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

Host Institution	Hokkaido University (HU)	Host Institution Head	Kiyohiro Houkin
Research Center	Institute for Chemical Reaction Design and Discovery (ICReDD)		
Center Director	Satoshi Maeda	Administrative Director	Koichiro Ishimori

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

I. Summary

ICReDD aims to "Revolutionize Chemical Reaction Design and Discovery" by fusing the fields of experimental chemistry, computational chemistry and information science. Its research activity has grown well, creating 406 papers, including 22 published in journals with IF higher than 20.0. To promote fusion research, seven flagship projects have been established; these projects have been successful in creating high impact fusion research outputs. ICReDD's organization has also operated steadily, having 69 researchers in total (39% foreign nationals). It utilizes a 2,600 m^2 space (plus an additional 5,500 m^2 space in the new building at the end of FY2022), and has secured its own financial resources equal to or greater than the WPI budget. ICReDD actively offers information on its activities through its website, SNS, etc. Moreover, researchers were accepted from both academia and industry through the MANABIYA system. ICReDD has strong cooperation with the University Executive Office. To help with its permanent establishment, ICReDD secured five positions (three associate professors, one female assistant professor, and one female associate professor) from the university. Further efforts to secure personnel and financial resources are in progress. Therefore, ICReDD is taking concrete steps towards "revolutionizing chemical reaction design and discovery" and its permanent establishment.

II. Items

1. Overall Image of Your Center

Our center, the "Institute for Chemical Reaction Design and Discovery (ICReDD)", aims to "Revolutionize Chemical Reaction Design and Discovery" by fusing the fields of experimental chemistry, computational chemistry and information science. Its research activity has grown well, creating 406 papers, including 22 published in journals with IF higher than 20.0. To provide strong support for the Center's effort, we established seven flagship projects. The projects are arranged hierarchically, with Project I as the foundation, and with the complexity of the chemical processes involved gradually increasing for Projects II-VII. By simultaneously pursuing these projects that tackle varying levels of complexity, both project-specific issues as well as common issues can be shared, which we expect will enable the comprehensive and rapid development of methods to describe chemical reactions. All the projects were evaluated at the end of FY2021 to decide whether to extend or not and how to enhance in the case the project is extended.

As of March 31, 2022, the number of PIs was 15, 39% of all researchers were foreign nationals, and 13% were female researchers (total of 69 researchers, split between the fields of Computation 18 (26%), Information 14 (20%), Experiment 37 (54%)). ICReDD has utilized the 2,600 m^2 space having experimental equipment and computers necessary for fusion research. In addition, construction of the new ICReDD building (5,500m^2) began (scheduled for completion at the end of FY2022). ICReDD operates with its own financial resources from the university, which are equal to or greater than the WPI budget. ICReDD's researchers have continued to receive competitive research funding steadily.

ICReDD offers information on the Center's activities through the Center's website, SNS, a "Monthly News Postcard", a "Quarterly News Poster", and an "Annual Report". Moreover, researchers were accepted from both academia and industry through the MANABIYA system.

The Research Support Division was set to further promote fusion research and to develop ICReDD toward its permanent establishment. ICReDD has strong cooperation with the University Executive Office to ensure that decisions made by the University are promptly reflected at the center. A "Fusion Research Coordinator" was established to enhance fusion research in ICReDD. The Advisory Board was established to receive recommendations on the future direction of the center from an international perspective.

In the past three and a half years, we have built a research and administrative structure that we think surpasses the initial vision of the center that we proposed at the time of applying for WPI. Our vision has also received vital support at all levels from Hokkaido University, including funding support for the construction of a new building and funding support for the establishment of tenure-track Junior PI posts. ICReDD is taking concrete steps towards "revolutionizing chemical reaction design and discovery."

2. Center's Research Activities

Our center aims to accelerate chemical reaction design and discovery by fusing experimental chemistry, computational chemistry, and information science. To realize this, we established seven flagship projects that can contribute to chemical processes that have important roles in a wide range of areas in our life and society, from single molecular systems to complex materials and biosystems. Our efforts have begun to bear fruit as explained below. With the newly established fusion research coordinator role, we will adjust the flagship projects' direction based on their progress.

(1) **Development and integration of advanced computational and informatics techniques** (Project I)

This project is the foundation of the center's research. The retrosynthetic analysis method by AFIR (QCaRA) was proposed and applied practically. We developed a prototype database platform, SCAN, which has begun to be combined with visualization and classification techniques of information science (RePathDB representation and SubMo-GNN). These will lead to predictions of new chemical reactions. Acceleration of the AFIR search using neural network potentials has also started to be worked on. Several informatics tools based on CGR, GNN and databases were also developed for the design of new chemical reactions.

(2) **Design and discovery of new synthesis methods** (Project II, III, IV, V)

Applicability of the QCaRA method was proved in the syntheses of difluoroglycine, unsymmetric bidentate phosphine derivatives, and so on. A recursive approach of computation and experiment realized the synthesis of N-α,α-difluorinated heterocycles, a dearomative dicarboxylation reaction using CO_2, etc. AFIR exhibited its capability to find transition states, leading to the understanding of the reaction mechanism of asymmetric organocatalysts and further optimization of transition metal catalysts. A new descriptor, CircuS was also developed and applied to predict highly enantioselective catalysts. As an alternative to chemical reactions in solvent, mechanochemical synthesis was explored and realized increasing reactivity, the reaction of insoluble compounds, mechanoredox reactions, and the synthesis of Grignard reagents by mechanical force.

(3) **Design and discovery of new materials** (Project VI)

Force-promoted degradation has been utilized for chemical reaction control and polymer material functionalization. The development of double network hydrogels (DN gel) that can be strengthened by bond scission and the reconstruction of new networks was achieved. DN gels with azo-crosslinkers were developed to produce a high concentration of mechanoradicals based on theoretical computation. Techniques for sensing mechanoradicals in generic polymers using a pre-fluorescent probe were also demonstrated.

(4) **Creation of innovative measurement and diagnostic methods** (Project VII)

Easy diagnosis of cancer is a focus of this project, in which the HARP phenomenon (cancer cells become cancer stem cells using a DN gel) was established. Subsequently, hydrogel plate kits were designed for efficient drug screening to identify therapeutic drugs from huge amounts of experiments together with the bandit algorithm.

Appropriate facilities and equipment have been established. The renovation of the Creative Research Institution Building has been completed and the 2,600 m^2 space has been effectively utilized to promote fusion research. We completed the design of the "International Research Center for Chemical Reaction Design and Discovery" that we will use from FY2023 to further promote fusion research. Research grants were also acquired by the center researchers including overseas PIs, reaching 2,460 million JPY as of FY2021.

These efforts resulted in 406 papers including high impact journals (IF>20: 22 papers; Nature(×3), Science(×5), Nature Nanotech.(×1), Adv. Mater.(×4), Nat. Biomed. Eng.(×1)), 74 TOP 10% papers, and 30 research press releases. We collaborated with domestic and international researchers as well, resulting in 121 collaborative papers within Hokkaido University, 162 domestic collaboration papers (9 inter-WPI collaboration papers), and 134 international collaboration papers. In addition, the center researchers received 39 awards, such as the Nobel Prize (List), the H.C. Brown Award (List), the Nagakura Saburo Award (Maeda), the Dirac Medal (Maeda), the CSJ Award (Gong), and the MEXT Commendation for Science and Technology (Gong, Sawamura).

3. Feeding Research Outcomes Back into Society

ICReDD's research results are steadily bearing fruit, including patent applications. The main achievements are as follows: 1) Our latest version of AFIR was made available for use in the GRRM20 software package, which was released from HPC Systems, Inc. in June 2021. 2) A mechanochemical synthetic method realized a cross-coupling reaction using insoluble substrates. These results are expected to lead to the development of light-emitting materials and electronic materials that cannot be synthesized by conventional synthesis in solution. 3) By collaboration with the HU Research and Education Center for Robust Agriculture, Forestry and Fisheries Industry, special light-converting materials were applied to the improvement of plant growth. 4) The HARP phenomenon has been used for clinical applications in cancer diagnostics, including the identification of novel cancer stem cell markers. We also designed a hydrogel kit for efficient experiments.

Each fiscal year, ICReDD held its International Symposium to introduce our vision and research. In 2021, we established the Akira Suzuki and ICReDD Awards, strengthening ICReDD's connection with the award winners and their institutions. A digital advertising campaign (Nature, Science, etc.) was also run to increase awareness of both the Akira Suzuki Award and the 4th International Symposium, mainly targeting the geographic regions of North American and Europe to maximize global visibility. A unique endeavor of ICReDD is the quarterly news poster "The CATALYST", which introduces our research to a high school level, non-scientist audience. A total of 7 issues have been created, including a special edition 6th issue that commemorated Prof. List winning the 2021 Nobel Prize in Chemistry. A recent effort has been made to promote our research more actively on our website and on Twitter. Mentioning journals in tweets has resulted in prominent journals following our Twitter account and retweeting us, increasing visibility to international audiences.

4. Generating Fused Disciplines

Under the leadership of the center's Director with the ICReDD slogan, we decided on new challenging themes, and launched the seven flagship projects. The director and the research strategy unit manager participated in each progress meeting, and discussed both short-term and long-term perspectives. The progress was shared with PIs in the monthly PI meetings. This helped us to share the ICReDD mission among all members in the center.

Regarding financial support, we prepared a start-up support system to allow young researchers to engage in challenging new research freely with their own ideas under the ICReDD slogan. We assigned 60.25 million JPY to 19 new faculty members and 68.2 million JPY to 24 projects. To promote new fusion research which can be supported by the system, various types of seminars (frank style seminars, fusion seminars, stirring seminars, seeds/needs seminars, and monthly seminars) were also held.

Regarding incubation space, we prepared mix-labs, a mix-office, and the ICReDD salon for daily communication and discussion to accelerate collaboration among different fields. Due to the COVID-19 situation, an online salon was also held to ensure communication.

For AFIR, which is a key technology in our center, a computing cluster with 4000 CPU cores has been prepared to allow experimentalists to perform calculations. A tutorial seminar on the use and development of AFIR was also held for theoretical and information scientists to accelerate their research and development through the use of AFIR.

5. Realizing an International Research Environment

An agreement is in place with the Univ of Strasbourg. Furthermore, the Max Planck Institute, Duke Univ, Peking Univ, Stockholm Univ, Univ of Oslo, Queen's Univ, ICIQ, and Univ of North Carolina were strong collaborative institutions. We plan to conduct international public relations activities at each overseas HU's Office, particularly the North American and European offices, as well as industry-academia-government collaboration.

Personnel have steadily increased over the past three and a half years. At the end of March 2022, 27 of 69 researchers (39%) were foreign nationals and 9 (13%) were female. The ratio of research fields is 50% each in computational/information and experimental science. To further promote world-class international research activities, three young foreign researchers of international excellence were hired as associate professors through the HU's Tenure Track System. In addition, one female assistant professor was hired, and one female tenure-track associate professor position was opened for applications. Interviews on living environment with foreign researchers and PIs were conducted by the International Planning Unit staff, and a one-stop hospitality support system was established.

6. Making Organizational Reforms

ICReDD will become the core of HU's fourth mid-term objectives and plans as the flagship project. Since the establishment of ICReDD, HU has strongly supported ICReDD and has secured funds equal to or more than the WPI grant for its operation (FY2018: 363 million yen, FY2019: 1,026 million yen, FY2020: 1,388 million yen, FY2021: 1,989 million yen). The final decision-making authority for all matters related to our operation and management rests with the Director. Our administrative structure was reorganized with its long-term (post WPI funding) future in mind, and the Executive Director was made the Administrative Director to strengthen cooperation with the HU Headquarters. Monthly meetings are held with the President to discuss management, including future plans. We revised HU's salary regulations to allow for higher salaries to hire the talented researchers. To acquire top-level researchers who can advance the chemical reaction design and discovery fields, we have also implemented a cross-appointment system and have utilized this to employ a chief researcher at RIKEN and a professor at the Univ of Tokyo as principal investigators. Furthermore, we established regulations to provide center allowances to PIs etc. In FY2022, a new regulation was established to provide incentives based on the research performance and evaluation of center faculty members. HU established an integrated technical staff organization, the Office for Technical Support, to which technical staff members from various departments in HU were dually appointed. The consolidation of the centralized administrative system strengthened support for cross-divisional education and research activities. This office dispatched technical staff to assist in the maintenance and management of ICReDD's NMR. From FY2022, HU has reorganized and strengthened its industry-academia collaboration system with a focus on accepting researchers from industry and establishing a research consortium with industry. The system is now capable of systematically supporting ICReDD's acquisition of private funding and its permanent establishment.

7. Future Prospects

Our next challenge is how to utilize the research results and permanently sustain operations after WPI funding ends. We reviewed and evaluated the progress of all projects at the end of FY2021. We will discuss whether to add members, extend duration, expand scope, reconsider direction, or abolish each project based on the evaluations. We will actively develop international outreach activities beyond academia by strengthening cooperation with internal organizations and will promote an effective international strategy to invite many excellent researchers and students from abroad. To achieve this, a new Human Resource Development Unit and Research Strategy Unit will be established for 2023. Utilizing the MANABIYA system, the Human Resource Development Unit will develop strategies and roadmaps for graduate education, recurrent education, and contributions to the scientific community and society. The Research Strategy Unit will use MANABIYA to gather companies in related fields and expand its network to best match with these industries.

8. Host Institution's Concrete Plan toward Achieving the Center's Independence over the Next 5 Years (from its sixth year)

ICReDD will be positioned as a special research institute under the direct control of the President. It will be made a permanent research center that always promotes cutting-edge, world-class research while maintaining flexibility in its research themes, based on a new HU research strategy. As a framework for significantly developing ICReDD's cutting-edge research together with many researchers inside and outside of HU, a "Collaborative Research Platform" will be established to support and promote research and development based on outstanding research results and to realize collaborative research with researchers outside the center. This platform concept will dramatically develop and establish an international research hub based on cutting-edge research originating from HU. In addition, after the completion of the WPI funding period, existing graduate schools in HU will be reorganized and integrated in order to establishment the graduate school of "Chemical Reaction Design and Discovery", with plans to cement "Chemical Reaction Design and Discovery" and "MANABIYA" as educational organizations of HU. To incorporate world-class advanced research back into educational programs, we plan to establish a system for cross-disciplinary and interdisciplinary education that is not bound by the framework of existing research institutes and graduate schools, and to establish the "ICReDD Human Resource Development Unit". It is rare for an international research institute to have a human resource development unit, and this organizational reform will lead to ICReDD's further development as a research center and its contribution to HU.

9. Others

We will enhance diversity, safety, technology export control and research ethics education for all ICReDD researchers. A workshop on diversity with an expert from Queen's Univ will be scheduled in May. We regret to report the retraction of a paper from ICReDD, which was published in Science in 2020. We recognize the highly serious nature of the incident and will take all possible actions to prevent similar incidents in the future and to regain trust, starting with the reeducation on research ethics for all researchers at the Center in June.

10. Center's Response to Results of FY2021 Follow-up (including Site Visit Results)

ICReDD has positively responded to most of the points raised this year.

1) ICReDD plans to reorganize its flagship projects and to restructure them into a stronger and more strategic research execution structure.
2) A career path system for female researchers from student, postdoctoral researcher, assistant professor, and associate professor (JrPI) to professor (PI) will be established and role models will be shown.
3) ICReDD plans to establish a new international collaborative research platform to realize collaborative research with researchers outside the center. Furthermore, to make the salary system for faculty members internationally competitive, ICReDD has introduced a salary system that can provide incentives based on performance evaluations starting from FY2022.
4) An ICReDD joint symposium with the Faculty of Medicine was held to increase understanding and discussion between both fields and to find new opportunities for interdisciplinary cooperation. In FY2022, ICReDD will also conduct a Clinics-oriented chemistry consortium.
5) ICReDD will further enhance outreach. We will actively engage in monthly postcards for researchers, quarterly news posters for high school and undergraduate students, lectures for high school students or the general public, press releases, and press conferences. Also, we will establish recognition through strategic international public relations using Science, Nature, ACS, RSC, Wiley, etc. for promoting international symposia and the Akira Suzuki Awards.
6) HU will permanently maintain ICReDD (see item 8). The Executive Director was newly appointed as the Administrative Director to ensure that decisions made by HU are promptly reflected in the center's projects. To strengthen the research support system, the management organization was reorganized into the Research Support Division and four units were established: the Administrative Affairs Unit, the International Planning Unit, the Research Strategy Unit, and the Human Resource Development Unit. The Fusion Research Coordinator role was also established, and 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. HU also plans to request 8 faculty members in the 2023 budget request.

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

Host Institution	Hokkaido University (HU)	Host Institution Head	Kiyohiro Houkin
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 2022) situation of your WPI center.
* As a rule, keep the length of your report within the specified number of pages. (The attached forms are not included to this page count.)
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

1. Overall Image of Your Center (write within 2 pages including this page)

Describe the Center's current identity and overall image.

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

Chemical reactions are used in every facet of modern society. Examples of this include creating useful materials from cheap resources, developing pharmaceutical drug molecules from simple molecules, converting toxic pollutants into non-toxic molecules, and controlling biological functions. Consequently, it can be said that the development and control of chemical reactions is a central challenge for modern society. However, the development of chemical reactions requires enormous expense. It is said that hundreds of experiments are necessary to develop a single chemical reaction. The personnel required and monetary costs are massive. Moreover, the current situation is that revolutionary reactions are only discovered at roughly 10-year intervals. In this context, we named our center the "Institute for Chemical Reaction Design and Discovery", and with the motto of "Revolutionize Chemical Reaction Design and Discovery" we aim to solve problems by fusing the fields of experimental chemistry, computational chemistry and information science. First, we will make full use of computational chemistry and information science methods to innovate how chemical reactions are designed. At the same time, we will demonstrate the utility of these methods by applying them to the practical development of chemical reactions. Based on feedback and problems encountered during practical usage, we will further improve the computational and information science methods.

Research strategy and achievements: The center's activity has grown well, creating 406 papers, including 22 published in journals with IF higher than 20.0. To provide strong support for the Center's effort, we established seven flagship projects. The seven projects are arranged hierarchically, with Project I as the foundation, and with chemical process complexity gradually increasing for Projects II-VII. In Project I, we utilize an advanced suite of techniques to innovate chemical reaction design, combining our unique automated reaction path search and chemical reaction descriptor technologies with more generally used regression and neural network methodologies. Projects II, III, and IV target organic synthesis reactions, supramolecular catalysts, and mechanochemical methods, respectively, while Projects V, VI and VII focus on artificial enzymes, polymer materials, and cancer cells, respectively. By simultaneously pursuing these projects that tackle varying levels of complexity, both project-specific issues as well as common issues can be shared with Project I, which we expect will enable the comprehensive and rapid development of methods to describe chemical reactions.

Some promising results are summarized here. Project I has developed quantum chemistry-aided retrosynthetic analysis (QCaRA) methods based on automated reaction path search technology. In Project II, QCaRA has been utilized to discover reactions for making difluoroglycine derivatives, which are difficult to synthesize. We have succeeded in developing asymmetric organocatalyst synthesis methods that make full use of information science techniques and an automated synthesis robot. In Project IV, computational chemistry is being used to elucidate the process of mechanoradical generation in polymer materials, which has led to improved mechanoradical generation efficiency. In Project VII, the HARP phenomenon was established, in which hydrogels are able to revert cancer cells back into cancer stem cells. The progress of all the projects was evaluated at the end of FY2021 to decide whether to extend or not and how to enhance in case to extend.

Realizing an International Research Environment: 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 FY2021 (88 applications for 7 positions). As of March 31, 2022, the number of PIs was 15, 39% of all researchers were foreign nationals, and 13% were female researchers (total of 69 researchers, including 27 foreign nationals and

9 female researchers, split between the fields of Computation 18 (26%), Information 14 (20%), Experiment 37 (54%)). To further promote top-level international research activities, three internationally excellent young foreign researchers with potential to become PIs in the future were hired as Associate Professors through the Hokkaido University Ambitious Tenure Track System, a planned support to make ICReDD permanent. In addition, with the support of the university, one female assistant professor, who will be hired on April 1, 2022, was selected, and one tenure-track associate professor position (limited to female applicants) was opened for applications. In this way, female career paths from postdoctoral researcher to principal investigator will be realized and nurtured and role models, which are not available for other organizations, will be shown. Personnel have steadily increased over the past three and a half years. We strategically hired talented researchers through interviews with the center's director from top research institutions, such as such as Princeton Univ, Columbia Univ, UCLA, Johns Hopkins Univ, Univ of Manchester, the Max-Plank Inst, Univ of Strasbourg, with high competition. The ratio of research fields is 50% each in computational/information and experimental science, which covers sufficient all research fields to strengthen the Center's mission.

The renovation of the Creative Research Institution Building was completed and the 2,600 m^2 space was effectively utilized to promote fusion research. Experimental equipment and computers necessary for fusion research have been installed with unparalleled research environment. In addition, with university support, construction of the new ICReDD building (4 floors above ground, 5,500m^2) with advanced facilities began in October 2021 (scheduled for completion at the end of FY2022).

ICReDD operates with its own financial resources from the university, which are equal to or greater than WPI budget. ICReDD's PIs and other researchers have continued to receive competitive research funding steadily since its inception. Overseas PIs have also succeeded in obtaining Grants-in-Aid for Scientific Research.

Achievements of Center's outreach activities and MANABIYA system: In addition to promoting research results on the Center's website and SNS, the Center has published a "Monthly 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.

Researchers and companies were accepted through the MANABIYA system. So far, we accepted 9 applicants and led to 4 papers. MANABIYA(ACADEMIC)" invited applications in April and October 2021 and accepted 7 researchers out of 12 applicants (under the COVID-19 situation, 1 researcher was accepted online, 3 were accepted from domestic and 3 were postponed) who were trained in ICReDD techniques. MANABIYA(INDUSTRY) released the program GRRM20 in June 2021 from HPC Systems, Inc. under a program license agreement with the University, in which the latest features of the AFIR method are available. A system was established for the use of this program in MANABIYA(INDUSTRY). GRRM20 is a "technology needed in society" that companies also need, and selling it is one of ICReDD's contributions to society. We also required the first-time purchasers to participate in MANABIYA. In FY2021, the center accepted joint research from six private companies (21.18 million yen).

Making Organizational Reforms: The Administrative Division was reorganized into the Research Support Division to further promote fusion research and to develop ICReDD toward its permanent establishment. In order to strengthen cooperation with the University Executive Office and to ensure that decisions made by the University are promptly reflected at the center, the Executive Director was appointed as the Administrative Director, and the Research Support Division was reorganized into the "Administrative Affairs Unit" and the "International Planning Unit" under the supervision of the "Director of Research Support." In addition, a "Fusion Research Coordinator" was established to provide a direct connection between the Center Director and the research labs. This role enables the management and monitoring of the progress of the Center Director's policies while being in close contact with researchers. The Advisory Board online meetings were held on February 22 (US time) and 28 (European time) (3 members from Japan, 5 from overseas). The committee 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.

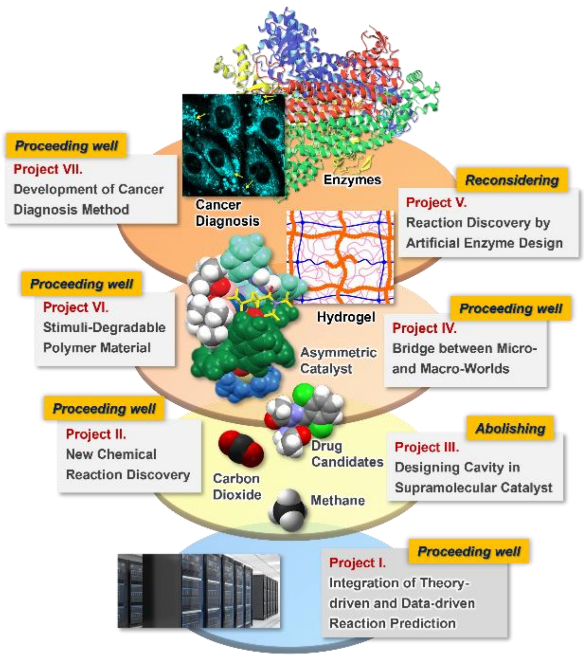
Summary: In the past three and a half years, we have built a research and administrative structure that we think surpasses the initial vision of the center that we proposed at the time of applying for WPI. In particular, the flagship projects have been instrumental in creating a strong fusion between experimental chemistry, computational chemistry and information science. Administratively, we have created a strong system built around the Center Director and Administrative Director. Our vision has also received vital support at all levels from Hokkaido University, including funding support for the construction of a new building and funding support for the establishment of three tenure-track Junior PI posts. We are also furthering our outreach efforts through an "on-the-job training"-style education system centered around the MANABIYA program. As a top-level research institute, ICReDD is taking concrete steps towards "revolutionizing chemical reaction design and discovery."

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

2-1. Research results to date

Give an overall picture of the Center's research activities. Select 10 representative research results achieved during the period from 2018 through March 2022. Number them [1] to [10] and provide a description of each.

・ In Appendix 1-1, list the papers underscoring each research achievement (up to 20 papers) and provide a description of each of their significance. And in Appendix 1-4 list the center's research papers published in 2021.



Our center the "Institute for Chemical Reaction Design and Discovery" aims to accelerate the chemical reaction discovery by fusing the fields of experimental chemistry, computational chemistry, and information science. To provide strong support for this effort, we established seven flagship projects, as shown in the figure on the right. The seven projects are arranged hierarchically, with Project I as the foundation, and with chemical processes complexity gradually increasing for Projects II-VII. In Project I, we utilize an advanced suite of techniques to innovate chemical reaction design, combining our unique automated reaction path search and chemical reaction descriptor technologies with more generally used regression and neural network methodologies. Project I includes the application of these chemical reaction design methods to the other projects, as well as the further development of these methodologies based on feedback that arises during implementation in other projects. Projects II, III, and IV target organic synthesis reactions, supramolecular catalysts, and mechanochemical methods, respectively, while Projects V, VI and VII focus on artificial enzymes, polymer materials, and cancer cells, respectively. By simultaneously pursuing these projects that tackle varying levels of complexity, both project-specific issues as well as common issues with implementation can be shared with Project I, which we expect will enable the comprehensive and rapid development of methods to describe chemical reactions. In addition to the flagship projects, we set several bottom-up projects launched by young researchers.

The ten representative research outputs below are from either the flagship or bottom-up projects. Results of well-proceeding projects (I, II, IV, VI, and VII) are presented. In other words, these projects have achieved the expected level of progress in the first four years. The remaining project (III and V) have not proceeded well and will be abolished or reconsidered. Two bottom-up projects launched by young researchers are also presented below. For each topic, the corresponding project is indicated by Project-*n* (*n* = I–VII) or Bottom-up in the topic's title.

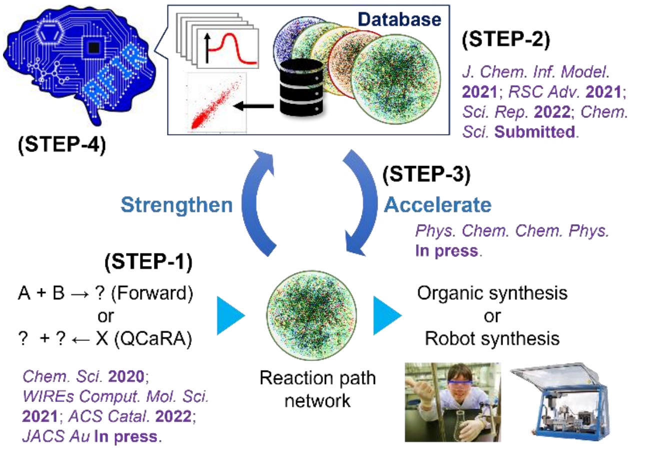
(1) Development and integration of advanced computational and informatics techniques

[1] **Development of reaction design tools** Project-I

An important mission of our institute is to develop computational chemistry and information science techniques that enable the purposeful design of chemical reactions. In Project I, the Maeda Group, Taketsugu Group, Komatsuzaki Group, Varnek Group, Takigawa Group, Yoshioka Group and Iwata Group are all working to develop these techniques, as well as a related platform.

We are currently constructing a system for designing chemical reactions based on reaction path network data, as shown in the scheme below (see the scheme also for related publications). At the heart of this scheme is the Artificial Force Induced Reaction (AFIR) method, which enables the generation of reaction path networks. As shown in the figure on the next page, this scheme has four steps: (**STEP-1**) using AFIR to automatically generate reaction path networks, (**STEP-2**) creating a database and platform for the reaction path networks generated in (STEP-1), (**STEP-3**) utilizing the database and platform from (STEP-2) to speed up the generation of reaction path networks, and (**STEP-4**) utilizing the database and platform from (STEP-2) to create AI that can predict reaction mechanisms. We already have results for steps 1 and 2. For step 1, we proposed the Quantum Chemistry-Aided Retrosynthetic Analysis (QCaRA) method and expanded its use to multi-step reactions (*JACS Au*, 2022). We have also developed virtual ligands that will be used to expand QCaRA usage to transition metal catalyst design (*ACS Catal.*, 2022). As will be explained in the next topic [2], we successfully used these methods to discover multiple small molecule transformations. In step

2, we are developing a data platform named SCAN and have finished a prototype. We have also published collaborative research on the visualization and classification of reaction path networks (*J. Chem. Inf. Model.*, 2021; *Sci. Rep.*, 2022). We are working on steps 3 and 4 in parallel as we further expand both our database and our techniques for predicting chemical reactions with reaction path networks.

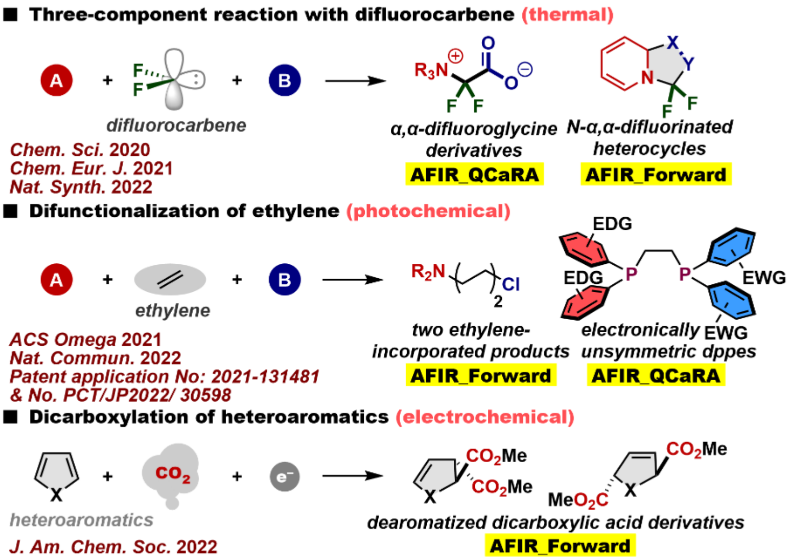


Computational and informatics approaches developed in Project I are being put to practical use in other projects. For example, topic [4] explains our efforts combining cheminformatics, quantum chemical computations and an automated synthesis robot to design highly selective asymmetric organocatalysts, while topic [5] discusses our work combining quantum chemical computations with cheminformatics to optimize catalysts.

(2) Design and discovery of new synthesis methods

[2] **Small molecule transformation** Project-II

By using esteemed computational technologies such as QCaRA (backward AFIR) and forward AFIR, the Mita group (the chief of the mix-lab) and the Maeda group have computationally designed and developed several three-component reactions (3CRs), as shown in the figure below.



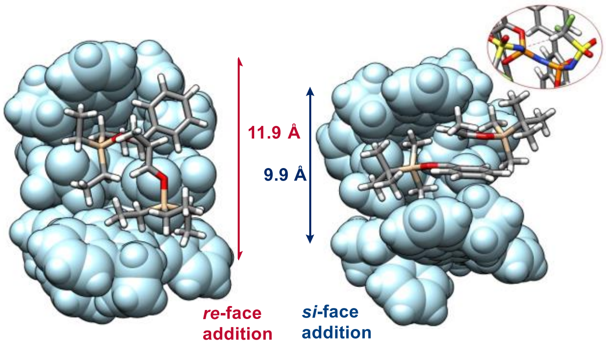
1) A new synthetic method of difluoroglycine, a bioisostere of natural glycine, was developed based on QCaRA (***Chem. Sci.***, 2020; ***Chem. Eur. J.***, 2021). The starting materials for the synthesis of difluoroglycine were computationally proposed, and then employed for the actual chemical synthesis of difluoroglycine. Next, a forward systematic AFIR search reacting $:CF_2$ with two other unsaturated components (C=O, C=N, C=C, or C≡C) was conducted. As a result, a new method for synthesizing of N-α,α-difluorinated heterocycles, which are attractive chemical structures in drug development, was designed and realized in experiment (*Nat. Synth.*, in revision).

2) The group is also interested in the use of ethylene gas, which is a fundamental C2 unit in industrial utilization. By using the AFIR forward search under radical conditions, an unprecedented photochemical reaction was developed where two ethylene molecules are incorporated into the substrate (***ACS Omega***, 2021). Moreover, the synthesis of symmetric as well as electronically and sterically unsymmetric 1,2-bis(diphenylphosphino)ethane (DPPE) derivatives, which are extremely useful for bidentate phosphine ligands, have been achieved based on the AFIR backward search (***Nat. Commun.***, 2022, patent: 2021-131481).

3) The dearomative dicarboxylation of stable heteroaromatics using CO_2 is highly challenging but represents a significantly powerful method for producing synthetically useful dicarboxylic acids. The group discovered that stable heteroaromatics could undergo unprecedented radical dearomative dicarboxylation under electrochemical reductive conditions based on results from AFIR. (***J. Am. Chem. Soc.***, 2022).

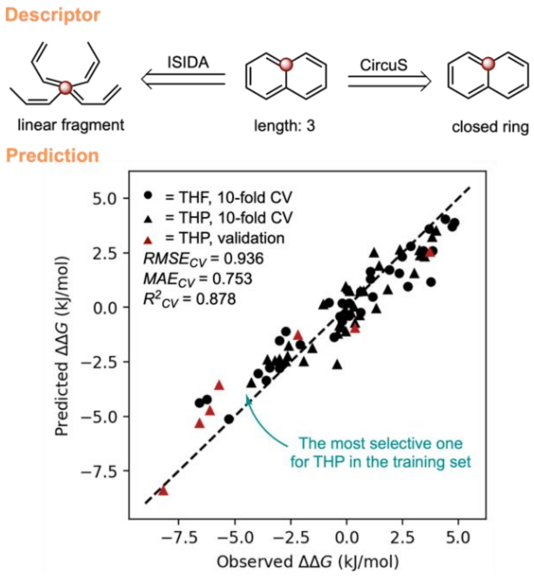
[3] **Theoretical investigation of asymmetric organocatalysis** Project-II

Understanding the reaction mechanism and origin of enantioselectivity is important in asymmetric catalysis because otherwise the concept cannot be generalized. Although it was possible to logically speculate about the mechanism and point out critical interactions of simple catalysts decades ago, more sophisticated catalysts possess relatively complex structures; hence rationalization is not an easy task. The List Group have been working on the development of organocatalysts, and tackled this challenge to address the peculiar switch of enantioselectivities in the Mukaiyama-aldol reaction, combined with theoretical calculations. It had been experimentally found that switching one of the fluorine into hydrogen provides a complete switch of enantioselectivity; however, the experimentalists did not have a clear understanding of the reason behind this observation. Tsuji in the List group performed a computational study using the GRRM program developed in the Maeda group and found that the intramolecular hydrogen bonding induced by the CF_2H group stabilizes certain conformations as shown in the above Fig., which preferentially provide the opposite enantiomer (***J. Am. Chem. Soc.***, 2021). In addition, Si-Stereogenic silyl ethers were synthesized using imidodiphosphorimidate catalysts. Tsuji again performed a computational study using the GRRM program and found that the nucleophile geometry has a relatively strong effect on the enantioselectivity (***J. Am. Chem. Soc.*** 2022). Based on these studies, computational designing of more selective catalysts is being investigated.



[4] **Chemoinformatics prediction of highly enantioselective catalysts** Bottom-up

Optimization of asymmetric catalysts typically requires a long time and considerable efforts because experimentalists often rely on trial-and-error and their chemical intuitions. To overcome this difficulty, several research groups introduced machine learning approaches into development of asymmetric catalysis. Their methodologies, however, require costly quantum calculations, and predicting higher enantioselective catalysts is still challenging. The List, Varnek, and Maeda Groups have been collaborating to predict highly selective catalysts using 2D descriptors, which could be more efficient than other standard 2D fingerprint descriptors, physical descriptors, or 3D descriptors, to represent structures of catalysts. During the preliminary studies, Tsuji in the List group and Sidorov and Gimadiev in the Varnek group found that ISIDA descriptors developed by the Varnek group performed far better than other fingerprint descriptors. With this preliminary success in hand, they envisioned that more precise description of cyclic fragments would be beneficial for representing hydrocarbon substituents of catalysts. To improve the descriptor for applications in asymmetric catalysis, they developed a new descriptor, Circular Substructures (CircuS), which enabled capturing cyclic fragments explicitly to represent catalyst structures more precisely as shown in the right Fig (top). Predictive models were constructed using the CircuS and applied to asymmetric synthesis of tetrahydrofuran ring to compare with pre-existing experimental data. Indeed, the prediction worked well as shown in the right Fig (bottom). After catalyst data for machine learning was quickly collected using a robotic synthetic system by Nagata in the Maeda group, the same scheme was applied to the synthesis of tetrahydropyran, and the predicted highly selective catalyst was examined experimentally. The predicted enantioselectivity of the most highly selective catalyst was 95:5, which was comparable to the experimental one, 95.5:4.5. Furthermore, some of predicted catalysts were unprecedented (***Angew. Chem. Int. Ed.,*** 2023). We established a seamless scheme utilizing experiments and machine learning to gather the corresponding data semi-automatically and perform predictions. This scheme will be applied not only to reactions similar to those we tried this time but also to more challenging reactions with low yield/selectivity in combination with large-scale screening.



[5] **Design of transition metal catalyst** Project-II

Organoboron compounds are very important as essential intermediates for the synthesis of pharmaceuticals and organic EL materials. The Ito group has successfully developed a computational chemistry-driven catalyst for the precise and selective synthesis of organoboron compounds. They used AFIR-based DFT calculations, which is the key technique in the center and advised by theoreticians, to calculate the transition state of the base reaction and consider the factors necessary for selectivity, a) design a new asymmetric ligand based on this consideration, b) confirm the improved performance through catalytic reaction experiments, and c) further computationally investigate the transition state of this new catalyst. By repeating this cycle of (a,b,c), a semi-rational design of asymmetric ligands was conducted (***Nat. Commun.***, 2018). The newly developed ligands are also effective in the previously impossible enantioconvergent asymmetric boron substitution reaction of alkyl halides, yielding the target compound with high enantioselectivity (***Angew. Chem. Int. Ed.***, 2019). To improve the performance of the ligand, a large silyl substituent was introduced into the quinoxaline backbone (Si-QuinoxP*), which is usually considered unimportant for design purposes, and the design was aimed at non-covalent interactions to the reaction center. The Si-QuinoxP* enabled direct enantioconvergent borylation and kinetic optical resolution of allyl-type substrates, which were considered challenging (***J. Am. Chem. Soc.***, 2021). Furthermore, the Si-QuinoxP*, designed based on computational chemistry, gave thermodynamically more unstable cis-borylcyclopropanes enantioselectively in the borylation cyclopropanation of allyl-type substrates (***J. Am. Chem. Soc.***, accepted). The selectivity is fully explained by DFT calculations and provides important insight into the effects of chiral ligands.

Assisted by computational chemistry, they have also succeeded in developing a new method for the synthesis of poly-substituted allylborane compounds, which were previously impossible to synthesize (***J. Am. Chem. Soc.***, 2021). Another achievement was the borylation of hydrosilanes and the generation of silyl anions from the resulting silylboranes (***J. Am. Chem. Soc.***, 2020), as well as the world's first successful synthesis of optically active silylboranes with nearly perfect optical purity (manuscript in preparation).

[6] **Chemical reaction induced by mechanical force** Project-IV

Organic synthesis is based on dissolving reactants in a solvent and conducting reactions in solution. In this project, the Ito group will find new reactions and achieve mechanochemical syntheses that are more efficient than solution systems by employing a grinding machine called a ball mill without using a solvent. Since this research field is very new and there are many unknown factors, computational and informatics science will be used to deepen our understanding of mechanochemical reactions and speed up the research.

Cross coupling reactions such as the Suzuki-Miyaura reaction are very useful chemical transformations, which together with the similar Buchwald-Hartwig reaction account for 30% of reactions used in the pharmaceutical field. The Ito group investigated the efficient implementation of such reactions in a ball mill and found an additive (1,5-cod) that significantly increases the reaction activity (***Nat. Commun.***, 2019; ***Chem. Sci.***, 2019), which was helped by Hasegawa group. This discovery led to further investigations, resulting in selective couplings that proceed only under solid conditions (***J. Am. Chem. Soc.***, 2020), and faster reactions (400-fold) and coupling of insoluble compounds (***J. Am. Chem. Soc.***, 2021) at high temperatures. Theoretical studies on the reactivity of solid-state reactions are underway with Yamamoto in Rubinstein group (manuscript in preparation).

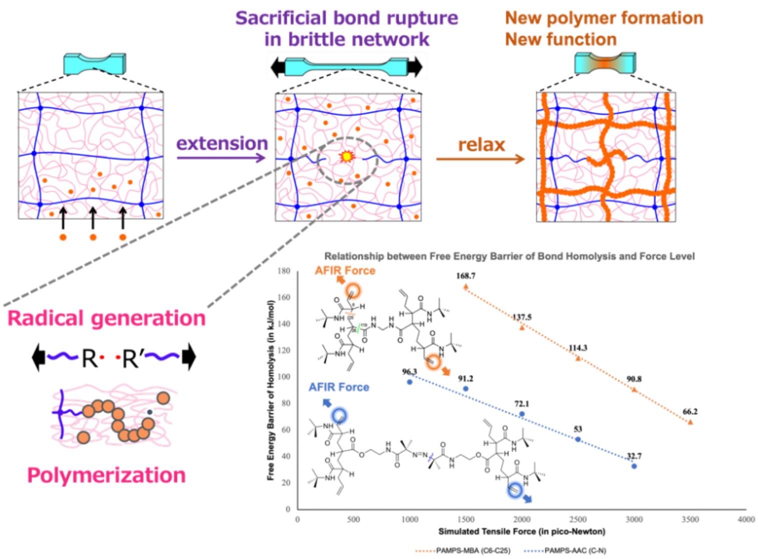
Ferroelectric materials exhibit the piezoelectric effect and generate an electric potential when mechanically stimulated. Taking advantage of this feature, the Ito group found for the first time in the world that mechanoredox reactions based on the piezoelectric effect proceed when ferroelectric materials and organic materials are milled together (***Science***, 2019, ***Angew. Chem. Int. Ed.***, 2020).

Organometallic compounds of main group elements are important reaction intermediates. The Grignard reagent, first reported 120 years ago, is a typical example and widely used worldwide. However, this reagent had to be synthesized in solution. The Ito and Maeda groups have found the first method to synthesize this reagent under ball-milling conditions (***Nat. Commun.***, 2021). They further deduced its structure using AFIR and DFT calculations and determined the structure with XAFS measurements using synchrotron radiation. This paper received over 18,000 views within 3 months of publication and was selected as one of the top 25 papers in *Nat. Commun.* in 2021.

(3) Design and discovery of new materials

[7] **Force-promoted degradation for controlled chemical reaction and polymer material functionalization** Project-VI

In general, force-promoted degradation by bond rupture inevitably causes local stress concentration and thereby catastrophic crack propagation at a macroscopic material level. This means that force-promoted degradation is uncontrollable, and chemically active species are not well-generated throughout the whole material, mostly occurring on the broken surfaces. In contrast, in a double network material, the stress concentration and crack propagation of the brittle network are suppressed by the presence of the soft and ductile network. Therefore, the double network systems can be potentially an excellent platform to directly apply the molecular level force-controlled chemical reaction to macroscopic materials for functionalization. The Gong group, Ito group, and Maeda group have been working on the development of force-promoted degradation for chemical reaction control and polymer material functionalization. Gong group developed the double network hydrogels as a platform of force-promoted degradation for controlled chemical-reaction (mechanoradical polymerization) and material functionalization (***Science***, 2019). Follow-up systematic studies quantified the force-driven internal chemical degradation in double network hydrogels (***Macromolecules*** 2020; ***Macromolecules*** 2020; ***Proc. Natl. Acad. Sci. USA***, 2021). Furthermore, Kubota and Jin in the Ito group and Maeda group demonstrated the sensing techniques of mechanoradicals in conventional polymers using a radical trapping molecule (***Angew. Chem. Int. Ed.***, 2021). The Gong group has been developing techniques for visualizing internal fractures in double network hydrogels using a mechanoradical trapping fluoroprobe (under preparation). The Maeda group theoretically investigated weak azo-crosslinkers for efficient force-promoted degradation (see Fig.), and Nakajima in the Gong group achieved a mechanoradical concentration, which is 5 times higher than that in the traditional crosslinker and significantly accelerated the radical polymerization kinetics in double network gels (***J. Am. Chem. Soc.***, 2022). The force-induced bond exchange reaction and long-term degradation and mechanism has been investigated via the collaboration of these three groups. Through these studies, the Maeda group established a theoretical approach to simulate mechanoradical generation (utilized in the above publications and the methodology paper is under preparation).



[8] **Understanding of formation/property/reaction of polymer network** Project-VI

The Rubinstein and Gong groups study the formation of polymer networks by free radical polymerization. To understand the kinetics of the network formation by free radical polymerization, the Rubinstein group has developed a model of coarse-grained molecular dynamics simulations. Their theoretical prediction is consistent with the simulation results. The Gong group is establishing a temperature-concentration superposition method that could probe the fast relaxation of network using rheometer. They have been working on a challenging topic extracting single chain behavior from the statistical ensemble response of a polymer network, together with Indei in Hokkaido University. They developed a double-network based "network force fingerprinting" method that connects single macromolecule force-extension behavior to the stress-elongation dependence of the corresponding network. This method catches individual chemical features of polymers well, and should serve as a powerful tool for the rational design of network materials with desired mechanical performances (submitted).

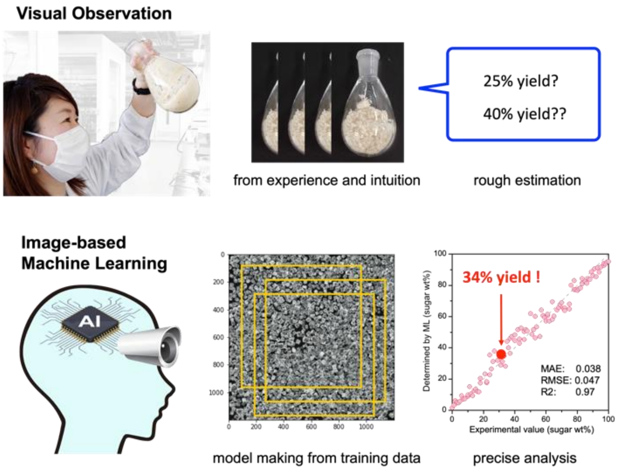
Based on such knowledge and techniques, they also worked on the brittle first network of double network hydrogels incorporating a unique mechanophore in collaboration with Prof. Craig at Duke University and other international members. This mechanophore has a ring-like structure that opens and lengthens by force and thereby toughens the double network hydrogels (***Science***, 2021).

(4) Creation of innovative measurement and diagnosis methods

[9] **Development of Cancer Diagnosis Method** Project-VII

Even though modern medical care is remarkably developed, easy diagnosis and treatment of cancer and development of technologies that contribute to them are indispensable. The Tanaka group, Gong group, and Komatsuzaki group have been working on the development of such technologies. Tanaka, Tsuda and Gong confirmed prototype HARP (Hydrogel activating reprogramming) phenomenon in 2018, where cancer cells become cancer stem cells within 24 hours using PAMPS-based double network gel (***Nat. Biomed. Eng.***, 2021, International patent: PCT/JP2018/005884, USA patent: 16/487,247). Cancer stem cells (CSCs) are the source of cancer recurrence and are therapeutic targets, and the HARP phenomenon could be applied for CSC detection. During the establishment of the HARP phenomenon, they analyzed cellular attachment and surface properties of double network gels (***Macromolecules***, 2019). For the interaction between hydrogel and cells, integrin was also shown to function as a mechanoreceptor (***Biochem. Biophys. Res. Commun.***, 2020). Novel reservoir function of the hydrogels was recognized by accumulating thrombospondine into hydrogels for cellular differentiation (***J. Biomed. Mater. Res. A,*** 2021). In addition to these basic progresses, clinical applications for cancer diagnosis including identification of new CSC markers and drug screening for identification of therapeutic drug to eradicate CSCs are important issues. These require a basic platform of hydrogel plates kits and a huge number of experiments. A hydrogel kit was designed for efficient performance of the experiments (Submitted patent: JP2021/151208) by a collaboration of the Tanaka and Gong groups with researchers in the Faculty of Advanced Life Science, and the bandit algorithm was applied for drug screening by the Komatsuzaki group. In addition, the Komatsuzaki group developed an AI-assisted Raman microscope and applied it to discriminate CSCs. The group also developed a platform to infer the underlying causal inference of many-body interactions to apply it to cell tracking data (***Sci. Adv.***, 2022).

[10] **Image-based machine learning for quantitative analysis of reactions** Bottom-up



In the field of experimental science, automation has been developed mainly for reaction screening and data measurement and processing. However, there still exists a large gap between experimental science and information (theoretical) science. When experimentalists develop and discuss reaction conditions, reaction yields are the most important and easy-to-understand parameter. While determination of reaction yields is generally a time-consuming process, well-trained researchers sometimes can predict rough reaction yields just by looking at the reaction flask, because they have sufficiently experienced good and bad batches. Based on this, Inokuma hypothesized that the experimentalists' experiences and intuition could be shared with non-experts through image-based machine learning as illustrated in the above Fig.. He started with non-experts to collaborate with Takigawa, Hu, Hijikata and Pirillo to establish systems for predicting molar ratio between two chemicals, which is a standard way to calculate yields. They first worked on mixtures of sugar and dietary salt, which it is very difficult to distinguish at a glance. After collecting images of the mixtures using a digital microscope, they performed image processing (Data Augmentation), such as image cropping, rotation/flipping operations, and contrast adjustment, to increase the number of training datasets (from 100 pictures to 12000 sub-images) for model making. Using the trained model of machine-learning, the team was able to predict the ratio of sugar and salt within a mean averaged error (MAE) of 3.8 wt% which is significantly more precise than analysis with naked eyes. While making a reliable machine-learning model requires at least 200 images, the trained model on GoogleColab allowed quick prediction (~10 sec.) of mixture ratio from test images. The same approach was also applied to mixtures of α-glycine and γ-glycine (a combination of crystalline polymorphs), crude product mixtures of pyrolysis reaction, and determination of enantiomeric excess between D- and L-tartaric acids with excellent accuracy, MAE ≤7% (manuscript in preparation). This image-based machine-learning system will help design and discover new chemical reactions by accelerating the analysis of reaction yields.

2-2. Research environment including facilities and equipment

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

Facilities and equipment appropriate for a world-class research center have been established. The renovation of the Creative Research Institution Building has been completed and the 2,600 m^2 space has been effectively utilized to promote fusion research. Experimental equipment and computers necessary for fusion research in line with the center's mission, such as laser scanning confocal Raman microscopes, luminescence and fluorescence imaging systems, high-resolution time-of-flight mass spectrometry systems, and high-performance computational information processing systems, have been installed as essential shared facilities for research. In addition, we completed the design of the "International Research Center for Chemical Reaction Design and Discovery" (new building, 4 floors above ground, 5,500 m^2), which was requested to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) as part of its budget request for the improvement of facilities for national universities, and construction work began in October 2021 (to be completed by the end of FY2022). With this, the lab space per PI in ICReDD will be roughly double that of the average space give to a PI in the university. President's discretionary expense will cover half of the construction cost. The new building will have a huge mixed office and mixed lab with unparalleled advanced facilities in line with the center's mission, to further promote research via daily communication. In addition, there will be a kid's room (innovation space) and a lounge space for casual communication. There will also be a discussion space and a communication space where all members can freely and comfortably discuss their research.

ICReDD has been affected by the COVID-19 pandemic for two years, and has been working at home, while developing an environment and installing equipment for online meetings. This enabled daily communication with overseas PIs as soon as we think of it and increased the level of fusion in ICReDD research. The research environment was also improved through ICReDD internal seminars, international seminars, interdepartmental symposiums, international symposiums, communication through online salons, start-up support for new faculty members, and start-up support for fusion research.

2-3. Competitive and other funding

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

ICReDD operates with its own financial resources from the university, which are equal to or greater than WPI budget. ICReDD's PIs and other researchers have continued to receive competitive research funding steadily since its inception. PIs have been selected for large research grants such as JST-ERATO, JST-CREST, AMED-CREST, AMED-P-CREATE, JST-ImPACT, and JST PRESTO. The total amount of these funds was 203 million yen in 2018, 668 million yen in 2019, 934 million yen in 2020, and 655 million yen in 2021. Representative competitive research funds in FY2021 are JST-ERATO (1), JST-CREST (7), JST-START (1), JST-MIRAI (1), JST-FOREST (1), JST-PRESTO (4), AMED-P CREATE (1) etc. In addition, our PIs proofread applications for Grants-in-Aid for Scientific Research to improve the acceptance rate. As results, the amounts of Grants-in-Aid for Scientific Research acquired have increased year by year (FY2018: 78 million yen, FY2019: 159 million yen, FY2020: 148 million yen, FY2021: 182 million yen), and overseas PIs have also succeeded in obtaining Grants-in-Aid for Scientific Research.

2-4. State of joint research

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

Since the establishment of the center, we have been actively collaborating with domestic and international researchers as well as promoting fusion research within the center, leading to papers in collaborations within Hokkaido University (121), domestic collaborations (162, including 9 inter-WPI collaborations), and international collaborations (134, 33% of papers from the center). 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, and five attached institutes in Mar. 2022 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.

Representative domestic collaborative research

The center conducted on a wide range of topics from single molecules to biological complex systems which were expanded to the outside of the center as well. For example, in complex biological issue, Tanaka, Tsuda, Wang et al. utilized their techniques to characterize the new SARS-CoV-2 variants under the framework of Genotype to Phenotype Japan (G2P-Japan) (***Nature***, 2022; ***Nature***, 2022), which is relevant to social needs. Hijikata and Pirillo elucidated the origin of the characteristic elasticity of a metal-organic framework by theoretical calculation in collaboration with RIKEN and the University of Tokyo (***Nature***, 2021). Hijikata and Pirillo also revealed the unique dynamics of novel carbon materials (***Science***, 2019) in collaboration between WPIs, showing full use of theoretical calculation in the synthesis of novel materials. Taketsugu and Iwasa reported theoretical understanding and analysis based on calculations in the development of precise spectroscopic methods at the single molecular level (***Science***, 2021; *Nat. Nanotech.*, 2020) in collaboration with RIKEN and others.

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Representative international collaborative research

Inokuma, Ide, Hijikata, Jenny, and Yoneda, together with Jonathan L. Sessler of the University of Texas at Austin, USA succeeded for the first time in the world in synthesizing and isolating calix[3]pyrrole, which was considered to be highly distorted from theoretical calculations (***J. Am. Chem. Soc.***, 2021). This work can open a new way to synthesize unstable compounds and was highlighted in Science magazine. In addition, Hijikata and Pirillo collaborated with Roland A. Fischer at the Technical University of Munich, Germany, under the JSPS bilateral program, and theoretically explained the role of water on selective gas adsorption in a metal-organic framework (***ACS Appl. Mater. Interfaces***, 2020) to develop practical materials. Taketsugu together with Oliver Schalk of the University of Copenhagen, Denmark, theoretically revealed the photochemical reaction (photodecomposition) of *o*-nitrophenol, which is one of the constituent molecules of the air pollutant PM 2.5, showing the origin of nitrite in the atmosphere (***J. Phys. Chem. Lett.***, 2021). These achievements have been published in press releases and disseminated widely. Huang started to work as a Jr. PI in 2021 and has already reported on photoisomerization of indigo compounds with S. Hecht et al. in Germany (***Chem. Eur. J.***, 2022). Theoretical analysis was conducted for further development of series of indigo compounds. Thus, the number of collaborations outside Japan and their Publications are steadily increasing.

PIs are located outside the center in the U.S., France, Germany, the University of Tokyo, and RIKEN, and agreements have been signed with some of the research institutions to which these PIs belong to strengthen collaboration. We have already reported co-authored papers on the fusion of theory and information with the University of Tokyo and the University of Strasbourg (***J. Chem. Inf. Model.***, 2021; ***Sci. Rep.***, 2022). Thus, the strengthened collaboration has led to scientific results. Gong and Rubinstein are members of the NSF Center for the Chemistry of Molecularly Optimized Networks, and reported a paper utilizing this network (***Science***, 2021). Through these agreements and network, we promote further research collaborations by stimulating exchanges at researcher level.

Collaborative research under MANABIYA

The center launched its own joint research and educational system, MANABIYA, and started to accept applications. So far, 9 applications have been accepted and led to 4 papers. Results of MANABIYA within Hokkaido University include the development of oxidative functionalization of low reactive tetraalkylsilanes (***J. Am. Chem. Soc.***, 2021), the development of hydrogenation of alkenes using cobalt redox catalyst and ascorbic acid (***Nat. Commun.***, 2021), and the elucidation of the ring-flip mechanism of overcrowded ethylenes (***Bull. Chem. Soc. Jpn.***, 2022) were reported. A participant from Waseda University reported the chiral diene-catalyzed enantioselective [4+2] cycloaddition via the reaction mechanism of the Pt(II)/Pt(IV) cycle (***Org. Chem. Front.***, 2021). After the COVID-19 pandemic, we more actively accept applications from overseas to promote international collaboration.

2-5. Appraisal by society and scientific organizations

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

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

ICReDD has world-class researchers as Principal Investigators (PIs) and has received outstanding awards such as the Nobel Prize in Chemistry (List), the H.C. Brown Award (List), the Nagakura Saburo Award (Maeda), the Dirac Medal (Maeda), the Chemical Society of Japan Award (Gong), the Minister of Education, Culture, Sports, Science and Technology's (MEXT) Commendation for Science and Technology (Gong, Sawamura). In FY2021, the center members have presented their research in 16 invited lectures at international conferences and 13 awards have been granted. Since the establishment of ICReDD, 46 invited lectures were given at international conferences and 39 awards were received.

In 2021, the center has also achieved outstanding research achievements. 184 papers were published in peer-reviewed journals, which is four times (12 papers per PI) the number of papers published by professors of the University per year (3 papers). 12 papers in journals with IF > 20, 47 papers in journals with 20 > IF >10). One paper was published in Nature (IF: 49.962), two in Science (IF: 47.728), one in Advanced Materials (IF: 30.849) and one in Nature Biomedical Engineering (IF: 25.671). The center has also published 406 total papers, including 74 TOP 10% papers (18% of 406 total papers, university average 9%), 116 highly cited papers (IF 9 or more), and 30 research press releases since 2018.

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

3-1. Applications of research results

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

ICReDD's research results, conducted under ICReDD's center strategy, are steadily bearing fruit, including patent applications. Since its inception, joint research and patent applications have increased (industry-academia collaboration papers 2018: 0, 2019: 4, 2020: 4, 2021: 12). 46 research news articles are featured on the website. The main achievements are as follows:

1) The program license agreement for the AFIR method to perform automated searches of chemical reaction paths by quantum chemical calculations was concluded. In this way, the AFIR method, which accelerates the understanding and prediction of chemical reactions, is now available to use in GRRM20. In June 2021, GRRM20 was released from HPC Systems Inc. under a program license agreement with the University. By March 2022, 16 licenses (1,233 cores) have been sold and 14 inquiries (1,200 cores) have been received (ICReDD's licensing income totals 8.64 million yen).
2) To realize the Suzuki-Miyaura cross-coupling reaction using insoluble aromatic halides as a reaction substrate, Professor Ito has established a synthetic method called high-temperature ball milling, in which ball milling is performed while heating the reaction vessel with a heat gun. The desired coupling products were obtained from insoluble pigments and dyes, which cannot be handled by conventional methods due to their extremely low solubility. These results are expected to lead to the development of new chemical products, pharmaceuticals, organic light-emitting materials, and organic electronic materials that cannot be synthesized by conventional organic synthesis in solution.
3) Professor Hasegawa collaborated with researchers at the Hokkaido University Research and Education Center for Robust Agriculture, Forestry and Fisheries Industry to apply special light-converting materials to the improvement of plant growth. The application of these materials as a thin film on greenhouse surfaces enables the conversion ultraviolet rays from the sun, which normally are not utilized in photosynthesis, into visible light that plants can use to create additional energy.
4) Focusing on the properties of hydrogels, Professors Tanaka and Gong succeeded in converting cancer cells back to cancer stem cells within 24 hours and filed a patent application. Clinical applications in cancer diagnosis, including the identification of novel cancer stem cell markers, have been realized, and this research has been covered 10 times by the press and TV programs. They also designed a hydrogel kit for efficient experiments and filed a patent application. Furthermore, in collaboration with Informatics, the company developed an AI-assisted Raman microscope and applied it to the identification of cancer cells and cancer stem cells. We developed an informatics platform to infer causality from cell tracking data. This could lead to the development of anti-cancer stem cell drugs and personalized medicine. Furthermore, Professor Gong's research on double-network hydrogels is expected to be implemented in society as automobile tires, self-healing materials expected to have medical applications, adhesives for the marine environment, and high-strength protectors, in addition to cancer stem cell induction, and has been featured 40 times by the press and TV programs.

3-2. Achievements of Center's outreach activities

* Describe what was accomplished in the center's outreach activities during the period from 2018 through March 2022 and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 5, describe the concrete contents of these outreach activities and media reports or coverage of the activities.

Each fiscal year, ICReDD held the ICReDD International Symposium, inviting researchers from Japan and overseas to introduce them to the vision and research of ICReDD. In 2018 and 2019, the symposium was held in Sapporo. In 2020 and 2021, the symposium was scheduled to be held at international locations (University of Strasbourg and Duke University, respectively) to further increase international awareness of ICReDD. However, due to the COVID-19 pandemic, the 2020 and 2021 International Symposia were held as virtual events. Despite the three time zones of Japan, the U.S., and Europe, the 2021 Symposium had 255 live participants from 11 countries, and numerous on-demand viewers.

Since 2018, ICReDD 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 FY2019 and FY2020 was created to convey the vision and recent progress of ICReDD to domestic and international audiences. Other ICReDD goods were created to attract attention to our booth at events, including pens 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 international events such as the 2019 World Conference of Science Journalists and the 2020 Annual AAAS Meeting to increase

ICReDD's global visibility, as well as at outreach events like the WPI Science Symposium to inspire high school students. Videos were created to introduce a majority of ICReDD PIs and these were posted on our YouTube channel.

In 2021, ICReDD established the Akira Suzuki and ICReDD Awards, which honor prominent chemists in both experimental chemistry and computational chemistry or information science. The inaugural awards were given to Professor Stephen L. Buchwald from the Massachusetts Institute of Technology and Professor David J. Wales from the University of Cambridge, strengthening ICReDD's connection with these two prominent scientists and their institutions. The MIT Chemistry department posted on Twitter about the award while mentioning @ICReDDconnect, garnering a high level of interaction (520 engagements) among an international audience. A digital ad campaign was also run to increase awareness of both the Akira Suzuki Awards and the 4th ICReDD International Symposium. Digital ads were posted on the websites of respected scientific journal publishers (Springer Nature, Science/AAAS, ACS, RSC) with ads mainly targeting the geographic regions of North America and Europe to maximize global visibility.

Other outreach efforts include our monthly research news postcard series (22 in total), which promote our latest research to a mailing list of hundreds of people, including over 70 international addresses. A unique endeavor at ICReDD is our quarterly news poster "The CATALYST", which explains concepts of chemistry in an easy-to-understand manner, while also introducing ICReDD research to a high school level, non-scientist audience to a mailing list of 220. A total of 7 issues have been issued, including a special edition 6th issue that commemorated ICReDD Specially Appointed Professor Benjamin List winning the 2021 Nobel Prize in Chemistry. Video interviews (5 videos, 10,390 views) and bilingual exhibition panels commemorating his Nobel Prize were created in collaboration with CoSTEP and the university PR. The panels are exhibited in numerous locations on the university campus.

ICReDD also promotes itself on social media, including Facebook, Twitter, LinkedIn and Instagram. A recent effort has been made to more actively promote ICReDD research on the ICReDD website and on Twitter. Since October 2021, in addition to 4 English language press releases, 15 research news articles (prepared in both English and Japanese) were posted on the ICReDD HP. Tweets related to these research articles have received roughly 86,000 impressions and over 2300 engagements. Growth for this period has averaged 20 followers per month, a 33% increase over our previous highest growth period. Mentioning journals in ICReDD research tweets has resulted in prominent journals such as JACS and ACS Catalysis following the ICReDD Twitter account and retweeting us, increasing ICReDD's visibility to the international audiences of these respected journals. Traffic on ICReDD's website saw an increase in traffic of 116%, partially due to the Nobel Prize. Still, ignoring the Nobel Prize spike in traffic, the increased research promotion has contributed to a 48% increase in website traffic in the last 5 months.

4. Generating Fused Disciplines (within 3 pages)

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

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

In 2019, under the leadership of the center's Director with the ICReDD slogan "Revolutionize chemical reaction design and discovery", we decided on new, challenging themes that are not an extension of the PI's past research, such as (1) Development and integration of advanced computational and informatics techniques, (2) Design and discovery of new synthesis methods, (3) Design and discovery of new materials, and (4) Creation of innovative measurement and diagnosis methods, and launched the 7 flagship projects. These projects hold monthly progress meetings, and the manager of the Research Strategy Unit (currently Fusion Research Coordinator) and the Center Director participate in these regular meetings to monitor progress, and the manger reports on each meeting at the director's meeting to discuss the direction of each research from a short-term perspective. The discussions are communicated to project members through the manager, and the direction of each research is adjusted. From a long-term perspective, the manager and the Executive Director meet annually with each PI to confirm and share the director's thoughts on the mission of the center, and discuss progress and issues related to each project.

In addition, at the regular monthly PI meetings, all PIs report on the research progress of their own group, which enables for PIs to share and discuss progress among PIs, leading to the discovery of new fusion research in top-down manner.

In FY2021, the progress report meetings for all flagship projects were held for all member of the center, because it was an appropriate time to consider future further development. Based on these reports, we will reorganize the flagship projects and rebuild a system that can carry out research more powerfully and strategically. We decided to establish We decided to establish an new independent fusion research coordinator from in the Research Strategy Unit, who was the unit manager , to work on promotion of fusion research and support researchers by looking out over the center from FY2022.

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

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

Start-up support

In contrast to top-down research by the Center Director and PIs, the new faculty start-up and fusion research start-up supports are operated to allow researchers to challenge new research freely with their own ideas under the ICReDD slogan. The new faculty start-up support is freely available to researchers to create an environment in which they can smoothly start new fusion research with ICReDD members by assigning the support to newly appointed faculty members. 10 members (31.5 million JPY in total) in FY2019, 7 members (22.05 million JPY in total) in FY2020, and 2 members (6.7 million JPY in total) in FY2021 received such support. The fusion research start-up support is based on a research proposal from researchers, and the Center Director decides on their acceptance/rejection, thereby supporting the smooth acquisition of external funding and results for new fusion research. In particular, the director highly evaluates challenging proposals consisting of research teams from three fields, theory, information, and experiment, and assigns the fusion research start-up support to those highly evaluated proposals. 8 proposals (37.5 million JPY in total) in FY2019, 7 proposals in FY2020 (13.15 million JPY), and 9 proposals in FY2021 (17.55 million in total) were funded, leading to 14 and 3 research grants from the government and foundations, respectively. Parts of scientific achievements are described 4-3.

Various types of seminars

Since the establishment of the center, various types of seminars have been held to match the level of understanding of different fields among researchers. From FY2018 to FY2019, a short frank presentation and discussion was held once a week during lunch time to remove barriers among three different fields. Faculty members also gave 30-minute presentations on their own expertise once a month, followed by one hour or more of discussion and mixing. In addition, a web page was created to introduce the research of individual researcher and to assist new members in finding research partners/topics. These created opportunities for all members of the center to get to know each other and find collaborators. Fusion seminars were subsequently initiated to further share each researcher's background research progress. The fusion seminars helped researchers understand the differences in research styles among the three fields. Together with the fusion seminar, we started the stirring seminar in order to share basic knowledge required to understand different fields in FY2020. In the stirring seminar, researchers in different fields are paired up, and one researcher prepares a presentation of his/her research field to be understood by people in different fields, and the other researcher explains his/her presentation. This helped both presenters and listeners deepen their understanding of different fields. In parallel with the above, seeds/needs seminars were also started to report on the progress of each researcher's research while also highlighting either proposals for researchers in different fields or requests for contributions to resolving problems of the presenter, with the aim of creating bottom-up fusion research. Although all seminars were conducted via ZOOM due to COVID-19 from FY2020, we continue to hold monthly seminars and started seminars that we invite researchers from outside the center including abroad (ICReDD internal seminars, external seminars, international seminars, etc.) by taking advantage of the ease of online seminars. In particular, international seminars were held to internationalize the center.

Support for AFIR

For AFIR, which is a key technology in our center, a computer environment with the huge number of cores (4000 cores) has been prepared to allow experimentalists to perform calculations for their own investigating systems. The computer systems are shared and fully used by researchers in the three fields for 24 hours daily. In addition, a tutorial seminar on the use and development of AFIR was held in FY2021 for theoretical and information scientists to accelerate their research and development This seminar resulted in achievements of [1], [2], [3], [6], and [7] in 2-1.

Research Environment

In order to realize an environment where researchers in computational and information science can watch experimental laboratories and experimental researchers can study and discuss the results of computation, the first mix-lab was launched in FY2018, where researchers in the three fields of computation, information, and experiment can work on their research together and also can communicate through daily conversations leading to the spontaneous discussions on collaborations. In FY2019, a second mix-lab and mix-office were launched, followed by the ICReDD salon, which is a place for relaxed communication among researchers, and in FY2020, the third and fourth mix-labs were launched to involve researchers more, 104 researchers and students were placed. To compensate for the decrease in face-to-face communication due to COVID-19, an online salon is also held twice a week using zoom (77 times in total), maintaining an environment that allows us freely to communicate, chat, and discuss research topics. In addition, a chief is assigned to each room to ensure smooth operations in each room and the creation of fusion research, including coordination of problems caused by differences in research styles between different fields. An equipment management committee meeting is held once a month to ensure efficient operation of experimental equipment throughout the center. These operations are scheduled to continue after we move to the new building (scheduled to be completed in April 2023) to further accelerate fusion research. In an effort to promote fusion research more, the newly established fusion research coordinator will act to match up researchers, encourage frequent discussions, and provide support for smooth launch of research through the start-up support system.

4-3. Results of research in fused research fields

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

- In Appendix 1-2, list up to 10 of the Center's main papers on interdisciplinary research that substantiate the above record of results, and describe their content.

Various measures we took successfully stimulated researchers and have led to various types of fusion research. Here, we describe examples of fusion research categorized into three types (**A**, **B**, and **C**).

A. Fusion research between theoretical chemistry and information science
Management and exploration of reaction path networks

With the rapid growth of calculation capabilities and fast exploration of the potential energy surface of reactions with GRRM/AFIR, manual analysis of all the generated data becomes cumbersome. Based on the newly developed CGRdb management system (*J. Chem. Inf. Model.*, 2021,), designed specifically for handling reactions, the Varnek and Maeda groups developed RePathDB (*J. Chem. Inf. Model.*, 2021), a combined graph/relational database management system for management and exploration of reaction path networks, which reduces network complexity significantly by representing transition states as Condensed Graphs of Reaction (CGR). This helps us to use huge size of database generated by AFIR.

B. Fusion research between theoretical chemistry and experimental chemistry
Computational and experimental iterative validation approach

To develop and utilize a strategy for creating new reactions using computation, integrative research was launched by a computation team (Harabuchi in Maeda group) that conducted reaction path searches with the AFIR method, and an experimental team (Mita, Hayashi, Takano, You) that investigated reactions based on the computational results. Due to these efforts, we have reported two approaches that leveraged the AFIR method to dictate the direction of the experiments for the radical difunctionalization of gaseous ethylene (*ACS Omega*, 2021) and the carboxylation of a palladacycle (*Chem. Asian J.*, 2021). These results represent the significant potential of AFIR for accelerating prediction-based reaction development.

Ring-opening reaction of newly synthesized highly-strained calix[3]pyrrole analogues

Inokuma and Ide (experimentalists) have unraveled the mystery of the previously unsynthesized calix[3]pyrrole molecule, composed of three pyrrole rings in collaboration with Hijikata and Pirillo (theoreticians) through daily scientific conversation. The calix[3]pyrrole synthesized from chain polyketones was found to have a large distorted structure, indicating a significant factor in its destabilization(*J. Am. Chem. Soc.*, 2021). Namely, the synthetic strategy overcame the instability of the calix[3]pyrrole which was suggested by theoretical calculation. They also synthesized calix[3]pyrrole analogues composed of pyrroles and/or furans and determined the mechanism of ring cleavage(*Chem. Eur. J.*, 2022). This achievement can open the way to synthesize unstable compounds.

Detection of mechano-radicals

The Ito and Maeda groups developed a novel strategy for introducing a luminophore into generic polymers facilitated by mechanical force to enable us to detect bond dissociation in polymer materials. They utilized polymeric mechano-radical formed in situ under ball-milling conditions to promote a radical-radical coupling reaction between the mechano-radical and a prefluorescent nitro-oxide reagent. The prefluorescent probe was ball-milled with the polystyrene, and a clear emission enhancement was observed. Photophysical properties of the yielded polymeric materials and a computational study indicated that the generated mechano-radicals coupled with the prefluorescent probe, inducing the strong emission. In addition, several generic polymer materials also showed the similar transitions (*Angew. Chem. Int. Ed.*, 2021).

Development of photo-functional materials

One of the research themes in Eu(III) complexes is manipulation of π-4f charge transfer excitation. This area of research is relatively unestablished, though those complexes could lead to the development of next-generation photofunctional metal complexes. Through cooperative efforts, the Hasegawa and Taketsugu groups successfully understood the fundamental effect of coordination geometry in Eu(III) complexes on the excited dynamics containing π–4f charge transfer excited states, and they demonstrated LMCT-dependent energy transfer processes of seven- and eight-coordinated Eu(III) complexes for the first time. (*J. Phys. Chem. A*, 2021). In addition, the Hasegawa group developed a chiral lanthanide lumino-glass with extra-large circularly polarized luminescence for which the glass structure is crucial and was revealed by Maeda group for further development (*Commun. Chem.*, 2020). This achievement can contribute to developing photonic security devices.

C. Fusion research between information science and experimental chemistry

Two projects, prediction of more highly enantioselective catalysts and image-based quantitative chemical reaction analysis, were described in Section 2-1. In addition to these, Sidorov in the Varnek group and Nagata in the Maeda group also have been collaborating. Generative models are becoming popular in drug design and other fields; however, generation of reactions is still uncommon. Using special SMILES-based Condensed Graph of Reaction representation, reaction can be generated more easily, which was demonstrated on the example of Suzuki-Miyaura coupling (*Sci. Rep.*, 2021). Among thousands of generated reactions, feasible ones can be picked out by special filters, including quantum chemical calculations of their thermodynamics. However, experimentally these may still be difficult to perform, which has inspired them on the project of predicting optimal conditions for chemical reactions, fluorination reactions for the use of fluorinated agents in PET imaging.

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

5-1. International Circulation of Best Brains

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

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

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

Professors Varnek, Rubinstein and List (Nobel Prize in Chemistry 2021) joined as PIs. Advisory board meetings were held online with 8 prominent researchers (3 from Japan and 5 from overseas): Hisashi Yamamoto (Chubu Univ, experimental), Cathleen Crudden (Queen's Univ, experimental), Feliu Maseras (ICIQ, theory), Fahmi Himo (Stockholm, theory), Shigeyoshi Sakaki (Kyoto Univ, theory), Peng Liu (Univ of Pittsburgh, theory), Alexander Tropsha (Univ of North Carolina, Information), and Shin-ichi Minato (Kyoto Univ, Information). We held two **international seminars**, which were able to be held more easily thanks to the new online meeting environment implemented in FY2021. Speakers for the seminars were Carsten Bolm (RWTH Aachen University) and David Balcells (Hylleraas Centre for Quantum Molecular Sciences, Univ of Oslo). Such seminars will be held regularly in the future.

International participants in the **International Symposium** were as follows (underlined are the Advisory Board): First (March 2019) Alexandre Varnek (PI), Benjamin List (PI). Second (194 participants, 24 foreign nationals) (November 2019) Vladimir Gevorgyan (Univ of Texas), Andrei Yudin (Univ of Toronto), Mu-Hyun Baik (KAIST), Fahmi Himo (Stockholm Univ), Jianbo Wang (Peking

Univ), Djamalddin Musaev (Emory Univ), Luisa De Cola (Univ of Strasbourg), Peng Liu (Univ of Pittsburgh). Third (279 participants, 118 foreign nationals) (February 2021) Jean-Marie Lehn, Jean-Pierre Sauvage, Paolo Samori and Alexandre Varnek (PI) (Univ of Strasbourg), and Peter Schreiner (Justus Liebig Univ), Feliu Maseras (ICIQ), Scott Denmark (Univ. of Illinois), Kendall Houk (UCLA). Fourth (255 participants, 42 from 10 foreign countries) (March 2022) Stephen Buchwald (MIT), David Wales (Cambridge Univ), Ron Elber (UT Austin), Rigoberto Hernandez (Johns Hopkins Univ), Matthew Sigman (Univ of Utah), Benjamin List (PI).

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

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

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

Since the center was established, foreign researchers have been hired through international recruitment by Nature, Science, JREC-IN, etc., and through the connections of PIs. Personnel have steadily increased over the past three and a half years. In 2019: 33 were employed (225 applicants), in 2020: 14 were employed (186 applicants), and in 2021: 11 were employed (88 applicants). We have hired researchers from top research institutions such as Princeton University, Columbia University, UCLA, Johns Hopkins University, The University of Manchester, the Max-Plank Institute, the University of Strasbourg, ENS de Lyon, and Monash University. Nationalities are from the U.S., France, Germany, Italy, Russia, Singapore, Philippines, Turkey, South Korea, Taiwan, India, China, etc. Foreign researchers now account for 40% of ICReDD's researchers, and young researchers under 40 years old account for 68%. At the end of March 2019, 4 of 18 researchers (22%) were foreign nationals and 3 (17%) were female. At the end of March 2020, 22 of 59 researchers (37%) were foreign nationals and 6 (10%) were female. At the end of March 2021, 24 of 66 researchers (36%) were foreign nationals and 7 (11%) were female. At the end of March 2022, 27 of 69 researchers (39%) were foreign nationals and 9 (13%) were female. The ratio of research fields is 50% each in computation/information and experimental scientist, which is in line with the center's plan since experimental researchers are needed for each output the center aims to achieve.

One Research strategy unit manager (currently Fusion research Coordinator; Specially Appointed Associate Professor) for the purpose of fusion research support were employed in the end of FY2018. 3 Co-PIs under 40 years old that work with the overseas PIs were employed from FY2019. The University provided permission to employ four full-time Tenure-Track Associate Professors and one assistant professor and recruitment started in FY2021. To start with, 3 associate professors and one female assistant professor under 40 years old were employed, and the remaining one female associate professor will be employed during FY2022.

Promotion activities for ICReDD faculty members and postdoctoral researchers have been showing positive outcomes. To enhance ICReDD's research, specially appointed Assistant Professors and lecturers were promoted to Associate Professor positions outside the center (one in Gong's group, one in Hasegawa's group and one in Komatsuzaki group in 2021, and two in Ito's group in 2020 and 2021). Also, five of the postdoctoral researchers, who had been achieving significant results in one of the core research projects, were promoted to Assistant Professor during the past three and a half years. In addition, 16 postdoctoral researchers and faculty members have left ICReDD for new positions. After ICReDD, many of them have returned to their home countries and succeeded in gaining new positions.

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

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

Agreements are in place with the University of Strasbourg, the University of Tokyo, and Chubu University. Furthermore, the Max Planck Institute, 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. We plan to continue to collaborate with these research institutions and conclude exchanges and agreements in a planned and concrete manner in cooperation with the University's International Cooperation Organization. We also plan to conduct active international public relations activities for ICReDD at each overseas Hokkaido University Office, particularly the North American and European offices, as well as engage in industry-academia-government collaboration. We will strengthen international public relations in cooperation with the University's Public Relations Office and initiate fundraising activities, including the creation of a mechanism to obtain external funding.

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

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

Four regular international symposiums that were held are listed in 4-6.

ICReDD has held four international symposia and four interdepartmental symposia in the past three and a half years. In 2021, the international Akira Suzuki Awards were established to recognize outstanding researchers. A number of seminars and symposium were held in order to ensure opportunities for regular and active communication in a cross-disciplinary manner among ICReDD's young researchers, to advance future fusion research, and to solicit and propose new collaborative research. These events include four interdepartmental symposiums (Faculty of Science (December 2020), Faculty of Engineering (April 2021), Faculty of Medicine (October 2021), and five attached institutes (March 2022)), two international seminars (December 2021, February 2022), and six ICReDD seminars. In addition, the ICReDD Online Salon was held twice a week (77 times in total) as an opportunity for regular communication.

A summary of our four international symposiums is as follows:

・First (130 participants) (March 12, 13, 2019) and Kenichiro Itami (Nagoya Univ), Shin-ichi Minato (kyoto Univ), Hisashi Yamamoto (Chubu Univ), and ICReDD PIs: Satoshi Maeda, Hajime Ito, Alexandre Varnek, Benjamin List.

・Second (194 participants) (November 27, 28, 29, 2019) Vladimir Gevorgyan (Univ of Texas), Andrei Yudin (Univ of Toronto), Mu-Hyun Baik (KAIST), Fahmi Himo (Stockholm Univ), Jianbo Wang (Peking Univ.), Djamalddin Musaev (Emory Univ), Luisa De Cola (Univ of Strasbourg), Peng Liu (Univ of Pittsburgh), Masahiro Yamanaka (Rikkyo Univ), and ICReDD PIs: Yasuchika Hasegawa, Satoshi Maeda, Masaya Sawamura.

・Third (279 participants) (February 22, 23, 24, 2021) Peter Schreiner (Justus Liebig Univ), Feliu Maseras (ICIQ), Scott Denmark (Univ of Illinois), Kendall Houk (UCLA), Miki Haseyama (Aoyama Gakuin Univ), Jean-Marie Lehn (Nobel laureate), Jean-Pierre Sauvage (Nobel laureate), Paolo Samori and Alexandre Varnek (PI) (Univ of Strasbourg), and ICReDD PIs: Satoshi Maeda, Tetsuya Taketsugu, Hajime Ito, Jian-pin Gong.

・Fourth (255 participants) (March 12, 13, 14, 2022) Stephen Buchwald (MIT, Akira Suzuki Award winner), David Wales (Cambridge Univ, ICReDD Award winner), Ron Elber (UT Austin), Rigoberto Hernandez (Johns Hopkins Univ.), Matthew Sigman (Univ. of Utah), and ICReDD PIs: Benjamin List (Nobel laureate), Tamiki Komatsuzaki, Tetsuya Taketsugu, Hajime Ito, Masaya Sawamura, Satoshi Maeda.

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

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

Interviews with foreign researchers and PIs were conducted by the International Planning Unit staff, 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 ICReDD'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, ICReDD 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 checks the situation in case of fever, contacts the public health center, and provides up-to-date information on vaccination.

5-4. Others

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

In such an international environment, Japanese researchers can gain international experience on a daily basis. We provided many opportunities for presentations at seminars, interdepartmental symposiums, and international symposiums, as well as lectures to the public as instructors. As details in 5-2-1, ICReDD secured five positions (three associate professors, one female assistant professor, and one female associate professor) from the university to create career paths for young researchers. Further efforts to secure positions are in progress. In this way, female career paths from postdoctoral researcher to principal investigator will be realized and nurtured and role models, which are not available for other organizations, will be shown.

6. Making Organizational Reforms (within 3 pages)

6-1. Decision–making system in the center

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

The final decision-making authority for all matters related to the operation and management of ICReDD rests with the Center Director. ICReDD's administrative structure was reorganized with its long-term (post WPI funding) future in mind, and the Executive Director was made the Administrative Director to strengthen cooperation with the University Headquarters. This reorganization has allowed the Center Director to focus more on research and less on administration. Administrative meetings also support the Center Director's leadership in research. Monthly meetings are held with the President to discuss management, including future plans, and important matters are decided at the ICReDD Steering Committee meetings. The center also supports the Center Director's leadership through discussions at bi-weekly director meetings and monthly PI meetings attended by PO.

The 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 ICReDD'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 February 22nd (US time) and 28th (European time). The committee 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. Specially, while actively recruiting doctoral students, it was suggested that outreach to and recruitment of middle and high school students would be effective in improving the employment and gender ratio of researchers.

The mission of the center is communicated to all members through interviews with researchers conducted by the Center Director. Laboratory chiefs are appointed in mixed laboratories and mixed offices, and laboratory management is conducted so that the Center Director's policies are promptly communicated. The "Fusion Research Coordinator" is directly connected to the research division so that the Center Director's policies can be managed, and progress monitored in close proximity to the researchers. Authority has been delegated to the Future Plan WG, Equipment Management WG, and New Building Preparation WG so that they can manage the center by the direction of the Center Director.

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

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

We have Japanese/English bilingual staff handling public relations, support for researchers traveling to Japan and living in Japan, research cooperation (application for external funding, dual employment), human resources and general affairs, and accounting. The Administrative Division, led by administrative staffs who promote the use of English in their work, has been reorganized as the Research Support Division from FY2022. To strengthen cooperation with the University Executive Office and to ensure that decisions made by the University are promptly reflected at ICReDD, the Executive Director was appointed as the Administrative Director. The Research Support Division is under the supervision of the new Research Support Division Director and consists of the

Administrative Affairs Unit and the International Planning Unit. The Administrative Affairs Unit, led by the Administrative Office Manager, consists of four staff members in charge of general affairs and five staff members in charge of accounting. The nine staff members in the Administrative Affairs Unit consist of five full-time administrative staff members and four contract staff members (fluent in English) dispatched from the university. The International Planning Unit, which is responsible for inviting outstanding researchers and students from overseas and conducting international outreach activities beyond the academic community, is staffed by one assistant professor (Ph.D., from the U.S.) and two contract employees, all of whom are fluent in English, and work strongly with the university's International Relations Organization, Public Relations, CoSTEP and URA in public relations. This unit also provides daily life support for foreign researchers. In addition, a "Fusion Research Coordinator" was established to provide a direct connection between the Center Director and the research labs. This role enables the management and monitoring of the progress of the Center Director's policies while being in close contact with researchers. In 2023, a "Research Strategy Unit" for supporting research capabilities and industry-academia collaboration, and a "Human Resource Development Unit" for education will be in place. Utilizing the MANABIYA system, the Human Resource Development Unit will develop strategies and roadmaps for graduate education, recurrent education, and contributions to the scientific community and society. The Research Strategy Unit will use MANABIYA to gather companies in related fields and expand its network in order to best match with these industries. It also functions to gather the needs of industry and society. We will enhance the value of research results through efforts in education and communication to society.

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

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

ICReDD revised the Hokkaido University's salary regulations to allow for higher salaries in order to hire talented researchers and distinguished professors such as Prof. List. To acquire top-level researchers who can advance the field of chemical reaction design and discovery, we have also implemented a cross-appointment system and have utilized this to employ a professor at RIKEN and one at the University of Tokyo as principal investigators.

ICReDD has established regulations to provide center allowances to the Center Director, deputy director, PIs, administrative director, and executive director. In FY2022, a new regulation was established to provide incentives based on the research performance and evaluation of center faculty members, for whom no evaluation system was previously in place. The Center Director will decide who is eligible and how much they will receive. The results of the performance evaluation will be 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.

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. This consolidation of the centralized administrative system aims to strengthen the support system for cross-divisional education and research activities. At ICReDD's request, the Office for Technical Support dispatched technical staff to assist in the maintenance and management of ICReDD's equipment (nuclear magnetic resonance equipment).

From FY2022, the University has reorganized and strengthened its industry-academia collaboration system with a focus on accepting researchers from industry and establishing a research consortium with industry. From this reorganization, the university is now capable of supporting ICReDD's acquisition of private funding which will enable its permanent establishment.

6-4. Support by Host Institution

The following two items concern the support that the host institution provides the Center. Describe the measures that the host institution has taken to sustain and advance the Center's project. That include the item of support that it committed to at the time of the initial project proposal submittal.

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

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

Since the establishment of ICReDD, Hokkaido University has strongly supported ICReDD and has secured funds equal to or more than the WPI grant for its operation (FY2018: 363 million yen, FY2019: 1,026 million yen, FY2020: 1,388 million yen, FY2021: 1,989 million yen). The President and the ICReDD Executive Board hold regular monthly meetings to discuss operations, including future plans to establish ICReDD as a sustainable research center. To allocate resources more effectively and flexibly, ICReDD is working to reform its structure, strengthen its financial base, and improve communication throughout the university. Specifically, the university has provided the following supports:

1) The university provided discretionary funds (at least 10 million yen per year) that can be used freely by the Center Director and are further supported with access to the resources of relevant

organizations such as the Institute for International Collaboration and the Institute for Promotion of Collaborating with Regional Businesses.

2) The university and the Dean have made arrangements to reduce the teaching and administrative of ICReDD PIs duties in their respective the university departments. To reduce the educational and administrative burden on the departments of each PI, the university provided labor costs (50 million yen per year) for the corresponding departments as a form of compensation.

3) The university provided ICReDD 2,600 ㎡ of space in the Creative Research Institution Building and covered fees for the space including utility cost, etc. the university provided land on the north side of the campus, where industry-academia collaboration research facilities are concentrated, to build a new research building (5,500 ㎡) by the end of FY2022. When ICReDD's researchers used shared university equipment, the university covers the fee for its use and provides a suitable research environment so that researchers can start their research immediately after their arrival.

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

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

ICReDD will become the core of the university's fourth mid-term objectives and mid-term plan as the flagship research project to achieve the university's near-future strategy of establishing a "global brain circulation center for world-class research".

In October 2020, the new "President's Policy: Aiming to be an Incomparable University – Towards the Fourth Period of Mid-Term Objectives and Mid-Term Plan" declared that Hokkaido University should be a world-class university and, at the same time, a university that truly "contributes to solving global issues" by leveraging its geographical strengths and geopolitical uniqueness in terms of historical background, and its cooperation with Hokkaido, Sapporo City, neighboring regions, and Japan. Based on these declarations, the University has set forth the following six visions for its mid-term objectives, aiming to become "an incomparable university" that contributes to solving the world's problems (achieving the SDGs). ICReDD will contribute to four of these six visions: 1) a research university, 2) an educational university, 3) A socially collaborative university, and 5) A data-driven university.

(1) A research university: We will establish a system to lead the way in solving domestic and international problems and creating innovations by both improving basic research capabilities and promoting applied research such as social implementation of research results.
(2) An educational university: We will reform education at both undergraduate and graduate school levels by reviewing the entrance examination system, cultivating cross-cultural understanding and international communication skills, and developing advanced human resources with the ability to contribute to society. We will also aim for a next-generation higher education system that includes entrepreneurship education and recurrent education.
(3) A socially collaborative university: We will dramatically advance social collaboration and act as a major player in social change toward building a decarbonized and inclusive society through entrepreneurship and regional development.
(4) A new university management: Establish a solid management structure with the ability to interact and act through the realization of high-quality internal control, the establishment of a collaborative relationship between faculty and staff, and the promotion of university-wide motivation management through the reform of work styles by utilizing DX and other tools.
(5) A data-driven university: Reforms to promote data-driven education, research, and industry-university collaboration will be carried out to create the University's strengths via academic fusion fields and new academic and industry-university collaborations.
(6) Sustainable financial ecosystem: While strengthening financial capabilities such as increasing self-revenue including managerial income, the financial foundation for stable, independent, and sustainable university management will be passed on to the next generation through judicious selection and consolidation of expenditures.

6-5. Others

6-5-1. System for fostering young researcher (e.g. start-up funding)

Start-up supports for new appointments and fusion research: Start-up support for new appointments (6.7 million yen for new positions) and start-up support for fusion research to challenge bottom-up fusion projects (8 projects (7.55 million yen) and 1 group project (10 million yen) for a total of 17.55 million yen) were awarded. These projects led to the acquisition of Grants-in-Aid for Scientific Research.

Pre-checking system for the grant application: We conducted a pre-checking system to review and revise the applications for Grants-in-Aid for Scientific Research, etc. before submission. 35% of the applications for Grants-in-Aid for Scientific Research were granted for FY2022 (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.

	Scientific Research A	Scientific Research B	Scientific Research C	Scientific Research on Innovative Areas	Early-Career Scientists	Total	Average of adoptions for the center	Average of adoptions for the university
FY2022 number of adoptions/applications	0/0	1/4	1/4	0/0	4/9	6/17	35.3%	39.7%
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%

6-5-2. Participation of female researchers

・ On the transition in the number of female researchers, enter the figures in Appendices 3-1 and 3-2.

ICReDD's future vision of the center aims to achieve a gender balance of 25%. All PI-groups are asked to have at least one female. With the support of the university, we 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) will be established and role models will be 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. We will also actively recruit female students using the University Fellowship System, and establish a strong, collaborative relationship with the Promotion Office of Research Environment for Diversity.

7. Future Prospects (within 2 pages)

7-1. Policy and plan for achieving the Center's research objectives in the future

In the past three and a half years, we have built a research and administrative structure that we think surpasses the initial vision of the center that we proposed at the time of applying for WPI. In particular, the flagship projects have been instrumental in creating a strong fusion between experimental chemistry, computational chemistry and information science. The seven projects are arranged hierarchically, with Project I as the foundation, and with the complexity of the chemical processes involved gradually increasing for Projects II-VII. ICReDD will continuously produce high impact fusion research outputs while tackling the flagship projects. Administratively, we have created a strong system built around the Center Director and Administrative Director. Our vision has also received vital support at all levels from Hokkaido University, including funding support for the construction of a new building and funding support for the establishment of three tenure-track Jr. PI posts. We are also furthering our outreach efforts through an "on-the-job training"-style education system centered around the MANABIYA program.

To sustain our research productivity, we reviewed and evaluated the progress of several bottom-up projects as well as all the flagship projects at the end of FY2021. We have been discussing whether to add members, extend duration, expand scope, reconsider direction, or abolish each project based on the evaluations. For example, we decided to continue projects I and II by expanding the design scope and applications. The fusion between computational and experimental sciences in project VI is going well, and we are going to expand its scope to control polymer mechanoradicals for broader applications. The bottom-up project for designing organocatalysts conducted by the List group, Varnek group, and Maeda group showed promising progress by establishing an ideal fusion research framework and thus is going to be added as a new flagship project. On the other hand, project V did not proceed well due to an inappropriate choice of the target reaction and will be reconsidered starting with the target selection. The revised overall picture is under construction. Further creations of fusion research projects will also be done either in a top-down or bottom-up fashion, making effective use of ICReDD's start-up budget proposal system.

ICReDD will continue to take on the challenge of internationalization. By expanding its international network, ICReDD will promote exchange of researchers and doctoral students with overseas research institutions. To achieve this, a new Human Resource Development Unit and Research Strategy Unit will be established for 2023. The Human Resource Development Unit will link MANABIYA (ACADEMIC) to the advanced graduate education system of the university, the "Advanced Training Course for Smart Materials Science" (SMatS) Program, and develop strategies and roadmaps for graduate education, recurrent education, and contributions to the scientific community and society. In order to return cutting-edge research to the field of education, we will establish a system for cross-disciplinary and interdisciplinary education that is not bound by the framework of existing research institutes and graduate schools. We will establish human resource development that will serve as a model case for next-generation higher education through a multifaceted approach for both students and working people, both in Japan and abroad.

The Research Strategy Unit (RSU) will use MANABIYA (INDUSTRY) to attract companies in related fields and expand its network in order to best match ICReDD research with these industries. The RSU also functions to gather the needs of industry and society.

7-2. Center's plan to maintain its posture as a globally visible institute after WPI funding ends

ICReDD has reviewed its research support structure for the second half of the WPI funding period, as its composition has increased, and fusion research has made steady progress since its inception in 2018. We will actively develop international outreach activities beyond academia by strengthening cooperation with internal organizations such as the Institute for International Collaboration, the Promotion of Business-Regional Collaboration, URA, and the Promotion Office of Research Environment for Diversity, and promote an effective international strategy to invite many excellent researchers and students from abroad.

In order to secure permanent operating funds, we aim to obtain joint research and large competitive funds such as Grants-in Aid for Scientific Research "the Promotion of Joint International Research (International Leading Research)" and have made plans to establish an educational system to foster world-class researchers. Hokkaido University and ICReDD have prepared the FY2023 budget request for education and research organization reforms consisting of "Next Generation Human Resource Development Led by ICReDD," "List Sustainable DX Catalyst International Collaborative Research Platform," and "Automated Organic Synthesis System to Accelerate Data Construction for New Catalyst Design," and will establish these reforms as permanent initiatives.

FY2023 Estimated Budget Request

Education organization reform to foster world-class researchers: "Next Generation Human Resource Development Led by ICReDD"

Summary: The Institute for Chemical Design and Discovery (ICReDD), an international research center of the university, will establish the following three human resource development initiatives and hire four new faculty members: (1) graduate education through a five-year integrated degree program for the practical study of chemical reaction design and discovery, (2) strengthening hosting researchers and students from overseas research institutions through the use of an "on-the-job" training program, (3) recurrent education system for working people by utilizing a certificate program.

Research organization reform: "List Sustainable DX Catalyst International Collaborative Research Platform"

Summary: The 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 ICReDD, which combine computational science, information science, and experimental science. This International Collaborative Research Platform will be established to promote this next generation DX organocatalytic chemistry. This International 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. In addition, four new faculty members will be hired to accept mid- and short-term researchers and international students from domestic and overseas research institutions, and joint research will be actively conducted. In addition, we will also strengthen industry-academia collaboration by working to solve problems in industry and promote demonstration experiments and social implementation. Furthermore, we 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.

8. Host Institution's Concrete Action Plan toward Making its center an autonomous research institute in the second half of the grant period (from the

6th year of the center's operation)

Describe the Host Institution's plan for realizing a research system including the allocation of resources (e.g. personnel, infrastructure) that will sustain the Center as a "top world-level research institute" after its WPI funding period ends. To enable this, describe the assets that the Host Institution will provide the Center (e.g. expected acquisition of external funding, allocation of personnel, provision of budgets). Describe actions that the Host Institution has taken toward achieving the Center's independence up to the point of this midterm evaluation.

ICReDD will be maintained as a permanent organization linked to the university administration. It will be positioned as a special research institute under the direct control of the President, which will maintain continuous research activities. This special research institute 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. This strategy is part of the mid-term objectives and mid-term plan of the university.

For this purpose, from the 6th year onward, as collaborative research sufficient for social implementation progresses, we will reorganize the "Creative Research Institution (CRIS)," a university-wide organization that oversees cross-departmental research, to incorporate research fields beyond ICReDD's core areas (computational science, information science, and experimental science) and to further promote and develop research.

As a framework for significantly developing ICReDD's cutting-edge research together with many researchers inside and outside the university, an "International Collaborative Research Platform" will be established to support and promote research and development based on outstanding research results and to realize organic collaborative research with researchers outside the center. As a first step, starting in FY2023, the platform will be headed by Nobel laureate Prof. List, who will combine ICReDD's advanced technologies (computational science, information science, and experimental science) with digital transformation (DX) technologies such as robotics, machine learning, and artificial intelligence. We plan to establish a cutting-edge international research exchange platform to promote the next generation of organocatalytic chemistry. This platform concept will dramatically develop and establish an international research hub based on cutting-edge research originating from the University with the participation of relevant researchers from both inside and outside the University. It will be an unprecedented framework for strengthening research capabilities that will lead to the establishment of an international research center. The University's research centers serve as incubators for new cutting-edge research, and this collaborative research platform will result in a seamless expansion and development of that cutting-edge research. In the future, we hope that the progress of cutting-edge research at the University will lead to the creation of a second and third collaborative research platform that will serve as a new driving force to improve the research prowess and international recognition of the University, following this initial collaborative research platform based on Prof. List's research.

In addition, 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 after the completion of the WPI funding period, 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, we plan to establish a system for cross-disciplinary and interdisciplinary education that is not bound by the framework of existing research institutes and graduate schools. We will establish the "ICReDD Human Resource Development Division" 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. No other international research institute in the university has a human resource development division, and this organizational reform will lead to ICReDD's further development as a research center and its contribution to the entire university.

In addition, since ICReDD's research activities are linked to various pressing social issues in today's changing society, the results from ICReDD's research should inspire related research in the humanities and social sciences, especially in bioethics and public policy. In addition, ICReDD's research activities will be related to Hokkaido University's goal of integrating of science and engineering with the humanities and social sciences, including topics such as intellectual property, safety assessment, science and technology ethics, and international operational standards for technology.

Staffing Plan

In order to maintain ICReDD as a permanent institute, Hokkaido University has made a plan to assign 10 world-class Senior Principal Investigators (PIs) and 6 Young Principal Investigators (PIs) to the center.

Ten senior PIs will be assigned one assistant or associate professor and one post-doctoral researcher each, and six young PIs will be assigned one post-doctoral researcher each. A plan was established to provide a total of 16 young PIs, assistant professors, and associate professors with voluntary funds from the university before the end of the WPI funding period. Based on this plan, 4 tenure-track associate professors and 1 assistant professor have already been assigned to ICReDD as of April 2022, and we plan to ensure ICReDD's permanence by providing 11 positions out of the required 16 by the end of the grant period in FY2027.

In addition, Hokkaido University will gradually secure personnel before the end of the subsidy period by taking measures to hire necessary faculty members. The university will also utilize various financial resources and reforms, such as giving ICReDD the authority to make requests for estimates. The university has already prepared the FY2023 budget request for the education and research organizational reforms, "List Sustainable DX Catalyst International Collaborative Research Platform" and "Next Generation Human Resource Development Led by ICReDD" and plans to request 8 new faculty members.

Funding Plan

Since the establishment of ICReDD, Hokkaido University has secured funds equal to or more than the WPI grant (700 million yen) for its operation (1,335 million yen in FY2021: 275 million yen for personnel expenses, 154 million yen for project promotion expenses (facility use, utilities, equipment usage fees, Center Director discretionary expenses, educational burden reduction expenses, etc.), and 906 million yen for new equipment and buildings. Based on a review of the appropriate scale to make ICReDD permanent, it was estimated that an additional budget of 200 million yen per year would be required to maintain the current project promotion and facility expenses while gradually increasing the number of regular university faculty members based on the above personnel plan, in accordance with the gradual decrease in WPI grants from FY2023. From FY2023, ICReDD plans to gradually become independent and secure continuous research activities by increasing the proportion of the university's voluntary cost burden. Specifically, starting in FY2022, the university reorganized and strengthened its industry-academia collaboration system with a focus on accepting researchers from industry and establishing a research consortium with industry. From this point on, the reorganized industry-academia system will support ICReDD's acquisition of private funding and its permanent establishment.

As described above, ICReDD is the flagship project for realizing the University's near-future strategy of becoming a "Global Brain Circulation Center for World-Class Research," and is the core of the University's fourth mid-term objectives and mid-term plan. Going forward, ICReDD will continue to be the driving force behind the transformation of Hokkaido University into a truly international center of education and research.

9. Others (within 1 page)

Diversity, safety, technology export control, and research ethics are key issues. We will establish special safety, technology export control and research ethics education appropriate for diversity and interdisciplinary fields.

We will enhance diversity, safety and technology export control and research ethics education for all ICReDD researchers. This training will also provide an opportunity to explain the mission to researchers. For foreign researchers, the differences between the rules in Japan and their home countries will also be explained. Via this training, researchers will be able to keep these issues in mind as they pursue their research and gain an understanding of international and domestic stakeholders. Additionally, a workshop on diversity is planned for May 25 with an expert speaker from Queen's University. It is also important to inform society, local communities, and the public at large about our commitment to diversity, safety, technology export control, and research ethics.

We regret to report the retraction of a paper from ICReDD, which was published in Science in 2020 [*Science*, **2020**, *369*, 970-974]. It is very much embarrassing to know that there is suspicion of falsification of experimental data in a joint paper by the Sawamura group and the Maeda group. Accordingly, we are taking appropriate measures, including the retraction of the Science paper and further investigations on some related papers. We recognize the highly serious nature of the incident and will take all possible actions to prevent similar incidents in the future and to regain trust, starting with the reeducation on research ethics of all researchers at the center in June.

10. Center's Response to Results of FY 2021 Follow-up (including Site Visit Results)

* Describe the Center's response to results of FY 2021 follow-up. Note: If you have already provided this information, please indicate where in the report.

1) Continue efforts to achieve top-level science based on the fusion of computational / informational / experimental sciences. The 7 flagship projects have been a very active vehicle for achieving this purpose.

   In March 2022, progress report meetings on all flagship projects were held for all members of ICReDD. Based on these reports, ICReDD plans to reorganize its flagship projects in the next period and to restructure them into a stronger and more strategic research execution structure. Some projects will add or replace members, and some will change projects. A fusion research coordinator, independent from the Research Strategy Unit, will be established to promote fusion research in close coordination with researchers starting in FY2022.

2) ICReDD needs to address the issue of gender balance. In FY 2020, 13 researchers were newly hired (9 foreigners, one female). 24 of 66 researchers are foreign nationals and 7 are female, which is still very low. A plan for how to support younger female scientists must be put in place as well as a plan for promoting and recruiting female PIs. There has to be more successful role models for young female researchers. ICReDD has the opportunity to gain international recognition by elevating Japanese female researchers.

   ICReDD's future vision of the center aims to achieve a gender balance of 25%. All PI-groups are asked to have at least one female. With the support of the university, we 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) will be established and role models will be 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. We will actively recruit female students using the University Fellowship System and establish a strong collaborative relationship with the Promotion Office of Research environment for Diversity in order to implement these plans.

3) Continue efforts toward increasing international visibility through the recruitment of talented young researchers. The Center is advised to bring in more researchers and students from established top-institutes abroad.

   ICReDD will improve its visibility through its website, SNS, News postcard, CATALYST News poster, Annual Report, international public relations, international seminars, the Akira Suzuki Awards, international symposiums, and the MANABIYA system. In addition, with the Nobel Prize in Chemistry awarded to Professor List, ICReDD plans to establish a new international collaborative research platform through the establishment of the List International Collaborative Research Center for Organocatalysis. The MANABIYA system will actively accept researchers and students from top-level overseas university and research institutions, as well as researchers from overseas companies. In order to make the salary system for faculty members internationally competitive, ICReDD has introduced a salary system that provides incentives based on performance evaluations starting from FY2022.

4) There seems to be some difficulties among clinicians and chemists in sharing the deeper meaning of scientific knowledge when collaborating to advance cancer diagnosis. ICReDD should encourage them to establish a mechanism for promoting better communication.

   On October 15, 2021, ICReDD Joint Symposium with Faculty of Medicine was held with the aim to foster understanding and discussion between experts in the field of chemical reaction design and the field of medicine, in hopes of finding new opportunities for interdisciplinary collaboration. In FY2022, ICReDD will also conduct a Clinics-oriented chemistry consortium. ICReDD has decided that this consortium will be held periodically, where ICReDD researchers present their materials and clinicians evaluate them for possible medical applications. In this meeting, an ICReDD researcher presents about their fusion research. Clinicians are free to participate, but those who are likely to be closely related to the research topic will be asked in advance to attend. In addition, during regular interviews with each researcher, the director will ensure that each researcher understands the content of areas outside of their area of expertise.

5) In tune with ICReDD's important mission, it will be important for the Center to develop more active programs for outreach beyond the academic community, which will help demonstrate the societal value of basic research.

In FY2021, ICReDD researchers lectured at the "Forum with Nobel laureates" organized by the Yomiuri Shimbun and at "Academic Fantasista" organized by the Hokkaido Shimbun. Researchers also participated in a number of media events, including an episode of NHK's "Science ZERO" (TV program) related to Professor List being awarded the Nobel Prize in Chemistry. ICReDD will further enhance outreach. We will actively engage in monthly postcards for researchers, quarterly news posters for high school and undergraduate students, lectures for high school students or the general public, press releases, and press conferences. Also, we will establish recognition through strategic international public relations using Science, Nature, ACS, RSC, Wiley, etc. for promoting international symposia and the Akira Suzuki Awards. We will also establish new international collaborations through the upcoming List Organocatalysis International Collaborative Research Platform.

6) To establish ICReDD as a permanent research institution beyond the WPI funding period, a clear and concrete plan will be required. An important item will be to increase the number of research and administrative positions that belong to ICReDD.

ICReDD will be positioned as a special research center under the direct control of the President and will maintain continuous research activities. After a period of about 10 years of research activities, we plan to permanently establish ICReDD as a dynamic research center based on a new research strategy that is part of the university's mid-term objectives and mid-term plan. The research space is 7500 m^2, consisting of new ICReDD Building (5500 m^2) and the Creative Research Institution Building (2000 m^2), and we estimate that we would need to secure financial resources of 200 million yen per year in order to maintain the research center at its current size. In order to permanently maintain the center at its current scale, we plan to assign 1 full-time associate professor and 1 post-doctoral fellow to each of the 10 Senior PIs, and 1 post-doctoral fellow to each of the 6 Junior PIs (10 top PIs, 16 faculty members and 16 post-doctoral fellows). With university support, 4 tenure-track associate professors and 1 assistant professor have already been assigned as of April 2022. Furthermore, the university plans to increase the proportion of its own expenses and take measures to hire necessary faculty members by utilizing various financial resources such as budget requests. The University plans to request 8 faculty members in the 2023 budget request and ramp up to 16 faculty members in FY2027. To 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 newly 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. 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, promote collaboration agreements with other institutions, and to establish joint research projects; and the "Human Resource Development Unit", which is in charge of graduate school education, recurrent education, and creating strategies and roadmaps for contributing to the scientific community and society. Additionally, the "Fusion Research Coordinator" 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. In this way, we plan to secure the personnel necessary to establish ICReDD as a permanent research institution.

Appendix 1-1 List of Papers Underscoring Each Research Achievement

* List papers underscoring each research achievement [1] ~ [10] listed in the item 2-1 "Research results to date" of 2. "Advancing Research of the Highest Global Level" (up to 20 papers) and provide a description of the significance of each (within 10 lines).
* For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. If a paper has many authors, underline those affiliated with the Center.
* If a paper has many authors (say, more than 10), all of their names do not need to be listed.
* Place an asterisk (*) in front of those results that could only have been achieved by a WPI center.

[1] **Development of reaction design tools**

*1. <u>Timur Gimadiev</u>, Ramil Nugmanov, Dinar Batyrshin, Timur Madzhidov, <u>Satoshi Maeda</u>, <u>Pavel Sidorov</u>, <u>Alexandre Varnek;</u> Combined graph/relational database management system for calculated chemical reaction pathway data (*J. Chem. Inf. Model.*, 2021, **61**, 554–559)

Quantum chemical calculations are widely used to generate extensive data sets for machine learning applications; however, generally, these sets only include information on equilibrium structures and some close conformers. Exploration of potential energy surfaces provides important information on ground and transition states, but analysis of such data is complicated due to the number of possible reaction pathways. In this work, the authors present RePathDB, a database system for managing 3D structural data for both ground and transition states resulting from QC calculations. This tool allows one to store, assemble, and analyze reaction pathway data. It combines relational database CGRdb for handling compounds and reactions as molecular graphs with a graph database architecture for pathway analysis by graph algorithms. Original condensed graph of reaction technology is used to store any chemical reaction as a single graph.

*2. Tomohiro Nakamura, Shinsaku Sakaue, Kaito Fujii, <u>Yu Harabuchi</u>, <u>Satoshi Maeda</u>, <u>Satoru Iwata;</u> Selecting molecules with diverse structures and properties by maximizing submodular functions of descriptors learned with graph neural networks (*Sci. Rep.*, 2022, **12**, 1124)

Selecting diverse molecules from unexplored areas of chemical space is an essential task for discovering novel molecules and reactions. This paper proposes a new approach, called SubMo-GNN, for selecting a subset of diverse molecules from a given molecular list. SubMo-GNN has been developed by combining machine learning and mathematical optimization. Specifically, graph neural network (GNN) is used for learning vector representation of molecules, and submodular function maximization is for a diverse-selection framework. Computational experiments confirm that SubMo-GNN successfully selects diverse molecules from the QM9 dataset regarding the property-based criterion while performing comparably to existing methods regarding standard structure-based criteria. Young researchers in Iwata-G and Maeda-G did the development.

3. William Bort, Igor I. Baskin, <u>Timur Gimadiev</u>, Artem Mukanov, Ramil Nugmanov, <u>Pavel Sidorov</u>, Gilles Marcou, Dragos Horvath, Olga Klimchuk, Timur Madzhidov, <u>Alexandre Varnek;</u> Discovery of novel chemical reactions by deep generative recurrent neural network (*Sci. Rep.*, 2021, **11**, 3178)

The creativity of Artificial Intelligence (AI) in terms of generating de novo molecular structures opened a novel paradigm in compound design. The authors showed that AI may be as successfully taught to enumerate novel chemical reactions that are stoichiometrically coherent. A sequence-to-sequence autoencoder with bidirectional Long Short-Term Memory layers was trained on newly developed SMILES/CGR strings, encoding reactions of the USPTO database. The autoencoder latent space was visualized on a generative topographic map. Novel latent space points were sampled around a map area populated by Suzuki reactions and decoded to corresponding reactions. Additional chemical filters assessing the feasibility of novel reaction, including quantum chemical calculations, are employed to pinpoint the most relevant among them.

4. Wataru Matsuoka, <u>Yu Harabuchi</u>, <u>Satoshi Maeda;</u> Virtual ligand-assisted screening strategy to discover enabling ligands for transition metal catalysis (*ACS Catal.*, 2022, **12**, 3752–3766)

The ligand screening, in which an optimal ligand for a reaction of interest is identified from an enormous and diverse set of candidate molecules, is of particular importance in the development of transition metal catalysis. This paper proposes a new strategy called "virtual ligand-assisted (VLA) screening" that enables practical in silico ligand screening based on transition-state theory. VLA allows us to identify the optimal electronic and steric effects for a reaction of interest through a highly efficient parameter-based ligand screening, thereby affording guiding principles for rational ligand design. Computational experiments indicate that VLA screening would be highly promising for streamlining the ligand screening process. Dr. Matsuoka of Maeda-G, an experimental chemist who took his Ph.D. under the guidance of Prof. Itami of ITbM, did the development, from the design of the computational strategy to the code writing and reaction path calculations.

[2] **Small molecule transformation**

*5. Tsuyoshi Mita, Yu Harabuchi, Satoshi Maeda; Discovery of a synthesis method for a difluoroglycine derivative based on a path generated by quantum chemical calculations (*Chem. Sci.*, 2020, **11**, 7569–7577)

The AFIR method with density functional theory automatically searched reaction paths toward an input molecule (a target compound etc.). In combination with graph theory and chemoinformatics, all the calculated reaction paths were closely scrutinized in the light of the obtained activation and ground state energies, proposing energetically accessible reaction routes and starting material pairs. Based on these results, α,α-difluoroglycine, a bioisostere of natural glycine, was retrosynthesized, proposing reasonable three basic starting materials like NR_3 (amine), $:CF_2$ (difluorocarbene), and CO_2 (carbon dioxide). Subsequently, when NMe_3 (R = Me), $^-CF_2Br$, which is a reasonable difluorocarbene precursor, and CO_2 were mixed experimentally to afford the difluoroglycine derivative ($Me_3N^+{-}CF_2{-}CO_2^-$) in high yield.

*6. Hiroki Hayashi, Hideaki Takano, Hitomi Katsuyama, Yu Harabuchi, Satoshi Maeda, Tsuyoshi Mita; Synthesis of difluoroglycine derivatives from amines, difluorocarbene, and CO_2: Computational design, scope, and applications (*Chem. Eur. J.*, 2021, **27**, 10040–10047)

While the proof-of-principle for the synthetic route to α,α-difluoroglycine has already been confirmed (*Chem. Sci.*, 2020, 11, 7569–7577), this paper describes the mechanism, scope, and applications of this difluoroglycine synthesis. First, the authors unveiled the detailed reaction mechanism of the difluoroglycine synthesis by the AFIR method including the use of ammonia as an amine source. Furthermore, the group expanded the substrate scope not only to include *tert*-akylamines, but also heteroaromatic compounds such as pyridine, (iso)quinoline, imidazole, thiazole, and pyrazole derivatives. Moreover, supported by the computational analysis, the authors designed and evaluated a new carbene precursor that allows generating difluorocarbene at 0 °C without any additives. The authors also demonstrate a new radical reaction of the products and a synthetic application of an imidazolium product as an *N*-heterocyclic carbene ligand for Ag and Rh complexes.

*7. Yong You, Wataru Kanna, Hideaki Takano, Hiroki Hayashi, Satoshi Maeda, Tsuyoshi Mita; Electrochemical dearomative dicarboxylation of heterocycles with highly negative reduction potentials (*J. Am. Chem. Soc.*, 2022, **144**, 3685–3695)

The dearomative dicarboxylation of stable heteroaromatics using CO_2 is a very powerful method for producing synthetically useful dicarboxylic acids. The authors discovered a new electrochemical protocol using the CO_2 radical anion. The developed reaction produces unprecedented *trans*-oriented 2,3-dicarboxylic acids from indole derivatives that exhibit highly negative reduction potentials. On the basis of the calculated reduction potentials, *N*-protected indoles with reduction potentials up to −3 V smoothly undergo the desired dicarboxylation. Other heteroaromatics with the reduction potentials more than −3 V served as effective substrates for such dicarboxylations. The dicarboxylated products thus obtained can be derivatized into useful synthetic intermediates for biologically active compounds in few steps. The present electrochemical approach uses calculated reduction potentials as a guide for the development of a new electrochemical carboxylation.

[3] **Theoretical investigation of asymmetric organocatalysis**

8. Tynchtyk Amatov, Nobuya Tsuji, Rajat Maji, Lucas Schreyer, Hui Zhou, Markus Leutzsch, Benjamin List; Confinement-controlled, either syn- or anti-selective catalytic asymmetric mukaiyama aldolizations of propionaldehyde enolsilanes (*J. Am. Chem. Soc.*, 2021, **143**, 14475–14481)

While protected aldols with either syn- or anti- stereochemistry are versatile intermediates in many natural product syntheses, traditional stereoselective approaches to such aldols typically require several non-strategic operations. The authors described two highly enantioselective and diastereoselective catalytic Mukaiyama aldol reactions of the enolsilanes of propionaldehyde with aromatic aldehydes. The reactions directly deliver valuable silyl protected propionaldehyde aldols in a catalyst-controlled manner, either as syn- or anti- isomer. They have identified a privileged IDPi catalyst motif that is tailored for controlling these aldolizations with exceptional selectivities, and demonstrated how a single atom modification in the inner core of the IDPi catalyst, replacing a CF_3 with a CHF_2, leads to a dramatic switch in the enantiofacial differentiation of the aldehyde. The origin of this remarkable effect was investigated by using AFIR and attributed to the tightening of the catalytic cavity via unconventional C–H hydrogen bonding of the CHF_2.

[5] **Design of transition metal catalyst**

9. Hiroaki Iwamoto, Kohei Endo, Yu Ozawa, Yuta Watanabe, Koji Kubota, Tsuneo Imamoto, Hajime Ito; Copper(I)-catalyzed enantioconvergent borylation of racemic benzyl chlorides enabled by quadrant-by-quadrant structure modification of chiral bisphosphine ligands (*Angew. Chem. Int. Ed.*, 2019, **58**, 11112–11117)

The design of catalytic enantioselective reactions and asymmetric ligands is generally difficult, and few have succeeded in their rational design using computational chemistry. The authors have succeeded in semi-rational design of asymmetric ligands by repeating detailed analysis of the reaction mechanism by DFT calculations, ligand design based on the analysis, and experimental verification (*Nature Commun.* 2019, **10**, 111). Based on this results, the first Cu(I)-catalyzed enantioselective borylation of racemic benzyl chlorides has been realized by a quadrant-by-quadrant structure modulation of QuinoxP*-type bisphosphine ligands. This reaction converts racemic mixtures of secondary benzyl chlorides into the corresponding chiral benzylboronates with high enantioselectivity (up to 92 % ee). The experimental mechanistic investigations suggest the formation of a benzylic radical intermediate. The DFT calculations indicate the optimal bisphosphine-Cu(I) catalyst involves noncovalent interactions that recognize the radical intermediate to afford high levels of enantioselectivity.

10. Hiroaki Iwamoto, Yu Ozawa, Yuta Watanabe, Tsuneo Imamoto, Hajime Ito; Backbone-modified C_2-symmetrical chiral bisphosphine TMS-QuinoxP*: asymmetric borylation of racemic allyl electrophiles (*J. Am. Chem. Soc.*, 2021, **143**, 6413–6422)

A novel C_2-symmetrical P-chirogenic bisphosphine ligand bearing silyl substituents on the ligand backbone, (*R*,*R*)-5,8-TMS-QuinoxP*, has been developed. This ligand showed higher reactivity and enantioselectivity for the direct enantioconvergent borylation of cyclic allyl electrophiles than the original ligand, (*R*,*R*)-QuinoxP*. The kinetic resolution of linear allyl electrophiles was also achieved using (*R*,*R*)-5,8-TMS-QuinoxP* with high selectivity. Interlocking structures between the phosphine and silyl moieties of (*R*,*R*)-5,8-TMS-QuinoxP* are crucial of the high selectivity and reactivity. The results of DFT calculations revealed that the entropy effect causes destabilization of the dimer species in the catalytic cycle to improve the reactivity. Furthermore, in the direct enantioconvergent case, the DFT calculations indicated a significant enantioselective discrimination around the carbon–carbon double bonds as a key for the borylation from both enantiomers of racemic allyl electrophiles.

11. Yu Ozawa, Kohei Endo, Hajime Ito; Regio- and stereoselective synthesis of multi-alkylated allylic boronates through three-component coupling reactions between allenes, alkyl halides, and a diboron reagent (*J. Am. Chem. Soc.*, 2021, **143**, 13865–13877)

Multisubstituted allylic boronates are attractive and valuable synthetic intermediates for the rapid and stereoselective construction of densely substituted carbon skeletons, but their synthesis are still difficult. The authors report the first synthetic approach for differentially 2,3,3-trialkyl-substituted allylic boronates with stereodefined tetrasubstituted alkene structure. Copper(I)-catalyzed regio- and stereoselective three-component coupling reactions among *gem*-dialkylallenes, alkyl halides, and $B_2(pin)_2$ afforded the desired allylic boronates. The further allylboration of aldehydes furnished the corresponding homoallylic alcohols that bear a quaternary carbon in diastereoselective manner. The results of the DFT calculations revealed that the coordination of a boryl copper(I) species to the allene substrate as well as the borylcupration step are important for the selectivity.

[6] **Chemical reaction induced by mechanical force**

*12. Koji Kubota, Tamae Seo, Katsumasa Koide, Yasuchika Hasegawa, Hajime Ito; Olefin-accelerated solid-state C–N cross-coupling reactions using mechanochemistry (*Nat. Commun.*, 2019, **10**, 111)

The development of palladium-catalyzed cross-coupling reactions is of great importance in the synthesis of bioactive molecules, pharmaceuticals and organic materials. Although the significant advancement has been achieved in cross-coupling chemistry, these solution-based reactions usually require significant amounts of dry and degassed organic solvents, which has led to serious problems with regard to solvent waste. In this study, we developed the first broadly applicable mechanochemical protocol for a solid-state palladium-catalyzed carbon–nitrogen bond forming cross-coupling reaction, so-called Buchwald-Hartwig amination. The key finding of this study is that olefin additives can act as efficient molecular dispersants for the palladium-based catalyst in solid-state media, facilitating the challenging solid-state cross-coupling. Beyond the immediate utility of this protocol, our finding could inspire the development of industrially attractive solvent-free palladium-catalyzed cross-coupling processes for other valuable synthetic targets.

13. Koji Kubota, Yadong Pang, Akira Miura, Hajime Ito; Redox reactions of small organic molecules using ball milling and piezoelectric materials (*Science*, 2019, **366**, 1500 – 1504)

When piezoelectric materials are subjected to mechanical pressure or strain, electricity is generated instantaneously on its surface. This well-known phenomenon has been widely utilized in a wide variety of scientific fields and even in everyday life. We imagined that when piezoelectric materials are used under ball milling conditions, electric potentials should be generated in response to mechanical impact provided by ball milling, and thus the redox reaction of organic molecules could be carried out in the solid-state. This conceptually new approach would establish a powerful platform for using mechanical force in organic synthesis. In this study, the authors developed a "mechanoredox system" using ball milling and piezoelectric materials. This approach was successfully applied to the development of force-promoted arylation and borylation reactions with aryldiazonium salts under mechanochemical conditions. These mechanoredox reactions completed in a much shorter time than the corresponding photoredox-catalyzed reactions.

*14. Rina Takahashi, Anqi Hu, Pan Gao, Yunpeng Gao, Yadong Pang, Tamae Seo, Julong Jiang, Satoshi Maeda, Hikaru Takaya, Koji Kubota, Hajime Ito; Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis (*Nat. Commun.*, 2021, **12**, 6691)

The Grignard reagents have been widely used as the most versatile carbon nucleophiles in organic synthesis since its first synthesis was reported in 1900. Direct insertion of magnesium metal to organic halide represents the most straight forward route for their preparation. Although this is an established method in organic synthesis, this approach usually requires the use of dry organic solvents, long reaction times, strict control of the reaction temperature, and inert-gas-line techniques. In this study, the aurhots achieved the general mechanochemical synthesis of magnesium-based carbon nucleophiles (Grignard reagents in paste form) in air using a ball milling technique. These nucleophiles can be used directly for one-pot nucleophilic addition reactions with various electrophiles and nickel-catalyzed cross-coupling reactions under solvent-free conditions. Direct spectroscopic evidence for the formation of magnesium-based carbon nucleophiles under mechanochemical conditions was obtained using NEXAFS spectroscopy.

[7] **Force-promoted degradation for controlled chemical reaction and polymer material functionalization**

15. Takahiro Matsuda, Runa Kawakami, Ryo Namba, Tasuku Nakajima, Jian Ping Gong; Mechanoresponsive self-growing hydrogels inspired by muscle training (*Science*, 2019, **363**, 504–508)

The authors proposed a strategy for developing "self-growing" materials in response to repetitive mechanical stimuli through mechanochemical reaction. The authors adopted a chemically cross-linked double network hydrogel that enables permeability to small molecules and efficient chemical reactions in the material. Force-induced polymer strand scission in the brittle network generates mechanoradicals that can trigger polymerization. As one radical can polymerize thousands of monomers, this is an efficient method for the reconstruction of new network. Double network hydrogels provided with a sustained monomer supply undergo self-growth, and the materials are substantially strengthened under repetitive loading through a structural destruction-reconstruction process. This work may pave the way for the development of self-growing gel materials for applications such as soft robots and intelligent devices.

*16. Koji Kubota, Naoki Toyoshima, Daiyo Miura, Julong Jiang, Satoshi Maeda, Mingoo Jin, Hajime Ito; Introduction of a luminophore into generic polymers via mechanoradical coupling with a prefluorescent reagent (*Angew. Chem. Int. Ed.*, 2021, **60**, 16003–16008)

Mechanical stimulation of polymers causes main-chain scission and generates free radicals (mechanoradicals), which has been focused on as a key process of polymer degradation, and significant progress has been made in parallel in force-mediated polymerization. In this context, the preparation of functional polymers such as luminescent polymeric materials via mechanoradical transformations has not yet been explored systematically. Such a new approach would potentially allow the direct preparation of functional polymers from chemically stable generic polymers. The authors developed a new strategy for introducing a luminophore into generic polymers facilitated by mechanical force using polymeric mechano-radical with a pre-fluorescent nitro-oxide reagent. Photophysical properties of the yielded polymeric materials and computational study indicated that the generated mechano-radical coupling with the pre-fluorescent probe. Several generic polymers also showed the similar transitions.

*17. Zhi Jian Wang, Julong Jiang, Qifeng Mu, Satoshi Maeda, Tasuku Nakajima, Jian Ping Gong; Azocrosslinked double-network hydrogels enabling highly efficient mechanoradical generation (*J. Am. Chem. Soc.*, 2022, **144**, 3154–3161)

The authors expand on their prior research (Matsuda, et al, Science, 2019) that shows much higher concentration mechanoradicals can be generated by the bond scissors (~10^{-5} M) in the double network (DN) than in the single network gels (~10^{-7} – 10^{-6} M). To further increase the mechanoradical concentration, they combined with DFT simulation and experiment results, and showed that azoalkane group is easy to break under the macroscopic force applied to the material. This work further showed that by incorporating weak azoalkane crosslinker in the DN gels, mechanoradical concentration can reach 10^{-4} M. The improved mechanoradicals accelerate the polymerization rate and should expand the application of force-response DN gels in biomedical devices and soft robots.

[9] **Development of Cancer Diagnosis Method**

*18. Jun Suzuka, Masumi Tsuda, Lei Wang, Shinji Kohsaka, Karin Kishida, Shingo Semba, Hirokazu Sugin, Sachiyo Aburatani, Martin Frauenlob, Takayuki Kurokawa, Shinya Kojima, Toshihide Ueno, Yoshihiro Ohmiya, Hiroyuki Mano, Kazunori Yasuda, Jian Ping Gong, Shinya Tanaka; Rapid reprogramming of tumour cells into cancer stem cells on double-network hydrogels; (*Nat. Biomed. Eng.*, 2021, **5**, 914–925)

For complete cure of cancer patients, eradication of cancer stem cells (CSCs) is required; however, the detection of CSCs is extremely difficult. The authors established a novel technique for rapidly inducing CSCs using a double-network (DN) hydrogel. By placing six human cancer cells onto DN gels, sphere formations and elevation of stemness markers were observed within 24 hours, with high tumourigenicity in SCID mice. The DN gels rapidly modulated cellular gene expression *via* TRP/osteopontin/Shh/tyrosine kinase (TK) signalling axis, and facilitated reprogramming of differentiated cancer cells towards CSCs, which is designed as HARP (hydrogel activated reprogramming) phenomena. The DN gels could reveal CSC-specific expression of the TK receptor, suggesting the possible eradication of CSCs by a TK inhibitor. This rapid detection system of CSCs could be useful for the prediction of therapeutic reagents for complete eradication of CSCs in cancer patients, leading to the development of an innovative method for diagnosis of CSCs using hydrogel.

*19. Martin Frauenlob, Daniel R. King, Honglei Guo, Seiichiro Ishihara, Masumi Tsuda, Takayuki Kurokawa, Hisashi Haga, Shinya Tanaka, Jian Ping Gong; Modulation and characterization of the double network hydrogel surface-bulk transition (*Macromolecules*, 2019, **52**, 6704–6713)

The hydrogel chemical structure at the gel-solution interface is important towards practical use, especially in tough double network (DN) hydrogels that have promising applications as structural biomaterials. In this work, the authors regulated the surface chemical structure of DN hydrogels and the surface-bulk transition by the molding substrate used for the synthesis of the 2nd network. They found that the polymerization on a repulsive substrate leads to the formation of a thin layer of 2nd network on the surface of DN hydrogels, which makes the surface different from the bulk. By controlling the 2nd network polymerization conditions and molding substrate, the surface-bulk transition region can be regulated, so that either only the 2nd network or both networks are present at the DN hydrogel surface. Through these findings, they gained a new insight on the structure formation at the DN hydrogel surface, and this leads to easy regulation of the hydrogel surface structure and properties.

20. Sulimon Sattari, Udoy S. Basak, Ryan G. James, Louis W. Perrin, James P. Crutchfield, Tamiki Komatsuzaki; Modes of information flow in collective cohesion; (*Sci. Adv.*, 2022, **8**, eabj1720)

Quantum chemistry (QC) starts from the existence of equation of motion but for much complex systems such as cells, e.g., cell-cell interactions or molecular interaction in cells, only what we can access is experimental data such as cell tracking. The abiding question is how each individual influences the collective in terms of very limited resource by experiments. Time-delayed mutual information and transfer entropy have been commonly used to quantify mutual influence. The authors showed that these information measures have substantial pitfalls in measuring information flow between systems from their trajectories. They decomposed the information measures into three distinct modes of information flow to expose the role of individual and group memory, and found decomposed information modes between a single pair of systems reveal the nature of mutual influence involving many-body nonadditive interactions. The work addresses the fundamental issue by the quantitative methods to unravel complex interactions even among cells such as QC did for molecules.

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

* List **up to 10 papers** underscoring each interdisciplinary research activity and give brief accounts (within 10 lines).
* For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. If a paper has many authors, underline those affiliated with the Center.
* If a paper has many authors (say, more than 10), all of their names do not need to be listed.

1. Timur Gimadiev, Ramil Nugmanov, Aigul Khakimova, Adeliya Fatykhova, Timur Madzhidov, Pavel Sidorov, Alexandre Varnek; CGRdb2.0: A python database management system for molecules, reactions, and chemical data (*J. Chem. Inf. Model.*, 2021, DOI: 10.1021/acs.jcim.1c01105)
   This work introduces CGRdb2.0 — an open-source database management system for molecules, reactions, and chemical data. CGRdb2.0 is a Python package connecting to a PostgreSQL database that enables native searches for molecules and reactions without complicated SQL syntax. The library provides out-of-the-box implementations for similarity and substructure searches for molecules, as well as for reactions in two ways — based on reaction components and based on the Condensed Graph of Reaction approach, the latter significantly accelerating the performance. In benchmarking studies with the RDKit database cartridge, the authors demonstrate that CGRdb2.0 performs searches faster for smaller data sets, while allowing for interactive access to the retrieved data.

2. Timur Gimadiev, Ramil Nugmanov, Dinar Batyrshin, Timur Madzhidov, Satoshi Maeda, Pavel Sidorov, Alexandre Varnek; Combined graph/relational database management system for calculated chemical reaction pathway data (*J. Chem. Inf. Model.*, 2021, **61**, 554–559)
   Quantum chemical calculations are widely used to generate extensive data sets for machine learning applications; however, generally, these sets only include information on equilibrium structures and some close conformers. Exploration of potential energy surfaces provides important information on ground and transition states, but analysis of such data is complicated due to the number of possible reaction pathways. In this work, the authors present RePathDB, a database system for managing 3D structural data for both ground and transition states resulting from QC calculations. This tool allows one to store, assemble, and analyze reaction pathway data. It combines relational database CGRdb for handling compounds and reactions as molecular graphs with a graph database architecture for pathway analysis by graph algorithms. Original condensed graph of reaction technology is used to store any chemical reaction as a single graph.

3. Hideaki Takano, Yong You, Hiroki Hayashi, Yu Harabuchi, Satoshi Maeda, Tsuyoshi Mita; Radical difunctionalization of gaseous ethylene guided by quantum chemical calculations: selective incorporation of two molecules of ethylene (*ACS Omega*, 2021, **6**, 33846–33854)
   Ethylene is a fundamental C_2 feedstock that is widely used for the industrial synthesis of polyethylenes and polyvinylchlorides. The authors reported a new strategy for the radical difunctionalization of ethylene supported by theoretical calculations. Initially, the group systematically screened heteroatom- and carbon-centered radicals that could react with ethylene. Using imidyl and sulfonyl radicals that have low activation barriers toward ethylene, the authors conducted experiments to reveal that these two heteroatom radicals can be efficiently introduced into ethylene under blue LED irradiation. These reaction systems led to the selective incorporation of two molecules of ethylene into the substrates. Furthermore, supported by computational estimations of the reactivity of each radial intermediate, the group developed new three- and four-component reactions using styrene or methyl acrylate instead of the second equivalent of ethylene.

4. Wataru Kanna, Yu Harabuchi, Hideaki Takano, Hiroki Hayashi, Satoshi Maeda, Tsuyoshi Mita; Carboxylation of a palladacycle formed via C(sp^3)–H activation: theory-driven reaction design (*Chem. Asian J.*, 2021, **16**, 4072–4080)
   A palladacycle(II), generated from 8-methylquinoline via C(sp^3)–H activation, has frequently featured in the scientific literature, albeit that its reactivity toward CO_2, an abundant, inexpensive, and non-toxic chemical, remains elusive. The authors have theoretically discovered potential carboxylation pathways of the palladacycle using the AFIR method. The theoretical results suggest that the reduction of the palladacycle(II) to Pd(I) is crucial to promote the carboxylation. Based on these computational findings, the authors employed various reductants such as a stoichiometric

amount of a one-electron reductant (Cp^*_2Co), a photoredox catalyst under blue LED irradiation, and reductive electrolysis ((+)Mg/(–)Pt), all of which afforded the desired carboxylated product in high yields. These findings can serve as part of critical guidelines for the development of unprecedented Pd(II)-catalyzed $C(sp^3)$–H carboxylation reactions with CO_2.

5. Yuya Inaba, Yu Nomata, Yuki Ide, Jenny Pirillo, Yuh Hijikata, Tomoki Yoneda, Atsuhiro Osuka, Jonathan L. Sessler, Yasuhide Inokuma; Calix[3]pyrrole: A missing link in porphyrin-related chemistry (*J. Am. Chem. Soc.*, 2021, **143**, 12355–12360)
   A long-standing question in porphyrin chemistry is why pyrrole monomers selectively form tetrapyrrolic macrocycles, whereas the tripyrrolic macrocycles are never observed. Calix[3]pyrrole is a missing link molecule that might hold the key to this enigma; however, it has remained elusive. The authors reported the synthesis and strain-induced transformations of calix[3]pyrrole and its furan analogue, calix[3]furan. Crystallographic and theoretical analyses reveal that these three-subunit systems possess the largest strain energy among known calix[*n*]-type macrocycles. The ring-strain triggers transformation of calix[3]pyrrole into first calix[6]pyrrole and then calix[4]pyrrole under porphyrin cyclization conditions. The present results help explain the absence of naturally occurring three-pyrrole macrocycles and the fact that they are not observed as products or intermediate during classic porphyrin syntheses.

6. Yuya Inaba, Yu Kakibayashi, Yuki Ide, Jenny Pirillo, Yuh Hijikata, Tomoki Yoneda, Yasuhide Inokuma; Strain-induced ring expansion reactions of calix[3]pyrrole-related macrocycles (*Chem. Eur. J.*, 2022, **28**, e202200056)
   The recent discovery of calix[3]pyrrole, a porphyrinogen-like tripyrrolic macrocycle, has provided an unprecedented strain-induced ring expansion reaction into calix[6]pyrrole. The authors synthesized calix[*n*]furan[3-*n*]pyrrole (n=1~3) macrocycles to investigate the reaction scope and mechanism of the ring expansion. Single crystal X-ray analysis and theoretical calculations revealed that macrocyclic ring strain increases as the number of inner NH sites increases. While calix[1]furan[2]pyrrole exhibited almost quantitative conversion into calix[2]furan[4]pyrrole quickly, less-strained calix[2]furan[1]pyrrole and calix[3]furan were inert. However, *N*-methylation of calix[2]furan[1]pyrrole induced a ring-expansion reaction that enabled the isolation of a linear reaction intermediate. The mechanism analysis revealed that the ring expansion consists of regioselective ring cleavage and subsequent cyclodimerization.

7. Koji Kubota, Naoki Toyoshima, Daiyo Miura, Julong Jiang, Satoshi Maeda, Mingoo Jin, Hajime Ito; Introduction of a Luminophore into Generic Polymers via Mechanoradical Coupling with a Prefluorescent Reagent (*Angew. Chem. Int. Ed.*, 2021, **60**, 16003–16008)
   Mechanical stimulation of polymers causes main-chain scission and generates free radicals (mechanoradicals), which has been focused on as a key process of polymer degradation, and significant progress has been made in parallel in force-mediated polymerization. In this context, the preparation of functional polymers such as luminescent polymeric materials via mechanoradical transformations has not yet been explored systematically. Such a new approach would potentially allow the direct preparation of functional polymers from chemically stable generic polymers. The authors developed a new strategy for introducing a luminophore into generic polymers facilitated by mechanical force using polymeric mechano-radical with a pre-fluorescent nitro-oxide reagent. Photophysical properties of the yielded polymeric materials and computational study indicated that the generated mechano-radical coupling with the pre-fluorescent probe. Several generic polymers also showed the similar transitions.

8. Pedro Paulo Ferreira da Rosa, Shiori Miyazaki, Haruna Sakamoto, Yuichi Kitagawa, Kiyoshi Miyata, Tomoko Akama, Masato Kobayashi, Koji Fushimi, Ken Onda, Tetsuya Taketsugu, and Yasuchika Hasegawa; Coordination geometrical effect on ligand-to-metal charge transfer-dependent energy transfer processes of luminescent Eu(III) complexes (*J. Phys. Chem. A*, 2021, **125**, 209–217)
   Photophysical properties of europium (Eu(III)) complexes are affected by ligand-to-metal charge transfer (LMCT) states. In this paper, seven- and eight-coordinated Eu(III) complexes were synthesized for geometrical-induced LMCT level control. The contribution percentages of π–4f mixing in HOMO and LUMO at the optimized structure in the ground state were calculated using DFT (LC-BLYP). The Eu–O distances and their π–4f mixed orbitals affect the energy level of LMCT

states in Eu(III) complexes. The energy transfer processes between LMCT and Eu(III) ion were investigated using temperature-dependent and time-resolved emission lifetime measurements of $^5D_0 \rightarrow {}^7F_J$ transitions of Eu(III) ions. Based on the experimental and theoretical approaches, the LMCT-dependent energy transfer processes of seven- and eight-coordinated Eu(III) complexes are demonstrated for the first time.

9. Yuichi Kitagawa, Satoshi Wada, M. D. Jahidul Islam, Kenichiro Saita, Masayuki Gon, Koji Fushimi, Kazuo Tanaka, Satoshi Maeda, Yasuchika Hasegawa; Chiral lanthanide lumino-glass for a circularly polarized light security device
Commun. Chem., 2020, 3, 119–123
Artificial light plays an essential role in information technologies such as optical telecommunications, data storage, security features, and the display of information. This paper reported a chiral lanthanide lumino-glass with extra-large circularly polarized luminescence (CPL) for advanced photonic security device applications. The chiral lanthanide glass is composed of a europium complex with the chiral β-diketonate ligand and the achiral glass promoter. The glass phase transition behavior of the Eu(III) complex is characterized using differential scanning calorimetry. The transparent amorphous glass shows CPL with extra-large dissymmetry factor of $g_{CPL} = 1.2$. The brightness of the lumino-glass is one thousand times larger than that of Eu(III) luminophores embedded in polymer films of the same thickness at a Eu(III) concentration of 1 mM. The structure of the characteristic lumino-glass is revealed by quantum chemical calculations.

10. William Bort, Igor I. Baskin, Timur Gimadiev, Artem Mukanov, Ramil Nugmanov, Pavel Sidorov, Gilles Marcou, Dragos Horvath, Olga Klimchuk, Timur Madzhidov, Alexandre Varnek; Discovery of novel chemical reactions by deep generative recurrent neural network (*Sci. Rep.*, 2021, **11**, 3178)
The creativity of Artificial Intelligence (AI) in terms of generating de novo molecular structures opened a novel paradigm in compound design. The authors showed that AI may be as successfully taught to enumerate novel chemical reactions that are stoichiometrically coherent. A sequence-to-sequence autoencoder with bidirectional Long Short-Term Memory layers was trained on newly developed SMILES/CGR strings, encoding reactions of the USPTO database. The autoencoder latent space was visualized on a generative topographic map. Novel latent space points were sampled around a map area populated by Suzuki reactions and decoded to corresponding reactions. Additional chemical filters assessing the feasibility of novel reaction, including quantum chemical calculations, are employed to pinpoint the most relevant among them.

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

*Prepare the information below during the period from the start of the center through March 2022.

1. Major Awards

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

Date	Recipient's name	Name of award
Announced:2022/2/10 Awarded:2022/4/11	Satoshi MAEDA	Nagakura Saburo Award for 2021
Announced:2021/12/22 Awarded:2022/3/24	Jian Ping GONG	The Chemical Society of Japan (CSJ) Award for 2021
Announced:2021/12/22 Awarded:2022/3/24	Satoshi MAEDA	The CSJ Award for Creative Work
Announced:2021/10/6 Awarded:2021/12/10	Benjamin LIST	The Nobel Prize in Chemistry 2021
Announced:2021/9/27 Awarded: March 2022	Benjamin LIST	the 2022 Herbert C. Brown Award for Creative Research in Synthetic Methods sponsored by the Purdue Borane Research Fund and the Herbert C. Brown Award Endowment.
2021/5/20	<u>Jian Ping GONG</u>, Katsuhiko TSUNODA, Kohzo ITO, Hideaki YOKOYAMA, and Kenji URAYAMA	The 33rd Award of the Society of Rubber Science and Technology, Japan
2021/5/19	Yasuchika HASEGAWA	The Rare Earth Society of Japan Award (Shiokawa Award)
2021/4/6	Masaya SAWAMURA	The 2020 Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology: Prizes for Science and Technology
2020/5/15	Yu HARABUCHI	The 1st prize for Outstanding Young Researcher, Japan Society of Theoretical Chemistry
2019/12/12	Yasuhide INOKUMA	Asian Rising Stars Lectureship
2019/04/17	Jian Ping GONG	The 2019 Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology: Prizes for Science and Technology
2019	Michael RUBINSTEIN	Soft Matter and Biological Physical Chemistry Award, Royal Society of Chemistry
2019/3/17	Tetsuya TAKETSUGU	The CSJ Award for Creative Work
2018/2/14	Masaya SAWAMURA	Synthetic Organic Chemistry Award
2018/12/25	Satoshi MAEDA	World Association of Theoretical and Computational Chemists, The Dirac Medal 2019

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

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

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
2021/12/19	Hajime ITO	Versatile soft crystals: Aryl gold(I) isocyanide derivatives	The 2021 International Chemical Congress of Pacific Basin Societies
2021/12/8	Benjamin LIST	Asymmetric Organocatalysis	2021 Nobel Prize Lectures
2021/11/2	Hajime ITO	Mechanoresponse of Luminescent Gold(I) Isocyanide and NHC Complexes	The 11th Asian Photochemistry Conference (APC 2021)
2021/10/12	Hajime ITO	Computer-Aided Reaction Design for Asymmetric Cu(I)-catalyzed Borylation	3rd Chinese Chemical Society Conference on Boron Science (CCS-CBS)
2021/7/7	Hajime ITO	Solid-State Cross-Coupling and Mechanoredox Reaction	Yonsei University Innovative Materials for Sustainable Future
2021/6/27-7/1	Ichigaku TAKIGAWA	A machine-learning view on heterogeneous catalyst design and discovery.	2021 Telluride Workshop on Computational Materials Chemistry, Telluride Science Research Center, Telluride, Colorado, USA
2021/3/19	Benjamin LIST	Very Strong and Confined Chiral Acids: Universal Catalysts for Asymmetric Synthesis?	Chemical Record Lecture 2021
2020/12/8	Hajime ITO	Rise of Mechanochemical Organic Synthesis	MRMforum2020 (Keynote Lecture)
2020/11/23-26	Tetsuya TAKETSUGU	Visualization of reaction path, global reaction route map, and on-the-fly trajectories	New Horizons in Scientific Software: from Legacy Codes to Modular Environments (NHISS 2020)
2020/9/17-23	Tetsuya TAKETSUGU	On-the-fly molecular dynamics approach to excited-state branching reaction	The 6th Quantum Science (QS) symposium – The Main Symposium of ICCMSE 2020 – Computational Chemistry and Computational Physics
2020/7/1	Michael RUBINSTEIN	Polymer physics	Invited Lecture at Garcia Program of Stony Brook University
2019/12/12	Yasuhide INOKUMA	Aliphatic Polyketones for Clay-Play Like Molecular Synthesis	The 18th Asian Chemical Congress
2019/12/10	Jian Ping GONG	Self-growing hydrogels by repetitive mechanical training	CEMS International Symposium on Supramolecular Chemistry and Functional Materials 2019
2019/11/07	Benjamin LIST	Very Strong and Confined Acids Enable a General Approach to Asymmetric Lewis Acid Catalysis	Plenary Speaker XXII SINAQO (Argentine Symposium on Organic Chemistry), Mendoza, Argentina
2019/10/02	Michael RUBINSTEIN	Mysteries of Mucus Physical Properties	5th International Symposium on "Multivalency in Chemistry and Biology"
2019/7/15	Satoshi MAEDA	Systematic Generation and Analysis of Reaction Path Networks by the Artificial Force Induced Reaction Method	10th Triennial Congress of the International Society for Theoretical Chemical Physics (ISTCP 2019)
2019/7/11-13	Shinya TANAKA	Engineered hydrogels for rapid induction of cancer stem cells	The 38th Sapporo International Cancer Symposium
2019/5/23-24	Yasuchika HASEGAWA	Eu(III) and Tb(III) Coordination polymers with strong luminerscence and photo-functional properties	International Conference on Photocatalysis and Photoenergy 2019 (ICoPP2019)
2019/2/18	Alexandre VARNEK	Chemography Concept in Chemical Space Analysis	Invited lecture; Institute of Supramolecular Science and Engineering
2018/11/1	Satoshi MAEDA	Reaction Path Network and its Analysis	The 18th Japan-Korea Joint Symposium on Organometallic and Coordination Chemistry

Appendix 1-4 2021 List of Center's Research Results

Refereed Papers

- List only the Center's papers published in 2021. (Note: The list should be for the calendar year, not the fiscal year.)

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

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

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

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

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

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

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

A. WPI papers

1. Original articles

(1) Akiyama, S.; Oyama, N.; Endo, T.; Kubota, K.; Ito, H. A Copper(I)-Catalyzed Radical-Relay Reaction Enabling the Intermolecular 1,2-Alkylborylation of Unactivated Olefins. *Journal of the American Chemical Society* **2021**, 143 (13), 5260-5268, DOI: 10.1021/jacs.1c02050.

(2) Amatov, T.; Tsuji, N.; Maji, R.; Schreyer, L.; Zhou, H.; Leutzsch, M.; List, B. Confinement-Controlled, Either syn- or anti-Selective Catalytic Asymmetric Mukaiyama Aldolizations of Propionaldehyde Enolsilanes. *Journal of the American Chemical Society* **2021**, 143 (36), 14475-14481, DOI: 10.1021/jacs.1c07447.

(3) Ando, R.; Jin, M.; Ito, H. Charge-transfer crystal with segregated packing structure constructed with hexaarylbenzene and tetracyanoquinodimethane. *CrystEngComm* **2021**, 23 (33), 5564-5568, DOI: 10.1039/d1ce00726b.

(4) Basak, U. S.; Sattari, S.; Hossain, M. M.; Horikawa, K.; Komatsuzaki, T. An information-theoretic approach to infer the underlying interaction domain among elements from finite length trajectories in a noisy environment. *Journal of Chemical Physics* **2021**, 154 (3), 12, DOI: 10.1063/5.0034467.

(5) Bollinger, J. A.; Grest, G. S.; Stevens, M. J.; Rubinstein, M. Overlap Concentration in Salt-Free Polyelectrolyte Solutions.

Macromolecules **2021**, 54 (21), 10068-10073, DOI: 10.1021/acs.macromol.1c01491.

(6) Bort, W.; Baskin, II; Gimadiev, T.; Mukanov, A.; Nugmanov, R.; Sidorov, P.; Marcou, G.; Horvath, D.; Klimchuk, O.; Madzhidov, T.; et al. Discovery of novel chemical reactions by deep generative recurrent neural network. *Scientific Reports* **2021**, 11 (1), 15, DOI: 10.1038/s41598-021-81889-y.

(7) Bowser, B. H.; Wang, S.; Kouznetsova, T. B.; Beech, H. K.; Olsen, B. D.; Rubinstein, M.; Craig, S. L. Single-Event Spectroscopy and Unravelling Kinetics of Covalent Domains Based on Cyclobutane Mechanophores. *Journal of the American Chemical Society* **2021**, 143 (13), 5269-5276, DOI: 10.1021/jacs.1c02149.

(8) Chong, S. G.; Yoneda, T.; Ide, Y.; Neya, S. Reversible Redox System of 2-Oxypyritriphyrin(1.2.1) Accompanying Interconversion between 3-Pyridone and 3-Hydroxypyridine Units. *Chemistry-An Asian Journal* **2021**, 16 (9), 1077-1080, DOI: 10.1002/asia.202100200.

(9) Cui, W.; Huang, Y. W.; Chen, L.; Zheng, Y.; Saruwatari, Y.; Hui, C. Y.; Kurokawa, T.; King, D. R.; Gong, J. P. Tiny yet tough: Maximizing the toughness of fiber-reinforced soft composites in the absence of a fiber-fracture mechanism. *Matter* **2021**, 4 (11), 3646-3661, DOI: 10.1016/j.matt.2021.08.013.

(10) da Rosa, P. P. F.; Miyazaki, S.; Sakamoto, H.; Kitagawa, Y.; Miyata, K.; Akama, T.; Kobayashi, M.; Fushimi, K.; Onda, K.; Taketsugu, T.; et al. Coordination Geometrical Effect on Ligand-to-Metal Charge Transfer-Dependent Energy Transfer Processes of Luminescent Eu(III) Complexes. *Journal of Physical Chemistry A* **2021**, 125 (1), 209-217.

(11) Dong, C. L.; Fan, H. L.; Tang, F.; Gao, X. B.; Feng, K.; Wang, J. H.; Jin, Z. X. Mussel byssus cuticle-inspired ultrastiff and stretchable triple-crosslinked hydrogels. *Journal of Materials Chemistry B* **2021**, 9 (2), 373-380, DOI: 10.1039/d0tb01993c.

(12) Ebisawa, S.; Tsutsumi, T.; Taketsugu, T. Geometric analysis of anharmonic downward distortion following paths. *Journal of Computational Chemistry* **2021**, 42 (1), 27-39, DOI: 10.1002/jcc.26430.

(13) Fa, S. X.; Adachi, K.; Nagata, Y.; Egami, K.; Kato, K.; Ogoshi, T. Pre-regulation of the planar chirality of pillar 5 arenes for preparing discrete chiral nanotubes. *Chemical Science* **2021**, 12 (10), 3483-3488, DOI: 10.1039/d1sc00074h.

(14) Fan, H. L.; Cai, Y. R.; Gong, J. P. Facile tuning of hydrogel properties by manipulating cationic-aromatic monomer sequences. *Science China-Chemistry* **2021**, 64 (9), 1560-1568, DOI: 10.1007/s11426-021-1010-3.

(15) Fan, H. L.; Wang, J. H.; Gong, J. P. Barnacle Cement Proteins-Inspired Tough Hydrogels with Robust, Long-Lasting, and Repeatable Underwater Adhesion. *Advanced Functional Materials* **2021**, 31 (11), 8, DOI: 10.1002/adfm.202009334.

(16) Fujii, T.; Kitagawa, Y.; Hasegawa, Y.; Imoto, H.; Naka, K. Drastic Enhancement of Photosensitized Energy Transfer Efficiency of a Eu(III) Complex Driven by Arsenic. *Inorganic Chemistry* **2021**, 60 (12), 8605-8612, DOI: 10.1021/acs.inorgchem.1c00577.

(17) Fujimori, T.; Kobayashi, M.; Taketsugu, T. Energy-based automatic determination of buffer region in the divide-and-conquer second-order Moller-Plesset perturbation theory. *Journal of Computational Chemistry* **2021**, 42 (9), 620-629, DOI: 10.1002/jcc.26486.

(18) Fujimura, A.; Kitagawa, Y.; Hasegawa, Y.; Doi, T.; Fushimi, K. Active-Passive Transition of an Fe-6 mass% Cr Surface in Acidic Sodium Sulfate Solutions Under a Laminar Flow Condition Evaluated by Ellipso-Microscopy and Channel Flow Electrode Method. *Journal of the Electrochemical Society* **2021**, 168 (5), 11, DOI: 10.1149/1945-7111/abfb96.

(19) Fujimura, M.; Kusaka, S.; Masuda, A.; Hori, A.; Hijikata, Y.; Pirillo, J.; Ma, Y. S.; Matsuda, R. Trapping and Releasing of Oxygen in Liquid by Metal-Organic Framework with Light and Heat. *Small* **2021**, 17 (22), 8, DOI: 10.1002/smll.202004351.

(20) Fushimi, K.; Okuyama, H.; Ohshimizu, K.; Shoji, S.; Kitagawa, Y.; Hasegawa, Y. In-situ Observation of Corrosion Initiation Occurring on NaCI Nanoparticles-deposited Carbon Steel Surfaces. *Tetsu to Hagane-Journal of the Iron and Steel Institute of Japan* **2021**, 107 (12), 1011-1019, DOI: 10.2355/tetsutohagane.TETSU-2021-049.

(21) Gao, M.; Nakahara, M.; Lyalin, A.; Taketsugu, T. Catalytic Activity of Gold Clusters Supported on the h-BN/Au(111) Surface for the Hydrogen Evolution Reaction. *Journal of Physical Chemistry C* **2021**, 125 (2), 1334-1344, DOI: 10.1021/acs.jpcc.0c08826.

(22) Gao, M.; Wang, B.; Tsuneda, T.; Lyalin, A.; Taketsugu, T. Catalytic Functionalization of Hexagonal Boron Nitride for Oxidation and Epoxidation Reactions by Molecular Oxygen. *Journal of Physical Chemistry C* **2021**, 125 (35), 19219-19228, DOI: 10.1021/acs.jpcc.1c04661.

(23) Gimadiev, T. R.; Lin, A.; Afonina, V. A.; Batyrshin, D.; Nugmanov, R. I.; Akhmetshin, T.; Sidorov, P.; Duybankova, N.; Verhoeven, J.; Wegner, J.; et al. Reaction Data Curation I: Chemical Structures and Transformations Standardization. *Molecular Informatics* **2021**, 40 (12), 15, DOI: 10.1002/minf.202100119.

(24) Gimadiev, T.; Nugmanov, R.; Batyrshin, D.; Madzhidov, T.; Maeda, S.; Sidorov, P.; Varnek, A. Combined Graph/Relational Database Management System for Calculated Chemical Reaction Pathway Data. *Journal of Chemical Information and Modeling* **2021**, 61 (2), 554-559, DOI: 10.1021/acs.jcim.0c01280.

(25) Habiba, U.; Sugino, H.; Yordanova, R.; Ise, K.; Tanei, Z.; Ishida, Y.; Tanikawa, S.; Terasaka, S.; Sato, K.; Kamoshima, Y.; et al. Loss of H3K27 trimethylation is frequent in IDH1-R132H but not in non-canonical IDH1/2 mutated and 1p/19q codeleted oligodendroglioma: a Japanese cohort study. *Acta Neuropathologica Communications* **2021**, 9 (1), 11, DOI: 10.1186/s40478-021-01194-7.

(26) Hamama, W. S.; Ghaith, E. A.; Ibrahim, M. E.; Sawamura, M.; Zoorob, H. H. Synthesis of 4-Hydroxy-2-pyridinone Derivatives and Evaluation of Their Antioxidant/Anticancer Activities. *ChemistrySelect* **2021**, 6 (7), 1430-1439.

(27) Han, R.; Diao, J. Y.; Kumar, S.; Lyalin, A.; Taketsugu, T.; Casillas, G.; Richardson, C.; Liu, F.; Yoon, C. W.; Liu, H. Y.; et al. Boron nitride for enhanced oxidative dehydrogenation of ethylbenzene. *Journal of Energy Chemistry* **2021**, 57, 477-484, DOI: 10.1016/j.jechem.2020.03.0272095-4956/.

(28) Hasebe, M.; Tsutsumi, T.; Taketsugu, T.; Tsuneda, T. One-to-One Correspondence between Reaction Pathways and Reactive Orbitals. *Journal of Chemical Theory and Computation* **2021**, 17 (11), 6901-6909, DOI: 10.1021/acs.jctc.1c00693.

(29) Hasegawa, Y.; Sato, N.; Hayashi, J.; Kitagawa, Y.; Fushimi, K. Thermo-Sensitive Eu-III Coordination Polymers with Amorphous Networks. *ChemistrySelect* **2021**, 6 (12), 2812-2816, DOI: 10.1002/slct.**2021**00531.

(30) Hayama, K.; Takahashi, R.; Kubota, K.; Ito, H. Copper(I)-catalyzed Stereoselective Silylative Dearomatization of Indoles and Pyrroles Using Silylboronates. *Chemistry Letters* **2021**, 50 (2), 289-292, DOI: 10.1246/cl.200725.

(31) Hayashi, H.; Takano, H.; Katsuyama, H.; Harabuchi, Y.; Maeda, S.; Mita, T. Synthesis of Difluoroglycine Derivatives from Amines, Difluorocarbene, and CO2: Computational Design, Scope, and Applications. *Chemistry-A European Journal* **2021**, 27 (39), 10040-10047, DOI: 10.1002/chem.202100812.

(32) Hayashi, J.; Shoji, S.; Kitagawa, Y.; Fushimi, K.; Hasegawa, Y. Amide-bridged Eu(III) coordination polymer for stable luminescent glass material. *Materials Letters* **2021**, 297, 4, DOI: 10.1016/j.matlet.2021.130012.

(33) Hinokuma, S.; Iwasa, T.; Kon, Y.; Taketsugu, T.; Sato, K. Effects of support materials and Ir loading on catalytic N2O decomposition properties. *Catalysis Communications* **2021**, 149, 5, DOI: 10.1016/j.catcom.2020.106208.

(34) Hinuma, Y.; Takigawa, I.; Kohyama, M.; Tanaka, S. A simplified methodology for the modeling of interfaces of elementary metals. *AIP Advances* **2021**, 11 (11), 13, DOI: 10.1063/5.0063715.

(35) Holec, J.; Cogliati, B.; Lawrence, J.; Berdonces-Layunta, A.; Herrero, P.; Nagata, Y.; Banasiewicz, M.; Kozankiewicz, B.; Corso, M.; Oteyza, D. G.; et al. A Large Starphene Comprising Pentacene Branches. *Angewandte Chemie-International Edition* **2021**, 60 (14), 7752-7758, DOI: 10.1002/anie.202016163.

(36) Hossain, S.; Miyajima, S.; Iwasa, T.; Kaneko, R.; Sekine, T.; Ikeda, A.; Kawawaki, T.; Taketsugu, T.; Negishi, Y. Ag23Pd2(PPh3)(10)Cl-7 (0): A new family of synthesizable bi-icosahedral superatomic molecules. *Journal of Chemical Physics* **2021**, 155 (2), 10, DOI: 10.1063/5.0057005.

(37) Huang, H. B.; Sato, H.; Pirillo, J.; Hijikata, Y.; Zhao, Y. S.; Cheng, S. Z. D.; Aida, T. Accumulated Lattice Strain as an Internal Trigger for Spontaneous Pathway Selection. *Journal of the American Chemical Society* **2021**, 143 (37), 15319-15325, DOI: 10.1021/jacs.1c06854.

(38) Ikeda, S.; Takeda, R.; Fujie, T.; Ariki, N.; Nagata, Y.; Suginome, M. Protected amino acids as a nonbonding source of chirality in induction of single-handed screw-sense to helical macromolecular catalysts. *Chemical Science* **2021**, 12 (25), 8811-8816, DOI: 10.1039/d1sc01764k.

(39) Imada, H.; Imai-Imada, M.; Miwa, K.; Yamane, H.; Iwasa, T.; Tanaka, Y.; Toriumi, N.; Kimura, K.; Yokoshi, N.; Muranaka, A.; et al. Single-molecule laser nanospectroscopy with micro-electron volt energy resolution. *Science* **2021**, 373 (6550), 95-+, DOI: 10.1126/science.abg8790.

(40) Inaba, Y.; Nomata, Y.; Ide, Y.; Pirillo, J.; Hijikata, Y.; Yoneda, T.; Osuka, A.; Sessler, J. L.; Inokuma, Y. Calix 3 pyrrole: A Missing Link in Porphyrin-Related Chemistry. *Journal of the American Chemical Society* **2021**, 143 (31), 12355-12360, DOI: 10.1021/jacs.1c06331.

(41) Ishi, Y.; Shimizu, A.; Takakuwa, E.; Sugiyama, M.; Okamoto, M.; Motegi, H.; Hirabayashi, S.; Cho, Y.; Iguchi, A.; Manabe, A.; et al. High-grade neuroepithelial tumor with BCL6 corepressor-alteration presenting pathological and radiological calcification: A case report. *Pathology International* **2021**, 71 (5), 348-354, DOI: 10.1111/pin.13083.

(42) Islam, M. J.; Kitagawa, Y.; Tsurui, M.; Hasegawa, Y. Strong circularly polarized luminescence of mixed lanthanide coordination polymers with control of 4f electronic structures. *Dalton Transactions* **2021**, 50 (16), 5433-5436, DOI: 10.1039/d1dt00519g.

(43) Iwai, T.; Goto, Y.; You, Z. S.; Sawamura, M. A Hollow-shaped Caged Triarylphosphine: Synthesis, Characterization and Applications to Gold(I)-catalyzed 1,8-Enyne Cycloisomerization. *Chemistry Letters* **2021**, 50 (6), 1236-1239, DOI: 10.1246/cl.210176.

(44) Iwamoto, H.; Ozawa, Y.; Takenouchi, Y.; Imamoto, T.; Ito, H. Backbone-Modified C-2-Symmetrical Chiral Bisphosphine TMSQuinoxP*: Asymmetric Borylation of Racemic Allyl Electrophiles. *Journal of the American Chemical Society* **2021**, 143 (17), 6413-6422, DOI: 10.1021/jacs.0c08899.

(45) Jancarik, A.; Mildner, D.; Nagata, Y.; Banasiewicz, M.; Olas, J.; Kozankiewicz, B.; Holec, J.; Gourdon, A. Synthesis and Absorption Properties of Long Acenoacenes. *Chemistry-A European Journal* **2021**, 27 (48), 12388-12394, DOI: 10.1002/chem.202101577.

(46) Jin, M.; Ando, R.; Jellen, M. J.; Garcia-Garibay, M. A.; Ito, H. Encapsulating N-Heterocyclic Carbene Binuclear Transition-Metal Complexes as a New Platform for Molecular Rotation in Crystalline Solid-State. *Journal of the American Chemical Society* **2021**, 143 (2), 1144-1153, DOI: 10.1021/jacs.0c11981.

(47) Kamei, Y.; Seino, Y.; Yamaguchi, Y.; Yoshino, T.; Maeda, S.; Kojima, M.; Matsunaga, S. Silane- and peroxide-free hydrogen atom transfer hydrogenation using ascorbic acid and cobalt-photoredox dual catalysis. *Nature Communications* **2021**, 12 (1), 9, DOI: 10.1038/s41467-020-20872-z.

(48) Kanna, W.; Harabuchi, Y.; Takano, H.; Hayashi, H.; Maeda, S.; Mita, T. Carboxylation of a Palladacycle Formed via C(sp(3))-H Activation: Theory-Driven Reaction Design. *Chemistry-An Asian Journal* **2021**, 16 (24), 4072-4080, DOI: 10.1002/asia.202100989.

(49) Kato, K.; Seki, T.; Ito, H. (9-Isocyanoanthracene)gold(I) Complexes Exhibiting Two Modes of Crystal Jumps by Different Structure Change Mechanisms. *Inorganic Chemistry* **2021**, 60 (15), 10849-10856, DOI: 10.1021/acs.inorgchem.1c00881.

(50) Kato, K.; Takaba, K.; Maki-Yonekura, S.; Mitoma, N.; Nakanishi, Y.; Nishihara, T.; Hatakeyama, T.; Kawada, T.; Hijikata, Y.; Pirillo, J.; et al. Double-Helix Supramolecular Nanofibers Assembled from Negatively Curved Nanographenes. *Journal of the American Chemical Society* **2021**, 143 (14), 5465-5469, DOI: 10.1021/jacs.1c00863.

(51) Katono, N.; Tsuda, M.; Suzuka, J.; Oda, Y.; Wang, L.; Tanei, Z.; Tanino, M.; Ohata, T.; Nagabuchi, E.; Ishida, Y.; et al. Involvement of BMP and WNT Signals Leading to Epithelial-Mesenchymal Transition in Colon Adenocarcinoma with Heterotopic Ossification. *Annals of Clinical and Laboratory Science* **2021**, 51 (2), 271-276.

(52) Kim, Y.; Iwai, T.; Fujii, S.; Ueno, K.; Sawamura, M. Dumbbell-Shaped 2,2 '-Bipyridines: Controlled Metal Monochelation and Application to Ni-Catalyzed Cross-Couplings. *Chemistry-A European Journal* **2021**, 27 (7), 2289-2293, DOI: 10.1002/chem.202004053.

(53) Kinoshita, S. N.; Harabuchi, Y.; Inokuchi, Y.; Maeda, S.; Ehara, M.; Yamazaki, K.; Ebata, T. Substitution effect on the

nonradiative decay and trans -> cis photoisomerization route: a guideline to develop efficient cinnamate-based sunscreens. *Physical Chemistry Chemical Physics* **2021**, 23 (2), 13, DOI: 10.1039/d0cp04402d.

(54) Kitagawa, Y.; Kumagai, M.; da Rosa, P. P. F.; Fushimi, K.; Hasegawa, Y. Long-Range LMCT Coupling in Eu-III Coordination Polymers for an Effective Molecular Luminescent Thermometer**. *Chemistry-A European Journal* **2021**, 27 (1), 264-269, DOI: 10.1002/chem.202002628.

(55) Kitagawa, Y.; Matsuda, K.; da Rosa, P. P. F.; Fushimi, K.; Hasegawa, Y. Long-lived emission beyond 1000 nm: control of excited-state dynamics in a dinuclear Tb(iii)-Nd(iii) complex. *Chemical Communications* **2021**, 57 (65), 8047-8050, DOI: 10.1039/d1cc03596g.

(56) Kitagawa, Y.; Naito, A.; Fushimi, K.; Hasegawa, Y. Bright sky-blue fluorescence with high color purity: assembly of luminescent diphenyl-anthracene lutetium-based coordination polymer. *RSC Advances* **2021**, 11 (12), 6604-6606, DOI: 10.1039/d0ra10795f.

(57) Kitagawa, Y.; Naito, A.; Fushimi, K.; Hasegawa, Y. First Tribo-Excited Chemical Reaction of a Stacked Lanthanide Coordination Polymer with an in Situ Reaction Monitor. *Chemistry-A European Journal* **2021**, 27 (7), 2279-2283, DOI: 10.1002/chem.202004485.

(58) Kobayashi, M.; Fujimori, T.; Taketsugu, T. Automatic Determination of Buffer Region in Divide-anc-Conquer Quantum Chemical Calculations. *Journal of Computer Chemistry-Japan* **2021**, 20 (2), 48-59, DOI: 10.2477/jccj.2021-0025.

(59) Kozawa, K.; Sekai, M.; Ohba, K.; Ito, S.; Sako, H.; Maruyama, T.; Kakeno, M.; Shirai, T.; Kuromiya, K.; Kamasaki, T.; et al. The CD44/COL17A1 pathway promotes the formation of multilayered, transformed epithelia. *Current Biology* **2021**, 31 (14), 3086-+, DOI: 10.1016/j.cub.2021.04.078.

(60) Kubota, K.; Miura, D.; Takeuchi, T.; Osaki, S.; Ito, H. Synthesis of Chiral alpha-Amino Tertiary Boronates via the Catalytic Enantioselective Nucleophilic Borylation of Dialkyl Ketimines. *ACS Catalysis* **2021**, 11 (11), 6733-6740, DOI: 10.1021/acscatal.1c01689.

(61) Kubota, K.; Toyoshima, N.; Miura, D.; Jiang, J. L.; Maeda, S.; Jin, M.; Ito, H. Introduction of a Luminophore into Generic Polymers via Mechanoradical Coupling with a Prefluorescent Reagent. *Angewandte Chemie-International Edition* **2021**, 60 (29), 16003-16008, DOI: 10.1002/anie.202105381.

(62) Li, X. Y.; Cui, K. P.; Kurokawa, T.; Ye, Y. N.; Sun, T. L.; Yu, C. T.; Creton, C. T.; Gong, J. P. Effect of mesoscale phase contrast on fatigue-delaying behavior of self-healing hydrogels. *Science Advances* **2021**, 7 (16), 9, DOI: 10.1126/sciadv.abe8210.

(63) Li, Y. K.; Babin, M. C.; Debnath, S.; Iwasa, T.; Kumar, S.; Taketsugu, T.; Asmis, K. R.; Lyalin, A.; Neumark, D. M. Structural Characterization of Nickel-Doped Aluminum Oxide Cations by Cryogenic Ion Trap Vibrational Spectroscopy. *Journal of Physical Chemistry A* **2021**, 125 (43), 9527-9535, DOI: 10.1021/acs.jpca.1c07156.

(64) Lian, W. Z.; Fan, Z. W.; Cui, K. P.; Yin, P. C.; Yang, J. S.; Jiang, H.; Tang, L. Q.; Sun, T. L. Tough Hydrogels with Dynamic H-Bonds: Structural Heterogeneities and Mechanical Performances. *Macromolecules* **2021**, 54 (19), 8996-9006, DOI: 10.1021/acs.macromol.1c01064.

(65) Liu, Z. Z.; Hui, C. Y.; Jagota, A.; Gong, J. P.; Kiyama, R. A surface flattening method for characterizing the surface stress, drained Poisson's ratio and diffusivity of poroelastic gels. *Soft Matter* **2021**, 17 (31), 7332-7340, DOI: 10.1039/d1sm00513h.

(66) Matsuda, T.; Kawakami, R.; Nakajima, T.; Hane, Y.; Gong, J. P. Revisiting the Origins of the Fracture Energy of Tough Double-Network Hydrogels with Quantitative Mechanochemical Characterization of the Damage Zone. *Macromolecules* **2021**, 54 (22), 10331-10339, DOI: 10.1021/acs.macromol.1c01214.

(67) Matsuoka, K.; Komami, N.; Kojima, M.; Mita, T.; Suzuki, K.; Maeda, S.; Yoshino, T.; Matsunaga, S. Chemoselective Cleavage of Si-C(sp(3)) Bonds in Unactivated Tetraalkylsilanes Using Iodine Tris(trifluoroacetate). *Journal of the American Chemical Society* **2021**, 143 (1), 103-108, DOI: 10.1021/jacs.0c11645.

(68) Matsuura, S.; Taguchi, J.; Seki, T.; Ito, H. Synthesis and Optical Properties of C,N-Swapped Boranils Derived from Potassium Acyltrifluoroborates. *Bulletin of the Chemical Society of Japan* **2021**, 94 (5), 1547-1552, DOI: 10.1246/bcsj.20210024.

(69) Meng, W. J.; Kondo, S.; Ito, T.; Komatsu, K.; Pirillo, J.; Hijikata, Y.; Ikuhara, Y.; Aida, T.; Sato, H. An elastic metal-organic crystal with a densely catenated backbone. *Nature* **2021**, 598 (7880), 298-+, DOI: 10.1038/s41586-021-03880-x.

(70) Mine, S.; Takao, M.; Yamaguchi, T.; Toyao, T.; Maeno, Z.; Siddiki, S.; Takakusagi, S.; Shimizu, K.; Takigawa, I. Analysis of Updated Literature Data up to 2019 on the Oxidative Coupling of Methane Using an Extrapolative Machine-Learning Method to Identify Novel Catalysts. *ChemCatChem* **2021**, 13 (16), 3636-3655, DOI: 10.1002/cctc.202100495.

(71) Miura, T.; Hagiwara, K.; Nakamuro, T.; Nagata, Y.; Oku, N.; Murakami, M. Regioselective 1,3-Dipolar Cycloaddition of Nitriles with Nitrile Imines Generated from Tetrazoles. *Chemistry Letters* **2021**, 50 (1), 131-135, DOI: 10.1246/cl.200634.

(72) Miura, T.; Oku, N.; Shiratori, Y.; Nagata, Y.; Murakami, M. Stereo- and Enantioselective Synthesis of Propionate-Derived Trisubstituted Alkene Motifs. *Chemistry-A European Journal* **2021**, 27 (11), 3861-3868, DOI: 10.1002/chem.202004930.

(73) Miyamoto, M.; Taketsugu, T.; Iwasa, T. A comparative study of structural, electronic, and optical properties of thiolated gold clusters with icosahedral vs face-centered cubic cores. *Journal of Chemical Physics* **2021**, 155 (9), 8, DOI: 10.1063/5.0057566.

(74) Mizuno, Y.; Takigawa, M.; Miyashita, S.; Nagahata, Y.; Teramoto, H.; Komatsuzaki, T. An algorithm for computing phase space structures in chemical reaction dynamics using Voronoi tessellation. *Physica D-Nonlinear Phenomena* **2021**, 428, 17, DOI: 10.1016/j.physd.2021.133047.

(75) Murata, Y.; Matsunagi, K.; Kashida, J.; Shoji, Y.; Ozen, C.; Maeda, S.; Fukushima, T. Observation of Borane-Olefin Proximity Interaction Governing the Structure and Reactivity of Boron-Containing Macrocycles. *Angewandte Chemie-International Edition* **2021**, 60 (26), 14630-14635, DOI: 10.1002/anie.202103512.

(76) Nagahata, Y.; Hernandez, R.; Komatsuzaki, T. Phase space geometry of isolated to condensed chemical reactions. *Journal of Chemical Physics* **2021**, 155 (21), 17, DOI: 10.1063/5.0059618.

(77) Nagano, M.; Kohsaka, S.; Hayashi, T.; Ueno, T.; Kojima, S.; Shinozaki-Ushiku, A.; Morita, S.; Tsuda, M.; Tanaka, S.; Shinohara, T.; et al. Comprehensive molecular profiling of pulmonary pleomorphic carcinoma. *NPJ Precision Oncology* **2021**, 5 (1), 9, DOI: 10.1038/s41698-021-00201-3.

(78) Nakajima, T.; Hoshino, K.; Guo, H. L.; Kurokawa, T.; Gong, J. P. Experimental Verification of the Balance between Elastic Pressure and Ionic Osmotic Pressure of Highly Swollen Charged Gels. *Gels* **2021**, 7 (2), 14, DOI: 10.3390/gels7020039.

(79) Nakajo, T.; Kumagai, J.; Kusaka, S.; Hori, A.; Hijikata, Y.; Pirillo, J.; Ma, Y. S.; Matsuda, R. Triplet Carbene with Highly Enhanced Thermal Stability in the Nanospace of a Metal-Organic Framework. *Journal of the American Chemical Society* **2021**, 143 (21), 8129-8136, DOI: 10.1021/jacs.1c02430.

(80) Nishimura, T.; Guo, H. L.; Kiyama, R.; Katsuyama, Y.; Gong, J. P.; Kurokawa, T. In Situ Evaluation of the Polymer Concentration Distribution of Microphase-Separated Polyelectrolyte Hydrogels by the Microelectrode Technique. *Macromolecules* **2021**, 54 (23), 10776-10785, DOI: 10.1021/acs.macromol.1c01435.

(81) Nitta, Y.; Schalk, O.; Igarashi, H.; Wada, S.; Tsutsumi, T.; Saita, K.; Taketsugu, T.; Sekikawa, T. Real-Time Probing of an Atmospheric Photochemical Reaction by Ultrashort Extreme Ultraviolet Pulses: Nitrous Acid Release from o-Nitrophenol. *Journal of Physical Chemistry Letters* **2021**, 12 (1), 674-679, DOI: 10.1021/acs.jpclett.0c03297.

(82) Nonoyama, T.; Wang, L.; Kiyama, R.; Kashimura, N.; Yasuda, K.; Tanaka, S.; Kurokawa, T.; Gong, J. P. Fast in vivo fixation of double network hydrogel to bone by monetite surface hybridization. *Journal of the Ceramic Society of Japan* **2021**, 129 (9), 584-589, DOI: 10.2109/jcersj2.21084.

(83) Nonoyama, T.; Wang, L.; Tsuda, M.; Suzuki, Y.; Kiyama, R.; Yasuda, K.; Tanaka, S.; Nagata, K.; Fujita, R.; Sakamoto, N.; et al. Isotope Microscopic Observation of Osteogenesis Process Forming Robust Bonding of Double Network Hydrogel to Bone. *Advanced Healthcare Materials* **2021**, 10 (3), 6, DOI: 10.1002/adhm.202001731.

(84) Noro, S.; Meng, Y.; Suzuki, K.; Sugiura, M.; Hijikata, Y.; Pirillo, J.; Takahashi, K.; Nakamura, T. A Temporarily Pore-Openable Porous Coordination Polymer for Guest Adsorption/Desorption. *Inorganic Chemistry* **2021**, 60 (7), 4531-4538,

DOI: 10.1021/acs.inorgchem.0c03420.

(85) Ohmura, T.; Morimasa, Y.; Ichino, T.; Miyake, Y.; Murata, Y.; Suginome, M.; Tajima, K.; Taketsugu, T.; Maeda, S. Mechanism of 2,6-Dichloro-4,4 '-bipyridine-Catalyzed Diboration of Pyrazines Involving a Bipyridine-Stabilized Boryl Radical. *Bulletin of the Chemical Society of Japan* **2021**, 94 (7), 1894-1902, DOI: 10.1246/bcsj.20210145.

(86) Ohtani, R.; Yoshino, H.; Yanagisawa, J.; Ohtsu, H.; Hashizume, D.; Hijikata, Y.; Pirillo, J.; Sadakiyo, M.; Kato, K.; Shudo, Y.; et al. Flexibility Control of Two-Dimensional Coordination Polymers by Crystal Morphology: Water Adsorption and Thermal Expansion. *Chemistry-A European Journal* **2021**, 27 (72), 18135-18140, DOI: 10.1002/chem.202103404.

(87) Okumura, T.; Takahashi, R.; Hagita, K.; King, D. R.; Gong, J. P. Improving the strength and toughness of macroscale double networks by exploiting Poisson's ratio mismatch. *Scientific Reports* **2021**, 11 (1), 13, DOI: 10.1038/s41598-021-92773-0.

(88) Orlov, A. A.; Marcou, G.; Horvath, D.; Cabodevilla, A. E.; Varnek, A.; de Meyer, F. Computer-Aided Design of New Physical Solvents for Hydrogen Sulfide Absorption. *Industrial & Engineering Chemistry Research* **2021**, 60 (23), 8588-8596, DOI: 10.1021/acs.iecr.0c05923.

(89) Ousaka, N.; Yamamoto, S.; Iida, H.; Iwata, T.; Ito, S.; Souza, R.; Hijikata, Y.; Irle, S.; Yashima, E. Encapsulation of Aromatic Guests in the Bisporphyrin Cavity of a Double-Stranded Spiroborate Helicate: Thermodynamic and Kinetic Studies and the Encapsulation Mechanism. *Journal of Organic Chemistry* **2021**, 86 (15), 10501-10516, DOI: 10.1021/acs.joc.1c01155.

(90) Ozawa, Y.; Endo, K.; Ito, H. Regio- and Stereoselective Synthesis of Multi-Alkylated Allylic Boronates through Three-Component Coupling Reactions between Allenes, Alkyl Halides, and a Diboron Reagent. *Journal of the American Chemical Society* **2021**, 143 (34), 13865-13877, DOI: 10.1021/jacs.1c06538.

(91) Parajuli, G.; Tekguc, M.; Wing, J. B.; Hashimoto, A.; Okuzaki, D.; Hirata, T.; Sasaki, A.; Itokazu, T.; Handa, H.; Sugino, H.; et al. Arid5a Promotes Immune Evasion by Augmenting Tryptophan Metabolism and Chemokine Expression. *Cancer Immunology Research* **2021**, 9 (8), 862-876, DOI: 10.1158/2326-6066.cir-21-0014.

(92) Parisi, D.; Buenning, E.; Kalafatakis, N.; Gury, L.; Benicewicz, B. C.; Gauthier, M.; Cloitre, M.; Rubinstein, M.; Kumar, S. K.; Vlassopoulos, D. Universal Polymeric-to-Colloidal Transition in Melts of Hairy Nanoparticles. *ACS Nano* **2021**, 15 (10), 16697-16708, DOI: 10.1021/acsnano.1c06672.

(93) Pradipta, A. R.; Ahmadi, P.; Terashima, K.; Muguruma, K.; Fujii, M.; Ichino, T.; Maeda, S.; Tanaka, K. Targeted 1,3-dipolar cycloaddition with acrolein for cancer prodrug activation. *Chemical Science* **2021**, 12 (15), 5438-5449, DOI: 10.1039/d0sc06083f.

(94) Preobrajenski, A. B.; Lyalin, A.; Taketsugu, T.; Vinogradov, N. A.; Vinogradov, A. S. Honeycomb Boron on Al(111): From the Concept of Borophene to the Two-Dimensional Boride. *ACS Nano* **2021**, 15 (9), 15153-15165, DOI: 10.1021/acsnano.1c05603.

(95) Rakhimbekova, A.; Akhmetshin, T. N.; Minibaeva, G. I.; Nugmanov, R. I.; Gimadiev, T. R.; Madzhidov, T. I.; Baskin, II; Varnek, A. Cross-validation strategies in QSPR modelling of chemical reactions. *SAR and QSAR in Environmental Research* **2021**, 32 (3), 207-219, DOI: 10.1080/1062936x.2021.1883107.

(96) Rawat, V. K.; Higashida, K.; Sawamura, M. Nickel-Catalyzed Homocoupling of Aryl Ethers with Magnesium Anthracene Reductant. *Synthesis-Stuttgart* **2021**, 53 (18), 3397-3403, DOI: 10.1055/a-1509-5954.

(97) Rawat, V. K.; Higashida, K.; Sawamura, M. Use of Imidazo 1,5-a pyridin-3-ylidene as a Platform for Metal-Imidazole Cooperative Catalysis: Silver-Catalyzed Cyclization of Alkyne-Tethered Carboxylic Acids. *Advanced Synthesis & Catalysis* **2021**, 363 (6), 1631-1637, DOI: 10.1002/adsc.202001515.

(98) Saito, M.; Morioka, M.; Izumiyama, K.; Mori, A.; Ogasawara, R.; Kondo, T.; Miyajima, T.; Yokoyama, E.; Tanikawa, S. Phlegmonous gastritis developed during chemotherapy for acute lymphocytic leukemia: A case report. *World Journal of Clinical Cases* **2021**, 9 (22), 6493-6500, DOI: 10.12998/wjcc.v9.i22.6493.

(99) Sasai, K.; Tabu, K.; Saito, T.; Matsuba, Y.; Saido, T. C.; Tanaka, S. Difference in the malignancy between RAS and GLI1-transformed astrocytes is associated with frequency of p27(KIP1)-positive cells in xenograft tissues. *Pathology Research and Practice* **2021**, 223, 7, DOI: 10.1016/j.prp.2021.153465.

(100) Sato, K.; Miyahara, S.; Tsujimaru, K.; Wada, Y.; Toriyama, T.; Yamamoto, T.; Matsumura, S.; Inazu, K.; Mohri, H.; Iwasa, T.; et al. Barium Oxide Encapsulating Cobalt Nanoparticles Supported on Magnesium Oxide: Active Non-Noble Metal Catalysts for Ammonia Synthesis under Mild Reaction Conditions. *ACS Catalysis* **2021**, 11 (21), 13050-13061, DOI: 10.1021/acscatal.1c02887.

(101) Schneemann, A.; Jing, Y.; Evans, J. D.; Toyao, T.; Hijikata, Y.; Kamiya, Y.; Shimizu, K.; Burtch, N. C.; Noro, S. Alkyl decorated metal-organic frameworks for selective trapping of ethane from ethylene above ambient pressures. *Dalton Transactions* **2021**, 50 (30), 10423-10435, DOI: 10.1039/d1dt01477c.

(102) Semba, S.; Kitamura, N.; Tsuda, M.; Goto, K.; Kurono, S.; Ohmiya, Y.; Kurokawa, T.; Gong, J. P.; Yasuda, K.; Tanaka, S. Synthetic poly(2-acrylamido-2-methylpropanesulfonic acid) gel induces chondrogenic differentiation of ATDC5 cells via a novel protein reservoir function. *Journal of Biomedical Materials Research Part A* **2021**, 109 (3), 354-364, DOI: 10.1002/jbm.a.37028.

(103) Seo, T.; Toyoshima, N.; Kubota, K.; Ito, H. Tackling Solubility Issues in Organic Synthesis: Solid-State Cross-Coupling of Insoluble Aryl Halides. *Journal of the American Chemical Society* **2021**, 143 (16), 6165-6175, DOI: 10.1021/jacs.1c00906.

(104) Shibata, T.; Shiozawa, N.; Nishibe, S.; Takano, H.; Maeda, S. Pt(ii)-Chiral diene-catalyzed enantioselective formal 4+2 cycloaddition initiated by C-C bond cleavage and elucidation of a Pt(ii)/(iv) cycle by DFT calculations. *Organic Chemistry Frontiers* **2021**, 8 (24), 6985-6991, DOI: 10.1039/d1qo01467f.

(105) Shida, N.; Takenaka, H.; Gotou, A.; Isogai, T.; Yamauchi, A.; Kishikawa, Y.; Nagata, Y.; Tomita, I.; Fuchigami, T.; Inagi, S. Alkali Metal Fluorides in Fluorinated Alcohols: Fundamental Properties and Applications to Electrochemical Fluorination. *Journal of Organic Chemistry* **2021**, 86 (22), 16128-16133, DOI: 10.1021/acs.joc.1c00692.

(106) Shimosaraya, N.; Sotani, T.; Miyagi, Y.; Mondarte, E. A. Q.; Suthiwanich, K.; Hayashi, T.; Nagata, Y.; Sogawa, H.; Sanda, F. Tyrosine-based photoluminescent diketopiperazine supramolecular aggregates. *Soft Matter* **2021**, 18 (1), 137-145, DOI: 10.1039/d1sm01206a.

(107) Shirakura, H.; Hijikata, Y.; Pirillo, J.; Yoneda, T.; Manabe, Y.; Murugavel, M.; Ide, Y.; Inokuma, Y. Insoluble pi-Conjugated Polyimine as an Organic Adsorbent for Group 10 Metal Ions. *European Journal of Inorganic Chemistry 2021*, **2021** (17), 1705-1708, DOI: 10.1002/ejic.202100172.

(108) Shirakura, H.; Manabe, Y.; Kasai, C.; Inaba, Y.; Tsurui, M.; Kitagawa, Y.; Hasegawa, Y.; Yoneda, T.; Ide, Y.; Inokuma, Y. Isopyrazole-Masked Tetraketone: Tautomerism and Functionalization for Fluorescent Metal Ligands. *European Journal of Organic Chemistry 2021*, **2021** (30), 4345-4349, DOI: 10.1002/ejoc.202100784.

(109) Singh, S.; Taketsugu, T.; Singh, R. K. Hydration, Prediction of the pK(a), and Infrared Spectroscopic Study of Sulfonated Polybenzophenone (SPK) Block-Copolymer Hydrocarbon Membranes and Comparisons with Nafion. *ACS Omega* **2021**, 6 (48), 32739-32748, DOI: 10.1021/acsomega.1c04484.

(110) Sugie, Y.; Yoshida, Y.; Mertig, N.; Takemoto, T.; Teramoto, H.; Nakamura, A.; Takigawa, I.; Minato, S. I.; Yamaoka, M.; Komatsuzaki, T. Minor-embedding heuristics for large-scale annealing processors with sparse hardware graphs of up to 102,400 nodes. *Soft Computing* **2021**, 25 (3), 1731-1749, DOI: 10.1007/s00500-020-05502-6.

(111) Sugiyama, K.; Saita, K.; Maeda, S. A reaction route network for methanol decomposition on a Pt(111) surface. *Journal of Computational Chemistry* **2021**, 42 (30), 2163-2169, DOI: 10.1002/jcc.26746.

(112) Sun, K. W.; Sugawara, K.; Lyalin, A.; Ishigaki, Y.; Uosaki, K.; Taketsugu, T.; Suzuki, T.; Kawai, S. Heterocyclic Ring-Opening of Nanographene on Au(111). *Angewandte Chemie-International Edition* **2021**, 60 (17), 9427-9432, DOI: 10.1002/anie.202017137.

(113) Sun, K.; Ueno, M.; Imaeda, K.; Ueno, K.; Sawamura, M.; Shimizu, Y. Visible-Light-Driven alpha-Allylation of Carboxylic Acids. *ACS Catalysis* **2021**, 11 (15), 9722-9728, DOI: 10.1021/acscatal.1c02558.

(114) Suzuka, J.; Tsuda, M.; Wang, L.; Kohsaka, S.; Kishida, K.; Semba, S.; Sugino, H.; Aburatani, S.; Frauenlob, M.; Kurokawa, T.; et al. Rapid reprogramming of tumour cells into cancer stem cells on double-network hydrogels. *Nature Biomedical Engineering* **2021**, 5 (8), 914-925, DOI: 10.1038/s41551-021-00692-2.

(115) Svirskiy, G. I.; Generalov, A. V.; Vinogradov, N. A.; Brykalova, X. O.; Vereshchagin, A. V.; Levin, O. V.; Lyalin, A. G.; Preobrajenski, A. B.; Vinogradov, A. S. Electronic structure of the Ni(Salen) complex studied by core-level spectroscopies. *Physical Chemistry Chemical Physics* **2021**, 23 (18), 11015-11027, DOI: 10.1039/d1cp00511a.

(116) Takahashi, K.; Satoshi, M. Mining hydroformylation in complex reaction network via graph theory. *RSC Advances* **2021**, 11 (38), 23235-23240, DOI: 10.1039/d1ra03395f.

(117) Takahashi, R.; Hu, A. Q.; Gao, P.; Gao, Y. P.; Pang, Y. D.; Seo, T.; Jiang, J. L.; Maeda, S.; Takaya, H.; Kubota, K.; et al. Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nature Communications* **2021**, 12 (1), 10, DOI: 10.1038/s41467-021-26962-w.

(118) Takahashi, R.; Seo, T.; Kubota, K.; Ito, H. Palladium-Catalyzed Solid-State Polyfluoroarylation of Aryl Halides Using Mechanochemistry. *ACS Catalysis* **2021**, 11 (24), 14803-14810, DOI: 10.1021/acscatal.1c03731.

(119) Takano, H.; Shibata, T. Versatile Transformations of Biphenylenes by Transition-Metal Catalysts and Application for the Synthesis of Polycyclic Hydrocarbons. *Journal of Synthetic Organic Chemistry Japan* **2021**, 79 (9), 849-858,

(120) Takano, H.; You, Y.; Hayashi, H.; Harabuchi, Y.; Maeda, S.; Mita, T. Radical Difunctionalization of Gaseous Ethylene Guided by Quantum Chemical Calculations: Selective Incorporation of Two Molecules of Ethylene. *ACS Omega* **2021**, 6 (49), 33846-33854, DOI: 10.1021/acsomega.1c05102.

(121) Takenaka, M.; Taketsugu, T.; Iwasa, T. Theoretical method for near-field Raman spectroscopy with multipolar Hamiltonian and real-time-TDDFT: Application to on- and off-resonance tip-enhanced Raman spectroscopy. *Journal of Chemical Physics* **2021**, 154 (2), 14, DOI: 10.1063/5.0034933.

(122) Takeuchi, T.; Shishido, R.; Kubota, K.; Ito, H. Synthesis of hydrosilylboronates via the monoborylation of a dihydrosilane Si-H bond and their application for the generation of dialkylhydrosilyl anions. *Chemical Science* **2021**, 12 (35), 11799-11804, DOI: 10.1039/d1sc01440d.

(123) Tanei, Z.; Saito, Y.; Ito, S.; Matsubara, T.; Motoda, A.; Yamazaki, M.; Sakashita, Y.; Kawakami, I.; Ikemura, M.; Tanaka, S.; et al. Lewy pathology of the esophagus correlates with the progression of Lewy body disease: a Japanese cohort study of autopsy cases. *Acta Neuropathologica* **2021**, 141 (1), 25-37, DOI: 10.1007/s00401-020-02233-8.

(124) Tao, S. S.; Xu, H.; Xu, Q.; Hijikata, Y.; Jiang, Q. H.; Irle, S.; Jiang, D. L. Hydroxide Anion Transport in Covalent Organic Frameworks. *Journal of the American Chemical Society* **2021**, 143 (24), 8970-8975, DOI: 10.1021/jacs.1c03268.

(125) Tentaku, T.; Atobe, R.; Tsutsumi, T.; Satoh, S.; Harabuchi, Y.; Taketsugu, T.; Sekikawa, T. Switching the relaxation pathway by steric effects in conjugated dienes. *Journal of Physics B-Atomic Molecular and Optical Physics* **2021**, 54 (17), 8, DOI: 10.1088/1361-6455/ac274c.

(126) Tokuchi, K.; Kitamura, S.; Maeda, T.; Watanabe, M.; Hatakeyama, S.; Kano, S.; Tanaka, S.; Ujiie, H.; Yanagi, T. Loss of FAM83H promotes cell migration and invasion in cutaneous squamous cell carcinoma via impaired keratin distribution. *Journal of Dermatological Science* **2021**, 104 (2), 112-121, DOI: 10.1016/j.jdermsci.2021.09.007.

(127) Tomomasa, R.; Arai, Y.; Kawabata-Iwakawa, R.; Fukuoka, K.; Nakano, Y.; Hama, N.; Nakata, S.; Suzuki, N.; Ishi, Y.; Tanaka, S.; et al. Ependymoma-like tumor with mesenchymal differentiation harboring C11orf95-NCOA1/2 or -RELA fusion: A hitherto unclassified tumor related to ependymoma. *Brain Pathology* **2021**, 31 (3), 14, DOI: 10.1111/bpa.12943.

(128) Tsuda, M.; Noguchi, M.; Kurai, T.; Ichihashi, Y.; Ise, K.; Wang, L.; Ishida, Y.; Tanino, M.; Hirano, S.; Asaka, M.; et al. Aberrant expression of MYD88 via RNA-controlling CNOT4 and EXOSC3 in colonic mucosa impacts generation of colonic cancer. *Cancer Science* **2021**, 112 (12), 5100-5113, DOI: 10.1111/cas.15157.

(129) Tsutsumi, T.; Ono, Y.; Taketsugu, T. Visualization of reaction route map and dynamical trajectory in reduced dimension. *Chemical Communications* **2021**, 57 (89), 11734-11750, DOI: 10.1039/d1cc04667e.

(130) Venkata, S. P.; Cui, K. P.; Guo, J. Y.; Zehnder, A. T.; Gong, J. P.; Hui, C. Y. Constitutive modeling of bond breaking and healing kinetics of physical Polyampholyte (PA) gel. *Extreme Mechanics Letters* **2021**, 43, 13, DOI: 10.1016/j.eml.2021.101184.

(131) Venkata, S. P.; Cui, K. P.; Guo, J. Y.; Zehnder, A. T.; Gong, J. P.; Hui, C. Y. Constitutive modeling of strain-dependent

bond breaking and healing kinetics of chemical polyampholyte (PA) gel. *Soft Matter* **2021**, 17 (15), 4161-4169, DOI: 10.1039/d1sm00110h.

(132) Wang, Z.; Zheng, X. J.; Ouchi, T.; Kouznetsova, T. B.; Beech, H. K.; Av-Ron, S.; Matsuda, T.; Bowser, B. H.; Wang, S.; Johnson, J. A.; et al. Toughening hydrogels through force-triggered chemical reactions that lengthen polymer strands. *Science* **2021**, 374 (6564), 193-+, DOI: 10.1126/science.abg2689.

(133) Xiao, R.; Mai, T. T.; Urayama, K.; Gong, J. P.; Qu, S. X. Micromechanical modeling of the multi-axial deformation behavior in double network hydrogels. *International Journal of Plasticity* **2021**, 137, 19, DOI: 10.1016/j.ijplas.2020.102901.

(134) Xu, L.; Urita, A.; Onodera, T.; Hishimura, R.; Nonoyama, T.; Hamasaki, M.; Liang, D. W.; Homan, K.; Gong, J. P.; Iwasaki, N. Ultrapurified Alginate Gel Containing Bone Marrow Aspirate Concentrate Enhances Cartilage and Bone Regeneration on Osteochondral Defects in a Rabbit Model. *American Journal of Sports Medicine* **2021**, 49 (8), 2199-2210, DOI: 10.1177/03635465211014186.

(135) Yamamoto, J.; Matsui, A.; Gan, F.; Oura, M.; Ando, R.; Matsuda, T.; Gong, J. P.; Kinjo, M. Quantitative evaluation of macromolecular crowding environment based on translational and rotational diffusion using polarization dependent fluorescence correlation spectroscopy. *Scientific Reports* **2021**, 11 (1), 11, DOI: 10.1038/s41598-021-89987-7.

(136) Yamamoto, T.; Sakaue, T.; Schiessel, H. Slow chromatin dynamics enhances promoter accessibility to transcriptional condensates. *Nucleic Acids Research* **2021**, 49 (9), 5017-5027, DOI: 10.1093/nar/gkab275.

(137) Yamauchi, Y.; Kameda, H.; Omori, K.; Tani, M.; Cho, K. Y.; Nakamura, A.; Miyoshi, H.; Tanaka, S.; Atsumi, T. Severe infection including disseminated herpes zoster triggered by subclinical Cushing's disease: a case report. *BMC Endocrine Disorders* **2021**, 21 (1), 6, DOI: 10.1186/s12902-021-00757-y.

(138) Yamazaki, T.; Yamamoto, T.; Yoshino, H.; Souquere, S.; Nakagawa, S.; Pierron, G.; Hirose, T. Paraspeckles are constructed as block copolymer micelles. *EMBO Journal* **2021**, 40 (12), 19, DOI: 10.15252/embj.2020107270.

(139) Yang, D. S.; Bao, P. Q.; Yang, Z.; Chen, Z. X.; Sakaki, S.; Maeda, S.; Zeng, G. X. Pincer-Type Phosphorus Compounds with Boryl-Pendant and Application in Catalytic H-2 Generation from Ammonia-Borane: A Theoretical Study. *ChemCatChem* **2021**, 13 (18), 3925-3929, DOI: 10.1002/cctc.202100661.

(140) Ye, Y. N.; Cui, K. P.; Hong, W.; Li, X. Y.; Yu, C. T.; Hourdet, D.; Nakajima, T.; Kurokawa, T.; Gong, J. P. Molecular mechanism of abnormally large nonsoftening deformation in a tough hydrogel. *Proceedings of the National Academy of Sciences of the United States of America* **2021**, 118 (14), 5, DOI: 10.1073/pnas.2014694118.

(141) Ye, Y. N.; Haque, M. A.; Inoue, A.; Katsuyama, Y.; Kurokawa, T.; Gong, J. P. Flower-like Photonic Hydrogel with Superstructure Induced via Modulated Shear Field. *ACS Macro Letters* **2021**, 10 (6), 708-713, DOI: 10.1021/acsmacrolett.1c00178.

(142) Yoshimaru, S.; Sadakiyo, M.; Maeda, N.; Yamauchi, M.; Kato, K.; Pirillo, J.; Hijikata, Y. Support Effect of Metal-Organic Frameworks on Ethanol Production through Acetic Acid Hydrogenation. *ACS Applied Materials & Interfaces* **2021**, 13 (17), 19992-20001, DOI: 10.1021/acsami.1c01100.

(143) You, Z. S.; Higashida, K.; Iwai, T.; Sawamura, M. Phosphinylation of Non-activated Aryl Fluorides through Nucleophilic Aromatic Substitution at the Boundary of Concerted and Stepwise Mechanisms. *Angewandte Chemie-International Edition* **2021**, 60 (11), 5778-5782, DOI: 10.1002/anie.202013544.

(144) Yu, C. T.; Cui, K. P.; Guo, H. L.; Ye, Y. N.; Li, X. Y.; Gong, J. P. Structure Frustration Enables Thermal History-Dependent Responsive Behavior in Self-Healing Hydrogels. *Macromolecules* **2021**, 54 (21), 9927-9936, DOI: 10.1021/acs.macromol.1c01461.

(145) Yue, Y. F.; Norikane, Y.; Gong, J. P. Ultrahigh-Water-Content Photonic Hydrogels with Large Electro-Optic Responses in Visible to Near-Infrared Region. *Advanced Optical Materials* **2021**, 9 (9), 9, DOI: 10.1002/adom.202002198.

(146) Zabolotna, Y.; Ertl, P.; Horvath, D.; Bonachera, F.; Marcou, G.; Varnek, A. NP Navigator: a New Look at the Natural Product Chemical Space. *Molecular Informatics* **2021**, 40 (9), 13, DOI: 10.1002/minf.**2021**00068.

(147) Zabolotna, Y.; Volochnyuk, D. M.; Ryabukhin, S. V.; Horvath, D.; Gavrilenko, K. S.; Marcou, G.; Moroz, Y. S.; Oksiuta,

O.; Varnek, A. A Close-up Look at the Chemical Space of Commercially Available Building Blocks for Medicinal Chemistry. *Journal of Chemical Information and Modeling*, **2021**, 15, Article; Early Access. DOI: 10.1021/acs.jcim.1c00811.

(148) Zankov, D.; Polishchuk, P.; Madzhidov, T.; Varnek, A. Multi-Instance Learning Approach to Predictive Modeling of Catalysts Enantioselectivity. *Synlett* **2021**, 32 (18), 1833-1836, DOI: 10.1055/a-1553-0427.

(149) Zhang, P. L.; Tsuji, N.; Ouyang, J.; List, B. Strong and Confined Acids Catalyze Asymmetric Intramolecular Hydroarylations of Unactivated Olefins with Indoles. *Journal of the American Chemical Society* **2021**, 143 (2), 675-680, DOI: 10.1021/jacs.0c12042.

(150) Zhang, T.; Kitagawa, Y.; Moriake, R.; da Rosa, P. P. F.; Islam, M. J.; Yoneda, T.; Inokuma, Y.; Fushimi, K.; Hasegawa, Y. Hybrid Eu-III Coordination Luminophore Standing on Two Legs on Silica Nanoparticles for Enhanced Luminescence. *Chemistry-A European Journal* **2021**, 27 (58), 14438-14443, DOI: 10.1002/chem.202102156.

(151) Zheng, Y.; Kiyama, R.; Matsuda, T.; Cui, K. P.; Li, X. Y.; Cui, W.; Guo, Y. Z.; Nakajima, T.; Kurokawa, T.; Gong, J. P. Nanophase Separation in Immiscible Double Network Elastomers Induces Synergetic Strengthening, Toughening, and Fatigue Resistance. *Chemistry of Materials* **2021**, 33 (9), 3321-3334, DOI: 10.1021/acs.chemmater.1c00512.

(152) Zheng, Y.; Matsuda, T.; Nakajima, T.; Cui, W.; Zhang, Y.; Hui, C. Y.; Kurokawa, T.; Gong, J. P. How chain dynamics affects crack initiation in double-network gels. *Proceedings of the National Academy of Sciences of the United States of America* **2021**, 118 (49), 8, DOI: 10.1073/pnas.2111880118.

2. Review articles

(153) Basak, U. S.; Sattari, S.; Hossain, M.; Horikawa, K.; Komatsuzaki, T. Transfer entropy dependent on distance among agents in quantifying leader-follower relationships. *Biophysics and Physicobiology* **2021**, 18, 131-144. DOI: 10.2142/biophysico.bppb-v18.015.

(154) Cui, K. P.; Gong, J. P. Aggregated structures and their functionalities in hydrogels. *Aggregate* **2021**, 2 (2). DOI: 10.1002/agt2.33.

(155) Danielsen, S. P. O.; Beech, H. K.; Wang, S.; El-Zaatari, B. M.; Wang, X. D.; Sapir, L.; Ouchi, T.; Wang, Z.; Johnson, P. N.; Hu, Y. X.; et al. Molecular Characterization of Polymer Networks. *Chemical Reviews* **2021**, 121 (8), 5042-5092. DOI: 10.1021/acs.chemrev.0c01304.

(156) Fan, H. L.; Gong, J. P. Bioinspired Underwater Adhesives. *Advanced Materials* **2021**, 33 (44). DOI: 10.1002/adma.202102983.

(157) Hirota, A.; AlMusawi, S.; Nateri, A. S.; Ordonez-Moran, P.; Imajo, M. Biomaterials for intestinal organoid technology and personalized disease modeling. *Acta Biomaterialia* **2021**, 132, 272-287. DOI: 10.1016/j.actbio.2021.05.010.

(158) Inokuma, Y.; Inaba, Y. Polyketone-Based Molecular Ropes as Versatile Components for Functional Materials. *Bulletin of the Chemical Society of Japan* **2021**, 94 (9), 2187-2194. DOI: 10.1246/bcsj.20210223.

(159) Kitagawa, Y.; da Rosa, P. P. F.; Hasegawa, Y. Charge-transfer excited states of pi- and 4f-orbitals for development of luminescent Eu(iii) complexes. *Dalton Transactions* **2021**, 50 (42), 14978-14984. DOI: 10.1039/d1dt03019a.

(160) Kitagawa, Y.; Tsurui, M.; Hasegawa, Y. Bright red emission with high color purity from Eu(iii) complexes with pi-conjugated polycyclic aromatic ligands and their sensing applications. *RSC Advances* **2021**, 12 (2), 810-821. DOI: 10.1039/d1ra08233g.

(161) Kubota, K.; Ito, H. Development of Selective Reactions Using Ball Milling. *Journal of Synthetic Organic Chemistry Japan* **2021**, 79 (5), 492-502.

(162) Long, R.; Hui, C. Y.; Gong, J. P.; Bouchbinder, E. The Fracture of Highly Deformable Soft Materials: A Tale of Two Length Scales. In Annual Review of Condensed Matter Physics, Vol 12, **2021**, Mackenzie, A. P., Marchetti, M. C. Eds.; *Annual Review of Condensed Matter Physics*, Vol. 12; **2021**; pp 71-94.

(163) Madzhidov, T. I.; Rakhimbekova, A.; Afonina, V. A.; Gimadiev, T. R.; Mukhametgaleev, R. N.; Nugmanov, R. I.; Baskinc, II; Varnekkd, A. Machine learning modelling of chemical reaction characteristics: yesterday, today, tomorrow. *Mendeleev*

Communications **2021**, 31 (6), 769-780. DOI: 10.1016/j.mencom.2021.11.003.

(164) Maeda, S.; Harabuchi, Y. Exploring paths of chemical transformations in molecular and periodic systems: An approach utilizing force. *Wiley Interdisciplinary Reviews-Computational Molecular Science* **2021**, 11 (6). DOI: 10.1002/wcms.1538.

(165) Muratov, E. N.; Amaro, R.; Andrade, C. H.; Brown, N.; Ekins, S.; Fourches, D.; Isayev, O.; Kozakov, D.; Medina-Franco, J. L.; Merz, K. M.; et al. A critical overview of computational approaches employed for COVID-19 drug discovery. *Chemical Society Reviews* **2021**, 50 (16), 9121-9151. DOI: 10.1039/d0cs01065k.

(166) Nonoyama, T.; Gong, J. P. Tough Double Network Hydrogel and Its Biomedical Applications. In Annual Review of Chemical and Biomolecular Engineering, Vol 12, **2021**, Doherty, M. F., Segalman, R. A. Eds.; *Annual Review of Chemical and Biomolecular Engineering*, Vol. 12; **2021**; pp 393-410.

(167) Ohmiya, H.; Sawamura, M. Copper-Catalyzed Reactions of Alkylboranes. *Bulletin of the Chemical Society of Japan* **2021**, 94 (1), 197-203. DOI: 10.1246/bcsj.20200283.

(168) Reyes, R. L.; Iwai, T.; Sawamura, M. Construction of Medium-Sized Rings by Gold Catalysis. *Chemical Reviews* **2021**, 121 (14), 8926-8947. DOI: 10.1021/acs.chemrev.0c00793.

(169) Yue, Y. F.; Gong, J. P. Structure and Unique Functions of Anisotropic Hydrogels Comprising Uniaxially Aligned Lamellar Bilayers. *Bulletin of the Chemical Society of Japan* **2021**, 94 (9), 2221-2234. DOI: 10.1246/bcsj.20210209.

3. Proceedings

(170) Tabata, K.; Nakumura, A.; Komatsuzaki, T. Classification Bandits: Classification Using Expected Rewards as Imperfect Discriminators. Cham, **2021**; Springer International Publishing: pp 57-69.

4. Other English articles

(171) King, D. R.; Gong, J. P. Hierarchical toughening: A step toward matching the complexity of biological materials. *Chem* **2021**, 7 (5), 1153-1155. DOI: 10.1016/j.chempr.2021.04.013.

(172) Reyes, R. L.; Sato, M.; Iwai, T.; Suzuki, K.; Maeda, S.; Sawamura, M. Asymmetric Remote C-H Borylation of Aliphatic Amides and Esters with a Modular Iridium Catalyst. *Synthesis-Stuttgart* **2021**, 53 (01), A6-A10. DOI: 10.1055/s-0039-1691227.

(173) Tsuneda, T.; Taketsugu, T. Reply to the 'Comment on "Theoretical investigations on hydrogen peroxide decomposition in aquo"' by W. H. Koppenol, *Phys. Chem. Chem. Phys*., **2021**, 23, DOI: 10.1039/D1CP03545B. Physical Chemistry Chemical Physics **2021**, 23 (45), 26006-26008. DOI: 10.1039/d1cp04003k.

B. WPI-related papers

1. Original article

(174) Kanyiva, K. S.; Marina, T.; Nishibe, S.; Shibata, T. Metal-Free Aminoiodination of Alkynes Under Visible Light Irradiation for the Construction of a Nitrogen-Containing Eight-Membered Ring System. *Advanced Synthesis & Catalysis* **2021**, 363 (11), 2746-2751. DOI: 10.1002/adsc.202100019.

(175) Das, S.; Mitschke, B.; De, C. K.; Harden, I.; Bistoni, G.; List, B. Harnessing the ambiphilicity of silyl nitronates in a catalytic asymmetric approach to aliphatic beta(3)-amino acids. *Nature Catalysis* **2021**, 4 (12), 1043-1049. DOI: 10.1038/s41929-021-00714-x.

(176) Diaz-Oviedo, C. D.; Maji, R.; List, B. The Catalytic Asymmetric Intermolecular Prins Reaction. *Journal of the American Chemical Society* **2021**, 143 (49), 20598-20604. DOI: 10.1021/jacs.1c10245.

(177) He, G. L.; List, B.; Christmann, M. Unified Synthesis of Polycyclic Alkaloids by Complementary Carbonyl Activation**. *Angewandte Chemie-International Edition* **2021**, 60 (24), 13591-13596. DOI: 10.1002/anie.202102518.

(178) Obradors, C.; List, B. Azine Activation via Silylium Catalysis. *Journal of the American Chemical Society* **2021**, 143 (18), 6817-6822. DOI: 10.1021/jacs.1c03257.

(179) Ouyang, J.; Bae, H.; Jordi, S.; Dao, Q. M.; Dossenbach, S.; Dehn, S.; Lingnau, J. B.; De, C. K.; Kraft, P.; List, B. The Smelling Principle of Vetiver Oil, Unveiled by Chemical Synthesis. *Angewandte Chemie-International Edition* **2021**, 60 (11), 5666-5672. DOI: 10.1002/anie.202014609.

(180) Schwengers, S. A.; De, C. K.; Grossmann, O.; Grimm, J. A. A.; Sadlowski, N. R.; Gerosa, G. G.; List, B. Unified Approach to Imidodiphosphate-Type Bronsted Acids with Tunable Confinement and Acidity. *Journal of the American Chemical Society* **2021**, 143 (36), 14835-14844. DOI: 10.1021/jacs.1c07067.

(181) Zhou, H.; Zhang, P. L.; List, B. The Silicon-Hydrogen Exchange Reaction: Catalytic Kinetic Resolution of 2-Substituted Cyclic Ketones. *Synlett* **2021**, 32 (19), 1953-1956. DOI: 10.1055/a-1670-5829.

(182) Zhu, C. D.; Mandrelli, F.; Zhou, H.; Maji, R.; List, B. Catalytic Asymmetric Synthesis of Unprotected beta(2)-Amino Acids. *Journal of the American Chemical Society* **2021**, 143 (9), 3312-3317. DOI: 10.1021/jacs.1c00249.

2. Review article

(183) Kennemur, J. L.; Maji, R.; Scharf, M. J.; List, B. Catalytic Asymmetric Hydroalkoxylation of C-C Multiple Bonds Focus Review. *Chemical Reviews* **2021**, 121 (24), 14649-14681. DOI: 10.1021/acs.chemrev.1c00620.

3. Proceedings

(184) Yamamoto, K.; Kawamura, K.; Ando, K.; Mertig, N.; Takemoto, T.; Yamaoka, M.; Teramoto, H.; Sakai, A.; Takamaeda-Yamazaki, S.; Motomura, M. STATICA: A 512-Spin 0.25M-Weight Annealing Processor With an All-Spin-Updates-at-Once Architecture for Combinatorial Optimization With Complete Spin-Spin Interactions. *IEEE Journal of Solid-State Circuits* **2021**, 56 (1), 165-178. DOI: 10.1109/jssc.2020.3027702.

4. Other English article

None

Appendix 2 FY 2021 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 FY2021>					**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	42	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	57	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	65	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	53	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	66	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	45	Specially Appointed Associate Professor, Institute for Chemical Reaction Design and Discovery, Hokkaido University Researcher, Center for Advanced Intelligence Project, RIKEN	Ph.D., Machine Learning	30	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	57	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	53	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	54	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	60	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	54	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	53	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	40	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	60	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	57	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 2021

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

Not applicable.

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

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

Academic degree and specialty

Effort **%**

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

Research and education history

Achievements and highlights of past research activities

Achievements

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

a) Recipient of international awards

b) Member of a scholarly academy in a major country

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

d) Editor of an international academic journal

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

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

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

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

Appendix 3-1 FY 2021 Records of Center Activities

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

1-1. Number of researchers and other center staffs

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

a) Principal Investigators

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

(number of persons)

	At the beginning of project	At the end of FY 2021	Final goal (Date: March, 2023)
Researchers from within the host institution	11	12	12
Researchers invited from abroad	3	3	3
Researchers invited from other Japanese institutions	0	0	0
Total principal investigators	14	15	15

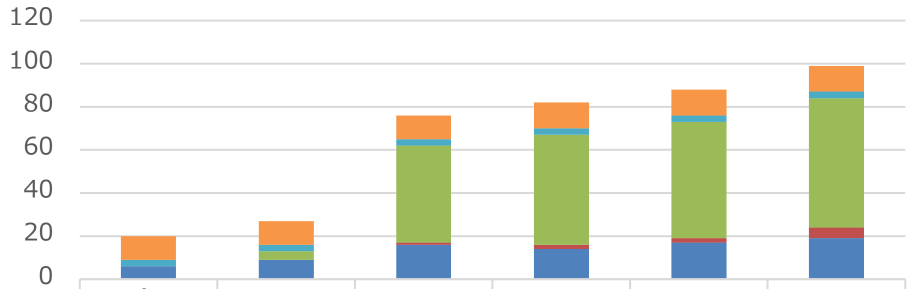
b) Total members

	At the beginning of project		At the end of FY 2021		Final goal (Date: March, 2023)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	14		69		75	
Overseas researchers	3	21	27	39	34	45
Female researchers	1	7	9	13	12	16
Principal investigators	14		15		15	
Overseas PIs	3	21	3	20	3	20
Female PIs	1	7	1	7	1	7
Other researchers	0		39		39	
Overseas researchers	0	0	12	31	13	33
Female researchers	0	0	3	8	5	13
Postdocs	0		15		21	
Overseas postdocs	0	0	12	80	18	86
Female postdocs	0	0	5	33	6	29
Research support staffs	0		2		5	
Administrative staffs	6		17		19	
Total number of people who form the "core" of the research center	20		88		99	

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

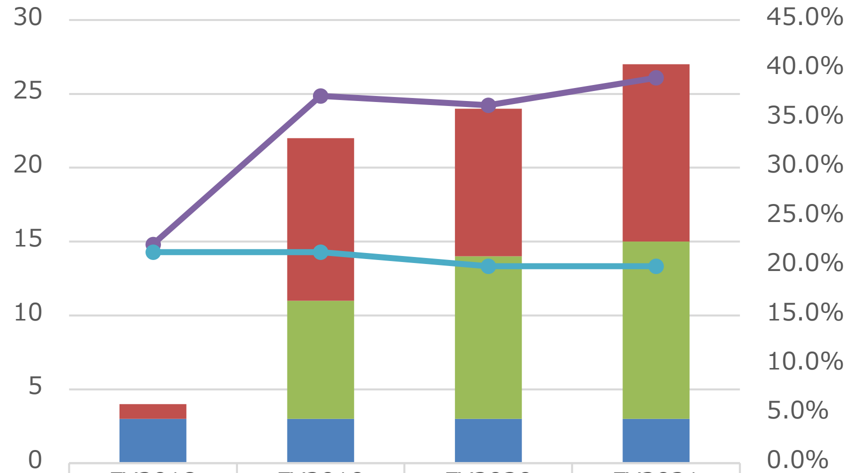
*Make a graph of the annual transition in the number of center personnel since the start of project.

Transition of Personnel



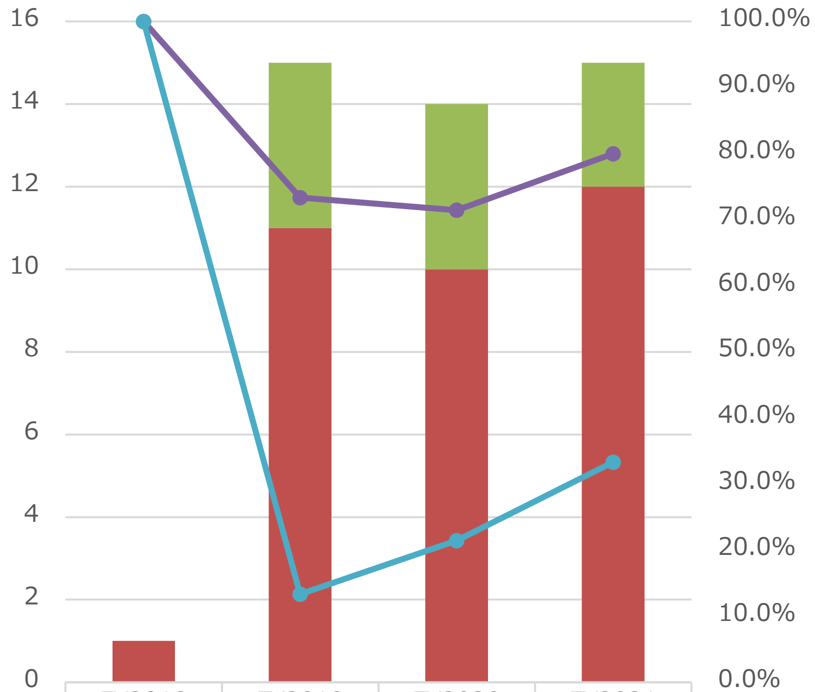
	At beginning	FY2018	FY2019	FY2020	FY2021	Final goal
PI : Researchers from within host institution	11	11	11	12	12	12
PI : Researchers invited from abroad	3	3	3	3	3	3
PI : Researchers invited from other Japanese institutions	0	0	0	0	0	0
Other researchers (incl. postdocs)	0	4	45	51	54	60
Research support staffs	0	0	1	2	2	5
Administrative staffs	6	9	16	14	17	19

Number/Ratio of Overseas Researchers



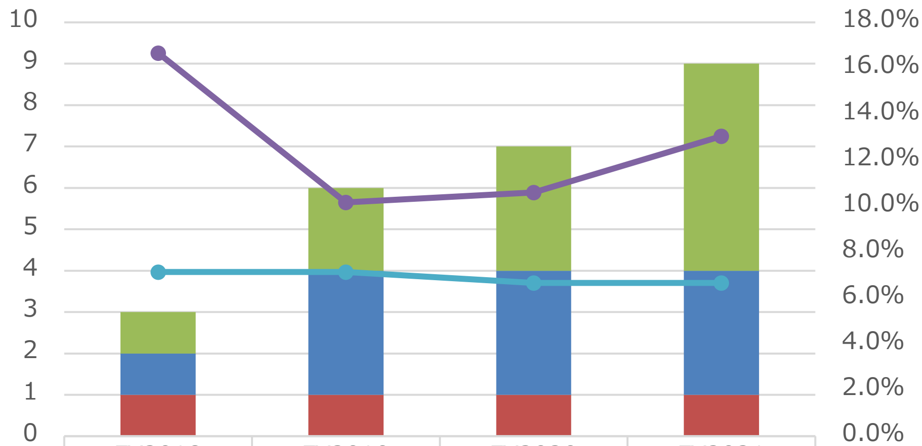
	FY2018	FY2019	FY2020	FY2021
Overseas postdocs	1	11	10	12
Overseas non-PI researchers	0	8	11	12
Overseas PIs	3	3	3	3
Ratio of oversea researchers	22.2%	37.3%	36.4%	39.1%
Ratio of oversea PIs	21.4%	21.4%	20.0%	20.0%

Number/Ratio of Overseas Postdoc



	FY2018	FY2019	FY2020	FY2021
Japanese postdocs	0	4	4	3
Overseas postdocs	1	11	10	12
Ratio of overseas postdocs	100.0%	73.3%	71.4%	80.0%
Ratio of female postdocs	100.0%	13.3%	21.4%	33.3%

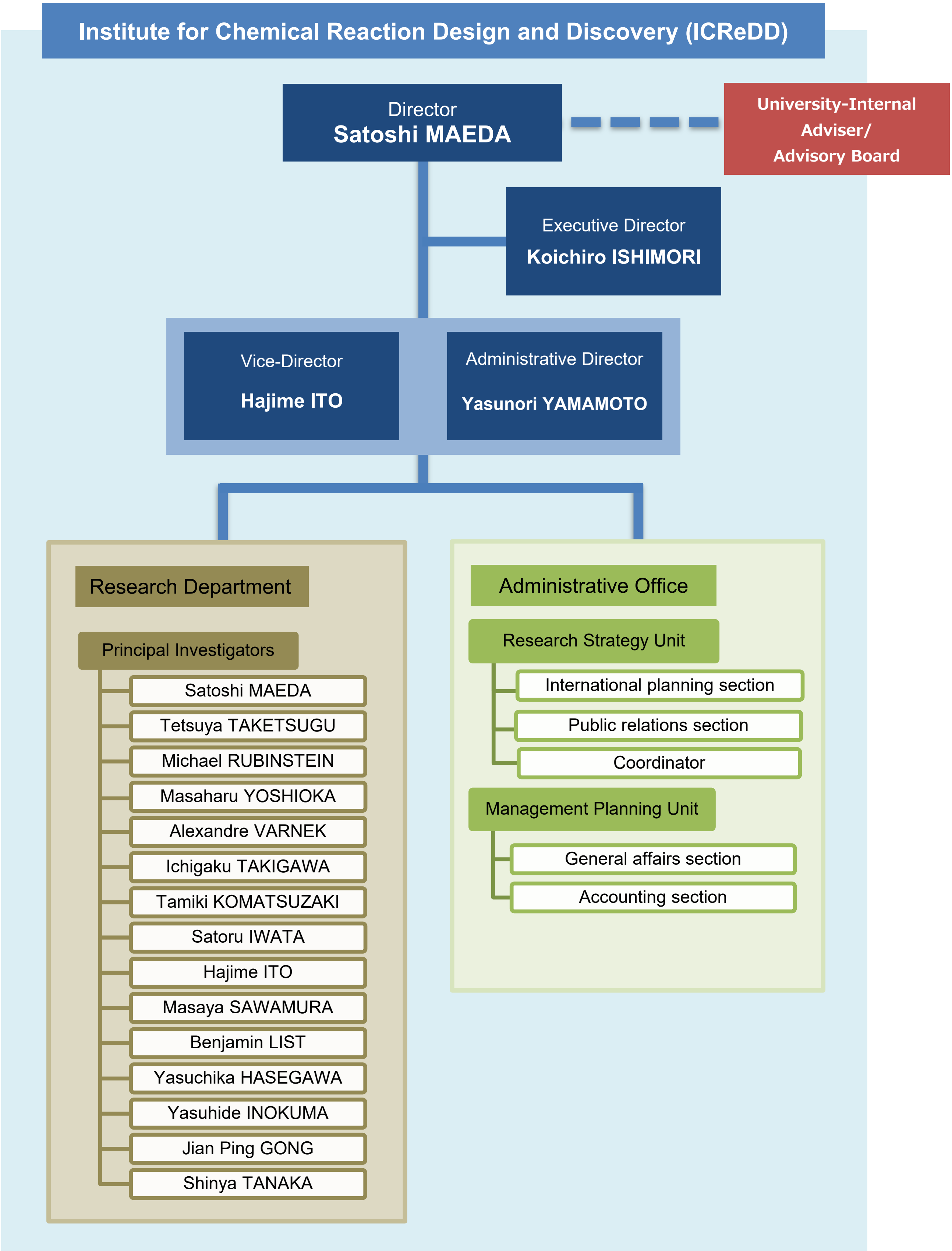
Number/Ratio of Female Researchers



	FY2018	FY2019	FY2020	FY2021
Female postdocs	1	2	3	5
Female non-PI researchers	1	3	3	3
Female PIs	1	1	1	1
Ratio of female researchers	16.7%	10.2%	10.6%	13.0%
Ratio of female PIs	7.1%	7.1%	6.7%	6.7%

Appendix 3-3 Diagram of Management System

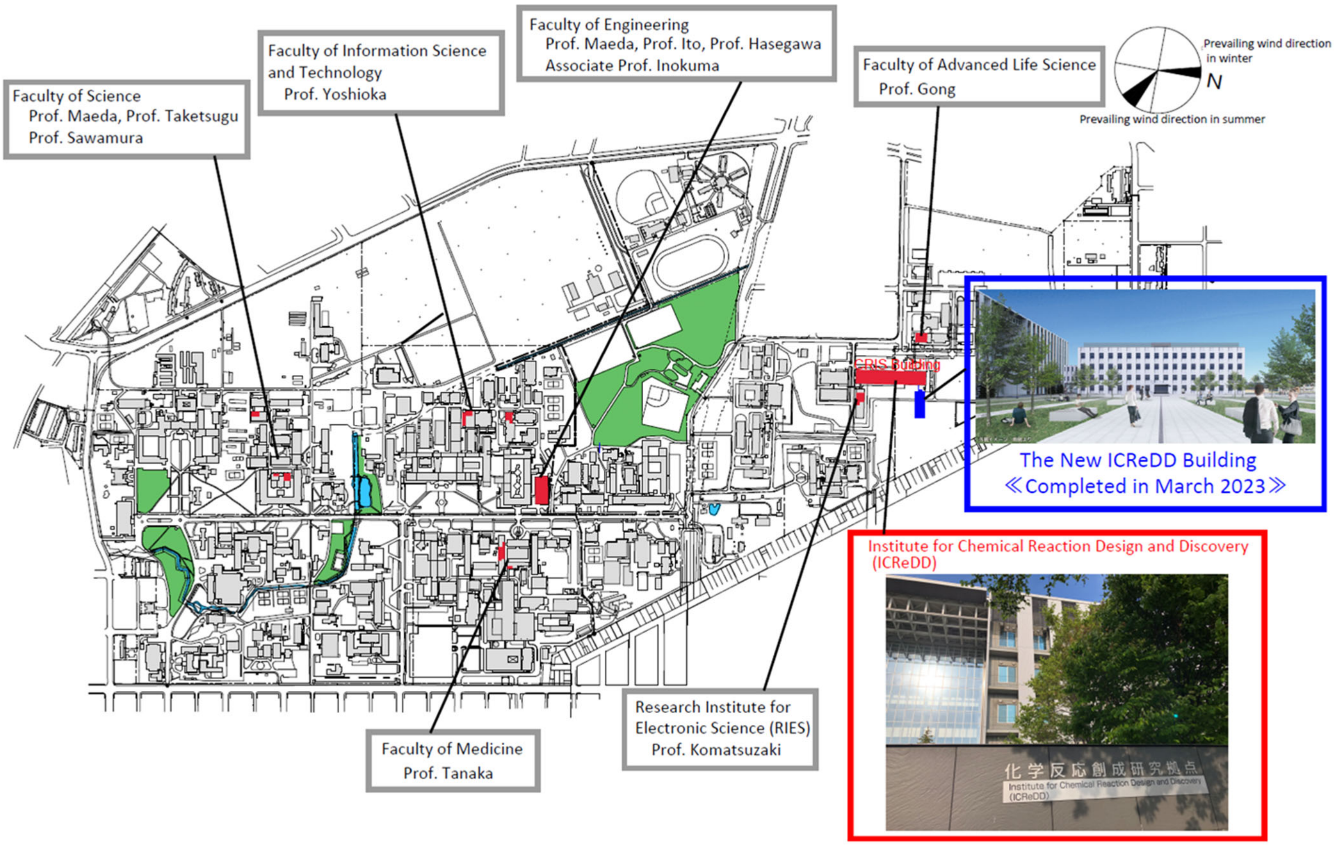
- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such as the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



Appendix 3-4　Campus Map

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

As of March 31, 2022



In March 2023, the new ICReDD building will be completed where all PIs will be gathered.

Appendix 3-5 Project Expenditures in FY2021

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, Executive Director, Administrative Director	34	11
	Principal investigators (no. of persons): 14	116	8
	Part-time faculty members (no. of persons): 14	101	0
	Specially appointed faculty members (no. of persons): 25	187	187
	Postdoctoral fellows (no. of persons): 13	52	52
	Other researchers (no. of persons): 1	5	5
	Research support staff (no. of persons): 1	1	1
	Administrative staff (no. of persons): 16	68	26
	Center allowance	19	19
	Subtotal	583	309
Project activities	Startup research project costs	15	15
	Research Strategy Unit costs	7	7
	Center operating costs	6	6
	Environmental improvement costs	12	8
	Facility rental fees	54	0
	Utility costs	25	0
	Puclic equipments usage fees	2	0
	Others	69	0
	Subtotal	190	36
Travel	Domestic travel costs	1	1
	Overseas travel costs	1	1
	Travel cost for scientists on transfer (no. of domestic scientists/oversea scientists): 0/1	1	1
	Subtotal	3	3
Equipment	Facility improvement costs	902	25
	Facility/equipment procurement costs	356	327
	Subtotal	1,258	352
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	203	0
	KAKENHI	140	0
	Commissioned research projects, etc.	235	0
	Joint research projects	18	0
	Ohers (donations, etc.)	59	0
	Subtotal	655	0
Total		2,689	700

Costs (Million yens)

WPI grant in FY 2021

	Costs
Costs of establishing and maintaining facilities	25
Repairing facilities (Number of facilities:1 , 90 m²)	25
Costs of equipment procured	327
High Resolution Time of Flight Mass Spectrometry System (Number of units:1)	35
Glove Box and Inert Gas Purification System (Number of units:2)	26
High Performance Computing and Information Processing System (Number of units:1)	65
Luminescence and Fluorescence In Vivo Imaging System (Number of units:1)	47
Laser Scanning Confocal Raman Microscope System (Number of units:1)	48
Others	106

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

2) Costs of satellites

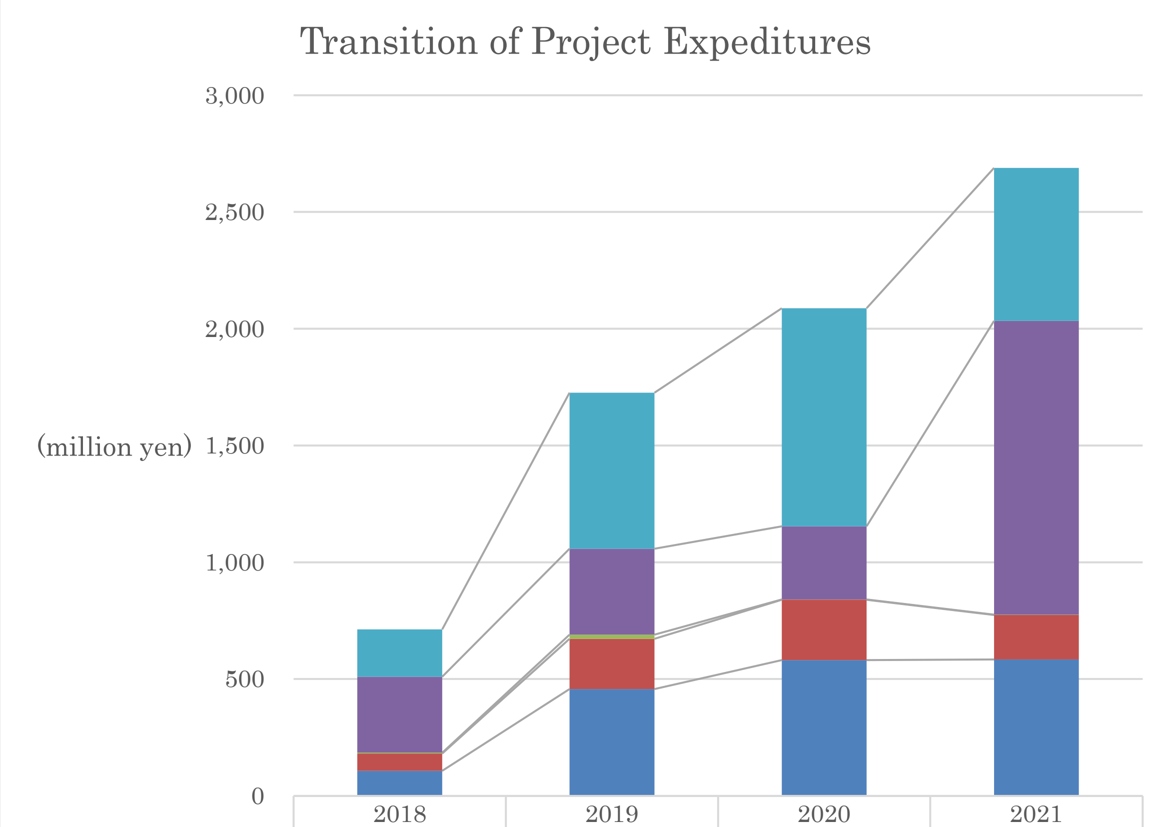
Appendix 3-5

(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 staffs (no. of persons):OO		
	Administrative staffs (no. of persons):OO		
	Subtotal	0	0
Project activities	Subtotal		
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		0	0

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

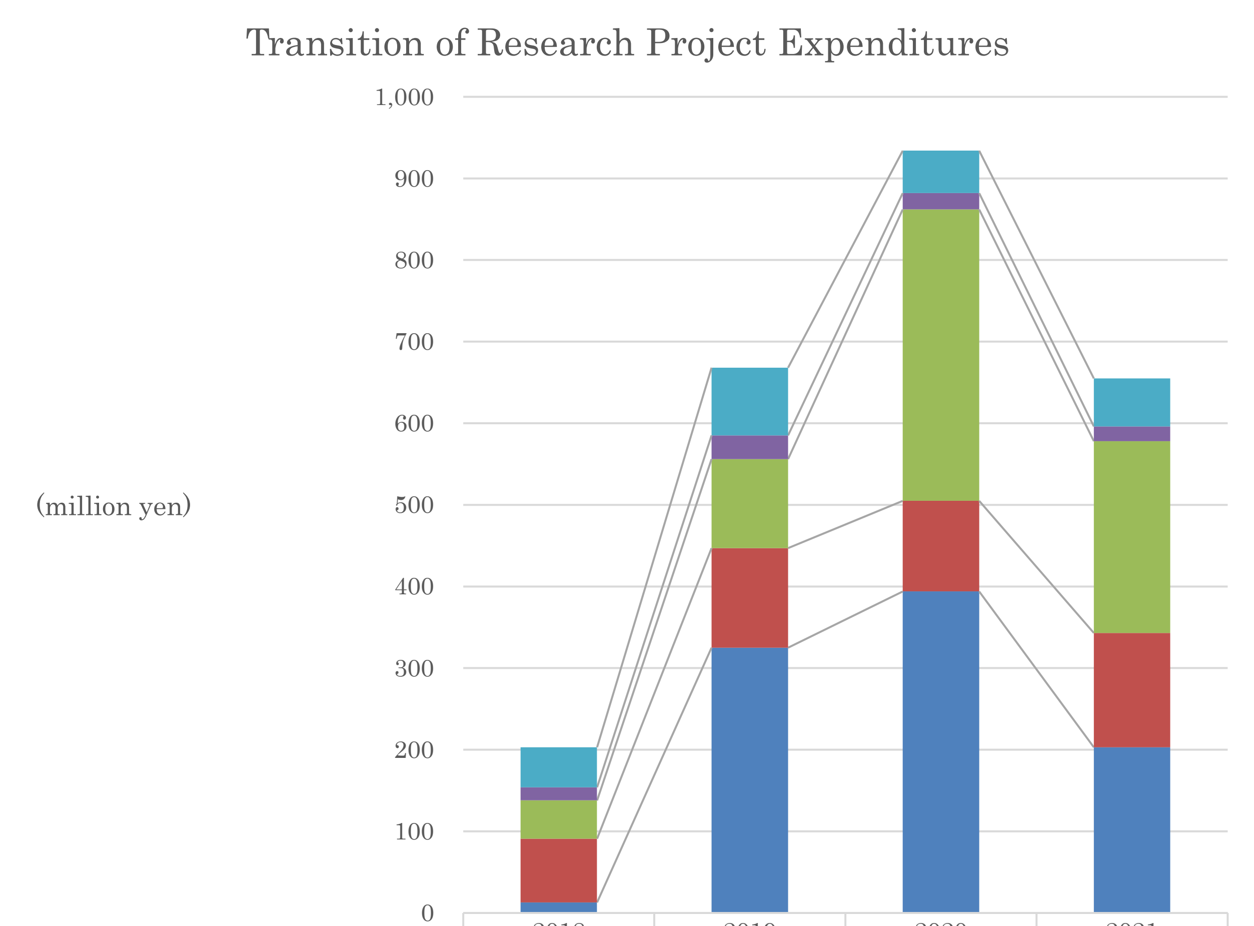
*Make a graph of the transition in the number of overall project funding.



	2018	2019	2020	2021
Research Projects	203	668	934	655
Equipment	325	368	313	1,258
Travel	4	18	1	2
Project Activities	74	215	259	190
Personnel	107	457	581	584

ICReDD uses WPI grants for the formation and development of the center, including for hiring specially appointed faculty members, postdoctoral fellows and administrative staff members, start-up costs, costs related to holding symposium and publicity, and the purchase of large common equipment.

Space charges, utilities, fees for the use of common equipment on campus, expenses related to the construction of the new building and personnel costs for the PI were contributed by the university.



	2018	2019	2020	2021
Others (donations, etc.)	49	83	52	59
Joint research projects	16	29	20	18
Comissioned research projects, etc.	47	109	357	235
KAKENHI	78	122	111	140
Project supported by other government subsidies, etc. *1	13	325	394	203

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

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

FY2018

・Name: Grant-in-Aid for Scientific Research (S), JSPS
Total Amount: 48,490,000 JPY (acquired by Jian Ping Gong)

・Name: Strategic Basic Research Programs (CREST), JST
Total Amount: 39,260,000 JPY (acquired by Satoshi Maeda)

・Impulsing Paradigm Change through Disruptive Technologies Program (ImPACT), JST
Total Amount: 30,000,000 JPY (acquired by Jian Ping Gong)

FY2019

・Name: Strategic Basic Research Programs (ERATO), JST
Total Amount: 179,889,500 JPY (acquired by Satoshi Maeda)

・Name: Grant-in-Aid for Scientific Research (S), JSPS
Total Amount: 45,370,000 JPY (acquired by Jian Ping Gong)

・Name: Strategic Basic Research Programs (CREST), JST
Total Amount: 39,260,000 JPY (acquired by Satoshi Maeda)

FY2020

- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 304,416,000 JPY (acquired by Satoshi Maeda)

- Name: Grant-in-Aid for Scientific Research (S), JSPS
  Total Amount: 34,450,000 JPY (acquired by Jian Ping Gong)

- Name: Strategic Basic Research Programs (CREST), JST
  Total Amount: 31,980,000 JPY (acquired by Hajime Ito)

FY2021

- Name: Strategic Basic Research Programs (ERATO), JST
  Total Amount: 178,034,400 JPY (acquired by Satoshi Maeda)

- Name: Grant-in-Aid for Scientific Research (S), JSPS
  Total Amount: 35,880,000 JPY (acquired by Jian Ping Gong)

Appendix 4-1 FY 2021 Status of Collaboration with Overseas Satellites

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

1. Satellites and partner institutions

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

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes

< 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		
Queen's University		

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

2. Coauthored Papers

- List the refereed papers published in FY 2021 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1-4. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1-4 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2022 and not described in Appendix 1-4.

Overseas Satellite 1 Name (Total: OO papers)
1)
2)
3)
4)

Overseas Satellite 2 Name (Total: OO papers)
1)
2)
3)
4)

3. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2021. 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
FY2021					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2021					

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
FY2021					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2021					

Not applicable.

Appendix 4-2 FY 2021 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: OO

	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								
2								
3								
4								
5								
6								
7								
8								
9								
10								

Appendix4-3 Postdoctoral Positions through Open International Solicitations

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

Fiscal year	number of applications	number of selection
FY 2018	-	-
	<-, -%>	<-, -%>
FY 2019	225	15
	<208, 92%>	<11, 73%>
FY 2020	186	6
	<180, 97%>	<5, 83%>
FY 2021	88	7
	<86, 98%>	<7, 100%>

Hokkaido University
Institute for Chemical Reaction Design and Discovery (ICReDD)

Appendix 4-4 Status of Employment of Postdoctoral Researchers

Enter the information below during the period from the start of the center through the end of FY 2021.

- For each person, fill in the spaces to the right. More spaces may be added.
- Leave "Position as of April 2022" blank if unknown.
- Enter the host institution name and the center name in the footer.

Japanese Postdocs

Employment period	Position before employed at WPI center		Next position after WPI center		Position as of April 2022*	
	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located
2019/4/1-2019/7/31	Japan Society for the Promotion of Science (JSPS) Research Fellows	Japan	Research Center of Mathematics for Social Creativity Research Institute for Electronic Science Hokkaido University・Assistant Professor	Japan	Research Center of Mathematics for Social Creativity Research Institute for Electronic Science Hokkaido University・Assistant Professor	Japan
2019/4/1-2020/3/31	Japan Society for the Promotion of Science (JSPS) Research Fellows	Japan	Japan Society for the Promotion of Science (JSPS) Research Fellows	Japan	Waseda Research Institute for Science and Engineering・Junior Researcher	Japan
2020/4/1-2021/9/30	Japan Society for the Promotion of Science (JSPS) Research Fellows	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan

2019/4/1-2022/3/31	Graduate School of Biostudies, Kyoto University ・Ph.D. student	Japan	Single-Cell Genome Information Analysis Core,Institute for the Advanced Study of Human Biology,Kyoto University・Program-Specific Researcher	Japan	Single-Cell Genome Information Analysis Core,Institute for the Advanced Study of Human Biology,Kyoto University・Program-Specific Researcher	Japan

Overseas Postdocs

Employment period	Position before employed at WPI center		Next position after WPI center		Position as of April 2022*		Nationality
	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	
2019/4/15-2019/6/28	Sapala Organics Private Limited・Guest Researcher	India	Laxai Life Sciences・Associate Scientist	India	University of Parma, Department of Chemistry, Life Sciences and Environmental Sustainability・Researcher	Italy	India
2019/3/1-2019/12/31	Institute of Transformative Bio-Molecules, Nagoya University ・Postdoctoral Fellow	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan	Italy
2017/9/1-2020/3/31	Faculty of Advanced Life Science, Hokkaido University・Postdoctoral Fellow	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Associate Professor	Japan	China

2018/10/1-2020/4/30	Faculty of Science, Hokkaido University・Postdoctoral Fellow	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Specially Appointed Assistant Professor	Japan	Philippines
2019/11/11-2020/11/24	Sorbonne University・Ph.D.	France	Nanyang Technological University・Postdoctoral Research Fellow	Singapore	Nanyang Technological University Postdoctoral Research Fellow	Singapore	China
2019/4/1-2020/12/25	Manipal University・Assistant Professor	India	PI Industries Ltd ・Senior Research Scientist	India	PI Industries Ltd Senior Research Scientist	India	India
2019/10/1-2020/12/22	Graduate School of Environmental Science, Hokkaido University・Doctoral Student	Japan	Ahsanullah University of Science and Technology ・ Faculty Member	Bangladesh	Bangladesh Council of Scientific and Industrial Research (BCSIR) Postdoctoral Researcher	Bangladesh	Bangladesh
2020/3/1-2021/1/29	Institute of Microbial Chemistry・Postdoctoral Fellow	Japan	Syngene International・Senior Research Investigator	India			India
2021/1/4-2021/2/26	Indian Institute of Technology・Doctoral Researcher	India	unattached	India			India
2020/4/1-2021/3/31	Graduate School of Chemical Sciences and Engineering, Hokkaido University・Doctoral Student	Japan	Jiangsu Hansoh Pharmaceutical Group・	China			China
2021/1/4-2021/8/20	Indian Institute of Science Education and Research・Senior Research Fellow	India	unattached	India	Institute for Chemical Reaction Design and Discovery, Hokkaido University・Postdoctoral Fellow	Japan	India

2019/11/1-2021/10/31	Kazan State University・Junior Researcher	Russia	BIOCAD ・Senior Chemoinformatics Data Scientist	Russia	BIOCAD ・ Senior Chemoinformatics Data Scientist	Russia	Russia
2021/1/18-2022/2/28	Chengdu University・Assistant Professor	China	Chengdu University・Assistant Professor	China	Chengdu University・Assistant Professor	China	China
2019/4/1-2022/3/31	National Institute of Science Education and Research Bhubaneswar・National Postdoctoral Fellow	India	unattached	India			India

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

*Prepare the information below during the period from the beginning of the Center through March 2022.

1. Name of an Agreement: Memorandum of Understanding between Institute for Chemical Reaction Design and Discovery, Hokkaido University and Faculty of Chemistry, The University of Strasbourg
   Dates of an Agreement: 19/01/2021
   Counterpart of an Agreement: Faculty of Chemistry, The University of Strasbourg
   Summary of an Agreement
   : a) Exchange of faculty members and research staff
   b) Joint research activities
   c) Support of research lectures, workshops and symposia
   d) Sharing of research materials, information and academic publications

2. Name of an Agreement:
   Dates of an Agreement:
   Counterpart of an Agreement:
   Summary of an Agreement:

3. Name of an Agreement:
   Dates of an Agreement:
   Counterpart of an Agreement:
   Summary of an Agreement:

Appendix4-6 Holding International Research Meetings

* Indicate up to two of most representative international research conferences or symposiums each financial year and give the number of participants using the table below.

FY2018-FY2019: 2 meetings

Date	Meeting title and Place held	Number of participants
March 12-13, 2019	The 1st ICReDD International Symposium FMI Hall, Hokkaido University (Sapporo)	From domestic institutions: 202 From overseas institutions: 3
November 27-29, 2019	The 2nd ICReDD International Symposium FMI Hall, Hokkaido University (Sapporo)	From domestic institutions: 379 From overseas institutions: 24

FY2020: 1 meeting

Date	Meeting title and Place held	Number of participants
February 22-24, 2021	The 3rd ICReDD International Symposium (Online)	279 (Online*) *From domestic :161 From overseas :118

FY2021: 2 meetings

Date	Meeting title and Place held	Number of participants
December 12-15, 2021	4th International Symposium on Photofunctional Chemistry of Complex Systems (ISPCCS2021), Kailua-Kona, Hawaii 96740 USA	148 (Onsite, Online) From domestic institutions: 6 (onsite)
March 12-13, 2022	The Inaugural Akira Suzuki Award Ceremony & 4th ICReDD International Symposium Akira Suzuki Hall, Hokkaido University (Sapporo + Online)	255 (Onsite, Online) From domestic institutions: 213 From overseas institutions: 42

Appendix 5 List of Achievements of Center's Outreach Activities between FY 2018 – 2021

* Using the table below, show the achievements of the Center's outreach activities from FY2018 through FY2021 (number of activities, times held).
*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 below, 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.

Activities	FY2018	FY2019	FY2020	FY2021
	(number of activities, times held)			
PR brochure, pamphlet	5	2	7	5
Lectures, seminars for the general public	1	4	10	2
Teaching, experiments, training for elementary, secondary and high school students		3	3	1
Science cafe		1		
Open house		3		
Participating, exhibiting in events	3	9	1	2
Press releases	4	9	11	13
Publications of the popular science books			3	
Others (IYPT event)	1			
Others (ICReDD Goods)	7	2	7	
Others (HP, SNS)	2			
Others (SNS)		2	3	5
Others (Videos)		12		
Others (Award Medal)				1
Others (Research News Articles on ICReDD Web)		1		15

Appendix 5 List of Media Coverage of Projects Carried out between FY 2018 – 2021

* Select main items of press releases, media coverage, and reports for FY 2018-2021 (especially by overseas media)

1) Japan

No.	Date	Type of the media (e.g., newspaper, magazine, television)	Description
1	2018/10/28	TV	PI (Maeda): Mornig News (domestic) "Interview to Director of WPI-ICReDD", NHK Sapporo
2	2019/1/11	Newspaper	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Nikkei Sangyo Shimbun
3	2019/1/11	Online news	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, National Institute for Environmental Studies web
4	2019/1/12	TV	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, NHK
5	2019/1/15	Newspaper	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Nikkan Kogyo Shimbun
6	2019/1/24	Online news	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Highlighted in Chem Station
7	2019/2/1	TV	PI (Gong): Research introduction regarding the paper, “Mechanoresponsive Self-growing Hydrogels Inspired by Muscle Training”, NHK Sapporo
8	2019/2/1	Newspaper(digital)	PI (Gong): Research introduction regarding the paper, “Mechanoresponsive Self-growing Hydrogels Inspired by Muscle Training”, Asahi Shimbun Digital
9	2019/2/4	Newspaper	PI (Gong): Article regarding the paper, “Mechanoresponsive Self-growing Hydrogels Inspired by Muscle Training”, The Nikkei
10	2019/3/28	Online news	PI (Komatsuzaki): Reports on a new type of industries-universities collaboration between Hitachi on annealing computing. （https://social-innovation.hitachi/ja-jp/case_studies/hitachi_hokudai_labo）, Hitachi Website
11	2019/3/28	Online news	Interview with Tamiki Komatsuzaki on Hitachi Website
12	2019/3/30	TV	PI (Hasegawa): Hasegawa prepared red-luminescent transparency film including Eu(III) complex for agriculture. Under collaboration between coordination chemistry, photochemistry, plant cultivation and cell-biology, effective promotion of luminescent film for plant growth was observed., HBC

13	2019/4/24	Newspaper	Article on ICReDD research press release (01/02/2019) about self-toughening hydrogel in Hokkaido Shimbun
14	2019/6/1	Pamphlet	Article on ICReDD research in Intelligent Measurement Analysis (issued by JST)
15	2019/7/1	Magazine	Interview with Satoshi Maeda in "Chemistry" (化学)
16	2019/7/19	Newspaper	Article on ICReDD-organised symposium in Hokkaido Iryou Shimbun
17	2019/10/26	Online news	Article on ICReDD research press release (01/02/2019) about self-toughening hydrogel in Diamond Weekly (Shu-kan Daiamondo)
18	2019/10/28	Newspaper	Article on ICReDD in Yomiuri Shimbun
19	2019/11/15	Newspaper	Article on ICReDD research press release (12/11/2019) about seawater glue gel in Yomiuri Shimbun
20	2019/11/19	Online news	Article on ICReDD research press release (12/11/2019) about seawater glue gel in Environmental Information Media "Environmental Observatory" (環境情報メディア「環境展望台」)
21	2019/11/25	TV	TV segment on ICReDD research on NHK Sapporo
22	2019/11/26	Online news	Article on ICReDD research in Jiji.com
23	2019/12/6	Online news	Article on ICReDD research on New Atlas
24	2019/12/8	TV	TV segment on ICReDD research on NHK Sapporo
25	2019/12/23	Newspaper	Article on ICReDD research (10.1126/science.aay8224) on redox mechanochemistry in Nikkan Kogyo Shimbun
26	2019/12/27	TV	TV segment on ICReDD research (10.1126/science.aay8224) on redox mechanochemistry on NHK
27	2019/12/27	Newspaper	Article on ICReDD research press release (01/02/2019) about self-toughening hydrogel in Yomiuri Shimbun

28	2020/1/8	Newspaper	Article on ICReDD research press release (12/11/2019) about seawater glue gel in Hokkaido Shimbun
29	2020/1/15	Newspaper	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Zaikei shimbun
30	2020/1/15	Online news	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Optronics
31	2020/1/28	Newspaper	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Nikkei Sangyo Shimbun
32	2020/2/1	Pamphlet	Article on ICReDD research in Japanese Scientists in Science 2019 (サイエンス誌に載った日本人研究者)
33	2020/2/7	Newspaper	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Nikkei Sangyo Shimbun
34	2020/2/15	TV	TV segment on ICReDD research on TV-Hokkaido
35	2020/7/29	Newspaper	Article on Prof. Tanaka's research on "Second cancers increase in older age groups", Hokkaido Shimbun (「重複がん　高齢で増加」)
36	2020/8/21	TV	Article on ICReDD research press release (2020/8/20) about functionalization for remote C–H bonds on NHK news Ohayo Hokkaido
37	2020/8/21	Newspaper	Article on ICReDD research press release (2020/8/20) about functionalization for remote C–H bonds in Japan Chemical Daily
38	2020/8/27	online news	Article on ICReDD research press release (2020/8/26) about luminescent lanthanide molecular in OPTRONICS online
39	2020/8/27	online news	Article on ICReDD research press release (2020/8/26) about luminescent lanthanide molecular in CHEMNET TOKYO online
40	2021/1/20	Newspaper	Article on ICReDD research press release (2020/6/23) about the mechanism of photochemical smog-causing PM2.5 in Nikkan Kogyo Shimbun
41	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in Nihon Keizai shimbun
42	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in Hokkaido shimbun

43	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in Yahoo news
44	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in Nikkan Kogyo Shimbun
45	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in jiji.com
46	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in 47news
47	2021/3/30	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in Hokkoku Shimbun
48	2021/3/31	online news	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in NHK news web
49	2021/3/31	newspaper	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel in Nihon Keizai shimbun
50	2021/4/6	Newspaper	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel, Yomiuri Shimbun
51	2021/4/9	Newspaper	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel, Hokkaido Iryo Shimbun
52	2021/4/14	Online news	Article on Prof. Gong's research on Doublle-Network Gel, ”A facile mechanochemical technique to visualize polymer chain breakage in hydrogel", Advanced In Engineering
53	2021/4/20	Newspaper	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel, Hokkaido Shimbun
54	2021/4/21	Newspaper	Article on ICReDD research press release (2021/3/30) about reversion of cancer cell to the cancer stem cell by hydrogel, Nikkan Kogyo Shimbun
55	2021/5/26	Newspaper	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, Nikkei Shimbun
56	2021/5/27	Newspaper	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, Iryo Shimbun Degital
57	2021/5/26	Online news	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, BIGLOBE News

58	2021/5/28	Online news	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, POTALFIELD News
59	2021/5/26	Online news	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, business network.jp
60	2021/5/27	Online news	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, Daigaku Journal Online
61	2021/7/9	Newspaper	Article on ICReDd research press release (2021/5/26) about industry-university joint research on Pathology Diagnosis by AI, Hokkaido Iryo Shimbun
62	2021/10/2	TV	ICReDD's PI, Prof. Tanaka appeared on the program *Good Morning Hokkaido* which covered his research on cancer stem cells and hydrogels, NHK
63	2021/10/7	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Hokkaido Shimbun
64	2021/10/7	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemstry, Hokkaido Shimbun
65	2021/10/7	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Hokkaido Shimbun (evening edition)
66	2021/10/7	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Yomiuri Shimbun
67	2021/10/8	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Asahi shimbun
68	2021/10/8	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Nikkei shimbun
69	2021/10/8	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Hokkaido Shimbun
70	2021/10/8	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Mainichi Shimbun
71	2021/10/8	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry, Yomiuri Shimbun
72	2021/10/10	TV	ICReDD's PI, Prof. Hasegawa appeared on the program "SDG Solutions~Building the Future with Research", Hokkaidod Broadcasting Corporation (HBC)

73	2021/10/12	Newspaper	Article on the 2021 Nobel Prize in Physics, Phisiology or Medicine, and Chemistry, Asahi shimbun
74	2021/10/16	Newspaper	Article on the announcement of Prof. List's 2021 Nobel Prize in Chemistry and international collaborative researches conducted in Japan, Yomiuri Shimbun
75	2021/11/17	Online news	News article on the establishment of the Akira Suzuki Awards and the inaugural award recipients, Chem Station
76	2021/11/18	Online news	Article on ICReDD research press release (2021/11/17) about synthesizing Grignard reagents by mixing reactants in a ball mill with minimal organic solvent usage, Nikkei Press Release
77	2021/11/28	Newspaper	Article on the "Nobel Forum"organized by the Yomiuri Shimbun where ICReDD director Prof. Maeda participated as a panellist., Yomiuri Shimbun
78	2021/11/28	Newspaper	Article on the "Nobel Forum", Yomiuri Shimbun
79	2021/12/1	Magazine	Feature Article on the 2021 Nobel Prize in Chemistry, Monthly science magazine "Kagaku"
80	2021/12/9	Newspaper	Article on the award ceremony of Prof. List's 2021 Nobel Prize in Chemistry, Hokkaido Shimbun
81	2021/12/9	Newspaper	Article on the award ceremony of Prof. List's 2021 Nobel Prize in Chemistry, Hokkaido Shimbun
82	2021/12/9	Newspaper	Article on the establishment of Akira Suzuki Awards and the inaugural award recipients, Yomiuri Shimbun
83	2021/12/15	Newspaper	Article on Major News in Medicine and Health in 2021. Prof. Tanaka's research on cancer stem cells was picked up as one of major news items, Hokkaido Shimbun
84	2021/12/17	Newspaper	Article on the establishment of Akira Suzuki Awards and the inaugural award recipients, Nikkei shimbun
85	2021/12/17	Newspaper	Article on the establishment of Akira Suzuki Awards and the inaugural award recipients, Hokkaido University
86	2021/12/17	Newspaper	Article on the establishment of Akira Suzuki Awards and the inaugural award recipients, Tomakomai Mimpo
87	2021/12/17	newspaper	Article on Prof. Tanaka's research on the Delta variant, Hokkaido Iryo Shimbun

88	2021/12/19	TV	ICReDD's Co-PI, Assist. Prof. Tsuji appeared on the feature program on the 2021 Nobel Prize in Chemistry, NHK
89	2021/12/23	Newspaper	Article on the Inaugural Akira Suzuki Awards ceremony, Yomiuri Shimbun
90	2021/12/25	Newspaper	Featured Article part 1 on the "Nobel Forum", Yomiuri Shimbun
91	2021/12/25	Newspaper	Featured Article part 2 on the "Nobel Forum", Yomiuri Shimbun
92	2021/12/29	Newspaper	Article on Hokkaido's NewsTop 10 (HU's Prof. List's 2021 Nobel Prize in Chemistry), Nikkei shimbun
93	2021/12/30	Newspaper	Article on Prof. Tanaka's research on the Omicron variant, Asahi Shimbun
94	2022/1/5	Newspaper	Article on Prof. Tanaka's research on the Omicron variant, Yomiuri Shimbun
95	2022/2/6	Newspaper	Interview Article to Prof. Tanaka, also mentioned about the collaborative research on cancer stem cells with Prof. Gong, Hokkaido Shimbun
96	2022/2/22	Online news	Article on ICReDD research press release (2022/2/22) about CO2 recycling and efficient drug development—tackling two problems with one reaction, Nikkei Press Release
97	2022/2/25	Newspaper	Article on the ICReDD director Prof. Maeda awarded the Inaugural Nagakura Saburo Award, Kagaku Shimbun
98	2022/3/8	Newspaper	Article on the governance of Hokkaido University introducing the interdiciplinary research project of ICReDD and Prof. List's 2021 Nobel Prize in Chemistry, Nikkei shimbun
99	2022/3/14	Online news	Article on ICReDD research press release (2022/3/14) about Virtual Ligand-Assisted Screening Strategy to Discover Enabling Ligands for Transition Metal Catalysis, Nikkei Press Release

2) Overseas

No.	Date	Type of the media (e.g., newspaper, magazine, television)	Description
1	2019/1/10	Magazine	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Nature Research BEHIND THE PAPER

2	2019/1/15	Magazine	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Selected as Nature Communications Editor's Highlights
3	2019/1/31	Magazine	PI (Gong) : Self-growing material could make muscles that become stronger with use" https://www.newscientist.com/article/2192376-self-growing-material-could-make-muscles-that-become-stronger-with-use/ New Scientist
4	2019/1/31	Magazine	PI (Gong) : "Stretchy hydrogel heals like muscle Material made from intertwined polymers gets stronger when stressed" https://cen.acs.org/materials/Stretchy-hydrogel-heals-like-muscle/97/i5 Chemical＆Engineering News
5	2019/2/1	Online news	PI (Taketsugu): "Current generation via quantum proton transfer" https://www.scienceworldreport.com/articles/60521/20190201/current-generation-via-quantum-proton-transfer.htm Science World Report
6	2019/2/1	Online news	PI (Gong) : "Fitnesstraining für Künstliche Fasern" https://www.wissenschaft-aktuell.de/artikel/Fitnesstraining_fuer_kuenstliche_Fasern1771015590666.html Wissenschaft aktuell (Germany)
7	2019/2/1	Online news	PI (Gong) : "Self-growing polymers repair themselves when fractured" https://www.chemistryworld.com/news/self-growing-polymers-repair-themselves-when-fractured/3010066.article Chemistry World
8	2019/2/3	Online news	PI (Gong) : "Hydrogel material flexes its muscles" https://physicsworld.com/a/hydrogel-material-flexes-its-muscles/ Physics World
9	2019/2/5	Online news	PI (Gong): "Hydrogel wächst mit seinen Aufgaben" https://chemreporter.de/2019/02/05/hydrogel-waechst-mit-seinen-aufgaben/ Der Chemische Reporter (Germany)
10	2019/2/8	Online news	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Highlighted in Technology News

11	2019/2/11	Online news	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Highlighted in Converter News
12	2019/2/11	Online news	PI (Ito): Cross-Coupling in Solid Using Mechanochemistry, Highlighted in Technology Networks
13	2019/5/27	Magazine	Article on ICReDD in QS Wow News print edition
14	2019/7/30	Online news	Article on ICReDD research press release (24/05/2019) about flexible alkaloidal scaffold synthesis in Phys.org (reach: 5,102,926)
15	2019/7/31	Online news	Article on ICReDD research press release (24/05/2019) about flexible alkaloidal scaffold synthesis in ScienceDaily (reach: 7,093,051)
16	2019/7/31	Online news	Article on ICReDD research press release (24/05/2019) about flexible alkaloidal scaffold synthesis in The Medical News (reach: 1,652,128)
17	2019/8/6	Online news	Article on ICReDD research press release (24/05/2019) about flexible alkaloidal scaffold synthesis in Technology Networks (reach: 315,028)
18	2019/10/7	Online news	Article on ICReDD research press release (19/07/2019) about all-benzene catenane and trefoil knot in Nanowerk (reach: 75,074)
19	2019/10/7	Online news	Article on ICReDD research press release (19/07/2019) about all-benzene catenane and trefoil knot in Phys.org (reach: 5,523,020)
20	2019/10/7	Online news	Article on ICReDD research press release (19/07/2019) about all-benzene catenane and trefoil knot in ScienceDaily (reach: 6,914,300)
21	2019/11/12	Online news	Article on ICReDD research press release (12/11/2019) about seawater glue gel in Daily Mail (reach: 59,623,497)
22	2019/11/12	Online news	Article on ICReDD research press release (12/11/2019) about seawater glue gel in SciTech Daily (reach: 1,419,752)
23	2019/11/13	Online news	Article on ICReDD research press release (12/11/2019) about seawater glue gel in Phys.org (reach: 4,985,649)
24	2019/11/13	Online news	Article on ICReDD research press release (12/11/2019) about seawater glue gel in ScienceDaily (reach: 7,255,533)
25	2019/12/3	Scientific journal	Article on ICReDD research (10.1002/adma.201905878) on rigidity-switching hydrogel in Nature Reviews Materials

26	2019/12/19	Magazine	Article on ICReDD research press release (12/11/2019) about seawater glue gel in Asia Research News print edition
27	2019/12/20	Online news	Article on ICReDD research press release (20/12/2019) about redox mechanochemistry in Phys.org (reach: 6,014,128)
28	2019/12/20	Online news	Article on ICReDD research press release (20/12/2019) about redox mechanochemistry in ScienceDaily (reach: 6,825,295)
29	2019/12/21	Online news	Article on ICReDD research press release (20/12/2019) about redox mechanochemistry in Chemical & Engineering News (reach: 282,868)
30	2020/1/21	Online news	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Nanowerk (reach: 165,628)
31	2020/1/21	Online news	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Technology (reach: 98,439)
32	2020/1/22	Online news	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in eeNews Europe (reach: 65,958)
33	2020/1/22	Online news	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Phys.org (reach: 6,014,128)
34	2020/1/24	Online news	Article on ICReDD research press release (14/01/2020) about high-efficiency photosensitizer in Photonics.com (reach: 91.919)
35	2020/1/28	Online news	Article on ICReDD research in Innovation News Network
36	2020/2/26	Online news	Article on ICReDD research press release (05/02/2020) about MOF carbohydrate gas separation in Nanowerk (reach: 103,525)
37	2020/2/26	Online news	Article on ICReDD research press release (05/02/2020) about MOF carbohydrate gas separation in Phys.org (reach: 5,078,145)
38	2020/2/27	Online news	Article on ICReDD research press release (05/02/2020) about MOF carbohydrate gas separation in ScienceDaily (reach: 6,547,254)
39	2020/6/5	TV	ARD alpha Campus Talks: “Catalysis for the World” (“Katalyse für die Welt”)
40	2020/6/23	Online news	Article on ICReDD research press release (2020/6/23) about photochemical reaction process using near-IR in ChemViews Magazine

41	2020/8/20	Online news	Article on ICReDD research press release (2020/8/20) about functionalization for remote C–H bonds in EurekAlert
42	2020/8/24	Magazine	Article on ICReDD research press release (2020/8/20) about functionalization for remote C–H bonds in C&E News
43	2020/12/16	Journal	Article on ICReDD research press release (2020/8/20) about functionalization for remote C–H bonds in synform
44	2021/5/19	Online news	Article on ICReDD research press release (EN) (2021/5/18) Toward overcoming solubility issues in organic chemistry, Science Daily (Reach: 6,198,579) https://www.sciencedaily.com/releases/2021/05/210518114217.htm
45	2021/5/18	Online news	Article on ICReDD research press release (EN) (2021/5/18) Toward overcoming solubility issues in organic chemistry, Phys.org (Reach: 4,752,602) https://phys.org/news/2021-05-solubility-issues-chemistry.html
46	2021/5/18	Online news	Article on ICReDD research press release (EN) (2021/5/18) Toward overcoming solubility issues in organic chemistry, EurekAlert! (Reach:1,420,178) http://www.eurekalert.org/pub_releases/2021-05/hu-tos051821.php
47-58	Various	Online news	12 other articles on ICReDD research press release (EN) (2021/5/18) Toward overcoming solubility issues in organic chemistry, various online sources (Reach: 1,838,925 http://www.eurekalert.org/pub_releases/2021-05/hu-tos051821.php
59	2021/6/10	Online news	Article on ICReDD research press release (EN) (2021/6/11) New method makes generic polymers luminescent, EurekAlert! (Reach: 1,443,020) http://www.eurekalert.org/pub_releases/2021-06/hu-nmm061021.php
60	2021/6/11	Online news	Article on ICReDD research press release (EN) (2021/6/11) New method makes generic polymers luminescent, Phys.org (Reach: 4,711,309) https://phys.org/news/2021-06-method-polymers-luminescent.html
61	2021/6/15	Online news	Article on ICReDD research press release (EN) (2021/6/11) New method makes generic polymers luminescent, Science Daily (Reach:5,811,454) https://www.sciencedaily.com/releases/2021/06/210614093831.htm
62-74	Various	Online news	13 other articles on ICReDD research press release (EN) (2021/6/11) New method makes generic polymers luminescent in in various online sources (Reach:1,665,857)

75	2021/9/16	Online news	Article on ICReDD research press release (EN) (2021/9/16) Pyrrole chemistry: Good things come in threes, Phys.org (Reach: 4,916,743) https://phys.org/news/2021-09-pyrrole-chemistry-good-threes.html
76	2021/9/17	Online news	Article on ICReDD research press release (EN) (2021/9/16) Pyrrole chemistry: Good things come in threes, ScienceDaily (Reach:3,955, 977) https://www.sciencedaily.com/releases/2021/09/210916114630.htm
77	2021/9/17	Online news	Article on ICReDD research press release (EN) (2021/9/16) Pyrrole chemistry: Good things come in threes, AZoM.com (Reach: 416,586) https://www.azom.com/news.aspx?newsID=56812
78-81	Various	Online news	4 other articles on ICReDD research press release (EN) (2021/9/16) Pyrrole chemistry: Good things come in threes, various online sources (Reach: 300,987)
82	2021/11/18	Online news	Article on ICReDD research press release (EN) (2021/11/18) 120-year-old reaction turned on its head with environment-friendly, paste-based method, SciTechDaily (Reach: 2,365,303) https://scitechdaily.com/revolutionary-chemistry-120-year-old-reaction-turned-on-its-head/
83	2021/11/18	Online news	Article on ICReDD research press release (EN) (2021/11/18) 120-year-old reaction turned on its head with environment-friendly, paste-based method, ScienceDaily (Reach: 5,350,825) https://www.sciencedaily.com/releases/2021/11/211118061319.htm
84	2021/11/19	Online news	Article on ICReDD research press release (EN) (2021/11/18) 120-year-old reaction turned on its head with environment-friendly, paste-based method, Phys.org (Reach: 4,300,839) https://phys.org/news/2021-11-year-old-reaction-environment-friendly-paste-based-method.html
85-97	Various	Online news	13 other articles on ICReDD research press release (EN) (2021/11/18) 120-year-old reaction turned on its head with environment-friendly, paste-based method, various (Reach: 2,023,854)
98	2022/1/18	Online news	Article on ICReDD research press release (EN) (2022/1/14) Blue LEDs light the way toward sustainable development, Phys.org (Reach:3,903,192) https://phys.org/news/2022-01-blue-sustainable.html

99	2022/1/24	Online news	Article on ICReDD research press release (EN) (2022/1/14) Blue LEDs light the way toward sustainable development, Markets Insider Business Insider (Reach:5,222,575) https://markets.businessinsider.com/news/commodities/leds-combined-with-copper-may-be-key-to-developing-new-medicines--electronics-10952428
100	2022/1/24	Online news	Article on ICReDD research press release (EN) (2022/1/14) Blue LEDs light the way toward sustainable development, MINING.com (Reach: 831181) https://www.mining.com/leds-combined-with-copper-may-be-key-to-developing-new-medicines-electronics/
101-112	Various	Online news	12 other articles on ICReDD research press release (EN) (2022/1/14) Blue LEDs light the way toward sustainable development, various (Reach:1,494,949)
113	2022/2/2	Online news	Article about Akira Suzuki Awards and 4th ICReDD Symposium, Computational Chemistry Daily https://paper.li/compchemdaily?edition_id=c3240b00-841d-11ec-8671-fa163e65ae25
114	2022/2/22	Online news	Article on ICReDD research press release (EN) (2022/2/22) CO2 recycling and efficient drug development—tackling two problems with one reaction, Science Daily (Reach: 4,707,188) https://www.sciencedaily.com/releases/2022/02/220222135423.htm
115	2022/2/23	Online news	Article on ICReDD research press release (EN) (2022/2/22) CO2 recycling and efficient drug development—tackling two problems with one reaction, Phys.org (Reach: 4,137,772) https://phys.org/news/2022-02-co2-recycling-efficient-drug-tackling.html
116	Various	Online news	Article on ICReDD research press release (EN) (2022/2/22) CO2 recycling and efficient drug development—tackling two problems with one reaction, Technology Networks. (Reach: 707,078)
117-127	Various	Online news	11 other articles on ICReDD research press release (EN) (2022/2/22) CO2 recycling and efficient drug development—tackling two problems with one reaction, Various (Reach: 530,113) https://www.eurekalert.org/news-releases/944197

128	2022/3/14	Online news	Article on ICReDD research press release (EN) (2022/3/14) Chemical reaction design goes virtual, EurekAlert! (Reach: 874,477) https://www.eurekalert.org/news-releases/946137
129	2022/3/15	Online news	Article on ICReDD research press release (EN) (2022/3/14) Chemical reaction design goes virtual, Phys.org (Reach: 3,840,122) https://phys.org/news/2022-03-chemical-reaction-virtual.html
130	2022/3/15	Online news	Article on ICReDD research press release (EN) (2022/3/14) Chemical reaction design goes virtual, scienceDaily (Reach: 4,484,264) https://www.sciencedaily.com/releases/2022/03/220314095724.htm
131	Various	Online news	11 other articles on ICReDD research press release (EN) (2022/3/14) Chemical reaction design goes virtual, various (Reach: 1,141,374)

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

1. Contributions from host institution

(1) Fund, Personnel

* Regarding "Fund" entry, describe with reference to the items in the Progress Report (Jisseki-hokoku-sho) based on Article 12 of the Grant Guidelines (Kofu-yoko).

* Don't include competitive funding obtained by researchers (used as research project funding)

(FY 2018-2021)

<Fund> **(million yen)**

Fiscal Year	2018	2019	2020	2021
Personnel	98	225	260	275
Faculty members	66	164	209	217
Full-time	66	164	209	217
Concurrent	0	0	0	0
Postdocs	0	0	0	0
RA etc.	0	0	0	0
Research support staffs	0	0	0	0
Administrative staffs	32	61	51	58
Full-time	32	61	51	58
Concurrent	0	0	0	0
Project activities	45	111	183	154
Travel	0	0	0	0
Equipment	17	23	11	906
Research projects	13	230	260	95
Total	173	589	714	1,430

<Personnel> **(person)**

Fiscal Year	2018	2019	2020	2021
Personnel	21	30	27	36
Faculty members	13	21	21	27
Full-time	13	21	21	27
Concurrent	0	0	0	0
Postdocs	0	0	0	0
RA etc.	0	0	0	0
Research support staffs	0	0	0	0
Administrative staffs	8	9	6	9
Full-time	8	9	6	9
Concurrent	0	0	0	0

Appendix6-1 Host Institution's Commitment

1. Contributions from host institution

(2) Provision of land and/or building(s), lab space, etc.

Laboratory space

Hokkaido University (HU) provided ICReDD space 2,600 ㎡ in the Creative Research Institution Building and space charges including utility costs, etc. HU completed the design of the "International Research Center for Chemical Reactions Design and Discovery" (new building, 4 floors above ground, 5,500 ㎡), which was requested to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) a portion of the building cost for the improvement of facilities for national universities, and construction work began in October 2021 (to be completed by the end of FY2022). President's discretionary expense will cover half of the construction cost. The new building is designed with consideration for the Sustainable Development Goals (SDGs), and will achieve energy savings of approximately 50% compared to the standard (= ZEB Ready).

Personnel and salaries

1) The HU has been covering the salaries of 13 PIs, 3 Jr. PIs, 13 research collaborators, and the Executive director of ICReDD.
2) 6 administrative staff through assignment from the University's human resources.
3) The HU secured 4 full-time tenure-track associate professors and 1 full-time assistant professor to ICReDD as of April 2022. Female assistant professor and female tenure-track associate professor positions are also included in these positions. Through these positions, a career path system for female researchers from student, post-doctoral fellow, assistant professor, associate professor (JrPI) to professor (PI) will be established and a role model will be presented.

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

The final decision-making authority for all matters related to the operation and management of ICReDD rests with the Center Director. The President and the ICReDD Director hold regular monthly meetings to discuss operations, including future plans to establish ICReDD as a sustainable research center. The reorganization was considered with a view to making it permanent, and the structure will be reorganized with the Executive Director as the Administrative Director to strengthen cooperation with the University Headquarters. ICReDD will be positioned as a special research district under the direct control of the President and will maintain continuous research center activities; after about 10 years of research activities, it will be re-established as a permanent and dynamic research center based on a new research strategy positioned, for example, in the mid-term objectives and mid-term plan.

Decision-making system

The HU established the Institute rule, "Hokkaido University Institute for Chemical Reaction Design and Discovery Rules". All matters concerning the operation and management of the Center fall under the purview of the Director. The HU also established "Hokkaido University Institute for Chemical Reaction Design and Discovery Steering Committee Rules" to organize the system, which enables the Director to exercise strong leadership in the Center concerning important matters such as personnel and execution of the budget.

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

Costs to corresponding departments and assignment of students

1) The HU and the Dean have made arrangements to reduce the PI's teaching and administrative duties in his/her department.
2) To reduce the educational and administrative burden on the departments of each PI, the HU provided labor costs (50 million yen per year) for the corresponding departments as a form of compensation.
3) All the HU PIs are holding strong ties with their original departments, and undergraduate and graduate students are assigned in the same way before establishing ICReDD.

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

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

As denoted by 2, the HU authorized that the Director has the authority to make decisions over the appointment of personnel, the Center's budget, and research priorities in addition to other matters. The Steering Committee authorizes the Director to make final decisions, thus it is the place for discussion and acts as an advisor to the Director. The HU assigned administrative staff who are eligible in English and are composed of personnel with excellent ability, experience in a variety of areas. All the administrative information is provided in both English and Japanese.

The HU revised the University's salary regulations to allow for higher salaries in order to hire the talented researchers. The HU has established regulations to provide center allowances to the center director, deputy director, PIs, administrative director, and executive director. FY2022, a new regulation will be established to provide incentives based on the research performance and evaluation of center faculty members; the determination of eligibility and the amount of the incentive are left to the discretion of the Director.

To acquire top-level researchers who can advance the Chemical reaction design and discovery fields, we have implemented a cross-appointment system and have utilized this to employ a professor at RIKEN and the University of Tokyo as principal investigator. In addition, an agreement was signed with the Graduate School of Information Science and Technology, the University of Tokyo, to which the principal investigator belonged, to promote research related to ICReDD.

5. Utilities and other infrastructure support provided by host institution

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

As denoted by 1, the HU provided ICReDD space 2,600 ㎡ in the Creative Research Institution Building and space charges including utility cost, etc. The HU will provide land on the north side of the campus, where industry-academia collaboration research facilities are concentrated, to build a new research building (5,500 ㎡) there by the end of FY2022. Thus, the HU is providing ICReDD with sufficient space including the original laboratory spaces of the HU PIs. When ICReDD's researchers used shared university equipment, the HU pays a fee for its use and provides a suitable research environment so that researchers can start their research immediately after their arrival.

6. Support for other types of assistance

ICReDD will be maintained as a permanent organization in conjunction with the HU administration. Positioned as a special research institute under the direct control of the President, ICReDD will maintain continuous research activities, and after about 10 years of research activities, it will be made permanent as a research center that constantly promotes cutting-edge, world-class research without fixing the assignment of researchers, based on a new research strategy positioned in the mid-term objectives and mid-term plan, etc.

The HU provided discretionary funds (at least 10 million yen per year) that can be used freely by the center director and supported by providing access to resources of relevant organizations such as the Institue for International Collaboration and the Insititute for Promotion of Collaborating with Regional Businesses.

The HU established an integrated technical staff organization, Office for Technical Support, to which technical staff members from various departments in the HU were dually appointed, and the consolidation of the centralized administrative system within its operating structure to strengthen the support system for cross-divisional education and research activities. In response to a request from ICReDD, the Office for Technical Support dispatched technical staff to assist in the maintenance and management of ICReDD's equipment (nuclear magnetic resonance equipment).

The HU secured four tenure-track associate professors and one assistant professor to ICReDD as of April 2022. In the future, one regular associate professors and one post-doctoral researcher will be assigned to the ten PIs of the Center's Top Researchers. 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, we will make a gradual increasing from FY2023 after the Interim evaluation toward the 16 faculty members in FY2027. The HU will give ICReDD the authority to make a budget request, and will make an estimated request for "human resource development department" with a view to establishing a graduate school in the future, and "List's cooperation research platform" for further development of research and enhancement of domestic and international research hub functions to request eight new faculty members. By increasing the ratio of the voluntary expenses of the university after the sixth year, the ICReDD will gradually become independent and secure ongoing research activities.

"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”.

From FY2022, the HU has reorganized and strengthened its industry-academia collaboration system with a view to accepting researchers from industry and establishing a research consortium with industry. From this, the system will be capable of systematically supporting ICReDD's acquisition of private funding, and can be maintained and made permanent while promoting fundraising.

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

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

<u>Medium-term Goals and Plans (FY2022-FY2026)</u>

Medium-term Goals

Strategically define areas of international presence to become a world-class research university. Establish an education and research environment (special research funds, special salary system, etc.) that will attract excellent researchers and students from Japan and abroad. Build a world-class institute with an accumulation of the most advanced education and research facilities, including data infrastructures, and accumulation of intellectual assets, including an international network and hub function that transcends industry-academia-government collaboration.

Medium-term Plan

Attract excellent researchers from Japan and abroad, based on the core functions and the international collaborative research utilizing the unique characteristics of the University, such as the "Institute for Chemical Reaction Design and Discovery (ICReDD)", which aims to form a world-class research center or research on zoonosis. Furthermore, establish a world-class research center linked to education by implementing graduate school education that reflects the cutting-edge research of the center in the curriculum.

◎<u>Medium-term Goals and Plans (FY2016-FY2021)</u>

Medium-term Goals

(2) Objectives regarding research implementation system, etc. ①Establish a system that will be the foundation for strengthening research capabilities.

Medium-term Plan

(2) Measures to achieve the goals concerning the research implementation system, etc. ①-3 Establish a research environment and support system to promote cutting-edge fusion research at the "Institute for Chemical Reaction Design and Discovery (ICReDD)", which was established in FY 2018 and aimed to build a world-class research center.