別紙様式３

学業及び研究等の進捗状況等報告書
Report of Research Progress and Future Research Plan

※ 本報告書は「4.指導教員からのコメント」を除き、北海道大学私費留学生特待プログラム」の HP に掲載します。（https://www.oia.hokudai.ac.jp/cier/own-scholarship/）
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氏名 Name	朱浩傑	学　年 Year	D3
所属学院等名 Graduate School	総合化学院		
所 属 専 攻 名 Major	総合化学		
所属研究室等名 Laboratory	構造化学研究室		
指導教員職・氏名 Supervisor	教授・石森浩一郎		

１．研究テーマ名 Research theme

Structural basis for the cooperative function of trigger factor–ClpX chaperone complex in protein unwinding

２．研究等の進捗状況等 Research progress, etc.

研究の概要、独創性、状況等を含めて具体的に記入のこと。

[Research]

In *E.coli*, a molecular chaperone, TF, consisting of three domains, TF^{RBD}, TF^{PPD}, and TF^{SBD}, is a ribosome-associated chaperone and plays important roles in the protein synthesis, facilitating folding and translocation of the newly synthesized proteins$^{(1)}$. On the other hand, misfolded or denatured proteins are unfolded by an ATP-dependent chaperone ClpX which consists of ClpX^{ZBD} and ClpX^{AAA}, and then degraded by ClpP protease$^{(2)}$. Recently, it was reported that misfolded substrates can be more efficiently unfolded by the direct interaction between TF and ClpX$^{(3)}$. However, how the TF-ClpX interaction accelerates the unfolding of substrates remains unclear. We used NMR titration experiments to investigate the TF-ClpX interaction and NOE experiments to examine the structure of the TF^{SBD}-ClpX^{ZBD} complex. The NMR titration experiments showed that the TF binding to ClpX is an ATP-dependent manner. The TF^{SBD}-ClpX^{ZBD} structure suggests that substrates are translocated from TF to ClpX, because the substrate binding sites on TF^{SBD} are occupied by ClpX^{ZBD} and the substrate binding sites on ClpX^{ZBD} are still exposed in the TF^{SBD}-ClpX^{ZBD} copmplex. Based on the TF-ClpX interaction pattern and the structural information, the models (Fig. 1) of the TF-ClpX complex were visualized by molecular docking for better understanding of the mechanism for the TF-ClpX interaction in the substrate unwinding. In the presence of ATP, the TF^{RBD} domain binds to the nucleotide-free ClpX^{AAA} subunit, while TF^{SBD} binds to ClpX^{ZBD}. The combination of TF^{SBD} and ClpX^{ZBD} induces the substrate translocation. When ATP was hydrolyzed, substrate-load ClpX^{ZBD} was released from TF^{SBD}, and TF^{SBD} as well as TF^{PPD} are expected to bind to the multiple ADP-bound ClpX^{AAA} subunits.

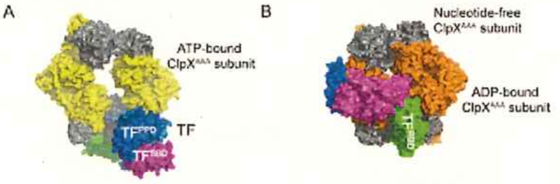

Fig. 1 The calculated models of TF-ClpX complex in the presence of ATP (A) and ADP (B).

(1) Hoffmann, A., et al., *Mol. Cell Res.*, **1803**, 6, 650-661 (2010). (2) Glynn, S.E., et al., *Cell*, **139**, 4, 744-756 (2009). (3) Kamran, R., et al., *Nat Commun.*, **12**, 1-18 (2021).

[Published paper]

K. Rizzolo, A. Y. H. Yu, A. Ologbenla, S. R. Kim, H. Zhu, K. Ishimori, G. Thibault, E. Leung, Y. W. Zhang, M. Teng, M. Haniszewski, N. Miah, S. Phanse, Z. Minic, S. Lee, J. D. Caballero, M. Babu, F. T. F. Tsai, T. Saio, W. A. Houry, Functional cooperativity between the trigger factor chaperone and the ClpXP proteolytic complex. Nat. Commun. 12, 1–18 (2021).

３．今後の研究計画等 Future research plan

現在までの進捗状況等を踏まえ、今後の研究発表等を含めて具体的に記入のこと。

Verification the substrate translocation between TF and ClpX

Because the substrate binding sites on TF^{SBD} are overlapped with ClpX^{ZBD} and the substrate binding sites on ClpX^{ZBD} are still exposed even in the TF^{SBD}-ClpX^{ZBD} complex, we proposed that substrates are released from TF^{SBD} and then captured by ClpX^{ZBD} in the TF^{SBD}-ClpX^{ZBD} complex. To verify this hypothesis, we plan to perform the NMR titration experiments for the protein complex consisting of ^{15}N-labeled PhoA, non-labeled TF^{SBD}, and non-labeled ClpX^{ZBD}. The addition of TF^{SBD} is expected to induce the resonance perturbations of ^{15}N-labeled PhoA, because PhoA is a substrate of TF. After the addition of TF^{SBD}, non-labeled ClpX^{ZBD} will be titrated. Because ClpX^{ZBD} and substrates compete to binds to TF^{SBD}, some of TF^{SBD} molecules binds to ClpX^{ZBD}, and thus some of PhoA molecules are expected to be released from TF^{SBD}, inducing the perturbed resonance of PhoA.

[To be submitted paper]

Haojie Zhu, Hiroyuki Kumeta, Kamran Rizzolo, Walid A. Houry, Koichiro Ishimori, and Tomohide Saio, Structural basis for cooperative function of trigger factor-ClpX chaperone complex in protein unwinding.

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氏名 Name	金　容俊	学　年 Year	D3
所属学院等名 Graduate School	総合化学院		
所属専攻名 Major	総合化学		
所属研究室等名 Laboratory	有機金属化学研究室		
指導教員職・氏名 Supervisor	澤村　正也		

１．研究テーマ名 Research theme

Design, Synthesis and Application of Dumbbell-Shaped Bipyridines as Ligands for Transition Metal Catalysis

２．研究等の進捗状況等 Research progress, etc.

研究の概要、独創性、状況等を含めて具体的に記入のこと。

※研究成果の発表・公表実績がある場合については学会名、掲載紙等の情報を含め詳細を記載すること

2,2'-Bipyridine (bpy) has been established as a prime ligand scaffold for Ni catalysis involving a single-electron redox process, which enables novel molecular transformations. In these Ni-bpy catalyses, catalytically active species are likely to be in the form of bpy-monochelated Ni complexes [Ni(bpy)], but dynamic coordination equilibria perturb the number of bpy ligands on the Ni atom. These coordination behavior may lead to a decrease in catalytic efficiency. I envisioned that distal steric effects of bpy C5 and C5'-substituents, which do not hamper the catalytic reactions by steric hindrance in the vicinity of the metal but develop outside the boundary of the catalytic space to allow selective monochelation to the metal center, could be an effective approach to improve the efficiency of the Ni catalysis.

I have reported the synthesis of a new class of 2,2'-bipyridine ligands (dsbpys) having dumbbell-like shapes with differently substituted triarylmethyl groups at the C5 and C5' positions and their applications as favorable ligands for the Ni-catalyzed cross-electrophile coupling and the Ni/photoredox-synergistically catalyzed decarboxylative coupling. Analysis of metal coordination behaviors of the bpy ligands by UV-vis absorption spectroscopy indicated the apparent monochelating nature of the dumbbell-shaped bpy ligands.

３．今後の研究計画等 Future research plan

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In detail, based on current progress, including a future research presentation plan.

In the future, the application of the dsbpys will be studied. I especially focus on catalytic applications. For example, application of the dsbpys in Ru, Ir, Fe, Pd catalysis are of highest interest.

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氏名 Name	馮智	学　年 Year	D３
所属学院等名 Graduate School	総合化学院		
所属専攻名 Major	総合化学専攻		
所属研究室等名 Laboratory	応用生物化学研究室		
指導教員職・氏名 Supervisor	大利　徹		

１．研究テーマ名 Research theme

Investigation of a Novel Epimerase in the Biosynthesis of a D-Tryptophan-Containing Lasso Peptide, MS-271

２．研究等の進捗状況等 Research progress, etc.

研究の概要、独創性、状況等を含めて具体的に記入のこと。
※研究成果の発表・公表実績がある場合については学会名、掲載紙等の情報を含め詳細を記載すること
In detail, including the outline, originality and so on.
*Please state the name of academic conferences, journals or transactions if you have presented your research or your research was published.

MS-271, produced by *Streptomyces* sp. M-271, is a lasso peptide natural product comprising 21 amino acid residues with a D-tryptophan (D-Trp) at its C terminus. Because lasso peptides are ribosomal peptides, the biosynthesis of MS-271, especially the mechanism of D-Trp introduction, is of great interest. Analysis of the MS-271 biosynthetic gene cluster (*msl*) revealed that the precursor peptide (MslA) contains all 21 amino acid residues of MS-271 including the C-terminal tryptophan. This suggested that the D-Trp residue is introduced by epimerization. Besides *mslA*, the cluster also contained gene for a macrolactam synthetase (*mslC*), precursor peptide recognition element (*mslB1*), cysteine protease (*mslB2*), disulfide oxidoreductases (*mslE*, *mslF*), and a protein of unknown function (*mslH*). I previously showed that the *msl* cluster contained all the necessary genes for MS-271 production, including a gene for a new peptide epimerase. Because it lacked obvious candidate genes for the epimerization of the tryptophan residue and MslH is a sole enzyme with unknown function, I speculated that MslH is responsible for the epimerization of the C-terminal Trp.

To test this hypothesis, I expressed *mslA* in the presence and absence of *mslH* and the chirality of the Trp residue in MslA was analyzed by modified Marfey's method. As the results, the formation of D-Trp was observed only when *mslH* was co-expressed with *mslA*. The MslH activity was also revealed by *in vitro* experiments using recombinant proteins. These results clearly demonstrated that MslH is a novel peptide epimerase that catalyzes the epimerization of the C-terminal Trp of the precursor peptide, MslA. Furthermore, I investigated the substrate receptivity of the modification enzymes, including MslH. Using the previously constructed MS-271 heterologous production system in *Streptomyces lividans*, I carried out heterologous expression of the *msl* cluster to produce MS-271 derivatives by altering the core peptide region of the *mslA* gene. After cultivation, production of MS-271 derivatives was successfully observed by LC-MS analysis and their C-terminal amino acids were determined as D configuration. As a result, I demonstrated that MslH had a broad substrate specificity toward the N-terminal region of the core peptide, which is potentially useful in peptide bioengineering.

学会発表

- Biosynthetic gene cluster of a D-Trp-containing lasso peptide, MS-271, Zhi Feng, Yasushi Ogasawara, Satoshi Nomura, Tohru Dairi. 第33回日本放線菌学会大会　2018年9月11~12日 武蔵野大学有明キャンパス

- Biosynthetic gene cluster of a D-Trp-containing lasso peptide, MS-271, Zhi Feng, Yasushi Ogasawara, Satoshi Nomura, Tohru Dairi. 日本農芸化学会 2019年度大会 2019年3月24~27日 東京農業大学世田谷キャンパス
- Biosynthetic gene cluster a D-Trp-containing lasso peptide, MS-271, Zhi Feng, Yasushi Ogasawara, Satoshi Nomura, Tohru Dairi. 2019 Cold Spring Harbor Asia Conference Chemical biology & Drug discovery, October 28-November 1, 2019, Suzhou, Jiangsu Province, China.
- Identification of the peptide epimerase MslH responsible D-amino acid introduction at the C-terminus of ribosomal peptides, Zhi Feng, Yasushi Ogasawara, Satoshi Nomura, Tohru Dairi. 2020年度日本農芸化学会北海道支部 2020年12月12~13日 札幌
- Identification of the peptide epimerase MslH responsible D-amino acid introduction at the C-terminus of ribosomal peptides, Zhi Feng, Yasushi Ogasawara, Satoshi Nomura, Tohru Dairi. 日本農芸化学会 2021年度大会 2021年3月18~21日 仙台

論文

- Zhi FENG *et. al.* Biosynthetic gene cluster of a D-tryptophan-containing lasso peptide, MS-271. *ChemBioChem* **2018**, *19*, 2045. (表紙絵にも採択)
- Zhi FENG *et. al.* Identification of the peptide epimerase MslH responsible for D-amino acid introduction at the C-terminus of ribosomal peptides. *Chem. Sci.* **2021**, *12*, 2567.

３．今後の研究計画等 Future research plan

現在までの進捗状況等を踏まえ、今後の研究発表等を含めて具体的に記入のこと。

In detail, based on current progress, including a future research presentation plan.

なし

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氏名 Name	Christida Estu Wastika	学 年 Year	D4
所属学院等名 Graduate School	Graduate School of Infectious Diseases		
所属専攻名 Major	Infectious Diseases		
所属研究室等名 Laboratory	Division of Molecular Pathobiology		
指導教員職・氏名 Supervisor	Prof. Hirofumi Sawa		

１．研究テーマ名 Research theme

Surveillance of arbovirus infection in Zambia and characterization of the untranslated regions of insect-specific flaviviruses

２．研究等の進捗状況等 Research progress, etc.

研究の概要、独創性、状況等を含めて具体的に記入のこと。
※研究成果の発表・公表実績がある場合については学会名、掲載紙等の情報を含め詳細を記載すること
In detail, including the outline, originality and so on.
*Please state the name of academic conferences, journals or transactions if you have presented your research or your research was published.

This semester, I summarized my research activities as a dissertation document and presented the dissertation to my advisors and public. I have got several questions related to arbovirus infection in nonhuman-primates, secondary structure of the untranslated regions of flaviviruses and their function during virus infection. At the end of the final discussion, I could address most of the questions. Finally, I could pass the dissertation screening process and graduated on May 25th, 2021.

３．今後の研究計画等 Future research plan

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In detail, based on current progress, including a future research presentation plan.

I will continue my research activity as a Post-Doctoral Research Associate (PDRA) at Liverpool School of Tropical Medicine, Liverpool, UK.

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氏名 Name	Xinluona Su	学　年 Year	D3
所属学院等名 Graduate School	Graduate School of Chemical Sciences and Engineering		
所属専攻名 Major	Chemical Sciences and Engineering division		
所属研究室等名 Laboratory	Chemical System Engineering		
指導教員職・氏名 Supervisor	Prof. Takao Masuda		

１．研究テーマ名 Research theme

Diffusion Mechanism of Hydrocarbons within Porous Materials in liquid, Sub-, and Super-Critical Fluids

２．研究等の進捗状況等 Research progress, etc.

研究の概要、独創性、状況等を含めて具体的に記入のこと。

※研究成果の発表・公表実績がある場合については学会名、掲載紙等の情報を含め詳細を記載すること

In detail, including the outline, originality and so on.

*Please state the name of academic conferences, journals or transactions if you have presented your research or your research was published.

Research meaning: Porous materials such as zeolite catalysts are crystalline alumino-silicate with ultra-fine nano-pores, the diameters of which are almost the same as those of minimum molecular diameters of lighter hydrocarbons. Therefore, the catalysts show unique catalysis caused by molecular sieving effect, and are widely used in the field of petrochemical processes. Understanding diffusion mechanisms of molecules in the catalysts are very important for understanding, since the degree of the diffusion limitations are observed differently by depending on molecular size and circumstance around the catalysts, such as gas, liquid, sub-critical and supercritical fluids. The information of the diffusion coefficient enables to analyze apparent reaction rate of zeolites and help to design the catalyst. Many research works have been reported, concerning hydrocarbons diffusivity within zeolites in vapor phase and liquid phase. Our group also reported the intracrystalline diffusivity of toluene, benzene and lighter hydrocarbons within MFI zeolites in the gas phase. In addition, researchers have also reported using different experimental methods (NMR, constant volumetric method, zero-length column and so on.) for measuring intracrystalline diffusivity within MFI-type zeolite in the liquid phase.

Originality: Although there are many important solid-liquid (vapor-liquid-solid) reaction systems with solid catalysts under high temperature and high-pressure condition such as heavy oil cracking, diffusivity of hydrocarbons within porous materials in liquid has few reported and in sub- and super-critical fluids have not been reported.

Research contents: In this study, measurement the diffusivity of hydrocarbons within porous materials (MFI-type and Y-type zeolites, etc.) in liquid, sub- and super-critical fluids of solvents by a constant volumetric method using Raman spectroscopy, and clarifies the diffusion mechanisms.

Published paper

(1) Xinluona Su, Yuta Nakasaka*, Ren Moriwaki, Takuya Yoshikawa, Takao Masuda, "Diffusion of phenolic compounds within high-silica MFI-type zeolite in the mesitylene solution" **Microporous Mesoporous Mater**, 2021. (just received)

Academic conferences

(1) Xinluona Su, Yuta Nakasaka *, Ryo Nakano, Yoshihiro Kubota, Satoshi Inagaki, Takao Masuda, "Measurement of Intracrystalline Diffusivity of Toluene within Silicalite-1 and K-ZSM-5 in Sub- and Super-critical Fluids" **APCChE 2019**, 23rd-27th/09/2019, Sapporo, Japan. (Presentation)

(2)Xinluona Su, Yuta Nakasaka *, Ryo Nakano, Yoshihiro Kubota, Satoshi Inagaki, Takao Masuda, "Diffusion of Toluene within Silicalite-1 and K-ZSM-5 in Sub- and Super-critical Fluids of cyclopentane" **International symposium on porous materials,** 17th-19th/11/2019,Tokyo, Japan. (Poster)

３．今後の研究計画等 Future research plan

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In detail, based on current progress, including a future research presentation plan.

In the future, diffusivity of phenol and toluene within Y-type zeolites will be measured in liquid of mesitylene, cyclopentane and cyclohexane and compared with MFI-type zeolites. If there is more time, find a solvent with a relatively low critical temperature and pressure such as CO_2.

- ✓ Diffusivity of phenol and toluene within Y-type zeolites will be measured in liquid of mesitylene, cyclopentane and cyclohexane: From March to May, 2021.
- ✓ Developed a device to using the sub- and super-critical fluids of CO_2 and explore effect of CO_2 pressure, pore size and Si/Al ratio of zeolites on diffusivity will be discussed: From June to August, 2021.
- ✓ Summary of results obtained and write a research papers. After modification publish the research papers: From March to August, 2021.
- ✓ Writing the dissertstion: From May to August, 2021.

Will be published:

1.Measurement of diffusivity of hydrocarbon within Silicalite-1, K-ZSM-5 and K-Y in Sub- and Super-critical Fluids.

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氏名 Name	Wiyanti Fransisca Simanullang	学年 Year	3
所属学院等名 Graduate School	Graduate School of Chemical Science and Engineering		
所属専攻名 Major	Chemical Science and Engineering Division		
所属研究室等名 Laboratory	Shimizu Laboratory		
指導教員職・氏名 Supervisor	Associate Professor Shinya Furukawa		

1．研究テーマ名 Research theme

Developing highly active noble-metal alternative catalysts using surface modification method for hydrogenation/dehydrogenation reactions.

２．研究等の進捗状況等 Research progress, etc.

研究の概要、独創性、状況等を含めて具体的に記入のこと。

※研究成果の発表･公表実績がある場合については学会名、掲載紙等の情報を含め詳細を記載すること

In detail, including the outline, originality and so on.

*Please state the name of academic conferences, journals or transactions if you have presented your research or your research was published.

In these past few years, we have been successfully synthesized the highly active Ni-based catalysts as noble-metal alternative catalysts by dealloying Ni-Si intermetallic compounds (IMCs). In this study, we applied “surface dealloying” methodology to a series of Ni-based IMCs that only surface structure was chemically modified whereas the bulk structure was retained. We discovered that some Ni-Si IMCs treated with a diluted aqueous solution of hydrofluoric acid (HF) exhibited outstanding catalytic performances in the hydrogenation of unsaturated hydrocarbons.
This work was already published in The Royal Society of Chemistry, Chem.Commun.,2019,55,13999 and in American Chemistry Society, Inorg.Chem.2019,58,5406-5409.

Next, we developed the Ni-based catalysts supported on silica with silicon decoration using a simple impregnation method to obtain Ni species embedded in silica matrix. We found that Si-decorated Ni exhibited an outstanding performance over (de)hydrogenation of aromatic compounds up to 50 times higher in conversion and TOF than the standard Ni/SiO_2. Silica decoration on Ni supported silica increases the number of its step active site without lowering the activation energy.
This work was already published in The European Chemical Societies Publishing, ChemCatChem, 2021, 13, 1306-1310.

We then applied the silica-decoration methodology to NiZn alloy system to confirm that this method is applicable to Ni-based alloys as well as monometallic Ni. As a target reaction for Ni-based alloy, I focused on acetylene semi hydrogenation to ethylene. As a result, silica decoration increases the activity of NiZn on silica support (95% conversion) without lowering its selectivity (89% ethylene). We are currently working on the paper resubmission.

3．今後の研究計画等 Future research plan

現在までの進捗状況等を踏まえ、今後の研究発表等を含めて具体的に記入のこと。
In detail, based on current progress, including a future research presentation plan.

Currently, I am applying for researcher position in one of the research institute in my home country. I would like to develop silica decoration method on Ni alloy system with some other second metals. In the future, I am testing silica decoration on Ni-based supported on silica catalysts performance over hydrodeoxygenation reaction for green diesel production.