory space; equipment; land, etc.)
i) NU commits to accommodate the Center with research space equivalent to 6,000 m^2.	· In addition to the 5,165 m^2 of space provided by Nagoya University from FY2012, further space was provided on an as-needed basis, and a

ii) 7 PI candidates who work for NU already occupy approximately 3,000 m^2. NU will provide additional 1,500 m^2 by the end of FY2012, and the other 1,500 m^2 as soon as possible. iii) NU will rearrange and relocate the facilities of the existing departments and centers, and will establish the Center's core facility, making it possible to collaborate intensively with the researchers of other departments and research centers. iv) NU will reauthorize the University's Facility Management Plan and will make the Center's core facility a top priority.	total of 5,820 m^2 of space was provided to ITbM. ・ For ITbM's new building, a space was provided that was in close proximity to the School of Science, which is where many of Nagoya University's PIs are situated. Many of ITbM's biologists are originally affiliated to the Life Science Department. Thus, the Science E building of the Life Science Department is directly connected to ITbM's new building by a bridge to increase accessibility and promote further collaboration. ・ The School of Science has agreed to manage and operate ITbM's new building and will manage the entrance, CCTV for security and will be the correspondence in case of fires.
(6) Support for other types of assistance i) <u>NU has decided to assign a member of the Board of Trustees/Vice-President as the Administrative Director to bridge the gap between the Center and the University's headquarters</u>. ii) The Administrative Director will organize a team with his two associates and keep the administrative office active enough to enable the Center's research activities at a maximum performance. Two associates are: Associate Administrative Director for Management who is a high-level expert of administration affairs, and Associate Administrative Director for External Relations who has strong expertize in chemistry related science, with a good command of English. iii) We recognize one of the important aspects of WPI is to accelerate system reform of Japanese universities such as deregulation, internationalization, and so on. Intensive commitment of NU's leadership to the Center is critically important to accelerate the system reform in not only the Center but also the entire university.	(6) Support for other types of assistance ・ The Administrative Department is comprised of the Management Division dealing with administrative/accounting affairs and the Research Promotion Division consisting of scientists to promote ITbM's research. This enables interactive communication between the management staff and faculty. ・ During the launch of the center, Nagoya University's Trustee Yoshihito Watanabe served as the Administrative Director who liaised and coordinated with the university's executive board. Through these endeavors, the center's management system and guidelines were built. As of January 2014, Watanabe stepped down as the Administrative Director and the Head of Research Promotion Tsuyoshi Matsumoto assumed the role of the Administrative Director. Watanabe continues to be involved with ITbM as a Trustee and coordinates with the executive board. ・ The Director of Research Cooperation Department and the Manager of Research Support Division from Nagoya University Headquarters attend ITbM Steering Committee as observers to further strengthen cooperation with the university headquarters and provide advice when needed.

11. Efforts to improve points indicated as requiring improvement in application review and results of such efforts	
- Major points to be improved	- Efforts to improve them and results *If you have already described these in other parts of this report, please indicate where for reference.
The following points were recommended in the Follow Up Report in FY2014. 1. The Working Group suggests that ITbM hires one or two outstanding foreign junior PIs who will reside in Nagoya. We also encourage ITbM to hire additional female scientists at the senior level.	ITbM's answers for the recommendations are as follows. 1. Proceeding from a preliminary announcement of an increase in the WPI budget towards ITbM, ITbM has decided to allocate the budget towards open recruitment of a foreign PI. For the recruitment, ITbM will make efforts to increase applications from excellent, foreign female researchers. ITbM will start the open recruitment as soon as possible and will carry out the selection process within FY2015.
2. ITbM may consider building a strategic international network of outstanding researchers in this new field, for example by hosting a high impact international conference like the Tetrahedron Symposium and by implementing a short-stay program for prominent international researchers.	2. ITbM is strongly motivated towards actively building strategic international networks in the research community. The center has hosted two international symposia, ITbM's annual international symposium (ISTbM-2) and the 20th Nagoya Medal of Organic Chemistry. Last year, ITbM supported the 19th International Symposium on Homogeneous Catalysis, which was an international conference held at Canada where many prestigious chemists in the field of catalysis and organometallic chemistry gathered and presented their research. ITbM set up a booth and ITbM's research activities were advertised in the abstract booklets and in the slides. Cathleen Crudden, the Vice-Chair of the conference and Takashi Ooi outlined the research activities of ITbM in their presentations, which attracted the attention and gained support from many researchers attending the conference. In December 2015, Kenichiro Itami, Shigehiro Yamaguchi, Cathleen Crudden will each organize a symposium at Pacifichem 2015, an international chemistry conference to be held in Hawaii. The Pacifichem is a global conference with more than 12,000 attendees, and is co-organized by the Chemical Societies of Japan, USA, Canada, Australia, New Zealand, Korea, and China. ITbM will continue to make efforts to increase its presence in the international research community, and consider the opportunity to organize additional international conference(s) at Nagoya University. In addition, ITbM will consider planning a short-stay program for international researchers.

3. ITbM may address environmental/safety issues beyond the scope of current regulations. The Environment and Safety Committee may help prepare criteria on how to assess the "safety" of the transformative bio-molecules developed. In addition to the excellent research, ITbM also has to become a leader in public education and outreach in support of their research activities.	3. ITbM has organized and are receiving adequate advice from the Environment and Safety Committee, consisting of well-established researchers within and outside ITbM. Committee meetings are organized at least once a year, and are also called when necessary. In the 1st Environment and Safety Committee Meeting that was held in February 2014, it was pointed out that it is essential to disseminate ITbM's research and gain support from the public. Following this statement, ITbM has been actively involved in public events. For example, Tetsuya Higashiyama held a public seminar at Nagoya University's Open Lecture in 2014, entitled "A story to understand the essence of flowers". In addition, Toshinori Kinoshita has organized a science café at Nagoya in 2013. In December 2014, the NHK one-hour TV program "Chikyu (Earth) Agora" focused on ITbM, which emphasized the importance of safety in the course of developing the new organisms and chemicals.
4. ITbM requires additional expertise in structural biology and computational modeling to guide the rational design of the most promising small molecule leads. Therefore, a strategic collaboration with CSRS at RIKEN could significantly improve the chance for ITbM to discover small molecule leads that could be ultimately developed into in vivo products.	4. Both ITbM and CSRS have agreed to establish strong ties between their centers. In January 2015, both centers have entered a joint agreement for the two centers to collaborate and coordinate in research. The 1st ITbM-CSRS Joint Workshop (closed) was also organized and held at Nagoya University in January 2015, which was a great opportunity to exchange ideas and establish cooperative relationships. Both centers have agreed to share their chemical library resources, and collaboration will start between Toshinori Kinoshita of ITbM and CSRS Vice-Director Hiroyuki Osada. The collaboration between ITbM's Chemical Library Center and Principal Investigator Minami Matsui of the Biomass Engineering Program Cooperation Division at CSRS is also planned to begin.

12. FY 2014 funding

i) Overall project funding

(Unit: 1 million yen)

Cost Items	Details	Costs (1 million yen)
Personnel	Center director and Administrative director	26
	Principal investigators (no. of persons):10	84
	Other researchers (no. of persons):38	212
	Research support staffs (no. of persons):8	28
	Administrative staffs (no. of persons):26	69
	Total	419
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0
	Cost of dispatching scientists (no. of persons):0	0
	Research startup cost (no. of persons):21	66
	Cost of satellite organizations (no. of satellite organizations):0	0
	Cost of international symposiums (no. of symposiums):2	3
	Rental fees for facilities	14
	Cost of consumables	3
	Cost of utilities	0
	Other costs	44
	Total	130
Travel	Domestic travel costs	2
	Overseas travel costs	13
	Travel and accommodations cost for invited scientists (no. of domestic scientists):2 (no. of overseas scientists):10	1
	Travel cost for scientists on secondment (no. of domestic scientists):2 (no. of overseas scientists):4	2
	Total	18
Equipment	Depreciation of buildings	8
	Depreciation of equipment	415
	Total	423
Other research projects	Projects supported by other government subsidies, etc.	294
	Commissioned research projects, etc.	662
	Grants-in-Aid for Scientific Research, etc.	122
	Total	1078
Total		2068

WPI grant for FY 2014	598
Costs of establishing and maintaining facilities in FY 2014	2572
Establishing new facilities: Institute of Transformative Bio-Molecules (Number of facilities: 7,943m²) Costs paid:	2572
Repairing facilities (Number of facilities: , m²) Costs paid:	0
Others	0
Cost of equipment procured in FY 2014	448
Name of equipment: Analysis Server Number of units: 1Set Costs paid:	6
Name of equipment: Two-Photon Excitation Laser Number of units: Costs paid:	7
Name of equipment: Environment Control Room Number of units: 1Set Costs paid:	86
Name of equipment: Laboratory Benches and Office Furniture Number of units: 1Set Costs paid:	41
Name of equipment: Fume Hood Number of units: 1Set Costs paid:	237
Name of equipment: Mass Spectrometry Instrument Number of units: 1Set Costs paid:	13
Others Number of units: 1Set Costs paid:	58

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (1 million yen)
Personnel	Principal investigators (no. of persons):	
	Other researchers (no. of persons):	
	Research support staffs (no. of persons):	
	Administrative staffs (no. of persons):	
	Total	0
Project activities		
Travel		
Equipment		
Other research projects		
Total		0