# ICReDD
# Annual Report

2019-2020

# Director's introduction

## Seeding a revolution:

# The first year of ICReDD

In the fiscal year 2020, ICReDD is setting out to tackle new challenges. We are working hard on setting up a system to, as our slogan states, "Revolutionize Chemical Reaction Design and Discovery" through a high-degree fusion of computational science, information science, and experimental science.

We are looking back at the fiscal year 2019 as one that was full of intense preparation to set up from scratch an institute worth of being a WPI center. In particular, the research is expected to be at the world's top level and to be carried out as true fusion research among all the groups, 14 groups in the case of ICReDD. This task is not achieved simply as a fact of being awarded a WPI project, even though some of the world's best research groups are assembled at ICReDD.

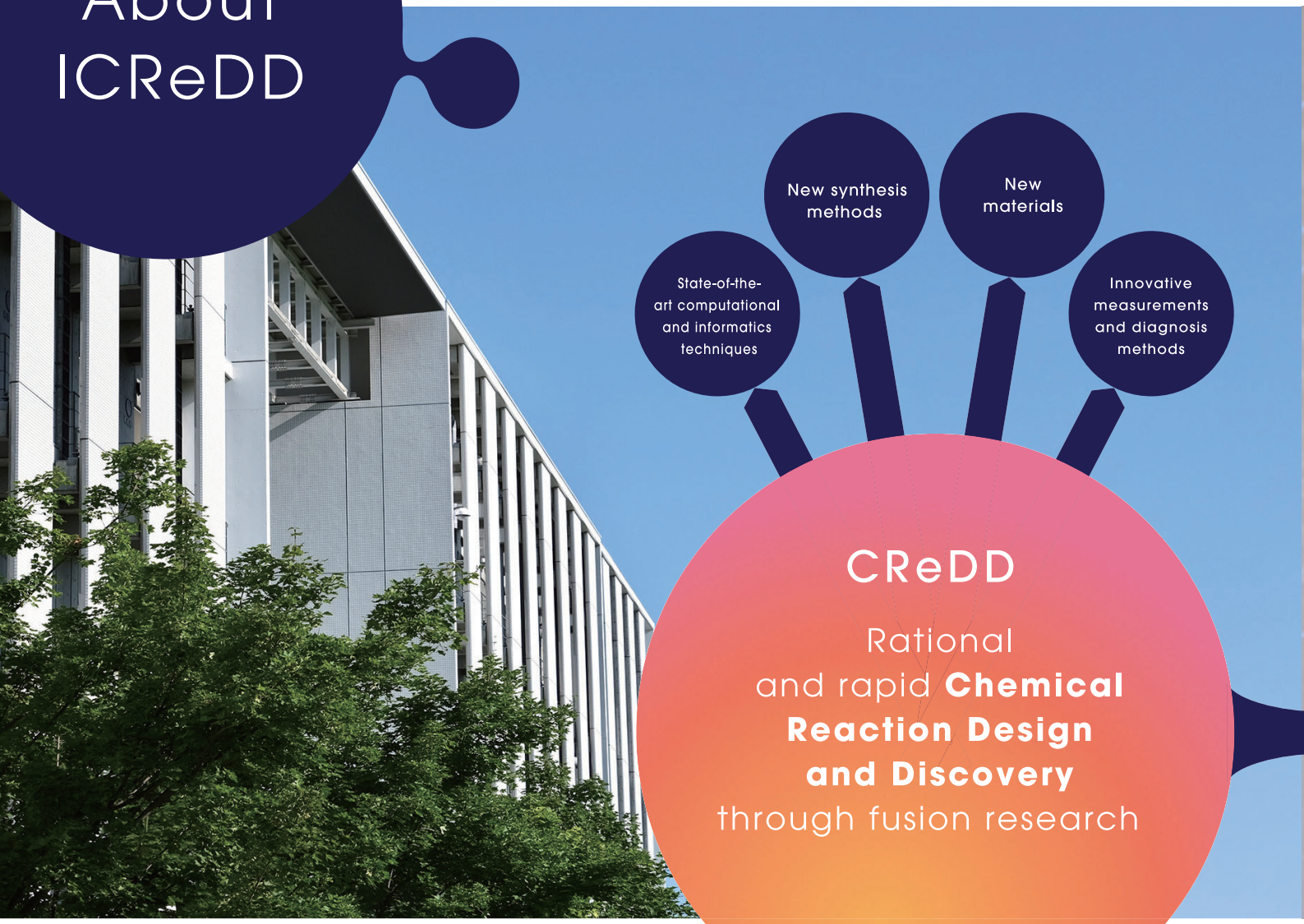
First, a large number of new members have joined the institute since April 2019. In order for all members of the center, including new members, to move forward with fusion research, one mixed lab was completed in April 2019, one mixed office in January 2020, and another mixed lab in March 2020. In addition to the above, a discussion space called the ICReDD Salon has also been developed. These facilities provide young researchers at the center with an excellent opportunity to promote fusion research. In addition, the various forms of fusion seminars held in the ICReDD Salon provided an opportunity to deepen mutual understanding amongst the different researchers in the center. In fact, the research seeds generated in these places have already begun to grow into new projects at the center.

Just having the right people and place was not enough to start a high-level fusion research. Therefore, we launched several flagship fusion research projects by soliciting ideas and holding discussions within the center. As a consequence, the development of chemical reactions led by computational science and information science is beginning to produce budding success stories.

The management structure has been strengthened with the addition of Professor Koichiro Ishimori as Executive Director and Professor Kuniharu Ishiro as an advisor, starting in the middle of the 2019 academic year. With their help, we are working on initiatives to further promote fusion research within and outside of ICReDD, such as through the MANABIYA system. It must be added that we also benefit from the guidance of the Evaluation Committee and the WPI Program Committee. In the fiscal year 2020, we will continue establishing an institute that truly meets the standards of the WPI program.

MAEDA Satoshi
Center Director

# About ICReDD




## About ICReDD

ICReDD is the Institute for Chemical Reaction Design and Discovery, a WPI center at Hokkaido University where researchers from different disciplines combine their strengths to take full control over chemical reactions. We use computational science, information science, and experimental science to develop new methods, new materials, and new applications across all fields where chemical reactions are important. Our researchers come together under one roof, with the expertise of each becoming a resource for the work of the other. We foster a regular, personal exchange across research laboratories on all levels from postdocs to principal investigators and work in shared facilities as well as participate in common activities such as seminars, retreats, or lunch gatherings.

## About MANABIYA

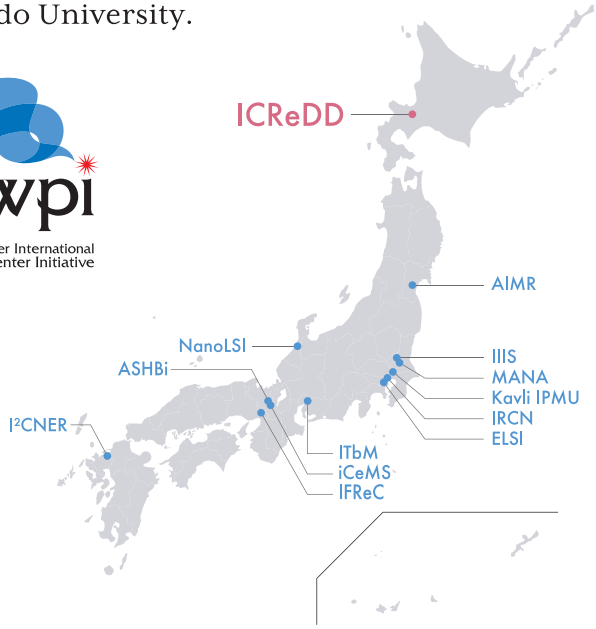
MANABIYA is a newly set-up strategic framework at ICReDD that enables us to develop an international collaborative research environment. It is a system to foster a new generation of researchers proficient in the three fields of computational, information


and experimental science by inviting them to study at ICReDD for up to three months, and to form collaborative relationships with academia and industries in Japan and overseas. By thus developing the new interdisciplinary academic field of "Chemical Reaction Design and Discovery" (CReDD) worldwide, we aim at making ICReDD an internationally recognized research institution, and discover new research seeds.

## About WPI

The World Premier International Research Center Initiative (WPI) was launched in 2007 by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in a drive to build within Japan "globally visible" research centers that boast a very high research standard and outstanding research environment, sufficiently attractive to prompt frontline researchers from around the world to want to work in them. ICReDD was established in October 2018 at Hokkaido University.

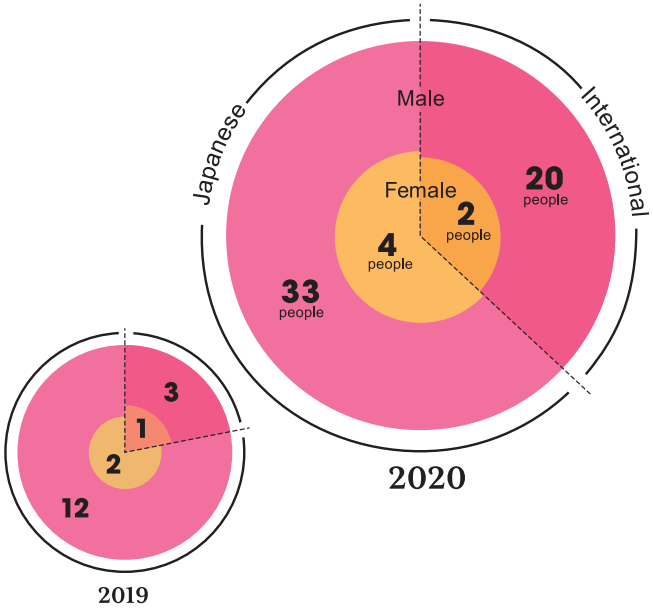
wpi
World Premier International Research Center Initiative



# Researchers and facilities

## Researcher composition

ICReDD is comprised of 59 researchers, 22 (36%) of which are foreign nationals, and 6 (10%) are female (as of 31 March 2020). We have 14 PIs, 3 of which are overseas (at the University of Strasbourg, the Max Planck Insitute for Coal Research, and Duke University), 30 faculty members, and 15 postdocs.




## Management

In order to realize the mission of the center and to contribute to its further development, we established a Steering Committee for the creation of an ambitious strategy, an Executive Committee to assist the Center Director in his decision making, an Advisory Board consisting of four foreign and three domestic researchers to lend advice for the improvement of our international presence, and PI Meetings to exchange opinions and for sharing ICReDD's vision, mission and research & management strategy among all groups.

**Computational science**


HARABUCHI Yu


HIJIKATA Yuh


IWASA Takeshi


KOBAYASHI Masato


HANE Yukiko


HASEGAWA Yasuchika


LYALIN Andrey


MAEDA Satoshi


ONO Yuriko


ISLAM Md Jahidul


ITO Hajime


ÖZEN Cihan


PIRILLO Jenny


KITAGAWA Yuichi


KUBOTA Koji


LIST Benjamin


RUBINSTEIN Michael


SUZUKI Kimichi

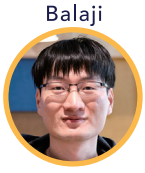

PANDUR VENKATESAN Balaji


REYES Ronald L.


TAKETSUGU Tetsuya


YAMAMOTO Tetsuya


GIMADIEV Timur


HU Sheng


KOMATSUZAKI Tamiki


MIZUNO Yuta


NAGAHATA Yutaka


SCHENZ Daniel

**Information science**


TERAMOTO Hiroshi


TSITSVERO Mikhail


CUI
Kunpeng


FAN
Hailong


GONG
Jian Ping


HIGASHIDA
Kosuke


HIROTA
Akira


HU
Anqi


IMAJO
Masamichi


INOKUMA
Yasuhide


JIN
Mingoo


KATO
Kenta


KUMAR
Sonu

**Experimental** science


MITA
Tsuyoshi


MURUGAVEL
Muthuchamy


NAGATA
Yuuya


NAKAJIMA
Tasuku


SARKAR
Parantap


SAWAMURA
Masaya


SEKI
Tomohiro


SHIMIZU
Yohei


TANAKA
Shinya


TSUDA
Masumi


TSUJI
Nobuya


YONEDA
Tomoki


ZHANG
Teng


SIDOROV
Pavel


TABATA
Koji


TAKIGAWA
Ichigaku


VARNEK
Alexandre


YOSHIOKA
Masaharu

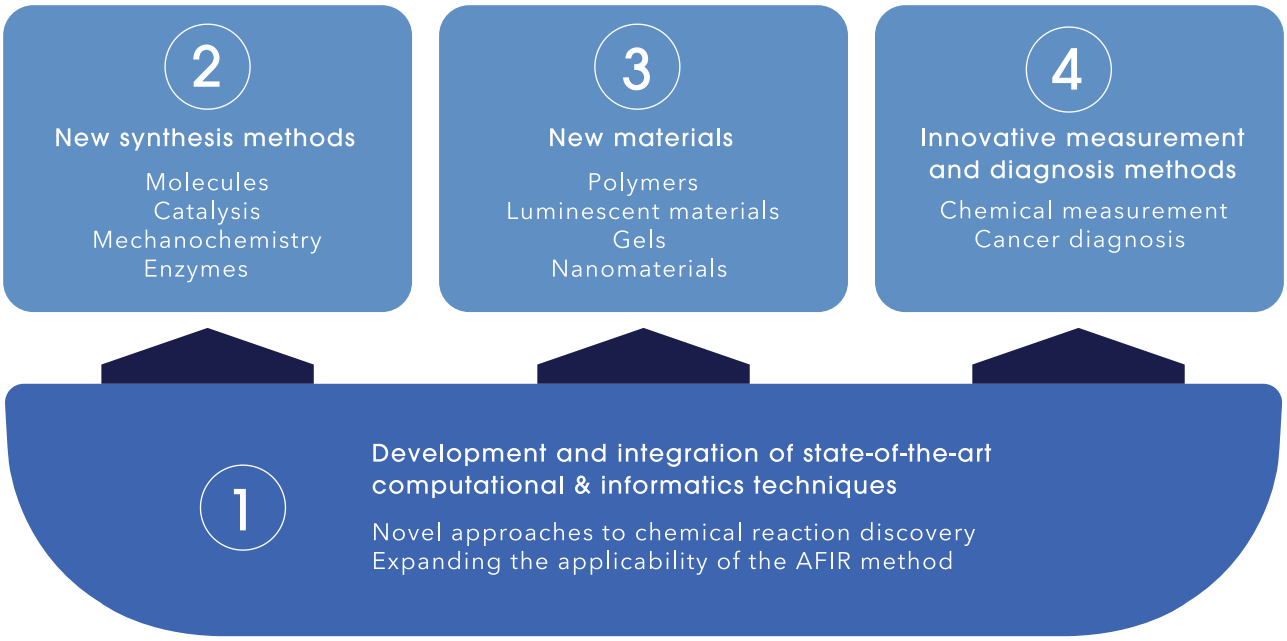
## Researcher support

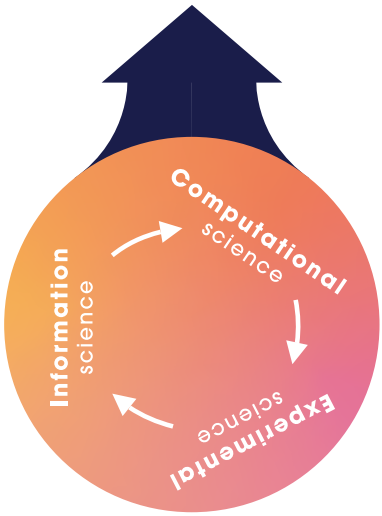
To support newly recruited researchers, we established a start-up funding system and provide guidance for applying for external grants with the aim of helping the newly hired researchers achieve outstanding results during their tenure, and to become prime candidates for faculty and post-doctoral positions at other international research institutions. In addition, we installed a hospitality system to help our international researchers with settling in and with getting a foothold in their daily life in Japan.

## Facilities

The currently developed research space of about 1,400 $m^2$ features an analytical instrument room, a large computer server room, a dry mixed office for researchers with a focus on computational and information science, and two wet mixed labs for those focusing on experimental science. An additional 1,200 $m^2$ of research space was secured with top-down financial support from the university's executive department. ICReDD offers open access to all equipment for cutting-edge research in computational science, information science and experimental science to all of our researchers. Our working spaces are shared to maximize cross-disciplinary communication and knowledge exchange.

# Research areas




The mission of ICReDD is the in-depth understanding and efficient development of chemical reactions through the interdisciplinary research of scientists from computational science, information science, and experimental science. Our aim is to enable humanity to purposefully craft chemical reactions to any design, not to leave the discovery of chemical reactions to serendipity or experience-guided intuition. To vastly accelerate the development of new reactions, we combine scientists from three fields to develop new synthesis methods, new materials, and new applications across all scientific fields. In particular, we have been developing the "Artificial Force-Induced Reaction" (AFIR) method that allows the exploration of the full chemical reaction network to discover unknown paths to desired products. The method can be applied to a wide range of reactions such as organic synthesis reactions, photoreactions, nanoparticle catalysts, heterogeneous catalysts, and phase transition reactions. The huge amount of data produced by the method needs to be managed by advanced information technology methods such as path enumeration, data mining, and machine learning that help to pinpoint promising reaction pathways. This approach is complemented by experimental chemists from a variety of fields who verify the proposed reactions, develop new experimental methods, and find applications.

In our first fiscal year we defined our four main research areas spanning all research groups at ICReDD, and established an interdisciplinary research environment where the expertise of each becomes a resource for the work of the other.

## ICReDD's four main research areas

### Development and integration of state-of-the-art computational & informatics techniques

In the past fiscal year, we developed new computation and informatics technologies for the discovery of new chemical reactions, and found generalizations and accelerations of reaction path search methods.

### Design and discovery of new synthesis methods

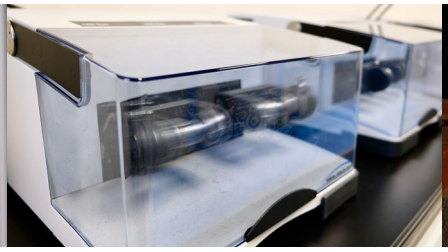
We developed synthetic methods at various levels of chemical complexity. In small-molecule transformations, the dream of quantum chemists to create new chemical synthesis methods from quantum chemical calculations is becoming a reality. We combine quantum chemical calculations and information science techniques to explore new catalytic functions for catalytic chemical reactions. Chemical reactions driven by mechanical stimuli have been analyzed to optimize their design. Finally, we are developing a computational method to screen enzymatic reactions from the process of substrate binding to the chemical transformation at the reaction site.

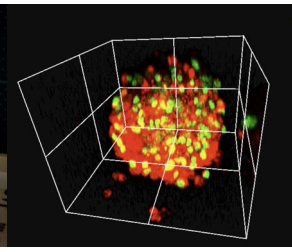
### Design and discovery of new materials

The control over chemical reactions is an essential prerequisite in the production of modern and functional materials. We are currently examining polymeric, luminescent, gel, and nano-materials to understand what kind of computation- and informatics-guided design strategies can be adopted. Among them, we succeeded in designing useful nano-materials with computation-driven approaches and have developed gel materials with a broad diversity of functions, from adhesion in sea water to the re-programming of cellular gene expression.

### Creation of innovative measurement and diagnosis methods

Many measurement technologies are based on a series of chemical reactions. In the past fiscal year, the efforts to develop a cancer stem cell detection and drug discovery kit stand out.



## The research environment at ICReDD

To accelerate the emergence of true fusion research, we established a new mixed office and two new mixed labs, which catalyze spontaneous, every-day scientific communication across disciplines. In these 3 rooms, researchers from the three fields are seated in a mixed fashion. This environment is a strong support in the spirit of our mission for all of the members to integrate the knowledge and skills of each group, which is important to initiate fusion research with new ideas. In addition, we established a range of different seminar series that enable our researchers to learn about each other's expertise and background as well as to discover inspiration and demands for new research approaches.

Over the following pages, we highlight four concrete research developments at ICReDD that exemplify the high standard and interdisciplinary nature of our work.

# Research achievements

Research area:


## The efficient development of an entirely new and useful chemical reaction

Developing deliberately chosen chemical reactions is the main aim of ICReDD. In the past fiscal year the institute demonstrated its ability to do this with the synthesis of α,α-difluoroglycine, a fluorinated amino acid whose increased lipophilicity and reduced degradability make it more bioactive and bioavailable over its natural counterpart. Although it is thus a compound with many promising applications, no efficient synthesis method had been known.

In an exemplary all-ICReDD collaboration between computational chemists Satoshi Maeda and Yu Harabuchi and experimental chemist Tsuyoshi Mita, an appropriate set of starting compounds and reaction paths was found by the newly developed reverse-synthetic AFIR method and then modified from the original computational suggestion with experimental considerations in mind and with computational evaluation of the modifications at each step. They finally arrived at a predicted yield of 99.99% in a single-step reaction of the readily available components $NMe_3$ (a tertiary amine), the $CF_2$ (difluorocarbane) precursor $^-CF_2Br$, and $CO_2$ (carbon dioxide). In the experimental verification, the unstable nature of the product made its isolation the most time-consuming step. However, thanks to the reassurance from the computational prediction, the desired product could finally be synthesized with a high 96% yield and purified after esterification with 80% yield after a total of only 2 months of experimental investigation.

This is a new and useful chemical reaction that could not have been developed conventionally, as the cost and time required for the reaction development as well as the uncertainty of the endeavor often prove prohibitive. However, the input of experimental expertise during the computational prediction and the reassurance of the validity of the experimental approach afforded by the computational prediction allowed the focused and efficient development of this totally new reaction. Therefore, this success is the result of scientific integration possible to this degree only at ICReDD.

Original article
Discovery of a synthesis method of difluoroglycine derivative based on a path generated by quantum chemical calculations
(T Mita, Y Harabuchi, S Maeda: *Chemical Science*, 2020)
DOI: 10.1039/DOSCO2089C

https://www.doi.org/10.1039/DOSCO2089C

# Development of a catalyst for highly specific C–H bond activation

The site-specific, enantioselective activation of C($sp^3$)–H bonds was a longstanding problem in organic synthesis, despite the importance this ability would have for the creation of pharmaceutical, agrochemical, and other chemical products. As a result of the combination of computational and experimental chemistry, ICReDD researchers opened up this door in the past fiscal year by the site-specific and highly enantioselective insertion of a boryl moiety in the place of such a methylene C–H bond in hydrocarbon chains.

The researchers in the Sawamura and Maeda groups created an Ir-BINOL-based monophosphite catalytic system and analyzed the enantioselectivity of the reaction using quantum chemical calculations, revealing that a narrow chiral reaction pocket in the catalyst is responsible for the differentiation between otherwise equivalent C–H bonds. This insight also enabled them to establish a highly enantioselective borylation protocol for N-adjacent C($sp^3$)–H bonds, giving them access to chiral α-aminoboronates, a significant class of bioactive isostructural boron analogues of amino acids. As an immediate practical outcome, this protocol allows the remarkably streamlined synthesis of the anticancer drug bortezomib. More fundamentally, these developments are the foundation for the creation of synthetic modular catalysts for the activation of remote C–H bonds, affording a degree of control over chemical reactions usually restricted to biological enzymatic systems.

The control over chemical reactions in many cases requires the use of an appropriate or even custom-designed catalyst, which makes the design of specific catalysts a central endeavor within ICReDD. However, the ability to tailor a synthetic catalyst to a targeted chemical reaction depends much on both the experimental ability to produce various catalytic systems as well as on our mechanistic understanding of the function of the catalyst, and thus on a concerted combination of experimental expertise and quantum chemical calculations as can only be realized at ICReDD.

Original article
Iridium-Catalyzed Asymmetric Borylation of Unactivated Methylene C($sp^3$)–H Bonds
(R Reyes *et al.*: *JACS*, 2019)
DOI: 10.1021/jacs.9b01952

https://www.doi.org/10.1021/jacs.9b01952

Research area:

Research area:


## Creating a material to prevent cancer recurrence

Cancer tissues often harbor cancer stem cells that are not affected by conventional anti-cancer treatments, which is the cause for cancer recurrence and a major hurdle in the complete eradication of cancers. At the same time, these stem cells are specific to each patient and their destruction requires the application of individualized drugs. In the past fiscal year ICReDD researchers at the Gong and Tanaka groups developed a double-network hydrogel consisting of PAMS and PDMAAm that was able to induce stem cell formation within 24 hours in all cancer tissues cultivated on it. Researchers working at both groups characterized the physical and chemical properties of the gels that induce the formation of cancer stem cells and thus became able to control the gene expression patterns of the cancer cells through the properties of the substrate. This paves the way for the establishment of the new research field of "material genomics".

The immediate consequence of this discovery is that these gels provide a testing ground for finding drugs that are able to target these stem cells specifically, which is an ongoing research project with ICReDD researchers at the Komatsuzaki group. Together, these developments are part of the effort to create a cancer stem cell detection and drug discovery kit with the prospect of dramatically increasing the 5-year survival rate of cancer patients, especially of those with a currently very low survival rate such as glioblastoma patients (10% 5-year survival rate compared to 65% for all cancer patients).

This highly promising research was only possible in consequence of the interdisciplinary human connections at ICReDD. The spatial proximity of researchers of different fields fosters interactions seeding breakthrough research, but also serves to broaden the horizons of the researchers by introducing them to results and methods far removed from their conventional work.

Original article
Modulation and Characterization of the Double Network Hydrogel Surface-Bulk Transition
(M Frauenlob *et al.*: *Macromolecules*, 2019)
DOI: 10.1021/acs.macromol.9b01399

https://www.doi.org/10.1021/acs.macromol.9b01399

# Machine Learning for chemical reaction discovery

Both computational and experimental chemists have amassed an unsurveyable amount of data. Information scientists at ICReDD have developed Machine Learning techniques to enable researchers to discover patterns and thus new possibilities in the existing treasure trove of data.

While Machine Learning algorithms have been used to predict chemical structures in form of SMILES strings with desired properties, the computational handling of chemical reactions has hitherto been challenging because they usually involve several reactants and products. ICReDD researchers in the Varnek group have applied the concept of Condensed Graphs of Reactions, that can capture the whole reaction in a single pseudo-molecule, to develop reaction-specific SMILES/CGR strings. In the past fiscal year the researchers succeeded in training a neural network on the reactions extracted from the United States patent database, and targeting Suzuki reactions in particular, they could find more than 400 new reactions with unknown reaction centers, as well as 30 new reactions with an unknown first environment of the reaction center. Together, they point the way to exploring feasible but completely unknown, new chemical reactions.

The researchers are now working on improving the feasibility check of their algorithms using both quantum chemical computations and the expertise of ICReDD's experimentalists, as well as improving the success rate of the algorithm together with the Machine Learning experts of the institute. Other current efforts to improve the ICReDD ecosystem include the development of a database enabling rapid search by substructures or similarity in the mass of AFIR-generated reactions, and of quantitative models that can predict the enantioselectivity of organic catalysts. The speed of the development of highly useful data science tools for the development of chemical reactions is possible only at ICReDD, where scientists from different fields work together on the same challenges and can thus benefit from each other's expertise.

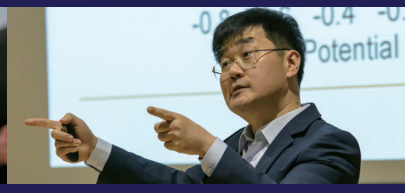
Original article
Discovery of Novel Chemical Reactions by Deep Generative Recurrent Neural Network
(P Sidorov *et al.*: *ChemRxiv*, 2020)
DOI: 10.26434/chemrxiv.11635929.v1

https://www.doi.org/10.26434/chemrxiv.11635929.v1

Research area:

# International symposium

## The future is here


Under the motto "Toward Interdisciplinary Research Guided by Theory and Calculation", ICReDD hosted its 2nd International Symposium in Sapporo from November 27 until November 29.

The speakers from fields as varied as synthetic chemistry, photochemistry, computational chemistry, and information science were united in asking the question: "How can computational chemistry inform experimental practice?"

Synthetic chemist Professor Andrei Yudin from the University of Toronto acknowledged: "There is a huge potential for computation and theoretical prediction," while Professor Djamaladdin Musaev from Emory University, who specializes in the design of highly active catalysts with the help of computation, phrased it like this: "You have to use computation and experiments together. We have to be not experimentalists or 'computationalists', but scientists!" And electrochemist Professor Mu-Hyun Baik from the Korean Advanced Institute of Science and Technology even went as far as to ask the question how computational chemists would design chemical experiments to get fully controllable, theory-guided experimental conditions, stating: "Computational chemistry will lead experimentalists to new concepts in chemical reactions."

We also held a poster session where young scientists took center stage and an introduction to the AFIR method by ICReDD Director Professor Satoshi Maeda.

One audience member asked: "When in the future will theory finally take the lead in chemistry and lead to predictions of unknown chemical reactions?" Various lecturers answered to this with: *"The future is here."* Experimentalists already include computational techniques to various degrees as standard tools in their every-day work, and computational chemists as well as information scientists have long grown past merely rationalizing chemical reactions to influencing experimental designs and predicting new ones based on calculation and data interpretation. ICReDD, then, is the manifestation of the emergence of an integrated, theory-led chemistry.

We are grateful to all speakers and attendees for making this symposium a lively discussion! Thank you for leaving us with exciting questions to expand our research together with our newfound friends!

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including the 2019 Commendation for Science and Technology by MEXT: Prizes for Science and Technology

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87

4 in journals with IF≥20;
14 in journals with 20>IF≥10

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2

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TV 4

newspapers 10

scientific journal feature 1

magazines 3

online news 29

external pamphlets 2


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