World Premier International Research Center Initiative (WPI)

Summary of Research Center Project

* Compile in English within A4 2 pages.

Center name: Institute for Chemical Reaction Design and Discovery (ICReDD)

Host institution: Hokkaido University

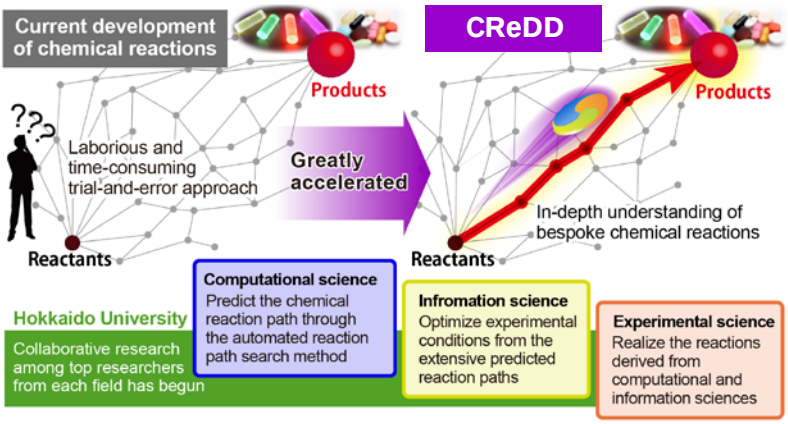
Head of host institution: Toyoharu Nawa (President)

Prospective center director: Satoshi Maeda, Professor, Faculty of Science

Prospective administrative director: Yasunori Yamamoto, Specially Appointed Associate Professor, Faculty of Engineering

1) Overall Framework of the Center Project

The ultimate goal of the Institute for Chemical Reaction Design and Discovery (ICReDD) is to acquire an in-depth understanding of chemical reactions by analyzing complex networks of chemical reaction paths in order to accelerate the efficiency of the development of new chemical reactions. These new chemical reactions will generate advanced materials and reduce the use of energy and natural resources, which is indispensable for a prosperous and sustainable future of humanity. **We aim to accomplish this objective in a research environment that integrates computational, information, and experimental sciences.** Considering that the current trial-and-error approach to the development of new chemical reactions is time-consuming and inefficient, new methods for the development of bespoke chemical reactions should be a key factor toward revolutionizing the entire field of science. By using state-of-the-art reaction path search methods based on quantum chemical calculations and collaborating with information and experimental scientists, we hope to establish the new academic field "Chemical Reaction Design and Discovery (CReDD)", which will provide substantial knowledge on chemical reactions that allows efficiently developing advanced chemical reactions and materials.

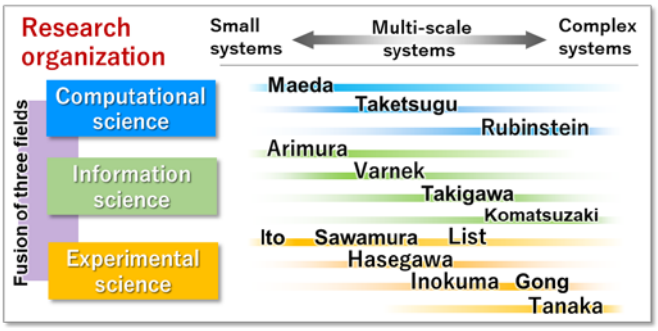


2) Content of Research

The development of new reactions by CReDD can be subdivided into three categories, depending on the size of the target molecules. The 1st category aims to create reactions that add high value to abundant and/or inexpensive resources (small molecules; ~100 atoms), e.g. synthesis of amino acids from CO_2. The 2nd category is concerned with the synthesis of high-tech materials (macromolecules; ~10,000 atoms), e.g. synthesis of highly efficient light-emitting materials and ultrahigh-strength carbon materials for space elevators. In the 3rd category, CReDD will be used to investigate cellular and biochemical reactions, and some of the materials developed in the 2nd category will be used in advanced medical care (complex molecules; > 10,000 atoms), e.g. for the establishment of new diagnostic tools and treatment strategies. In collaboration with information science, Prof. Maeda's automated reaction path search method (AFIR) can be used to identify optimal synthetic paths to target structures. The real material that is significantly important and desired by human society will be synthesized by experimental scientists on the basis of the theoretical prediction.

3) Interdisciplinary Research

AFIR allows the extraction of the molecular behavior that is crucial for chemical reactions. Still, when AFIR is applied to more realistic systems, the time required to carry out the necessary complex calculations is relatively long. This obstacle could potentially be circumvented using established methods in information science (e.g. high-speed algorithms), which should dramatically reduce the time and cost for these



calculations. Subsequently, experimental scientists will carry out the practical verification of the proposed reactions, and the experimental results will be analyzed and used as data feedbacked for the information scientists to extract new insights and apply these to the chemical reaction design. The success of CReDD would not only benefit areas that are directly related to the chemical industry, but also the global environment, life sciences, and society in general. The CReDD should thus act as an initiator and incubator for rapid, productive, and innovative research based on chemical reactions that affect all aspects of society.

4) International Research Environment

Three world-leading researchers from foreign research institutes have been invited to participate in the ICReDD. Research groups will be established for foreign PIs, and **Co-PIs** and research staff will be employed to support and manage the research groups in close collaboration with the foreign PIs, given that the latter will also serve at their home institutions. Recruitment at the ICReDD will be based on a competitive, international selection process, and **~30% of the researchers will be foreign**. We will establish an international hospitality support system for foreign researchers. Hokkaido University has already established **the Global Institution for Collaborative Research and Education (GI-CoRE)**, which consists of several centers. Among these, especially the Soft Matter GI-CoRE and the Information Science GI-CoRE will be incorporated into the ICReDD as key sub-organizations. **We aim to establish the MANABIYA (an old Japanese word for "school") system** in the ICReDD to educate young researchers and graduate students on collaborative research that integrates computational, information, and experimental sciences in order to realize a global circulation system for world-class scientists in the integrative research area CReDD. We will build a broad collaboration network through the ICReDD research.

5) Center Management and System Reform

Project management: The director, Prof. Maeda, will serve for a minimum of 10 years, seconded by the vice director, Prof. Ito. Decision-making rights regarding central matters of institute management (e.g. recruitment and budgetary discretion) will rest exclusively with the director of the ICReDD. Depending on the progress of research, the roles of each PI will be reviewed and evaluated periodically by the director, and appropriate incentives and/or replacements will be implemented. Dr. Yamamoto, who has extensive experience in collaborative industry research and intellectual property management will serve as the administrative director. With URA support from the headquarters, the ICReDD will function as an organization directly connected to the university administration. The research support department will create a research environment that allows researchers and students to engage in their research without administrative interruptions.

Research environments and establishing an independent research center: A collaborative research space including the MANABIYA system and the Inter-science Café space will be installed in the Creative Research Institution building (CRIS). The CRIS Global Facility Center will manage instruments purchased at the ICReDD. Using the support system of each PI's affiliated department will reduce the burden of administrative work for the PIs and ensure that research and education is their prime concern. At the launch, the ICReDD will have secured operational funding from the university that is at least equivalent to the WPI grant. CReDD and MANABIYA will eventually be transformed into **the new "Graduate School of Chemical Reaction Design and Discovery"**. We will also create a permanent organization for the acquisition of private funding by e.g. hosting researchers from industry and establishing research consortia. The ICReDD will incorporate research areas beyond its three core fields, such as humanities and social sciences, which are required for the promotion of research and the reformation of CRIS. By sharing new management systems acquired through the WPI, the ICReDD will finally contribute to the reorganization of the University.

World Premier International Research Center Initiative (WPI)

Research Center Project

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Center name: Institute for Chemical Reaction Design and Discovery (ICReDD)

Host institution: Hokkaido University

Head of host institution: Toyoharu Nawa (President)

Prospective center director: Satoshi Maeda, Professor, Faculty of Science

Appendix 1: "Biographical Sketch of the Prospective Center Director" (to be attached)

Appendix 2: "References (recommendations) for the prospective center director by distinguished international researcher(s) in the center's target field" (to be attached)

Prospective administrative director: Yasunori Yamamoto, Specially Appointed Associate Professor, Faculty of Engineering

Appendix 3: "Biographical Sketch of the Prospective Administrative Director" (to be attached)

1) Overall Framework of the Center Project

* Cleary and concisely describe your center's mission statement as a WPI center, its identity, and its goals toward achieving the objectives of the WPI program.

[Summary of the Research Center]

The ultimate goal of the Institute for Chemical Reaction Design and Discovery (ICReDD) is to acquire an in-depth understanding of chemical reactions by analyzing complex networks of chemical reaction paths in order to accelerate the efficiency of the development of new chemical reactions. These new chemical reactions will generate advanced materials and help to reduce the use of energy and natural resources, which is indispensable for a prosperous and sustainable future of humanity. We aim to accomplish this objective via the **establishment of a research environment that integrates computational, information, and experimental sciences.**

Considering that the current trial-and-error approach to the development of new chemical reactions is time-consuming and highly inefficient, developing methods for the controlled development of bespoke chemical reactions should be a key factor toward revolutionizing the entire field of science. Using state-of-the-art reaction path search methods based on quantum chemical calculations and collaborating with information and experimental scientists, we hope to establish the new academic field "Chemical Reaction Design and Discovery (CReDD)", which will hopefully enable us to acquire substantial knowledge on chemical reactions and thus allow us to efficiently develop advanced chemical reactions and materials. Moreover, we aim to **establish the MANABIYA (an old Japanese word for "school") system in the ICReDD to educate young researchers and graduate students on collaborative research** that integrates computational, information, and experimental sciences in order to realize a global circulation system for world-class scientists in the integrative research area CReDD.

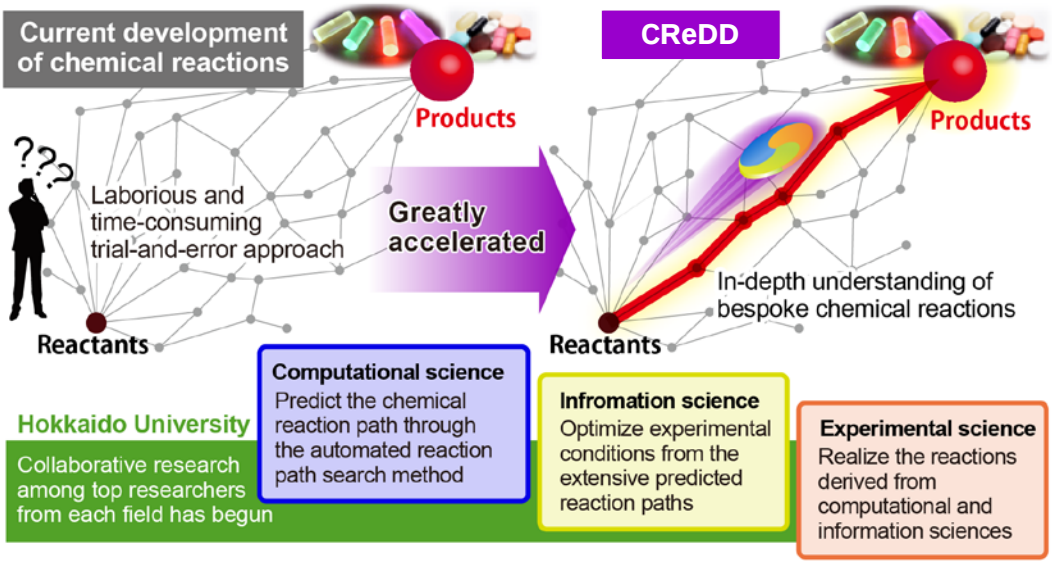
[The Necessity of Establishing the Research Center]

Chemical reactions provide access to the multitude of chemical compounds (e.g. agrochemicals, pharmaceuticals, and materials) that have allowed humanity to prosper. However, the development of new chemical reactions is usually time-consuming and laborious, while the probability of success is

uncertain at best. In order to shorten the development period, many studies have until recently applied theoretical and computational science in an attempt to better understand chemical reactions and to design new reactions. However, it remains incredibly complicated to understand the fundamental aspects of chemical reactions based on the quantum dynamic behavior of atoms and molecules. Furthermore, conventional quantum chemical calculations occupy vast amounts of computation resources, rendering this approach less than efficient. Yet, the demand for new chemical reactions has never been higher in the context of e.g. the chemical industry, global resource exploitation, the environment, and human healthcare. **Unless significantly more efficient methods for the development of new chemical reactions will be established, it should be difficult to maintain the current growth of humanity while maintaining or increasing the current standard of living.**

[Strategy to Establish the Research Center and Specific Goals]

To solve these problems, we will establish the new field "Chemical Reaction Design and Discovery (CReDD)" in order to efficiently develop and understand new chemical reactions by combining computational, information, and experimental sciences. By establishing the Institute for Chemical Reaction Design and Discovery (ICReDD), which would be the first of its kind, we will promote cutting-edge, integrated collaborative research, and establish a new era of research on chemical reactions. The development of chemical reactions based on experimental trial-and-error typically requires several decades in order to develop a single new chemical reaction. To circumvent this obstacle, Prof. Maeda, the prospective director of the ICReDD, has developed the "automated reaction path search (AFIR)" as a new method for the computational search of chemical reactions. Although this method is highly innovative and predicts the desired chemical reactions with high precision, it still requires vast amounts of computation resources. To address this issue, we want to use information science and the expertise from international leading researchers hosted by Hokkaido University in order to identify important reaction paths in a manner that allows high-speed calculations. Internationally leading experimental scientists at Hokkaido University (e.g. authors of top 1% paper(s) in high-impact journals and/or highly cited authors) will carry out the experimental validation of the chemical reaction development.



The experimental scientists will also provide feedback for the computational and information scientists, which will help to improve the understanding of the reaction network. Via the integrated method described above, it should be possible to identify promising experiments in advance, i.e., the exploration of the reaction path network can be prioritized according to the predictions. The time required for the development of new reactions should thus be reduced substantially compared to conventional methods that rely on trial and error. Additionally, with this method, it should be possible to understand the complicated transformation of many substances, which is relevant for other academic fields related to chemical reactions. Especially for the three core areas of research (computational, information, and experimental sciences), Hokkaido University has already established itself as a prominent global institution that would provide a strong foundation on which the goals of CReDD can be achieved. At the proposed ICReDD, we further plan to establish the MANABIYA system, which is a crucial strategic aspect in order to ensure the development of world-class human resources. **Via the MANABIYA fostering system, the IRCD will establish national and international collaborations with other research centers by i) developing a new area of research (CReDD), ii) restructuring the organization of Hokkaido University, and iii) establishing the new graduate school "School of Chemical Reaction Design and Discovery".** The integrated research on CReDD should lead to the development of highly efficient chemical reactions that should afford high-value-added chemicals with applications in agro- and environmental chemistry, pharmaceutical and materials science, medical technology, as well as energy and resource management. The target reactions and molecules are carefully selected based on the impact to the society through discussion among broad research communities and with many companies.

2) Content of Research

2) -1 Research fields

* Write in your target research field(s)
* Describe the importance of the target research field(s), including the domestic and international R&D trends in that research domain and neighboring field(s), and describe the scientific and/or social significance of the field(s).
* Describe the value of carrying out research in the field(s) as a WPI center (e.g., Japan's advantages in the subject fields, the project's international appeal as an initiative that challenges world-level science issues, and the future prospects of the research)
* List up to 5 centers either in Japan or overseas that are advancing research in fields similar to the center's field(s), and evaluate research levels between your center and those centers.
* Appendix 4: "Up to 10 English-written papers (review papers are also acceptable) closely related to the center's project and their list" (to be attached)

[Establishment of the Research Field Chemical Reaction Design and Discovery]

The objective of our institute is to establish the new research field "Chemical Reaction Design and Discovery (CReDD)" in order to gain a fundamental understanding of the intricacies of chemical reactions, which represent very complicated quantum dynamical phenomena, and to develop new chemical reactions at high speed. The development of chemical reactions may help to alleviate serious social problems such as increasing industrial waste and food shortages and contribute to a more sustainable future society. **For that purpose, we aim to integrate computational, information, and experimental sciences. Among these three scientific areas, collaborations between two of these three fields is relatively common, while collaborations between all three areas remain elusive.** The proposed ICReDD is designed to fully integrate world-leading research at Hokkaido University on reaction path search (computational science), mathematical and statistical modeling (information science), and cutting-edge experimental verification of the proposed models and pathways in order to realize a prediction-based design and rapid development of bespoke chemical reactions.

The ICReDD will also play a central role in the development of world-leading young researchers who master techniques in computational, information, and experimental sciences. **In the ICReDD, all reaction paths for the synthesis of target compounds from feedstock chemicals will be systematically investigated *de novo*. This is an unprecedented approach that stands in sharp contrast to existing informatics projects.** Materials informatics and chemoinformatics projects such as the materials genome initiative in the USA, the materials research by information integration initiative of the National Institute for Materials Science (NIMS) and the Novel Materials Discovery (NOMAD) laboratory in the EU generally design target materials rather than reactions, which is similar to the operational principle of AIMR (Tohoku WPI). Literature-based projects such as PubChem in the USA, Reaxys (Elsevier), and SciFinder (American Chemical Society) search for *known* reactions.

In contrast, the focus of the ICReDD will be placed on *discovering a variety of unknown reactions*, which will fundamentally change the system of field integration and collaborative research. Although several established WPIs, such as the ITbM (Nagoya WPI) and the MANA (NIMS WPI) continuously develop new purpose-orientated molecules and materials using chemical reactions, these are obtained using classical trial-and-error approaches. In contrast, the integrated approach of the ICReDD should lead to numerous new reactions, each of which should efficiently generate bespoke chemicals and materials. **The potential of this approach to deliver successful collaborative research is highly promising. The ICReDD**

should therefore become a benchmark for rapid, productive, and innovative research on new chemical reactions. The ICReDD will also play a crucial role to promote these innovative and integrative research methods to a higher level by disseminating the results beyond immediate institutional boarders.

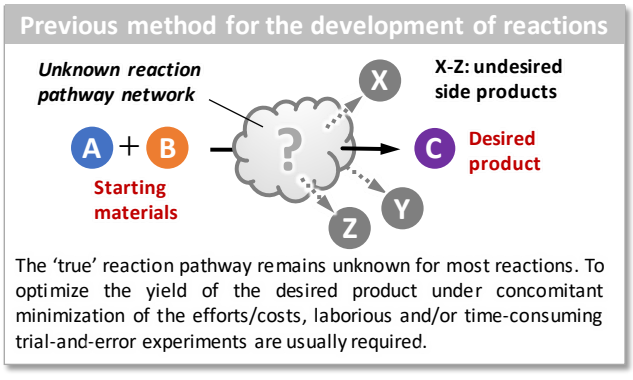
2)-2 Research Objectives and Plans

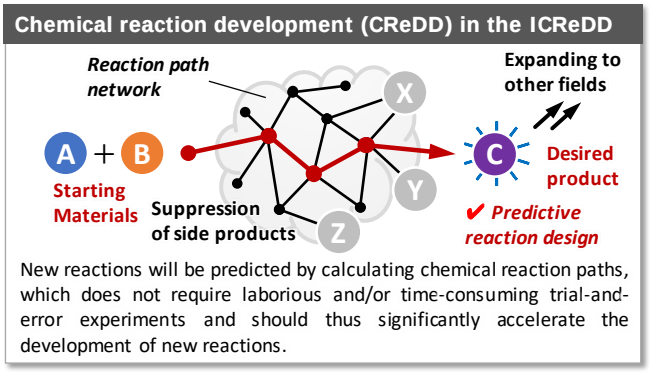
* Describe in a clear and easy-to-understand manner by the general public the research objectives that your project seeks to achieve by the end of its grant period (in 10 years). In that process, what world-level scientific and/or technological issues are you seeking to solve? What will be the expected impact of the scientific advances you aim to achieve on society in the future?
* Describe concretely your research plan to achieve these objectives and any past achievements related to your application.

[Objectives of Chemical Reaction Design and Discovery (CReDD)]

The extremely advanced materials that propel modern societies cannot be obtained for free, as they always represent the product of chemical processes that turn bulk and/or feedstock chemicals into value-added compounds using chemical reactions as tools. The objective of CReDD is the development of new chemical reactions that allow the effective synthesis of target compounds under concomitant minimization of the use of exhaustible resources (materials and energy). **The development of new reactions in the context of CReDD can be subdivided into three categories, depending on the size of the target molecules.** In the first category CReDD aims to create reactions that add high value to abundant resources and/or low-value substances (**small molecules of ~100 atoms**), while the second category is concerned with the synthesis of high-tech materials (**macromolecules of ~10,000 atoms**). The third category (after ~8 years) is concerned with the use of CReDD for cellular and biochemical reactions, whereby some of the materials developed in category 2 will be applied to advanced medical care **(complex molecules > 10,000 atoms**). **In the early stage of the ICReDD, we will select model reactions for proof of concept. Then, in the middle to the later stage, reactions that have a significant impact on the society will be carefully selected based on the discussion with the broad scientific community members and companies.**

The key technique to be used in the CReDD is the automated reaction path search method (AFIR) that has been developed by Prof. Maeda, who is the prospective director of the ICReDD. AFIR allows the accurate prediction of various reaction pathways to produce value-added target molecules from simpler starting materials. In order to apply this method effectively to relatively large molecules, which would conventionally incur prohibitively high costs for calculations and produce extremely complex experimental data, suitable information science tools (e.g. mathematical models and statistical analysis techniques) will be developed and applied. As the complexity of such models and techniques increases with increasing size





of the target molecules, CReDD will initially be concerned with relatively simple molecular systems (category 1) and subsequently advance to more complex systems (categories 2 and 3).

1. Category 1: Reactions that Add High Value to Small Molecules (~100 atoms)

In this category, chemical reactions will be created that add high value to small molecules. The focus of CReDD in this category rests on reactions that provide e.g. food or pharmaceuticals from abundant and inexpensive raw materials, such as industrial waste, air, and seawater. Prof. Maeda has already discovered a reaction path that allows the synthesis of amino acids from CO_2. Expanding this method, CReDD aims to develop e.g. reactions for the synthesis of peptides from CO_2 and of pharmaceuticals from crude oil components. We envision a future in which abundant food and medicine is produced from abundant low-value sources and supplied all over the world in order to save human lives, especially those of children suffering from famine and/or diseases.

2. Category 2: Reactions for the Synthesis of New Materials (~10,000 atoms)

Expanding CReDD to synthesize molecules of ~10,000 atoms can afford e.g. highly efficient light-emitting materials, exhaust gas cleaning catalysts, dynamic responsive soft materials, and ultrahigh-strength materials. For the development of catalysts, detailed reaction path searches will be conducted for the catalytic reactions in order to construct accurate reaction models at the catalytically active center. Moreover, for example, the synthesis of “self-evolving” gels and polymers will be examined, as these are able to easily change their physical properties (e.g. hardness, absorption, emission) in response to external stimuli (e.g. light, heat, mechanical stress). Chemical reactions developed in this category will provide polypeptide pharmaceuticals, as well as materials for accident- and pollution-free vehicles and ultrahigh-strength space crafts and stations.

3. Category 3: Applications of New Materials to Advanced Medical Care (>10,000 atoms)

In the third category we will use CReDD to investigate cellular and biological reactions for applications in advanced medical care. The functioning of the human body relies on many complex biological reactions such as the chemical modification of DNA and proteins. A disturbance or imbalance of these reaction systems often induces a variety of human diseases that include autoimmune disorders and cancer, which may lead to human death. In order to uncover mechanisms of human diseases, we will use CReDD and biocompatible materials based on some of the stimuli-responsive materials developed in category 2.* Following the development of mathematical models and biocompatible materials to control the cellular events, new diagnostic tools and treatment strategies will be established for various human diseases with mechanical genomics by the end of the funding period.

*Cancer cells are one of the major targets of the research. For rapid and complete eradication of cancers, mechanisms of cancer stem cells (CSCs) induced by hydrogels developed in category 2 should be clarified by the AFIR method, with respect to a regulation of monomeric hydrogels. Novel strategy of liquid biopsy targeting circulating tumor cells will be developed using the materials collaborating with researchers of National Cancer Center Research Institute (Tokyo), leading to early detection and diagnosis of cancer. As clinical cancer therapy, precision medicine should be performed at Hokkaido

University Hospital, including Oncology group, using oncogene panels such as MSK-IMPACT collaborating with Dr. Marc Ladanyi (Memorial Sloan-Kettering Cancer Center, MSKCC, New York, USA), who is a developer of the panel. In addition, chemical libraries that have been developed at Hokkaido University are available for drug screening for identifying CSCs-targeted anticancer drugs. One ultimate goal is to predict and prevent human diseases through CReDD.

2)-3 System for advancing the research

* Describe the center's research organization (including its research, support and administrative components) and your concept for building and staffing the organization.
* Describe your concrete plan for achieving the center's final staffing goal, including steps and timetables.
* If the center will form linkage with other institutions, domestic and/or foreign, *by establishing satellite functions*, provide the name(s) of the partner institution(s), and describe their roles, personnel composition and structure, and the collaborative framework with the center project (e.g., contracts to be concluded, schemes for resource transfer).
* If the center will form linkage with other institutions, domestic and/or foreign, *without establishing satellite functions*, provide the names of the partner institutions and describe their roles and linkages within the center project.
* Appendix 5: "List of Principal Investigators" (If there are changes from the PI list in the first screening application documents, describe the points changed and reasons.) (to be attached)
* Appendix 6: "Biographical sketch of principal investigator" (to be attached)
* Appendix 7: "Composition of personnel in center" (to be attached)
* Appendix 8: "Letters from researchers invited from abroad or other Japanese institutions expressing their intent to participate in the center project" (to be attached)

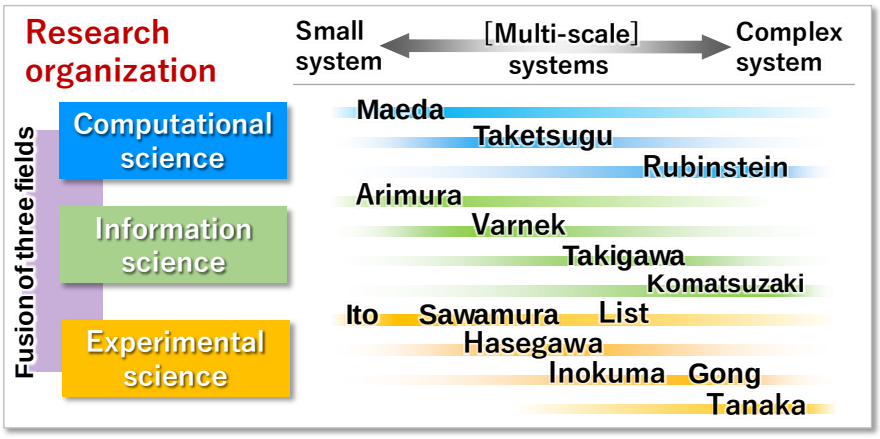
[Research Organization]

Computational Science: The designated director of the ICReDD, **Prof. Maeda**, heads an internationally leading research group concerned with computational chemistry; Prof. Maeda has developed the automated reaction path search method (AFIR) (*PCCP* **2013**; top 1% paper), which will be used to **predict reaction path networks for various chemical reactions.** The establishment of the reaction path network is crucial for the integrated nature of this initiative. In cases where reactions involve an excited state, **Prof. Taketsugu**, who has extensive experience in calculating photoreaction processes, will perform high-precision calculations. **Prof. Rubinstein (Duke University)**, a specialist in the computational science of polymer models, will examine complex reaction system categories s including macromolecules (polymers and gels). In addition to these PIs, we will appoint associate professors and (post)doctoral research fellows who are familiar with computational science in order to model macromolecules and complex systems based on the results from the high-precision calculations on reactions involving small molecules.

Information Science: As chemical reactions have far-reaching implications at the micro, meso, and macro level, information science will use statistical and mathematical models to analyze and unveil complex multi-layer hierarchical systems with cross-layer coordination. This should **allow bridging the gap between different hierarchical layers (from quantum and physical chemistry to biophysics to cell biology)** and also disentangling the complex nature of chemical reaction networks that has been exposed by Prof. Maeda's research. **Prof. Arimura** (data mining), who is a world-leading expert on scalable data mining, will lead the design of efficient algorithms for the discovery of knowledge in the computational and experimental data that will have been accumulated in the ICReDD's cross-sectional research. **Prof. Varnek (chemoinformatics, University of Strasbourg)** will integrate computational

and experimental sciences in category 1 using state-of-the-art chemoinformatics methods for molecular screening and reaction design. **Prof. Komatsuzaki** (mathematical science), who is experienced in the analysis of chemical reaction networks, will work on the mathematical modeling of macromolecules and complex systems. **Prof. Takigawa**, an expert in machine learning, will establish data-driven predictive models based on machine learning and data science to extract the maximum of information from the diverse kinds of available data. This approach should provide a rational strategy for the optimal design of experiments as well as the design and discovery of bespoke functional materials and life-science-related molecules.

Experimental Science: Experimental scientists will **create the CReDD output via the implementation of reactions at the various hierarchical levels.** For the development of high-value-added reactions (category 1), we target a broad variety of molecules that range from pharmaceuticals to functional materials. **Vice Director Prof. Ito** (synthetic chemistry) and **Prof. Sawamura** (catalysis) will address transition-metal-catalyzed reactions, while **Prof. List (reaction design, Max Planck Institute for Coal Chemistry)**, who is world-renowned expert on reaction design, will investigate catalytic organic reactions for the efficient development of reactions without having to rely on trial-and-error methods. In category 2, **Prof. Hasegawa** (optical material science) will develop high-performance light-emitting materials based on the predictions of the excited-state calculations performed by Prof. Taketsugu, while **Prof. Gong** (polymer science), who is a gel materials expert, will create stimuli-responsive materials that e.g. toughen upon exposure to mechanical stimuli and that can decompose or deteriorate in a controlled manner. **Prof. Inokuma** (structural chemistry) will perform structural analyses of the obtained macromolecules and provide feedback for the collaborators concerned with information science. The thus obtained experimental information will help to the reduce the calculation costs in category 2. During the experimental verification of category 3, **Prof. Tanaka** (tumor pathology), who is an expert in disease-function analysis, will investigate complex cell responses using the new materials obtained in category 2. In collaboration with information science researchers, he aims to effectively find hidden biochemical reaction systems that are hampered by diseases. The experimental researchers will then develop innovative regenerative medical strategies that do not require genetic engineering, novel diagnostic tools for cancer to overcome cell variation, and biocompatible materials that can control cellular responses.



Integrated Research Center and Collaboration Organizations: The ICReDD will host ~100 members, which includes ~30 coordinators and support staff. We will invite foreign PIs using a cross-appointment system and encourage the creation of sub-research groups that host full-time Co-PIs and (post)doctoral research fellows at Hokkaido University, which will provide significant valuable leadership training for younger researchers. PIs will invite and host foreign researchers in order to further their professional development in the three core areas of CReDD, and to promote human-resource development and collaborative research. **In order to disseminate CReDD internationally, we plan to implement the MANABIYA system, which consists of a continuous cycle of short-term visitors comprising approx. 20 foreign researchers and ~50 graduate students**. Since we can lead and accelerate research in other institutes, we will invite researchers (*without satellite functions*) from other WPI centers such as the ITbM (Nagoya University) and the MANA (NIMS), as well as from other foreign research institutes and companies to practically experience CReDD. We will also consult with Prof. Minato (Kyoto University), who is familiar with this area of research, to ensure that these collaborations proceed efficiently. **By focusing on the accelerated collaborative research, the ICReDD will hopefully become the premier international center of integrated computational, information, and experimental researches on chemical reactions.**

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

* Paste onto table a) in Appendix 7.

(persons)

	At beginning of project	At end of FY 2018	Final goal (Date: March, 2023)
Researches from within the host institution	11	11	11
Foreign researchers invited from abroad	3	3	3
Researchers invited from other Japanese institutions	0	0	0
Total principal investigators	14	14	14

b) Total number of members

* Paste onto table b) in Appendix 7.

	At beginning of project		At end of FY2018		Final goal (Date: March, 2023)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	14		32		53	
Overseas researchers	3	21.4	10	31.3	16	30.2
Female researchers	1	7.1	2	6.3	6	11.3
Principal investigators	14		14		14	
Overseas PIs	3	21.4	3	21.4	3	21.4
Female PIs	1	7.1	1	7.1	1	7.1
Other researchers	0		18		39	
Overseas researchers	0	—	7	38.9	13	33.3
Female researchers	0	—	1	5.6	5	12.8
Research support staffs	3		15		28	
Administrative staffs	6		10		10	
Total number of people	23		57		91	

Chemical reaction design and discovery

Computational science

● **Director MAEDA, Satoshi** (computational science)
Development of automated reaction path search methods
The Japan Society for the Promotion of Science (JSPS) Award, Banyu Chemist Award, Principle Investigator of Core Research Evolutional Science and Technology (CREST)
Publications: e.g. *Science*, *JACS*, and *Angew. Chem.*

● **TAKETSUGU, Tetsuya** (quantum chemistry)
Development of light-emitting materials by calculation of excited states
NIMS Global Research Center for Environment and Energy Based on Nanomaterials Science (GREEN)
Publications: e.g. *Science*, *JACS*, and *Adv. Mater.*

● **RUBINSTEIN, Michael** (polymer physics)
Duke University and Hokkaido University Distinguished Professor, Co-chair Gordon Research Conference
Modeling of various polymeric systems
Advisory Board member of *Soft Matter*
Publications: e.g. *Nature*, *Nature Materials*, and *Science*.

Information science

● **ARIMURA, Hiroki** (data mining)
Listing, selection, and high-speed search of small to medium-sized molecules
Director of Global COE (Centers of Excellence) Program, Grants-in-Aid for Specially Promoted Research, Principal Investigator

● **VARNEK, Alexandre** (chemoinformatics) University of Strasbourg
Reaction databases and molecular screening
Vice-president of the French Society of Chemoinformatics
Publications: e.g. *JACS*

● **TAKIGAWA, Ichigaku** (machine learning)
Reaction network modeling and data-driven predictions
Principle Investigator of Precursory Research for Embryonic Science and Technology (PRESTO)
Publications: e.g. *Nature Comm.*

● **KOMATSUZAKI, Tamiki** (mathematical science)
Mathematical modeling of macromolecule systems and data-driven science
Editorial Board member of *Sci. Rep.*, Director of CREST
Publications: e.g. *PRL*, *PNAS*, *Nature Comm.*, and *Nature Chem. Bio.*

Experimental science

● **Vice Director ITO, Hajime** (synthetic chemistry)
Development of new reactions including multi-element reactions and small molecules
CSJ Award for Creative Work, Principle Investigator of PRESTO, Funding Program for Next Generation World-Leading Researchers (NEXT)
Publications: e.g. *Nature Chem.*, *Nature Comm.*, *JACS*, and *Angew. Chemie.*

● **SAWAMURA, Masaya** (catalysis) Hokkaido University Distinguished Professor
Development of new catalytic reactions involving transition metals and/or small molecule
CSJ Award for Creative Work, Nagoya medal (Silver medal), ACT-C, Principle Investigator of PRESTO
Publications: e.g. *Nature*, *Nature Chem.*, and *Science*.

● **LIST, Benjamin** (reaction design) Max-Planck Institute for Coal Chemistry
Development of new reactions with organocatalysts and/or small molecules
Thomson Reuters Highly Cited Researcher, Editorial Advisory Panel member of *Nature Comm.*, Editor-in-Chief of *Synlett*
Publications: e.g. *Nature*, *Science*, *Nature Chem.*, *Chem. Rev.*, and *JACS*.

● **HASEGAWA, Yasuchika** (optical materials science)
Development of light-emitting materials with high brightness and high durability, macromolecules
CSJ Award for Creative Work, Prizes for Science and Technology from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT)
Publications: e.g. *JACS*, *Sci. Rep.*, and *Angew. Chem.*

● **INOKUMA, Yasuhide** (structural chemistry)
Development of functional crystalline and polymer materials, macromolecules
Nagase Special Prize, The Young Scientists' Prize by MEXT, Principle Investigator of PRESTO
Publications: e.g. *Nature*, *Nature Chem.*, *JACS*, and *Angew. Chem.*

● **GONG, Jing-Ping** (polymer chemistry) Hokkaido University, Distinguished Professor
Development of biocompatible/Self-evolving gels, and macromolecules
RSC Fellow, CSJ Award for Creative Work, Award of the Japanese Society of Polymer Science, Grants-in-Aid for Scientific Research (S), Grants-in-Aid for Specially Promoted Research, Principal Investigator, Editorial Board member of *Macromolecules*, *Polymer*, *Soft Matter*
Publications: e.g. *Science*, *Nature Mater.*, and *Nature Comm.*

● **TANAKA, Shinya** (tumor pathology)
Cell control by new material(s), machine learning, and complex molecules
Director of the Japanese Society of Pathology, Incitement Award of the Japanese Cancer Association, Incitement Award of the Japanese Society of Pathology, Associate Editor of *Brain Tumor Pathol.*
Publications: e.g. *Nature Str. Mol. Biol.*

Advisor and collaborative researcher

MINATO, Shin-ichi (information science) Kyoto University
Research Director of ERATO, Visiting Professor at Hokkaido University

2)-4 Securing research funding

Past record

* Give the total amount of research funding (e.g., competitive funding) secured by the principal investigators who will join the center project. Itemize by fiscal year (FY2013-2017).

Past record of the total amount of research funding acquired by the 11 domestic PIs (total number of PIs: 14) between FY 2013 and FY 2017:
¥471,573,750 (FY2017); ¥525,511,632 (FY2016); ¥359,291,752 (FY2015); ¥361,013,030 (FY2014); ¥463,468,450 (FY2013); ¥2,180,858,614 (Total FY2013-FY2017)

Funding prospects after the establishment of the center

* Based on the past record, describe your concrete prospects for securing resources that match or exceed the WPI grant (FY2018-2022).
* Calculate the total amount of research funding (e.g., competitive funding) based on the amount of funding that the researchers will allocate to the center project. Be sure that the funding prospects are realistically based on the past record.

To establish the ICReDD, we plan to secure a maximum of ¥560,000,000 in research funding. The domestic PIs have already acquired ~¥470,000,000 in 2017. With the addition of junior researchers, who have acquired ~¥140,000,000 in 2017, and external funds obtained by the foreign PIs, we will be able to fully cover the anticipated costs for the proposed research activities. Further commitments, including supplies from the host organization, will secure operational funding at least similar to that of the WPI grant (*cf.* the appropriation plan). The age range of the PIs (30s–50s) will ensure continuous research funding of several million yen. Additionally, we will apply for publicly available funds in the fields of chemistry and information science, and initiate research consortia with companies in order to actively acquire research funds from the private sector.

3) Interdisciplinary Research

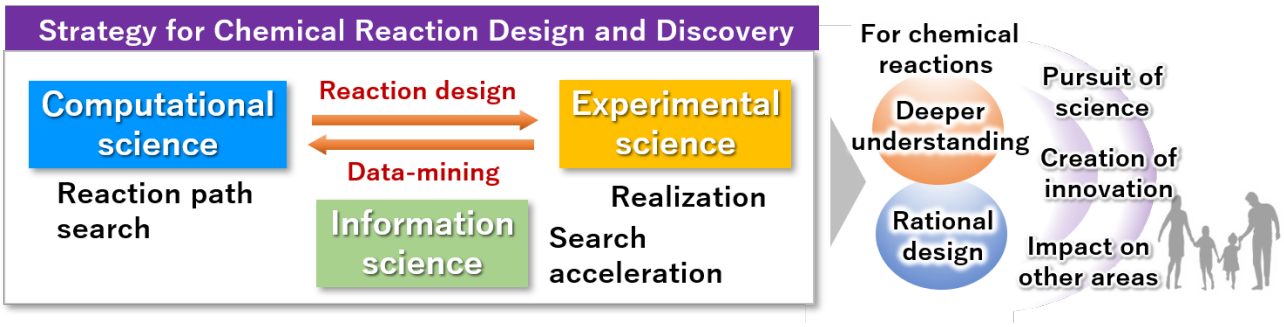
* Describe the fused research domains, why interdisciplinary research is necessary and important in the target field(s), and what new field(s) can be expected to be created by way of this project. Describe your concrete strategy for fusing different research domains and creating new field(s) by the fusion.

[Necessity and Significance of Integrated Research]

Given their particular importance for human activity and sustenance, it is hardly surprising that industry branches related to chemical reactions have a combined annual impact of 500 trillion yen (4 trillion USD). The rational design of chemical reactions based on a better understanding how they procced should allow carrying out these operations more efficiently. **However, using quantum chemistry to examine chemical reactions is very expensive and time-consuming as the numerous combinations of possible chemical reaction patterns usually require prolonged calculations.** Prof. Maeda's automated reaction path search method allows calculating virtual forces between molecules that are next to each other or separated (artificial force-induced reaction; AFIR), which enables the extraction of the molecular behavior that is crucial for chemical reactions. Still, when this method is applied to more complex 'realistic' systems, the time required to carry out the necessary complex calculations is relatively long. This obstacle could potentially be circumvented by taking advantage of established methods in information

science such as high-speed algorithms and pattern calculations, which should dramatically reduce the calculations. Subsequently, experimental scientists will carry out the practical verification of the proposed reactions in collaboration with the computational and information scientists. In addition, experimental results will be analyzed and used as a data feedbacked for the information scientists to extract new insights and apply these to the chemical reaction design.

The proposed academic field of "Chemical Reaction Design and Discovery (CReDD)" aims to understand and design bespoke chemical reactions by integrating three different areas of research. The success of CReDD would not only benefit areas that are directly related to chemical reactions, but also the global environment, life sciences, and society in general, as most industrial productions depend on substances obtained from chemical reactions. The creation of CReDD as an academic research area and the foundation of a WPI dedicated to CReDD should thus act as an initiator and incubator for ripple effects that affect all aspects of society. Collaborative research of prospective PIs for the ICReDD at Hokkaido University has already produced significant preliminary results that could be used as the foundation for ICReDD.



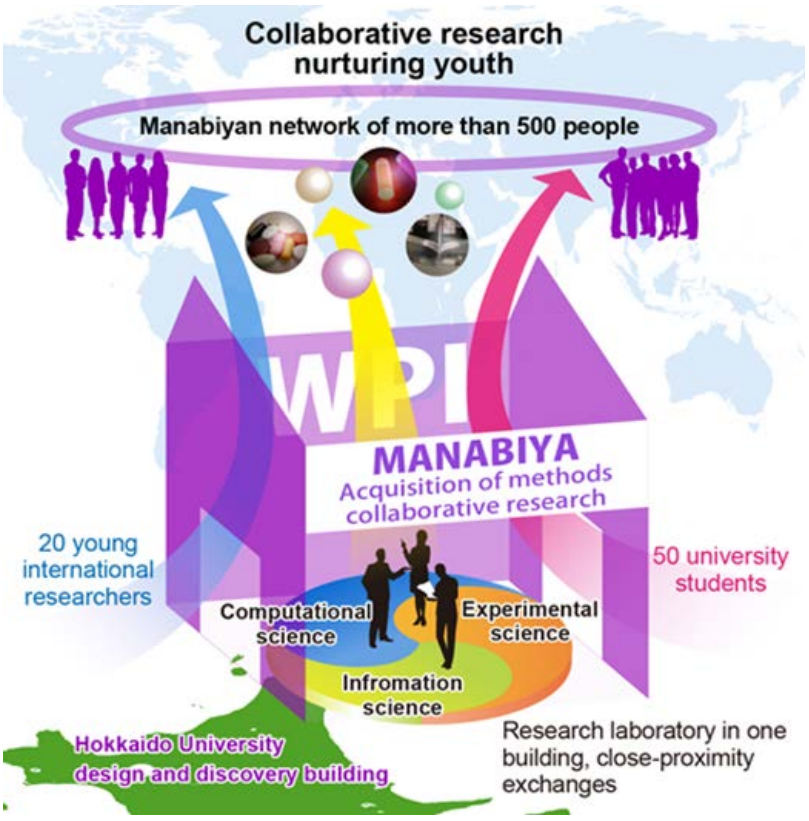
For example, Profs. Maeda (computational science) and Ito (experimental science), the designated director and vice director of ICReDD, have already discovered new reaction mechanisms for highly complex reactions using the AFIR method (JACS **2015**). Prof. Taketsugu (computational science) has already developed new functional materials in collaboration with Profs. Ito (experimental science) and Hasegawa (experimental science; JACS **2017**). Prof. Takigawa (information science) is a world leader in the development of new catalytic reactions using computational science and machine learning in collaboration with experimental scientists at Hokkaido University (RSC Advances **2016**). However, to truly integrate these three areas of research and to firmly establish CReDD, the collaborating scientists must work together in a research center in order to foster cross-fertilization and maximize synergistic effects. At this integrative research institute, we will not only accomplish groundbreaking research, but also train and educate a future generation of internationally oriented researchers that will be experts in all three research areas.

[Strategies for Advancing Integrated Research]

Research activities will take place at the **"Hokkaido University Creative Research Institution (CRIS) Building,"** and the close proximity of researchers will result in frequent information exchange

and collaboration. We will invite young researchers from national and international institutes for periods of 1-3 months in order to familiarize them with this new collaborative approach to develop new reactions. This **MANABIYA system will invite approximately 20 foreign researchers and 50 graduate students (MANABIYANs).** These researchers will be trained in the new collaborative methods and they will hopefully return to their home institutions to apply them there. **After 10 years, the MANABIYAN network should comprise >500 researchers** in a balanced mixture of experienced global leaders and young researchers, which should support the further development of this new field. We will also provide opportunities for "science tea meetings" with researchers from different disciplines to regularly meet in a relaxed environment to promote frequent exchange (**Inter-science Café**). Additionally, we will also provide high-quality video conference systems that are continuously connected in order to facilitate exchange and collaboration with foreign satellite institutes.

At Hokkaido University, the majority of graduate schools and research institutes are located on a single campus, which is different from many other Japanese universities, rendering the collaborative inter-disciplinary research highly efficient.



4) International Research Environment

4)-1 System for advancing international research

* Describe your concrete plan for building an international research center including the makeup of its foreign researchers, establishment of oversea satellites, or similar functions. Include a time schedule for the plan.
* Describe concretely your strategy for staffing foreign researchers (e.g., postdoc positions) through open international solicitations. Describe the procedures you will use to do so.

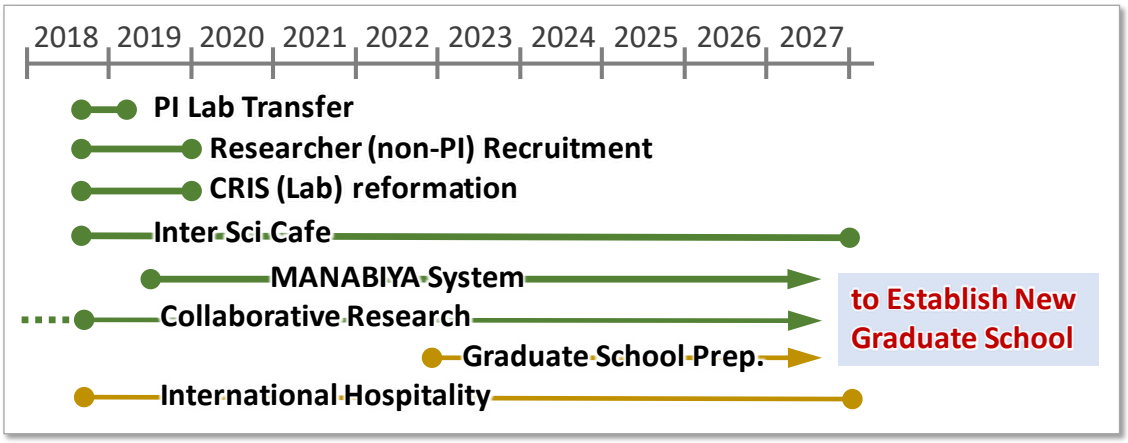
We have invited three world-leading researchers from foreign research institutes to participate in the proposed ICReDD. Prof. Rubinstein (Duke University, USA) is a globally acclaimed researcher in theoretical polymer physics. Since 2016, he has worked as a visiting professor at the Global Institute for Collaborative Research and Education (GI-CoRE; Hokkaido University), where he has recently been appointed as Distinguished Professor. Currently, he is in the process of developing collaborative research related to soft matter. Prof. Varnek (University of Strasbourg, France) is a world-renowned researcher in chemoinformatics, who also focuses on the dissemination and education of chemical informatics. Prof. List (Max Planck Institute for Coal Research, Germany) is a leading experimental scientist in reaction design, especially in the context of organic catalysts.

Foreign PIs stays in ICReDD for enough period, e. g. two months, contribute the fusion research in cooperation with Co-PIs by frequently using TV-conference to increase the percentage of time they spend on site. Since foreign PIs will simultaneously serve at their home institutions and the ICReDD, **we will establish research groups for foreign PIs within our center and employ Co-PIs and research staff** (i.e., specially appointed associate and assistant professors as well as postdoctoral fellows) to support and manage the research groups in close collaboration with the foreign PIs. All specially appointed associate/assistant professors and postdoctoral fellows employed at the ICReDD will be selected through a competitive, international recruitment process, and **~30% of these researchers will be foreign.** The aforementioned Co-PI system has had great success at the WPI of Nagoya University (ITbM), and a similar scheme was used in the SMART program between the Massachusetts Institute of Technology and the National University of Singapore. With this system, world-renowned foreign PIs will establish research teams at the ICReDD in collaboration with Co-PIs, creating outstanding research environments that promote interdisciplinary interaction. Such an inspirational environment should allow the continuous fostering of young researchers, who represent the future of the scientific community and technology development. Foreign PIs will also invite young foreign researchers to participate in the ICReDD via the aforementioned MANABIYA system.

In 2014, as part of its mid-to-long-term strategy, Hokkaido University has established **the Global Institution for Collaborative Research and Education (GI-CoRE)**, with a faculty organization scheme that is under the direct control of the president of the university. This institution has launched six GI-CoRE centers in research fields that are considered to be the strengths of the university and promoted organized international collaborative research with voluntary funding. Among these centers, especially the Soft Matter GI-CoRE and the Information Science GI-CoRE are currently used as centers of collaborative research that would be connected to the ICReDD. **These GI-CoRE centers will be carefully incorporated into the ICReDD as key sub-organizations.** In the Soft Matter GI-CoRE, Prof. Gong will serve as a representative to promote strong collaborative research. Furthermore, we will continue to

promote and support systematic collaboration with Duke University (Soft Matter GI-CoRE) and the University of Massachusetts Amherst (Information Science GI-CoRE). We will also collaborate closely with Emory University (computational chemistry), the Swiss Federal Institute of Technology in Zurich (ETH Zurich; experimental science), Peking University (experimental science), and Stockholm University (experimental science) through collaborative research and the MANABIYA system, thus generating an environment that encourages international collaboration while promoting interactions among researchers. We will try to expand the collaboration network further by actively interacting with researchers both in Japan and abroad.

Collaborating international institutes	Country	MANABIYA	Collaborative research	Official inter-university agreement
University of Strasbourg [Foreign PI]	France	✔	✔	✔
Max Planck Institute for Coal Research [Foreign PI]	Germany	✔	✔	
Duke University [Foreign PI]	U.S.A.	✔	✔	✔ Soft Matter GI-CoRE
ESPCI	France	✔	✔	✔ Soft Matter GI-CoRE
University of Massachusetts Amherst	U.S.A.	✔	✔	✔ Information Science GI-CoRE
Swiss Federal Institute of Technology in Zurich (ETH)	Switzerland	✔	✔	✔
Stockholm University	Sweden	✔	✔	✔
Emory University	U.S.A.	✔	✔	
Peking University	China	✔	✔	✔



4) -2 Establishment of international research environment

* Describe your concrete strategy for establishing an international research environment, administration system, and support system (e.g., appointment of staff and provision of startup funding) to accommodate researchers from overseas.
* Concretely describe how the center will provide an environment in which researchers can work comfortably on their research by being exempted from duties other than research and related educational activities, and how they will be provided adequate staff support to handle paperwork and other administrative functions. Include your procedure and time schedule.

* Describe your strategy, procedure and timing for periodically holding international research conferences or symposiums (at least once a year).

Start-up research funds will be provided for the foundation of the research groups of the foreign PIs to establish research environments that allow a start of the research activity that is as frictionless as possible. As **English will be the working language in the ICReDD**, all members of staffs that are endowed with management tasks and the operation of the ICReDD must be fluent in English in order to ensure sufficient support for research activities, collaborations, publications, and administrative work. The already established GI-CoRE and the associated centers at Hokkaido University will thereby provide support for foreign researchers. Furthermore, we will establish **an international hospitality support system** that provides assistance for foreign PIs and their families regarding non-research-oriented issues such as visas and housing in order to ease the transition and promote research efficiency. This system will utilize the resources of the already established GI-CoRE and the Institute for International Collaboration at Hokkaido University. We will also implement **an international promotion program** to enable effective collaboration between foreign researchers and Japanese researchers and their students. We plan to frequently invite world-class researchers to the ICReDD and host **annual international symposia**. Part of the **MANABIYA system** will be a short-term exchange program between young foreign researchers and Japanese graduate students in order to promote diversification within the ICReDD and to establish and nurture an international network.

5) Center Management and System Reform

5)-1 Project management

* Describe the role of the center director and the administrative director.
* Concretely describe your concept for establishing an administrative organization, the center's decision-making system and how authority is allocated between the center director and the host institution.
* Concretely describe how the center will adopt a rigorous system for evaluating research and will introduce a system for merit-based compensation (e.g., annual salary scheme). Describe your procedures and timing for operationalizing these systems.

The goals and concepts of the ICReDD with the WPI program at its core will be consistently developed by the designated full-time director, Prof. Maeda, who is despite his youth a world-leading computational scientist. Prof. Maeda will serve for a period of at least 10 years, seconded by Prof. Ito, a world-renowned experimental scientist with extensive experience in organizational operations, who will serve as the vice director. The ICReDD will be established within the Creative Research Institution (CRIS) building and form a center dedicated to the fusion of globally leading computational, information, and experimental sciences in order create an internationally competitive research/education environment. **Decision-making rights regarding central matters of institute management such as recruitment of personnel and budgetary discretion will rest exclusively with the director of the ICReDD, who will also preside over a university-allocated budget of at least 10 million yen per year that can be freely used by the director.** Upon the launch of the program, we will build a co-management system to support the ICReDD's young director based on the extensive experience of the vice director. In the medium-to-long term, the director will establish a system of top-down decision-making. **To support the decision-making process of the director, a steering committee, composed of the vice director, the**

administrative director, and the university research administrators (URAs), will be established. The attendance of PIs at steering committee meetings is not required so that the PIs can focus exclusively on research. However, PIs may directly advise the director about any concerns if and when necessary. Based on the performance-evaluation system that has already been introduced at Hokkaido University, **we will construct a salary scheme that is centered on research performance and ability. Depending on the progress of research, the roles of each PI will be reviewed and evaluated periodically by the director, and appropriate incentives and/or replacements will be implemented.**

[Research Support Department]

Specially appointed Associate Professor Yamamoto, who has extensive experience in university research, collaborative industry research, intellectual property management, and leading educational programs, will serve as the administrative director of the ICReDD. With URA support from the headquarters, the ICReDD will function as an organization directly connected to the university administration. We will also establish a section for WPI procedures employing full-time staff members to provide a smooth transition during the program's initial stages and to support continued research activities. We will establish an "International Planning Section" to support foreign PIs, researchers, students, and to organize international symposia. The "Public Relations Section" will provide services and support for the management of e.g. websites and the organization of events, while a "Research Promotion Section" will select researchers and students, and organize collaborative work between industrial partners, the government, and the university. The research support department will ensure that the research environment is suitable for researchers and students to comfortably engage in their research without administrative interruptions.

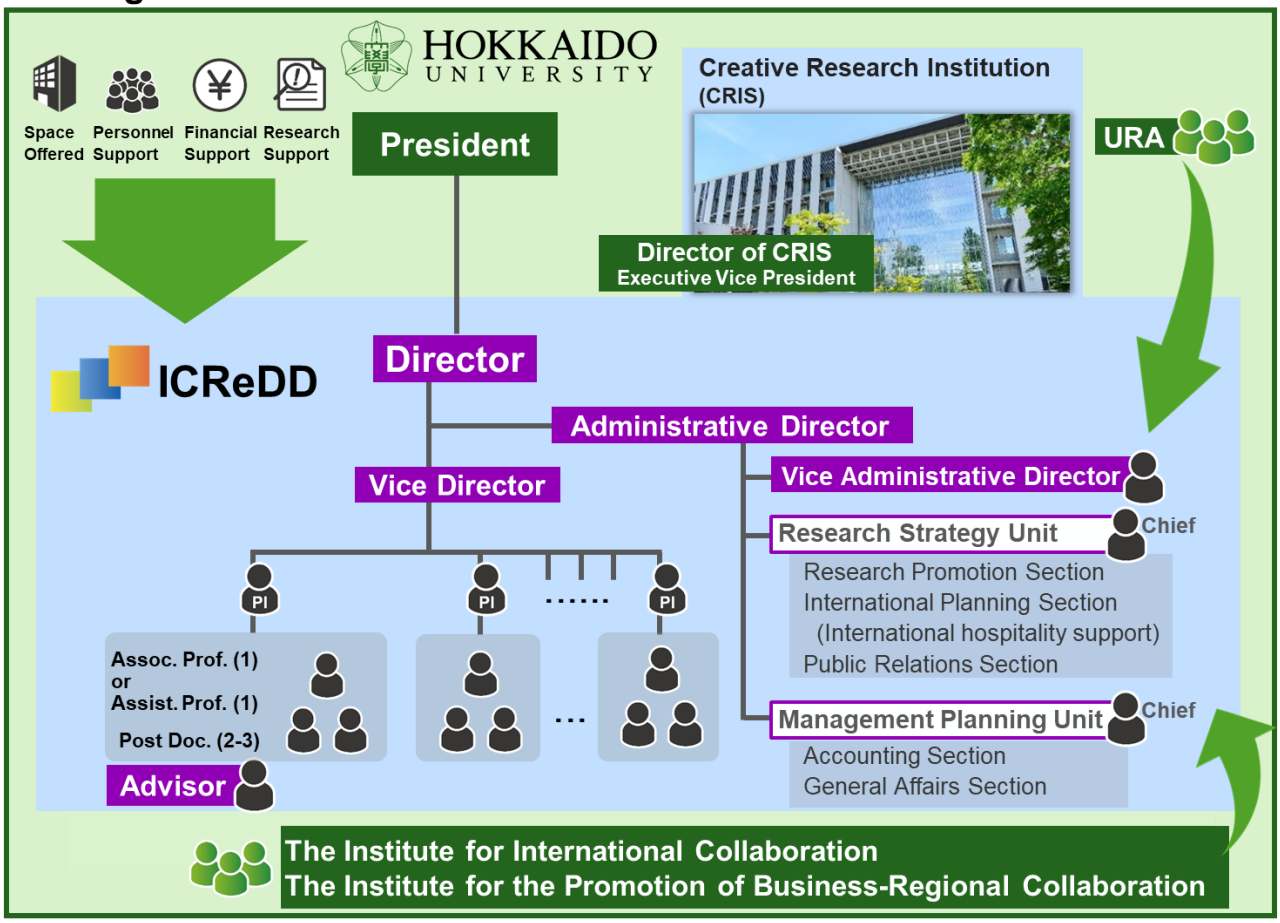
5)-2 Research environments

* Concretely describe how equipment and facilities, including laboratory space, will be provided in a manner appropriate for a "world premier international center." Include your procedure and timing.
* Concretely describe how the center will consider to arrange for its researchers to participate in the education of graduate students.
* Describe your measures other than the above to ensure that world's top researchers from around the world can comfortably devote themselves to their research within an international and competitive environment at the center.

Initially, we will secure a collaborative research space in the Frontier Applied Science Research Building in addition to the PI's laboratories. The university has already committed to renovate 1,000 m^2 of the CRIS building to serve as the ICReDD's core space. After the second year of the program, we will progressively expand the space within the CRIS. In order to realize the director's vision in which researchers and graduate students gather from all over the world, synergistically integrate knowledge that is beyond their respective disciplines, engage in collaborative research, and thus establish a world-leading research institute, we will implement the "MANABIYA" system and the "Inter-science Café" space. **PIs and researchers will educate graduate students, who are invited to the "MANABIYA" from the PI's laboratories and other national and international institutes for periods of 1-3 months, to master the new reaction development methods established in the ICReDD.** We aim to have a

continuous cycle of short-term visitors that comprises 20 foreign researchers and ~50 graduate students, and to establish a new graduate school that provides intellectual resources based on the discoveries of the ICReDD. The "Inter-science Café" will serve as a space for researchers to casually gather in a relaxed environment in order to promote interdisciplinary discussions. The director will thus spearhead the development of an internationally leading research institute that continually exchanges researchers. The MANABIYA system will promote diversification within the ICReDD and establish an international network. The international hospitality support system by utilizing the resources of the already established GI-CoRE and the Institute for International Collaboration at Hokkaido University, will provide assistance for the foreign PIs and their families regarding non-research-oriented issues such as visas and housing to ease the transition. As a result, the foreign PIs will be disengaged from the affairs of daily life and it will promote the efficiency of their research activities. The outstanding researchers at the ICReDD will be appointed following a competitive selection process and offered tenured faculty positions in order to ensure the continuation of internationally leading education and research at Hokkaido University (*cf.* form 5-4-2). In addition to the use of shared instruments [currently there are ~160 cutting-edge instruments at the CRIS Global Facility Center (GFC)] and financial support from the university regarding analytical fees, **the GFC will maintain and manage analytical instruments purchased at the institute, which allows the PIs to focus exclusively on research.** The Institute for International Collaboration will prepare and support the living environment for foreign researchers employed at the center and their family members.

The Organization of ICReDD



5)-3 Establishing an independent research center in sync with reorganizing the host institution

* Concretely describe how your proposal seeks to establish a new center that will achieve independence within 10 years and how the project will advance synchronization between WPI center support and reform of the host institution's existing organization?
* With prior consent from the host institution, describe concretely the host institution's mid-to-long-term plan and schedule for achieving the center's independent operation within the host institution, including adjustments to the existing organization and/or acquisition of external funding.

The ICReDD will be established as a permanent organization in collaboration with the university administration. For that purpose, we will use the organizational reform of the “Creative Research Institution (CRIS, established in 2002)”, which is a university-wide organization that supervises cross-departmental research in order to integrate the ICReDD as an independent institute within the university organization in the future. **After the sixth year, with sufficient progress of the collaborative research to carry out social implementations, we will i) incorporate research fields beyond the ICReDD’s core areas (computational, information and experimental sciences) in order to further promote and develop CReDD, and ii) start reforming the CRIS.** The results obtained from research in the ICReDD should also inspire related research in humanities and social sciences, especially in the context of life ethics and public policy, given that the research activities in the ICReDD will be connected to a wide variety of pressing social issues in today's changing society. **This cross-fertilization should directly lead to the reorganization of Hokkaido University through the integration of humanities and social sciences with science and engineering, which concerns aspects of e.g. intellectual property, safety evaluations, science and technology ethics, and international operation standards of technology.** Using the support system of each PI’s affiliated department will reduce the burden of administrative work for the PIs and ensure that research and education is their prime concern. At the launch of the program, the ICReDD will secure operational funding (including laboratory costs for PIs and research space) from the university that is at least equivalent to the WPI grant. 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 (*cf.* form 5: Host Institution's Commitment). CReDD 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”**. The necessary reorganization and integration of existing graduate school(s) will begin after the sixth year of the program. **We also will create a permanent organization for the acquisition of private funding by e.g. hosting researchers from industry and establishing research consortia with industrial partners.** Concretely, managers at Institute for the Promotion of Business-Regional Collaboration, Hokkaido University, will mediate between researchers at ICReDD and corporation members of the research consortia to promote research collaboration. (*cf.* form 5-9-2).

The ICReDD will thus become the core of the university's third medium-period target and the medium-term plan as the flagship project to achieve the university's near-future strategy of establishing a "global brain circulation center for world-class research”. In the long-term, the ICReDD will be the driving force that transforms Hokkaido University into a truly international center for education and research.

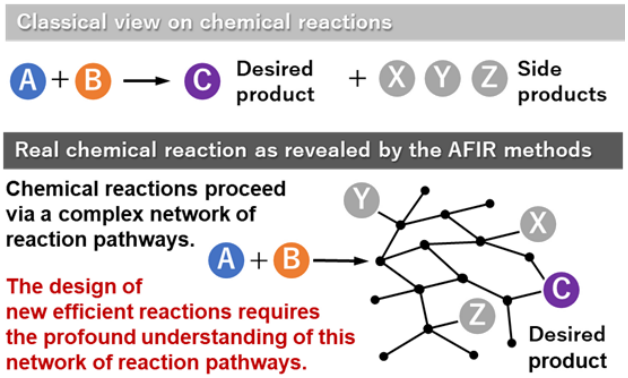
Center Director's Vision

Hokkaido University Prof. Satoshi Maeda

The development of new chemical reactions is intrinsically entangled with the prosperity of humanity and the preservation of the environment. One of the most notable chemical reactions discovered in the last century was the Haber-Bosch process, which catalytically synthesizes ammonia (NH_3) from nitrogen (N_2) and hydrogen (H_2). Also known as "the reaction that turns air into bread," the Haber-Bosch process enables the mass production of fertilizer, which helped overcoming the global food shortages at the beginning of the 20th century. A more recent example of such transformative chemical reactions with profound impact are cross-coupling reactions, the discovery of which was awarded with the 2010 Nobel Prize in Chemistry. These reactions are used to produce approximately 20% of all medicinal reagents, and almost all liquid crystalline and organic electroluminescent materials. The industrial use of these chemical reactions contributes ~60 trillion yen per annum to the global economy. **The development of new chemical reactions thus significantly affects the evolution of society.** However, the currently used methods for the design and development of bespoke chemical reactions is highly inefficient. Usually, these methods are based on trial and error, which is not only very laborious and time-consuming, but the discovery of truly innovative reactions is relatively rare. **As the development and implementation of new chemical reactions often takes decades in reality, fundamentally new scientific approaches are required.**

The goal of this initiative is to establish the scientific field of "Chemical Reaction Design and Discovery (CReDD)", which should allow the efficient development of chemical reactions through a combination of computational, information, and experimental sciences. CReDD will elevate the state-of-the-art methods for the development of chemical reactions to the next level by (1) establishing design guidelines for chemical reactions based on quantum-chemical calculations, (2) understanding the complexity of chemical reactions and designing new reactions via informatics methods, and (3) experimentally validating the theoretically proposed reactions. Quantum-chemical calculations that will be implemented at the proposed Institute for Chemical Reaction Design and Discovery (ICReDD) are different from previous approaches that have been employed to verify *known* reaction mechanisms. Quantum-chemical calculations that are capable of unveiling *unknown* pathways should represent a scientific advancement of substantial magnitude. A key technology that enables such calculations is the "automated reaction path search (AFIR) method" developed by Prof. Maeda, the designated director of the institute, who is an internationally renowned pioneer in this area. Merely 10 years ago, automatic searches for chemical reaction paths based on quantum-chemical calculations were considered impossible. However, Prof. Maeda proposed the idea of applying a virtual mechanical force to reaction systems in order to unveil potential pathways. Based on this idea, he developed the world's first general method to systematically predict *unknown* reaction paths. This method is not only of academic interest, and several companies are currently conducting collaborative research with Prof. Maeda.

It is highly remarkable that when the AFIR method is used for the analysis of chemical reactions, the results often show that these reactions proceed via paths that are very different from those initially anticipated. Simple chemical formulae reveal a large volume of uncharted **reaction path networks**, which show all possible pathways from the reactants to the major product and minor byproducts. Understanding reaction path networks will ultimately allow discovering unknown pathways to targeted product and blocking those to undesired byproducts. For the bespoke design of chemical reactions, **it is thus inevitable to study reaction path networks and identify controllable reaction pathways.**



In addition, the AFIR method also addresses the considerable challenge of 'complexity'. Even simple reactions that include only few atoms may exhibit very complicated reaction-path networks, rendering the differentiation between significant and insignificant reaction paths highly difficult. Thus, the aid of information science is essential in order to identify promising reaction paths. The faculty at Hokkaido University hosts numerous internationally renowned researchers in e.g. path enumeration, data mining, and machine learning, who could help analyzing such complex networks. By including the knowledge of information scientists, this initiative aims to understand intricate reaction-path networks and extract important factors that should be considered prior to the experimental stage. Simultaneously, large volumes of previously obtained experimental data will be examined and meaningful data will be forwarded to computational scientists in order to simplify the calculations required to obtain the reaction-path networks.

Theoretical predictions become meaningful only after they have been experimentally proven, however. In this initiative, we aim to merge experimental science with computational and information sciences on a globally leading level. The hitherto insufficient conceptual understanding that chemical reactions proceed via an extensive network of chemical reaction paths has left experimental scientists with no other alternative but to continue the laborious, expensive, and inefficient processes of trial and error. In contrast, CReDD (1) uses the AFIR method to calculate chemical reaction-path networks, and (2) applies concepts of information science in order to extract meaningful information for experiments, thus narrowing down optimal experimental conditions. This approach enables "pinpointing" promising experiments, which should considerably shorten the time required to develop chemical reactions. As the majority of the experimental scientists who will join this initiative have already collaborated with computational or information scientists, synergy among scientists from different backgrounds will be easily attained. In addition, information science provides a feedback loop, in which data obtained by the experimental scientists is circulated back to the computational scientists; the synergetic effects from the combination of three fields should lead to the improvement and refinement of CReDD.

The development of CReDD will enable the discovery of reactions that afford (1) high-value-added chemicals (small to medium size molecules), (2) new materials (macromolecules), and (3) state-of-the-art medical technology (complex systems). Reactions of the type (1) create useful chemical agents from low-value materials, e.g. via the synthesis of biologically relevant molecules from CO_2. Reactions of the type (2) produce materials with advanced functionality, e.g. highly luminescent or stimuli-responsive materials. Finally, reactions of the type (3) afford advanced materials for applications in a clinical context, e.g. improved biomedical materials leading to reagents for regenerative medicine and diagnosis. These reactions vary widely in complexity and environments for the reacting molecule(s). To cover this broad scope, we will strategically assemble a team of researchers from different disciplines. As a practical example, let us explain one of reactions predicted by automated reaction path searches. A path of amino acid synthesis from CO_2, which is a high-value-added chemical synthesis, has been predicted by Prof. Maeda in 2004. However, due to the lack of CReDD, the amino acid synthesis could not be realized experimentally until 2016. In similar situations, **CReDD will be able to provide experimental scientists with the most promising prospective reactions from the reaction path network by applying information-science-based approaches. The target reaction will be carefully selected based on social demand.**

Another goal of this initiative is to generate, nurture, and train a new generation of researchers who master all three subjects, i.e. computational, information, and experimental sciences, so that CReDD can be developed further in the future. **The continued relevance of CReDD will be ensured by sharing the results of this initiative with the world via the foundation of the MANABIYA (Japanese for 'school') system, where researchers from outside the proposed WPI will have the opportunity to collaborate and benefit from the innovative technology and knowledge developed there.** Specifically, foreign experimental researchers will have the opportunity to join MANABIYA and learn about e.g. the AFIR method and machine learning by collaborating with WPI researchers. These researchers will use the knowledge and techniques acquired at the proposed WPI upon returning to their home institutes. Through MANABIYA, our WPI will become a global research hub that continuously welcomes researchers from all over the world. This will allow our institute to not only thrive, but also to contribute to the research of other universities, research institutes, and companies that develop chemical reactions. **In the future, the MANABIYA system will evolve into the new "Graduate School of Chemical Reaction Design and Discovery". Furthermore, sharing the management system of excellence acquired through the WPI, the ICReDD will reform Hokkaido University.**

Reaction development that relies solely on the trial-and-error approach is too time-consuming to solve current global problems that include pollution as well as the scarcity of energy and resources. CReDD will revolutionize the traditional approach to developing reactions by fusing computational, information, and experimental sciences. We strive to spread the benefits of this approach by establishing a global WPI and integrating other disciplines. Our sincere hope is that our WPI may contribute to a brighter and more prosperous future for all of humanity.

World Premier International Research Center Initiative (WPI)

Host Institution's Commitment

June 1st, 2018

To MEXT

National University Corporation Hokkaido University
Toyoharu Nawa, President

Signature

I confirm that the measures listed below will be carried out faithfully and concretely as follows regarding the "Institute for Chemical Reaction Design and Discovery (ICReDD)" if it is adopted under the World Premier International Research Center Initiative.

Concrete Measures

・Describe the concrete measures that the host institution will take to satisfy the following requirements.

1) For the center to become a truly "world premier international research center" and independent by the time WPI support ends, the host institution must clearly define the center's role within its own mid-to-long-term strategy and provide its comprehensive support from the time that the funded project starts.

※Describe the center's role within host institution's own mid-to-long-term strategy.

The mid-to-long-term strategy of Hokkaido University is based on several progressive schemes related to research and education towards the internationalization of the university. In 2002, the Creative Research Institution (CRIS) was established to promote interdisciplinary research under a trans-departmental scheme. In 2014, Hokkaido University defined its vision for the near future, i.e., until its 150th anniversary in 2026, as contributing to the resolution of pressing global issues, which are outlined in the 'Future Strategy for the 150th Anniversary of Hokkaido University'. In order to accomplish the objectives, the Global Institution for Collaborative Research and Education (GI-CoRE) was founded in order to promote international collaborative research and education based on the characteristic strengths and distinctive features of Hokkaido University. The immediate objective of GI-CoRE is to become a research center of excellence that acts as a hub for world-class researchers. The ultimate objective of GI-CoRE is to reform and globalize Hokkaido University by the end of the third medium-term as specified by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT). For that purpose, Hokkaido University has developed the proposal for the World Premier International Research Center Initiative "Institute for Chemical Reaction Design and Discovery (ICReDD)" as a flagship initiative to substantially improve the research performance of Hokkaido University in collaboration with already established GI-CoRE projects and to provide maximum research support to achieve its near-future vision. The ICReDD will be incorporated into the CRIS framework and thus be able to make full use of already established infrastructure and resources to promote the proposed WPI.

Following the approval of the ICReDD, Hokkaido University will revise its third mid-term goals and plans in order to clarify its commitment to the WPI. Hokkaido University will use the momentum of the ICReDD as a driving force to transform the entire university into an internationally outstanding center for research and education that contributes to the resolution of pressing global issues.

2) Providing a mid-to-long-term policy for amending the plan on the direction of the host institution's organization and operation, one that includes the reform of the institution's existing organization in ways that will achieve the center's independence and create a permanent place for it within the organization. A concrete plan and schedule must be set and carried out for restructuring the host institution's organization.

※Describe both a mid-to-long-term policy for amending the plan on the direction of the host institution's organization and operation and provide a concrete plan and schedule.

Hokkaido University will establish the ICReDD within the CRIS framework and establish close collaborations with the Information Science GI-CoRE and the Soft Matter GI-CoRE to provide maximum support for this international research center. In order to become a world-leading research center and generate results that may change the future of humanity, this WPI will advance the research implementation and involve further research collaborations outside the ICReDD's core areas (computational, information, and experimental sciences). To manage such a progressive performance of the ICReDD, CRIS will be reorganized into an institution that pioneers novel interdisciplinary research. The following measures will be implemented in order to maximize the performance of the ICReDD via the restructuring of already existing organizations within the university in the foreseeable future.

1. Upon launching the proposed program, Hokkaido University would provide physical and financial resources (research space, utility fees, and the usage of equipment owned by the open facility center) that at least equal the WPI project grant. In order to gradually promote the independence of the ICReDD and to ensure its permanent establishment as an integral part of Hokkaido University, the university plans to increase the ratio of its own contribution to the ICReDD budget starting from the sixth year.
2. In order to ensure that the ICReDD sustainably continues its research activities independently, the university will provide financial support starting from the sixth year for tenure positions that will be offered to outstanding WPI researchers. These will be appointed following a rigorous selection process based on research activities such as high-impact publications and receipt of competitive funds. The university will also provide the ICReDD with full access to its financial infrastructure, i.e., the opportunity to request budget estimates and to apply for competitive cross-departmental funding.
3. From the sixth year onwards, preparation for establishment of the new "Graduate School of Chemical Reaction Design and Discovery" will be launched, which will be based on the intellectual resources obtained from the discoveries of the ICReDD; the university will begin the reorganization and integration of existing graduate school(s) in cooperation with WPI-related departments.
4. The university will support the formation of consortia that involve companies and research institutions that collaborate with the ICReDD in order to promote industrial collaborations and establish a system to attract independent funding for the ICReDD.
5. After ten years, the ICReDD will become a permanent independent research organization within the university. The university's evaluation committee will assess the ICReDD's approach and reapply successful systems and methods, such as research and education systems, to other departments of the university.

3) Provide sufficient support for carrying out the center's operation and research activities, including necessary personnel, financial, and system support.

The university will provide physical and financial support that is at least equal to that of the WPI grant via the following measures.

1. In October 2017, the university established a WPI task force that is staffed by full-time clerical

employees and two university research administrators (URAs). Provided the success of this application, the university will successively increase the number of office management personnel and transform the management office into the WPI administration office. In order to guarantee smooth program management, and given the international orientation of the ICReDD, the university will hire full-time clerical employees who are fluent in English for the ICReDD.

2. The university has already provided research funds (10 million yen) and research space (120 m^2) to the designated director of the ICReDD in order to initiate interdisciplinary integrated research. After the launch of the ICReDD, the university will initially provide further space (1,000 m^2) at the CRIS, which will be expanded progressively.
3. To reduce the educational and administrative burden on the departments of each PI, the university will take measures to provide labor costs (~50 million yen per year) for the corresponding departments as a form of compensation. The university has also established a "specially appointed professor (re-employment of retired instructors) system" to ease the educational strain on researchers who participate in larger projects. Furthermore, the university will also revise related provisions as and when necessary, e.g. the employment of researchers taking advantage of various financial resources.
4. When researchers at the ICReDD use shared university equipment, the university will pay any usage fees and provide a suitable research environment so that researchers can start their research immediately after their arrival.

4) Provide necessary support to achieve the independence of the center and sustain its research at a top world level after the WPI grant period ends.

After the end of the supporting program, the ICReDD will continue to operate as an independent research department and implement the results obtained from this initiative to promote the sustainable development of human resources engaged in CReDD. Furthermore, industrial collaborations will be established and promoted to practically implement the results obtained from the ICReDD. To achieve this goal, the following steps will be taken.

1. From the 5th year, the university will provide the ICReDD with the opportunity to request budget estimates, which will allow the IRCD to establish an independent financial base.
2. After the end of the grant period, outstanding researchers at the ICReDD will be appointed following a competitive selection process and offered tenured faculty positions in order to ensure the continuation of internationally leading education and research at Hokkaido University.
3. To promote research collaborations and to establish a system that attracts independent funding for the ICReDD, the university will support the establishment of research consortia between the ICReDD and corporations that are engaged in CReDD.

5) Provide a system that will in practice allow the center director to make decisions in implementing the center project, including personnel and budgets, and that will secure the autonomy of its operation.

Even though the ICReDD will eventually become a permanent part of CRIS, the university will initially implement exceptional rules until the ICReDD becomes an independent institute in order to provide the director of the ICReDD with all decision-making rights regarding important matters of institute management such as recruitment and budgetary discretion. To support the director in the decision-making process, the university will set up a management committee that includes vice directors, administrative directors, and URAs.

Furthermore, the university will establish discretionary funds (at least 10 million yen per year) that can be used freely by the director of the ICReDD.

6) Provide support to the center director by coordinating with other departments regarding the

assigning of researchers to the center and the creating of an effective environment for the center within the host institution. Needed adjustments to do so should be made proactively while giving consideration to their effect on the educational and research activities of those departments.

The university will set up an environment in which the participating PIs from each department in the ICReDD can concentrate on WPI research. Coordination with the individual departments will be led by the president and the vice president in charge.

1. To reduce the educational and administrative burden on the departments of each PI, the university will take measures to cover occurring labor expenses for the corresponding departments as a form of compensation. Additionally, a "specially appointed professor (re-employment of retired instructors) system" has been established.
2. The university will revise and adapt existing systems to provide access to a variety of financial resources in order to employ permanent researchers that will support the ICReDD permanently.

7) Offer cooperation in flexibly applying, revising, or supplementing the host institution's internal systems as needed for the center to effectively implement new management methods unfettered by conventional modes of operation (e.g. English-language environment, merit-based pay, top-down decision making, linkage to graduate school education).

In order to ensure a continuous circulation of internationally leading researchers in this ICReDD, its organizational structure will be based on flexible management in order to prioritize research activities. The necessary system reform initiatives will be executed via the ICReDD steering committee; the director, the vice director, the administrative director, and the URAs who work at ICReDD under the supervision of vice president.

1. The ICReDD will capitalize on the soft infrastructure that has already been established by previous GI-CoRE activities, e.g. a framework for collaboration among departments and foreign institutions, expertise for global cooperation with companies, approaches to develop new educational programs, and livelihood support services for international researchers and their families.
2. Initially, the ICReDD will operate a joint management system, i.e., the designated director leads the decision-making process, supported by the vice director, who has a different research background and extensive experience in organizational management, which should help to establish a top-down decision-making system for the management of an interdisciplinary research center in the medium-to-long term.
3. The ICReDD will introduce a system to evaluate the progress of performance led by the director of the ICReDD. This system will consist of a self-assessment process that is centered on indicators related to research output as well as flexible management of the institutional budget.
4. The president of Hokkaido University will transfer full authority to the director of the ICReDD regarding decisive actions that include the reorganization of the personnel structure should the collaborative and institutional progress require such action.
5. The university will preferentially hire administrative staff for the ICReDD that is fluent in English in order to promote the use of English in the office environment.

8) Secure, provide and deliver the necessary infrastructure for the center to carry out its activities (e.g. research space, facilities, land).

Provisions for the ICReDD, such as the use of the university campus infrastructure including the CRIS building, are outlined below.

1. Initially, the university will provide 1000 m^2 of space in the CRIS, which will be renovated prior to use. This research space will be expanded progressively during the period of the WPI.
2. The university will provide the fees requiring to analyze synthesized samples in the context of the

ICReDD, as well as the usage fees for the open facility system, which provides access to cutting-edge equipment such as the world's only isotope imaging microscopy system and high-resolution NMR spectrometers that are managed by the university.

3. The university will set up a common space (Inter-Science Café), where all WPI researchers can gather for lunch meetings every month in order to exchange ideas across different disciplines in English, whereby especially young researchers will be encouraged to disseminate their research progress.

9) Provide other types of assistance to give the center maximum support in achieving its concepts and objectives and in becoming a world premier international research center in both name and deed.

Hokkaido University will provide unreserved support for the implementation of the plans of the ICReDD by integrating its goals and plan into that of the third medium-term of the university, which should help to nurture and establish the institute as a permanent and integral part of the university.

1. In order to promote advanced integrated operations between the ICReDD and the university, the URAs will be granted the status of deputy administrative directors, which should facilitate communication with the president and the vice president in charge.
2. In addition to providing access to the CRIS infrastructure, the university will support the ICReDD by providing access to resources of other relevant organizations, such as the Institute for International Collaboration and the Institute for the Promotion of Collaborations with Regional Businesses.
3. The university will help to realize the objectives of the ICReDD by collaborating with projects that concern university reforms and making the most of its results. This includes seminars to promote the acquisition of competitive funding for early career researchers by the MEXT Program for Promoting the Enhancement of Research Universities (started in FY 2013) and collaborations regarding public relations with the Global Relations Office, which was established through the MEXT Top Global University Project (started in FY 2014).

10) The host institution is to self-evaluate the results of the system reforms achieved by the center and distribute the results that it evaluates highly to all of its departments.

The university's evaluation committee will assess the performance of the ICReDD and reapply successful systems and approaches, such as research and education systems, e.g. the "MANABIYA" system to other departments of the university. Especially, the research results obtained in the ICReDD will be transformed into educational activities via collaborations with closely related divisions in the university in order to train scientific leaders who may contribute to solving important global issues. On the basis of educational resources obtained from ICReDD activities such as the MANABIYA system, this initiative strives to reform and generate a new interdisciplinary graduate school that will integrate basic science, drug discovery, and medicinal technology, as well as materials and energy science.

Thus, the ICReDD should become the impulse and driving force for the restructuring of Hokkaido University into a truly international world-class center for research and education.

11) (For host institutions that already have an existing WPI center) Fully support and sustain the existing center and advance its development as a top world-level research institute while being concurrently capable of fully supporting the new center.

Not applicable.

12) (For host institutions that already have an existing WPI center) Take the initiative to spread the existing center's good system reform results to other departments throughout the institution and thus applied them to its own reform.

Not applicable.

World Premier International Research Center Initiative (WPI)
FY2018 the Second Screening Proposal

List of Principal Investigators

・If the number of principal investigators exceeds 10, add columns as appropriate.
・Place an asterisk(*) by the name of the investigators who are considered to be ranked among the world's top researchers.
・Give age as of 1 April 2018.
・For investigators who cannot participate in the center project from its beginning, indicate the time that their participation will start in the "Notes" column.
・If there are changes from the PI list in the first screening application documents, describe the points changed and reasons in the "Notes" column.
・Include principal investigators affiliated with satellite institutions. Give the name of their satellite institutions in the "Notes" column.
・Fill in the achievements of each PI in the "Biographical Sketch of Principal Investigator."

	Name	Age	Current affiliation (Department/ School/Institution)・Title	Specialization	Effort * (%)	Notes
1	Satoshi Maeda*	38	Department of Chemistry, Faculty of Science, Hokkaido University・Professor	Computational Chemistry	80%	Director
2	Hajime Ito*	50	Division of Applied Chemistry, Faculty of Engineering, Hokkaido University・Professor	Organometallic Chemistry	80%	Vice-director
3	Hiroki Arimura*	52	Division of Computer Science and Information Technology, Graduate School of Information Science and Technology, Hokkaido University・Professor	Computer Science	80%	
4	Jian Ping Gong*	56	Department of Advanced Transdisciplinary Science, Faculty of Advanced Life Science, Hokkaido University・Distinguished Professor	Soft Matter, Polymer Science,	80%	
5	Yasuchika Hasegawa*	49	Division of Applied Chemistry, Faculty of Engineering, Hokkaido University・Professor	Coordination Chemistry, Photochemistry	80%	
6	Yasuhide Inokuma	36	Division of Applied Chemistry, Faculty of Engineering, Hokkaido University・Associate Professor	Structural Organic Chemistry, Coordination Polymers	80%	
7	Tamiki Komatsuzaki*	53	Research Center of Mathematics for Social Creativity・Director/ Research Institute for Electronic Science, Hokkaido University・Professor	Molecular Data Science, Information Theory	80%	
8	Benjamin List*	50	The Max-Planck-Institut für Kohlenforschung・Professor and Director	Organic chemistry, Organocatalysis	20%	
9	Michael Rubinstein*	61	Departments of Mechanical Engineering & Materials Science, Biomedical Engineering, Chemistry and Physics, Duke University・Professor	Theoretical Polymer Science, Soft Matter	20%	
10	Masaya Sawamura*	56	Department of Chemistry, Faculty of Science, Hokkaido University・Distinguished Professor	Organometallic Chemistry, Asymmetric Catalysis	80%	
11	Tetsuya Taketsugu*	53	Department of Chemistry, Faculty of Science, Hokkaido University・Professor	Ab Initio Reaction Dynamics	80%	
12	Ichigaku Takigawa	41	Division of Computer Science and Information Technology, Graduate School of Information Science and Technology, Hokkaido University・Associate Professor	Machine Learning, Data Mining and Bio/Cheminformatics	80%	
13	Shinya Tanaka*	53	Department of Cancer Pathology, Faculty of Medicine, Hokkaido University・Professor	Pathology	80%	
14	Alexandre Varnek*	62	Faculty of Chemistry, University of Strasbourg・Professor	Cheminfomatics	20%	

* Percentage of time that the principal investigator will devote to working for the center vis-à-vis his/her total working hours. (Activities carried out using competitive funding can be included as effort as long as they correspond to the purpose of the WPI center and are conducted for the center.)