World Premier International Research Center Initiative (WPI)
FY 2022 WPI Project Progress Report (The center selected in and before FY2020)

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Research Center	Institute for Chemical Reaction Design and Discovery (ICReDD)		
Center Director	Satoshi Maeda	Administrative Director	Koichiro Ishimori

Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2023) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.
- Prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

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

1. Advancing Research of the Highest Global Level

To achieve sustainable development goals through the realization of Society 5.0, new chemical reactions are needed to create novel functional molecules and high-performance materials, and even medical treatments for intractable diseases. However, the design and discovery of new chemical reactions has relied on serendipity or experience-guided intuition, which has been a bottleneck in innovation for the new society. In the center, the computational research team, which is capable of simulating various types of chemical reactions, is engaged in the development of practical chemical reaction design techniques through close cooperation with information and experimental teams. To address various problems in highly complex chemical processes, the information team, which covers diverse fields ranging from chemical and materials informatics to combinatorial optimization, knowledge engineering, and mathematical modeling, was established by bringing together top information scientists in these fields. The experimental team also consists of top scientists from diverse backgrounds, such as organic synthesis, materials chemistry, polymer physics, and medical science. The center is engaged in developing "chemical reaction design and discovery" strategies for various application fields through high-level fusion research combining computational, informatics, and experimental techniques owned by these teams. Through these efforts, the center will revolutionize chemical reaction design and discovery. The achievements for FY2022 are as follows: 139 papers were published in peer-reviewed journals (36 papers in journals with an IF > 10). Two papers were published in *Nature* (IF: 69.5), one in *Science* (63.832), two in *Cell* (IF: 66.85), one in *Advanced Materials* (IF: 32.086) and five in *Nature Communications* (IF: 17.694). The center members have presented their research in 28 invited lectures at international conferences and 17 awards have been granted. The total amount of research funding was 848 million JPY. Representative grants are JST-ERATO, JST-CREST, AMED-P-PROMOTE, etc.

2. Generating Fused Disciplines

Promotion of fusion research: The center was working on several flagship projects and bottom-up projects. These projects are evaluated yearly, and then, promising ones were expanded or promoted from bottom-up to flagship project. These projects were carried out under the Center Director's initiative with the Fusion Research Coordinator leading the project together with project leader.

Fusion research achievements in FY2022: Maeda-group (computation) together with Dr. Mita (experimental lab-chief) published multiple papers on the development of new synthetic methods utilizing quantum chemical reaction path networks (*Nat. Synth.* 2022, *Nat. Commun.* 2022). List-group (experiment) and Varnek-group (information) achieved an informatics-driven discovery of new organocatalysis (*Angew. Chem.* 2023). Gong-group (experiment, material), Ito-group (experiment, organic), and Maeda-group (computation) developed a fluorescence probe to rapidly detect mechanoradicals in hydro-gel materials (*J. Am. Chem. Soc.* 2023).

Start-up support for fusion research: In FY2022, start-up support for fusion research to take on challenging bottom-up fusion projects (10 projects (10 million yen) and 1 group project (10 million yen) for a total of 20 million yen) were awarded. These projects led to the acquisition of Grants-in-Aid for Scientific Research; 6 projects (30.6 million yen) were granted.

Pre-checking system for the grant application: The center conducted a pre-checking system to review and revise the applications for Grants-in-Aid for Scientific Research, etc. before submission. 41% of the applications for Grants-in-Aid for Scientific Research were granted for FY2023 (university average 38%). The amounts of Grants-in-Aid for Scientific Research obtained have been increasing every year. FY2022: 219 million yen, and overseas PIs and Jr-PIs have also succeeded in obtaining Grants-in-Aid for Scientific Research.

3. Realizing an International Research Environment

Number of researchers: The center conducted an international call for applications for new specially appointed faculty members and postdoctoral researchers to be hired at the center and received 190 applications for 16 positions from Japan and abroad in FY2022. As of March 31, 2023, the number of PIs was 15 including 3 foreign PIs, 45% of all researchers were foreign nationals,

and 15% were female researchers (total of 80 researchers, including 36 foreign nationals and 12 female researchers, split between the fields of Computation (20 researchers, 25%), Information (15 researchers, 19%), and Experiment (45 researchers, 56%).

Symposiums and seminars: The center has held the ICReDD international symposium, inviting researchers from Japan and overseas to introduce them to the vision and research of the center. The 2nd Akira Suzuki awards ceremony & the 5th ICReDD international symposium was held on January 11, 2023. This symposium had 361 registrations (59 overseas registrations from 19 countries), 115 live participants (103 domestic and 12 overseas), 36 poster sessions and numerous on-demand viewers. In FY2022, the center held eight international seminars, which were able to be held more easily thanks to the online meeting environment. These events include two interdepartmental symposiums, eight international seminars, two research ethics seminars, two diversity seminars, and five research seminars. In addition, special lecture with Nobel Laureate Professor List, the center increased recognition of the center within the university (100 in-person participants) and among other universities and in industry in Japan and abroad (177 online participants). The ICReDD Online Salon as lunch & evening seminar was held 30 times in total as an opportunity for regular communication.

Establishing collaborative agreements: In FY2022, an agreement was put in place with the Max Planck Institute. This will lead to further expansion of research exchanges with MPI, a world-class research center. (Total number of agreements: 4)

Fostering young researchers by MANABIYA: Researchers were accepted through the MANABIYA system. "MANABIYA (ACADEMIC)" invited applications from April 2022 and accepted 13 researchers (10 were accepted from domestic and 3 were accepted from abroad) out of 17 applicants, who were trained in the center's techniques. With the removal of Covid travel restrictions, the number of applicants from overseas is expected to increase in FY2023.

4. Making Organizational Reforms

Evaluation system of center faculty members: In FY2022, a new regulation was established to provide incentives based on the research performance and the discretionary evaluation by annual interview of center faculty members, for whom no evaluation system was previously in place. The results of the self-performance evaluation, and discretionary performance evaluation by annual interview with the Center Director are used to determine the salary increase or decrease by one or two steps from the base annual salary for the following year, which has not yet been done in any other departments in the University.

Establishment of ICReDD fellow system: The center established a new position called the ICReDD fellow. The center provides ICReDD fellows with our resources and collaborate with them. This system is expected to expand the scope of ICReDD's research both inside and outside the university and serve as an incubation system for new PIs.

Establishment of Equipment Management Center: To prevent misconduct and further accelerate fusion research, a new department will be established to manage experimental data and to ensure the reliability of the data published in the paper by cross-checking with raw data from third-party experts. Such a system is expected to lead to a university-wide development to ensure the integrity of research.

Establishment of Human Resource Development Unit: The center established the "Human Resource Development Unit" which is in charge of fostering researchers, graduate students, and industrial researchers using MANABIYA, as well as creating strategies and roadmaps for the center's graduate and recurrent education. From FY2023, the university already hired a full professor and specialized faculty with extensive teaching and research experience for this unit.

Prevention of research misconduct: To prevent misconduct, in addition to thorough ethics education within the center (attend the center's own research ethics education seminars upon hiring and once a year on a regular basis), the Equipment Management Center established by hiring a researcher holding a PhD with expertise in the field will manage data on equipment at the center and check all figures for submission against the raw data, and efforts will be made to make the center can be openly discussed, will prevent misconduct by facilitating an environment in which research results.

5. Efforts to Secure the Center's Future Development over the Mid- to Long-term

The University has strongly supported the center and has secured funds equal to or more than the WPI grant for its operation (FY2022: 2,657 million yen). The center will be made a permanent research center that always promotes cutting-edge, world-class research based on a new adaptive research strategy involving periodically changing researchers and research themes. In FY2022, the center has launched a consortium called the "Clinical Platform for Chemical Reaction Collaboration" in partnership with the School of Medical Science. The center has just launched the "List-DX Catalyst Collaboration Research Platform (List-Platform)" and the "Mitsui Chemicals-ICReDD Innovative Chemical Reaction Design Laboratory (Mitsui Chemicals-ICReDD Laboratory)" in FY2023. The university highly evaluates the center's achievements, such as a management system that clearly separates research and administrative organization, like a Center Director and Administrative Director, a careful performance evaluation system, a hospitality system, the assignment of faculty members specializing in fusion research (Fusion Research Coordinator), and instrument management faculty to prevent research misconduct, and ICReDD fellow system.

6. Others

As a result of a Twitter campaign using @ function to mention the recipients' departments, tweets about the Akira Suzuki Awards ceremony were retweeted multiple times by prestigious universities abroad, reaching over 20,000 impressions in total and connecting the center's brand with a more international audience. As a result of focusing on disseminating new research, 10 English language press releases were distributed to news platforms, resulting in an estimated 7.75 million views. The 10 English releases plus 15 highlight articles resulted in 5400 unique pageviews, with over 700 people driven directly from Tweets about research.

* Describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 viewpoints, place emphasis on the following:
  (1) Whether research is being carried out at a top world-level (including whether research advances are being made by fusing disciplines).
  (2) Whether a proactive effort continues to be made to establish itself as a "truly" world premier international research center.
  (3) Whether a steadfast effort is being made to secure the center's future development over the mid- to long-term.

1. Advancing Research of the Highest Global Level

* Among the research results achieved by the center, concretely describe those that are at the world's highest level. In Appendix 1, list the center's research papers published in 2022.
* Regarding the criteria used when evaluating the world level of center, note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

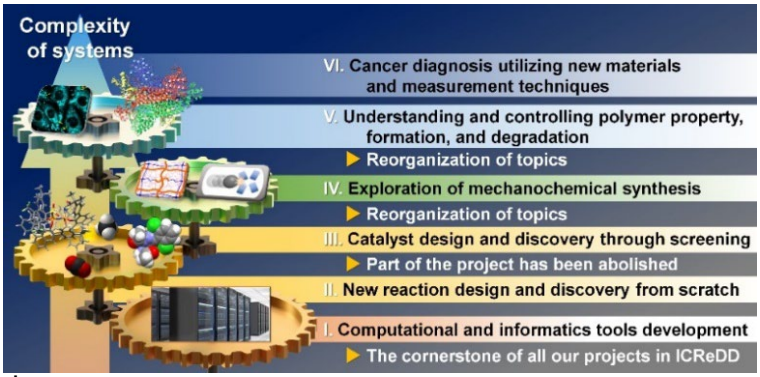
I. The center's scientific mission

To achieve sustainable development goals through the realization of Society 5.0, new chemical reactions are needed to create novel functional molecules and high-performance materials, and even medical treatments for intractable diseases. However, the design and discovery of new chemical reactions has relied on serendipity or experience-guided intuition, which has been a bottleneck in innovation for the new society. The center's mission is to establish "chemical reaction design and discovery" strategies and to enable humanity to purposefully design chemical reactions without relying on serendipity or experience-guided intuition. The center combines computational science, information science, and experimental science to develop new synthetic methods, new materials, and new applications in all areas of our society. In the center, the computational research team, which is capable of simulating various types of chemical reactions, is engaged in the development of practical chemical reaction design techniques through close cooperation with information and experimental teams. To address various problems in highly complex chemical processes, the information team, which covers diverse fields ranging from chemical and materials informatics to combinatorial optimization, knowledge engineering, and mathematical modeling, was established by bringing together top information scientists in these fields. The experimental team also consists of top scientists from diverse backgrounds, such as organic synthesis, materials chemistry, polymer physics, and medical science. In the center, we are engaged in developing "chemical reaction design and discovery" strategies for various application fields through high-level fusion research combining computational, informatics, and experimental techniques owned by these teams. Through these efforts, the center will revolutionize chemical reaction design and discovery.

II. Overview of the center's research

We initiated seven flagship projects in FY2020 and have been working on them ever since. These projects have been instrumental in achieving high-impact research results in line with our Center's goal of advancing fusion research. At the end of FY2021, to examine the research policy and strategy for the second half of the grant period based on the research results of the first half of the grant period to date, we evaluated these projects to determine their feasibility for further expansion, continuation, restructuring, or termination. In the second half of the grant period, we will apply the more advanced computational and information processing methods developed in the first half of the grant period to more complex systems, aiming to demonstrate that our innovative chemical reaction creation strategy will lead to new developments and innovations in the fields of medicine, drugs, and materials design. After the evaluation process, we decided to continue six flagship projects.

Among them, Project I is the most important project in ICReDD. It is closely related to all the other projects and provides computational acceleration tools for them. During monthly meetings, all computational and informatics groups come together to share successes and failures based on their contributions to the other flagship projects. This feedback loop allows us to stay abreast of the latest state-of-the-art computational and informatics tools being used in these projects and helps us to further develop these tools. The other projects have a hierarchical complexity. The complexity increases in the order of the project number. In other words, the number of atoms involved in the reaction treated in each project increases in that order. Working simultaneously on these projects of varying complexity will allow us to build a comprehensive set of tools that can be applied to a wide range of problems in the chemical and materials sciences.



The list of these projects is shown below:

Project-I: **Computational and informatics tools development**. We consistently make Project I the cornerstone of all our projects. All computational and informatics PIs work with Project I and provide feedback on the application of their tools to other projects. This feedback loop

strengthens our foundation and helps accelerate all of our projects. The goal of this project is to create a set of *in silico* reaction design strategies that can be tailored to individual cases. In the first half of the WPI period, Project I contributed to the development of the QCaRA/AFIR approach, which combines the AFIR method with a graph-theory-based method for calculating reaction yields, leading to the first-principle discovery of previously unexplored chemical reactions. In addition, a cheminformatics-based approach to predicting the enantioselectivity of organocatalysis has contributed to the discovery of new catalysis. Two goals for the second half of the WPI period are the development of a method for designing an appropriate organometallic catalyst for a given chemical transformation (related to Project II) and the design of a high performance organocatalyst that achieves asymmetric activation of unfunctionalized molecules (related to Project III).

Project-II: New reaction design and discovery from scratch. We continue to work on a project to predict new reactions from scratch using reaction path networks based on quantum chemical calculations (former Project II). So far, we have demonstrated several successful examples of (non-catalytic) small molecule synthesis. In the future, we will focus our efforts on the discovery of catalysis. This can be done in part on the basis of the achievements in non-catalytic reactions made in the first half of the WPI period, but is a much more complex matter requiring the further development of computational and informatics tools. The goal of this project is to establish a systematic design framework for discovering an organometallic catalyst that can achieve previously unexplored chemical transformations.

Project-III: Catalyst design and discovery through screening. Project III replaces the Supramolecular Catalytic Reaction Space Design project (former Project III) that we were working on. In its current form, the project involves finding the optimal substituents for certain transformations in molecular catalysts. For example, we aim to improve the enantioselectivity of List's IDPi catalyst for various chemical transformations by using a computational and informatics based approach to screen and optimize the substituents of the catalyst. The goal of this project is to achieve an asymmetric activation of unfunctionalized molecules with the assistance of a computational and informatics approach. Such a transformation is highly difficult to achieve by an organocatalyst and is an appropriate target for the second half of the WPI period.

Project-IV: Exploration of mechanochemical synthesis. Project IV is related to the Bridging Micro- and Macro-World project (former Project IV), but focuses exclusively on mechanochemical synthesis using ball mills. It is an ideal target for our computational and informatics tools because of its rapidly growing importance and the large amount of unexplored knowledge that remains. This synthetic method has proven to be a promising tool in organic synthesis. However, its applicability and understanding have not yet been sufficiently explored. The goal of this project is to expand its applicability, elucidate unexpected species unique to this synthesis, and construct a theory for modeling the effects of mechanical impact. Based on the rational design of mechanochemical reactions we will investigate target reactions such as the cross-coupling of solid materials, synthesis of new organometallic reagents like Grignard reagents in the solid state, and the decomposition and recycling of polymer materials.

Project-V: Understanding and controlling polymer property, formation, and degradation. Project V is an extension of the Polymer Degradation Project (former Project VI) that we have been working on. The project, in its current form, involves the design of polymer properties through simulation, the visualization of polymer mechanoradicals, the exploitation of polymer mechanoradicals, the design of polymer sequences to maximize desired properties, and more. Two goals of this project are to improve the performance of muscle-like double network hydrogels and to utilize plastic materials in the synthesis of useful materials.

Project-VI: Cancer diagnosis utilizing new materials and measurement techniques. We will continue our work on developing cancer diagnostic methods using new materials and measurement techniques (former Project VII). In particular, we will further investigate the hydrogel-activated reprogramming phenomenon (HARP) that was discovered during the first half of the WPI period. Two goals of this project are to understand HARP properly and to achieve its clinical applications by a fusion team of materials scientists, information scientists, and medical scientists.

In addition, in partnership with the School of Medical Science, we have launched a consortium called the Clinical Platform for Chemical Reaction Collaboration. Through this consortium, we aim to accelerate the use of our chemical products in medical diagnosis and treatment.

Bottom-up project: Furthermore, we have provided opportunities for young researchers to propose new ideas and launch related bottom-up projects. The launch of each bottom-up project is supported by an internal budget called Fusion Research Start-up. Based on their results, successful bottom-up projects are promoted as flagship projects, while underperforming flagship projects are evaluated and may be discontinued. This approach allows us to consistently deliver high-impact results while encouraging the activities of our young researchers.

III. Achievements and progress on the center research

Below, preliminary reports and interdisciplinary collaborations are marked as follows.

* Preliminary report (confidential)

† Interdisciplinary collaboration within the center

‡ Interdisciplinary collaboration with groups outside the center

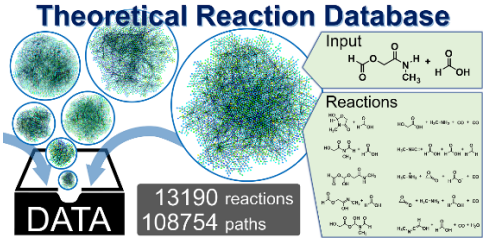
Below, achievements and progress on the above six flagship projects I-VI and two bottom-up projects are showcased.

(1) Achievements and progress on the Project-I: Computational and informatics tools development

The development and integration of fundamental computational and informatics methods are key issues in developing strategies for computational and informatics driven chemical reaction design and discovery. In FY2022, the achievements and progress are on three topics: an automated reaction path search method called quantum chemistry aided retrosynthetic analysis (QCaRA)/artificial force induced reaction (AFIR) (QCaRA/AFIR) method to trace back the synthesis path and its application to a natural product (**1-1**), the development of AFIR method for photo-redox catalyzed radical reactions (**1-2**), and the development of highly accurate machine learning potentials to accelerate AFIR searches (**1-3**).

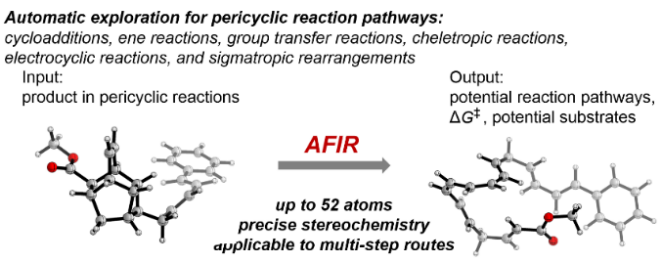
†1-1) Retrosynthetic analysis of a natural product using QCaRA/AFIR

Maeda group proposed the QCaRA/AFIR method which generates a reaction path network including thousands of elementary steps and predicts hundreds or more chemical reactions along with their theoretical yields (***JACS Au.*** 2022). **Maeda group** also proposes QCaRA-based theoretical reaction database construction. Seven reaction-path networks containing 13,190 reactions, and 108,754 reaction paths were published through the platform SCAN (searching chemical action and networks). In addition to well-known reactions, numerous unexplored reactions with high, medium, low, near-zero, or zero yields have been identified. The QCaRA-based theoretical reaction database will provide information on hitherto unexplored reactivities, especially those that are experimentally inaccessible (***submitted*** 2023).



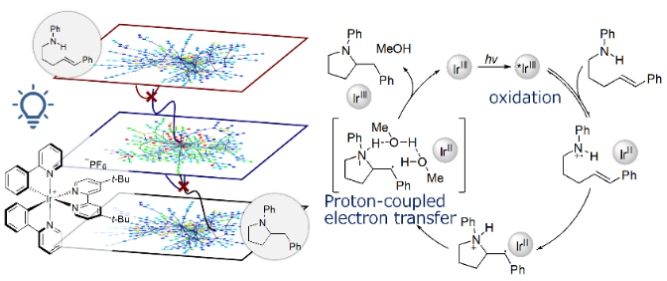
Mita (**mix-lab chief**) and **Maeda group** have demonstrated the expanded use of QCaRA/AFIR in predicting pericyclic reactions with accurate stereoselectivity based solely on information about the target product molecule. This automated reaction path search method's ability to accurately predict a molecule's stereochemistry is unprecedented. This study serves as a proof of concept that the AFIR method has the potential to discover novel reactions with specific stereochemistry.

The AFIR method successfully traced all categories of pericyclic reactions, including cycloadditions, ene reactions, group-transfer, cheletropic, electrocyclic, and sigmatropic reactions, via concerted reaction pathways, and obtained starting materials computationally with the correct stereochemistry. Furthermore, the AFIR was used to predict whether the identified reaction pathway could be expected to occur in good yield relative to other possible reactions of the identified starting material. To showcase its practical utility, this state-of-the-art technology was applied to the retrosynthetic analysis of a natural product with a relatively high number of atoms (52 atoms: endiandric acid C methyl ester). This compound was first synthesized by Nicolaou in 1982, and the AFIR provided the corresponding starting polyenes with the correct stereospecificity via three pericyclic reaction cascades (one Diels-Alder reaction as well as 6π and 8π electrocyclic reactions) (***J. Am. Chem. Soc.*** 2022, selected as the journal cover). This work was selected as the cover of the journal and has attracted a lot of attention, being featured in the JACS Spotlight and Science journal blog.



†1-2) Developing AFIR Method for photoredox-catalyzed radical reactions

Photoredox catalysts are often used in radical-based reactions to achieve chemical transformations that are challenging for typical thermal reactions. However, these reactions involve competition between bond rearrangement reaction paths and substrate-catalyst electron transfer reaction pathways, making it difficult to determine the mechanism of these reactions. Although quantum chemical calculations can provide an atomic-level picture of the mechanism, transition metal photoredox catalysts are generally over 80 atoms in size, which can create a significant barrier in terms of calculation costs.

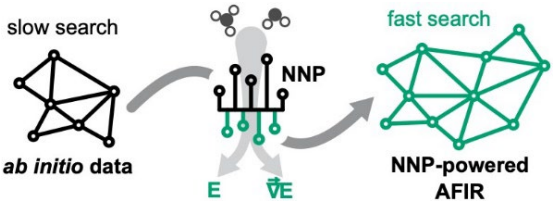


Maeda group and **Mita** (**mix-lab chief**) developed a method to describe the reaction path of

the substrate and the substrate-catalyst electron transfer in a simpler manner. By adjusting the substrate molecule's potential energy surface based on the redox potential of the catalyst, the search for reactions involving single electron transfer by the AFIR method becomes possible without calculating the large catalyst in the reaction system.

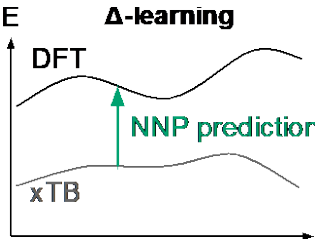
This method clarifies the entire mechanism of Knowles hydroamination and shows that electron transfer processes and proton transfer processes proceed in a concerted fashion. Calculation demonstrated that the relative importance of the reaction paths leading forward to the product and backward to the starting materials is dependent on the redox potential of the catalyst, and therefore the redox potential may influence the product yield of the reaction. The method is expected to be especially useful for the screening of photoredox catalysts (***Angew. Chem., Int. Ed.*** 2022, selected as the journal cover).

***†1-3) AFIR search powered by Neural Network Potentials**



The AFIR method allows to efficiently explore reaction path networks for predicting reaction yields and elucidating reaction mechanisms. Recently, the kinetic-based navigation method was developed to optimize the reaction path network exploration, by focusing on the kinetically important pathways. Despite these efforts, such exploration still requires in practice a large amount of accurate energy and gradients calculations. Therefore, the computational cost of the AFIR search is still large, due to expensive *ab initio* calculations, which limits the application of the AFIR search to systems with up to 30 atoms. Furthermore, cheaper but less accurate potentials, such as semiempirical methods, are not particularly compatible with the kinetic-based navigation method, whose efficiency depends on accurate reaction barriers predictions during the search.

Recent advances in Neural Network Potentials (NNP) offer many examples of highly accurate predictions at a significantly lower cost than their corresponding *ab initio* calculations, provided that sufficient training data is available. By replacing *ab initio* calculation with fast NNP predictions, an NNP-powered reaction path search can therefore combine the search efficiency of the AFIR + kinetic-based navigation with the performance of NNP predictions, enabling the application of the AFIR method to large systems.

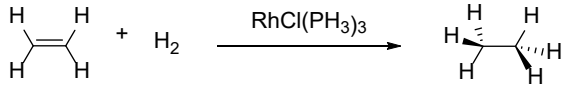


Varnek group and **Maeda group** have developed an NNP-AFIR interface and NNP-based models to support AFIR-based reaction path search, where strong exploration forces are involved.

Indeed, typical NNP models are not compatible with the artificial forces involved during an AFIR search. Therefore, robust NNP-based models were designed by including xTB predictions through a Δ-learning scheme. This was recently illustrated on hydrogenation reactions using Wilkinson's catalyst:

A preliminary reaction path search was done at the DFT level, using the AFIR method with kinetic-based navigation, and NNP models were trained on the resulting reaction network. All trained NNP models displayed accurate predictions on pre-obtained geometries. However, typical NNP models performed badly when used to run an AFIR search, with the generation of broken geometries wrongly capturing the reaction yield (i.e., leaky holes behavior).

Therefore, novel NNP(+xTB) models were designed and implemented by combining NNP predictions with robust physics-based semiempirical calculations, using a Δ-learning approach. Unlike conventional NNP, these NNP(+xTB) models were found sufficiently robust for powering an AFIR search. In particular, the AFIR search with kinetic-based navigation powered by a sufficiently trained NNP(+xTB) model was found to reproduce the reaction yield obtained at the DFT level (***submitted***).



Potential used	NNP	NNP (+xTB)	DFT	xTB only
Reaction yield (300 K)	0%	96.47%	100%	1.42%

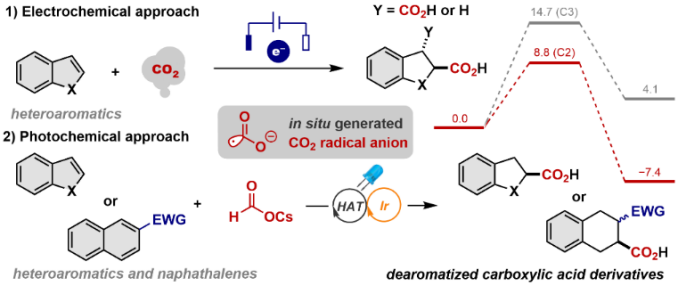
(2) Achievements and progress on the Project-II: New reaction design and discovery from scratch

To verify our models and to construct more useful models, we tackled several real-world chemical problems using AFIR. In FY2022, novel chemical transformations were discovered for CO_2 incorporation reactions (**2-1**) and for the double functionalization of ethylene and propellane (**2-2**).

†2-1) CO_2 incorporation reactions

Mita (**mix-lab chief**) and **Maeda group** have developed an electrochemical dearomative carboxylation method for stable heteroaromatics such as indole, benzofuran, and benzothiophene derivatives, using CO_2. This method is a powerful tool for producing synthetically useful carboxylic

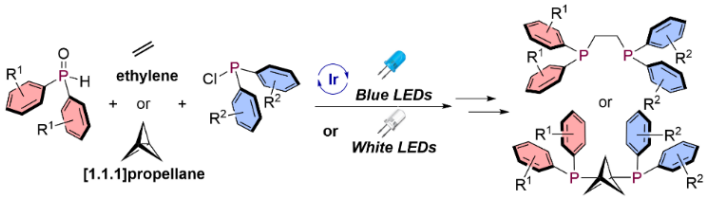
acid derivatives. However, these types of transformations are still underdeveloped, and concise methodologies with high efficiency have not been reported. To address this, the authors developed a new electrochemical protocol using $CO_2^{\bullet-}$, which produces unprecedented 2-carboxylic acid and *trans*-2,3-dicarboxylic acids from stable heteroaromatic derivatives. They designed substrates for carboxylation based on the calculated reduction potentials and the addition step of $CO_2^{\bullet-}$ by the AFIR method. The mono and dicarboxylated products thus obtained can be easily derivatized into useful synthetic intermediates for biologically active compounds in just a few steps. (***J. Am. Chem. Soc.*** 2022).



Mita (**mix-lab chief**) and **Maeda group** have developed a method that uses cooperating catalysts (hydrogen atom transfer (HAT)/photoredox Ir catalysis) under photochemical conditions. In this process, highly reactive $CO_2^{\bullet-}$ derived from an inexpensive formate salt (HCO_2Cs) reacted with stable heteroaromatics such as benzofuran, benzothiophene, and indole derivatives to produce synthetically useful α-oxy, α-thio, and α-amino acid derivatives in moderate to high yield, which are potentially useful in drug development. In addition, when using electron-deficient naphthalene derivatives, both single-electron reduction and Giese-type nucleophilic addition occur simultaneously to produce carboxylated tetrahydronaphthalene deriv-atives in good yield. (***ACS Catal.*** 2023, selected as the journal cover).

†2-2) Double functionalization of ethylene and [1.1.1]propellane to synthesize electronically unsymmetric 1,2-bisphosphine ligands

Ethylene is an important molecule with a worldwide production of around 170 million tons annually. While it is commonly used for industrial-scale synthesis of polyethylene and polyvinyl chloride, its application for fine chemicals (useful small molecules) has been limited compared to other alkenes.



However, **Mita** (**mix-lab chief**) and **Maeda group** predicted the retrosynthetic pathways of 1,2-Bis(diphenylphosphino)ethane (DPPE) by the AFIR, revealing ethylene and two phosphinyl radicals. Through experimental demonstration, they discovered a new double functionalization of ethylene with various P-radicals generated by a photoredox catalyst under light irradiation. In this synthetic protocol, two electronically different phosphines could be incorporated on both termini of ethylene, producing unsymmetric 1,2-bis(diarylphosphino)ethanes that have the potential to be used as novel bidentate phosphine ligands for transition-metal catalysts (***Nat. Commun.*** 2022 & **PCT/JP2022/30598**).

As an application of this synthetic method, straight-shaped symmetrical and asymmetrical diphosphine molecules were successfully synthesized by replacing ethylene with [1.1.1]propellane (***Angew. Chem., Int. Ed.*** 2023).

(3) Achievements and progress on the Project-III: Catalyst design and discovery through screening

In its current form, the project involves finding the optimal substituents and conditions for the catalyst through a computational screening process. In FY2022, we made progress in improving the enantioselectivity of List's IDPi catalyst for a known chemical transformation by using cheminformatics to screen and optimize the catalyst's substituents and conditions.

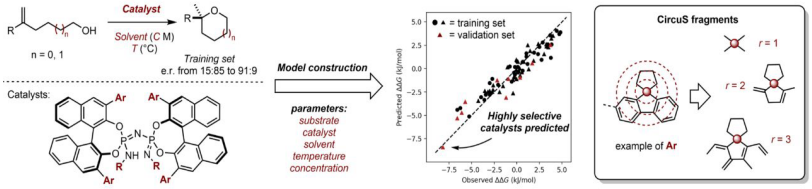
†3-1) Predicting highly enantioselective catalysts using tunable fragment descriptors

Catalyst optimization processes typically rely on inductive and qualitative assumptions of chemists based on screening data. While machine learning models using molecular properties or calculated3D structures enable quantitative data evaluation, costly quantum chemical calculations are often required. In contrast, readily available binary fingerprint descriptors are time-and cost-efficient, but their predictive performance remains insufficient. To help address this challenge, **List group**, **Pavel group**, **Varnek group**, and **Nagata** (**experimental scientist**) have demonstrated a machine learning method that utilizes advanced yet efficient 2D chemical descriptors to accurately predict highly selective asymmetric catalysts—without the need for quantum chemical computations.

For a computer to learn chemical information, molecules are usually represented as a collection of descriptors, which often consist of small parts, or fragments, of those molecules. However, computationally cheaper 2D descriptors have struggled to accurately represent complex catalyst structures, leading to inaccurate predictions. To improve this issue, researchers developed

new **Circu**lar**S**ubstructure (CircuS) 2D descriptors that explicitly represent cyclic and branched hydrocarbon structures, which are common in catalysis. Training data was obtained through experiments via a streamlined, semi-automatic process utilizing a synthesis robot. This experimental data was then converted into descriptors and used to train the A.I. model.

Fast and robust predictive models using 2D descriptors particularly suited for asymmetric catalysis. Highly selective catalysts were predicted and validated using training data with only moderate selectivities. They used the fully trained model to virtually test 190 catalysts not part of the training data. In this set, the model was able to predict highly selective catalysts after only having been trained on the data of catalysts with moderate selectivity, showing an ability to extrapolate beyond the training data. The catalyst predicted to have the highest selectivity was then tested experimentally, exhibiting a selectivity nearly identical to the prediction. Obtaining high selectivity is especially crucial for the design of new medicines, and this technique provides chemists with a powerful framework for optimizing selectivity that is efficient in both computational and labor cost (***Angew. Chem., Int. Ed.***, 2023).

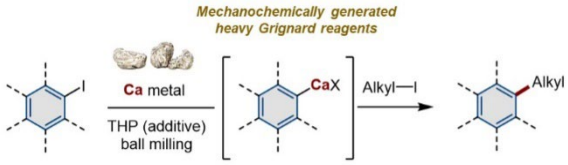


(4) Achievements and progress on the Project-IV: Exploration of mechanochemical synthesis

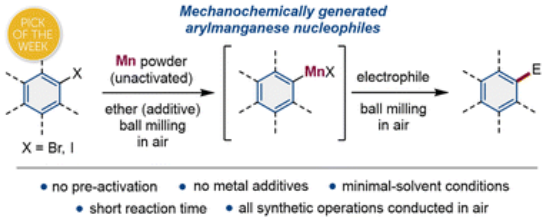
Ball mill mechanochemical synthesis has emerged as a promising tool in organic synthesis. However, despite its growing importance, little is understood about this new method. In FY2022, we uncovered novel tools and catalyst design strategies related to ball mill synthesis, including a calcium-based Grignard reagent formation method, an arylmanganese nucleophiles formation method, and a ligand design strategy unique to ball mill synthesis.

†4-1) Mechanochemical synthesis with the ball mill technique

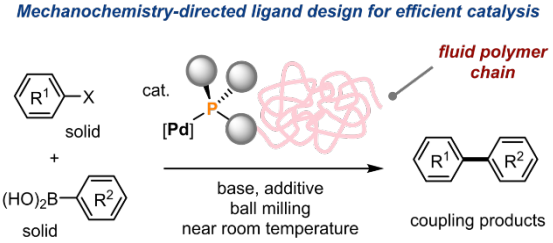
Ito-group and **Maeda group** has addressed this issue by developing a streamlined way to make organocalcium reagents so-called "heavy Grignard" without the need for a pre-activation step. In the mechanochemical method developed here, an organohalide and commercially available calcium are put inside a ball mill with a small amount of organic solvent additive. The mechanical impact of the ball provides enough energy to activate the calcium without the need for harsh conditions, dry organic solvents, or strict temperature control. With this operationally simple method in hand, researchers successfully demonstrated the first example of the alkylation of arylcalcium halides with alkyl electrophiles. Importantly, the use of calcium instead of magnesium for this reaction resulted in a significantly higher yield of the desired product. This work demonstrates the promise of calcium-based Grignard reagents, showing they can result in novel reactivity and improved yield. Additionally, the mechanochemical protocol reported here provides researchers with a simple, non-toxic method for creating heavy Grignard reagents, opening the door for further investigation into this largely unexplored field (***Angew. Chem., Int. Ed.***, 2022).



Ito-group showed that a mechanochemical ball-milling protocol facilitates the generation of various arylmanganese nucleophiles from aryl halides and commercially available, unactivated manganese metal without the need for complicated pre-activation processes and metal additives. These manganese-based carbon nucleophiles can be used directly for one-pot addition reactions with various electrophiles and palladium-catalyzed cross-coupling reactions under bulk-solvent-free mechanochemical conditions. Importantly, all experimental operations can be conducted under atmospheric conditions. They experimentally found that this new method enables solvent-free reactions with unique selectivity and reactivity (***Chem. Sci.***, 2023).



Ito-group reported a mechanochemical-directed catalyst design: the polyethylene glycol molecules form a region between the solid materials behaving like a molecular-level fluid phase, where mechanochemical Suzuki-Miyaura cross-coupling reactions proceeded much more efficiently and without the problematic aggregation of palladium. In addition to achieving significantly higher product yields, the reaction proceeded effectively near room

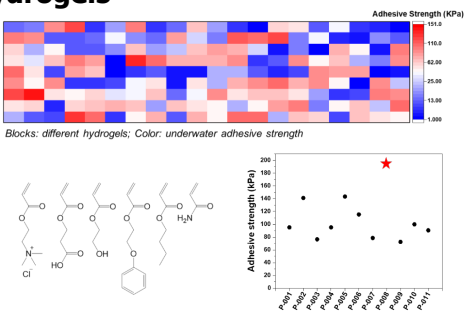


temperature — the previously best-performing alternative required heating to 120°C. Similar cross-coupling reactions are widely used in research and the chemical industry. We believe it could be adapted for many other reactions, and also for catalysts using other elements from the transition metals of the periodic table. The wider adoption of the process, and others like it, could eventually bring significant savings in costs and energy consumption in commercial chemical processes while allowing more environmentally friendly large-scale production of many useful chemicals (***J. Am. Chem. Soc.*** 2023).

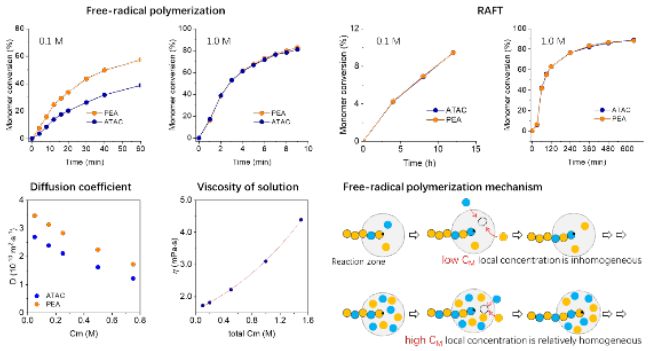
(5) Achievements and progress on the Project-V: Understanding and controlling polymer property, formation, and degradation

The project includes the design of polymer properties through simulation, the visualization of polymer mechanoradicals, the use of polymer mechanoradicals, and the design of polymer sequences to maximize desired properties. In FY2022, we had progress in the design of polymer sequences using informatics and simulations (**5-1**) and the visualization of polymer mechanoradicals using a new mechanoprove and elucidation of the behavior of radicals by AFIR (**5-2**).

***†5-1) Sequence-controlled underwater adhesive hydrogels**



Mimicking the primary structure of functional proteins is a straightforward strategy to design the chemical composition of polymers for functional material development. To efficiently develop novel protein-inspired underwater adhesives, **Gong group** and **Takigawa group** proposed on a strategy that using data-mining and machine-learning. They have collected 24,707 adhesive proteins of ~200 kinds of organisms from protein database. **Takigawa group** analyzed the consensus sequence of these proteins by data mining and analyze the pairwise frequencies of adjacent sub-group residues. 5 most frequently appeared pairs are identified for 180 species. To design the adhesive hydrogel materials, **Gong group** selected 6 acylate monomers with functional groups similar to the 6 sub-groups of amino acids. A total of 180 hydrogel samples with monomer fractions the same as that of 5 top frequencies in the 180 species were fabricated and their underwater adhesiveness were tested. **Takigawa group** analyzed the relationship between the measured adhesive strengths of these hydrogels and their monomer fraction by machine learning and provided some optimized monomer fractions, which are predicted with better adhesive performance. According to the optimized monomer fractions, **Gong group** further fabricated 11 hydrogel samples and measured their underwater adhesive strengths. It has been found that all of these 11 hydrogels exhibited high adhesion with the adhesive strength over 80 kPa to negatively charged substrates. Most noteworthy is the sample of P-008 that has the highest underwater adhesive strength (194.6 kPa) greater than that of the previous 180 samples. This result demonstrates that the data-driven molecular design of novel adhesive hydrogels is efficient. More detailed experiments are undergoing (H. Fan, H. Sheng, et al., ***in preparation***).



Custom synthesis of copolymer with required monomer sequences is a central challenge in polymer chemistry. The sequence is determined by the selective propagation of monomers during polymerization, which is governed by the quantity called as reactivity ratios of monomers (r). **Gong group** found that the reactivity ratios of cationic and aromatic monomers highly depend on the monomer concentrations by using free-radical polymerization, but is independent of monomer concentration when using the RAFT method. To understand the underlying mechanism, **Maeda group** performed DFT calculation, and has clarified that the energy barriers of the transition state of each monomer addition to the polymer are similar, indicating that the monomers have no addition preference chemically. To study the effect of solvation of monomers, which influence the diffusivity of monomers and thereby polymerization kinetics, **Rubinstein group** performed molecular dynamics simulations by utilizing a coarse-grained model, and has clarified that the solvation difference to different monomers decreases with the increase of monomer concentration, and hence, the apparent reactivity ratios change with the monomer concentration. These results clarified that in the free-radical polymerization that has a very high reaction kinetics, the monomer reactivity ratios are dominated by the monomer diffusion kinetics, depending on monomer concentration. While in the RAFT polymerization that has a slow reaction kinetics, the monomer reactivity ratios are dominated by chemical reaction energy barrier, independent of

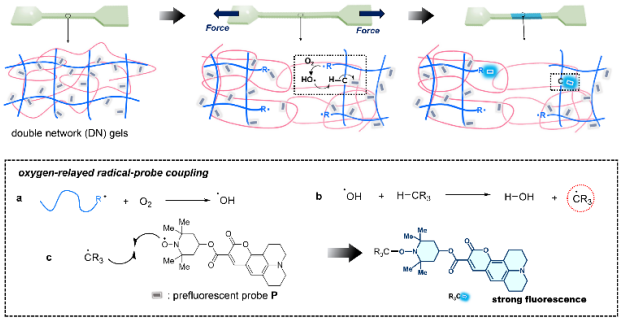
monomer concentrations. The understanding of reaction mechanism assists **Gong group** to control the monomer sequence of copolymerization and to obtain hydrogel materials with required functions.

*†5-2) Visualisation of mechanoradicals in hydrogel media

Visualization of mechanochemical damages especially molecular-scale bond scission in polymeric materials is of great industrial and academic significance. **Jin group**, **Maeda group**, **Ito group**, and **Gong group** discovered that the radical-trapping prefluorescent probe P can efficiently detect mechanoradicals in DN hydrogels even in air with abundant amounts of oxygen which usually quench the radicals. Moreover, the hydrophobicity P should be immobilized on polymer network in water and therefore should have low efficiency on trapping mechanoradicals on the cleavaged polymer strands.

To elucidate the mechanism, they theoretically estimated the reaction of oxygen with the mechanoradicals. Their calculation suggested that the oxygen reacts with mechanoradical to form peroxide radical and the peroxide further abstracts the H atom from nearby C-H bond to generate a new carbon centred radical, which would be trapped by the probe P and initiate luminescence. The above-mentioned carbon radical which carries the -OOH functional group may undergo further intramolecular reaction to generate an OH radical and a closed-shell species.

The OH is highly mobile and meanwhile highly reactive. It may transfer to other parts of the polymer network and abstract H atom there from a C-H bond. Therefore, oxygen may ampliphier and spread the radical species to promote the efficient radical traping of P. To experimentally verify such effect of oxygen, we performed the mechanoradical probing experiment in deoxygenated DN hydrogel. We found that in contrast to the DN gel in open air that showed clear emission change in necking region where large amount of mechanoradicals were generated, the deoxygenated DN gel hardly showed emission change in necking region. This result is in consistent with theoretical prediction. The results answered the questions why the hydrophobic P can detect the mechanoradicals efficiently in hydrogels in the presence of oxygen (***J. Am. Chem. Soc.***, 2023).

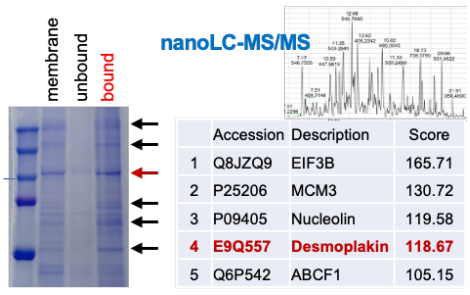


(6) Achievements and progress on the Project-VI: Cancer diagnosis utilizing new materials and measurement techniques

We have continued to investigate the hydrogel-activated reprogramming phenomenon (HARP), which was discovered during the first half of the WPI period. Understanding HARP and its potential clinical applications are pressing issues to be addressed in this project. In FY2022, we had progress in the investigation on the gel-side factors on the cancer stem cells (CSCs) generation and discovered that PNaSS gel can induce CSCs efficiently.

*†6-1) PNaSS gel induces cancer stem cells (CSCs) with invasiveness

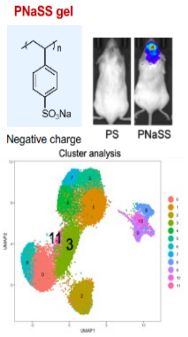
Tanaka group and **Gong group** previously reported rapid reprogramming from cancer cells to CSCs using hydrogel, named hydrogel activated reprogramming (HARP) phenomenon. In order to elucidate the underlying molecular mechanisms, we analyzed the gel-side factors and cell-side factors on the CSC generation. As gel-side factors, we varied the electric modulus of the hydrogel from 5 to 187 kPa in 7 steps, and proved that the efficiency of CSC generation was highest at 10 kPa, which is almost equal as *in vivo* tumor tissue stiffness. NanoLC-MS/MS analysis demonstrated that six kinds of membrane proteins including Desmoplakin bound to the hydrogel with 10 kPa, suggesting to function as candidate mechanoreceptors. Meanwhile, the optimum electric charge of the gel for CSC generation varied according to the type of cancer cells. As cell-side factors, activated Ras-transformed cells induced CSCs, whereas activated Src-transformed cells failed, indicating an influence of oncogenes. Furthermore, we analyzed the effect of CSCs generation by adding a CSC niche environment to the hydrogel, and found that low-nutrient environment and direct contact with vascular endothelial cells may promote reprogramming of cancer cells.



	Accession	Description	Score
1	Q8JZQ9	EIF3B	165.71
2	P25206	MCM3	130.72
3	P09405	Nucleolin	119.58
4	E9Q557	Desmoplakin	118.67
5	Q6P542	ABCF1	105.15

Tanaka group and **Gong group** recently found that the PNaSS (poly(sodium p- styrene sulfonate) gel can induce CSCs more efficiently. All cancer cells cultured on the PNaSS gel had enhanced expression of the stem cell markers and acquired tumorigenicity *in vivo*, suggesting to acquire the characteristics of CSCs. Of note, the cell membrane on the PNaSS gel was greatly expanded, and it is expected to enhance the cell motility. Brain tumor cells cultured on the PNaSS for 1 week revealed that mitochondrial respiration was enhanced, whereas glycolysis was decreased,

indicating that the cells cultured on the PNaSS gel are Quiescent CSCs with enhanced oxidative phosphorylation. To analyze the characteristics of the CSCs on the PNaSS gel, the analyses of cell metabolism and single-cell RNAseq (scRNA-seq) analysis were performed. The gene expression profile of cultured cells on PS dish, classical neurosphere (NS) culture, DN gel, and PNaSS gel were divided into 11 clusters, and the cells on PNaSS gel were distributed in clusters 3 and 11. They include the extracellular matrix collagens, as well as THY1 and SPARC. Thus, PNaSS gels may induce CSCs with enhanced cell motility, that exist at the invasive front niche for CSCs, which might contribute to the development of treatments that can overcome the treatment resistance and metastasis / recurrence (***Manuscript in preparation***).



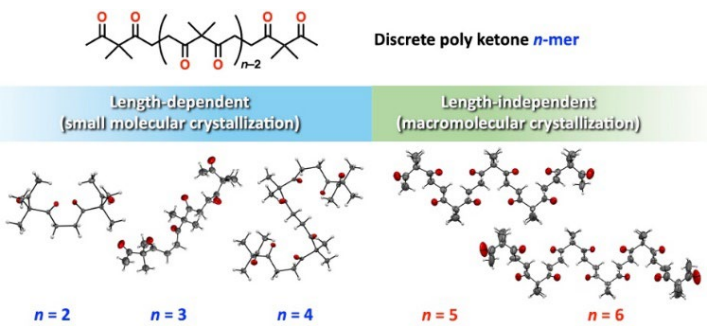
(7) Achievements and progress on Bottom-up projects

Bottom-up projects are initiatives led by our young researchers, and two outstanding projects from FY2022 are highlighted below. Inokuma, the youngest PI, collaborated with Hijikata, the former Fusion Research Coordinator, on the first project, which explored potential applications of polyketones, the first systematic synthesis of which was achieved by Inokuma. The second project was led by Tanigawa, a former member of the Tanaka group, in collaboration with the Gong group, and focused on the use of hydrogels to heal damaged brains.

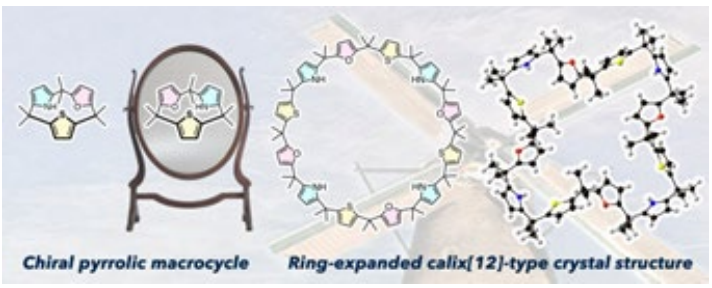
†7-1) Discrete polyketones for fundamental understanding of polymer crystallization and for application to novel macrocyclic compounds

When molecules form a crystal, the way in which they arrange themselves can affect many different physical properties, including melting point, folding, and light absorption. For crystallization fashion of molecules, it has been known that small molecules widely change their crystal packing and solid-state conformations depending on even slight differences of substituents or molecular size (Small molecular crystallization). However, polymers often adopt common packing and conformations regardless of chain length (Macromolecular crystallization). There must be the critical chain length above which crystallization behavior stays macromolecular for each oligomers/polymers. Investigating this critical length is key for understanding how material properties change with the transition from small, individual molecules to large polymer macromolecules. However, it is challenging to investigate these changes due to the difficulty of synthesizing and crystallizing samples purely consisting of a discrete chain length.

Inokuma group and **Hijikata (Computational scientist)** investigated the critical chain length for a polyketone compound based on an acetylacetone derivative. The benefit of using such a polyketone is that the polymer chain can be extended in a controlled, selective fashion from only one end of the chain. This enabled to synthesize pure samples of molecules with a discrete chain length in the range of 2-20 repeating subunits. Utilizing single crystal and powder X-ray diffraction (XRD) data, the team found the critical chain length was a surprisingly short five subunits. Below this length, distinct crystal packing and chain conformation were observed for each chain length. At or above the length of 5-mer, similar XRD patterns were observed regardless of chain length. Single crystal XRD analysis revealed that 5- and 6-mers adopted similar helical conformations and packing structures. Calculations of an infinitely long chain also showed a helical structure, supporting the idea that packing structure does not change beyond the critical chain length of five. This determination aided in explaining melting point behavior. Unpredictable melting point changes occurred below the critical chain length and were attributed to the different molecular packing arrangements. As the polymer chain increased above the critical length, the melting point changes became more stable, gradually increasing with chain length. This approach could be extended to other polymers in order to understand property changes and determine the optimal chain length of a material for a given application (***Chem. Sci.***, 2022).



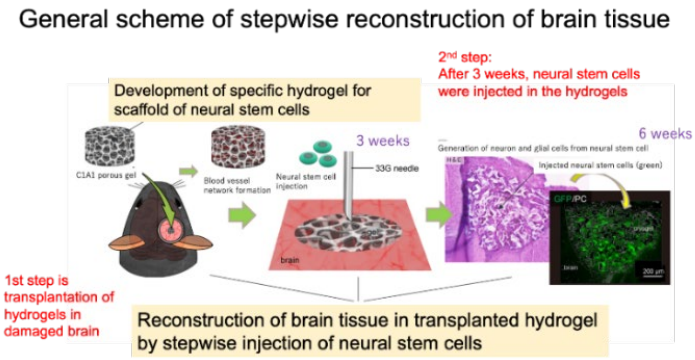
Cyclic analogues of discrete polyketones were utilized to produce novel porphyrin-related macrocyclic compounds. Calixpyrroles are useful host compounds that bind various molecules and ions. Despite their rich host-guest chemistry, inherently chiral



calixpyrrole analogues that might show chiral molecular recognition or unusual reactivity have not been synthesized because rapid ring flipping motion of heteroarene units renders the macrocycle virtually achiral. **Inokuma group** and **Hijikata (Computational scientist)**, and Jonathan L. Sessler group at the University of Texas-Austin have synthesized calix[1]furan[1]pyrrole[1]thiophene, which is a unique, inherently chiral calix[3]pyrrole analogue that features three different heteroarene subunits. Owing to the proximal arrangement of three aromatic rings, ring flipping motion leading to racemization was enough slow to allow chiral separation of enantiomers. *N*-Methylation on the pyrrole unit resulted in complete suppression of ring flipping so that enantiomers could be obtained as optically pure forms to allow single crystal X-ray analysis. Molecular dynamics (MD) simulations revealed that flipping of thiophene ring is the rate-determining step. When *N*-methylation was performed in the presence of chiral ammonium salt, the reaction proceeded in a enantioselective fashion, although *ee* was modest. Interestingly, unusual reactivity of calix[1]furan[1]pyrrole[1]thiophene provided a new synthetic access to larger calixpyrrole-type macrocycles: calix[9] and [12]-analogues. When calix[1]furan[1]pyrrole[1]thiophene was treated with trifluoroacetic acid, strain-induced ring expansion reaction occurred to give its cyclic oligomers. The team succeeded to isolate up to calix[12]pyrrole analogue, calix[4]furan[4]pyrrole[4]thiophene, and determined its crystal structure. The crystallographic data revealed that the calix[12]-analogue adopted windmill-like conformation. This crystal structure is, to date, the largest calixpyrrole-type macrocycle to be analyzed by XRD (***Angew. Chem., Int. Ed.***, 2023).

†7-2) Healing the brain: hydrogels enable neuronal tissue growth

While growing brains may sound like something out of a science fiction movie, **Tanigawa of Tanaka group** and **Gong group** have made a step in that direction. They used hydrogel materials, in combination with neural stem cells, to grow new brain tissue. This is important since, when tissue in our brain is damaged, the neuronal tissue does not have the same regenerative capacity as other parts of our body such as skin.

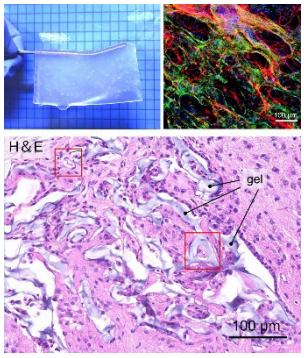


The main reason for difficulty of regeneration of brain tissue is loss of scaffold for cellular regeneration caused by cerebral hemorrhage, infarction, or brain tumor resection. General scheme is shown in the right panel. This is the stepwise strategy in which hydrogel was transplanted in the brain cavity and 3 weeks later, neural stem cells were injected into the hydrogel. Injected cells were visualized with green fluorescence.

The first step for researchers was to develop a hydrogel material in which neural stem cells could survive(shown in the right panel, upper left photo).

They found that a neutral gel made with equal parts positively and negatively charged monomers resulted in the best cell adhesion (designated as C1A1 gel, ratio of cation to anion is 1 to 1). Researchers then adjusted the ratios of crosslinker molecules to achieve a stiffness similar to that of brain tissue as several kilo-Pascal; pores were then created in the gel in which cells could be cultured with several hundred micrometer. The researcher confirmed the neural stem cells could grow in this soft porous C1A1 hydrogels with some differentiation of neuronal cells and glial cells in vitro (shown in right panel, upper right photo).

Once the gels were optimized, they were soaked with a vascular endothelial growth factor VEGF to encourage blood vessel growth, and then implanted in damaged areas of the brain in a mouse model. After three weeks, researchers found that immune cells and neuronal cells from the surrounding host brain tissue had entered the hydrogel and that blood vessels had grown.



At this point, researchers injected neural stem cells into the hydrogel. After 40 days, stem cell survival rate was high, and some had differentiated into new astrocyte cells or neuronal cells. It was observed that host cells infiltrated the hydrogel, while some new neuronal cells from the hydrogel migrated to the surrounding brain tissue, showing some degree of integration between the hydrogel and host brain tissue.

The stepwise nature of the process was key, as implanting the hydrogel and transplanting the neural stem cells at the same time proved unsuccessful. This study marks an important step toward developing therapies involving brain tissue regeneration; the next steps involve studying the optimal transplant timing and the effect of the inflammatory response on transplanted cells leading to the functional recovery (***Sci. Rep.*** 2023, Altmetric 245 on Mar 28, 2023).

2. Generating Fused Disciplines

* Describe the content of measures taken by the center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields. If any, describe the interdisciplinary research/fused discipline that have resulted from your efforts to generate fused disciplines. You may refer to the research results described concretely in "1. Advancing Research of the Highest Global Level."

Promotion of fusion research: The center is working on several flagship projects. Each project involves groups from two or more disciplines. Setting and working on such flagship projects together has been a strong driving force to promote interdisciplinary fusion in the center. In addition, the center holds a call for ideas from young researchers in the center and provide them with an opportunity to lead a bottom-up project. These flagship and bottom-up projects are evaluated yearly. Then, promising ones are expanded or promoted from bottom-up to flagship project. Conversely, ones that are not proceeding well are terminated or restarted as a bottom-up project. These projects are carried out under the Center Director's initiative. To do that, the center sets a position called "Fusion Research Coordinator" in 2022. The Fusion Research Coordinator joins periodic meetings of all these projects and reports their progress to the Center Director. If necessary, the Fusion Research Coordinator participates in a project themselves and leads the project together with project's leader. Moreover, all researchers in the center have an opportunity to report their progress, including interactive discussions, twice every year to the Center Director, the Administrative Director, and the Fusion Research Coordinator. The following outputs demonstrate the effectiveness of our strategy and prove that the strategy works well for achieving our goal of "revolutionizing chemical reaction design and discovery".

Fusion research achievements in FY2022: Maeda-group (computation) together with Dr. Mita (experimental lab-chief) published multiple papers on the development of new synthetic methods utilizing quantum chemical reaction path networks (*Nat. Synth.* 2022, *Nat. Commun.* 2022). List-group (experiment) and Varnek-group (information) achieved an informatics-driven discovery of new organocatalysis (*Angew. Chem.* 2023). Gong-group (experiment, material), Ito-group (experiment, organic), and Maeda-group (computation) developed a fluorescence probe to rapidly detect mechanoradicals in hydro-gel materials (*J. Am. Chem. Soc.* 2023).

Papers in collaborations: In 2022, the center has achieved outstanding research achievements. 139 papers including 22 TOP 10% papers (16% of 139 total papers, university average 9%) and 40 highly cited papers (IF 9 or more) were published in peer-reviewed journals which is three times (9 papers per PI) the number of papers published by professors of the University per year (3 papers). 8 papers in journals with IF > 20, 28 papers in journals with 20 > IF >10. Two papers were published in Nature (IF: 69.5), one in Science (IF: 63.832), two in Cell (IF: 66.85), one in Advanced Materials (IF: 32.086) and five in Nature Communications (IF: 17.694). Since the establishment of the center, the center has been actively collaborating with domestic and international researchers as well as promoting fusion research within the center, leading to papers in collaboration within Hokkaido University (39), domestic collaborators (56), and with international collaborators (38; 27% of papers from the center) in 2022.

Interdepartmental joint symposiums: After the joint symposium with Faculty of Science in Dec. 2020, the joint symposiums were also held with Faculty of Engineering in Apr. 2021, Faculty of Medicine in Oct. 2021, five attached institutes in Mar. 2022, Faculty of Pharmaceutical Sciences in Sep. 2022, and Research Faculty of Agriculture in March 2023 to ensure opportunities for regular and active communication across disciplines, to promote future fusion research, and to invite and propose new joint research in our university.

Start-up support for new appointments and fusion research: In FY2022, start-up support for new appointments (15 million yen for 5 new positions) and start-up support for fusion research to take on challenging bottom-up fusion projects (10 projects (10 million yen) and 1 group project (10 million yen) for a total of 20 million yen) were awarded. These projects led to the acquisition of Grants-in-Aid for Scientific Research.

Pre-checking system for the grant application: The center conducted a pre-checking system to review and revise the applications for Grants-in-Aid for Scientific Research, etc. before submission. 41% of the applications for Grants-in-Aid for Scientific Research, including "Transformative Research Areas B", were granted for FY2023 (see below). The amounts of Grants-in-Aid for Scientific Research obtained have been increasing every year. FY 2018: 78 million yen, FY 2019: 159 million yen, FY 2020: 148 million yen, FY 2021: 182 million yen, FY2022: 219 million yen, and overseas PIs and Jr-PIs, and young researchers have also succeeded in obtaining Grants-in-Aid for Scientific Research.

	Scientific Research A	Scientific Research B	Scientific Research C	Scientific Research on Innovative Areas	Transformative Research Areas A	Transformative Research Areas B	Early-Career Scientists	Total	Average of adoptions for the center	Average of adoptions for the university
FY2023 number of adoptions / applications	0/0	0/4	0/4	0/0	0/0	4/4	7/15	11/27	40.7%	38.3%
FY2022 number of adoptions / applications	0/0	1/4	1/4	0/0	1/3	0/3	4/9	7/23	30.4%	37.1%
FY2021 number of adoptions / applications	0/1	2/6	3/5	1/1	-	-	6/14	12/27	44.4%	38.0%
FY2020 number of adoptions / applications	0/1	1/3	0/1	1/3	-	-	3/7	5/15	33.3%	37.1%

Securing research funding: The center's PIs and other researchers have continued to receive competitive research funding steadily since its inception. The total amount of these funds was 203 million yen in 2018, 668 million yen in 2019, 934 million yen in 2020, 655 million yen in 2021, and 848 million yen in FY2022. Representative competitive research funds in FY2022 are Grants-in-Aid for Scientific Research "Fund for the Promotion of Joint International Research (International Leading Research)" (1) and "Scientific Research S" (1), JST-ERATO (1), JST-CREST (5), JST-START (2), JST-MIRAI (1), AMED-P-PROMOTE (1) etc.

3. Realizing an International Research Environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:
- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers (in Appendix 2); exchanges with overseas entities (in Appendix 4); number and state of visiting researchers (in Appendix 5)
- Proactive efforts to raise the level of the center's international recognition
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

(1) **Number of researchers**: The center conducted an international call for applications for new specially appointed faculty members and postdoctoral researchers to be hired at the center and received many applications from Japan and abroad in FY2022 (190 applications for 16 positions). As of March 31, 2023, the number of PIs was 15 including 3 foreign PIs, 45% of all researchers were foreign nationals, and 15% were female researchers (total of 80 researchers, including 36 foreign nationals and 12 female researchers, split between the fields of Computation (20 researchers, 25%), Information (15 researchers, 19%), and Experiment (45 researchers, 56%). The ratio of research fields is 50% each in computational/information and experimental science, which sufficiently covers all research fields to strengthen the center's mission.

(2) **ICReDD International symposium**: Since 2021, the center established the Akira Suzuki and ICReDD Awards, which honor prominent chemists in both experimental chemistry and computational chemistry or information science. The 2nd awards were given to Professor John F. Hartwig from University of California, Berkeley and Professor Kendall N. Houk from University of California, Los Angeles, strengthening the center's connection with these two prominent scientists and their institutions. Each fiscal year, the center has held the ICReDD international symposium, inviting researchers from Japan and overseas to introduce them to the vision and research of the center. The fifth ICReDD international symposium was held on January 11, 2023. This symposium had 361 registrations (59 overseas registrations from 19 countries), 115 live participants (103 domestic and 12 overseas), 36 poster sessions and numerous on-demand viewers. Speakers were John F. Hartwig (UC Berkeley, Akira Suzuki Award winner), Kendall N. Houk (UC Los Angeles, ICReDD Award winner), Dean J. Tantillo (UC Davies), Alán Aspuru-Guzik (Univ. Toronto), Cathleen M. Crudden (Queen's Univ.), and ICReDD's Tsuyoshi Mita and Hajime Ito.

(3) **International seminars**: In FY2022, the center held eight international seminars, which were able to be held more easily thanks to the online meeting environment. Speakers for the seminars were Michael J. Krische (University of Texas at Austin, July 20), Han Hao (University Toronto, July 22), Matthew J. Fuchter (Imperial College London, September 9), Senmiao Xu (Suzhou Research Institute of LICP, September 20), Jye-Shane Yang (National Taiwan University, October 27), Bernd M. Schmidt (Heinrich Heine University Düsseldorf, January 18), Igor Larrosa (The University of Manchester, March 9), and Dmitri Federov (National Institute of Advanced Industrial Science and Technology (AIST), March 29). Such seminars will be held regularly in the future.

(4) **Other seminars and symposiums**: A number of seminars and symposium were held in order to ensure opportunities for regular and active communication in a cross-disciplinary manner among the center's young researchers, to advance future fusion research, and to solicit and propose new collaborative research. These events include two interdepartmental symposiums (Faculty of Pharmaceutical Sciences (September 2022) and Research Faculty of Agriculture (March 2023)), eight international seminars, and nine ICReDD seminars (two research ethics seminars (Robert J Gellar (July 13) and Jun Fudano (July 28)), two diversity seminars (Heidi Penning (Equity Advisor, Queen's University, May 25), Aiko Fukazawa (iCeMS, July 19)), five research seminars (Ruben Staub (ICReDD, April 22), Wei Li (ICReDD, August 31), Ryota Isshiki (ICReDD, November 30), Makoto Yamashita (Nagoya University, October 11) and Masahiro Murakami (Kyoto University, December 7)). In addition, the ICReDD Online Salon as lunch & evening seminar was held 30 times in total as an opportunity for regular communication.

(5) **Support for inviting many excellent researchers and students from abroad**: The center assigned administrative staff who are capable in English and are composed of personnel with excellent ability and experience in a variety of areas. All the administrative information is provided in both English and Japanese. Interviews by the International Planning Unit staff with foreign researchers and PIs were conducted, and a one-stop support system was established. The administrative department provides a wide range of support daily by staff who can respond

in both English and Japanese. Many documents related to the daily lives of foreign researchers and their families and university administrative procedures are translated into English by center's administrative department. Emphasis is placed on support for foreign researchers at the time of employment (coming to Japan) and at the time of retirement, and careful explanations are provided in English about Japanese taxes and social insurance systems. To create an environment in which foreign researchers can concentrate on their research, The center provides language support for contracts and necessary living procedures when looking for private apartments and helps them to settle in Sapporo. Support for child enrollment, communication support with schools, and Japanese language courses for learning Japanese are also introduced. For preschool children, assistance is provided in guiding them through nursery school and kindergarten procedures, contacting the schools with inquiries, and so on. As for health care support for the individual and his/her family, advice on hospital selection, explanation and accompaniment to appointments, and support for pregnant women during childbirth are provided. In response to the new corona virus, the center also checked the situation in case of fever, contacts the public health center, and provides up-to-date information on vaccination.

(6) **Establishing collaborative agreements**: In FY2022, an agreement was put in place with the Max Planck Institute. In addition, the University of Strasbourg, the University of Tokyo, and Chubu University. Furthermore, Duke University, Peking University, Stockholm University, University of Oslo, Queen's University, and ICIQ (Institut Català d'Investigació Química (Institute of Chemical Research of Catalonia)) were strong collaborative institutions. The center plans to continue to collaborate with these research institutions.

(7) **Fostering young researchers by MANABIYA**: Researchers were accepted through the MANABIYA system. "MANABIYA(ACADEMIC)" invited applications from April 2022 and accepted 13 researchers (under the COVID-19 situation, 10 were accepted from domestic and 3 were accepted from abroad) out of 17 applicants, who were trained in the center's techniques.

4. Making Organizational Reforms

* Describe the system reforms made to the center's research operation and administrative organization, along with their background and results.
* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.
* Describe the center's operation and the host institution's commitment to the system reforms.

(1) **Evaluation system of center faculty members**: In FY2022, a new regulation was established to provide incentives based on the research performance and discretionary evaluation by annual interview of center faculty members, for whom no evaluation system was previously in place. The results of the self-performance evaluation, and discretionary performance evaluation based on annual interview with the Center Director are used to determine the salary increase or decrease by one or two steps from the base annual salary for the following year, which has not yet been done in any other departments in the University. Performance evaluations (S, A, B, C and D) were conducted for 18 of 22 faculty members, excluding those who arrived and left during FY2022. 3 faculty members received a two-level salary increase as evaluation value S, 6 faculty members received a one-level salary increase as evaluation value A, 7 faculty members received no revision salary as evaluation value B and 2 faculty members received a one-level salary decrease as evaluation value C.

(2) **Establishment of ICReDD fellow system**: In FY2023, the center established a new position called the ICReDD fellow to expand ICReDD's research activities inside and outside the university and to serve as an incubation system for new PIs. The center provides ICReDD fellows with our resources and collaborate with them. When a senior PI is replaced or new developments in research are needed, the most suitable ICReDD fellow is selected. ICReDD fellows are potential candidates for future senior PIs. The center will be made a permanent research center that always promotes cutting-edge, world-class research based on a new adaptive research strategy involving periodically changing researchers and research themes.

(3) **The decision-making system**: The mission of the center is communicated to all members through interviews at hiring and annually with researchers conducted by the center director. Laboratory chiefs were appointed in mixed laboratories and mixed offices, and laboratory management is conducted so that the Center Director's policies are promptly communicated. Under the direct supervision of the Center Director, the "Fusion Research Coordinator," established since FY2022 and directly connected to the research division, actively promotes and plans fusion research and advises on the progress of the research. Authority had been delegated to the Future Plan WG, Equipment Management WG, so that they can manage the center by the direction of the center director. The regularly scheduled Advisory Board Meetings were established to obtain advice, recommendations, and evaluations from experts on future prospects, strategies, and approaches to solving problems in order to realize the center's vision and create a world-class research center, thereby contributing to the future management of the center. The Advisory Board online meetings were held on March 22nd (European time) and 30th (US time). The board members reviewed the progress and follow-up reports from an

international perspective and made recommendations on the future direction of the center and provided advice on how to promote research. Specifically, the members suggested that (1) the major research goals of the center should be clarified, (2) an environment in which research data can be openly discussed is important for ensuring research transparency and preventing research misconduct, (3) it is important to ensure independence of young researchers from senior PIs, (4) the ICReDD fellow system is expected to improve the gender balance of the center, and (5) it is also important for the PI to be affiliated with both the department and the center, as is currently the case in the center, to develop research.

(4) **Strengthen the research support system**: The management organization was reorganized into the Research Support Division to better clarify research support and administration. The "Executive Director" was already appointed as the "Administrative Director" to ensure stronger cooperation with the University Executive Office and to ensure that decisions made by the University are promptly reflected in the center's projects, which steadily strengthened the governance of the center. The Research Support Division was reorganized into the following four units: the "Administrative Affairs Unit", which is responsible for general affairs and accounting; the "International Planning Unit", which invites outstanding overseas researchers and students and conducts international outreach beyond the academic community in cooperation with the Institute for International Collaboration; the "Research Strategy Unit", which works with the URA and the Institute for the Promotion of Business-Regional Collaboration to obtain large-scale funds, promotes collaboration agreements with other institutions, and establish joint research projects with companies; and the "Human Resource Development Unit", which is a new unit in charge of fostering researchers, graduate students, and industrial researchers using MANABIYA, as well as creating strategies and roadmaps for the center's graduate and recurrent education. The center established this "Human Resource Development Unit" with an aim to establish a graduate school in the future. "Chemical Reaction Design and Discovery" and "MANABIYA" will also be firmly rooted in the university's organizational structure via the establishment of the "Graduate School of Chemical Reaction Design and Discovery". Since the center will have its own graduate school, which is different from the current graduate school, the ICReDD graduate school will have an influence on the development of young researchers at other research institutes, etc., and add new and attractive content such as MANABIYA, which is a laboratory visit in a different field, to the regular graduate school curriculum. Additionally, the "Fusion Research Coordinator" and "Equipment Management Center" is directly connected to the research division, so that the Center Director's policies are managed, and progress is monitored in close concert with researchers.

(5) **Prevention of research misconduct**: The center recognizes that the center bears a serious responsibility for managing the research misconduct committed by one of its past researchers. In the second half of the WPI funding period, in addition to thorough ethics education within the center (attend the center's own research ethics education seminars upon hiring and once a year on a regular basis), a new department established by hiring a researcher holding a PhD with expertise in the field will manage data on equipment at the center and check all figures for submission against the raw data, and efforts will be made to make the center a global standard in terms of research transparency. Furthermore, by facilitating an environment in which research results can be openly discussed, the center will prevent misconduct and further accelerate fusion research.

5. Efforts to Secure the Center's Future Development over the Mid- to Long-term

* Address the following items, which are essential to mid- to long-term center development:
- Future prospects with regard to the research plan, research organization and PI composition; prospects for fostering and securing of next-generation researchers
- Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure
- Measures to sustain the center as a world premier international research center after program funding ends
- Host institution's organizational reforms carried out for the center's autonomous administration simultaneously with the creation of the center.

The university highly evaluates the center's achievements and plans to expand it to other departments of the university, such as a management system that clearly separates research and administrative organization, like a Center Director and Administrative Director, a careful performance evaluation system that provides incentives to faculty members, a hospitality system that supports the daily life of foreign researchers, and the assignment of faculty members specializing in fusion research (Fusion Research Coordinator) and instrument management faculty to prevent research misconduct.

(1) **Financial support**: Since the establishment of the center, The University has strongly supported the center and has secured funds equal to or more than the WPI grant for its operation (FY2018: 358 million yen, FY2019: 1,026 million yen, FY2020: 1,388 million yen, FY2021: 1,904 million yen, FY2022: 2,657 million yen). The university also provides the center with full access to its financial infrastructure, i.e., the opportunity to request budget estimates

and to apply for competitive cross-departmental funding. The University strongly supports new developments in the center's research and, in 2022, it has accepted an estimated budget request from the center for "List-Platform" for further development of research and enhancement of domestic and international research hub functions. This budget was requested from the government, which was adopted and the platform was launched from FY2023. The university supported the formation of consortia that involve companies that collaborate with the center in order to promote industrial collaborations and established a system to attract independent funding for the center. Since June 2021, GRRM20 was launched by HPC Systems, Inc. under a program license agreement with the University, and license income has been increasing year by year. From FY2023, a five-year large-scale joint research project (250 million yen in total) with Mitsui chemicals was launched. The center will conduct recurrent education by using MANABIYA (INDUSTRY) to attract companies in related fields and expand its network in order to best match the center's research with these industries. In this way, from FY2023, the center plans to gradually become independent and secure continuous research activities by increasing the proportion of the university's voluntary cost burden.

(2) **Personnel support**: In order to ensure that the center sustainably continues its research activities independently, the university provided financial support starting for tenure positions that were offered to outstanding WPI researchers. These were appointed following a rigorous selection process based on research activities such as high-impact publications and receipt of competitive funds. Based on this plan, 4 tenure-track associate professors and 1 assistant professor have already been assigned to the center as of April 2023. Furthermore, two specially appointed faculty members will be secured in FY2023 with the establishment of the List-Platform. In the future, one regular associate professors and one post-doctoral researcher will be assigned to each senior PI of the center. Six young PIs will be assigned one post-doctoral fellow each. Taking measures to hire necessary faculty members by utilizing various financial resources such as budget requests, the university will make a gradual increasing to ten associate professors assigned to each senior PI, and 6 young PIs from FY2023.

(3) **Participation of female researchers**: The future vision of the center aims to achieve a gender balance of 25%. All PI-groups are asked to have at least one female. The university secured positions for a female assistant professor and a tenure-track associate professor. Through these positions, a career path system for female researchers from student, postdoctoral researcher, assistant professor, and associate professor (Jr. PI) to professor (PI) was established and role models were shown. Finally, they will be established as PIs of the center and inject a fresh, young perspective into the center's research direction and leadership. The center will also actively recruit female students using the University Fellowship System, and establish a strong, collaborative relationship with the Office of Diversity, Equity, and Inclusion.

(4) **Technical support**: The university established an integrated technical staff organization, the Office for Technical Support, to which technical staff members from various departments in the university were dually appointed, and the consolidation of the centralized administrative system within its operating structure strengthens the support system for cross-divisional education and research activities. In response to a request from the center, the Office for Technical Support dispatched technical staff, performing duties in cooperation with the equipment management faculty members to assist in the maintenance and management of the center's equipment (nuclear magnetic resonance equipment) under the coordination with the Equipment Management Unit. The university provided the fees required to analyze synthesized samples in the context of the center, as well as the usage fees for the open facility system, which provides access to cutting-edge equipment such as high-resolution NMR spectrometers that are managed by the university (FY2019: 850 thousand yen; FY2020: 1 million yen; FY2021: 2.5 million yen; FY2022: 2.3 million yen)

(5) **Establishment of graduate school**: From FY2023, the reorganization and integration of existing graduate schools in order to establish of the graduate school of "Chemical Reaction Design and Discovery" will be implemented, with plans to cement "Chemical Reaction Design and Discovery" and "MANABIYA" as educational organizations of the university. In order to incorporate the world's most advanced research back into educational programs, the university plans to establish a system for cross-disciplinary and interdisciplinary education that is not bound by the framework of existing research institutes and graduate schools. The center established the " Human Resource Development Unit" to design a human resource development framework that will function as a model case for next-generation higher education through a multilateral approach for students and working people regardless of national or international affiliation. From FY2023, the university already hired a full professor and specialized faculty with extensive teaching and research experience for the Human Resource Development Unit. No other international research institute in the university has such a human resource development unit, and this organizational reform will also lead to the center's further development as a research center to foster young researchers, which would contribute to the reformation of the entire university. Furthermore, the educational reform of a research institution having its own graduate school is worthy of attention not only for its impact within the university but also outside the university, and as an attempt to foster human resources to take responsibility for

the world-leading-edge research.

(6) **Research space**: The university already provided 2,600 m^2 of ICReDD space in the CRIS building and pays for the use of the space, including utilities. The center's research space was expanded from 2,600m^2 to 8,100m^2 in February 2023.The University provided land on the north side of the campus, where the CRIS building and industry-academia collaboration research facilities are concentrated, and a new research building (4 floors, 5,500 m^2) was completed, creating an environment where a total of over 100 researchers can conduct research under one roof. This includes an animal laboratory, an industry-academia collaboration laboratory and a fusion research office where 90 researchers can research in a single space.

6. Others

* Describe what was accomplished in the center's outreach activities last year and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.
* In addition to the above 1-5 viewpoints, if there is anything else that deserves mention regarding the center project's progress, note it.

(1) Each fiscal year, the center has held the ICReDD international symposium, inviting researchers from Japan and overseas to introduce them to the vision and research of the center. In 2021, the center established the Akira Suzuki and ICReDD Awards, which honor prominent chemists in both experimental chemistry and computational chemistry or information science. The 2nd annual awards were given to Professor Joh F. Hartwig from UC Berkeley and Professor Kendall N. Houk from UCLA. Despite the U.S. time zone (mid-night in Japan), the 2nd Akira Suzuki Awards Ceremony & the 5th ICReDD International Symposium had 361 registrations (59 overseas registrations from 19 countries), 115 live participants (103 domestic and 12 overseas), 36 poster sessions and numerous on-demand viewers. As a result of a Twitter campaign using @ function to mention the recipients' departments, tweets about the Akira Suzuki Award ceremony were retweeted multiple times by prestigious universities abroad (UCLA, UC-Berkeley), reaching over 20,000 impressions in total and connecting the center's brand with a more international audience. Furthermore, by holding a Special Lecture with Nobel Laureate Professor List on September 22 at Hokkaido University, the center increased recognition of the center within the university (100 in-person participants) and among other universities and in industry in Japan and abroad (177 online participants).

(2) The center has world-class researchers as Principal Investigators (PIs) and has received outstanding awards such as APS 2023 Polymer Physics Prize (Gong). In FY2022, the center members have presented their research in 28 invited lectures at international conferences and 17 awards have been granted.

(3) Since 2018, the center has created a number of promotional materials, including an institute pamphlet and a recruiting brochure targeted at overseas researchers. An English language Annual Report brochure for FY2022 was created to convey the vision and recent progress of the center to domestic and international audiences. the center's goods were created to attract attention to our booth at events, including pens, Clear files, and notepads, as well as outreach-focused handouts like our unique "word reactor" and "periodic table pen stand". These items have been handed out at many events such as outreach events like the WPI Science Symposium to inspire high school students.

(4) The center has published a "Monthly Research News Postcard" that provides monthly research highlights, a "Quarterly News Poster" that presents research content in an easy-to-understand manner, and an "Annual Report" to provide information on the center's annual research activities. Information was widely disseminated domestically and internationally. Our monthly research news postcard series promote our latest research to a mailing list of hundreds of people, including over 70 international addresses. A unique endeavor at the center is our quarterly news poster "The CATALYST", which explains concepts of chemistry in an easy-to-understand manner, while also introducing the center research to a high school level, non-scientist audience via a mailing list of 220. In FY 2023, 4 issues have been issued, including "How light interacts with molecules", "The strength and utility of polymers", "Chemistry in medicine", and "Controlling chemical reactions with temperature".

(5) The center also promotes itself on social media, including Facebook, Twitter, LinkedIn and Instagram. A recent effort has been made to more actively promote the center research on the center website and on Twitter. As a result of focusing on disseminating new research, 10 English language press releases were distributed to news platforms, resulting in an estimated 7.75 million views. The center HP coverage (10 English releases plus 15 highlight articles) resulted in 5400 unique pageviews, with over 700 people driven directly from Tweets about research.

(6) In addition to promoting research results on the center's website and SNS, a promotional video was created to introduce ICReDD's new building and is shown at our entrance hall. From FY2022, the center strengthened international public relations in collaboration with the University's Public Relations Office and launched fundraising activities, including the creation of a mechanism to obtain external funding.

7. Center's Response to Results of Last Year's Follow-up

* Transcribe the item from the "Actions required and recommendations" section in the site visit report and the Follow-up report, then note how the center has responded to them.
* If you have already provided this information, indicate where in the report.

1) ICReDD needs to set explicitly its goals and roadmaps for the Flagship Projects and the bottom-up projects. What has been achieved in the last 5 years and what is expected in the 2nd half of the funding period should be clearly articulated.

Project I is the most important project in the center because it is closely related to all the other projects and provides computational acceleration tools for them. All computational and informatics groups come together to share successes and failures based on their contributions to the other flagship projects. This feedback loop allows us to stay abreast of the latest state-of-the-art computational and informatics tools being used in these projects and helps us to further develop these tools.

The other projects have a hierarchical complexity. The complexity increases in the order of the project number. In the second half of the WPI period, the center will focus more on systems of higher complexity.

Project-II: New reaction design and discovery from scratch. So far, the center has demonstrated multiple successful examples of (non-catalytic) small molecule synthesis. Going forward, the center will be focusing our efforts on discovering organometallic catalysts that can achieve previously unexplored chemical transformations within this framework.

Project-III: Catalyst design and discovery through screening. The project entails finding the optimal catalyst's ligands and substituents through a computation-aided screening process. For example, the center aims to enhance the enantioselectivity of List's IDPi catalyst for various chemical transformations by utilizing a computation- and informatics-based approach to screen and optimize the catalyst's substituents.

Project-IV: Exploration of mechanochemical synthesis. Project IV focuses on mechanochemical synthesis using ball mills. This synthetic method has emerged as a highly promising tool in organic synthesis. However, its applicability and understanding have not been sufficiently explored yet. The goal of this project is to broaden its applicability, elucidate unexpected species unique to this synthesis, construct a theory for modeling the influences of mechanical impacts, and more.

Project-V: Understanding and controlling polymer properties, formation, and degradation. The project involves the design of polymer properties through simulation, visualization of polymer mechanoradicals, utilization of polymer mechanoradicals, the design of polymer sequences to maximize desired properties, and more. Two specific examples of our goals are to enhance the performance of muscle-like double-network hydrogels and to utilize plastic materials in the synthesis of useful materials.

Project-VI: Cancer diagnosis utilizing new materials and measurement techniques. The project focuses on developing cancer diagnosis methods that utilize new materials and measurement techniques. Specifically, the center will be conducting further research on the hydrogel-activated reprogramming phenomenon (HARP), which was discovered during the first half of the WPI period. Understanding HARP and its potential clinical applications are urgent topics to be addressed in this project, through a fusion team among materials scientists, informaticians, and medical doctors.

2) To elucidate the nature of the cancer stem cells that ICReDD has derived from their interactions with hydrogels, closer collaborations with experts in fundamental cancer biology and pathology are needed.

In collaboration with Dr. Mano, Director of the National Cancer Center, the effectiveness of the rapid cancer stem cell generation method using double network hydrogel (Hydrogel Activated Reprograming (HARP) phenomenon) was confirmed. The results confirmed that cancer stem cells obtained by this method have the same profile as those obtained by conventional methods. In order to further accelerate fusion research between chemistry and clinical medicine, the center has changed experimental science PIs from Prof. Sawamura to Prof. Ogawa (Chemical Biology) in FY2023 to realize efficient cancer treatment methods based on detailed chemical manipulations. In partnership with the School of Medical Science, the center has launched a consortium called the Clinical Platform for Chemical Reaction Collaboration. Through this consortium, the center aims to accelerate the use of our chemical products in medical diagnosis and treatment.

3) In its support plan, Hokkaido University should make clear whether the 10 senior PI positions belong to ICReDD.

After the funding period from WPI, the center will be established as a permanent research institute at Hokkaido University. Unlike conventional research institutes, the center will implement a dynamic personnel appointment system. This means that senior PIs at the center will have two laboratories:

one at the center and the other in a different department of Hokkaido University or a top institute outside of Hokkaido University. The university will provide one associate professor and one postdoctoral fellow to each senior PI's laboratory and support their activities at the center. Ten senior PI laboratories will be created in the center, and the budget to hire additional staffs (ten associate professors and ten postdoctoral fellows in total) will be covered by Hokkaido University. These ten senior PIs are top-level researchers who undergo annual evaluations and may be replaced based on their performance to ensure that the center maintains the highest level of excellence. From FY2023, the center established a new position called the ICReDD fellow as an incubation system for next PIs. When a senior PI is replaced or new research areas will need to be developed, the most suitable ICReDD fellow will be selected. In addition, the center plans to establish approximately six junior PI groups, led by rising stars in related fields. These junior PIs will be recruited from top institutes abroad and appointed as tenure-track associate professors. After several years, they are expected to become full professors in the other department of Hokkaido University after obtaining tenure, or to secure tenured positions at top institutes abroad. The university will provide each junior PI group with one postdoctoral fellow and a budget for managing their groups. Hokkaido University will cover the costs required to establish the junior PI groups, including the employment costs of the junior PIs. With this dynamic personnel circulation system, the center will maintain the highest level of scientific excellence always.

4) ICReDD needs to provide a clear strategy for balancing academic leadership with responsiveness to industry and commercialization opportunities. It is important for the Center to show that it has a strategy for maximizing its impact—both in terms of the academic world and in practical terms.

Since June 2021, "GRRM20" was launched from HPC Systems, Inc. under a program license agreement with the University, in which the latest features of the AFIR method are available. GRRM20 is a "technology needed in society" that companies also need, and selling it is one of the center's contributions to society. The center already established a system for the use of this program in MANABIYA (INDUSTRY). In FY2022, the center has launched a consortium called the "Clinical Platform for Chemical Reaction Collaboration" in partnership with the School of Medical Science. Through this consortium, the center aims to accelerate the utilization of our chemical products in medical diagnosis and treatment. Furthermore, the center has just launched the "List-DX Catalyst Collaboration Research Platform (List-Platform)" and the "Mitsui Chemicals-ICReDD Innovative Chemical Reaction Design Laboratory (Mitsui Chemicals-ICReDD Laboratory)" in FY2023. These initiatives will assist quick implementation of our research outputs in social and industrial applications.

The List-Platform will be headed by Professor List, a Nobel laureate, and will promote next generation organocatalytic chemistry that integrates computational science with digital transformation (DX) technologies such as robotics, machine learning, and artificial intelligence by applying the advanced technologies of the center, which combine computational science, information science, and experimental science. The List-Platform will establish five research groups, starting with basic theoretical research and extending to catalyst development, evaluation and optimization, drug discovery and materials development, and synthetic process development, and will mobilize the collective efforts of top-level researchers inside and outside the university. Furthermore, the center will invite world-class researchers from Japan and abroad as fellows to provide advice on research and share research results widely, aiming to become a leading international research exchange center for sustainable DX organocatalytic chemistry research.

In addition, the center will also strengthen industry-academia collaboration by working to solve problems in industry and promote demonstration experiments and social implementation. From FY2023, "Mitsui Chemicals-ICReDD Laboratory" was started for joint research focused on the swift, high-precision design of new reactions that will contribute to the development of high-performance materials and the creation of a recycling-oriented society, based on the center's strength in chemical reaction design and discovery, which integrates the three fields of computational science, information science, and experimental science, and Mitsui Chemicals' knowledge of materials development. Additionally, efforts will focus on achieving further advances in chemical reaction design and discovery via research and development of new computational science and information science technologies.

5) Hokkaido University is asked to submit an official report to the WPI Program Committee on the findings of its investigation on the scientific misconduct that occurred at ICReDD and on the reforms that the university will undertake to prevent reoccurrences.

Hokkaido University will submit an official report to the WPI Program Committee on the findings of its investigation on the scientific misconduct that occurred at the center and on the reforms that the university will undertake to prevent reoccurrences. Now, this report was reviewed by MEXT, JSPS, and Japan Science and Technology Agency (JST), and will be open and submit to WPI program committee after revising around June.

Appendix 1 FY 2022 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2022. (Note: The list should be for the calendar year, not the fiscal year.)

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

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

(2) Method of listing paper
   - List only refereed papers. Divide them into categories (e.g., original articles, reviews, proceedings).
   - For each, write the author name(s); year of publication; journal name, volume, page(s) (or DOI number), and article title. Any listing order may be used as long as format is consistent. (The names of the center researchers do not need to be underlined.)
   - If a paper has many authors (say, more than 10), all of their names do not need to be listed.
   - Assign a serial number to each paper to be used to identify it throughout the report.
   - If the papers are written in languages other than English, underline their serial numbers.
   - Order of Listing
      A. WPI papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles

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

(3) Submission of electronic data
   - In addition to the above, provide a .csv file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
   - The papers should be divided into A or B categories on separate sheets, not divided by paper categories.

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

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

A. WPI papers

1. Original articles

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4. Other English articles

(154) Keshavamurthy, S.; Komatsuzaki, T.; Leitner, D. Richard Stephen Berry (1931-2020). Resonance-Journal of Science Education 2022, 27 (1), 11-17, Biographical-Item. DOI: 10.1007/s12045-022-1290-9.

(155) Konishi, T.; Takahashi, Y.; Kazui, S.; Yasui, Y.; Saiin, K.; Naito, S.; Takenaka, S.; Mizuguchi, Y.; Tada, A.; Kobayashi, Y.; et al. Neoatherosclerosis with silent plaque rupture in a saphenous vein graft causing no re-flow phenomenon assessed by optical coherence tomography and histopathology. Cardiology Journal 2022, 29 (4), 718-719, Editorial Material. DOI: 10.5603/cj.2022.0063.

(156) Nagata, Y. Young Career Focus: Professor Yuuya Nagata (Hokkaido University, Sapporo, Japan). Synlett 2022, 33 (01), A3-A4, Editorial Material. DOI: 10.1055/s-0040-1720546.

(157) Taketsugu, T.; Ootani, Y. “Trajectory on-the-fly Molecular Dynamics Approach to Tunneling

Splitting in the Electronic Ground and Excited States in "Spectroscopy and Computation of Hydrogen-Bonded Systems" ed. M.J. Wojcik and Y. Ozaki, chapter 3, pp65-80, Wiley-VCH GmbH, 2022.

(158) Taketsugu, T.; Tsutsumi, T.; Harabuchi, Y.; Tsuneda, T. On-the-fly excited-state molecular dynamics study based on spin-flip TDDFT approach: photo-branching reaction of stilbene and stilbene derivatives in "Time-Dependent Density Functional Theory: Nonadiabatic Molecular Dynamics" ed. C. Zhu, chapter 2, pp38-72, Jenny Stanford Publishing, Singapore, 2022.

B. WPI-related papers

1. Original article

(159) Bilchak, C.R.; Jhalaria, M.; Adhikari, S; Midya, J.; Huan, Y.; Abbas, Z.; Nikoubashman, A.; Benicewicz, B.C.; Rubinstein, M.; Kumar, S.K. Understanding Gas Transport in Polymer-Grafted Nanoparticle Assemblies. Macromolecules, 2022, 55, 3011-3019. DOI: 10.1021/acs.macromol.1c02367

(160) Duan, M.; Díaz-Oviedo, C. D.; Zhou, Y.; Chen, X.; Yu , P.; List, B.; Houk, K. N.; Lan, Y. Chiral Phosphoric Acid Catalyzed Conversion of Epoxides into Thiiranes: Mechanism, Stereochemical Model, and New Catalyst Design. Angewandte Chemie International Edition 2022, 61, e202113204. DOI: 10.1002/anie.202113204

(161) Grest, G.S.; Ge, T.; Plimpton, S.J.; Rubinstein, M.; O'Connor, T.C. Entropic Mixing of Ring/Linear Polymer Blends. ACS Polymers Au, 2023, 3, 209-216. DOI: 10.1021/acspolymersau.2c00050

(162) Ghosh, S.; Erchinger, J. E.; Maji, R.; List, B. Catalytic Asymmetric Spirocyclizing Diels–Alder Reactions of Enones: Stereoselective Total and Formal Syntheses of α-Chamigrene, β-Chamigrene, Laurencenone C, Colletoic Acid, and Omphalic Acid. Journal of the American Chemical Society 2022, 144, 6703–6708. DOI: 10.1021/jacs.2c01971

(163) Hill, D.B.; Button, B.; Rubinstein, M.; Boucher, R.C. Physiology and Pathophysiology of Human airway Mucus. Physiological Reviews, 2022, 102 (4), 1757-1836. DOI: 10.1152/physrev.00004.2021

(164) Kato, T.; Radicioni, G.; Papanikolas, M.J.; Stoychev, G.V.; Markovetz, M.R.; Aoki, K.; Porterfield, M.; Okuda, K.; Barbosa Cardenas, S.M.; Gilmore, R.C.; Morrison, C.B.; Ehre, C.; Burns, K.A.; White, K.K.; Brennan, T.A.; Goodell, H.P.; Thacker, H.; Loznev, H.T.; Forsberg, L.J.; Nagase, T.; Rubinstein, M.; Randell, S.H.; Tiemeyer, M.; Hill, D.B.; Kesimer, M.; O'Neal, W.; Ballard, S.T.; Freeman, R.; Button, B.; Boucher, R. Mucus Concentration-Dependent Biophysical Abnormalities Unify Submucosal Gland and Superficial Airway Dysfunction in Cystic Fibrosis. Science Advances, 2022, 8, eabm9718. DOI: 10.1126/sciadv.abm9718

(165) Obradors, C.; Mitschke, B.; Aukland, M. H.; Leutzsch, M.; Grossmann, O.; Brunen, S.; Schwengers, S. A.; List, B. Direct and Catalytic C-Glycosylation of Arenes: Expeditious

Synthesis of the Remdesivir Nucleoside. Angewandte Chemie International Edition 2022, 61, e202114619. DOI:10.1002/anie.202114619

(166) Scharf, M. J.; List, B. A Catalytic Asymmetric Pictet–Spengler Platform as a Biomimetic Diversification Strategy Toward Naturally Occurring Alkaloids. Journal of the American Chemical Society 2022, 144, 15451–15456. DOI: 10.1021/jacs.2c06664

(167) Yamaguchi, Y.; Seino, Y.; Suzuki, A.; Kamei, Y.; Yoshino, T.; Kojima, M.; Matsunaga, S. Intramolecular Hydrogen Atom Transfer Hydroarylation of Alkenes toward delta-Lactams Using Cobalt-Photoredox Dual Catalysis. Organic Letters 2022, 24 (12), 2441-2445, Article. DOI: 10.1021/acs.orglett.2c00700.

(168) Zhou, H.; Zhou, Y.; Bae, H. Y.; Leutzsch, M.; Li, Y.; De, C. K.; Cheng, G.-J.; List, B. Organocatalytic Stereoselective Cyanosilylation of Small Ketones. Nature 2022, 605, 84–89. DOI: 10.1038/s41586-022-04531-5

2. Review articles
3. Proceedings
4. Other English articles

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

- List up to 10 main presentations during FY 2022 in order from most recent.
- For each, write the date(s), lecturer/presenter's name, presentation title, and conference name.

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
March 27, 2023	Yasuchika Hasegawa	Luminescent lanthanide coordination polymers and aggregates for future photonic materials	Aggregate webinar series 'Recent Progress in Developing Advanced Luminescent Materials'
March 26-30, 2023	M. Rubinstein	Conformation and dynamics of Active and Passive Associating Polymers	Division of Polymer Science & Engineering, ACS Spring Meeting, Indianapolis, IN
March 26-30, 2023	Ichigaku Takigawa	Exploring Practices in Machine Learning and Machine Discovery for Heterogeneous Catalysis	ACS Spring 2023 Symposium on AI-Accelerated Scientific Workflow, ACS 2023 Spring National Meeting, Indianapolis, USA
March 7, 2023	Jian Ping Gong	Toughening hydrogels with sacrificial bonds	APS Annual Meeting
March 7, 2023	M. Rubinstein	Three Faces of Polymer Entanglements	Division of Polymer Physics, American Physical Society Meeting, Las Vegas, NV
Feb. 19-23, 2023	Tetsuya Taketsugu	Understanding of chemical reaction mechanism and dynamics in terms of natural reaction orbital (NRO) and reaction space projector (ReSPer) approaches	10th Asia Pacific Association of Theoretical and Computational Chemists Conference (10th APATCC), Qui Nhon, Vietnam

Jan. 26, 2023	Jian Ping Gong	Challenges and Opportunities of Hydrogels	POLY-CHAR 2023
Nov. 25, 2022	Tasuku Nakajima	Self-Growing Gels Inspired by Metabolism	International Congress on Pure & Applied Chemistry (ICPAC) KK 2022, Sabah, Malaysia, （Online）
Jul. 14, 2022	Yasuhide Inokuma	Calix[3]pyrrole: Synthesis and strain induced reactions	Twelfth International Conference on Porphyrins and Phthalocyanines
Apr. 23, 2022	Jian Ping Gong	Force-triggered growth of double network hydrogels based on bond cleavage-induced polymerization	Accounts of Materials Research: Asia-Pacific Summit

3. Major Awards

- List up to 10 main awards received during FY 2022 in order from the most recent.
- For each, write the date issued, the recipient's name, and the name of award.
- In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
March 6, 2023	Jian Ping Gong	APS 2023 Polymer Physics Prize
Jan. 6, 2023	Nobuya Tsuji	The 2023 Thieme Chemistry Journals Award
Dec. 21, 2022	Koji Kubota	The Chemical Society of Japan Award for Young Chemists for 2022
Nov. 29, 2022	Andrey Lyalin	The 17th round of HPC Innovation Excellence Awards
Nov. 28, 2022	Ichigaku Takigawa	Top reviewer (Top 10%), The 36th Conference on Neural Information Processing Systems (NeurIPS 2022)
Oct. 1, 2022	Shinya Tanaka	The Hokkaido Medical Association Award and Hokkaido Governor's Award

Jul. 17, 2022	Ichigaku Takigawa	Outstanding reviewer (Top 10%), The 39th International Conference on Machine Learning (ICML 2022).
May 12, 2022	Tasuku Nakajima	The SRJ Young Researcher Award for 2021
Apr. 25, 2022	Ichigaku Takigawa	Highlighted reviewer, ICLR 2022. The 10th International Conference on Learning Representations (ICLR 2022).
Apr. 1, 2022	Yasuhide Inokuma	Research Promotion Award of NAGASE Science Technology Foundation

Appendix 2　FY 2022 List of Principal Investigators

NOTE:

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

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

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

<Results at the end of FY2022> **Principal Investigators Total: 15**

Name	Age	Affiliation (Position title, department, organization)	Academic degree, Specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center Director Satoshi MAEDA	43	Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Science, Hokkaido University	Ph.D., Computational Chemistry	80	October 2018	Usually stays at the center	
Tetsuya TAKETSUGU	58	Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Science, Hokkaido University	Ph.D., Quantum Chemistry	80	October 2018	Usually stays at the center	
Michael RUBINSTEIN	66	Professor, Duke University	Ph.D., Polymer Physics	20	October 2018	- Primarily stays at Partner institution - attends meeting (by online)	- Conducting interdisciplinary research - Recruitment of young researchers
Masaharu YOSHIOKA	54	Professor, Institute for Chemical Reaction Design and Discovery / Graduate School of Information Science and Technology, Hokkaido University	Doctor of Engineering, Knowledge Engineering	20	January 2020	Usually stays at the center	
Alexandre VARNEK	67	Professor, University of Strasbourg	Ph.D., Chemoinformatics	20	October 2018	- Primarily stays at Partner institution - attends meeting (by online)	- Conducting interdisciplinary research - Recruitment of young researchers
Ichigaku TAKIGAWA	46	Specially Appointed Professor, Institute for Chemical Reaction Design and Discovery, Hokkaido University Program-Specific Professor,Center for Innovative Research and Education in Data Science, Institute for Liberal Arts and Sciences, Kyoto University	Ph.D., Machine Learning	20	October 2018	- Generally stays at the center once a month (In FY 2020, due to COVID-19, participates in mainly by online) - attends meeting (by online)	
Tamiki KOMATSUZAKI	58	Professor, Institute for Chemical Reaction Design and Discovery / Research Center of Mathematics for Social Creativity, Research Institute for Electronic Science, Hokkaido University	Ph.D., Mathematical Science	80	October 2018	Usually stays at the center	
Satoru IWATA	54	Specially Appointed Professor, Institute for Chemical Reaction Design and Discovery, Hokkaido University Professor, Graduate School of Information Science and Technology, The University of Tokyo	Doctor of Science, Mathematical Engineering	20	November 2020	- Generally stays at the center once a month (In FY 2020, due to COVID-19, participates in mainly by online) - attends meeting (by online)	
Hajime ITO	55	Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Engineering, Hokkaido University	Doctor of Engineering, Synthetic Chemistry	80	October 2018	Usually stays at the center	
Masaya SAWAMURA	61	Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Science, Hokkaido University	Doctor of Engineering, Catalysis	80	October 2018	Usually stays at the center	
Benjamin LIST	55	Specially Appointed Professor, Institute for Chemical Reaction Design and Discovery, Hokkaido University Professor and Director, Max Planck Institute for Coal Research	Ph.D., Reaction Design	20	October 2018	- Primarily stays at Partner institution - attends meeting (by online)	- Conducting interdisciplinary research - Recruitment of young researchers
Yasuchika HASEGAWA	54	Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Engineering, Hokkaido University	Ph.D., Optical Materials Science	80	October 2018	Usually stays at the center	
Yasuhide INOKUMA	41	Associate Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Engineering, Hokkaido University	Ph.D., Structural Chemistry	80	October 2018	Usually stays at the center	
Jian Ping GONG	61	Professor, Institute for Chemical Reaction Design and Discovery / Faculty of Advanced Life Science, Hokkaido University	Doctor of Science, Doctor of Engineering, Polymer Chemistry	80	October 2018	Usually stays at the center	
Shinya TANAKA	58	Professor, Institute for Chemical Reaction Design and Discovery / Global Institution for Collaborative Research and Education / Faculty of Medicine, Hokkaido University	M.D., Ph.D., Tumor Pathology	80	October 2018	Usually stays at the center	

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

Principal investigators unable to participate in project in FY 2022

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

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age) **Ogawa Mikako (49)**

Affiliation and position (Position title, department, organization, etc.)
Professor
Institute for Chemical Reaction Design and Discovery, Hokkaido University, Japan
Graduate School of Pharmaceutical Sciences, Hokkaido University, Japan

Academic degree and specialty
Ph. D (Dr of Pharmaceutical Sciences), Kyoto University
Life sciences / Pharmaceuticals - analytical and physicochemistry

Effort **80 %**
* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history
1998.3 Bachelor of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Kyoto University
2000.3 Master of Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, Kyoto University
2007.1 Ph. D (Dr of Pharmaceutical Sciences), Kyoto University

2000.4. - 2001.9 Research Assistant, Department of Biofunctional Research, National Institute for Longevity Sciences
2001.10. - 2002.9 Research Scientist, Department of Investigative Radiology, National Cardio Vascular Center Research Institute
2002.10. - 2007.8 Assistant Professor, Photon Medical Research Center, Hamamatsu University School of Medicine
2007.9. - 2009.5 Visiting Fellow, Molecular Imaging Program, NCI/NIH
2009.6. - 2010.2 Assistant Professor, Medical Photonics Research Center, Hamamatsu University School of Medicine
2010.3. - 2015.3 Associate Professor, Medical Photonics Research Center, Hamamatsu University School of Medicine
2015.4. – present Professor, Graduate School of Pharmaceutical Sciences, Hokkaido University
2023.4. – present Professor, Principal Investigator, Institute for Chemical Reaction Design and Discovery, Hokkaido University

Achievements and highlights of past research activities
- She showed that atherosclerotic plaque instability can be quantitatively assessed with [18F]FDG. She received 2004 and 2006 First Place Award Outstanding Basic Science Investigations, Alavi-Mandell Award (2004, 2006), and SNM Cardiovascular Council First Place Basic Science Young Investigators Award (2006) from Society of Nuclear Medicine.
- She developed many activatable fluorescent imaging agents, based on FRET, pai-electron stacking, pH activation, etc., when she was a postdoc at NIH. She received Fellow award of research excellence from NIH (2008), Student Travel Award from Society of Molecular Imaging (2009), and First Place Poster in Molecular Imaging Track from Society of Nuclear Medicine (2010).
- She discovered a compound that is toxic only to cancer cells when irradiated with near-

infrared light. Photoimmuno therapy (PIT) using this compound has been investigated by Dr. Kobayashi at NIH, who is a co-investigator, and was conditionally approved in Japan in 2020, ahead of any other country in the world.

Achievements

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

a) Recipient of international awards

2004 First Place Award Outstanding Basic Science Investigations (Society of Nuclear Medicine), June 2005.
Alavi-Mandell Award (Society of Nuclear Medicine), June 2005.
SNM Cardiovascular Council First Place Basic Science Young Investigators Award (Society of Nuclear Medicine), June 2006.
2006 First Place Award Outstanding Basic Science Investigations (Society of Nuclear Medicine), June 2007.
Alavi-Mandell Award (Society of Nuclear Medicine), June 2007.
First Place Poster in Molecular Imaging Track (Society of Nuclear Medicine), June 2010.

b) Member of a scholarly academy in a major country

N/A

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

Invited speaker:

1. Activation of compounds in vivo using light, OPIC 2023, Yokohama, Apr. 2023.
2. Evaluation of Cancer Immunity and Development of Novel Radiolabeling Method with Astatin-211, EFMC-ISMC2022 (XXVII EFMC International Symposium on Medicinal Chemistry), Online, Sep. 2022.
3. Cytotoxic mechanism of near-infrared photoimmunotherapy (NIR-PIT), Pacifichem, Online, Dec. 2021.
4. Evaluation of energy metabolism in tumor microenvironment with [18F]FDG, and development of a new 18F-probe for evaluation of lactate metabolism, Pacifichem, Online, Dec. 2021.
5. Basics of PET imaging probes for atherosclerosis imaging, IAEA Workshop, Nagoya, Nov. 2021.
6. Evaluation of tumor microenvironment with [18F]FDG after immune checkpoint therapies, and development of a new 18F-probe for evaluation of lactate metabolism, The 11th China-Japan-Korea Symposium on Radiopharmaceutical Sciences (CJKSRS 2021), Online, Nov. 2021.
7. Cancer targeted phototherapy, based on photo-chemical reaction, The 7th international ALA and Porphyrin Symposium, Sapporo, Dec. 2019.
8. New cancer therapy using near infrared light, VI International Symposium Topical problems of biophotonics, St. Petersburg, Aug. 2017.
9. In vivo molecular imaging with fluorescence and Cerenkov luminescence, XVII International Symposium on Luminescence Spectrometry, Taipei, Nov. 2016.

d) Editor of an international academic journal

American Journal of Nuclear Medicine and Molecular Imaging, Senior Editorial Board

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

N/A

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

Project for Medical Device and Healthcare, AMED, 22hma322001h0001, 2022.12-2025.3
Grant-in-Aid for Scientific Research (B), JSPS, 22H03009, 2022.4—2026.3.
Grant-in-Aid for Scientific Research (B), JSPS, 19H03593, 2019.4—2022.3.
Grant-in-Aid for Scientific Research (B), JSPS, 16H05382, 2016.4—2019.3.
CREST, JST, JPMJCR1902, 2019.10—2025.3.
PREST, JST, JPMJPR15P5, 2015.10—2019.3.

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

1. Kobayashi H, Ogawa M, Alford R, Choyke PL, Urano Y. New strategies for fluorescent probe design in medical diagnostic imaging. Chem Rev 110(5), 2620-2640 (2009). [2140]

2. Mitsunaga M, Ogawa M, Kosaka N, Rosenblum LT, Choyke PL, Kobayashi H. Cancer cell-selective in vivo near infrared photoimmunotherapy targeting specific membrane molecules. Nat Med 17(12), 1685-1691 (2011). [913]
3. Urano Y, Sakabe M, Kosaka N, Ogawa M, Mitsunaga M, Asanuma D, Kamiya M, Young MR, Nagano T, Choyke PL, Kobayashi H. Rapid cancer detection by topically spraying a gamma-glutamyltranspeptidase-activated fluorescent probe. Sci Transl Med 3(110), 110ra119 (2011). [432]
4. Ogawa M, Ishino S, Mukai T, Asano D, Teramoto N, Watabe H, Kudomi N, Shiomi M, Magata Y, Iida H, Saji H. (18)F-FDG accumulation in atherosclerotic plaques: immunohistochemical and PET imaging study. J Nucl Med 45(7), 1245-1250 (2004). [415]
5. Asanuma D, Sakabe M, Kamiya M, Yamamoto K, Hiratake J, Ogawa M, Kosaka N, Choyke PL, Nagano T, Kobayashi H, Urano Y. Sensitive beta-galactosidase-targeting fluorescence probe for visualizing small peritoneal metastatic tumours in vivo. Nat Commun 6(6463 (2015). [294]
6. Kobayashi H, Longmire MR, Ogawa M, Choyke PL. Rational chemical design of the next generation of molecular imaging probes based on physics and biology: mixing modalities, colors and signals. Chem Soc Rev 40(9), 4626-4648 (2011). [230]
7. Longmire MR, Ogawa M, Choyke PL, Kobayashi H. Biologically optimized nanosized molecules and particles: more than just size. Bioconjug Chem 22(6), 993-1000 (2011). [187]
8. Ogawa M, Kosaka N, Choyke PL, Kobayashi H. H-type dimer formation of fluorophores: a mechanism for activatable, in vivo optical molecular imaging. ACS Chem Biol 4(7), 535-546 (2009). [178]
9. Ogawa M, Tomita Y, Nakamura Y, Lee MJ, Lee S, Tomita S, Nagaya T, Sato K, Yamauchi T, Iwai H, Kumar A, Haystead T, Shroff H, Choyke PL, Trepel JB, Kobayashi H. Immunogenic cancer cell death selectively induced by near infrared photoimmunotherapy initiates host tumor immunity. Oncotarget 8(6), 10425-10436 (2017). [177]
10. Sato K, Ando K, Okuyama S, Moriguchi S, Ogura T, Totoki S, Hanaoka H, Nagaya T, Kokawa R, Takakura H, Nishimura M, Hasegawa Y, Choyke PL, Ogawa M, Kobayashi H. Photoinduced Ligand Release from a Silicon Phthalocyanine Dye Conjugated with Monoclonal Antibodies: A Mechanism of Cancer Cell Cytotoxicity after Near-Infrared Photoimmunotherapy. ACS Cent Sci 4(11), 1559-1569 (2018). [160]
11. Ogawa M, Magata Y, Kato T, Hatano K, Ishino S, Mukai T, Shiomi M, Ito K, Saji H. Application of 18F-FDG PET for monitoring the therapeutic effect of antiinflammatory drugs on stabilization of vulnerable atherosclerotic plaques. J Nucl Med 47(11), 1845-1850 (2006). [155]
12. Ogawa M, Kosaka N, Longmire MR, Urano Y, Choyke PL, Kobayashi H. Fluorophore-quencher based activatable targeted optical probes for detecting in vivo cancer metastases. Mol Pharm 6(2), 386-395 (2009). [115]
13. Ogawa M, Regino CA, Choyke PL, Kobayashi H. In vivo target-specific activatable near-infrared optical labeling of humanized monoclonal antibodies. Mol Cancer Ther 8(1), 232-239 (2009). [111]
14. Ogawa M, Regino CA, Seidel J, Green MV, Xi W, Williams M, Kosaka N, Choyke PL, Kobayashi H. Dual-modality molecular imaging using antibodies labeled with activatable fluorescence and a radionuclide for specific and quantitative targeted cancer detection. Bioconjug Chem 20(11), 2177-2184 (2009). [109]
15. Satomi T, Ogawa M, Mori I, Ishino S, Kubo K, Magata Y, Nishimoto T. Comparison of Contrast Agents for Atherosclerosis Imaging Using Cultured Macrophages: FDG Versus Ultrasmall Superparamagnetic Iron Oxide. J Nucl Med 54(6), 999-1004 (2013). [91]

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

N/A

Appendix 3-1 FY 2022 Records of Center Activities

1. Researchers and center staff, satellites, partner institutions

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

- Regarding the number of researchers at the Center, fill in the table in Appendix 3-1a.

Special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working on the global circulation of world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established overseas, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
University of Strasbourg	Alexandre Varnek	
Max Planck Institute for Coal Research	Benjamin List	
Duke University	Michael Rubinstein	
ESPCI		
Swiss Federal Institute of Technology in Zurich		
Peking University		
Kyoto University, Graduate School of Informatics		
Chubu University, Molecular Catalyst Research Center		
The University of Tokyo, Graduate School of Information Science and Technology	Satoru Iwata	
Stockholm University		
University of Oslo		

2. Holding international research meetings

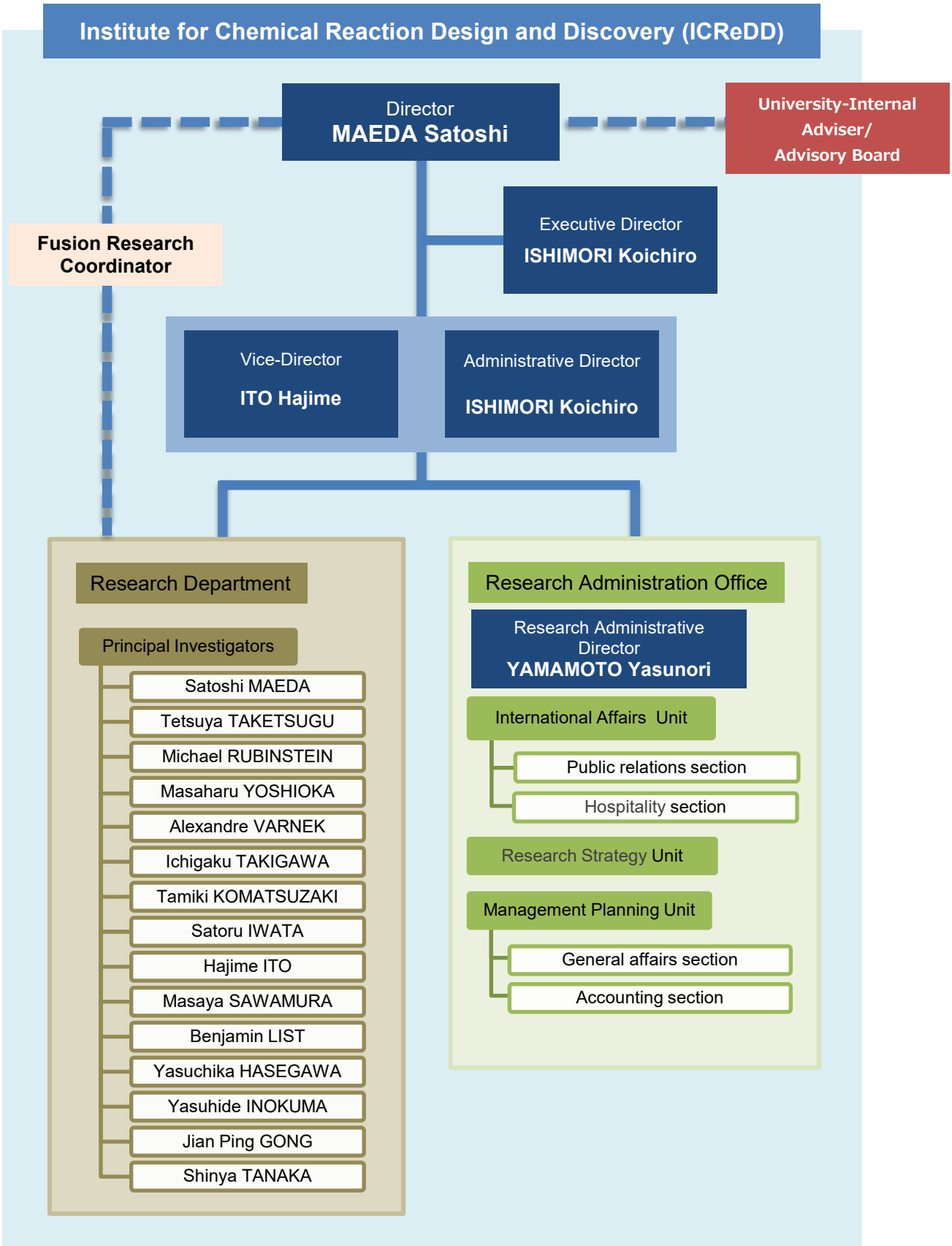
- Indicate the number of international research conferences or symposiums held in FY2022 and give up to three examples of the most representative ones using the table below.

FY 2022: 1 meeting

Major examples (meeting titles and places held)	Number of participants
The 2nd Akira Suzuki Awarsds Ceremony & the 5th ICReDD International Symposium (Online) January 11, 2023	115 (Online Live*) *From domestic :103 From overseas :12

3. Diagram of management system

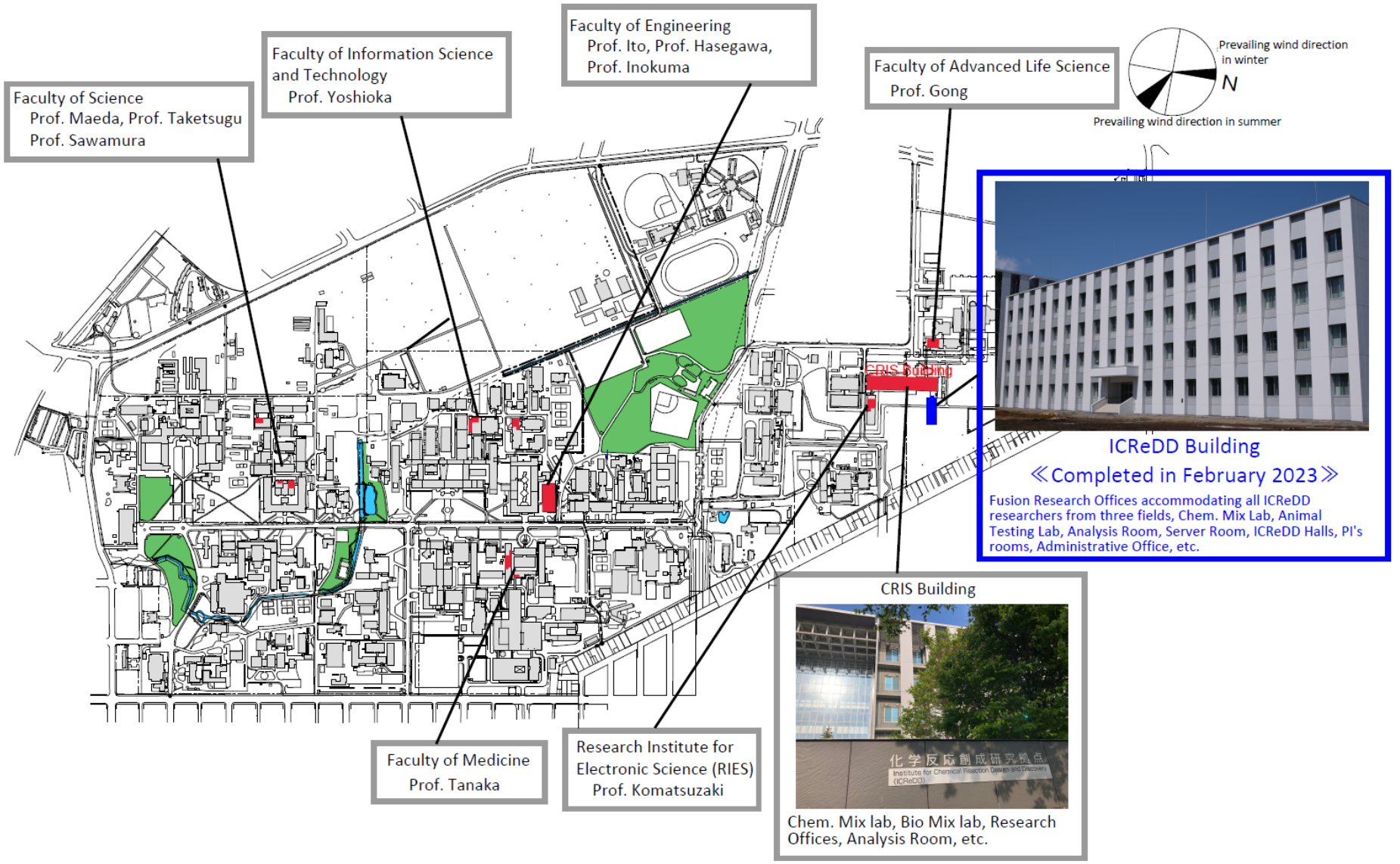
- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any new changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such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



4. Campus Map

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

As of March 31, 2023



5. Securing external research funding*

External research funding secured in FY2022

Total: 596,502,848 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes "KAKENHI," funding for "commissioned research projects," "joint research projects," and for others (donations, etc.) as listed under "Research projects" in Appendix 3-2, Project Expenditures.

・Name: Strategic Basic Research Programs (ERATO), JST
Total Amount: 295,914,400 JPY (acquired by Satoshi Maeda)

・Name: Grant-in-Aid for Scientific Research (S), JSPS
Total Amount: 46,280,000 JPY (acquired by Jian Ping Gong)

・Name: International Leading Research, JSPS
Total Amount: 38,740,000 JPY (acquired by Jian Ping Gong)

Appendix 3-1a FY 2022 Records of Center Activities

Researchers and other center staff

Number of researchers and other center staff

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

a) Principal Investigators

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

(number of persons)

	At the beginning of project	At the end of FY 2022	Final goal (March 2028)
Researchers from within the host institution	11	12	12
Researchers invited from overseas	3	3	3
Researchers invited from other Japanese institutions	0	0	0
Total principal investigators	14	15	15

b) Total members

	At the beginning of project		At the end of FY 2022		Final goal (March 2028)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	14		80		85	
Overseas researchers	3	21	36	45	38	45
Female researchers	1	7	12	15	21	25
Principal investigators	14		15		15	
Overseas PIs	3	21	3	20	7	47
Female PIs	1	7	1	7	2	13
Other researchers	0		43		45	
Overseas researchers	0	0	14	33	13	29
Female researchers	0	0	6	14	10	22
Postdocs	0		22		25	
Overseas postdocs	0	0	19	86	18	72
Female postdocs	0	0	5	23	9	36
Research support staffs	0		2		4	
Administrative staffs	6		17		19	
Total number of people who form the "core" of the research center	20		99		108	

	At the beginning of project		At the end of FY 2022		Final goal (March 2028)	
	Number of persons	%	Number of persons	%	Number of persons	%
Doctoral students	67		71		80	
Employed	17	25.4	20	28.2	48	60.0

※b) The number of doctoral students in the lower table can be duplicated in the upper table of overall composition.

Appendix 3-2 Project Expenditures

1) Overall project funding

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

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Center Director, Administrative Director, Research Administrative Director	25	11
	Principal investigators (no. of persons):9	81	0
	Full-time faculty members (no. of persons): 5	39	0
	Part-time faculty members (no. of persons): 13	61	0
	Specially appointed faculty members (no. of persons): 26	198	198
	Postdoctoral fellows (no. of persons): 18	74	66
	Other researchers (no. of persons): 1	5	5
	Research support staff (no. of persons): 3	2	2
	Administrative staff (no. of persons): 15	71	28
	Center allowance	19	19
	Subtotal	575	329
Project activities	Startup research project costs	42	28
	Outreach costs	7	7
	Center operating costs	7	6
	Environmental improvement costs	111	79
	Facility rental fees	47	0
	Utility costs	36	0
	Puclic equipments usage fees	2	0
	Others	69	0
	Subtotal	321	120
Travel	Domestic travel costs	2	2
	Overseas travel costs	1	1
	Travel cost for scientists on transfer (no. of domestic scientists):2 (no. of overseas scientists):1	1	1
	Subtotal	4	4
Equipment	Depreciation of buildings	1282	0
	Depreciation of equipment	294	247
	Subtotal	1576	247
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	247	0
	KAKENHI	163	0
	Commissioned research projects, etc.	332	0
	Joint research projects	42	0
	Ohers (donations, etc.)	60	0
	Subtotal	844	0
Total		3320	700

Costs (Million yens)

WPI grant in FY 2022	700
Costs of establishing and maintaining facilities	0
Establishing new facilities	0
(Number of facilities: , OO m²)	
Repairing facilities	0
(Number of facilities: , OO m²)	
Others	0
Costs of equipment procured	359
Nuclear Magnetic Resonance System	60
(Number of units:2)	
Ultra-sensitive Multifunctional Photoluminescence Spectrometer	299
(Number of units:1)	
Others	158

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

*1 運営費交付金(機能強化経費を含む)、国立大学改革強化推進補助金等の補助金、間接経費、その他大学独自の取組による学内リソースの配分等による財源
*2 科研費、受託研究費、共同研究費等によって人件費、旅費、設備備品等費を支出している場合も、その額は「研究プロジェクト費」として計上すること

2) Costs of satellites

(Million yens)

Cost items	Details	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):OO		
	Other researchers (no. of persons):OO		
	Research support staff (no. of persons):OO		
	Administrative staff (no. of persons):OO		
	Subtotal	0	0
Project activities	Subtotal		
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		0	0

Appendix 4 FY 2022 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2022 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2023 and not described in Appendix 1.

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

1)
2)
3)
4)

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

1)
2)
3)
4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2022. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

Overseas Satellite 2:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

Appendix 5　FY 2022 Visit Records of Researchers from Abroad

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

Total: 5

	Name	Age	Affiliation		Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
			Position title, department, organization	Country				
1	Francesco, PUCCETTI	28	PhD candidate, Institute of Organic Chemistry, RWTH Aachen University	Germany	PhD candidate, Organic Chemistry	Research internship in Spain, Germany and Croatia Graduation Award from the University of Florence, Italy	2022/5/2-7/31, 3 months	Participation in the MANABIYA (Academic) program
2	Isabell, JOHANSSON	28	PhD candidate, Department of Chemistry, Uppsala University	Sweden	PhD candidate, Structural Chemistry	Doctoral thesis expected to complete in 2023	2022/9/12-30, 2022/11/2-11, 1 month	Participation in the MANABIYA (Academic) program
3	Rassmus, ANDERSSON	32	PhD candidate, Department of Chemistry, Uppsala University	Sweden	PhD candidate, Structural Chemistry	Doctoral thesis expected to complete in 2024	2022/11/2-12/7, 1 month	Participation in the MANABIYA (Academic) program
4	Benjamin, LIST	54	Principal Investigator, Professor, ICReDD Director and Professor,	Germany	PhD, Chemical Synthesis and Catalysis	The Nobel Prize in Chemistry, Herbert C. Brown Award 2022 for Creative Research in Synthetic Methods, Member of the German National Academy of Science Leopoldina	2022/9/18-10/2, 2 weeks	Visit as principal investigator, giving lectures and participation in meetings
5	Alexandre, VARNEK	68	Principal Investigator, Professor, ICReDD Professor, University of	France	PhD, Physical Chemistry	Co-organizer of the biannual French-Japanese Workshop on Computational Methods in Chemistry, Invited Professorships in Australia and Israel	2022/12/1-3 3 days	Visit as principal investigator and participation in meetings
6								
7								
8								
9								
10								

Appendix 6 FY2022 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2022 by each activity.
* Describe the outreach activities in the "6. Others" of Progress Report, including those stated below that warrant special mention.

Activities	FY2022 (number of activities, times held)
PR brochure, pamphlet	3: Monthly post card J/E, Quarterly news poster J/E, Annual report J/E
Lectures, seminars for general public	1: "A Message to the Next Generation" (by Prof. List)
Open houses	1: Online lecture and lab tour (Ito lab., Sakura Science Exchange Program)
Participating, exhibiting in events	3: Japan SciCom Forum 2022 (participation by PR), WPI Science Symposium 2022, Japan-U.S. Science Communication and Policy Fellowship (participation by PR)
Press releases	15: Press releases (research)
Others (Research News Articles on ICReDD Web)	10
Others (SNS)	5: Twitter, Facebook, YouTube, Instagram, LinkedIn
Others（PR video）	1: Promotional video for ICReDD new building
Others (ICReDD Goods)	2: Pen, Clear file folder

*If there are any rows on activities the center didn't implement, delete that (those) row(s). If you have any activities other than the items stated above, fill in the space between parentheses after "Others" on the bottom with the name of those activities and state the numbers of activities and times held in the space on the right. A row of "Others" can be added, if needed.

Outreach Activities and Their Results

List up to three of the Center's outreach activities carried out in FY 2022 that have contributed to enhancing the brand or recognition of your Center and/or the brand of the overall WPI program, and describe its concrete contents and effect in narrative style. (Where possible, indicate the results in concrete numbers.)

-By holding a Special Lecture with Nobel Laureate Professor Ben List, we increased recognition of ICReDD within the university (100 in-person participants) and among other universities and in industry in Japan and abroad (177 online participants)

-As a result of a Twitter campaign using @ function to mention the recipients' departments, tweets about the Akira Suzuki Award ceremony were retweeted multiple times by prestigious universities abroad (UCLA, UC-Berkeley), reaching over 20,000 impressions in total and connecting ICReDD's brand with a more international audience.

-As a result of focusing on disseminating new research, 10 English language press releases were distributed to news platforms, resulting in an estimated 7.75 million views. ICReDD HP coverage (10 English releases plus 15 highlight articles) resulted in 5400 unique pageviews, with over 700 people driven directly from Tweets about research.

Appendix 7 FY 2022 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY2022.

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

1) Japan

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	2022/4/29	Newspaper	Article on the research paper retracted for alleged data falsification, Hokkaido Shimbun
2	2022/5/27	Newspaper	Article on ICReDD Research press release about "Carbon nanobelt synthesis successfully creates twisted "Möbius band"", Kagaku Shimbun
3	2022/6/13	Online magazine	Article on ICReDD Research press release about "Carbon nanobelt synthesis successfully creates twisted "Möbius band"", Keguan Japan https://www.keguanjp.com/kgjp_keji/kgjp_kj_newtech/pt20220613000002.html
4	2022/6/28	Online magazine	Article on ICReDD Research press release about "Carbon nanobelt synthesis successfully creates twisted "Möbius band"", Science Japan https://sj.jst.go.jp/news/202206/n0628-03k.html
5	2022/7/7	Newspaper	Article on the fraud in research papers, Hokkaido Shimbun
6	2022/8/9	Online news	Article on ICReDD Research press release about "In silico reaction screening with difluorocarbene for N-difluoroalkylative dearomatization of pyridines", Nikkei Press release
7	2022/8/24	Online news	Article on the new ICReDD building acquired the "ZEB Ready" certification, Nikkei Press Release
8	2022/8/26	Newspaper	Article on the new ICReDD building acquired the "ZEB Ready" certification, Nikkei Shimbun
9	2022/9/14	Newspaper	Article on Prof. List's visit to HU after receiving the Nobel Prize, Hokkaido Shimbun
10	2022/9/16	Online news	Article on ICReDD Research press release about "In silico reaction screening with difluorocarbene for N-difluoroalkylative dearomatization of pyridines", Spotlight Research, Chem-Station https://www.chem-station.com/blog/2022/08/dfc.html
11	2022/9/22	Newspaper	Article on Prof. List's visit to HU after receiving the Nobel Prize, Hokkaido Shimbun
12	2022/9/22	Newspaper	Article on the title "University Professor" bestowed to Prof. List, Yomiuri Shimbun
13	2022/9/23	Newspaper	Interview article of Prof. List after the lecture for young generations at HU, Hokkaido Shimbun
14	2022/9/29	Newspaper	Article on Prof. List's visit to MEXT, Hokkaido Shimbun

15	2022/10/27	Newspaper	Article on ICReDD Research press release about "Transparent film that promotes plant growth", Nikkan Kogyo Shimbun
16	2022/11/22	Newspaper	Article on SDGs' activities at HU, mentioning the new ICReDD building , Hokkaido Shimbun
17	2022/11/24	Online news	Article on the agreement between Mitsui Chemicals and ICReDD, Nikkei Press Release
18	2022/12/1	Online news	Article on ICReDD Research press release about "Quantum chemical calculations predict starting materials for organic compounds from scratch", Nikkei Press Release
19	2022/12/30	Online news	Article on ICReDD Research press release about “Plant growth acceleration using a transparent Eu3+-painted UV-to-red conversion film”, Spotlight Research, Chem-Station https://www.chem-station.com/blog/2022/11/eu.html
20	2023/1/10	Online news	Article on ICReDD Research press release about "A theory-driven synthesis of symmetric and unsymmetric 1,2-bis(diphenylphosphino)ethane analogues via radical difunctionalization of ethylene", Spoplight Research, Chem-Station https://www.chem-station.com/blog/2023/01/dppe.html
21	2023/1/11	Newspaper	Article on ICReDD Research press release about "Quantum chemical calculations predict starting materials for organic compounds from scratch", Kagaku Kogyo Niipou
22	2023/1/23	Newspaper	Article on ICReDD Research press release about "Squid/synthetic polymer double-network gel", Nikkan Kogyo Shimbun
23	2023/1/23	Online news	Article on ICReDD Research press release about "Squid/synthetic polymer double-network gel", TECH+ https://news.mynavi.jp/techplus/article/20230123-2572738/
24	2023/1/24	Online news	Article on ICReDD Research press release about "Squid/synthetic polymer double-network gel", Yahoo! News (Science) https://news.yahoo.co.jp/articles/d14f132baec7db4ff583db3683abdd2294a98512
25	2023/1/29	Newspaper	Article on ICReDD Research press release about "Squid/synthetic polymer double-network gel", Nikkei Shimbun
26	2023/3/9	Online news	Article on ICReDD Research press release about "Organic chemistry with machine learning using new descriptor to predict optimal catalysts", Chem-Station https://www.chem-station.com/blog/2023/03/tfd.html
27	2023/3/13	Newspaper	Article on ICReDD Research press release about "Newly developed gel reconstructs the neural tissue of the brain", Hokkaido Iryo Shimbun
28	2023/3/16	Online magazine	Article on ICReDD Research press release about "Photoredox/HAT-Catalyzed Dearomative Nucleophilic Addition of the CO2 RadicalAnion to(Hetero) Aromatics", Keguan Japan https://www.keguanjp.com/kgjp_keji/kgjp_ki_smkx/pt20230316000001.html
29	2023/3/28	Online magazine	Article on ICReDD Research press release about "Organic chemistry with machine learning using new descriptor to predict optimal catalysts", Science Japan https://sj.jst.go.jp/news/202303/n0328-01k.html

2) Overseas