World Premier International Research Center Initiative (WPI)
Executive Summary (For Extension Application Screening)

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

A. Progress Report of the WPI Center

I. Summary

ITbM was launched at Nagoya University (NU) as a unique research institute to develop innovative functional molecules "transformative bio-molecules" that make a marked change in the form and nature of biological science and technology. By taking full advantage of our cutting-edge molecular synthesis expertise and intense interactions with leading plant/animal biology research, ITbM has been conducting 'needs-inspired' basic research and explored new research areas of "plant chemical biology", "chemical chronobiology", and "chemistry-enabled live imaging".

The achievements of 2012.11-2019.3 (papers: 2012.11-2018.12)

- Journal publications: 770 peer-reviewed papers (191 papers = IF>10; 313 papers = IF>7; 51 Highly cited papers (Top 1%); 6 Hot papers (Top 0.1%),
  Nature x 5, *Science* x 7, *Cell* x 4, *Nature/Science sister journals* x 63)
- Awards and honors: 129
- Patent application: 120 (incl. 41 cases co-filed among several PI groups)
- Patent license agreement: 32
- Collaborative research with industries: 72
- Commercialization of molecules/catalysts: 15
- Spin-off ventures: 2 companies
- Total sum of external research funds: 7.45 billion yen

The synergy of ITbM researchers' high research profile and the new research style at ITbM has facilitated interdisciplinary research at a pace more rapidly than initially expected. ITbM's "Mix Labs" that mixes different disciplines has been highly effective, and has led to the development of a number of new bio-functional molecules and molecular technologies. The ITbM Research Award, established to promote interdisciplinary research proposed by young researchers, has accelerated collaborations in a bottom-up manner and most of the proposals have been making good progress to mature into ITbM's representative projects. Many of the research outcomes have been filed for patents and published as joint publications between different research groups. Their societal implementation is also in progress as represented by the development of molecules to combat parasitic plants *Striga*. ITbM launched a membership discussion forum "ITbM Consortium" in 2017 to provide matching opportunities with industries.

ITbM has been extending its global network to further advance its interdisciplinary research via extensive collaboration through researcher exchange. With the cutting-edge research outcomes, ITbM is now widely recognized as an international research hub of chem-bio research. ITbM is positioned as a flagship research institute of NU, and has induced system reforms of NU. In 2018, a new graduate program was launched with ITbM as a core, and ITbM will work proactively in nurturing PhD students who can pioneer new science at the interface of multiple disciplines.

ITbM has now become truly exciting and internationally visible institute where new interdisciplinary research fields emerge and new molecules are born every day. ITbM's unique "Mix" culture has led researchers from different fields to work together, take risks, think/act differently, thereby finding unique problems and solutions, discovering something new, and providing unique solutions to key global problems. Researchers world-wide have recognized the strength of ITbM. Our dream of changing the world with molecules is clearly bearing fruit, but the challenge continues.

II. Items

1. Overall Image of Your Center

ITbM has gathered top-researchers from the different disciplines including synthetic

chemistry, plant biology, animal biology, and theoretical sciences under one roof, who have been carrying out interdisciplinary research through extensive collaboration. In the 7 years, ITbM has grown to a size of 200 people including 13 PIs, 63 researchers, 62 support staff, and many PhD students. ITbM has also been proactive to appoint female researchers. Including three female PIs, 19 female researchers are on staff at ITbM, making up 25% of total researchers.

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

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

2. Advancing Research of the Highest Global Level

Research Activities

ITbM has been promoting 'needs-inspired' basic research to develop transformative bio-molecules that make a marked change in the form and nature of biological science and technology. ITbM has also pioneered a new molecular nanocarbon science using its state-of-art synthetic chemistry, which will be a new pillar of ITbM in the future. Selected achievements are summarized below.

Development of molecules toward combating *Striga*: The parasitic plant *Striga* has been causing huge damage on crop production in Africa. ITbM has been tackling to provide molecular solutions to the food security in Africa. The fluorescent probe molecule "Yoshimulactone" Green (YLG) was developed, which enabled disclosure on the mechanism of germination and elongation of the *Striga* parasite. Researchers have also identified strigolactone receptors in *Striga* by the use of YLG, which further led to the development of *Striga* germinator sphynolactone-7 (SPL7). SPL7 has two functional modules, which cooperatively acted on the specific strigolactone receptor, and activated it with a high-affinity to provoke *Striga* germination with potency in the *femtomolar* (10^{-15} molar) range. The SPL7 is effective for reducing *Striga* parasitism on practical crop (maize) without impinging on host strigolactone-related processes. To test these molecules in environmentally challenged fields, ITbM starts collaboration with KALRO to bring them into societal implementation.

Discovery of key molecules that regulate plant reproduction: Following the discovery of the long sought pollen tube attractant molecules LURE, ITbM has identified anew two key biomolecules AMOR and CALL1 that control plant fertilization. The AMOR is a sugar chain molecule that increases the fertilization efficiency. Interestingly, the essential part of the AMOR was proved to be a disaccharide unit via structure-activity relationship study. This is a quite interesting finding because any specific sugar-chain unit of plant extracellular matrix has not been identified as a bioactive molecule.

Recently the target protein of the LURE has been identified and the structure was elucidated by the crystallographic analysis. The discovery of a series of biomolecules is expected to lead to advances in research to improve plant fertilization efficiency.

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

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

Using drug-repurposing approach, molecules that can either shorten or lengthen the circadian rhythm in human cells have been developed. DHEA (dehydroepiandrosterone), which is a hormone also known as a common anti-aging supplement, demonstrated notable period-shortening activities. When DHEA was fed to mice, jet lag symptoms were significantly reduced. Further screening of known bioactive compounds may lead to the discovery of other effective compounds that can treat circadian clock disorders arising from jet lag. In the study of seasonal clock, medaka fish was found to show different behavior upon seasonal changes, and the reason was revealed as that the genes encoding photopigments vary dynamically among seasons. It was also suggested that plasticity in color perception is crucial for the emergence of seasonally regulated behaviors.

Imaging molecules: ITbM has developed molecules that exhibit exceptionally high resistance to photobleaching that can accelerate cutting-edge and super-resolution bio-imaging such as STED microscopy. Researchers have also developed molecules that exhibit high responsive property to environment polarity and have discovered near infrared emissive phospha-fluoresceins. These super high performance molecules are commercially available and expected to serve a significant role in leading the bio-imaging field. Indeed, the molecule named as PREX 710 can be used to stain mitochondria in living cells, which allowed long-term and multi-color imaging in the vis-NIR range. The PREX 710 exhibits the high fluorescence longevity and applicable to a single-molecule microscopy under physiological conditions.

Catalysis and rapid molecule synthesis: ITbM has established epoch-making synthetic methodologies that allow rapid synthesis and modification of biologically active molecules. These include next-generation cross-coupling catalysts, C-H coupling catalysts, asymmetric reactions, and rapid peptide/protein synthesis. For example, Ooi has developed a new reaction to directly install amines into carbonyl compounds using their unique phase-transfer catalyst. This unprecedented method leads to the rapid formation of optically active (chiral) α-aminocarbonyls, which are structural moieties found in many biologically active compounds. These synthesis technologies have been applied to ITbM's interdisciplinary research, and towards developing candidate molecules for medicines and agrochemicals.

Molecular nanocarbons: Chemists have tried to synthesize carbon nanobelts for more than 60 years, but none have succeeded until now. Itami has reported the first organic synthesis of a carbon nanobelt. Carbon nanobelts are expected to serve as a useful template for building carbon nanotubes and open a new field of nanocarbon science. Itami has also developed a fast way to form nanographenes in a controlled fashion. This simple and powerful method for nanographene synthesis could help generate a range of novel optoelectronic materials and biological applications.

Societal implementation of the research outcomes

ITbM has strategically created a wide range of networks consisting of domestic/international industries toward societal implementation of the research outcomes. As summarized above, ITbM has filed 120 patent applications, and its 34% have been derived from the interdisciplinary researches between chemistry and biology. Base on the patents, 2 ITbM-based ventures have also launched and 15 molecules are commercially available as tool reagents for researches. For example, LipiDye, a novel fluorescent dye that stains the lipid droplets located in cells with high sensitivity, has widely spread to not only academia but industries including medical, pharmaceutical, agrochemical and cosmetic companies. ITbM concluded the license agreement of SPL7, which induces suicide germination of *Striga* and has decided to commercialize as a reagent for researchers. SPL7 is expected to be utilized as an agrichemical application in Africa and other countries.

ITbM has been conducting many collaborative research projects with companies and has concluded 25 MTAs to further promote the societal implementation. To create the opportunities for academia-industry partnership, ITbM launched a membership discussion forum "ITbM Consortium" in 2018, where 'Seeds' and 'Needs' meet each other.

3. Generating Fused Disciplines

Under the strong leadership of the Director, all members at ITbM have been working beyond their discipline and developing interdisciplinary research spanning chemistry, plant/animal biology, and theoretical sciences toward making transformative molecules. ITbM has defined three flagship research areas as 'plant chemical biology', 'chemical chronobiology', and 'chemistry-enabled live imaging', and has been exploring the research projects via extensive collaboration of chemistry and biology.

ITbM's interdisciplinary research has been making significant progress under the "Mix" concept, and the center's initiatives to promote interdisciplinary research have been effective so far. The ITbM Research Award, established to foster interdisciplinary collaboration among young researchers and students, was granted to 4 new projects in FY2017. The ITbM Workshop and Tea

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

The synergy of ITbM researchers' high research profile with the new research style at ITbM has facilitated interdisciplinary research, and has resulted in a number of innovative achievements that can never be obtained without extensive interactions of the different disciplines. The success of the interdisciplinary research is represented by the joint publications and patents. So far, 49 papers and 41 patents are co-authored by multiple PIs, and 260 papers are published by international collaboration. The numbers have been constantly increasing. The *Striga* project is a representative case, which launched as a bottom-up collaboration led by a PhD student and has become a flagship project of ITbM organized by the team *Striga.* Now the team has many researchers and administrative staff and is tackling to provide a molecular solution to the food security of Africa.

4. Realizing an International Research Environment

ITbM has 5 world-leading overseas PIs. They have been actively contributing to the activities of ITbM. They are staying in Nagoya for 1-2 months per year and attending the site visits and annual international symposia, ISTbM. Even when they are absent from Nagoya, they have close contact with their respective Co-PIs and postdoctoral researchers through regular TV conferences or e-mails. They also send a few researchers of his/her institutes to ITbM.

ITbM has hired 82 postdocs from over the world, and 53 (65%) are non-Japanese. Out of the 59 postdocs who left ITbM, 31 found faculty positions in academia in Japan and overseas. Thus ITbM has been involved in a global brain circulation.

The Administrative Department consists of staff with good correspondence in both English and Japanese to handle various tasks. The RPD has staff to provide support to foreign researchers and their families.

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

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

5. Making Organizational Reforms

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

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

ITbM's high research performance has largely contributed to establish various initiatives of NU, such as being selected as "Designated National University" by MEXT (2018), a basic agreement with RIKEN. NU launched the new graduate program "Graduate Program of Transformative Chem-Bio Research (GTR)" with ITbM as a core. ITbM's Mix Lab will provide a superb place to nurture young researchers who pioneer new science.

NU has been strongly supporting ITbM by such as (1) covering salaries, (2) provision of space, (3) financial support towards construction of ITbM's building, (4) support towards the operation of the building, and (5) ITbM's priority to the use of hall of residence. To secure the employment of ITbM's faculties and staffs, NU makes an organizational reform in 2019. NU will launch "Institutes for Advanced Research Excellence", and position ITbM under this umbrella.

6. Others

Upon development of molecules that modulate biological system in plants and animals, ITbM recognizes the importance of communication with the general public widely so that ITbM always addresses the environmental and safety issues carefully. Accordingly, ITbM has set up an Environment and Safety Committee so that researchers at ITbM are constantly aware of these issues when conducting their research. ITbM provides special safety training for the ITbM researchers suitable for interdisciplinary environments.