10th Joint RSC-CSJ Symposium :
Chemistry for Complex Biological Systems

ROYAL SOCIETY OF CHEMISTRY

CSJ

September 7th, 2019
Tohoku University, Sendai, Japan

Welcome Address from CSJ President

Dear Colleagues,

Welcome to our 10th Joint CSJ RSC Symposium on "*Chemistry for Complex Biological Systems*".

This RSC-CSJ symposium is held every year based on our international cooperation agreement between the Royal Society of Chemistry; RSC and the Chemical Society of Japan; CSJ concluded in July 2010 to further our closer and personal relationship. So far, this symposium has been held as one of the international events on the sidelines of the CSJ Annual Meeting.

This year, our joint symposium celebrates its 10th running in total. In commemoration of this milestone, we try to make a new attempt. We decided to cooperate with "The 13th symposium on Biorelevant Chemistry" organized by two of CSJ Divisions (Division of Biofunctional Chemistry and Division of Biotechnology) and a grant-aided academic group titled "Chemistry for Multimolecular Crowding Biosystems". Prof. Hamachi, the leader of this academic group supported by MEXT gave a special consideration to provide a better experience for all of participants from the planning stage. The purpose of this group is to establish a new chemical approach for functional analysis and artificial regulation of biological molecules residing in crowded biosystems. Hence, we set the theme for this RSC-CSJ symposium as "Chemistry for Complex Biological Systems" after due deliberation. We also carefully selected 10 promising young researchers both from the UK and Japan, who have been derived from this cutting-edge field.

Additionally, we invited 33 active Japanese researchers in this specific area to participate in our symposium. It is also the first challenge to ask all participants to give a flush presentation as well as poster session to develop the deep and warm personal relationship with each other.

I would like to thank Professors John Brazier and Shigeki Kiyonaka for bringing in excellent people to the symposium. I believe this opportunity to sit together at the same table will provide a meaningful chance for sustainable collaboration between both countries.

Professor Maki Kawai
President of Chemical Society of Japan

Welcome Address from RSC President

Dear Colleagues,

It is my pleasure to welcome you to the 10th UK-Japan Symposium, celebrating a decade of this series of events jointly held by our valued partner the Chemical Society of Japan and the Royal Society of Chemistry.

We have worked closely with the Chemical Society of Japan for a number of years to support scientific collaboration and exchange between our two countries. In 2010 we formalised our relationship by signing an international cooperation agreement, which we renewed in 2015.

Interdisciplinary science and collaboration across borders are essential elements of successful scientific progress. Our theme for this joint symposium – chemistry for complex biological systems – will support and take advantage of both of those elements.

We hope that the presentations from our Japanese and UK speakers will stimulate the exchange of ideas and experiences between all participants and we thank each of the speakers and all the participants for their contributions to this symposium.

We particularly give thanks to Professor Shigeki Kiyonaka of Nagoya University and Professor Itaru Hamachi of Kyoto University, for their pivotal role in enabling this symposium.

Once again a very warm welcome to what promises to be an exciting scientific event. I hope that today offers yet more opportunities to build relationships and find new opportunities for researchers from the UK and Japan to collaborate on this important topic.

I wish you all an informative, productive and enjoyable day.

Professor Dame Carol Robinson
President, Royal Society of Chemistry

10th RSC-CSJ Joint Symposium
- Chemistry for Complex Biological Systems -

September 7th, 2019

Tohoku University, Sendai, Japan

9:00 - 09:10 Opening remarks
From the Chemical Society of Japan: Itaru Hamachi, Kyoto University
From the Royal Society of Chemistry: Stephen Rumbelow, Royal Society of Chemistry

(Chair: Shinya Tsukiji, Nagoya Institute of Technology)

9:10 - 09:45 **[JP1]** Shigeki Kiyonaka (Nagoya University)
New Chemogenetic Approaches for Artificially Controlling Neurotransmitter Receptor Function in Neuronal System

9:45 - 10:20 **[UK1]** Martin Fascione (University of York)
Organocatalyst-mediated Bioconjugation of Proteins

10:20 - 10:35 Break

(Chair: Hiroshi Murakami, Nagoya University)

10:35 - 11:10 **[JP2]** Yuki Goto (The University of Tokyo)
Artificial In Vitro Biosynthesis for Elaboration of Pseudo-natural Peptides

11:10 - 11:45 **[UK2]** Yu-Hsuan Tsai (Cardiff University)
Using Genetically Incorporated Unnatural Amino Acids to Study and Control Protein Function

11:45 - 12:20 One-min flash talk for poster presentation (31 presenters)

12:20 - 14:20 Lunch & Poster

(Chair: Shinsuke Sando, The University of Tokyo)

14:20 - 14:55 **[JP3]** Shinya Hagihara (RIKEN)
Dissection of Plant Hormone Signaling with Synthetic Molecules

14:55 - 15:30 **[UK3]** Rebecca Goss (University of St Andrews)
Blending Synthetic Chemistry with Synthetic Biology in vivo to Enable Access to New to Nature Natural Products

15:30 - 15:45 Break

(Chair: Moritoshi Sato, The University of Tokyo)

15:45 - 16:20 **[JP4]** Kenjiro Hanaoka (The University of Tokyo)
Construction of a Library of Asymmetric Si-rhodamine Fluorophores and its Application to Ratiometric Fluorescence Probes for pH

16:20 - 16:55 **[UK4]** Akane Kawamura (University of Oxford)
Development of Chemical Tools for Epigenetic Proteins

16:55 - 17:10 Break

(Chair: Hirohide Saito, Kyoto University)

17:10 - 17:45 **[JP5]** Hisae Tateishi-Karimata (Konan University)
Role for G-quadruplexes of Nucleic Acids During Tumor Progression

17:45 - 18:20 **[UK5]** John Brazier (University of Reading)
Expanding The i-motif – Why Does Sequence Matter?

18:20 - 18:30 Closing remarks
Shigeki Kiyonaka, Nagoya University
John Brazier, University of Reading

10th RSC-CSJ Joint Symposium is jointly sponsored by the Institute of Multidisciplinary Research for Advanced Materials; Tohoku University (IMRAM, or Tagen-Ken in Japanese) and Chemistry for Multi-Molecular Crowding Biosytems; MEXT Grant-in-Aid for Scientific Research on Innovative Areas FY2017-2021

Titles for Poster Presentations (in alphabetical order)

Speaker (Family-name-first)	Affiliation	Title of the Poster Presentation
ENDOH, Tamaki	Konan University	RNA-capturing Microsphere Particles (R-CAMPs) for Optimization of Functional RNAs
FUJIEDA, Nobutaka	Osaka Prefecture University	Artificial Metalloenzymes Bearing a Small Barrel Protein
FUJITA, Daishi	Kyoto University	Protein Stabilization and Refolding in a Chaperonin-inspired Synthetic Cage
HAYASHI, Gosuke	Nagoya University	Cysteinylprolyl Imide (CPI) Crypto-thioester for Chemical Protein Synthesis
HIRAYAMA, Tasuku	Gifu Pharmaceutical University	Development of Fluorescent Probes of Subcellular Labile Fe(II)
HORI, Yuichiro	Osaka University	Fluorogen/Protein Hybrid Probes for Detection of RNA Methylation
IMANISHI, Miki	Kyoto University	A Simple Screening System for Inhibitors of m6A-Regulatory Enzymes
INABA, Hiroshi	Tottori University	Modulation of Microtubules by Peptide-based Encapsulation of Nanostructures
ITOH, Yukihiro	Kyoto Prefectural University of Medicine	Identification of a KDM5C Inhibitor and Its Biological Evaluation
KATSUDA, Yousuke	Kumamoto University	Development of a Novel Tool to Regulate Gene Expression Level by Short Nucleic Acid
KISHIMURA, Akihiro	Kyushu University	Control of The Formation Process of Polypeptide Self-assemblies for Understanding Complex Biological Systems: From Nano-physiology to Artificial Cells
KOMATSU, Toru	The University of Tokyo	Establishment of Enzymomics Approach to Screen Disease-related Alternation of Enzymatic Functions
MIZUKAMI, Shin	Tohoku University	Development of Chemical Probes for Investigating Biomolucular Dynamics in Living Cells
MURAKAMI, Hiroshi	Nagoya University	TRAP Display for Selection of Synthetic Antibodies
MURAOKA, Takahiro	Tokyo University of Agriculture and Technology	Synthetic Promotors of Oxidative Protein Folding
NAGATOISHI Satoru	The University of Tokyo	Biophysics of the Protein-ligand Interactions to Regulate the Protein Functions

Speaker (Family-name-first)	Affiliation	Title of the Poster Presentation
NAKASE, Ikuhiko	Osaka Prefecture University	Biofunctional Peptide-modified Exosomes for Intracellular Delivery
NAKATA, Eiji	Kyoto University	DNA Binding Adaptors to Locate Multiple Enzymes on DNA Scaffold
SAITO, Hirohide	Kyoto University	Synthetic RNA Technologies to Program Cells
SANDO, Shinsuke	The University of Tokyo	Molecular Technologies to Control Cellular Functions and Fates
SATO, Moritoshi	The University of Tokyo	Manipulating Living Systems by Light
SATO, Shinichi	Tokyo Institute of Technology	Site-selective Antibody Chemical Modification Using Photocatalyst-proximity Labeling Reaction
SATO, Shinichi	Kyoto University	Live-cell Imaging of Multiple Endogenous mRNAs with Dhort RNAs and Small Molecules
SHOJI, Osami	Nagoya University	Use of Decoy Molecules to Trick Cytochrome P450s
TAKEZAWA, Yusuke	The University of Tokyo	Development of Cu(II)-responsive DNAzymes by Introducing a Metal-mediated Artificial Base Pair
TAKI, Masayasu	Nagoya University	Super-photostable Organelle Markers for Super-resolution Imaging
TAMURA, Tomonori	Kyoto University	Organelle-selective Lipid Labeling and Dynamic Imaging in Living Cells
TSUKIJI, Shinya	Nagoya Institute of Technology	Chemical Tools for Controlling Protein Localization in Living Cells
TSUTSUMI, Hiroshi	Tokyo Institute of Technology	Functionalized Supramolecular Peptide Hydrogels for 3D Culture of Cancer Cells
UCHINOMIYA, Shohei	Kyushu University	Live-cell Imaging of Activity of Fatty Acid Beta Oxidation Pathway with a Fluorescent Probe
WAKABAYASHI, Rie	Kyushu University	Size- and Morphology-controlled Co-assembly of Peptide Amphiphiles and Small Molecules for Intracellular Delivery

Shigeki Kiyonaka

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➢ Educational Background

1998 B.Sc., Kyushu University (supervisor: Profs. Itaru Hamachi and Seiji Shinkai)
2000 M.Sc., Graduate School of Engineering, Kyushu University (supervisor: Profs. Itaru Hamachi and Seiji Shinkai)
2002 Doctor of Engineering, Graduate School of Engineering, Kyushu University (supervisor: Prof. Itaru Hamachi)

➢ Professional Career

2003 PD, National Institute for Physiological Sciences, Japan (Prof. Yasuo Mori laboratory)
2005 Assistant professor, Kyoto University (Prof. Yasuo Mori laboratory)
2012 Associate professor, Kyoto University (Prof. Itaru Hamachi laboratory)
2019 Professor, Nagoya University

➢ Research Interests

1) Visualization of neurotransmitter receptors in neuronal system
2) Development of chemogenetics tools for understanding neuronal networks
3) Understanding cellular events under subcellular or suborganellar resolution

➢ Recent Publications

1. "On-cell coordination chemistry: Chemogenetic activation of membrane-bound glutamate receptors in living cells", Ryou Kubota, Shigeki Kiyonaka, Itaru Hamachi, *Methods Enzymol.* **2019**, *622*, 411.
2. "Ligand-Directed Chemistry of AMPA Receptors Confers Live-Cell Fluorescent Biosensors", Shigeki Kiyonaka, Seiji Sakamoto ,Sho Wakayama, Yuma Morikawa, Muneo Tsujikawa, Itaru Hamachi, *ACS Chem. Biol.* **2018**, *13*, 1880.
3. "Chemical labeling for visualizing native AMPA receptors in live neurons", Sho Wakayama, Shigeki Kiyonaka, Itaru Arai, Wataru Kakegawa, Shinji Matsuda, Keiji Ibata, Yuri L. Nemoto, Akihiro Kusumi, Michisuke Yuzaki, Itaru Hamachi, *Nat. Commun.* **2017**, *8*, 14850.
4. "Allosteric activation of membrane-bound glutamate receptors using coordination chemistry within living cells", Shigeki Kiyonaka, Ryou Kubota, Yukiko Michibata, Masayoshi Sakakura, Hideo Takahashi, Tomohiro Numata, Ryuji Inoue, Michisuke Yuzaki,Itaru Hamachi, *Nat. Chem.* **2016**, *8*, 958.
5. "Discovery of allosteric modulators for $GABA_A$ receptors by ligand-directed chemistry", Kei Yamaura, Shigeki Kiyonaka, Tomohiro Numata, Ryuji Inoue, Itaru Hamachi, *Nat. Chem. Biol.* **2016**, *12*, 822.
6. "Validating subcellular thermal changes revealed by fluorescent thermosensors", Shigeki Kiyonaka, Reiko Sakaguchi, Itaru Hamachi, Takashi Morii, Takenao Yoshizakik, Yasuo Mori, *Nat. Methods* **2015**, *12*, 801.
7. "Genetically encoded fluorescent thermosensors visualize subcellular thermoregulation in living cells", Shigeki Kiyonaka, Taketoshi Kajimoto, Reiko Sakaguchi, Daisuke Shinmi, Mariko Omatsu-Kanbe, Hiroshi Matsuura, Hiromi Imamura, Takenao Yoshizaki, Itaru Hamachi, Takashi Morii, Yasuo Mori, *Nat. Methods* **2013**, *10*, 1232.

New Chemogenetic Approaches for Artificially Controlling Neurotransmitter Receptor Function in Neuronal System

Shigeki Kiyonaka

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Understanding the molecular mechanisms of memory formation is a critically important in neuroscience. Recent studies have revealed that functions of neurotransmitter receptors are dynamically regulated in the memory formation. In contrast, disregulation of neurotransmitter receptors causes neurological disorders. For clarifying these mechanisms in brain tissues or live animals, development of new methods for regulating neurotransmitter receptors in target cells are highly desired. We have recently reported a new method for selective activation of glutamate receptors on live cells, by combination of point-mutagenesis with metal complex-mediated molecular recognition, termed coordination chemogenetics. Our concept relies on stabilization of the active conformation of the membrane receptors via coordination bonding of Pd^{2+} complexes with mutated amino acid residues, which enables allosteric activation of the receptor subtype in target cells. Using this strategy, chemogenetics activation of ion-channel-type and GPCR-type glutamate receptors has been successfully carried out in target cells or brain tissue. We expect that this method would be applicable for understanding neuronal circuits in the brain.

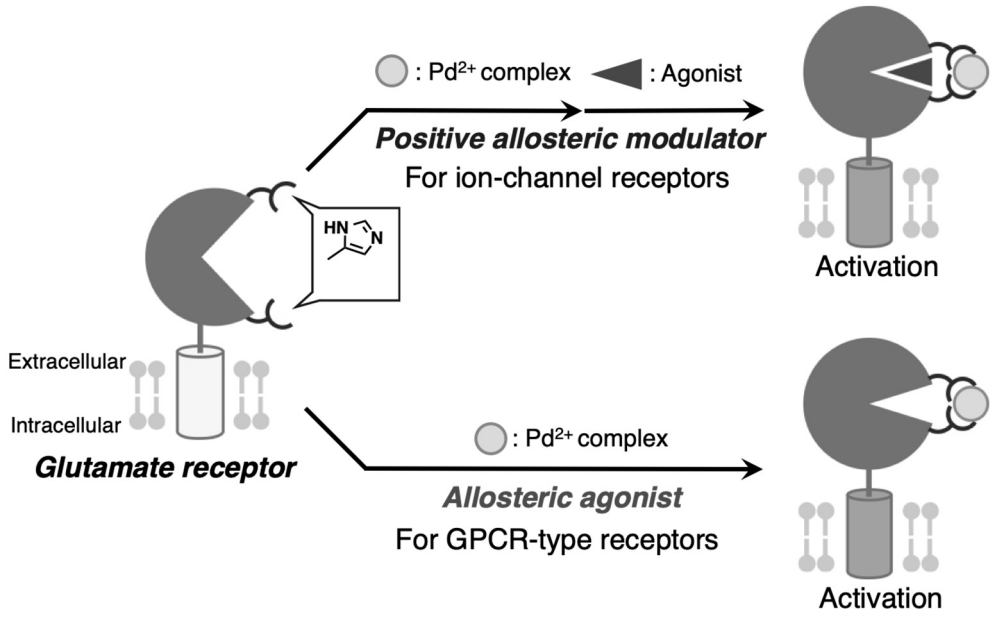

Figure 1. Schematic illustration of coordination chemogenetics for glutamate receptors.

Martin Fascione

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➢ Educational Background

2005 MChem., University of Leeds, UK
2009 Ph.D., School of Chemistry, University of Leeds (supervisor: Prof. W. Bruce Turnbull)

➢ Professional Career

2009-2012 EPSRC funded postdoctoral research associate, University of Leeds ("carbohydrate-binding-protein based virus-like particles"), with Dr. W. Bruce Turnbull
2012-2013 Marie Curie International Outgoing Fellow, University of British Columbia, Vancouver, Canada ("xylanases as models for understanding enzymatic catalysis"), with Prof. Stephen G. Withers, FRS
2013-2014 Marie Curie Research Fellow, YSBL, University of York ("mechanistic study of carbohydrate processing enzymes using protein semi-synthesis and x-ray crystallography"), with Prof. Gideon Davies, FMedSci, FRS
Aug 2014-present Lecturer in Chemical Biology, YSBL, Department of Chemistry, University of York, UK.

➢ Research Interests

1) Chemical glycobiology
2) Bioconjugation chemistry

➢ Awards

- Henry Ellison Scholarship, 2005, University of Leeds
- JB Cohen Prize, 2010, University of Leeds
- Marie Curie International Outgoing Research Fellowship 2012-2014

➢ Recent Publications

1. "Using automated glycan assembly (AGA) for the practical synthesis of heparan sulfate oligosaccharide precursor", Darshita Budhadev, Karinna Saxby, Julia Walton, Gideon Davies, Peter C. Tyler, Ralf Schworer, Martin A. Fascione, *Org. Biomol. Chem.* **2019**, *17*, 1817. DOI: 10.1039/C8OB02756K.
2. "Site-selective C-C modification of proteins at neutral pH using organocatalyst-mediated cross aldol ligations ", Richard J. Spears, Robin L. Brabham, Darshita Budhadev, Tessa Keenan, Sophie McKenna, Julia Walton, James. A. Brannigan, A. Marek Brzozowski, Anthony J. Wilkinson, Michael Plevin, Martin A. Fascione, *Chem. Sci.* **2018**, *9(25)*, 5585. DOI: 10.1039/c8sc01617h.
3. "Palladium-unleashed proteins: gentle aldehyde decaging for site-selective protein modification", Robin L. Brabham, Richard J. Spears, Julia Walton, Swati Tyagi, Edward A. Lemke, Martin A. Fascione, *Chem. Commun.* **2018**, *54*, 1501. DOI: 10.1039/C7CC07740H.

Organocatalyst-mediated Bioconjugation of Proteins

Richard J. Spears,[a] Robin L. Brabham,[a] Darshita Budhadev,[a] Tessa Keenan,[a] Sphie McKenna,[a] Julia Walton,[a] James. A. Brannigan,[a] A. Marek Brzozowski,[a] Anthony J. Wilkinson,[a] Michael Plevin,[a], and Martin A. Fascione[a,b]

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The bioconjugation of proteins with small molecules has revolutionised the fields of chemical medicine, chemical biology, and cell biology, enabling scientists to probe and perturb dynamic cellular processes. The general use of chemical methods for the functionalisation of proteins is still limited however as they often require complicated reaction partners and/or non-physiological pH, which is incompatible with many protein scaffolds. Herein we describe efficient organocatalyst-mediated reaction on proteins using simple chemical probes (Figure 1), which afford a range of stable C-C linked bioconjugates at physiological pH. This strategy is showcased in the 'chemical mimicry' of a previously inaccessible natural dual post-translationally modified protein, integral to the pathogenesis of the neglected tropical disease Leishmaniasis, and provides a facile route to differentially modified proteins under biologically compatible conditions.

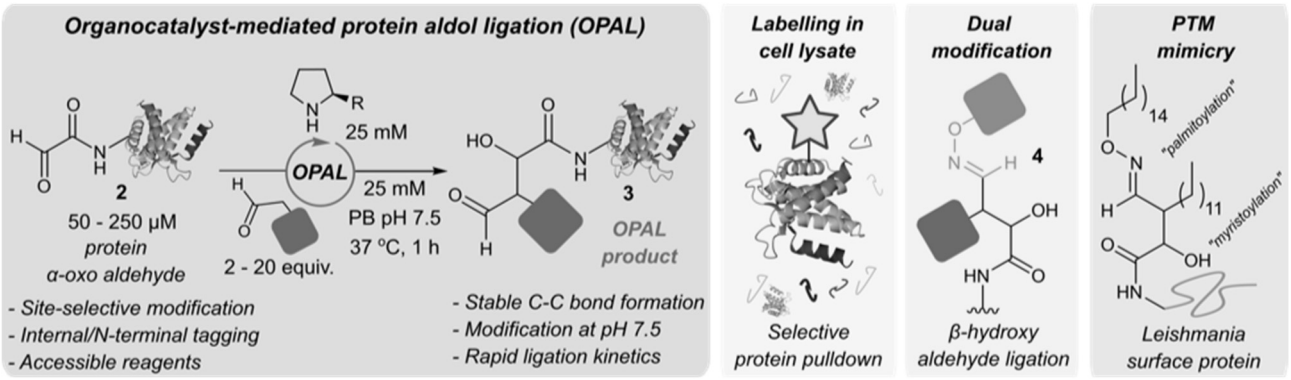
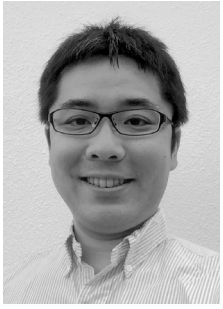


Figure 1.

Yuki Goto



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➢ Educational Background

2003 B.Sc., Kyoto University (supervisor: Prof. Isao Saito)
2005 M.Sc., Graduate School of Engineering, Kyoto University (supervisor: Prof. Kazuhiko Nakatani)
2008 Ph.D. in Engineering, Graduate School of Engineering, The University of Tokyo (supervisor: Prof. Hiroaki Suga)

➢ Professional Career

2008 Postdoctoral research associate, University of Illinois at Urbana-Champaign
JSPS Postdoctoral Fellow for Research Abroad (advisor: Prof. Wilfred A. van der Donk)
2009 Assistant professor, The University of Tokyo
2011 PRESTO researcher, JST (cross-appointed)
2016 Associate professor, The University of Tokyo

➢ Research Interests

1) In vitro engineering of biosynthetic pathways for facile synthesis of artificial compounds
2) Elaboration of bioactive pseudo-natural peptides

➢ Awards

2013 Young Scientists Prize, Minister of Education, Culture, Sports, Science and Technology
2016 Young Investigator Award, Japanese Peptide Society
2017 The Chemical Society of Japan Award For Young Chemists for 2017
2018 The 1st Bioindustry Research Award

➢ Recent Publications

1. "Ribosomal Synthesis of Backbone-Cyclic Peptides Compatible with In Vitro Display", Ryo Takatsuji, Koki Shinbara, Takayuki Katoh, Yuki Goto, Toby Passioura, Ryo Yajima, Yamato Komatsu, Hiroaki Suga, *J. Am. Chem. Soc.* **2019**, *141*, 2279.
2. "Engineering of RiPP pathways for the production of artificial peptides bearing various non-proteinogenic structures.", Yuki Goto, Hiroaki Suga, *Curr. Opin. Chem. Biol.* **2018**, *46*, 82.
3. "Dissection of goadsporin biosynthesis by *in vitro* reconstitution leading to designer analogues expressed *in vivo*", Taro Ozaki, Kona Yamashita, Yuki Goto, Morito Shimomura, Shohei Hayashi, Shumpei Asamizu, Yoshinori Sugai, Haruo Ikeda, Hiroaki Suga, Hiroyasu Onaka, *Nat. Commun.* **2017**, *8*, 14207.
4. "Expanding the amino acid repertoire of ribosomal polypeptide synthesis via the artificial division of codon boxes", Yoshihiko Iwane, Azusa Hitomi, Hiroshi Murakami, Takayuki Katoh, Yuki Goto, Hiroaki Suga, *Nat. Chem.* **2016**, *8*, 317.
5. "One-Pot Synthesis of Azoline-Containing Peptides in a Cell-free Translation System Integrated with a Posttranslational Cyclodehydratase ", Yuki Goto, Yumi Ito, Yasuharu Kato, Shotaro Tsunoda, Hiroaki Suga, *Chem. Biol.* **2014**, *21*, 766.
6. "Nonstandard Peptide Expression under the Genetic Code Consisting of Reprogrammed Dual Sense Codons", Yuki Goto, Megumi Iseki, Azusa Hitomi, Hiroshi Murakami, Hiroaki Suga, *ACS Chem. Biol.* **2014**, *8*, 2630.

Artificial In Vitro Biosynthesis for Elaboration of Pseudo-natural Peptides

Yuki Goto

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Naturally occurring peptides produced as secondary metabolites in microorganisms often have macrocyclic scaffolds with diverse modified backbone structures such as N-methylated amides, thioamides, heterocyclic backbones, and *β/γ*-amino acids. As such unique nonproteinogenic structures play important roles in diverse bioactivities of the natural peptides, peptides with the non-standard structures can be attractive candidates even for artificial bioactive peptides.

Many biosynthetic systems involved in the production of macrocyclic scaffolds and modified backbones have been discovered from nature to date. Although they are useful synthetic tools to produce specific natural products and their related analogs, it is generally difficult to be applied for the synthesis of de novo artificial molecules and their chemical libraries. Thus, versatile biosynthetic systems that facilitate production of diverse and artificial peptides with non-standard peptides had been demanded for development of novel bioactive peptides.

We have developed artificial *in vitro* biosynthesis systems by the combination of custom-made ribosomal synthesis (named FIT system) and various posttranslational modification strategies. The FIT system enables us to reprogram the genetic code to produce peptides with multiple non-canonical amino acids such as *N*-methylated amino acids and D-amino acids. We have demonstrated that chemical and enzymatic posttranslational modification of the resulting peptide successfully yielded various non-proteinogenic structured found in naturally occurring bioactive peptides. These artificial *in vitro* biosynthesis can be applied for construction of natural product-like peptide libraries with the complexity of more than a trillion members. By integrating this technology with an *in vitro* display system, the peptide libraries with various ring sizes and building blocks can be rapidly screened against drug targets, resulting in novel bioactive peptides. These works have demonstrated synthetic and pharmaceutical potentials of the artificial *in vitro* biosynthesis systems, leading to the elaboration of a new class of bioactive molecules so-called pseudo-natural peptides.

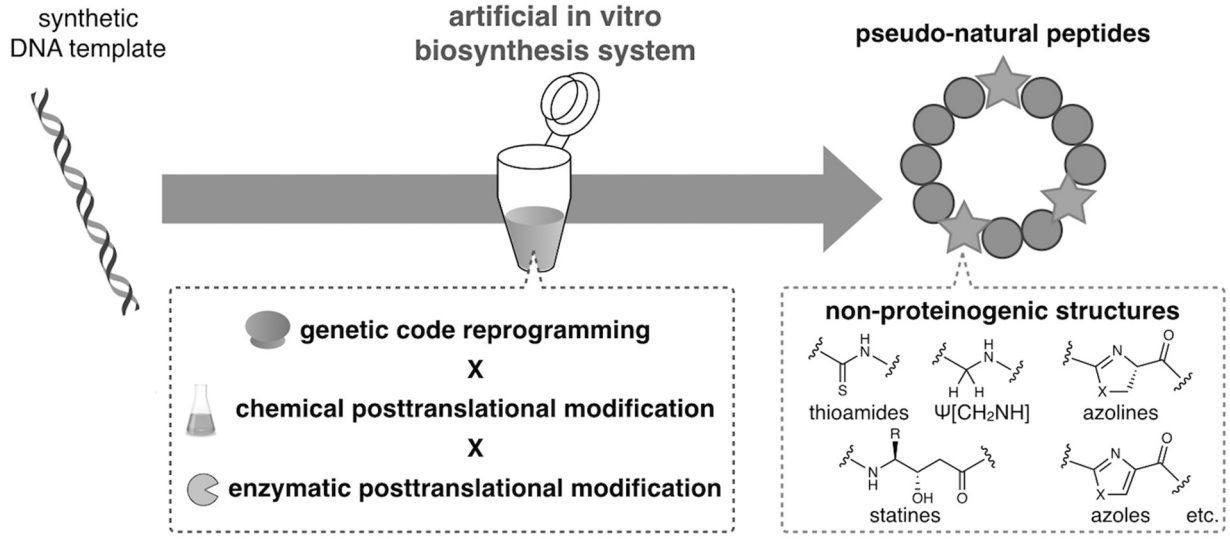
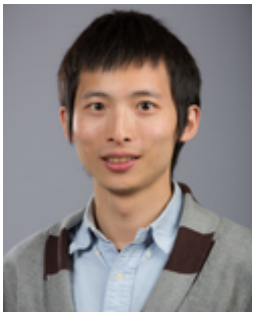


Figure 1. Artificial *in vitro* biosynthesis systems that can synthesize various pseudo-natural peptides containing diverse non-proteinogenic structures.

Yu-Hsuan Tsai



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- **Educational Background**

2006 B.Sc., National Taiwan University
2008 M.Sc., Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology Zurich (supervisor: Prof. Peter H. Seeberger)
2001 Doctor of Natural Science, Division of Biology, Chemistry, Pharmacy, Freie Universität Berlin (supervisor: Prof. Peter H. Seeberger)

- **Professional Career**

2006 - 2007 Research Assistant, Academia Sinica (Taipei, Taiwan)
2012 - 2014 Postdoc, Medical Research Council Laboratory of Molecular Biology (Cambridge, England)
2015 - now Lecturer, Cardiff University (Cardiff, Wales)

- **Research Interests**

1) Novel approaches for protein modulation
2) Protein post-translational modification in bacteria

- **Awards**

2001 Chinese Chemical Society Award
2012 MRC Career Development Fellowship
2017 GW4 Crucible
2018 British Science Association Media Fellowship

- **Recent Publications**

1. "Selective, rapid and optically switchable regulation of protein function in live mammalian cells", Yu-Hsuan Tsai, Sebastian Essig, John R. James, Kathrin Lang, Jason W. Chin, *Nat. Chem*. **2015**, *7*, 554.
2. Acetylome of *Acinetobacter baumannii* SK17 Reveals a Highly-Conserved Modification of Histone-like Protein HU", Jiahn-Haur Liao, Cheng-Han Tsai, Sanjay G. Patel, Jhih-Tian Yang, I-Fan Tu, Matteo Lo Cicero, Magdalena Lipka-Lloyd, Wan-Ling Wu, Wen-Jie Shen, Meng-Ru Ho, Chi-Chi Chou, Garima R. Sharma, Hiroki Okanishi, Louis Y. P. Luk, Yu-Hsuan Tsai*, Shih-Hsiung Wu*, *Front. Mol. Biosci*. **2017**, *4*, 77. DOI: 10.3389/fmolb.2017.00077.
3. "Switchable genome editing *via* genetic code expansion", Toru Suzuki, Maki Asami, Sanjay G. Patel, Louis Y. P. Luk, Yu-Hsuan Tsai, Anthony C. F. Perry, *Sci. Rep*. **2018**, *8*, 10051.
4. "Using genetically incorporated unnatural amino acids to control protein functions in mammalian cells", Alexander R. Nodling, Luke A. Spear, Thomas L. Williams, Louis Y. P. Luk, Yu-Hsuan Tsai, *Essays Biochem*. **2019**, *63*, in press (DOI: 10.1042/EBC20180042).

Using Genetically Incorporated Unnatural Amino Acids to Study and Control Protein Function

Yu-Hsuan Tsai

School of Chemistry, Cardiff University, Cardiff CF10 3AT, United Kingdom

Genetic code expansion (Figure 1) allows unnatural (non-canonical) amino acid incorporation into proteins of interest by repurposing the cellular translation machinery.[1] The development of this technique has enabled site-specific incorporation of many structurally and chemically diverse amino acids, facilitating a plethora of applications. Here I will show how genetic code expansion can be applied to regulate protein function in mammalian cells[2] and study protein post-translational modification.[3]

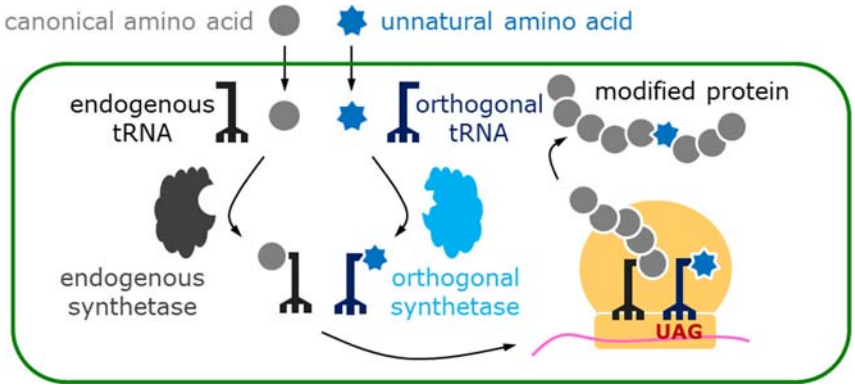

Figure 1. Concept of genetic code expansion.

References:

1. "Using genetically incorporated unnatural amino acids to control protein functions in mammalian cells", A. R. Nödling, L. A. Spear, T. L. Williams, L. Y. P. Luk, Y.-H. Tsai, *Essays Biochem*. **2019**, *63*, DOI: 10.1042/EBC20180042.
2. (a) "Selective, rapid and optically switchable regulation of protein function in live mammalian cells", Yu-Hsuan Tsai, Sebastian Essig, John R. James, Kathrin Lang, Jason W. Chin, *Nat. Chem*. **2015**, *7*, 554.
   (b) "Switchable genome editing via genetic code expansion", Toru Suzuki, Maki Asami, Sanjay G. Patel, Louis Y. P. Luk, Yu-Hsuan Tsai, Anthony C. F. Perry, *Sci. Rep*. **2018**, *8*, 10051.
3. "Acetylome of *Acinetobacter baumannii* SK17 Reveals a Highly-Conserved Modification of Histone-Like Protein HU", Jiahn-Haur Liao, Cheng-Han Tsai, Sanjay G. Patel, Jhih-Tian Yang, I-Fan Tu, Matteo Lo Cicero, Magdalena Lipka-Lloyd, Wan-Ling Wu, Wen-Jie Shen, Meng-Ru Ho, Chi-Chi Chou, Garima R. Sharma, Hiroki Okanishi, Louis Y. P. Luk, Yu-Hsuan Tsai*, Shih-Hsiung Wu*, *Front. Mol. Biosci*. **2017**, *4*, 77.

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➢ Educational Background

1998 B.Eng., Kyoto University (supervisor: Prof. Isao Saito)
2000 M.Eng., Graduate School of Engineering, Kyoto University (supervisor: Prof. Isao Saito)
2003 Doctor of Engineering, Graduate School of Engineering, Kyoto University (supervisor: Prof. Isao Saito)

➢ Professional Career

2003 RIKEN (PD)
2007 University of Geneva (PD)
2008 Assistant professor, Tohoku University
2013 Associate professor, Nagoya University
2018 Team Leader, RIKEN

➢ Research Interests

Plant chemical biology

➢ Awards

2015 Lecture Award, Bio-related Chemistry Symposium
2018 Mishima Kaiun Memorial Award

➢ Recent Publications

1. "Chemical hijacking of auxin signaling with an engineered auxin-TIR1 pair ", Naoyuki Uchida, Koji Takahashi, Rie Iwasaki, Ryotaro Yamada, Masahiko Yoshimura, Takaho A. Endo, Seisuke Kimura, Hua Zhang, Mika Nomoto, Yasuomi Tada, Toshinori Kinoshita, Kenichiro Itami, Shinya Hagihara, Keiko U. Torii, *Nat. Chem. Biol.* **2018**, *14*, 299.
2. "A super strong engineered auxin-TIR1 pair ", Ryotaro Yamada, Keiichiro Murai, Naoyuki Uchida, Koji Takahashi, Rie Iwasaki, Yasuomi Tada, Toshinori Kinoshita, Kenichiro Itami, Keiko U. Torii, Shinya Hagihara, *Plant Cell Physiol.* **2018**, *59*, 1538.
3. "Rapid and reversible root growth inhibition by TIR1 auxin signalling ", Matyáš Fendrych, Maria Akhmanova, Jack Merrin, Matouš Glanc, Shinya Hagihara, Koji Takahashi, Naoyuki Uchida, Keiko U. Torii, Jiří Friml, *Nat. Plants* **2018**, *4*, 453.
4. "Probing strigolactone receptors in Striga hermonthica with fluorescence ", Yuichiro Tsuchiya, Masahiko Yoshimura, Yoshikatsu Sato, Keiko Kuwata, Shigeo Toh, Duncan Holbrook-Smith, Hua Zhang, Peter McCourt, Kenichiro Itami, Toshinori Kinoshita, Shinya Hagihara, *Science* **2015,** *349*, 864.

Dissection of Plant Hormone Signaling with Synthetic Molecules

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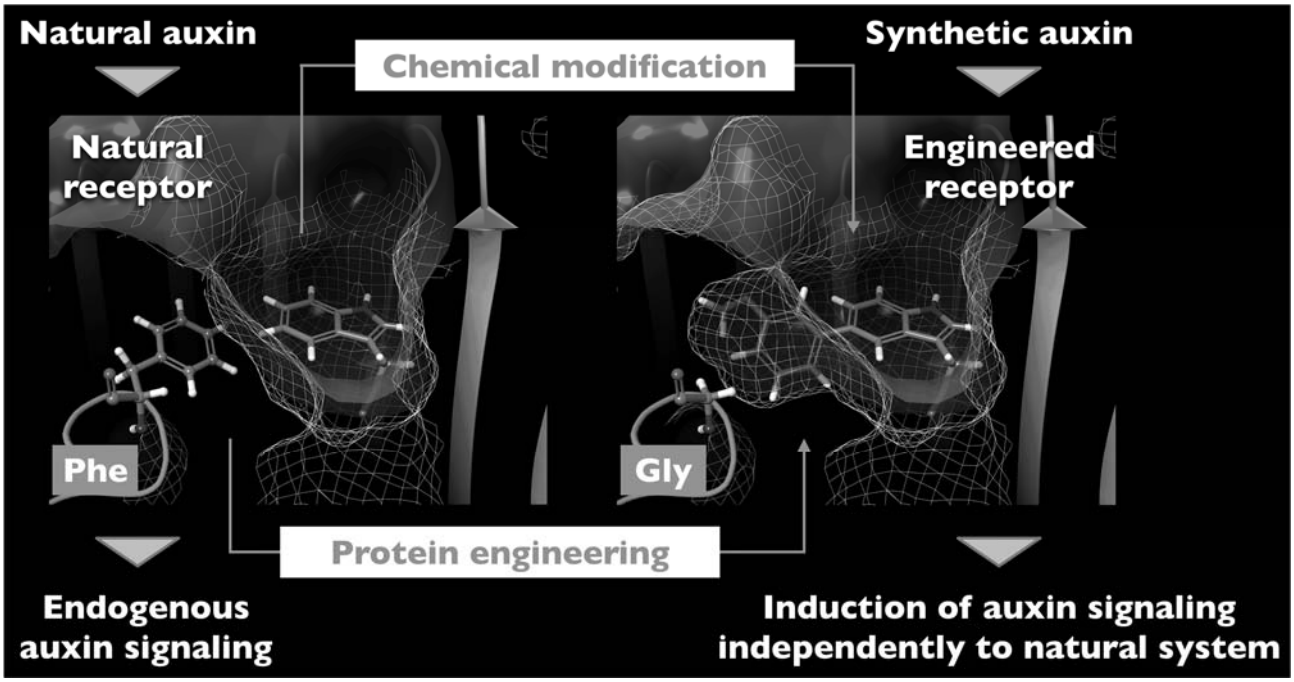
Molecular recognition in miscellaneous and crowding multimolecular biosystems plays an important role in biological functions. Especially, the specific interaction between plant hormone and its receptor protein is crucial for long-distance signal transduction that enables plants to rapidly adapt to environmental changes. Although recent biological studies have made substantial progress in our understanding of plant hormone signaling, delineating plant hormone response at molecular level remains a major challenge. In this presentation, we will show chemistry-based approaches to understand and regulate plant hormone signaling. Our studies successfully uncovered long-sought-after mechanism of auxin signaling.



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➢ Educational Background

1997 Degree Chemistry BSc Hons., University of Durham, UK
2001 PhD, School of Chemistry, University of Durham (supervisor: Prof. David O'Hagan)

➢ Professional Career

2000 Postdoctoral Research Associate, (Professors Staunton FRS and Leadlay FRS) University of Cambridge
2002 Teaching Fellow, School of Chemistry, University of Nottingham
2003 Proleptic lectureship University of Exeter
2005 Lecturer, then Senior Lecturer, then Reader, University of East Anglia
2012 Reader then Professor, School of Chemistry, University of St Andrews

➢ Research Interests

1) Blending synthetic biology with synthetic chemistry to make new to nature natural products of medicinal relevance
2) Biosynthetic elucidation of complex natural products
3) Developing Enzymes for Synthesis

➢ Awards and Honours

2003 Royal Society Dorothy Hodgkin Fellowship (~10 awarded each year across the UK in science)
2007 awarded the 2006 RSC Meldola Medal (awarded to the most promising UK chemist under the age of 32) in particular I was *"distinguished for excellent contributions at the interface of organic chemistry and molecular biology*"
2011 Thieme Chemistry Journal Award
2011 JSP award to participate at the Burgenstock Stereochemistry meeting
2011 Selected as the UK's under 40 Organic Chemistry delegate for EuCheM's Young Investigators Workshop
2013 Natural Product Report Emerging Researcher Lectureship
**Awarded for our pioneering new approach to natural product analogue generation "Genochemetics", which marries together Synthetic Biology and Synthetic Chemistry to access new bioactives of medicinal interest.*
2017-onwards Associate Editor for *Chem. Soc. Rev.*

➢ Recent Publications

1. "A natural solution to the photoprotection and isolation of the potent polyene antibiotic marinomycin", Christopher S. Bailey, Joseph S. Zarins-Tutt, Matthias Agbo, Hong Gao, Alberto Diego Taboada, Maoluo Gan, Emily R. Abraham, Grahame Mackenzie, P. Andrew Evans, Rebecca J. M. Goss, *Chem. Sci.* **2019**, DOI: 10.1039/C9SC01375J. (**Chem Sci Pick of the week, Highlighted in C&EN News. https://cen.acs.org/pharmaceuticals/Pollen-shells-protect-drugs-UV/97/i22*)
2. "Heck Diversification of Indole-Based Substrates under Aqueous Conditions: From Indoles to Unprotected Halo-tryptophans and Halo-tryptophans in Natural Product Derivatives", Cristina Pubill-Ulldemolins, Sunil V. Sharma, Christopher Cartmell, Jinlian Zhao, Paco Cµrdenas, Rebecca J. M. Goss, *Chem. Eur. J.* **2019**, DOI: 10.1002/chem.20190137.
3. "Buchwald Hartwig diversification of unprotected halotryptophans, halotryptophan containing tripeptides and the natural product barettin in aqueous conditions", Yohann J. G. Renault, Rosemary Lynch, Enrico Marelli, Sunil. V. Sharma, Cristina Pubill-Ulldemolins, Joshua A. Sharp, Chris Cartmell, Paco Cárdenas, Rebecca J. M. Goss, *Chem. Commun.* **2019**, accepted.

Blending Synthetic Chemistry with Synthetic Biology *in vivo* to Enable Access to New to Nature Natural Products

Rebecca J. M. Goss

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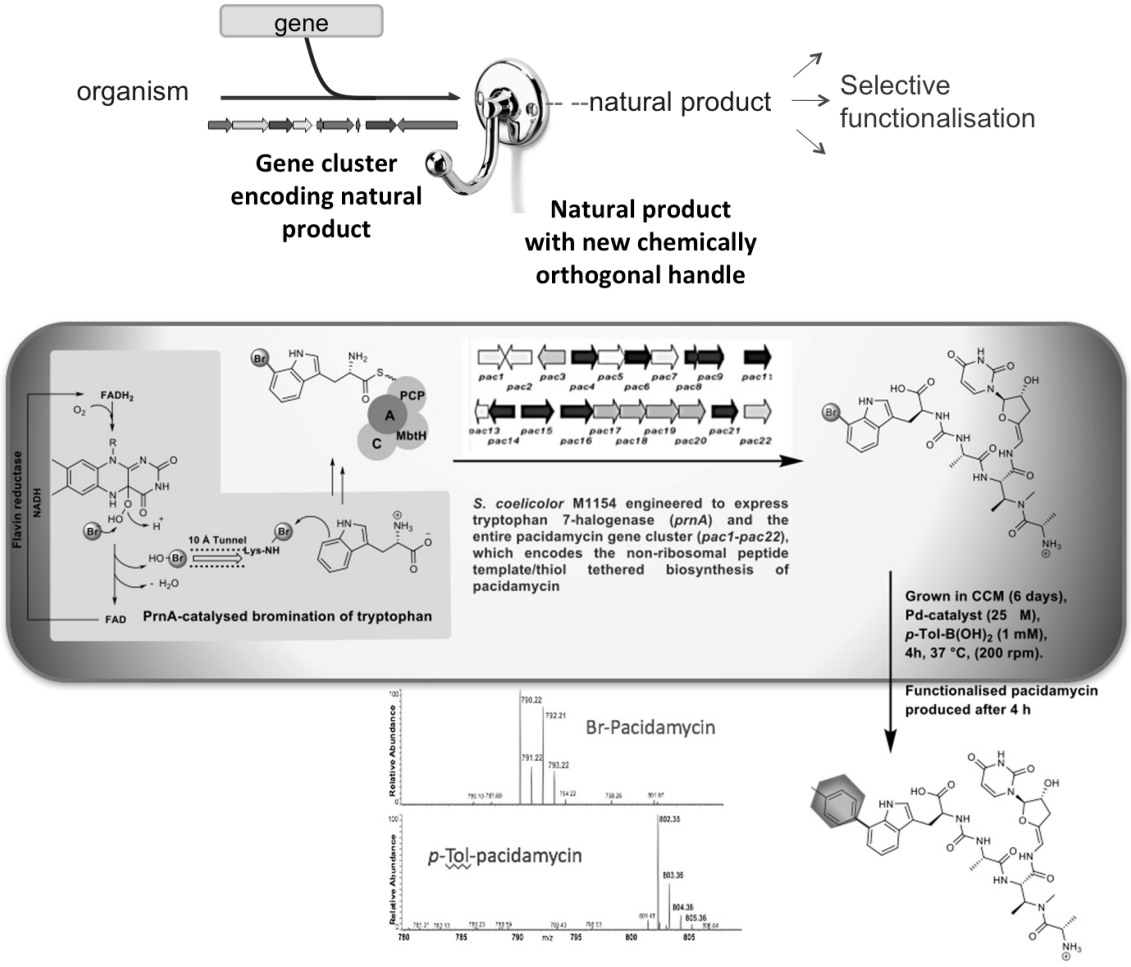
Natural products represent a treasure trove of medicinally relevant compounds: over the past 3 decades over 70% of antimicrobials and over 60% of antitumor agents entering clinical trials have been based on natural products. Generation of natural product analogues is an important area.

We have pioneered a new concept in which a gene is introduced to an organism and coerced to work in concert with an existing biosynthetic pathway. This installs a chemical handle that enables selective derivatisation of the natural product.[1-4] The selective modification of the new to nature natural product in the presence of the living cells that produce it will also be discussed.[5]



Scheme 1: GenoChemetics; gene insertion enables the installation of a reactive and chemically orthogonal handle into a natural product, permitting its selective functionalization and diversification.

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1. Abhijeet Deb Roy, Sabine Gruschow, Nickiwe Cairns, Rebecca J. M. Goss, *J. Am. Chem. Soc.* **2010**, *132(35)*, 12243.
2. M. J. Corr, S. V. Sharma, C. Pubill-Ulldemolins, R. T. Bown, P. Poirot, D. R. M. Smith, C. Cartmell, A. Abou Fayad, R. J. M. Goss, *Chem. Sci.* **2017**, *7*, 2039. DOI: 10.1039/c6sc04423a (Edge Article).
3. Duncan R. M. Smith, Agustinus R. Uria, Eric J. N. Helfrich, Daniela Milbredt, Karl-Heinz van PeeJorn Piel, Rebecca J. M. Goss, *ACS Chem. Biol.* **2017**, *12(5)*, 1281.
4. Enrico Marelli, Yohann Renault, Sunil V. Sharma, Steven P. Nolan, Rebecca J. M. Goss, *Chem. Eur. J.* **2017**, *23*, 3832. DOI:10.1002/chem.201700680.
5. Sunil V. Sharma, Xiaoxue Tong, Cristina Pubill-Ulldemolins, Christopher Cartmell, Emma J. A. Bogosyan, Emma J. Rackham, Enrico Marelli, Refaat B. Hamed, Rebecca J. M. Goss*, Nat. Commun.* **2017**, *8*, 229. DOI: 10.1038/s41467-017-00194-3.

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➢ Educational Background

2000 B.Sc., Faculty of Pharmaceutical Sciences, The University of Tokyo (supervisor: Prof. Tetsuo Nagano)
2002 M.Sc., Graduate School of Pharmaceutical Sciences, The University of Tokyo (supervisor: Prof. Tetsuo Nagano)
2005 Doctor of Pharmacy, Graduate School of Pharmaceutical Sciences, The University of Tokyo (supervisor: Prof. Tetsuo Nagano)

➢ Professional Career

2004 Research Fellow of the Japan Society for the Promotion of Science (JSPS Research Fellow) (DC2)
2005 Postdoctoral Fellow, University of Texas, Southwestern Medical Center, USA (supervisor: Prof. Thomas Kodadek)
2006 Research Fellow of the Japan Society for the Promotion of Science (JSPS Research Fellow) (SPD)
2007 Assistant professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo
2010 Lecturer, Graduate School of Pharmaceutical Sciences, The University of Tokyo
2011 Associate professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

➢ Research Interests

1) Fluorescence probes
2) Chemical tools for bioimaging and drug discovery

➢ Awards

2010 The Pharmaceutical Society of Japan Award for Young Scientists
2011 The Young Scientists' Prize, The Commendation for Science and Technology, by the Minister of Education, Culture, Sports, Science and Technology
2011 Inoue Science Research Award
2014 Nakatani Foundation Award
2014 ICBS Young Chemical Biologist Award (The International Chemical Biology Society)

➢ Recent Publications

1. "Design and Synthesis of an Activatable Photoacoustic Probe for Hypochlorous Acid", Takayuki Ikeno, Kenjiro Hanaoka*, Shimpei Iwaki, Takuya Myochin, Yoshiaki Murayama, Hisashi Ohde, Toru Komatsu, Tasuku Ueno, Tetsuo Nagano, Yasuteru Urano*, *Anal. Chem.* in press.
2. "Synthesis of unsymmetrical Si-rhodamine fluorophores and application to a far-red to near-infrared fluorescence probe for hypoxia", Kenjiro Hanaoka*, Yu Kagami, Wen Piao, Takuya Myochin, Koji Numasawa, Yugo Kuriki, Takayuki Ikeno, Tasuku Ueno, Toru Komatsu, Takuya Terai, Tetsuo Nagano, Yasuteru Urano*, *Chem. Commun.* **2018**, *54*, 6939.
3. "Development of a Series of Practical Fluorescent Chemical Tools to Measure pH Values in Living Samples", Shodai Takahashi, Yu Kagami, Kenjiro Hanaoka*, Takuya Terai, Toru Komatsu, Tasuku Ueno, Masanobu Uchiyama, Ikuko Koyama-Honda, Noboru Mizushima, Tomohiko Taguchi, Hiroyuki Arai, Tetsuo Nagano, Yasuteru Urano*, *J. Am. Chem. Soc.* **2018**, *140*, 5925.

Construction of a Library of Asymmetric Si-rhodamine Fluorophores and its Application to Ratiometric Fluorescence Probes for pH

Kenjiro Hanaoka

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Red to NIR-fluorescent Si-rhodamines (SiRs) are favorable long-wavelength fluorophores for bioimaging that retain the advantageous photophysical properties of conventional rhodamine dyes such as high photostability and high quantum yield (see our review article: *Chem. Asian J.*, **2017**, *12*, 1435). However, their chemical structures are limited to symmetrical ones, so further derivatization of the structure would expand the molecular design and applicable range of fluorescence probes based on SiRs. For this purpose, we newly developed a novel synthetic method of 4,4'-methylenebisaniline derivatives, and we successfully achieved the synthesis of various asymmetrical SiRs by using this reaction as a key step for constructing SiR fluorophores (*Chem. Commun.* **2018,** *54*, 6939).

Among synthesized asymmetric SiRs, we luckily discovered a compound that shows an absorption wavelength change of about 80 nm in response to pH change. We considered that this SiR scaffold could be an excellent scaffold for developing fluorescence probes for ratiometric pH measurements, because modification of the pK_a value and the absorption and emission wavelengths, as well as introduction of functional groups, can be easily performed. In biological systems, the pH in intracellular organelles is strictly regulated, and differences of pH are deeply related to key biological events such as protein degradation and intracellular trafficking. Ratiometric fluorescence imaging is useful for determination of precise pH values, but existing fluorescence probes have substantial limitations, such as inappropriate pK_a for imaging in the physiological pH range, inadequate photobleaching resistance, and insufficiently long excitation and emission wavelengths. So, we developed a versatile scaffold for ratiometric fluorescence pH probes, based on the above-mentioned pH-sensitive asymmetric SiR (*J. Am. Chem. Soc.* **2018,** *140*, 5925). We developed **SiRpH6.1** as a ratiometric pH fluorescence probe, and it has suitable pK_a and water solubility for imaging in acidic intracellular compartments; by using transferrin tagged with **SiRpH6.1**, we achieved time-lapse imaging of pH in endocytic compartments during protein trafficking for the first time. These chemical tools should be useful for studying the influence of intracellular pH on biological processes.

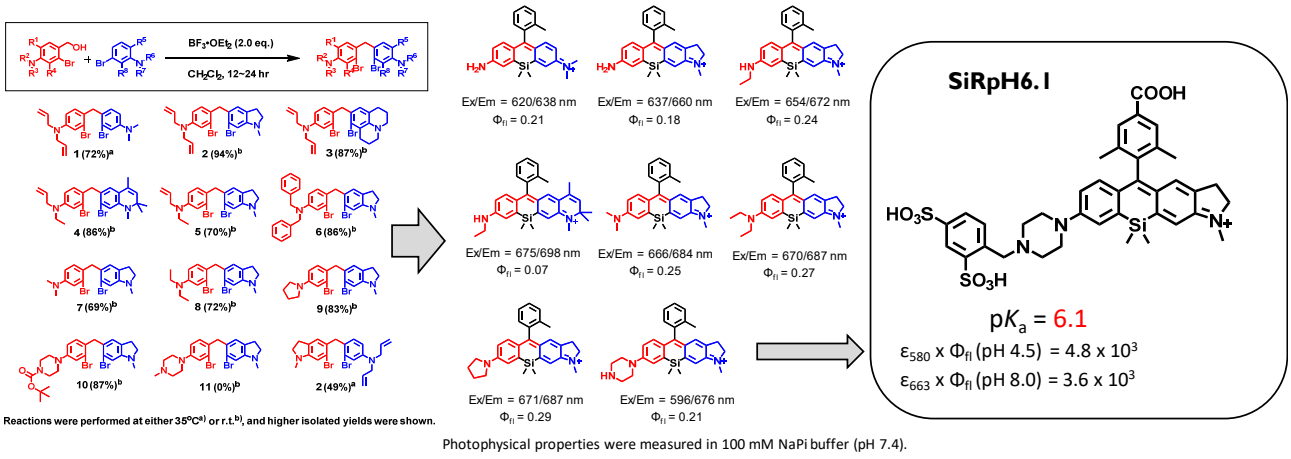

Figure 1. Established synthetic scheme for asymmetrical SiRs and their photophysical properties. Based on the synthesized asymmetrical SiR, a new ratiometric fluorescence probe for pH, **SiRpH6.1**, has been developed.

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- **Educational Background**
  2000 M.Chem (Hons), University of Oxford
  2005 D.Phil Pharmacology, University of Oxford (supervisor: Prof Edith Sim)

- **Professional Career**
  2006 Summit Therapeutics PLC (formerly VASTox PLC), Senior Scientist
  2009 Senior Postdoctoral Research Assistant, University of Oxford (Prof. Chris Schofield)
  2012 BHF CRE Senior Fellow, University of Oxford
  2013 Royal Society Dorothy Hodgkin Fellow, University of Oxford
  2016 University Research Lecturer, University of Oxford
  2019 Associate Professor, University of Oxford

- **Research Interests**
  1) Development of chemical probes / tools for studying enzymes involved in epigenetic regulation
  2) Biochemical and functional studies of histone demethylases
  3) Peptide-based inhibitor design

- **Recent Publications**

1. "Non-competitive cyclic peptides for targeting enzyme-substrate complexes", T. E. McAllister, T.-L. Yeh, M. I. Abboud, I. K. H. Leung, E. S. Hookway, O. N. F. King, B. Bhushan, S. T. Williams, R. J. Hopkinson, M. Münzel, N. D. Loik, R. Chowdhury, U. Oppermann, T. D. W. Claridge, Y. Goto, H. Suga, C. J. Schofield, A. Kawamura, *Chem. Sci.* **2018**, *9*, 4569. DOI: 10.1039/C8SC00286J.
2. "Highly selective inhibition of histone demethylases by de novo macrocyclic peptides", Akane Kawamura, Martin Münzel, Tatsuya Kojima, Clarence Yapp, Bhaskar Bhushan, Yuki Goto, Anthony Tumber, Takayuki Katoh, Oliver N. F. King, Toby Passioura, Louise J. Walport, Stephanie B. Hatch, Sarah Madden, Susanne Müller, Paul E. Brennan, Rasheduzzaman Chowdhury, Richard J. Hopkinson, Hiroaki Suga, Christopher J. Schofield, *Nat. Commun.* **2017**, *8*, 14773. DOI: 10.1038/ncomms14773.
3. "The Activity of JmjC Histone Lysine Demethylase KDM4A is Highly Sensitive to Oxygen Concentrations", Rebecca L. Hancock, Norma Masson, Kate Dunne, Emily Flashman, Akane Kawamura, *ACS Chem. Biol.* **2017** *12(4)*, 1011. DOI: 10.1021/acschembio.6b00958.
4. "Recent Progress in Histone Demethylase Inhibitors", Tom E. McAllister, Katherine S. England, Richard J. Hopkinson, Paul E. Brennan, Akane Kawamura, *J. Med. Chem.* **2016,** *59(4)*,1308. DOI: 10.1021/acs.jmedchem.5b01758.
5. "Arginine demethylation is catalysed by a subset of JmjC histone lysine demethylases", Louise J. Walport, Richard J. Hopkinson, Rasheduzzaman Chowdhury, Rachel Schiller, Wei Ge, Akane Kawamura, Christopher J. Schofield, *Nat. Commun.* **2016,** *7*, 11974. DOI: 10.1038/ncomms11974.

Development of Chemical Tools for Epigenetic Proteins

Akane Kawamura
University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom

Post-translational modifications (PTMs) on histone tails are of central importance in regulation of gene expression. Histone PTMs are dynamically modified and recognised by a wide range of epigenetic proteins. Abnormal histone modification patterns and dysregulation of epigenetic proteins are implicated in many diseases. Thus, there is significant interest in developing chemical tools to probe the biology of these epigenetic proteins. Methylation of lysines on histones is reversible, and regulated by histone methyltransferases (KMTs) and demethylases (KDMs). Despite the emerging importance of KDMs in cellular processes and the intense therapeutic interest in relation to diseases, developing chemical tools for KDMs have been challenging. The talk will provide an overview of our recent work on KDMs, with a particular focus on peptide-based strategies to develop chemical and mechanistic probes.

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➢ Educational Background

2003 B.Sc., Faculty of Science, Department of Chemistry, Konan University (supervisor: Prof. Naoki Sugimoto)
2005 M.Sc., Graduate School of Natural Science, Chemistry, Konan University (supervisor: Prof. Naoki Sugimoto)
2001 Doctor of Science, Graduate School of Natural Science, Life and Functional Material Science, Konan University (supervisor: Prof. Naoki Sugimoto)

➢ Professional Career

2005.4-2008.3	Research Fellow, Japan Society for the Promotion of Science, Japan
2008.4-2009.2	Researcher, Fine Co. Ltd., Japan
2008.4-2008.6	Visiting postdoctoral researcher, University of Illinois, USA
2010.7	Assistant Professor of Frontier Institute for Biomolecular Engineering Research (FIBER), Konan University
2016.4	Lecturer of Frontier Institute for Biomolecular Engineering Research (FIBER), Konan University

➢ Research Interests

1) Nucleic Acid Chemistry
2) Biochemistry and Biofunctionalchemistry

➢ Awards

2014 Lecture Award, The 95th CSJ (the Chemical Society of Japan) Annual Meeting
2014 Lecture Award, Bio-Related Chemistry Symposium
2017 Shiseido Science Grant Award
2019 CSJ award for Outstanding Young Women Chemist

➢ Recent Publications

1. "A–T base pairs are more stable than G–C base pairs in a hydrated ionic liquid", Tateishi-Karimata H, Sugimoto N., *Angew. Chem. Int. Ed.* **2012**, *51*, 1416.
2. "i-Motifs are more stable than G-quadruplexes in a hydrated ionic liquid", Hisae Tateishi-Karimata, Miki Nakano, Smritimoy Pramanik, Shigenori Tanaka, Naoki Sugimoto, *Chem. Commun.* **2015**, *51*, 6909.
3. "Newly characterized interaction stabilizes DNA structure: oligoethylene glycols stabilize G-quadruplexes CH–π interactions ", Hisae Tateishi-Karimata, Tatsuya Ohyama, Takahiro Muraoka, Peter Podbevsek, Adam M. Wawro, Shigenori Tanaka, Shu-ichi Nakano, Kazushi Kinbara, Janez Plavec, Naoki Sugimoto, *Nucleic Acids Res.* **2017**, *45*, 7021.
4. "Destabilization of DNA G-Quadruplexes by Chemical Environment Changes during Tumor Progression Facilitates Transcription", Hisae Tateishi-Karimata, Keiko Kawauchi, Naoki Sugimoto, *J. Am. Chem. Soc.* **2018**, *140*, 642.

Role for G-quadruplexes of Nucleic Acids During Tumor Progression

Hisae Tateishi-Karimata[a] and Naoki Sugimoto[a,b]

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[b]*Graduate School of Innovative Research in Science and Technology (FIRST), Konan University, 17-1-20 Minatojima-minamimachi, Kobe, 650-0047, Japan*

The DNA structures adopted are affected by their surrounding environments. The canonical DNA structure is a duplex; however, DNA can also form noncanonical structures of triplexes, G-quadruplexes, and cruciforms. The highly crowded intracellular environments mimicked by cosolutes such as polyethylene glycol (PEG) and stabilize noncanonical DNA structures and destabilize duplexes suggesting that noncanonical DNAs should have important roles in cells. Previous reports indicated that transcription by arrested or slipped prior to the formation of stable structures such as Z-form duplexes, triplexes, and G-quadruplexes in template DNA. We previously showed that the frequency of mutations resulting from arrest and slippage depends on the stability of the G-quadruplexes formed in the template DNAs. There are 300,000 sequences with the potential to form G-quadruplex structures in the human genome, with most of these sequences located in oncogenes or proto-oncogenes. G-quadruplex formation is highly responsive to surrounding conditions, particularly K^+ concentration. Malignant cancer cells have a much lower K^+ concentration than normal cells because of overexpression of a K^+ channel; thus, G-quadruplexes may be unstable in cancer cells. Here, we investigated physicochemically how changes of intracellular chemical environments influence G-quadruplex formation and transcription during tumor progression *in vitro* and in cells. *In vitro*, the stable G-quadruplex formation inhibits transcription in a solution containing 150 mM KCl (normal condition). As K^+ concentration decreases, which decreases G-quadruplex stability, transcript production from templates with

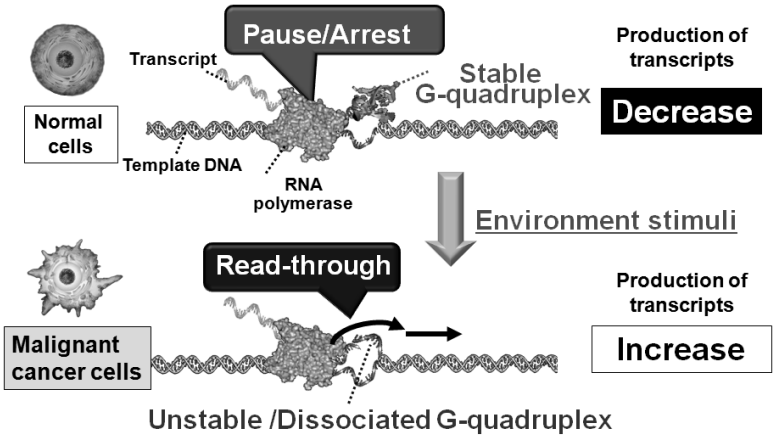

Figure 1. Schematic illustration of effects of G-quadruplex formation on transcription.

G-quadruplex-forming potential increases. In normal cells, the trend in transcript productions was similar to that in experiments in vitro, that is, transcription efficiency inversely correlated with G-quadruplex stability. Interestingly, higher transcript levels were produced from templates with G-quadruplex-forming potential in Ras-transformed and highly metastatic breast cancer cells (MDA-MB-231) than in non-transformed and control MCF-7 cells. These results suggest that in normal cells, K^+ ions attenuate the transcription of certain oncogenes by stabilizing G-quadruplex structures (Figure 1). The G-quadruplex-forming sequences at cancer related genes are located mainly in non-coding DNA region suggesting that the G-quadruplexes would have important roles during tumor progression.

Acknowledgment: This research was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and Japan Society for the Promotion of Science (JSPS), especially a Grant-in-Aid for Scientific Research on Innovative Areas "Chemistry for Multimolecular Crowding Biosystems" (JSPS KAKENHI Grant No. JP17H06351), and Grant-in-Aid for Scientific Research (C)(JP17K05941), Japan, Shiseido Female Researcher Science Grant, and Kawanishi Memorial Shinmaywa Education Foundation.

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➢ Educational Background

1999 MChem. Chemistry, University of Warwick
2004 PhD. Nucleic Acid Chemistry, University of Sheffield (supervisor: Dr. David Williams)

➢ Professional Career

2004 Postdoctoral Research Assistant, University of Liverpool (Prof. Rick Cosstick)
2006 JSPS Postdoctoral Research Fellow, Kyushu University (Prof Shigeki Sasaki)
2008 Lecturer in Pharmaceutical Chemistry, University of Reading
2017 Associate Professor in Pharmaceutical Chemistry, University of Reading
2017 Head of Pharmaceutics and Pharmaceutical Chemistry, Reading School of Pharmacy, University of Reading

➢ Research Interests

1) Nucleic Acid structure and function, in particular, the structure and function of i-motifs
2) Ruthenium complex binding to nucleic acid structures, including duplexes and higher order structures

➢ Recent Publications

1. "Structural Studies Reveal Enantiospecific Recognition of a DNA G-Quadruplex by a Ruthenium Polypyridyl Complex", Kane McQuaid, Holly Abell, Sarah P. Gurung, David R. Allan, Graeme Winter, Thomas Sorensen, David J. Cardin, John A. Brazier, Christine J. Cardin, James P. Hall, *Angew. Chem. Int. Ed.* **2019**, DOI:10.1002/anie.201814502.
2. "Topological impact of noncanonical DNA structures on Klenow fragment of DNA polymerase", Shuntaro Takahashi, John A. Brazier, Naoki Sugimoto, *PNAS* **2017**, *114 (36)*, 9605.
3. "The importance of loop length on the stability of i-motif structures", Gurung, S. P., Schwarz, C., Hall, J. P., Cardin, C. J. and Brazier, J. A. *Chem. Commun.* **2015**, *51(26)*, 5630.
4. "I-Motif formation in gene promoters: unusually stable formation in sequences complementary to known G-quadruplexes", John A. Brazier,* Arti Shaha, Geoffrey D. Brown, *Chem. Commun.* **2012**, *48 (87)*, 10739.

Expanding The i-motif –Why Does Sequence Matter?

John A. Brazier,[a] James P. Hall,[a] and Christine J. Cardin[b]

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[b]*Department of Chemistry, University of Reading, Reading, RG6 6AD, United Kingdom*

The i-motif is quadruplex structure that is formed by cytosine-rich sequences of DNA and is formed of cytosine: cytosine basepairs (Figure 1). Recently, the presence of the i-motif in the nucleus of human cells has been demonstrated using an antibody selected for its specificity to the i-motif structure.[1]

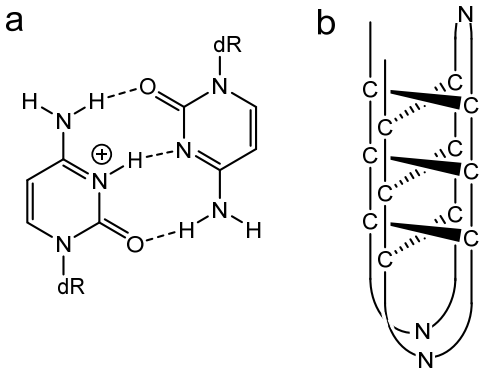

Figure 1. a) protonated-cytosine: cytosine base pair b) Schematic representation of an i-motif structure, where N denotes any DNA heterocyclic base.

This recent finding, along with the evidence that shows the role of the i-motif in modulating gene expression[2] and its ability to inhibit polymerases,[3] shows the importance in understanding more about this unusual structure. It is known from research on biologically derived sequences, that i-motifs formed by different sequences exhibit different thermal and pH stability.

We are interested in understanding how sequence plays a role in stability, and whether we can use sequence to provide recognition sites for binding events, whether that is small molecules, or larger biomolecules. We have shown that longer loops are inherently less stable than short loops,[4] but we have recently demonstrated that long loops provide a suitable binding area for a metal complex,[5] and could therefore be targeted and stabilized by binding molecules. We have also begun to understand that the requirement for 4 continuous cytosine tracts is not always required for i-motif formation and that these can be interrupted by non-cytosine bases.[6]

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