First Osaka University-EPFL International Symposium

Supported by Embassy of Switzerland in Japan and Nitto Denko Corporation

Research Symposium

Final Program and Abstracts

Icho-Kaikan

Osaka University

Suita, Osaka, Japan
December 2-4, 2013

大阪大学 OSAKA UNIVERSITY

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Nitto

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Science & Technology Office Tokyo
科学技術部

150 Anniversary of Diplomatic Relations between Switzerland and Japan
日本・スイス国交樹立記念

Welcome to the Research Symposium in the First Osaka University-EPFL International Symposium.

The objective of this research symposium is to provide an opportunity for discussing the novel developments, challenges, and the future perspectives in chemical biology, organic chemistry, and life science with researchers from Osaka University, EPFL, and Nitto Denko Corporation. The symposium will also provide you special session for funding opportunities and a Swiss promotion session.

I would like to express my appreciation for supports given by Osaka University, EPFL, and Embassy of Switzerland, Nitto Denko Corporation without whom this symposium would not have been possible

I look forward to fruitful discussions and interactions that will lead to future collaborations.

Prof. Koichi Fukase
Research Symposium director,
First Osaka University-EPFL International Symposium.

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Program

Monday, December 2nd

8:00-8:30	**Registration** (poster setting)
8:30-8:40	**Opening Greeting** (Osaka University /the Ambassador of Switzerland/ EPFL/ Nitto Denko Corporation)
8:40-8:45	**Speaker group photo shooting**
8:45-10:20	Session 1 (4talks) **Prof. Kai JOHNSSON (EPFL)** New Fluorescent Probes and Sensors **Prof. Kazuya KIKUCHI (Osaka)** Designed Chemical Probe for Highly Sensitive 19F MR Imaging **Prof. Takeharu NAGAI (Osaka)** Luminescent protein able to high speed imaging at single cell and whole body level **Dr. Ruud HOVIUS (EPFL)** A fluorogenic probe based on the solvatochromic dye Nile Red for wash-free labeling of SNAP fusion proteins on the cell surface
10:20-10:40	Coffee Break
10:40-11:55	Session 2 (3 talks) **Prof. Gerardo TURCATTI (EPFL)** From the Biomolecular Screening Facility at the EPFL to the Chemical Biology Screening platform for Switzerland **Prof. Koichi FUKASE (Osaka)** Visualization of Glycan-dependent Bio-dynamics of Glycoproteins, Glycan Dendrimers, and Living Cells by PET and Fluorescent Imaging

	Prof. Hiroaki SASAI (EPFL) Novel Catalytic Reaction Promoted by Pd-SPRIX Complex
11:55-12:05	**Group photo shooting session** (all participants)
12:05-13:20	**Lunch** (Restaurant Minerva 2F, only invited participants)
13:20-14:40	**Session 3** (Nitto Denko Corporation Session) Introductory presentation - overview of activities in Life Science - and 4 Scientific presentations
14:40-16:10	**Poster Session and Networking 1** (coffee and snacks around 3 pm)
16:10-17:20	**Funding opportunities for Swiss-Japan collaboration and fellowships** (JEUPISTE, SNSF, Osaka University, and EPFL)
17:20-17:30	Break
17:30-18:30	**Swiss promotion Session** (Embassy of Switzerland)
18:45-20:00	Swiss Apero with wine and cheese (Cafeteria Takumi)
19:45 -	
Dinner 1:	Professors of Osaka Univ. and EPFL
Dinner 2:	Nitto Denko Corporation and EPFL VPIV & International Relations

In parallel event: ***Swiss Information Booth*** *(12:00-17:00)*

Tuesday, December 3rd

8:30-8:35	**Announcements**
8:35-8:50	**Introduction of Osaka University and its research activities**
8:50-9:05	**Introduction of EPFL and its research activities**
9:05-10:20	**Session 4** (3 talks) **Prof. Harm-Anton KLOK (EPFL)** Combating Diseases with Peptide – Polymer Conjugates **Prof. Yasuhiro KAJIHARA (Osaka)** Chemical Synthesis of Misfolded and Correctly Folded Glycoproteins: A Unique Approach for the Study of Glycoprotein Quality Control **Prof. Kazuhiko NAKATANI (Osaka)** Small Organic Molecules regulating RNA Structure and Function
10:20-10:40	Coffee Break
10:40-11:55	**Session 5** (3 talks) **Prof. Beat FIERZ (EPFL)** Chromatin as a Dynamic Platform for Protein-Protein Interactions **Prof. Michio MURATA (Osaka)** Intermolecular Hydrogen Bonding between Amides of Sphingomyelin in Raft Model Membrane **Prof. Jieping ZHU (EPFL)** From Isonitrile to Heterocycles and potential Fluorescence probes
11:55-13:25	**Lunch** (lunch meeting among professors) Conference Room C, 3F
13:25-14:55	**Poster Session and Networking 2** (coffee and snacks around 2pm)
14:55-16:10	**Session 6** (3 talks) **Prof. Jérôme WASER (EPFL)** Hypervalent Iodine Reagents: New Tools for the Synthesis of

	Alkynes **Prof. Christian HEINIS (EPFL)** Development of Bicyclic Peptides for Therapeutic Application **Prof. Hiromichi FUJIOKA (Osaka)** Organic Synthesis Using Electrophilic Salt Intermediates: Alkyl ether from MOM Ethers and Mixed Acetals
16:10-16:20	**Concluding remarks** (Prof. Fukase and Prof. Zhu)

(17:00　Posters should be taken out)

Wednesday, December 4th　(optional participation)

10:00-12:00	**Lab visit** (The Institute of Scientific and Industrial Research, Osaka Univ.)
12:00-13:30	**Lunch**
13:30 -	**Industry visit: Nitto Denko Ibaraki Site**
16:00	**Hotel** (Senri Hankyu Hotel)

Session 1

Chaired and Presented by

Prof. Johnsson, Prof. Kikuchi, Prof. Nagai, and Dr. Ruud Hovius

NEW FLUORESCENT PROBES AND SENSORS

Kai JOHNSSON

Keywords: Fluorescent sensors, protein chemistry, live-cell imaging

ABSTRACT:
In the first part of my presentation I will introduce a highly permeable and biocompatible near-infrared fluorophore that can be specifically coupled to intracellular proteins in live cells and tissues using different labeling techniques. The fluorogenic character of the probe and its high brightness permit live-cell imaging experiments without washing steps. The fluorophore is ideally suited for live-cell superresolution microscopy approaches using either stimulated emission depletion (STED) or stochastic single-molecule localization nanoscopy. The excellent spectroscopic properties of the probe combined with its ease of use in live-cell applications make it a powerful new tool for bioimaging.
In the second part of my talk, I will talk about our attempts to introduce a new class of fluorescent sensor proteins that permit to visualize drug and metabolite concentrations in living cells with high spatial and temporal resolution.

Kai JOHNSSON, Ph.D

Professor
Kai Johnsson is Professor at the Institute of Chemical Sciences and Engineering of EPFL. His current research interests are the development and application of chemical approaches to study and manipulate protein function. His past achievements include the introduction of different approaches to specifically label proteins in living cells; among these the SNAP-tag and CLIP-tag have become popular in the biological community.

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Selected Publications

(1) "Selective Chemical Crosslinking Reveals a Cep57-Cep63-Cep152 Centrosomal Complex", Lukinaviclus, G.; Lavogina, D.; Orpinell, M.; Umezawa, K.; Reymond, L.; Garin, N.; Gonczy, P.; Johnsson, K., *Curr Biol* **2013**, *23*, 265.

(2) "A near-infrared fluorophore for live-cell super-resolution microscopy of cellular proteins", Lukinavicius, G.; Umezawa, K.; Olivier, N.; Honigmann, A.; Yang, G.; Plass, T.; Mueller, V.; Reymond, L.; Correa, I. R., Jr.; Luo, Z. G.; Schultz, C.; Lemke, E. A.; Heppenstall, P.; Eggeling, C.; Manley, S.; Johnsson, K., *Nature chemistry* **2013**, *5*, 132.

(3) "Tetrahydrobiopterin biosynthesis as an off-target of sulfa drugs", Haruki, H.; Pedersen, M. G.; Gorska, K. I.; Pojer, F.; Johnsson, K., *Science* **2013**, *340*, 987.

(4) Trefzer, C.; S'kovierova, H.; Buroni, S.; Bobovska, A.; Nenci, S.; Molteni, E.; Pojer, F.; Pasca, M. R.; Makarov, V.; Cole, S. T.; Riccardi, G.; Mikusova, K.; Johnsson, K. In *J Am Chem Soc* 2012; Vol. 134, p 912.

(5) "A Fluorescent Sensor for GABA and Synthetic GABA(B) Receptor Ligands", Masharina, A.; Reymond, L.; Maure, D.; Umezawa, K.; Johnsson, K., *J Am Chem Soc* **2012**, *134*, 19026.

(6) "A Semisynthetic Fluorescent Sensor Protein for Glutamate", Brun, M. A.; Tan, K. T.; Griss, R.; Kielkowska, A.; Reymond, L.; Johnsson, K., *J Am Chem Soc* **2012**, *134*, 7676.

Designed Chemical Probe for Highly Sensitive ^{19}F MR Imaging

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Keywords: Imaging, MRI, ^{19}F

ABSTRACT:
One of the great challenges in the post-genome era is to clarify the biological significance of intracellular molecules directly in living cells. If we can visualize a molecule in action, it is possible to acquire biological information, which is unavailable if we deal with cell homogenates. One possible approach is to design and synthesize chemical probes that can convert biological information to chemical output.

Magnetic resonance imaging (MRI) is an imaging modality adequate for *in vivo* studies. Therefore, many scientists are interested in the development of MRI probes capable of detecting enzyme activities *in vivo*. Because background signal is hardly detectable, ^{19}F-MRI probes are promising for *in vivo* imaging. A novel design strategy for ^{19}F-MRI probes to detect protease activities is proposed. The design principle is based on the paramagnetic relaxation effect from Gd^{3+} to ^{19}F. A peptide was synthesized, Gd-DOTA-DEVD-Tfb, attached to a Gd^{3+} complex at the N-terminus and a ^{19}F-containing group at the C-terminus. The ^{19}F-NMR transverse relaxation time (T_2) of the compound was largely shortened by the paramagnetic effect of intramolecular Gd^{3+}. The peptide was designed to have a sequence cleaved by an apoptotic protease, caspase-3. When the peptide was incubated with caspase-3, the peptide was cleaved and subsequently the Gd^{3+} complex and the ^{19}F-containing group were separated from each other. T_2, after cleavage, was extended to cancel the intramolecular paramagnetic interaction. T_2 is a parameter that can be used to generate contrasts in MR images. Using this probe as a positive contrast agent, the probe could detect caspase-3 activity spatially from an image using ^{19}F MRI.

Then sensitive detection using ^{19}F MRI for in vivo cell tracking was invesitigated. Following two key points are necessary for a highly sensitive ^{19}F MRI contrast agent: increasing the number of fluorine atoms within a probe, and free molecular motion of fluorine atoms to retain the long T_2. Herein, development of novel multifunctional nanoparticles that fulfill the requirements is described. The nanoparticles are composed of a core micelle filled with liquid perfluorocarbon and a silica shell, which can be chemically functionalized in organic solvents. The free rotation of fluorine atoms was maintained in the stable silica shell. Thereby, the T_2 did not change when the nanoparticle was attached to a macromolecule. These nanoparticles enabled the highly sensitive ^{19}F MRI detection of gene expression in living cells and tumor tissue in mice. These results show that the robust nanoparticles are suitable for in vivo applications, in terms of sensitivity, biocompatibility, and stability.

Kazuya KIKUCHI, Ph.D

Professor

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Postdoc at University of California, San Diego, USA (1994), and at The Scripps Research Institute, USA (1995).
Assistant Professor at Graduate School of Pharmaceutical Sciences, The University of Tokyo (1997).
Associate Professor at Graduate School of Pharmaceutical Sciences, The University of Tokyo (2000).
Professor at Graduate School of Engineering, Osaka University (2005).
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Selected Publications

1. S. Mizumkami, Y. Hori,and K. Kikuchi: Small-Molecule-Based Protein-Labeling Technology in Live Cell Studies: Probe-Design Concepts and Applications. Acc. Chem. Res. 46, in press (2013)

2. R. Baba, Y. Hori, S. Mizukami, and K. Kikuchi: Development of Fluorogenic Probe with Transesterification Switch for Detection of Histone Deacetylase Activity. J. Am. Chem. Soc. 134, 14310-3 (2012)

3. S. Mizukami, S. Watanabe, Y. Akimoto, and K. Kikuchi: No-Wash Protein Labeling with Designed Fluorogenic Probes and Application to Real-Time Pulse-Chase Analysis. J. Am. Chem. Soc., 134, 1623-9 (2012)

4. S. Mizukami, T. Yamamoto, A. Yoshimura, S. Watanabe, and K. Kikuchi: Covalent Protein Labeling with a Lanthanide Complex and its Application to Photoluminescence Lifetime-based Multicolor Bioimaging. Angew. Chem. Int. Ed. 50, 8750-2 (2011)

5. S. Mizukami, M. Hosoda, T. Satake, S. Okada, Y. Hori, T. Furuta, K. Kikuchi: Photocontrolled Compound Release System Using Caged Antimicrobial Peptide. J. Am. Chem. Soc. 132, 9524-5 (2010)

6. S. Mizukami, S. Watanabe, Y. Hori, and K. Kikuchi: Covalent Protein Labeling Based on Non-catalytic β-Lactamase and a Designed FRET Substrate. J. Am. Chem. Soc. 131, 5016-7 (2009)

7. S. Mizukami, R. Takikawa, F. Sugihara, M. Shirakawa, and K. Kikuchi: Dual Functional Probe to Detect Protease Activity for Fluorescence Measurement and ^{19}F MRI. Angew. Chem. Int. Ed. 48, 3641-3 (2009)

8. S. Mizukami, K. Tonai, M. Kaneko, and K. Kikuchi: Lanthanide-based Protease Activity Sensors for Time-resolved Fluorescence Measurements. J. Am. Chem. Soc. 130, 14376-7 (2008)

9. S. Mizukami, R. Takikawa, F. Sugihara, Y. Hori, H. Tochio, M. Wälchli, M. Shirakawa, and K. Kikuchi: Paramagnetic Relaxation-based ^{19}F MRI Probe to Detect Protease Activity. J. Am. Chem. Soc. 130, 794-5 (2008)

Luminescent protein able to high speed imaging at single cell and whole body level

Takeharu NAGAI ,
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Keywords: bioimaging, fluorescence, chemiluminescence, FRET, optogenetics

ABSTRACT:
Fluorescence imaging is widely used, but the dependence on external illumination prevents its universal application. For example it cannot be used to study light dependent biological processes such as photosynthesis. Moreover it is incompatible with the non-invasive imaging of whole organisms, or other applications where the cellular substrate is autofluorescent, saturated with photopigments or extremely photosensitive. Experimental conflicts arise when external illumination is essential in other biological technologies, such as optogenetics, chromophore-assisted light inactivation, or photolysis of caged compounds, preventing simultaneous use of fluorescence imaging. Finally sub W/cm^2 external illumination, which is general power density for fluorescence excitation in live cell imaging under the wide field microscopic observation, sometimes causes phototoxic effects in visualized substrates which alter cellular behavior and ultimately cause cell death. By contrast chemiluminescence generates a visible light signal by a localized chemical reaction without the need for external illumination. The k_{cat} values of conventional luciferases are ranging from 0.1 for Fluc (quantum yield=0.5) and aprox. 4.4 for RLuc8 (quantum yield=0.053). Provided that cells express several μM Rluc8, a typical concentration of transiently expressed protein, the power density of light emitted from the Rluc8-expressing cells could be calculated as approximately 0.1 μW/cm^2 which is 1/10^3 of general power density for fluorescence excitation in live cell imaging. It is therefore theoretically independent of the associated restrictions which limit biological application of fluorescence. However the 0.1 μW/cm^2 power density is not bright enough to image events on a biological scale with subsecond/micrometer accuracy. Therefore although the chemiluminescent protein including aequorin and luciferases have been used to image living cells, and organisms, the temporal and spatial resolution of this strategy is unable to match that of fluorescence. In luminous organisms such as the sea pansy *Renilla reniformis*, nature has solved this problem using BRET (bioluminescence resonance energy transfer), in which the excited energy of a luminescent substrate, coelenterazine, bound to *Renilla* luciferase (RLuc) (quantum yield=0.053) is efficiently transferred inter-molecularly to the acceptor *Renilla* green fluorescent protein (RGFP) (quantum yield=0.3) by a Förster resonance energy transfer (FRET) mechanism, thereby increasing the emitted photon number approximately 5 fold. Based on this natural inter-molecular BRET, intra-molecular BRET probes such as aequorin-GFP and BAF-Y have been developed. Although these allow live-cell imaging with improved resolution in space and time, they still underperform compared with FP-based probes because of low brightness. To overcome this drawback, *Renilla reniformis* luciferase (Rluc) was conducted on random mutagenesis to improve the intensity. Then, the luminescence intensity was further increased by fusion of the enhanced Rluc (eRluc) to a yellow fluorescent protein, Venus with high BRET efficiency. The chimeric protein, Nano-lantern, showed much brighter luminescence than the commercially available Rluc, enabling not only real-time imaging of intracellular structures in living cells with spatial resolution equivalent to fluorescence but also sensitive tumor detection in freely moving mice which has never been possible before. We then applied the intense luminescent protein to design Ca^{2+}, cAMP, and ATP indicators, thereby we succeeded imaging these bioactive molecules in environments where fluorescent indicators have failed. These super-duper luminescent proteins will revolutionize conventional bioimaging by allowing visualization of biological phenomena not seen before at the single-cell, organ, and whole-body level, in animals and plants.

Takeharu NAGAI, Ph.D

Professor

1998: Ph.D. Graduate School of Medicine, The University of Tokyo
1998-2001: Postdoc, Brain Science Institute, RIKEN.
2001-2005: PRESTO, JST
2005-2012: Professor, Research Institute for Electronic Science, Hokkaido University
2008- : PRESTO, JST
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Service and honors

- Committee member of Japan Society of Biophysics
- Editorial board member of BIOPHYSICS
- Editorial board member of MICROSCOPY
- Kihara memorial foundation award for applied science

Research Interest

- Minority Biology, Green Biology, Protein engineering

Selected Publications

1. Takemoto K. et al. SuperNova, a monomeric photosensitizing protein for chromophore assisted light inactivation. **Scientific Reports** 3, 2629 (2013)
2. Matsuda T. et al. Highlighted Ca^{2+} imaging with a genetically encoded 'caged' indicator. **Scientific Reports** 3, 1398 (2013).
3. Saito K. et al. Luminescent protein for high-speed single-cell and whole-body imaging. **Nature Communications** 3, 1262 (2012).
4. Zhao Y. et al. An expanded palette of genetically encoded Ca^{2+} indicators. **Science** 333, 1888-91 (2011).
5. Horikawa K et al. Spontaneous network activity visualized by ultrasensitive Ca^{2+} indicators, yellow Cameleon-Nano. **Nature Methods** 7, 729-32 (2010)
6. Tomosugi W. et al. An ultramarine fluorescent protein with increased photostability and pH insensitivity. **Nature Methods** 6, 351-3 (2009)
7. Matsuda T. et al. Direct measurement of protein dynamics inside cells using a rationally designed photoconvertible protein. **Nature Methods** 5, 339-45 (2008)
8. Okamoto K. et al. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bi-directional plasticity. **Nature Neuroscience** 7, 1104-12 (2004)
9. Nagai T. et al. Expanded dynamic range of fluorescent indicators for Ca^{2+} by circularly permuted yellow fluorescent proteins. **PNAS** 101, 10554-9 (2004)
10. Nagai T et al. A variant of yellow fluorescent protein with fast and efficient maturation for cell biological applications. **Nature Biotechnology** 20, 87-90 (2002)
11. Nagai T et al. Circularly permuted green fluorescent protein engineered to sense Ca^{2+}. **PNAS** 98, 3197-202 (2001)

A fluorogenic probe based on the solvatochromic dye Nile Red for wash-free labeling of SNAP fusion proteins on the cell surface

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Keywords: Membrane protein labelling, fluorogenic probe, SNAP tag, no-wash

ABSTRACT:

Homogeneous, no-wash methods for the labelling of proteins in cells offers several important advantages with respect to methods involving wash steps, e.g. speed or less stressful to the cells. Here, a fluorogenic probe for cell membrane proteins based on the solvatochromic dye Nile Red and SNAP-tag is introduced. It takes advantage of Nile Red, a solvatochromic molecule highly fluorescent in an apolar environment, like cellular membranes, but almost dark in a polar aqueous environment. The probe possesses a tuned affinity for membranes allowing its Nile Red moiety to insert into the lipid bilayer – and becoming fluorescent - only after the conjugation of the benzylguanine part of the probe to a membrane protein fusion of SNAP-tag. Human insulin receptor fused to SNAP-tag was specifically labeled at the surface of live cells using this probes. This work introduces a powerful turn-on probe for “no wash” specific targeting of SNAP fusion membrane proteins with interesting applications.

Ruud Hovius, Ph.D

Senior scientist

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Senior scientist at Laboratory of Protein Engineering, EPFL.
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Selected Publications

1. A. Keppler, S. Gendreizig, T. Gronemeyer, H. Pick, H. Vogel and K. Johnsson. A general method for the covalent labeling of fusion proteins with small molecules in vivo. Nature Biotechnology, 21(1) 86-89 (2003)

2. E. G. Guignet, et al. Reversible site-selective labeling of membrane proteins in live cells. Nature Biotechnology, 22(4) 440-444 (2004)

3. J. Grandl, et al. Fluorescent epibatidine Agonists for neuronal and muscle-type nicotinic acetylcholine receptors. Angewandte Chemie, 46(19), 3505-3508 (2007)

4. R. Schmauder, et al. Correlated optical and electrical single-molecule measurements reveal conformational diffusion from ligand binding to channel gating in the nicotinic acetylcholine receptor. ChemBioChem 12(16) 2431-2434 (2011)

5. L. Grasso, et al. Downscaling the analysis of complex transmembrane signaling cascades to closed attoliter volumes. PLoS ONE, 8(8) e70929 (2013)

Session 2

Chaired and Presented by

Prof. Turcatti, Prof. Fukase, and Prof. Sasai

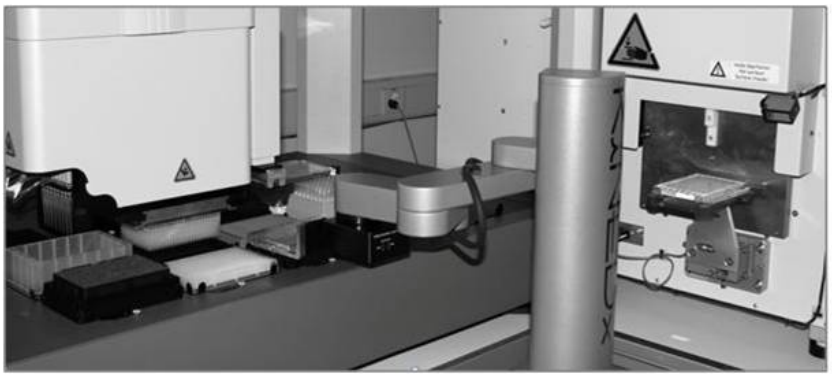
From the Biomolecular Screening Facility at the EPFL to the Chemical Biology Screening platform for Switzerland

Gerardo TURCATTI,
Biomolecular Screening Faclity, School of Life Sciences, EPFL
Station 15. Lausanne 1015, Switzerland

Keywords: Academic screening, Assay Automation, Assay Development, Chemical Biology, Gene Knockdown Screening, High Throughput screening, High Content Screening, siRNA, Systems Biology, Small Molecules.

ABSTRACT:

The Biomolecular Screening Facility (BSF) is a multidisciplinary laboratory created in 2006 for performing high throughput screening in life sciences-related projects. The screening platform was conceived and constructed according to a wide range of researchers needs rather than to privilege a particular biological discipline or therapeutic area. The BSF holds the necessary infrastructure, multidisciplinary expertise and flexibility for screening a variety of compound libraries including siRNAs and chemical collections (synthetic small molecules and natural products) in both cellular and biochemical target-based assays. In the frame of the NCCR-Chemical Biology, the BSF is hosting 'ACCESS', An Academic Chemical Screening Platform for Switzerland that provides the scientific community with chemical diversity, screening facilities and know-how in chemical genetics. In addition, the BSF applied research axes are driven by innovation in thematic areas related to bioactive compound discovery and preclinical drug discovery.



Gerardo TURCATTI, Ph.D

Senior Scientist. Director of the Biomolecular Screening Facility, EPFL. Project Leader of ACCESS (NCCR-Chemical Biology).

He graduated in Chemical Engineering at the University of Geneva and received his Ph.D in Sciences (Chemistry and Biochemistry) at the EPFL. More than 20 years industrial experience in Biotech and Pharma companies (Biogen, Glaxo, Serono and Manteia)

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Profile: Dr. Gerardo Turcatti, directs the academic technological platform, Biomolecular Screening Facility (BSF) at the EPFL (Swiss Federal Institute of Technology) he created in 2006. Previously he co-founded and acted as CTO of Manteia S.A., a Swiss-based company that developed revolutionary high throughput DNA sequencing technologies he transferred to Solexa and Lynx in 2004 (currently commercialized by Illumina Inc.) Prior to this experience, Dr Turcatti had a long multidisciplinary career in R&D divisions of Biotechnology and Pharmaceutical companies with extensive expertise in several Chemical Biology-related disciplines such as Drug Screening, Bio-analytical Chemistry, Receptor Biochemistry, DNA and Protein Chemistry. Dr Turcatti earned his Master in Chemical Engineering at the University of Geneva and his PhD in Chemistry and Biochemistry from the EPFL where he received the award for the best doctoral thesis of the year.

Selected Publications

1. Makhlouf Brahmi, M., Portmann, C., D'Ambrosio, D., Woods, T. M., Banfi, D., Reichenbach, P., Da Silva, L., Baudat, E., Turcatti, G., Lingner, J., and Gademann, K. (2013) Telomerase Inhibitors from Cyanobacteria: Isolation and Synthesis of Sulfoquinovosyl Diacylglycerols from Microcystis aeruginosa PCC 7806, *Chemistry – A European Journal 19*, 4596-4601.

2. Kühn, J., Shaffer, E., Mena, J., Breton, B., Parent, J., Rappaz, B., Chambon, M., Emery, Y., Magistretti, P., Depeursinge, C., Marquet, P., and Turcatti, G. (2012) Label-Free Cytotoxicity Screening Assay by Digital Holographic Microscopy, *ASSAY and Drug Development Technologies 11*, 101-107.

3. Magnet, S., Hartkoorn, R. C., Székely, R., Pató, J., Triccas, J. A., Schneider, P., Szántai-Kis, C., Orfi, L., Chambon, M., Banfi, D., Bueno, M., Turcatti, G., Kéri, G., and Cole, S. T. (2010) Leads for antitubercular compounds from kinase inhibitor library screens, *Tuberculosis 90*, 354-360

4.. Bentley, D. R.,et al., (2008) Accurate whole human genome sequencing using reversible terminator chemistry, *Nature 456*, 53-59.

5. Turcatti, G., Romieu, A., Fedurco, M. and Tairi A. (2008). A New Class of Cleavable Fluorescent Nucleotides: Synthesis and Optimization as Reversible Terminators for DNA Sequencing by Synthesis. *Nucl. Acids Res*. vol. 36, num. 4, p. e25, 200.

Visualization of Glycan-dependent Bio-dynamics of Glycoproteins, Glycan Dendrimers, and Living Cells by PET and Fluorescent Imaging

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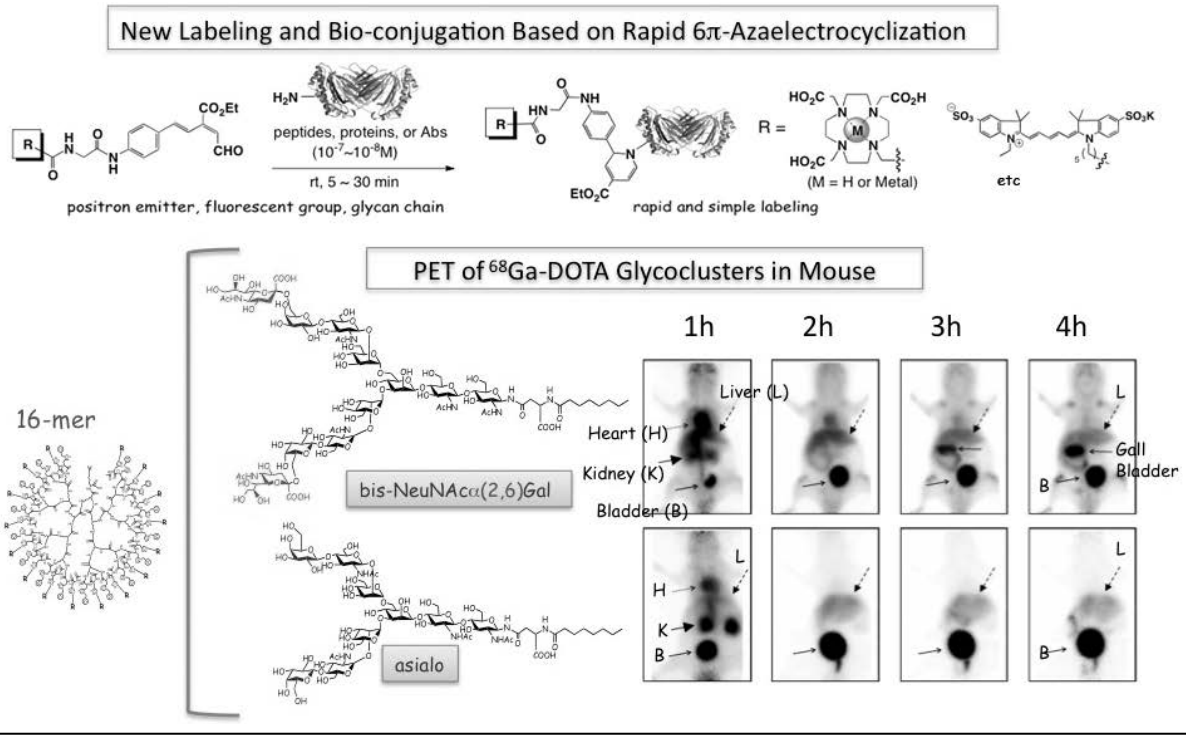
Keywords: PET imaging, Fluorescent imaging, Glycan, Dendrimer, Bioconjugation.

ABSTRACT:
New efficient labeling for peptides, proteins, and living cells using 6π-electrocyclization and the application to PET and fluorescent imaging and bioconjugation are described. The high reactivity of the conjugated aldehyde probe enabled the labeling at low concentration (~10^{-8} M) within a short period (10~30 min). PET imaging and fluorescence imaging of the labeled glycoproteins, glycodendrimers, and living cells successfully visualized the glycan-dependent bio-dynamics in whole-body system of mice or rabbits; Sia⟨(2,6)Gal glycans tend to retain in body, whereas asialoglycans and Sia⟨(2,3)Gal glycans tend to excreted rapidly through kidney and gallbladder. We also observed that bio-dynamics of glycodendrimers were significantly altered in tumor-implanted mice.
We then investigated a whole-body fluorescence imaging of tumor metastasis. Two kinds of cancer cells, i.e., human gastric cancer MKN45 and human colon cancer HCT116, and their transfected versions with the surface glycan-related genes, were fluorescently labeled and their trafficking and metastasis in BALB/c nude mice were imaged. The metastasis properties depending on glycan structures was clearly visualized over a month; the increased polylactosamine structure and the deficiency of fucosylation enhances the metastatic potential.
A new bioconjugation method was developed by using double azaelectrocyclization probe, which was sequentially reacted first with one peptide molecule and then with a protein or the amino groups on the surface of a live cell through double azaelectrocyclization to achieve highly efficient bioconjugation.



Koichi FUKASE, Ph.D

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EDUCATION: BS; Department of Chemistry, School of Science, Osaka University (1982),
Ph.D.; Department of Organic Chemistry, Graduate School of Science, Osaka University (1987)
RESEARCH EXPERIENCE: JSPS Fellow (1987-1988), Department of Chemistry, Graduate School of Science, Osaka University: Research Associate (1988-1996), Assistant Professor (1996-1998), Associate Professor (1998-2004), Professor (2004-present),
MEXT overseas fellow, Department of Chemistry, Columbia University (1994)
Email: koichi@chem.sci.osaka-u.ac.jp
Research field: synthetic organic chemistry, natural product chemistry, carbohydrate chemistry, bioorganic chemistry.
AWARDS: The Chemical Society of Japan Award for Creative Work (2011)

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Selected Publications

1. K. Tanaka, E. R. Siwu, K. Minami, K. Hasegawa, S. Nozaki, Y. Kanayama, K. Koyama, W. C. Chen, J. C. Paulson, Y. Watanabe, and K. Fukase: Noninvasive imaging of dendrimer-type *N*-glycan clusters: in vivo dynamics dependence on oligosaccharide structure. Angew. Chem. Int. Ed. Engl. 49(44), 8195-200 (2010).
2. K. Fukase and K. Tanaka: Bio-imaging and cancer targeting with glycoproteins and N-glycans. Curr. Opin. Chem. Biol. 16(5-6), 614-21 (2012).
3. N. Wang, C. Y. Huang, M. Hasegawa, N. Inohara, Y. Fujimoto, and K. Fukase: Glycan sequence-dependent Nod2 activation investigated by using a chemically synthesized bacterial peptidoglycan fragment library. Chembiochem 14(4), 482-8 (2013).
4. K. Tanaka, K. Moriwaki, S. Yokoi, K. Koyama, E. Miyoshi, and K. Fukase: Whole-body imaging of tumor cells by azaelectrocyclization: visualization of metastasis dependence on glycan structure. Bioorg. Med. Chem. 21(5), 1074-7 (2013).
5. Y. Fujimoto, K. Mitsunobe, S. Fujiwara, M. Mori, M. Hashimoto, Y. Suda, S. Kusumoto, and K. Fukase: Synthesis and biological activity of phosphoglycolipids from Thermus thermophilus. Org. Biomol. Chem. 11(30), 5034-41 (2013)
6. K. Tanaka, Y. Nakamoto, E. R. Siwu, A. R. Pradipta, K. Morimoto, T. Fujiwara, S. Yoshida, T. Hosoya, Y. Tamura, G. Hirai, M. Sodeoka, and K. Fukase: Development of bis-unsaturated ester aldehydes as amino-glue probes: sequential double azaelectrocyclization as a promising strategy for bioconjugation. Org. Biomol. Chem. 11(42), 7326-33 (2013)

Novel Catalytic Reaction Promoted by Pd-SPRIX Complex

Kazuhiro TAKENAKA, Suman C. MOHANTA, Yogesh D. DHAGE, Shinobu TAKIZAWA, Hiroaki SASAI
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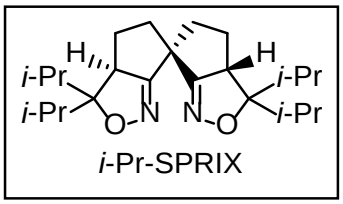
Keywords: Pd-enolate, enantioselective, catalyst, umpolung

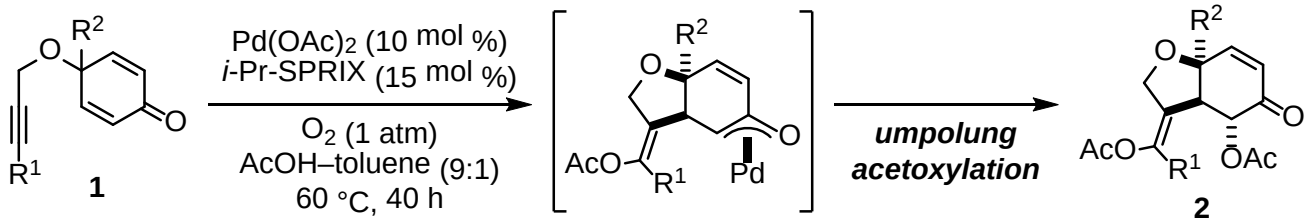
ABSTRACT:

π-Allyl Pd complexes are known to react with a variety of nucleophiles, whereas oxa-*π*-allyl Pd species (Pd enolates) commonly exhibit reactivity to an electrophile. Reactions of the Pd enolate with a nucleophile are therefore expected to be a novel and powerful synthetic protocol for carbonyl compounds. We have found that a unique ligand, SPRIX,[1,2] promotes the promising umpolung reaction which involves unusual nucleophilic interception of the Pd enolate. Thus, a cyclative diacetoxylation of alkynyl cyclohexadienones **1**[3] proceeded smoothly in the presence of Pd–*i*-Pr-SPRIX catalyst under an O_2 atmosphere (1 atm) in a 9:1 mixture of AcOH–toluene at 60 °C to produce densely functionalized benzofuranone derivatives **2** in good yields. Furthermore, the enantioselective reaction turned out to be accomplished by employing optically pure SPRIX.

In addition, a novel Pd(II/IV) catalysis to produce chiral 3-acetoxy-tetrahydrofuran derivatives from alkenyl alcohols will be discussed.[4]



i-Pr-SPRIX



up to 84% yield

1. G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa, and H. Sasai, *Bull. Chem. Soc. Jpn*. *82*, 285 (2009).
2. K. Takenaka, M. Akita, Y. Tanigaki, S. Takizawa, and H. Sasai, *Org. Lett. 13*, 3506 (2011) and references cited therein.
3. For a Pd-catalyzed cyclative acetoxylation of **1**, see: R. Tello-Aburto, and A. M. Harned, *Org. Lett. 11*, 3998 (2009).
4. K. Takenaka, Y. D. Dhage, and H. Sasai, *Chem. Commun. 49*, in press.

Hiroaki SASAI, Ph.D

Professor

The Institute of Scientific and Industrial Research (ISIR), Osaka University. Received Ph.D in applied chemistry at Keio University in 1985, Researcher at Sagami Chemical Research Center (1985-88), Assistant Professor at Hokkaido University (1988-92), Lecturer and Associate Professor at the University of Tokyo (1992-97), and Professor at Osaka University from 1997. Postdoc at University of California, Los Angeles, US in 1994.
Email: sasai@sanken.osaka-u.ac.jp

Awards
The Daicel Award in Synthetic Organic Chemistry in 1992, the Pharmaceutical Society of Japan Award for Young Scientists in 1995, the Fluka Prize “Reagent of the Year 1996”, the Chemical Society of Japan Award for Creative Work (2006), Ichimura Science Award (2006), and Molecular Chirality Award (2011).

LAB INFO
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Selected Publications

1. S. Takizawa, E. Rémond, F. A. Arteaga, Y. Yoshida, V. Sridharan, J. Bayardon, S. Jugé, and H. Sasai: P-Chirogenic organocatalysts: Application to the aza-Morita-Baylis-Hillman (aza-MBH) reaction of ketimines. Chem. Commun. 49, 8392-94 (2013)

2. S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, and H. Sasai: Organocatalyzed formal [2+2] cycloaddition of ketimines with allenoates: Facile access to azetidines with a chiral tetrasubstituted carbon stereogenic center. Org. Lett. 15, 4142-45 (2013)

3. S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders, and H. Sasai: Enantioselective synthesis of α-alkylidene-γ-butyrolactones: Intramolecular Rauhut-Currier reaction promoted by acid/base organocatalysts. Angew. Chem., Int. Ed. 51, 5423-26 (2012)

4. S. Takizawa, K. Kiriyama, K. Ieki, and H. Sasai: Bifunctional spiro-type organocatalyst with high enantiocontrol: Application to the aza-Morita–Baylis–Hillman reactions. Chem. Commun. 47, 9227-29 (2011)

5. S. Takizawa, N. Inoue, S. Hirata, and H. Sasai: Enantioselective synthesis of isoindolines: Organocatalyzed domino process based on the aza-Morita-Baylis-Hillman (aza-MBH) reaction. Angew. Chem. Int. Ed. 49, 9725-29 (2010)

6. T. Tsujihara, K. Takenaka, K. Onitsuka, M. Hatanaka, and H. Sasai: Pd^{II}/Pd^{IV} Catalytic enantioselective synthesis of bicyclo[3.1.0]hexanes via oxidative cyclization of enynes. J. Am. Chem. Soc. 131, 3452-53 (2009)

Session 3

Chaired and Presented by

Nitto Denko Corporation

Profile of NITTO DENKO Group and Life Science related R&D Activities

Yoshihisa NAKANO, ,
NITTO DENKO ASIA TECHNICAL CENTRE PTE LTD
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Keywords: life science, gene therapy, transdermal patch, medical device

ABSTRACT:
NITTO DENKO was founded in 1918 and will celebrate the 100th anniversary in 2018.
Corporate objective and vision are “Creation of New Value” and “Flexible Technology Company” respectively.
NITTO DENKO aims to become a company which can respond flexibly in any business fields based on their flexible technologies.
As of now, there are 109 group companies around the world and 80% of group companies is located overseas.
As for R&D, NITTO DENKO has 10 R&D bases globally and R&D centers which are conducting a life science related R&D activity are located in Japan, USA, Singapore and Switzerland.
NITTO DENKO’s core technologies are adhesion, coating, polymer function control and polymer analysis & evaluation technology.
NITTO DENKO Group is providing high-value added materials and products developed with these technologies in many business fields.
The early activity relate to life science in NITTO DENKO started in 1967 and NITTO DENKO has been bringing several life science related products to the market.
In particular, transdermal patches are useful for improving a patient’s QOL as a leading pharmaceutical product.
Over the last several years, NITTO DENKO has stepped into new research fields such as a gene therapy and an advanced medical device etc. in line with the market trend of lifestyle which is moving toward a preventive healthcare and advanced medical treatment.
There are several new technologies and products relate to life science being developed now in NITTO DENKO R&D centers around the world.

Global R&D Network for Life Science

Yoshihisa NAKANO

Managing Director

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The length of my stay in Singapore: 4 years
Technical background: Pharmaceutical Science

Selected Publications

1.

2.

3.

Novel Transdermal Drug Delivery System: PassPort™ System

Hirotoshi Adachi Ph.D.
Director, Life Science Research Center –US,
Nitto Denko Technical Corporation
11568 Sorrento Valley Rd., Suite 9, San Diego, CA 92130, USA

Keywords: Active Transdermal Therapeutic System (Active TTS), Drug Delivery System, PassPort™ System, Microporation, Dry-Patch, Large Molecule, Peptide and Protein

ABSTRACT:

The active transdermal therapeutic system (TTS) is a novel drug delivery technology to enhance drug penetration through the skin. As non-invasive active TTS, technologies such as iontophoresis and sonophoresis have been well known over the past decades. However, the use of these technologies has been limited to small molecules. Recently, advanced minimally-invasive active TTS such as microneedle and microporation technologies are focused on delivering large molecules.

Microporation technology utilizes energy to create micropores on the skin surface in order to systemically deliver biopharmaceutical medicines that include peptides, proteins, nucleic acids and vaccines. Nitto's microporation technology, the PassPort™ system, is a combination of a thermal ablation device and therapeutic transdermal dry-patch. The device consists of applicator and porator; the applicator delivers an electrical energy to a porator that converts current to heat and creates micropores. The dry-patch was invented specifically for use with the PassPort™ system; the drug is dispersed in a dry-state matrix. After application of PassPort™ system, the drug in a dry-patch is quickly dissolved by micropore exudates and then enters the body.

The PassPort™ system can enhance a delivery of both small and large molecules. One key feature of the technology is its ability to produce either an immediate or sustained pharmacokinetic (PK) profile – even for large molecules that are only available in injection forms. For example, the PassPort™ system has demonstrated basal insulin delivery in humans from a dry-patch formulation.

Overall, the PassPort™ system offers patient-friendly self-administration and is a good option for those experiencing difficulty taking medications. The technology can replace painful daily injections and reduce needle phobia that is often associated with poor patient compliance.

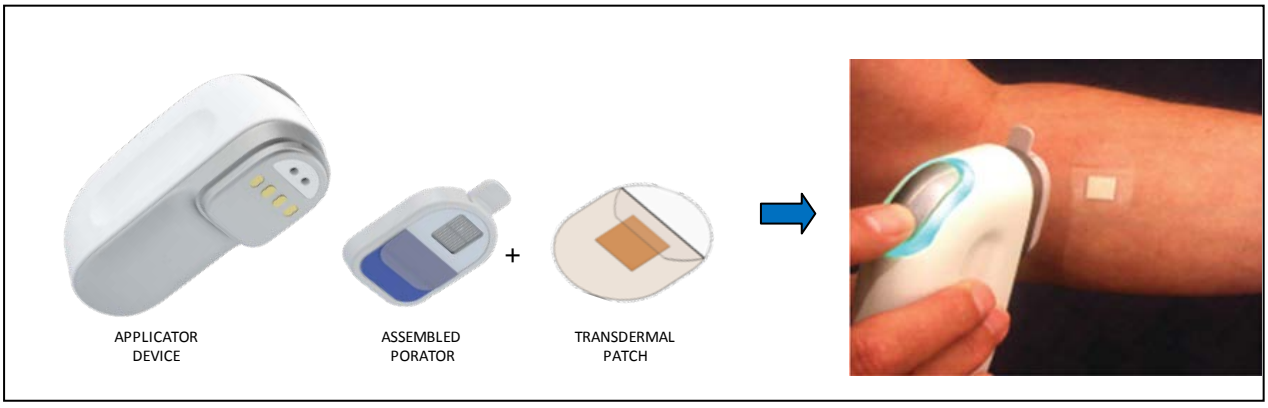

Figure: PassPort™ System

Hirotoshi Adachi, Ph.D.

Director
Life Science Research Center - US
Nitto Denko Technical Corporation

Graduated at Graduate School of Medical Pharmacy,
Kumamoto University and received Ph.D. in Pharmaceutical Sciences

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Dr. Adachi is a director of Life Science Research Center – US, Nitto Denko Technical Corporation. He is responsible for the development of novel transdermal technologies.

Dr. Adachi received his Ph.D. in Pharmaceutical Sciences at Kumamoto University in Japan in 1993. He has been working for pharmaceutical companies and collaborated with Prof. Richard Guy at University of Geneva in 2001.

He has over 20 years experiences in pharmaceutical companies in Japan and US, and credited with co-authoring about 20 articles and 30 patents related to transdermal drug delivery systems. He is specialized in directing transdermal technology development and CMC regulatory.

Selected Publications

1. Topical iontophoretic delivery of chlorhexidine, H. Adachi, Y.N. Kalia, R.H. Guy, N. Higo and A. Naik, Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., 28, 211-212, San Diego (USA), 2001.
2. Iontophoretic pulsatile transdermal deliverly of human parathyloid hormone (1-34), Yasuyuki Suzuki, Katsumi Iga, Shigeo Yanai, Yukihiro Matsumoto, Masahiro Kawase, Tunehiko Fukuda, Hirotoshi Adachi, Naruhito Higo and Yasuaki Ogawa, J. Pharm. Pharmacol., 53, 1227-1234, 2001.
3. Prevention of bone loss In ovariectomized rats by pulsatile transdermal iontophoretic administration of human PTH (1-34), Yasuyuki Suzuki, Yoshinori Nagase, Katsumi Iga, Masahiro Kawase, Masahiro Oka, Shigeo Yanai, Yukihiro Matsumoto, Shizue Nakagawa, Tunehiko Fukuda, Hirotoshi Adachi, Naruhito Higo and Yasuaki Ogawa, J. Pharm. Sci., 91, 350-361, 2002.

Selected Oral Presentations

1. Transdermal Drug Delivery Systems, INOVACOES NO TRATAMENTO DA PATOLOGIA MUSCULOESQUELETICA, Lisbon, Portugal, 2010.
2. Development strategy of topical and systemic transdermal drug delivery system, ROME REHABILITATION 2010 – S.I.C.D., Rome, Italy, 2010.

Patents

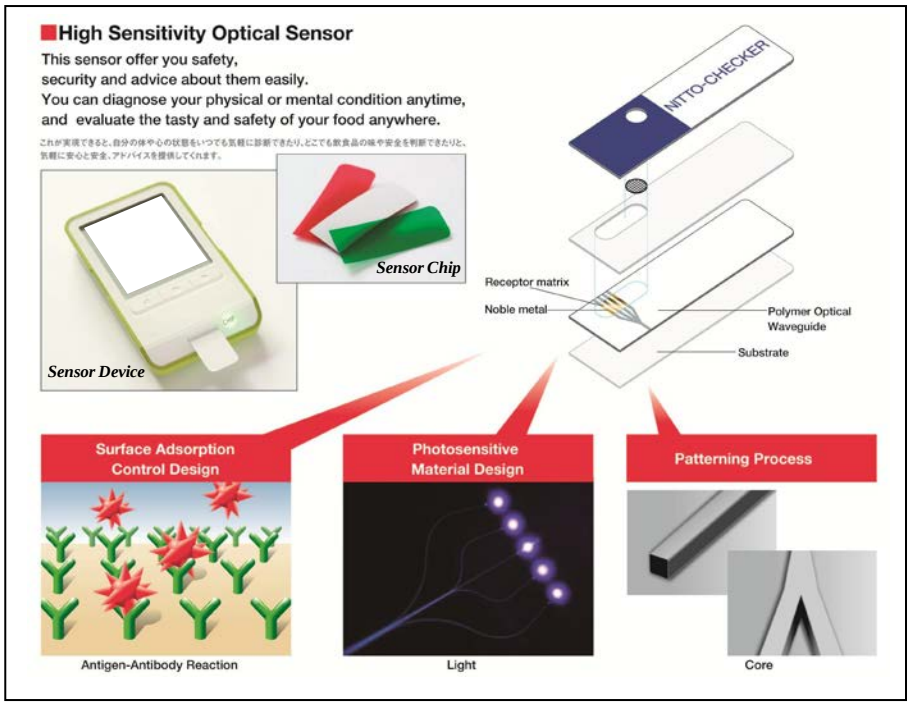
- 16 Published Applications and 9 Patents in the U.S.
- 27 PCT Applications
- 32 Published Applications and 21 Patents in Japan
- 7 Design Patents in Japan

High Sensitivity Handy Optical Bio-sensor combined Optical Waveguide and Surface Plasmon Resonance Design

Tomohiro KONTANI
NITTO DENKO CORPORATION
Life Science Research Center, Technology Section 2
Photonics Center 4F, Osaka University, 565-0871, Japan

Keywords: medical device, optical sensor, SPR, polymer optical waveguide, immune reaction

ABSTRACT:
NITTO DENKO has developed several optical sensing technologies in the world.
One of them is the mobile optical bio-sensor combined the polymer optical waveguide and surface plasmon resonance, also known as SPR.
Nitto's optical bio-sensor utilizes our accumulated technologies of the surface adsorption control design and the photosensitive material design, the patterning process.
In particular, the new material design of the polymer optical waveguide supported to achieve the similar high sensitivity to the commercial SPR system.
Our optical system attaches a high value to be user friendly.
We innovates the easy optics alignment design into the optical system.
So, Nitto's optical bio-sensor can show a good balance between the high sensitivity and the low cost, the small device.
Our optical bio-sensor will enable rapid diagnostic tests with a little sample.
We believe that the optical bio-sensor offers your safety, security and advice about them easily.
I hope you will be able to diagnose your physical or mental condition anytime, and evaluate the tasty and safety of your food anywhere.



Tomohiro KONTANI

Chief Researcher

NITTO DENKO CORPORATION
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Technology Section 2

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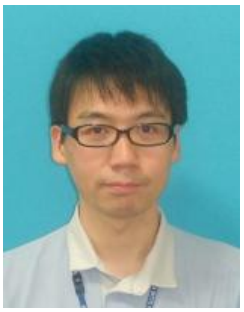
Technical background: Polymer Chemistry



Selected Publications

1.

2.

3.

Nitto's Formulation and Process Technology of The Transdermal Delivery System:

Hidetoshi KURODA, Tsuyoshi KASAHARA
Nitto Denko Corporation Medical Division Development Department
101 Sunada Shimonome Iwadeyama, Osaki City, Miyagi, 989-6493, Japan

Keywords: Transdermal Delivery System (TDS), Adhesive, Excipient, Permeation Enhancer, Skin Irritation, Drug Stability

ABSTRACT:

The first Transdermal Delivery System (TDS) was developed in 1979, since then 20 brand of TDS products have been launched in the world. Nitto has succeeded in development of 4 TDS products and our products have been widly accepted by customer depending on these unique properties. In this presentation, We expound the Nitto's key technologies for development of TDS products.

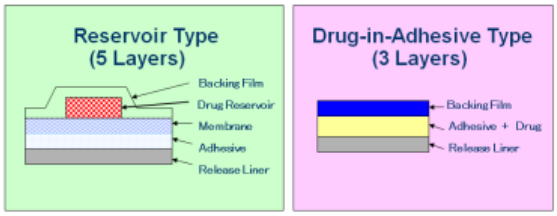


Fig. 1 Configuration of TDS

The TDS products are generally categorized in 2 types (Fig.1). As Fig.1 shown, Drug-in-Adhesive (DIA) type has advantages for material cost and processing depending on its simple configuration. However, in the stand point of controlled release of drug and ingredient loading capability, the Reservoir Type has greater advantage than DIA type. Nitto adopted DIA type because Nitto's has technology basis of adhesives and can design adhesives optimized for good drug release, stability and skin adhesion.

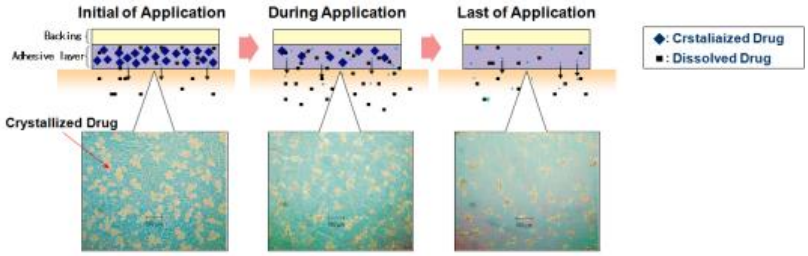


Fig. 2 Drug Release Mechanism of Crystal Reservoir System

In order to overcome the disadvantage of DIN, we developed key technologies, the "Crystal Reservoir System" and the "Gel Matrix System". On the "Crystal Reservoir System", drug was re-crystallized in adhesive layer purposefully by design. The crystallized drug behaves as if "reservoir of the drug" when the drug concentration decreased during application (Fig.2). By this phenomenon, drug release rate is controlled as steady rate. On the "Gel-Matrix System", the polymers in adhesive layer are crosslinked by crosslinker and layer of gel is formed. By the gel-forming, higher amount and more various ingredients including permeation enhancers can be loaded than non-cross linked adhesives.

Right now, Nitto has many drug candidates for TDS products under development; however, it's found that not all drug candidates can apply to the Nitto's key technologies. Recent pharmaceutical market moves into an era of macromolecular drugs like peptides, DNAs, and RNAs for the new action mechanism. Since it's considered very difficult for macromolecular drugs to be delivered into the human body through the skin, we should "evolve" the Nitto's key technologies or find the "Brand-New" technology for new macromolecular drug TDS.

Hidetoshi KURODA

Manager
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Profile:
Join Nitto Denko Corporation in 1994.
Area of Specialty: Design of Transdermal Delivery System, Synthesis and Evaluation of Medical Adhesive
Hobby: Fishing

Selected Publications

1. Nitto Denko Corporation. Kuroda, Hidetoshi. Manufacturing method of acrylic adhesives for medical application. JP4704586. 2011-06-15

2. Nitto Denko Corporation. Kuroda, Hidetoshi. Transdermal delivery system contains Nicotine. JP5000932. 2012-08-15

3. Nitto Denko Corporation. Kuroda, Hidetoshi. Production of a medical adhesive tape or other composition for percutaneous absorption of a drug. JP5021124. 2012-09-05

Nitto Molecular Targeting DDS

Ryouji TSUTSUMIUCHI
Manager
Planning & Management Dept.
Corporate Business Development Div.

Keywords: Unmet medical needs, Value proposition, Molecular Targeting DDS, Organ fibrosis

ABSTRACT:

As corporate business development division, we focus on creating new projects and establishment of new business with value proposition in response to social unmet needs.
With the key words of " Green " " Clean " and " Fine ", we strive new business development toward Year 2018 on the field of Energy management, Environmental recycling, and Life science.

As for the judging criteria of projects we embark, value proposition is identified and satisfied with unmet needs, and IP strategy and business model are established as indispensable items.
Furthermore, our technical probability is evaluated by outside authorities. We believe all of these are absolutely necessary activities in order to cultivate and establish new business field.

In today's joint workshop, we would like to present Molecular Targeting DDS for organ fibrosis, which Corporate Business Development Division is initiating in life science field.

It is known that numerous patients are suffering from organ fibrosis all over the world because of no approved efficacious therapy for it. For this unmet medical need, we are developing a therapy for liver cirrhosis together with Prof. Niitsu from Sapporo Medical University. Liver cirrhosis is one of the most urgently desired among organ fibrotic diseases.
Our innovative technology is realized by the collaboration with the invention of Prof. NIITSU and Nitto owned process material and technologies for oligonucleotide synthesis and drug delivery.
By these technologies, we made it possible to treat liver cirrhosis completely by targeting specific cells causing fibrosis.
Through our current studies, we have obtained fundamental IP in major countries which widely covers for principle of molecular targeting DDS.
Furthermore, non-clinical study (POC in animal study) was completed, and now we have been proceeding clinical study phase 1.

As the business deployment on novel therapeutic drug, we will pursue the possibilities for other intractable diseases, by utilizing the molecular targeting DDS technology platform in addition to various organ fibrosis.

Ryouji TSUTSUMIUCHI

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URL

End.

Selected Publications

1.

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Session 4

Chaired and Presented by

Prof. Klok, Prof. Kajihara and Prof. Nakatani

Combating Diseases with Peptide – Polymer Conjugates

Harm-Anton KLOK
École Polytechnique Fédérale de Lausanne (EPFL)
Institut des Matériaux and Institut des Sciences et Ingénierie Chimiques
Laboratoire des Polymères, Station 12, CH-1015 Lausanne, Switzerland

Keywords: Peptide – polymer conjugates; nanomedicine

ABSTRACT:
Peptides and proteins often combine unique self-assembly properties with very specific biological activities. From a therapeutic point of view, peptides and proteins are of interest, not only because of the possibilities to act as inhibitors or antagonists of biological processes (i.e. to act as therapeutics), but also because they provide opportunities e.g. for targeted delivery or to guide intracellular trafficking. Judiciously combining biologically active peptides or proteins with synthetic polymers provides opportunities to overcome problems related to the limited stability and plasma half life of peptides and proteins, to enhance the efficacy of polymer-drug conjugates and to augment the activity of peptide based therapeutics. This presentation will consist of two parts which will successively discuss: (i) polymer-modified HIV fusion inhibitors that show increased stabilities as compared to the unmodified peptides while maintaining activity and (ii) multivalent HIV entry inhibitors based on side-chain peptide – polymer conjugates which allow to augment the activity of the peptide.
.

Harm-Anton KLOK

Professor

Ph.D. in 1997 from the University of Ulm (Germany); Postdoctoral research: D. N. Reinhoudt (University of Twente) and S. I. Stupp (University of Illinois at Urbana–Champaign, USA); Project leader: Max Planck Institute for Polymer Research (Mainz, Germany; K. Müllen) 1999 - 2002.

Email: harm-anton.klok@epfl.ch; URL: http://lp.epfl.ch
Research interests: peptide/protein-based materials and nanomedicine, surface-initiated polymerization and polymer brushes, controlled/"living" polymerization and macromolecular engineering as well as dendritic and hyperbranched polymers.

Selected Publications

1. M. Danial, T. H. H. van Dulmen, J. Aleksandrowicz, A. J. G. Pötgens, H.-A. Klok, Site-specific PEGylation of HR2 peptides: Effects of PEG conjugation position and chain length on HIV-1 membrane fusion inhibition and proteolytic degradation, *Bioconjugate Chem.* **2012**, *23*, 1648 – 1660.
2. M. Danial, M. J. Root, H.-A. Klok, Polyvalent side chain peptide – synthetic polymer conjugates as HIV-1 entry inhibitors, *Biomacromolecules* **2012**, *13*, 1438 – 1447.
3. B. Apostolovic, S. P. E. Deacon, R. Duncan, H.-A. Klok, Hybrid polymer therapeutics incorporating bioresponsive, coiled coil peptide linkers, *Biomacromolecules* **2010**, *11*, 1187 - 1195.
4. B. Apostolovic, M. Danial, H.-A. Klok, Coiled coils: attractive protein folding motifs for the fabrication of self-assembled, responsive and bioactive materials, *Chem. Soc. Rev.* **2010**, *39*, 3541 – 3575.

Chemical Synthesis of Misfolded and Correctly Folded Glycoproteins: A Unique Approach for the Study of Glycoprotein Quality Control

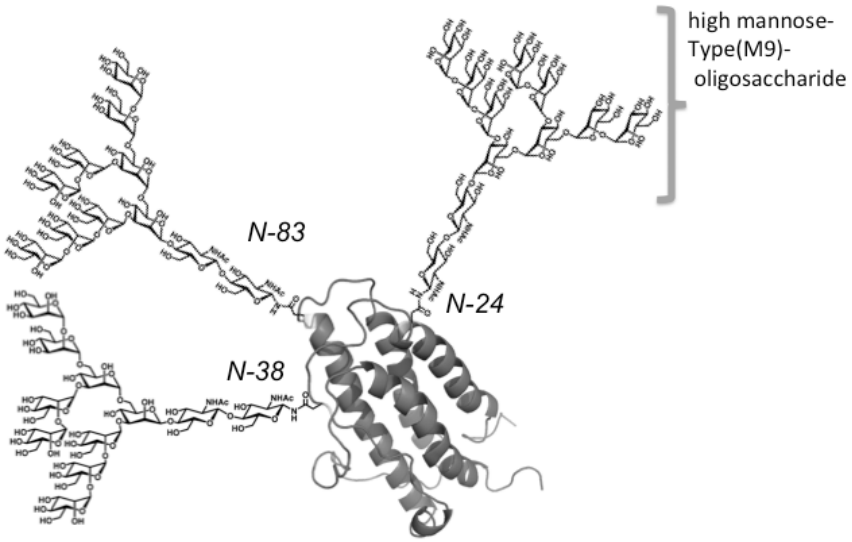
Yasuhiro Kajihara,
Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama-cho, Toyonaka, Osaka, 560-0043, Japan

Keywords: Glycoprotein, oligosaccharide, protein folding

ABSTRACT:
Biosynthesis of glycoproteins in the endoplasmic reticulum employs a quality control (QC) system, which discriminates and excludes misfolded malfunctional glycoproteins from correctly folded one. In the QC system, UDP-glucose:glycoprotein glucosyltransferase (UGGT) recognizes misfolded glycoprotein bearing high-mannose type N-glycan and glucosylate it so that the misfolded proteins can interact with molecular chaperones calnexin/calreticulin to attain correctly folded structure. As chemical tools to study glycoprotein quality control system at molecular level, we systematically synthesized misfolded and correctly folded homogeneous glycoproteins such as erythropoietin bearing high-mannose type oligosaccharide.

In order to synthesize the target glycoprotein, full-length glycosylpolypeptide chains was designed to divide into 6 segments and these were prepared by tert-Boc-SPPS. In terms of M9-highmannose oligosaccharide, corresponding glycopeptide was prepared from natural source and then converted into tert-Boc-Asn-M9-highmannose for tert-Boc-SPPS. Glycopeptide-□-thioester and peptide-□-thioesters thus obtained were successfully coupled by repetitive native chemical ligation. Subsequent folding experiments of chemically synthesized homogeneous glycopeptide yielded correctly folded glycoprotein with native disulfide bond patterns as well as misfolded glycoproteins with non-native disulfide bond patterns. Using these misfolded and correctly folded glycoproteins, we evaluated the ability of UGGT to discriminate between correctly and misfolded glycoproteins.

In this presentation, I would like to discuss the chemical synthesis of homogeneous glycoproteins and the ability of glycoprotein folding sensor enzyme, UGGT.



Erythropoietin (EPO) Bearing Highmannose-type Oligosaccharides

Yasuhiro Kajihara, Ph.D

Professor

Graduated at Graduate School of Science, Osaka University and received his PhD from Tokyo Institute of Technology in 1993. He spent two years at the Life Science Research Laboratory of Japan Tobacco Inc. as a post doctoral fellow. During this period he studied the synthesis of glycosyltransferase inhibitors and methods for sugar nucleotide synthesis. In 1995 he joined Yokohama City University as an Assistant Professor and was then promoted to Associate Professor in 2001 and Full Professor in 2007. At YCU, he developed chemoenzymatic synthesis of oligosaccharides as well as chemical synthesis of glycoproteins. In 2009 he moved to the Department of Chemistry at Osaka University.

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http://www.chem.sci.osaka-u.ac.jp/lab/kajihara/en_index.html

Selected Publications

1. M. Izumi, Y. Makimura, S. Dedola, A. Seko, A. Kanamori, M. Sakono, Y. Ito, Y. Kajihara, Chemical Synthesis of intentionally misfolded homogeneous glycoprotein: a unique approach for the study of glycoprotein quality control. *J. Am. Chem. Soc.*, 134, 7238-7241 (2012)
2. I. Sakamoto, K. Tezuka, K. Fukae, K. Ishii, K. Taduru, M. Maeda, M. Ouchi, K. Yoshida, Y. Nambu, J. Igarashi, N. Hayashi, T. Tsuji, Y. Kajihara, Chemical synthesis of homogeneous human glycosyl-interferon-beta that exhibits potent antitumor activity in vivo. *J. Am. Chem. Soc.*,134, 5428-5431.(2012)
3. M. Murakami, R. Okamoto, M. Izumi, Y. Kajihara, Chemical synthesis of an erythropoietin glycoform containing a complex-type disialyloligosaccharide. *Angew. Chem. Int. Ed.*, 51, 3567-3572 (2012)
4. R. Okamoto, K. Morooka, Y. Kajihara, A synthetic approach to a peptide alpha-thioester from unprotected peptide through cleavage and activation of a specific peptide bond by N-acetylguanidine. *Angew. Chem. Int. Ed.*, 51, 191-196 (2012)
5. Chemical Synthesis of a Glycoprotein having an Intact human complex-type sialyloligosaccharide under the Boc and Fmoc synthetic strategies. N. Yamamoto, Y. Tanabe, R. Okamoto, P. E. Dawson, Y. Kajihara, *J. Am. Chem. Soc.*,130, 501-510 (2008)
6. K. Hirano, D. Macmillan, K. Tezuka, T. Tsuji, Y. Kajihara, Design and Synthesis of Homogeneous Erythropoietin Analogue with Two Human Complex-Type Sialyloligosaccharides: Combined Use of Chemical and Bacterial Protein Expression Methods. *Angew. Chem. Int. Ed.*,48, 9557-9560 (2009)
7. C. Unverzagt, Y. Kajihara, Chemical assembly of N-glycoproteins: a refined toolbox to address a ubiquitous posttranslational modification, *Chem. Soc. Rev.*, 42, 4408-4420 (2013)

Small Organic Molecules regulating RNA Structure and Function:

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Keywords: small molecules, RNA, UTR, hairpin loop, regulation

ABSTRACT:
Having completed the human genome project, we have learned that many non-coding RNA (ncRNA) play important roles in regulating the function necessary for maintaining biological activities. MicroRNA and riboswitches are the representative of those functional ncRNA. Riboswitches are the cis-regulatory elements found in untranslated regions (UTR) of mRNA.[1] The binding of small organic molecules to the aptamer domain of the riboswitch modulates the secondary structure, which resulted in the ON and OFF of the expression of downstream gene. MicroRNA is a small single stranded RNA with the length of about 22 nucleotides can modulate the gene expression by the formation of RNA induced silencing complex at the 3'-UTR of the target gene.[2] microRNA was produced by the enzymatic digestion of primary microRNA and subsequently of pre-microRNA. Small organic molecules suppressing or enhancing the production of mature microRNA by the binding to pre-microRNA can in principle regulating the gene expression. On the basis of these potentials of small organic molecules binding to RNA, we have studied for the last five years on the small organic molecules binding to the hairpin and stem loops of hairpin RNA structure.
I will present our recent studies on
1) Small molecules binding between RNA hairpin loops
Our synthetic ligand bound between two hairpin loops of r(CGG)n and induced the change in the secondary structure, and
2) Modulation of gene expression by ligand binding to 5'-UTR
We have confirmed that luciferase activity was suppressed with the concentration dependent manner of ligand binding to 5'-UTR by using the cell-free in vitro translation system.
Detail of these studies will be discussed in the presentation.

Kazuhiko NAKATANI, Ph.D

Professor

The Institute of Scientific and Industrial Research, Osaka University.
1988 PhD Osaka City University

1985-1988 Research Associate, Columbia University, USA
1988-1991 Postdoctoral Fellow,
Sagami Chemical Research Center
1991-1993 Assistant Professor, Osaka City University
1993-1997 Assistant Professor, Kyoto University
1997-2005 Associate Professor, Kyoto University
2005 – Present Professor, Osaka University

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LAB INFO
http://www.sanken.osaka-u.ac.jp/labs/rbc/english/index_e.html
My lab is primarily focusing on the synthesis of small molecules that can regulate gene expression by binding DNA and RNA.

Selected Publications

1. A synthetic riboswitch that operates using a rationally designed ligand-RNA pair. Dohno, C.; Kohyama, I.; Kimura, M.; Hagihara, M.; Nakatani, K. Angew. Chem. Int. Ed. 2013, 52, 9976-9979.

2. G-quadruplex formation of entirely hydrophobic DNA in organic solvents. Shibata, T.; Dohno, C.; Nakatani, K. Chem. Commun. 2013, 49, 5501-5503.

3. Ligand-inducible formation of RNA pseudoknot. Matsumoto, S., Hong, C; Otabe, T.; Murata, A.; Nakatani, K. Bioorg. Med. Chem. Lett. 2013, 23, 3539-3541.

4. Structure-activity studies on the fluorescent indicator in the displacement assay for the screening of small molecules binding to RNA. Umemoto, S.; Im, S.; Zhang, J.; Hagihara, M.; Murata, A.; Harada, Y.; Fukuzumi, T.; Wazaki, T.; Sasaoka, S.; Nakatani, K. Chem. Eur. J. 2012, 18, 9999-10008.

5. Ligand-Assisted Complex of Two DNA Hairpin Loops. Hong, C.; Hagihara, M.; Nakatani, K. Angew. Chem. Int. Ed. 2011, 50, 4390-4393.

6. Ligand Inducible Assembly of a DNA Tetrahedron. Dohno, C.; Atsumi, H.; Nakatani, K. Chem. Commun. 2011, 47, 3499-3501.

Session 5

Chaired and Presented by

Prof. Fierz, Prof. Murata, and Prof. Zhu

Chromatin as a Dynamic Platform for Protein-Protein Interactions

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École Polytechnique Fédérale de Lausanne

Keywords: Protein semi-synthesis, expressed protein ligation, chromatin, biophysics

ABSTRACT:
Post-translational modifications (PTMs) of histone proteins play a crucial role in regulating chromatin function. Effector proteins interact with histone PTMs through specific interaction domains (reader domains)[1]. Thus, effectors are dynamically recruited to their target chromatin regions from a soluble and freely diffusible pool[2]. It is currently not well understood how low-affinity interactions between histone PTMs and reader domains (with dissociation constants in the range of 5-100 micromolar) can result in rapid and specific effector recruitment. A possible model involves kinetic capture of effectors by a high local concentration of histone PTMs. Fast rebinding kinetics increase the effector residence time and result in local effector accumulation.

To shed light on these recruitment processes, we are quantitatively investigating the molecular mechanism of dynamic protein localization through histone PTMs. To this end, we are developing defined *in vitro* systems which allowing us to measure the complex binding reactions of chromatin factors to chromatin fibers carrying varying concentrations of their cognate histone marks. Employing chemical protein semi-synthesis[3] and DNA engineering we construct chromatin fibers of a distinct architecture and carrying a defined set of histone PTMs. We then employ a set of spectroscopic methods to investigate the interaction of reader proteins with these designer chromatin fibers in a quantiative fashion and investigate the effect on chromatin structure as a result of effector binding.

Quantitative analysis of dynamic chromatin processes *in vitro* is required to gain a better understanding of these processes in the complex environment of a nucleus. We thus expect that our analyses will significantly advance our knowledge of key aspects of the molecular mechanisms at work in histone PTM mediated effector recruitment in transcription, repression and DNA repair.

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(3) Fierz, B.; Muir, TW. Nat Chem Biol 2012, 8, 417.

Beat FIERZ, Ph.D

Tenure track assistant professor

Graduated at University of Basel, Switzerland

2006, Ph.D in biophysical chemisty at the University of Basel

2007-2012, Postdoc at the Rockefeller University, New York, and Princeton University, New Jersey, USA in the laboratory of Prof. Tom W. Muir

2012, Tenure track assistant professor (Chaire Fondation Sandoz en chimie biophysique des macromolécules) at EPFL.

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http://lcbm.epfl.ch/

Selected Publications

1. D.-H. Kim, Z. Tang, M. Shimada, B. Fierz and B. Houck-Loomis et al. Histone H3 K27 trimethylation inhibits H3 binding and function of SET1-like H3K4 methyltransferase complexes, in Molecular and Cellular Biology, 2013.

2. B. Fierz, S. Kilic, A. R. Hieb, K. Luger and T. W. Muir. Stability of Nucleosomes Containing Homogenously Ubiquitylated H2A and H2B Prepared Using Semisynthesis, in Journal of the American Chemical Society, vol. 134, num. 48, p. 19548-51, 2012.

3. B. Fierz and T. W. Muir. Chromatin as an expansive canvas for chemical biology, in Nature chemical biology, vol. 8, num. 5, p. 417-27, 2012.

4. B. Fierz, C. Chatterjee, R. K. McGinty, M. Bar-Dagan and D. P. Raleigh et al. Histone H2B ubiquitylation disrupts local and higher-order chromatin compaction, in Nature chemical biology, vol. 7, num. 2, p. 113-9, 2011

Intermolecular Hydrogen Bonding between Amides of Sphingomyelin in Raft Model Membrane

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Department of Chemistry, Grad. School of Science, Osaka University

Keywords: *sphingomyelin | hydrogen bond | lipid rafts |solid state NMR*

ABSTRACT:

Sphingomyelin (SM) and cholesterol (Chol) form membrane microdomains characterized by a liquid ordered phase; this is often referred to as the lipid raft model. However, the molecular interactions responsible for formation of the ordered phase are not completely understood.

In this study, the presence or absence of stable intermolecular hydrogen bonds was examined for all possible pairs—SM/SM, SM/Chol, and Chol/Chol—using solid-state NMR (rotational-echo double resonance, REDOR) spectroscopy for isotope-labeled compounds. In the presence of Chol, significant intermolecular interaction was observed between the amide groups of SMs (**1** and **2**), while no interaction was detected between SM (**2** or **3**) and Chol (**6**) or between Chol (**5**) and Chol (**6**) (see Figure 1). These results suggest that a small cluster of SM molecules interconnected by hydrogen-bonds is present in the Chol-containing membrane. This cluster, together with the ordering effect of Chol on SM alkyl chains, may lead to formation of the ordered phase. Results also show that solid-state NMR techniques such as REDOR can be utilized to examine intermolecular interactions in model membranes and potentially reflect both their dynamic nature and mesoscopic structures. This is the first application of REDOR for direct detection of intermolecular lipid-lipid interactions in hydrated bilayer membranes. Although care is required for interpreting the results, dipolar-dipolar interactions in solid state NMR are shown to be a versatile tool for investigating the molecular basis of biomembranes.

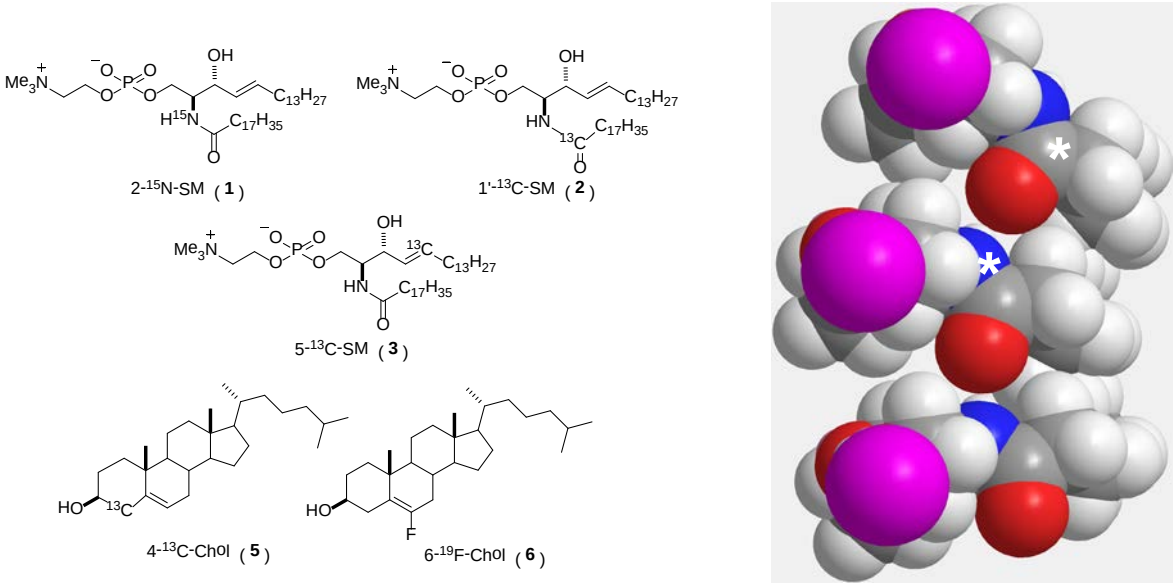

Figure 1. Labeled sphingomyelins and cholesterols used for solid-state NMR, left, and probably hydrogen bonding between sphingomyelin molecules, right. Asterisks denote hydrogen bonding pair of C=O and NH in the amide group of compounds **1** and **2**.

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Received Ph.D in Tohoku University in 1986,
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Assist. Professor at Facult. Agriculture, Tohoku Univ. 1985-1993.
Assoc. Professor at Dept. Chem. Univ. Tokyo 1993-1999
Professor at the current position 1999-.

LAB INFO
URL: http://www.chem.sci.osaka-u.ac.jp/lab/murata/
Our motto is: "To achieve something that no one has ever done or even attempted"
We are looking at endogenous small molecules such as lipids, sterols and peptides that form self-assemblies in membrane by means of NMR spectroscopy and synthetic organic chemistry. We are also interested in small exogenous molecules such as natural products that possess unique biological activities.

Selected Publications

1. A novel sperm-activating and attracting factor (SAAF) from the ascidian Ascidia sydneiensis. Matsumori, N., Hiradate, Y., Shibata, H., Oishi, T., Simma, S., Toyoda, M., Hayashi, F., Yoshida, M., Murata, M., Morisawa, M., *Org. Lett.*, **15,** 294-297 (2013).
2. Interaction between the marine sponge cyclic peptide theonellamide A and sterols in lipid bilayers as viewed by surface plasmon resonance and solid-state 2H nuclear magnetic resonance. Rafael, A. E., Matsumori, N., Murata, M. Nishimura, S., Kakeya, H., Matsunaga, S., Yoshida, M. *Biochemistry,* **52,** 2410-2418 (2013).
3. Head-to-tail interaction between amphotericin B and ergosterol occurs in hydrated phospholipid membrane. Umegawa, Y., Nakagawa, Y., Tahara, K. Tsuchikawa, H., Matsumori, N., Oishi, T. and Murata, M. *Biochemistry* **51,** 83-89 (2012).
4. Comprehensive molecular motion capture for sphingomyelin by site-specific deuterium labeling. Matsumori, M., Yasuda, T., Okazaki, H., Suzuki, T., Yamaguchi, T., Tsuchikawa, H., Doi, M., Oishi, T., Murata, M. *Biochemistry* **51,** 8363-8370 (2012).
5. Conformations of spermine in ATP complex: The structural basis for weak bimolecular interactions of major cellular electrolytes. Maruyoshi, M., Yamaguchi, T., Demura, T., Matsumori, N., Oishi, T. and Murata, M. *Chem. Eur. J.* **17,** 4788-4795 (2011).
6. Conformational change of spermidine upon interaction with adenosine triphosphate in aqueous solution. Maruyoshi, K., Nonaka, K., Sagane, T., Demurata, T., Matsumori, N. and Murata, M. *Chem. Eur. J.* **15,** 1618-1626 (2009).
7. Direct interaction between amphotericin B and ergosterol in lipid bilayers as revealed by 2H NMR. Matsumori, N., Tahara, K., Yamamoto, H., Morooka, A., Doi, M., Oishi, T. and Murata, M. *J. Am. Chem. Soc.* **131,** 11855-11860 (2009).
8. Orientation of fluorinated cholesterol in lipid bilayers analyzed by 19F tensor calculation and solid-state NMR. Matsumori, N., Kasai, Y., Oishi, T., Murata, M. and Nomura, K. *J. Am. Chem. Soc.* **130,** 4757-4766 (2008).
9. Complex formation of amphotericin B in sterol-containing membrane as evidenced by surface plasmon resonance. Mouri, R., Konoki, K., Matsumori, N., Oishi, T. and Murata, M. *Biochemistry,* **47,** 7807-7815 (2008).
10. Design and synthesis of ladder-shaped tetracyclic, heptacyclic, and decacyclic ethers and evaluation of the interaction with transmembrane proteins. Torikai, K., Oishi, T., Ujihara, S., Matsumori, N., Koniki, K. Murata, M. and Aimoto, S. *J. Am. Chem. Soc.* **30,** 10217-10226 (2008).

From Isonitrile to Heterocycles and potential Fluorescence probes

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Keywords: Isonitrile, multicomponent reactions, heterocycles, Diversty-oriented synthesis, Fluroscence probe

ABSTRACT:

Small polyfunctionalized heterocyclic compounds play important roles in drug discovery process and in isolation and structural identification of biological macromolecules. Indeed, analysis of drugs in late development or on the market shows that about 70% of them are heterocycles. With the progress achieved in the field of functional genomics and proteomics, more information about the structures and functions of biologically active macromolecules is becoming available. To match such a formidable advance in biological research, the identification and optimization of new small molecular chemical substances that can specifically interact with therapeutical targets is of utmost importance and constitute actually the bottleneck in medicinal chemistry. This observation has naturally provided the impetus for the renewed interests in the heterocyclic chemistry. Development of novel atom- and step-economic and greener synthetic routes for the construction of heterocycle rather than functionalization of the existing cyclic scaffold attracted consequently much attention from both academia and industrial researchers. It is reasonable to expect that ready access to diverse sets of heterocycles can not only help improving the known biological and pharmacokinetic properties of drugs, but also help discovering molecules that exhibit biological effects beyond those associated with the previous known macromolecules. We will briefly summarize our work on the development of novel multicomponent synthesis of heterocycles based on isonitrile chemistry. Particular attention will be paid on the new reactivity profile of isonitriles observed recently in the lab and their application to the synthesis of heterocycles with strong fluorescence emission properties.

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- 1980-1984, B.Sc, Hangzhou Normal University, P. R. of China
- 1984-1987, M.Sc (Prof Y.-L. Li), Lanzhou University, P. R. of China
- 1988-1991, Ph.D (Prof H.-P. Husson and Prof J.-C. Quirion), Univerisité Paris-Sud, France,
- 1991-1992, Post-Doct (Prof D. H. R. Barton), Texas A & M University, College Station, USA,
- 1992-2000, Chargé de Recherche, Institut de Chimie des Substances Naturelles, CNRS, France,
- 2000-2006, Director of Research 2nd class, Institut de Chimie des Substances Naturelles, CNRS, France,
- 2006-2010, Director of Research 1st class, Institut de Chimie des Substances Naturelles, CNRS, France,
- Sept 2010–, Full Professor, EPFL, Switzerland,

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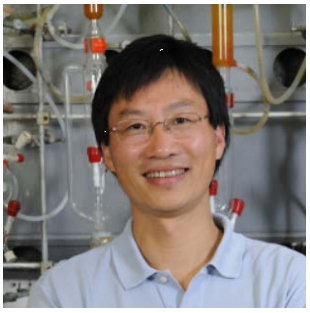

Selected Publications

1. Yao, B.; Wang, Q.; Zhu, J. *Angew Chem. Int. Ed*. **2013**, *52*, DOI: 10.1002/anie.201307738.
2. Buyck, T.; Wang, Q.; Zhu, J. *Angew Chem. Int. Ed*. **2013**, *52*, DOI: 10.1002/anie.201306663.
3. Piou, P.; Bunescu, A.; Wang, Q.; Neuville, L.; Zhu, J. *Angew Chem. Int. Ed*. **2013**, *52*, DOI: 10.1002/anie.201306532
4. Odabachian, Y.; Tong, Shuo, Wang, Q.; Zhu, J. *Angew Chem. Int. Ed*. **2013**, *52*, 10878-10882.
5. Xu, Z.; Wang, Q.; Zhu, J. *Angew Chem. Int. Ed*. **2013**, *52*, 3272-3276.

Session 6

Chaired and Presented by

Prof. Waser, Prof. Heinis and Prof. Fujioka

Hypervalent Iodine Reagents: New Tools for the Synthesis of Alkynes

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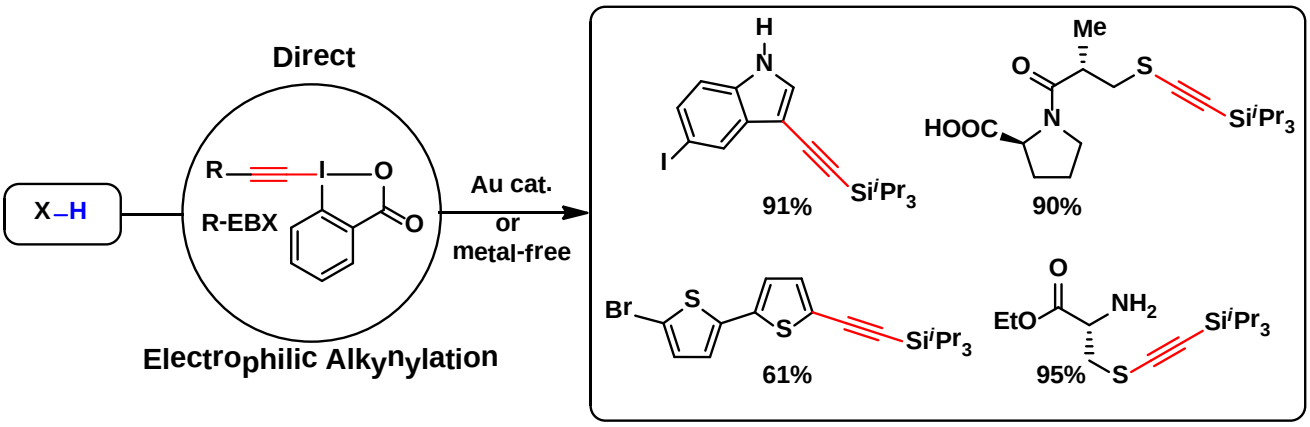
Keywords: Alkynes, Catalysis, Bioconjugation, Thiols, Heterocycles

Acetylenes are versatile functional groups in synthetic chemistry, chemical biology and materials science due to the numerous methods existing for further modification of the triple bond. Acetylene chemistry is usually based on nucleophilic alkyne synthons. Neglected for a long time, electrophilic synthons are a valuable alternative.[1] In particular, our group has been interested in the development of alkynylation methods using cyclic EthynylBenziodoXolone (EBX) hypervalent iodine reagents. Herein, the discovery of the exceptional reactivity of EBX reagents and the last results of our research in the area will be presented, including the first examples of gold-catalyzed C-H alkynylation and domino cyclization-alkynylation[2] and a highly efficient and practical alkynylation method for thiols, both on small organic molecules and biomolecules.[3]



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2. a) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. b) Y. Li, J. P. Brand, J. Waser, *Angew. Chem., Int. Ed.* **2013**, *52*, 6743.

3. R. Frei, J. Waser, *J. Am. Chem. Soc.* **2013**, *135*, 9620.

Jérôme Waser, Ph.D

Assistant Professor

Graduated at ETH Zurich, Switzerland and received his Ph.D in chemistry in 2006 with Prof. Erick M. Carreira.
Postdoc at Stanford University, USA, with Prof. Barry M. Trost from 2006 to 2007.

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Our current research efforts focus on: (1) The development of electrophilic alkynylation methods; (2) The use of cyclization and annulation reactions in the synthesis of bioactive compounds.

Selected Publications

1. R. Frei, A. Raja, R. Franke, F. Sasse, D. Staedler, S. Gerber-Lemaire and J. Waser: Total Synthesis and Biological Evaluation of Jerantinine E. Angew. Chem., Int. Ed. 52, ASAP. DOI: 10.1002/anie.201305533 (2013).

2. F. de Nanteuil and J. Waser: Synthesis of Aminocyclobutanes by Iron-Catalyzed [2+2] Cycloaddition. Angew. Chem. Int. Ed. 52, 9009-9013 (2013).

3. R. Frei and J. Waser: A Highly Chemoselective and Practical Alkynylation of Thiols, J. Am. Chem. Soc. 135, 9620-9623 (2013).

4. Y. Li, J. P. Brand, and J. Waser: Gold-Catalyzed Regioselective Synthesis of 2- and 3-Alkynyl Furans. Angew. Chem. Int. Ed. 52, 6743-6747 (2013).

5. F. de Nanteuil, and J. Waser: Catalytic [3+2] Annulation of Aminocyclopropanes for the Enantiospecific Synthesis of Cyclopentylamines. Angew. Chem. Int. Ed. 50, 12075-12079 (2011).

6. S. Nicolai, C. Piemontesi, and J. Waser: A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of Trachelanthamidine. Angew. Chem. Int. Ed. 50, 4680-4683 (2011).

Development of Bicyclic Peptides for Therapeutic Application

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Keywords: peptide, peptide macrocycle, peptide therapeutic, directed evolution, phage display

ABSTRACT:
My laboratory is engaged in the discovery and development of new peptide formats for the use in therapy. A major focus is the development of bicyclic peptide ligands of disease targets using a combinatorial approach based on phage display (please see the figure below). The bicyclic peptides combine key qualities of antibody therapeutics (high affinity and specificity) and advantages of small molecule drugs (access to chemical synthesis, diffusion into tissue, various administration options). We were able to generate bicyclic peptide antagonists or ligands with nanomolar or even picomolar binding affinity to a range of human disease targets including plasma kallikrein, urokinase-type plasminogen activator, coagulation factor XII, matrix metalloproteinase 2 and sortase A. Towards the therapeutic application of the peptides, we have extended their circulation time to several days in mice and we are now assessing the therapeutic effect of some of the peptides in vivo. An important activity of my research group is also the development of novel peptide macrocycle formats with even better binding properties.

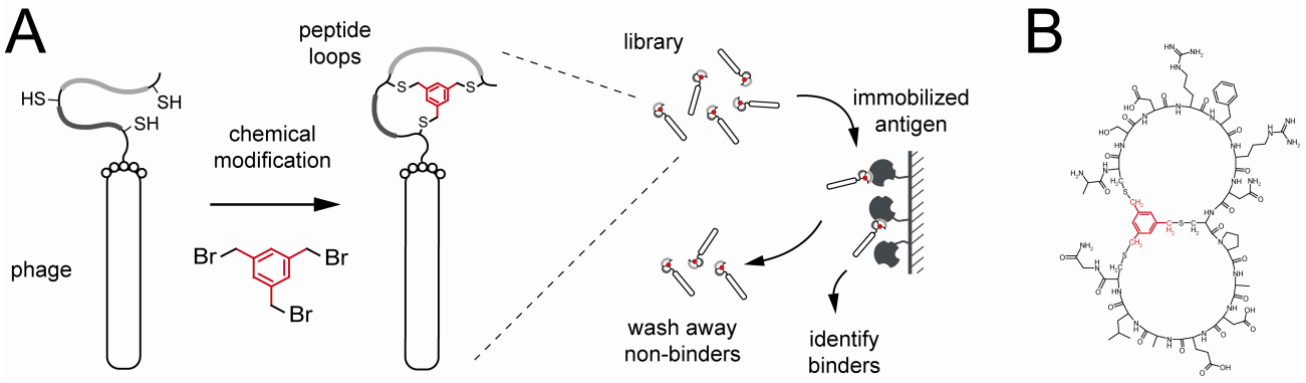

Figure: (A) Large libraries of random peptides (> 4 billion different peptides) are displayed on phage and cyclised in a chemical reaction (left). Binders to targets of interest are subsequently isolated in affinity selections (right). (B) Chemical structure of an isolated bicyclic peptide.

Christian HEINIS, Ph.D

Assistant Professor, EPFL in Lausanne, Switzerland

Studies in biochemistry/molecular biology at ETH Zurich in Switzerland; Ph.D in protein engineering in the group of Prof. Dr. Dario Neri at ETH Zurich; Post-doc in the group of Prof. Dr. Kai Johnsson at EPFL in Lausanne, Switzerland; Post-doc in the group of Sir Greg Winter at the LMB in Cambridge, UK.

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My laboratory is engaged in the discovery and development of new molecule designs for the use in therapy. A major focus is the development of bicyclic peptide ligands of disease targets using a combinatorial approach based on phage display.

Selected Publications

1. Chen, S.; Rebollo, I. R.; Buth, S. A.; Morales-Sanfrutos, J.; Touati, J.; Leiman, P. G.; Heinis, C. Bicyclic peptide ligands pulled out of cysteine-rich peptide libraries. *JACS* 2013, 135, 6562-6566
2. Baeriswyl, V.; Calzavarini, S.; Gerschheimer, C.; Diderich, P.; Angelillo-Scherrer, A.; Heinis, C. Development of a selective peptide macrocycle inhibitor of coagulation factor XII toward the generation of a safe anti-thrombotic therapy, *J. Med. Chem.* 2013, 56, 3742-3746
3. Chen, S.; Morales-Sanfrutos, J.; Angelini, A.; Cutting, B.; Heinis, C. Structurally diverse cyclisation linkers impose different backbone conformations in bicyclic peptides. *ChemBioChem* 2012, 13, 1032-1038
4. Baeriswyl, V.; Rapley, H.; Pollaro, L.; Stace, C.; Teufel, D.; Walker, E.; Chen, S.; Winter, G.; Tite, J.; Heinis, C. Bicyclic peptides with optimized ring size inhibit human plasma kallikrein and its orthologues while sparing paralogous proteases. *ChemMedChem* 2012, 7, 1173-1176
5. Angelini, A.; Morales-Sanfrutos, J.; Diderich, P.; Chen, S.; Heinis, C. Bicyclization and tethering to albumin yields long-acting peptide antagonists. *J. Med. Chem.* 2012, 55, 10187-10197
6. Angelini, A.; Diderich, P.; Morales-Sanfrutos, J.; Thurnheer, S.; Hacker, D.; Menin, L.; Heinis, C. Chemical macrocyclization of peptides fused to antibody Fc fragments. *Bioconj.Chem.* 2012, 23, 1856-1863
7. Angelini, A.; Cendron, L.; Chen, S.; Touati, J.; Winter, G.; Zanotti, G.; Heinis, C. Bicyclic peptide inhibitor reveals large contact interface with a protease target. *ACS Chem. Biol.* 2012, 7, 817-821
8. Heinis, C.; Rutherford, T.; Freund, S.; Winter, G. Phage-encoded combinatorial chemical libraries based on bicyclic peptides. *Nat. Chem. Biol.*2009, 5, 502-507

ORGANIC SYNTHESIS USING ELECTROPHILIC SALT INTERMEDIATES: ALKYL ETHERS FROM MOM ETHERS AND MIXED ACETALS

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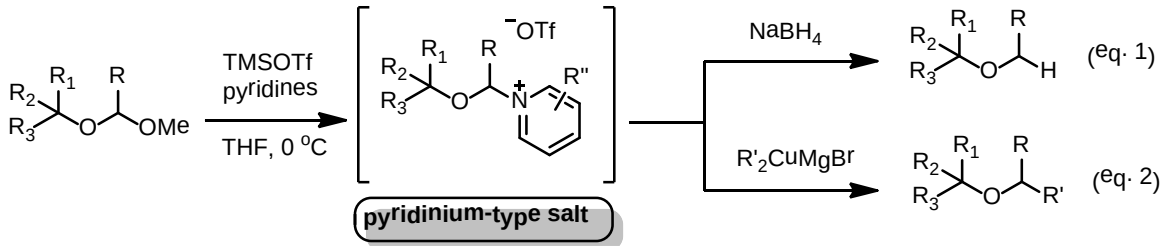
Keywords: electrophilic salt, alkyl ether, MOM ether, mixed acetal

Ether moieties are chemically and metabolically stable and often found in many pharmaceutical agents and biologically active compounds. The Williamson ether synthesis protocol, involving reactions between an alkoxide and an alkyl halide, is perhaps the best-known method to prepare them.[1] However, this protocol has critical limitations associated with use of strongly basic nucleophiles. In order to overcome the drawbacks of Williamson's method, various alternative methods have been developed. However, many of these methods often involve harsh conditions, have severe substrate limitations, or require the use of complicated procedure. Bode and co-workers have recently developed an efficient method for the preparation of alkyl ethers that utilizes methoxymethyl (MOM) ethers or their derivatives, exemplified by hydroxamic acid-derived acetals.[2] However, sp^3 *C*-nucleophiles (*e.g.*, alkyl groups) cannot be employed in this process. Therefore, the discovery of new, versatile and efficient procedures for alkyl ether synthesis remains a worthy goal in organic chemistry.

We developed mild and divergent two methods for the synthesis of alkyl ethers. Both methods proceed through the electrophilic salt intermediates. Thus, treatment of mixed acetals, MOM and methoxyethyl (ME) ethers with TMSOTf and pyridine-type base afforded the corresponding single pyridinium-type salts. Then, the reactions of them with $NaBH_4$ (eq. 1) or organocuprate (eq. 2) afforded the corresponding ethers in good yields. The features of the methods are as follows: 1) The reactions are very mild, and many acid-labile functional groups can survive, and 2) Sterically crowded alkyl ethers bearing various functional groups are synthesized in high yields.[3]



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2. C.-V. T. Vo, T. A. Mitchell, J. W. Bode, *J. Am. Chem. Soc.* **2011**, *133*, 14082.
3. Y. Minamitsuji, A. Kawaguchi, O. Kubo, Y. Ueyama, T. Maegawa, H. Fujioka, *Adv. Synth. Catal.*, **2012**, *354*, 1861.

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Hiromichi Fujioka received Ph. D. from Osaka University under the guidance of Professor Isao Kitagawa (1981). He worked with Professor Yoshito Kishi for two years at Harvard University, USA. In 1984, he got a position of assistant professor under Professor Yasumitsu Tamura at Osaka University. In 1992, he became an associate professor under Professor Yasuyuki Kita, the successor of Professor Tamura. Since 2008, he has been a full professor. His interests are the developments of new methodologies, reactions using reactive intermediates, and biologically active natural product synthesis.

Selected Publications

1. T. Maegawa, Y. Koutani, K. Otake, and H. Fujioka: Methylene Acetal Formation from 1,2- and 1,3-Diols Using an *O,S*-Acetal, 1,3-Dibromo-5,5-dimethylhydantoin and BHT. *J. Org. Chem.* 2013, 78, 3384-3390.
2. Y. Minamitsuji, A. Kawaguchi, Y. Ueyama, T. Maegawa, and H. Fujioka: A Mild and Versatile Method for the Synthesis of Alkyl Ethers from MOM Ethers and Application to the Preparation of Sterically Crowded Ethers, *Adv. Synth. Catal.* 2012, 354, 1861-1866.
3. A. Goto, K. Otake, O. Kubo, Y. Sawama, T. Maegawa, and H. Fujioka: Effects of Phosphorus Substituents on Reactions of α-Alkoxyphosphonium Salts with Nucleophiles. *Chem. Eur. J.* 2012, 18, 11423-11432.
4. H. Fujioka, K. Yahata, O. Kubo, Y. Sawama, T. Hamada, and T. Maegawa: Reversing Reactivity of Carbonyl Compounds via Phosphonium Salt: Enantioselective Total Synthesis of (+)-Centrolobine. *Angew. Chem. Int. Ed.* 2011, 50, 12232-12235.
5. H. Fujioka: O. Kubo, K. Senami, Y. Minamitsuji, and T. Maegawa: Remarkable effect of 2,2'-bipyridyl: mild and highly chemoselective deprotection of methoxymethyl (MOM) ethers in combination with TMSOTf (TESOTf)–2,2'-bipyridyl. *Chem. Commun.* 2009, 4429-4431.
6. H. Fujioka, T. Okitsu, Y. Sawama, N. Murata, R. Li, and Y. Kita: Reaction of the Acetals with TESOTf-Base Combination; Speculation of the Intermediates and Efficient Mixed Acetal Formation. *J. Am. Chem. Soc.* 2006, 128, 5930-5938.

Poster Presentations

Poster Session

*The presentations of odd number will be presented on December 2nd, and December 3rd for those of even number.

P1	Alberto SCHENA (EPFL) Nanolights to Illuminate Diagnostics and Cell Biology
P2	Yuichiro HORI (Osaka) Development of PYP–tag Mutants and Fluorogenic Probes for Rapid Imaging of Intracellular Proteins
P3	Toshiyuki KOWADA (EPFL) Development f pH–Activatable Fluorescent Probe and Intravital Imaging of Osteoclast
P4	Masahiro Nakano (Osaka) Monitoring Temperature inside a Single Cell with a Novel Genetically Encoded Fluorescent Temperature Indicator
P5	Yoshiyuki ARAI (Osaka) Kohinoor, a Photo–switichable fluorescent protein for superresolution imaging
P6	Yoshiyuki MANABE (Osaka) Synthetic Study of N–glycans Using Efficient Glycosylation
P7	Tsung–Che Chang (EPFL) Fully Synthetic Self–Adjuvanting Siayl–Tn Antigen Based Anticancer Vaccine
P8	Tue Minh–Nhat Nguyen (EPFL) Enantioselective Synthesis of α–Methylidene–γ– Butyrolactones: Intramolecular Rauhut–Currier Reaction Promoted by Acid/Base Organocatalysts
P9	Fernando ARTEAGA–ARTEAGA (EPFL) Enantioselective Organocatalyzed Formal [n+2] Cycloaddition of Ketimines

P10	Hirotoshi Adachi (Osaka) Novel Transdermal Drug Delivery System: PassPortTM System
P11	Chieko KITAURA (Osaka) Plant cell culture technology
P12	Tomohiro KONTANI (Osaka) Novel Biosensor – Current Concept and Key Findings –
P13	Ryouji TSUTSUMIUCHI (Osaka) Nitto Molecular Targeting DDS
P14	Hidetoshi KURODA (Osaka) Nitto's Formulation and Process Technology of the Transdermal Delivery System
P15	John MORAES (EPFL) Using RAFT polymerization to control the size of monodisperse, charge-stabilized core-shell particles
P16	Raoul PELTIER (EPFL) Peptide-Polymer Vehicles for intracellular, organelle-targeted drug delivery
P17	Masumi MURAKAMI (Osaka) Synthetic Study of Erythropoietin Glycoform Containing Three Complex-type Disialyloligosaccharides at the Native Positions
P18	Yasuhito Morishita (Osaka) Development of a concise synthetic strategy of β-mercapto amino acid derivatives
P19	Yuta MAKI (Osaka) Synthesis of Tri-antennary Complex-type Sialyl-tetradecasaccharide from Bi-antennary N-Glycan Isolated from Biological Source
P20	Asako MURATA (Osaka) Development of potential small-molecule inhibitors of pre-miRNA processing

P21	Takahiro OTABE (Osaka) Synthesis of RNA bulge binding small molecule and application to inhibitor of Dicer cleavage reaction
P22	Aurore DELACHAT(EPFL) Development and engineering of probes for bivalent epigenetic marks
P23	Hiroshi TSUCHIKAWA (Osaka) Stereocontrolled synthesis of the 5,5,6-bis-spiroacetal ring moiety of spirolide C
P24	Sébastien LETHU (EPFL) Design and Synthesis of Labeled Compounds for Conformation Analysis of Fatty Acids Bound to Proteins
P25	Bo Yao (EPFL) Pd(II)-Catalyzed Domino Reactions of Alkynes Under Aerobic Conditions: Facile Access to Potentially Bioactive Heterocycles
P26	Zhengren XU (EPFL) Total Synthesis of (±)-Goniomitine
P27	Reto FREI (EPFL) Total Synthesis and Biological Evaluation of Jerantinine E
P28	Inmaculada RENTERO REBOLLO (EPFL) Bicyclic peptide inhibitors of SrtA from Staphylococcus aureus
P29	Shiyu CHEN (EPFL) Bicyclic peptide ligands pulled out of cysteine-rich peptide libraries
P30	Kenichi MURAI (Osaka) Asymmetric bromolactonization based kinetic resolution of β-substituted olefinic carboxylic acids
P31	Kenzo YAHATA (Osaka) Selective Transformations of Carbonyl Functions Using in situ Protection Methodology

P32	Kojiro NAGATA (Osaka) Dioxygen Activation by Bio-Inspired Trinuclear Copper Complexes with a Cage Ligand

Alberto SCHENA
Graduate Student

Graduated in Organic Chemistry at the University of Pisa and at the Scuola Normale Superiore (Pisa, Italy) and former visiting scholar at the University of California, San Diego (UCSD, USA). Currently attending the graduate school of Chemistry and Chemical Engineering at the Swiss Federal Institute of Technology (EPFL) to develop semisynthetic luminescence-based biosensors for live cell imaging and MedTech diagnostics. Interests: fluorescence microscopy, luminescence-based probes, diagnostics.

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Nanolights to Illuminate Diagnostics and Cell Biology

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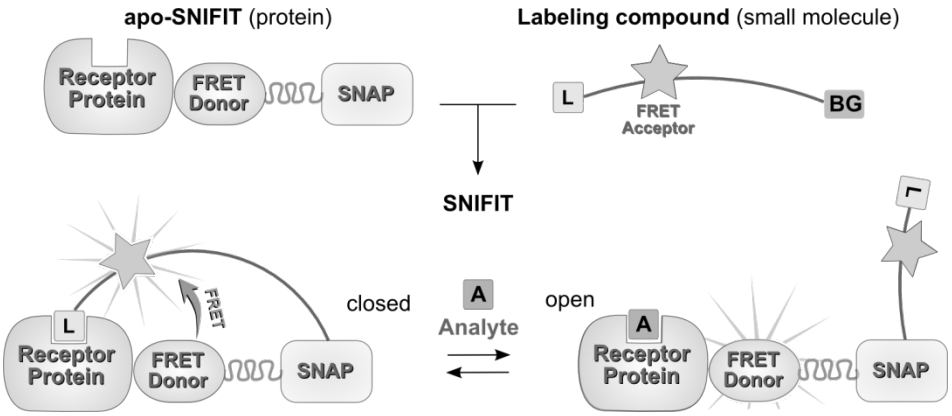
Keywords: biosensor, luminescence, FRET, diagnostics

ABSTRACT:

Optical biosensors can be used for a non-invasive direct monitoring and quantification of analytes to elucidate their action and biodistribution both *in vivo*, in their biological environment, or *ex vivo*, in collected samples. Suitable luminescent bioprobes as bright nanometric lights have been developed by us to confer desirable features such as specificity, robustness, fast response kinetic, low background and high signal change, to permit a rapid, reliable, localized analyte detection.
The discovery of several bioprobes with various analyte specificities, detection modes and readout principles will be described. They all rely on composite macromolecules constituted of a fusion protein, obtained by molecular biology techniques, specifically modified with polyfunctional molecules, prepared by organic synthesis. The protein and the molecule are adapted to confer specificity, to improve the signal and the kinetic of response or to tune the response range to the biologically relevant levels of the analyte.



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Development of PYP-tag Mutants and Fluorogenic Probes for Rapid Imaging of Intracellular Proteins

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Keywords: PYP-tag, fluorogenic probes

ABSTRACT:
Fluorescence protein imaging by synthetic probes is a powerful technique to analyze protein function and localization. In this technique, a specific pair of a protein tag and its fluorescence probe is utilized to image proteins in living cells. The advantage in this approach is that the timing of protein labeling is easily controlled. On the other hand, its drawback is that the fluorescence of free probes inside cells causes the reduction of the signal-to-noise ratio. To solve this problem, we previously developed a fluorogenic probe for labeling photoactive yellow protein (PYP) tag. PYP-tag is a small protein (14 kDa) derived from purple bacteria, and covalently binds to the thioester derivatives of cinnamic acid/coumarin. Owing to the fluorogenic properties of the probe, proteins of interest were clearly detected without the removal of free probes. However, the probe was not applicable to the live-cell imaging of intracellular proteins, because the probe was not cell permeable, .

In this research, we developed new cell-permeable probes containing coumarin-based PYP-ligands with environment-sensitive fluorogenic switch. The kinetic properties of protein labeling reactions were significantly improved and intracellular proteins were successfully imaged. Moreover, we created the mutants of PYP-tag to enhance labeling kinetics and brightness of the probes. In this conference, we will report the detail of probe/protein design, kinetic experiments and live-cell imaging.

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Y. Hori, K. Nakaki, M. Sato, S. Mizukami, and K. Kikuchi: Development of Protein Labeling Probes with Redesigned Fluorogenic Switch Based on Intramolecular Association and No-wash Live-cell Imaging. Angew. Chem. Int. Ed. 51, 5611-4 (2012)

Y. Hori, H. Ueno, S.Mizukami, and K. Kikuchi: Photoactive Yellow Protein-Based Protein Labeling System with Turn-on Fluorescence

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Dr. Toshiyuki Kowada was born in 1982 in Nara, Japan. He graduated at Graduate School of Engineering at Kyoto University and received his PhD in 2010 under the supervision of Prof. K. Ohe. He joined the laboratory of Prof. K. Kikuchi at Osaka University as a postdoctoral fellow. In 2011, he became a specially appointed assistant professor.

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Development f pH-Activatable Fluorescent Probe and Intravital Imaging of Osteoclast

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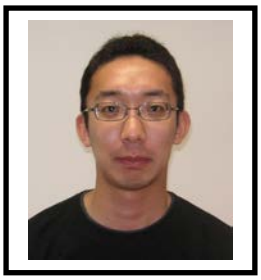
[2] Graduate School of Engineering, Osaka University

Keywords: BODIPY, Fluorescence imaging, Osteoclast

ABSTRACT:
Bone homeostasis in our body is regulated by the balance between osteoclastic bone resorption and osteoblastic bone formation. Because the upregulation of osteoclast activity will lead to bone diseases such as rheumatoid arthritis and osteoporosis, there has been much effort to clarify the osteoclast function. Among several methods for detecting osteoclast activity, fluorescence imaging has great potential for real-time imaging of osteoclast function because of its high sensitivity and spatiotemporal resolution. Thus, we have so far developed pH-activatable fluorescent probes for visualizing the acidic compartment created by bone-resorbing osteoclasts in vivo. As a result, we successfully visualized the bone-resorbing osteoclasts in living mice using the boron-dipyrromethene (BODIPY)-based pH-activatable fluorescent probe, BAp-E. However, unfortunately, time-lapse imaging of osteoclast activity was hardly achieved, because the fluorescence signals of BAp-E remarkably decreased during imaging experiments.

According to in vitro photostability test, the photobleaching of BAp-E should be mainly caused by reactive oxygen species (ROS), which were generated upon photoirradiation. To overcome this problem, we redesigned and synthesized the fluorescent probe with higher photostability. The improved probe showed lower reactivity against ROS compared to BAp-E and stably existed under long-time photoirradiation in vitro. We next performed the imaging of bone-resorbing osteoclasts in vivo using two-photon microscopy. Consequently, we succeeded in time-lapse imaging of osteoclast activity because of high photostability of the improved probe. Therefore, we strongly believe that our newly developed probe will help to clarify the osteoclast function in vivo.

Reference:
T. Kowada, J. Kikuta, A. Kubo, M. Ishii, H. Maeda, S. Mizukami, and K. Kikuchi: In Vivo Fluorescence Imaging of Bone-Resorbing Osteoclasts. J. Am. Chem. Soc. 133, 17772-6 (2011)



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Monitoring Temperature inside a Single Cell with a Novel Genetically Encoded Fluorescent Temperature Indicator

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Keywords: Fluorescent protein, Temperature

ABSTRACT:

Intracellular temperature is crucial role for many cellular processes such as gene expression and cellular metabolism. A lot of temperature indicators inside a cell are developed based on temperature sensitive synthetic chemicals or particles. However, most of them needs injection of the indicator to the cell by micro injection, and also they could not be applied to specific intracellular organelle, such as mitochondria and nucleus. Noninvasive indicator for monitoring of temperature changes in individual cells enables us to understand cellular processes and has possibility of finding new applications in biology and medicine. Fluorescent protein based genetically encoded indicators are noninvasive and powerful tools for monitor dynamics of specific cellular compartment, such as Ca^{2+} and ATP at the single cell level. Recently, green fluorescent protein based thermal imaging by measuring fluorescence polarization anisotropy was developed. However, to measure the fluorescence polarization anisotropy, a complicated fluorescence microscopy set-up is required.

To overcome these limitations, we developed a new genetically encoded fluorescent temperature indicator for monitoring temperature changing in a single living cell by combination a temperature sensitive fluorescent protein and a temperature less sensitive protein. This indicator needs only a single excitation wavelength and a detector for two fluorescence. To monitor the intracellular organelle specific temperature dynamics, we succeeded in expression the temperature indicator in mitochondria, nucleus, and plasma membrane. And also, we successfully monitored heat production in mitochondria of single cell with chemical stimulation.

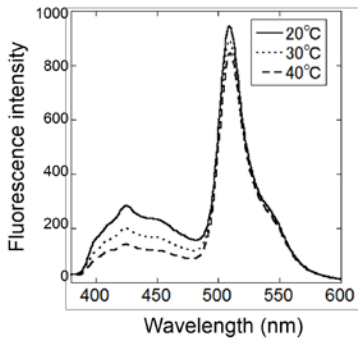

Fig.1. Temperature dependent spectra of the temperature indicator

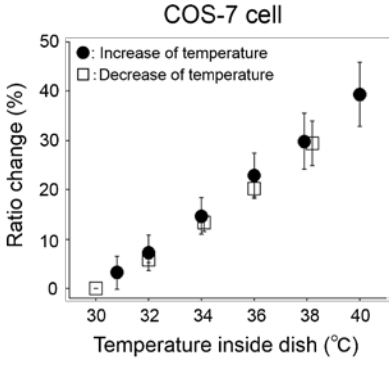

Fig.2. Temperature dependent emission ratio change of the temperature indicator in COS-7 cell.

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Kohinoor, a Photo-switichable fluorescent protein for superresolution imaging

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Keywords: Photo-switchable fluorescent protein, superresolution, nanoscopy

ABSTRACT:
Nanoscale imaging in light based microscopy is breakthrough in science that permit imaging well below the diffraction limit of light (<200-nanometer). Many fluorescence nanoscopy methods are utilizing rapid on and off photoswitching of fluorescent proteins either by controlled or stochastic switching manner for resolution enhancement. Although, the switching on/off traits of the only available fast reversibly switchable fluorescent proteins limit their utility in nanoscopy imaging owing to the coupling between switching-off and fluorescence excitation. Their utility is also restricted to selective nanoscopy methods using a complicated optics. Here we reported a fast switching and photostable reversibly photoswitchable fluorescent protein, Kohinoor, which has completely decoupled switch off and fluorescence excitation spectrum. Kohinoor's switching on and off traits required very simple optics for spatially targeted switching nanoscopy with resolution down to <85-nanometer. We also implemented Kohinoor for stochastic switching based nanoscopy with achievable localization precision potential 13 nm.

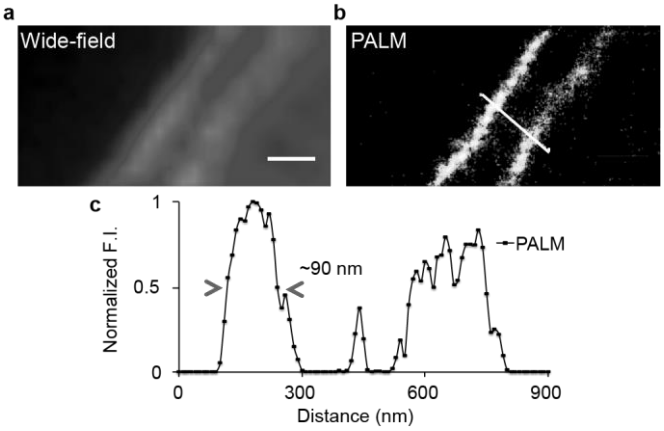

Figure 1. PhotoActivation Localization Microscopy (PALM) imaging of HeLa cell expressing Kohinoor-β-actin. a, Wide-field image of Kohinoor-β-actin. b, c, PALM image of Kohinoor-β-actin. c, Graph show the normalized fluorescence profile across the line in image. Scale bar is 2 μm

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Synthetic Study of *N*-glycans Using Efficient Glycosylation

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Keywords: *N*-glycan, glycosylation, microflow reactor

ABSTRACT:

Asparagine-linked oligosaccharides (*N*-glycans) on glycoproteins have high diversity and complexity and are involved in a variety of important physiological events, such as protein quality control, cell-cell recognition, adhesion, and signal transduction. We have investigated the synthesis of the complex-type *N*-glycans containing core fucose, bisecting glucosamine, or bis-sialylated motif to investigate their biological function (Fig.1). In our synthetic strategy, glycosyl-Asn structure was first synthesized by *N*-glycosylation under microfluidic condition, and the oligosaccharide chains were elongated. We have already synthesized tetrasaccharides containing core fucose or bisecting glucosamine, and these tetrasaccharides were successfully deprotected. Thus, the basic synthetic strategy of *N*-glycan was established. Next, we investigated the coupling between the reducing fragments and the non-reducing fragments. As a result, this glycosylation was achieved in good yield by using ether as a solvent. We also synthesized bis-sialylated tetrasaccharide using efficient α-sialylation under microfluidic condition and the control of hydrogen bonding effect.

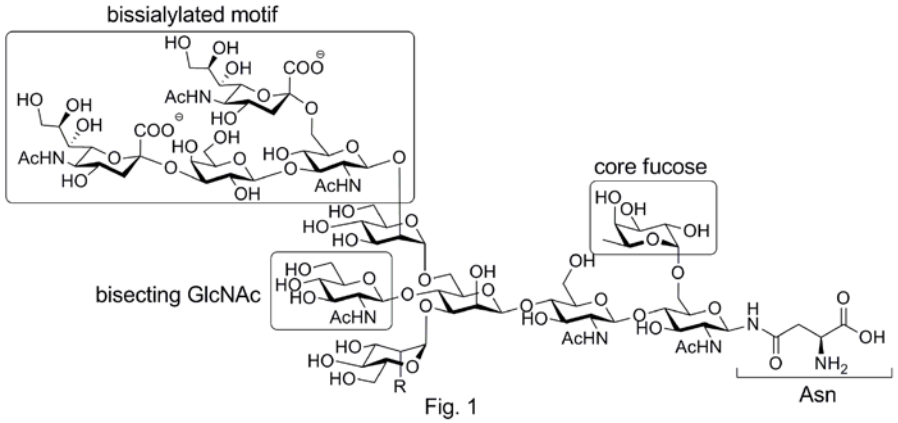

Fig. 1

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Fully Synthetic Self-Adjuvanting Siayl-Tn Antigen Based Anticancer Vaccine

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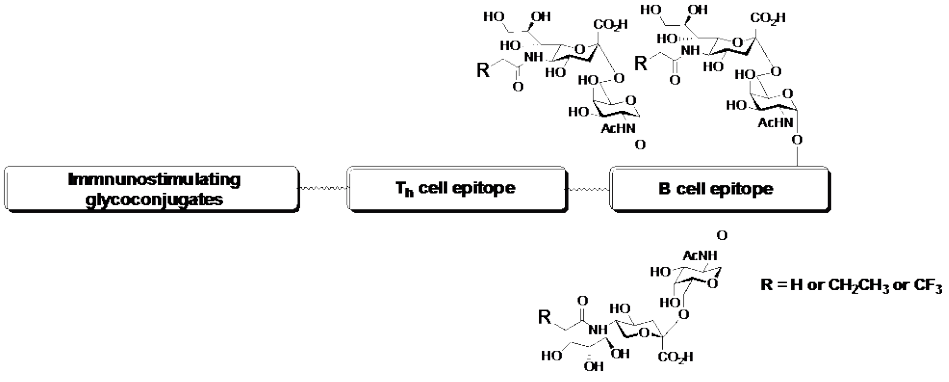
Keywords: Tumor-associated carbohydrate antigen, cancer vaccine, Sialylation.

ABSTRACT:

Sialyl-Tn (sTn) antigens are expressed in carcinoma-associated mucins, highly *O*-glycosylated and high molecular weight glycoproteins expressed on endodermal epithelial cells. The tumor-associated carbohydrate antigens (TACA) are low antigenicity, because they are self-antigens and consequently are tolerated by the immune system. In addition, carrier proteins such as keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA) conjugated with TACA can elicit a strong B cell response, which may lead to induce suppression of an antibody response against the carbohydrate epitope. On the other hand, modification of the C5 *N*-substitutent of sialic acid in sialic-acid-containing antigens has been shown to enhance their immunogenicity. One approach to improve the presentation of a TACA to relevant immune cells is to attach the antigen to a receptor ligand that can activate appropriate immune cells. TLR ligands, such as mono-phosphoryl lipid A (MPL) (TLR4 ligand), or bacterial lipopeptides (TLR2 ligand), were developed as an adjuvant for various virus vaccines, but there have appeared some issues on them. Our lab has newly developed adjuvants that control certain pathways of the immune system with the combination of some receptor ligands, which include Nod1, Nod2 or special-types of TLR4 ligands. We will thus combine these adjuvants with modified sTn to form a cancer vaccine. The synthesized vaccine would show more efficient class switch to IgG antibodies against tumor-associated carbohydrate epitopes.



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After completing my Undergraduate studies. I decided to continue my education in Japan. It has given me the opportunity to experience a culture that is very much different from the western world. My study here is support by the Japanese government, under the MEXT scholarship.

"Big things have small beginnings"

Enantioselective Synthesis of α-Methylidene-γ -Butyrolactones: Intramolecular Rauhut-Currier Reaction Promoted by Acid/Base Organocatalysts

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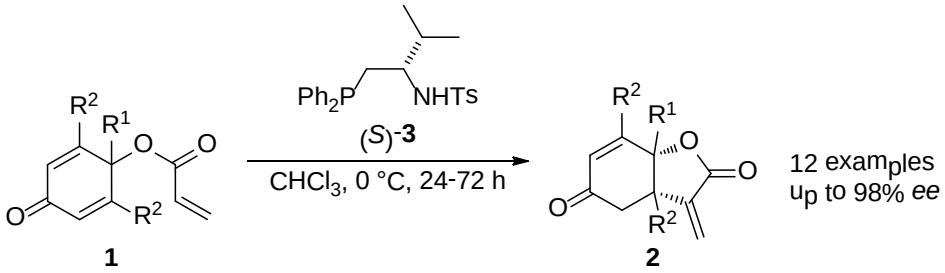
Keywords: Rauhut-Currier reaction; α-Methylidene-γ-butyrolactone; Acid-base organocatalyst;

ABSTRACT:
The Rauhut–Currier (RC) reaction is known to be a readily access to α-substituted enones via coupling of two different α,β-unsaturated carbonyl compounds, where one acts as a latent enolate. Although attractive systems based on achiral catalysis have been developed for the RC process, few examples of synthetically useful enantioselective RC transformations have been reported.[1,2] Highly selective construction of complex frameworks via the enantioselective RC reaction has been a challenge in asymmetric synthetic chemistry.
Herein we report the bifunctional organocatalyzed intramolecular RC reaction of the prochiral dienones **1**. Aliphatic and aromatic substituted starting materials **1** were cyclized to give α-methylidene-γ-butyrolactones **2** in good yields and high enantioselectivities.[3]



References:
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3) a) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 5423. b) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Suzuki, M.; Enders, D.; Sasai, H. *Tetrahedron,* **2013**, *69*, 1202.

Fernando

ARTEAGA-ARTEAGA

Ph.D. Student, D3

Master degree in Chemistry from University of Guanajuato, Mexico. Currently Ph.D. candidate at Graduate School of Science, Osaka University.

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After finish the Master course in March 2011 in Mexico, I came to Japan to join initially as a research student and then as a Ph. D. student from October 2011 in Sasai group. My study here in Japan is supported by the Japanese Government, under the MEXT scholarship.

My research is focus on the development and application of organocatalysis for the synthesis of important synthetic building blocks, such as amino acids related systems.

Chemistry is a wonderful tool that allows us touching the invisible matter.

Enantioselective Organocatalyzed Formal [n+2] Cycloaddition of Ketimines

Fernando ARTEAGA-ARTEAGA, Shinobu TAKIZAWA, Yasushi YOSHIDA, Michitaka SUZUKI and Hiroaki SASAI*
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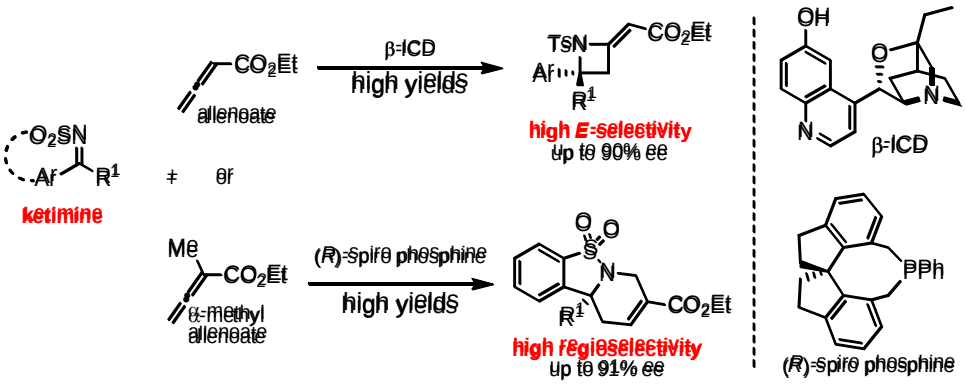
Keywords: [n+2] cycloaddition • ketimine • organocatalysis • chiral tetrasusbstituted carbon stereogenic center

ABSTRACT:
Simple construction of functionalized chiral molecules is a subject of intensive research.[1] Enantioselective synthesis using a domino process of ketimines with allenoates is a very attractive methodology for the preparation of nitrogen-containing heterocycles featuring a chiral tetrasubstituted carbon stereogenic center. Herein we report the enantioselective synthesis of azetidines and tetrahydropyridines through the formal [n+2] cycloaddition reactions. The acid-base organocatalyst β-ICD,[2] promoted the [2+2] cycloaddition affording azetidines with high enantioselectivities.[3] Furthermore, a spiro phosphine Lewis base smoothly performed the [4+2] annulation of cyclic ketimines with α-methyl allenoate in high enantio- and regioselectivity.



References:

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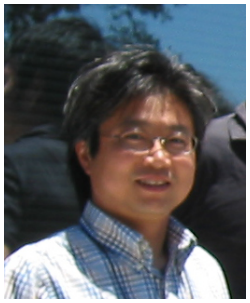
3) S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai, *Org. Lett.* **2013**, *15*, 4142.



Hirotoshi Adachi, Ph.D.
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Dr. Adachi is a director of Life Science Research Center – US, Nitto Denko Technical Corporation. He is responsible for the development of novel transdermal technologies.

Dr. Adachi received his Ph.D. in Pharmaceutical Sciences at Kumamoto University in Japan in 1993. He has been working for pharmaceutical companies and collaborated with Prof. Richard Guy at University of Geneva in 2001.

He has over 20 years experiences in pharmaceutical companies in Japan and US, and credited with co-authoring about 20 articles and 30 patents related to transdermal drug delivery systems. He is specialized in directing transdermal technology development and CMC regulatory.

Novel Transdermal Drug Delivery System: PassPort™ System

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Keywords: Active Transdermal Therapeutic System (Active TTS), Drug Delivery System, PassPortTM System, Microporation, Dry-Patch, Large Molecule, Peptide and Protein

ABSTRACT:

The active transdermal therapeutic system (TTS) is a novel drug delivery technology to enhance drug penetration through the skin. As non-invasive active TTS, technologies such as iontophoresis and sonophoresis have been well known over the past decades. However, the use of these technologies has been limited to small molecules. Recently, advanced minimally-invasive active TTS such as microneedle and microporation technologies are focused on delivering large molecules.

Microporation technology utilizes energy to create micropores on the skin surface in order to systemically deliver biopharmaceutical medicines that include peptides, proteins, nucleic acids and vaccines. Nitto's microporation technology, the PassPort™ system, is a combination of a thermal ablation device and therapeutic transdermal dry-patch. The device consists of applicator and porator; the applicator delivers an electrical energy to a porator that converts current to heat and creates micropores. The dry-patch was invented specifically for use with the PassPort™ system; the drug is dispersed in a dry-state matrix. After application of PassPort™ system, the drug in a dry-patch is quickly dissolved by micropore exudates and then enters the body.

The PassPort™ system can enhance a delivery of both small and large molecules. One key feature of the technology is its ability to produce either an immediate or sustained pharmacokinetic (PK) profile – even for large molecules that are only available in injection forms. For example, the PassPort™ system has demonstrated basal insulin delivery in humans from a dry-patch formulation.

Overall, the PassPort™ system offers patient-friendly self-administration and is a good option for those experiencing difficulty taking medications. The technology can replace painful daily injections and reduce needle phobia that is often associated with poor patient compliance.

Chieko KITAURA

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Joined Nitto Denko in 1997.
Engaged in development of diagnostic products, ginseng products,.
basic study of transdermal delivery of large molecules.

Graduated at Nara Institute of Science and technology and received MD in Bioscience.
BD in Horticulture was received at Osaka Prefecture University.

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Plant cell culture technology

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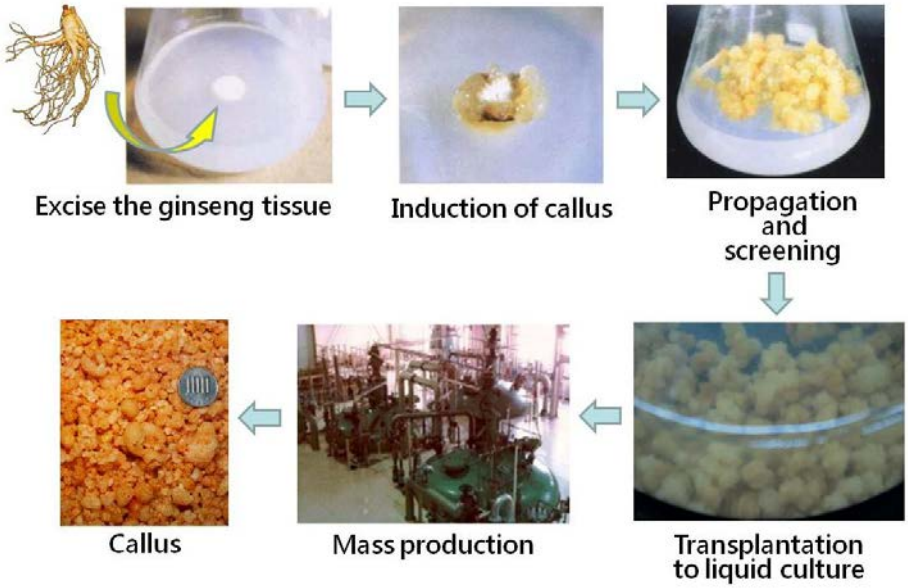
Keywords: Plant cell culture, Plant secondary metabolite, *Panax ginseng*, callus

ABSTRACT:
The large scale production of ginseng (*Panax ginseng* C.A. Meyer) with plant tissue culture technology was established in Nitto Denko Corp. in 1985. Commercial production was achieved at a scale of 20 to 25 thousand liters. Ginseng extract was derived from harvested cells and processed into health food. The sale of ginseng products was terminated last year, however, this unique technology was taken over in corporate R&D to launch the new business in a future.
The concept of this study is 'Create the new value with plant cell culture'. There are some strong advantages on cultured cells such as pathogen free or heavy metal free. Moreover tank cultivation enables unlimited propagation of plant cells, so it would be possible to supply precious plant resources without any concern about climate change or starvation of wild plants.
Currently we are dealing with not only ginseng, but also other beneficial plants. Ingredients accumulated by cell culture process will be analyzed by multivariate analysis to certify their distinctive feature. At the same time, we are looking for the collaboration partner to develop the new business using outcome of this technology.



Procedure of large-scale production of ginseng

Tomohiro KONTANI
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Technical background:
Polymer Chemistry

End.

Novel Biosensor
- Current Concept and Key Findings -

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Terukazu IHARA, Junko NAKANO
Life Science Research Center, Technology Section 2
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Keywords:
optical sensor, SPR, polymer optical waveguide, immune reaction

ABSTRACT:
NITTO DENKO has developed the mobile optical bio-sensor combined the polymer optical waveguide and surface plasmon resonance, also known as SPR.
Nitto's optical bio-sensor utilizes our accumulated technologies of the surface adsorption control design and the photosensitive material design, the patterning process.
In particular, the new material design of the polymer optical waveguide supported to achieve the similar high sensitivity to the commercial SPR system.
Our optical system attaches a high value to be user friendly.
We innovates the easy optics alignment design into the optical system.
So, Nitto's optical bio-sensor can show a good balance between the high sensitivity and the low cost, the small device.
Our optical bio-sensor will enable rapid diagnostic tests with a little sample.
We believe that the optical bio-sensor offers your safety, security and advice about them easily.
I hope you will be able to diagnose your physical or mental condition anytime, and evaluate the tasty and safety of your food anywhere.

Ryouji TSUTSUMIUCHI
Manager

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End.

Nitto Molecular Targeting DDS

Ryouji TSUTSUMIUCHI
Manager
Planning & Management Dept.
Corporate Business Development Div.

Keywords: Unmet medical needs, Value proposition, Molecular Targeting DDS, Organ fibrosis

ABSTRACT:
As corporate business development division, we focus on creating new projects and establishment of new business with value proposition in response to social unmet needs.
With the key words of “ Green “ “ Clean “ and “ Fine “, we strive new business development toward Year 2018 on the field of Energy management, Environmental recycling, and Life science.

As for the judging criteria of projects we embark, value proposition is identified and satisfied with unmet needs, and IP strategy and business model are established as indispensable items.
Furthermore, our technical probability is evaluated by outside authorities. We believe all of these are absolutely necessary activities in order to cultivate and establish new business field.

In today’s joint workshop, we would like to present Molecular Targeting DDS for organ fibrosis, which Corporate Business Development Division is initiating in life science field.

It is known that numerous patients are suffering from organ fibrosis all over the world because of no approved efficacious therapy for it. For this unmet medical need, we are developing a therapy for liver cirrhosis together with Prof. Niitsu from Sapporo Medical University. Liver cirrhosis is one of the most urgently desired among organ fibrotic diseases.
Our innovative technology is realized by the collaboration with the invention of Prof. NIITSU and Nitto owned process material and technologies for oligonucleotide synthesis and drug delivery.
By these technologies, we made it possible to treat liver cirrhosis completely by targeting specific cells causing fibrosis.
Through our current studies, we have obtained fundamental IP in major countries which widely covers for principle of molecular targeting DDS.
Furthermore, non-clinical study (POC in animal study) was completed, and now we have been proceeding clinical study phase 1.

As the business deployment on novel therapeutic drug, we will pursue the possibilities for other intractable diseases, by utilizing the molecular targeting DDS technology platform in addition to various organ fibrosis.

Hidetoshi KURODA

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Profile:
Join in Nitto Denko Corporation in 1994.
Area of Specialty:
Design of Transdermal Delivery System, Synthesis and Evaluation of Medical Adhesive
Hobby: Fishing

Nitto's Formulation and Process Technology of The Transdermal Delivery System:

Hidetoshi KURODA, Tsuyoshi KASAHARA
Nitto Denko Corporation Medical Division Development Department
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Keywords: Transdermal Delivery System (TDS), Adhesive, Excipient, Permeation Enhancer, Skin Irritation, Drug Stability

ABSTRACT:

The first Transdermal Delivery System (TDS) was developed in 1979, since then 20 brand of TDS products have been launched in the world. Nitto has succeeded in development of 4 TDS products and our products have been widly accepted by customer depending on these unique properties. In this presentation, We expound the Nitto's key technologies for development of TDS products.

The TDS products are generally categorized in 2 types, Reservoir type and Drug-in-Adhesive (DIA) type. DIA type has advantages for material cost and processing depending on its simple configuration. However, in the stand point of controlled release of drug and ingredient loading capability, the Reservoir Type has greater advantage than DIA type. Nitto adopted DIA type because Nitto's has technology basis of adhesives and can design adhesives optimized for good drug release, stability and skin adhesion.

In order to overcome the disadvantage of DIN, we developed key technologies, the "Crystal Reservoir System" and the "Gel Matrix System". On the "Crystal Reservoir System", drug was re-crystallized in adhesive layer purposefully by design. The crystallized drug behaves as if "reservoir of the drug" when the drug concentration decreased during application. By this phenomenon, drug release rate is controlled as steady rate. On the "Gel-Matrix System", the polymers in adhesive layer are crosslinked by crosslinker and layer of gel is formed. By the gel-forming, higher amount and more various ingredients including permeation enhancers can be loaded than non-cross linked adhesives.

Right now, Nitto has many drug candidates for TDS products under development; however, it's found that not all drug candidates can apply to the Nitto's key technologies. Recent pharmaceutical market moves into an era of macromolecular drugs like peptides, DNAs, and RNAs for the new action mechanism. Since it's considered very difficult for macromolecular drugs to be delivered into the human body through the skin, we should "evolve" the Nitto's key technologies or find the "Brand-New" technology for new macromolecular drug TDS.

John MORAES, Ph.D

Scientist

John graduated with an MSc from Victoria University of Wellington, New Zealand. He then completed a Ph.D at the University of Sydney, Australia in 2013. He has been a post-doctoral researcher at EPFL, Switzerland since April 2013.

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My primary interest is in the fine control over the architecture of polymer chains. This is particularly crucial when investigating the post-polymerization modification of polymer chains for use in biological applications where low-dispersity, readily-functionalizable chains are desired. I also have an interest in nanoparticle systems especially the characterization of functional groups grafted onto nanoparticles.

Using RAFT polymerization to control the size of monodisperse, charge-stabilized core-shell particles

John MORAES,[1,3] Kohji OHNO,[2] Guillaume GODY,[3] Thomas MASCHMEYER,[3] and Sebastien PERRIER[3]

[1] Laboratoire des Polymères, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland.
[2] Division of Materials Chemistry, Institute for Chemical Research, Kyoto University, Kyoto, Japan.
[3] School of Chemistry, The University of Sydney, Sydney, Australia.

Keywords: Controlled radical polymerization, silica nanoparticles, post-polymerization functionalization

ABSTRACT:
Controlled radical polymerization is an increasingly well-studied field of research as it allows fine control over the molecular weight and structure of polymers derived from radical reactions. Grafting such polymers to a nanoparticle scaffold using reversible addition-fragmentation chain transfer (RAFT) polymerization allows for the synthesis of well-defined core-shell particles from a range of monomers. Furthermore, using a functionalizable monomer such as 4-vinylbenzyl chloride (VBC) allows for post-polymerization modification of the polymer-grafter nanoparticles.

We here present the functionalization of silica nanoparticles using a RAFT agent containing a triethoxysilane anchoring group as well as a thiocarbonylthio group capable of mediating the polymerization of a wide range of monomers including VBC. We investigate the trade-off considerations of achieving a high molecular-weight polymer while maintaining end-group fidelity and show how the size of silica-grafted poly(VBC) particles may be tuned with polymerization conditions (Fig 1). We also demonstrate the incorporation of a fluorescent co-monomer into the particle shell and post-polymerization modification of the particles to achieve water-dispersible particles.

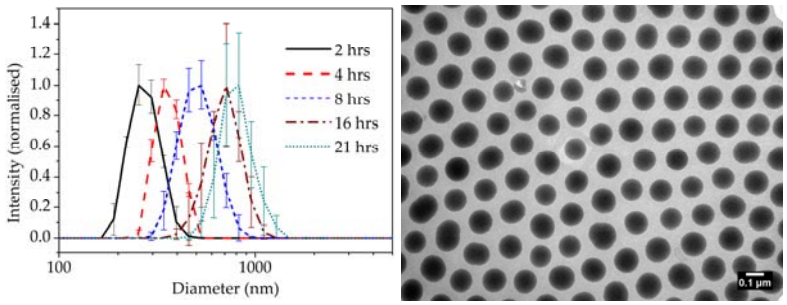

Fig 1: Particle size evolution and transmission electron micrograph of silica-grafted poly(VBC) particles. Scale bar is 0.1 µm.

Raoul PELTIER, Post-Doc.

Professor Harm-Anton KLOK

Graduated at University Paul Sabatier, Toulouse, France and received Ph.D in chemistry at the University of Auckland, New Zealand. He has been a post-doctoral researcher at the EPFL in Lausanne, Switzerland, since September 2011

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Specialized in peptide chemistry, I have a very multidisciplinary background that includes polymer science, nanotechnology and cellular biology.

Peptide-Polymer Vehicles for intracellular, organelle-targeted drug delivery:

Raoul PELTIER[1] and Harm-Anton KLOK[1]

[1]Laboratoire des Polymères, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Keywords: Peptide-Polymer Conjugates, Drug Delivery, Organelles Targeting

ABSTRACT:

During the past ten years, research in the area of drug delivery has focused at on the development of vehicles that can target specific cells in the body and on the use of such vehicles to specifically deliver a drug within these cells. Today, science is going one step further and the creation of vehicles that can target specific organelles within the cell is the new challenge. Polymer-peptide conjugates are perfectly suited for this purpose since they combine the advantages of both worlds. Polymers allow enhanced plasma half-life of the drug, improved solubility and the possibility of controlled release whereas the conjugation with peptide sequences can be used as cell-penetrating moieties or as targeting moieties that will guide the vehicles to the organelle of choice.

In this project, we aim at preparing such vehicles using 2-hydroxypropyl methacrylamide (PHPMA) as the polymer, the advantage being that the polymer is biocompatible, well-soluble in water, and relatively straightforward to functionalize Possible targeting peptides have been conjugated to this polymer, either via their C-terminus or the N-terminus of the peptide, and the resulting vehicles have been tested for their cellular internalisation behaviour and intracellular trafficking and accumulation.

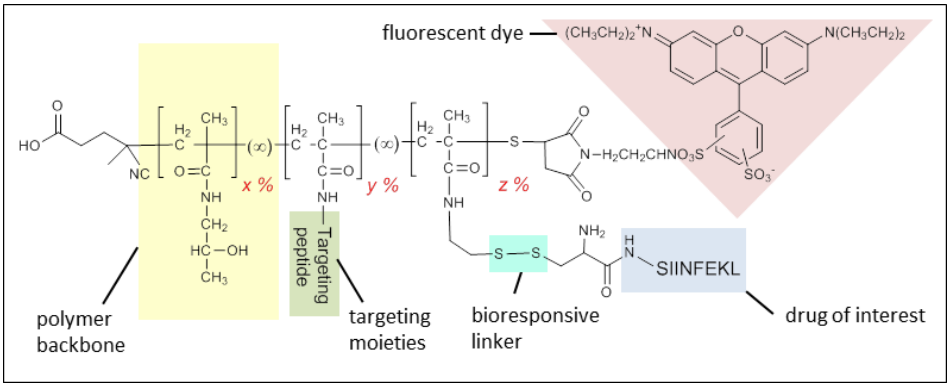

Figure 1. Polymer-peptide conjugate design for targeted intracellular drug delivery.

Masumi MURAKAMI
Doctoral student

I have been studying in carbohydrate and protein chemistry under the supervision of Prof. Kajihara. I have studied at Prof. Danishefsky Lab for a half year in New York.

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Likes: Sweets (Carbohydrate), watching movies (I love “Rain Man”, “Top Gun”, “Bourne” series and “Star Wars” series)

Synthetic Study of Erythropoietin Glycoform Containing Three Complex-type Disialyloligosaccharides at the Native Positions

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Keywords: Glycoprotein synthesis, Sialic acid, Erythropoietin

ABSTRACT:
Chemical synthesis is a powerful approach to investigate how post-translational modification of proteins, such as glycosylation, can affect protein functions. In modern procedures for chemical protein synthesis, the concept of peptide-peptide ligation plays an essential role. With this methodology the synthesis of glycopeptide-thioester building blocks is a key point to construct glycoproteins. However, widely used tert-Boc-based solid phase peptide synthesis (tert-Boc SPPS) is not applicable to the synthesis of glycopeptide-thioesters (Fig. a), which is essential for the synthesis of glycoproteins, because the oligosaccharides especially sialic acids are labile under the strong acidic conditions which are required for the cleavage/deprotection steps.

During our investigation, we uncovered that protection to the carboxylic acids of sialic acid residues makes the sialyl linkage stable under acidic conditions since the intramolecular catalytic reaction (Fig.b) is suppressed. Our extensive studies revealed that the protected sialyloligosaccharide could be used for synthesis of sialylglycopeptide-thioester. In addition, a sialylglycoprotein ,Erythropoietin (EPO) which consists of 166 amino acids (Fig c,d), bearing one disialyloligosaccharide at 83rd Asn were successfully achieved through chemical peptide synthesis and peptide-peptide ligations. We are now going to synthesize EPO glycoform bearing three disialyloligosaccharides at the native positions. We would like to present the synthesis of sialylglycopeptide-thioester and recent progress of this approach for EPO synthesis.

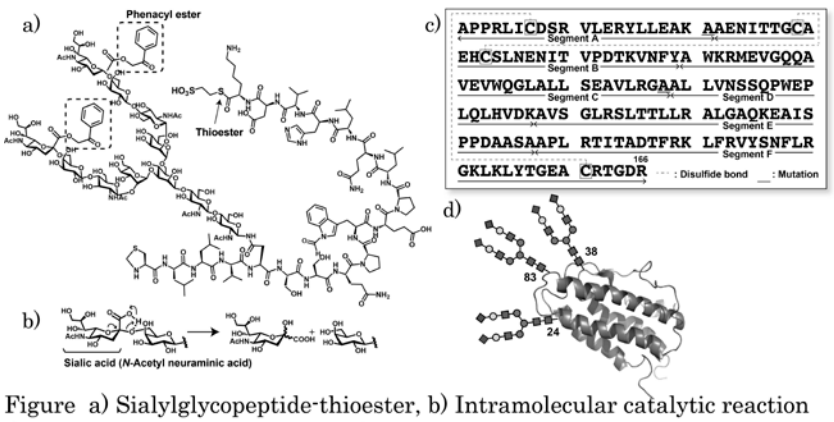
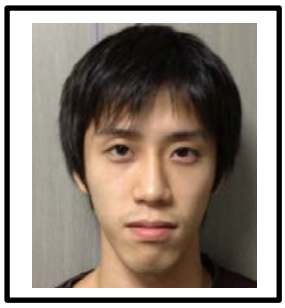


Figure a) Sialylglycopeptide-thioester, b) Intramolecular catalytic reaction
c) Amino acid sequence of EPO, d) Structure of EPO



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Guraduated from Osaka university

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Development of a concise synthetic strategy of β-mercapto amino acid derivatives

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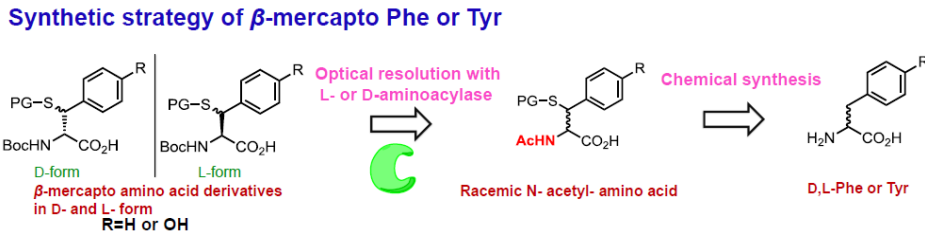
Department of chemistry, University of Osaka , Toyonaka, Osaka 560-0043, Japan

Keywords: peptide ligation, protein synthesis, amino acid derivative, enzymatic resolution

ABSTRACT:

Native Chemical Ligation (NCL) is a powerful method for chemical protein synthesis. NCL requires the coupling of peptide-$^{\alpha}$thioester and Cys-peptide which has Cys residue at its N-terminus. It is known that Cys residue is relatively rare amino acid residue in naturally occurring protein, therefore several methods have been developed to overcome the site limitation of NCL. Desulfurization strategy is one of the robust approach of these, which originally can convert Cys to Ala residue. Recently, the strategy is expanded to the other amino acid residues by using chemically prepared β-mercapto amino acid derivatives. However, in order to use these approaches, we have to prepare β-mercapto amino acid derivatives which usually require precise synthesis comprising several stereoselective reactions to suppress the epimerization of α position.

In this presentation, we would like to introduce a new concise synthesis of β-mercapto-derivatives for the synthesis of D- and L-protein. This strategy contains optical resolution step by D- and L- acylase that can de-acetylate D-amino acid or L-amino acid respectively.



Yuta MAKI
Student

Graduated at School of Science, Osaka University and studies in Graduate School of Sience, Osaka University.

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My favorite thing is climbing mountains (already completed most of the 10 highest mountains in Japan), and recently I started to enjoy taking pictures with a new camera.

Synthesis of Tri-antennary Complex-type Sialyl-tetradecasaccharide from Bi-antennary *N*-Glycan Isolated from Biological Source

Yuta MAKI[1], Ryo OKAMOTO[1], Masayuki IZUMI[1], Takeshi YAMAMOTO[2], Yasuhiro KAJIHARA[1]

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Keywords: Glycoprotein, Oligosaccharide

ABSTRACT:

The complex-type *N*-glycans have structural diversity because of their inherent branching. These oligosaccharyl structures can have an affect on the property and biological activity of glycoproteins.

We have examined the synthesis of natural highly branched complex-type *N*-glycans by use of bi-antennary complex-type *N*-glycan available in large scale from hen egg yolk. First, partial protection of bi-antennary oligosaccharide was examined, then benzylidenation of 4,6 positions of galactosides and mannosides was found to be applicable to the partial protection. With an extensive investigation, a suitable glycosyl acceptor, which has only two free hydroxyl groups, was obtained in 4 steps. Glycosylation of the oligosaccharyl acceptor with a lactosamine donor followed by systematic deprotection and subsequent enzymatic tris-sialylation yielded a desired human-type tri-antennary *N*-glycan.

In this presentation, we would like to show a detail of the experiments and the structural analysis of tri-antennary *N*-glycan synthesized by NMR techniques.

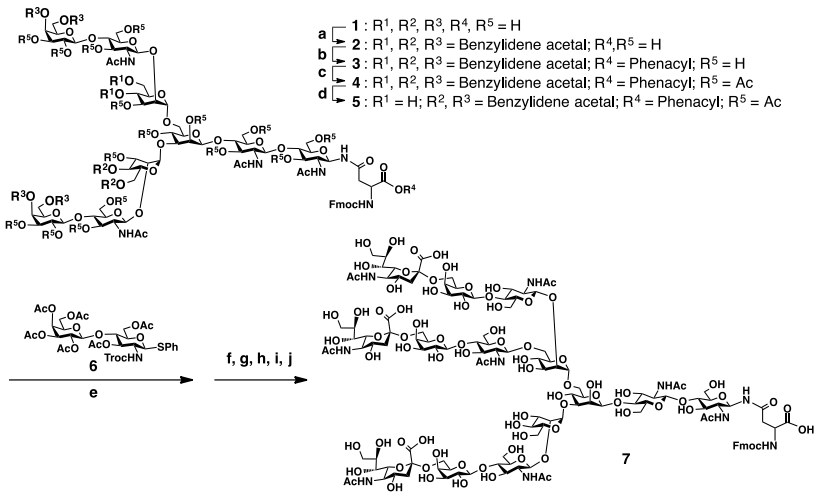

Figure. Synthesis of Complex-type Triantennary Oligosaccharide.
Reagents and conditions (a) $PhCH(OMe)_2$, CSA, DMF, rt. (b) Phenacyl bromide, $^iPr_2NEt$, DMF, rt.
(c) Ac_2O, pyridine, DMAP, rt. (d)60% AcOHaq., rt. (e)**6**, NIS, TfOH, DCM, 4A molecular sieves, 0 °C
(f) Zn, THF/ AcOH/ Ac_2O, 0 ºC to rt, (g) NaOHaq./ MeOH, 0 ºC to rt, (h) FmocOSu, Na_2CO_3, DMF/ H_2O, 0 ºC to rt,
(i) TFAaq., 0 ºC (j) α 2,6 Sialyltransferase, CMP-Neu5Ac, HEPES buffer, 37 ºC

Asako MURATA, Ph.D
Assistant Professor

Graduated from Graduate School of Frontier Sciences, The University of Tokyo and received Ph.D. in life science. Postdoc at Baylor College of Medicine, Texas, US and Kyoto University.

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I studied neurobiology as an undergraduate at University of Tsukuba, then I moved to the laboratory of Prof. Wada and Prof. Saigo at the University of Tokyo, where I learned organic synthesis and chemistry of nucleic acids. During the Ph.D. course, I found out how powerful chemicals can be as tools for biological research, and I started my research career as a Postdoc in the chemical biology laboratory of Prof. Uesugi at Kyoto University. I am interested in the interaction between RNA and small molecules and currently working on a project to develop a small-molecule ligand that modulate RNA function at Prof. Nakatani's laboratory in ISIR.

Development of potential small-molecule inhibitors of pre-miRNA processing

Asako MURATA, Ayako SUGAI, Yasue HARADA, Takahiro OTABE, Takeo FUKUZUMI, Kazuhiko NAKATANI
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Keywords: pre-miRNAs, inhibitors, Dicer digestion, Small molecule

ABSTRACT:

MicroRNAs (miRNAs) are involved in many biological processes including development, differentiation and carcinogenesis through translational repression by binding to a target mRNA. Inhibition of miRNA pathways by altering miRNA expression and/or maturation in cells would modulate gene expression, and enable us to understand miRNA regulatory effects on various biological processes. A small molecule that bind to precursor miRNA (pre-miRNA) and inhibit Dicer-catalyzed pre-miRNA processing will provide tools for modulating miRNA-mediated gene regulation.

We have previously reported the xanthone-based fluorescent indicators for detecting the interactions between RNA and small molecules [*J. Am. Chem. Soc.* **2010**, 132, 3660., *Chem. Eur. J*. **2012**, 18, 9999.]. Some of the 2,7-aminoalkoxy-substituted xanthone and thioxanthone derivatives preferentially bind to certain secondary structures of RNA such as loops and bulges rather than double-stranded regions. Since most pre-miRNAs have such secondary structures, we explored a possibility of inhibitory activity of the xanthone and thioxanthone derivatives against the dicing reaction upon their binding to pre-miRNA. Here we report that an aminoalkoxy-substituted thioxanthone derivative interferes Dicer-mediated processing of pre-miR-29a. X2SS, one of the thioxhanthone derivatives we synthesized, effectively suppressed the formation of both the intermediate and mature miR-29a, indicating the inhibitory effect of X2SS on pre-miRNA processing. Analysis of the dicing reaction of pre-miR-29a mutant revealed that binding of X2SS close to a cleavage site is capable of interfering the processing of pre-miR-29a. Moreover, we performed a screening with in-house chemical library for potential inhibitors of pre-miR-29a processing using X2SS as the fluorescent indicator. Since a small molecule that competes for X2SS binding site of pre-miR-29a and displace X2SS from pre-miR-29a would be readily used as an inhibitor for pre-miR-29a processing, X2SS offers advantages to be used as the fluorescent indicator. Information about the interaction between these xanthone derivatives and pre-miRNAs will enable us to design and develop new small molecule-based inhibitors for miRNA pathway.

Takahiro OTABE, D2

Graduated from Nihon University where I have taken the BSc course in organic chemistry. Now I am second grade student of doctoral course in Department of Chemistry, Graduate School of Science, Osaka University

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Synthesis of RNA bulge binding small molecule and application to inhibitor of Dicer cleavage reaction

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Keywords: small molecule, pre-miRNA, Dicer

ABSTRACT:

The microRNA (miRNA) is small molecule RNA like approximately 22 bases that Dicer produces a microRNA precursor after processing, and then approximately 1,000 kinds are confirmed in the Homo sapiens. miRNA is are after being incorporated into the RNA-induced silencing complex (RISC), they regulate gene expression by base pairing with the complementary mRNAs, thereby blocking translation and/or affecting the mRNA stability. They are found to be involved in a variety of cellular physiological processes like development, differentiation, apoptosis, proliferation and metabolism. In this study, we have tried that controlled the processing process with a small molecule.

We have developed a series of naphthyridine derivatives that can bind to single nucleotide bulges in DNA duplexes. Among these derivatives, *N,N*-bis(3-aminopropyl)-2,7-diamino-1,8-naphthyridine (DANP) was found to bind to cytosine and guanine bulges in dsDNA. The stabilizing effect of DANP on the complex with bulged dsRNA as determined by thermal melting analysis, however, was rather smaller than that observed for bulged dsDNA. The results of molecular modeling of RNA-DANP complex indicate that stacking interaction of DANP with the neighboring bases in the RNA duplex would be insufficient compared with that of DNA-DANP complex. We therefore designed BzDANP that has the same hydrogen-bonding surface as that of DANP but has an expanded aromatic plane in order to examine the effect of the molecular size and the π-stacking with the neighboring base pairs on binding affinity with RNA duplexes. We have shown the synthesis and the evaluation of binding capability BzDANP to dsRNA containing a single nucleotide bulge. A significant increase in melting temperature with dsRNA containing a single bulge was observed in presence of the BzDANP, suggesting the increased stabilizing effect of BzDANP on bulged dsRNA relative to DANP.

Next we explored a potential inhibitory of BzDANP against the dicing reaction of precursor-miRNA (pre-miRNA) upon binding to its secondary structures. Pre-miR-29a has a cytosine bulge near the putative cleavage sites by Dicer, so we expected that the binding of BzDANP to the bulge would interfere the dicing reaction of pre-miR-29a.

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Development and engineering of probes for bivalent epigenetic marks:

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Keywords: Bivalent chromatin, protein probe, designer nucleosome

ABSTRACT:
In embryonic stem (ES) cells, bivalent chromatin domains are marked with repressive (H3 lysine 27 methylation, H3K27me3) as well as activating (H3 lysine 4 methylation, H3K4me3) post-translational modifications (PTMs). Bivalent domains have been mostly studied with methods which require cell lysis, the use of large number of cells and the availability of specific antibodies. Our aim is to develop a genetically encoded probe that bind specifically to bivalent nucleosomes to be able to detect and follow the co-existence of H3K4me3 and H3K27me3 at the single cell level. This probe would weakly bind singly modified nucleosomes but strongly bind nucleosomes having both H3K4me3 and H3K27me3 allowing for the detection of bivalent nucleosomes.

We designed, expressed and optimized a genetically encoded multivalent protein probe called ChroProbe1 which consists of the improved version of YFP, Venus, intercalated between two binding domains, a PHD zinc finger and a Chromodomain. In order to validate and further optimize our probe, we used Expressed Protein Ligation (EPL) to synthesize two histones modified with H3K4me3 and H3K27me3 which were assembled with H2A, H2B, H4 and DNA to form nucleosomes. The binding of ChroProbe1 against these designer nucleosomes will serve as an *in vitro* validation model. ChroProbe1 will be expressed in cells and observed by fluorescence microscopy to detect and follow the presence of bivalent chromatin in a single cell. Genetically encoded probes like ChroProbe1 are powerful tools to study the functions and dynamics of bivalent chromatin at the single cell level.

Hiroshi TSUCHIKAWA, Ph.D
Assistant Professor

Received Ph.D in Science at Osaka University, Japan under the supervision of Prof. Michio Murata in December 2006. And a first postdoctoral fellow in Prof. Shigeo Katsumura lab. at Kwansei Gakuin University, Japan (2007.1-2009.3), then a second postdoctoral fellow in Prof. Mikiko Sodeoka lab. at REKEN, Japan (2009.4-2010.5)

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Stereocontrolled synthesis of the 5,5,6-bis-spiroacetal ring moiety of spirolide C:

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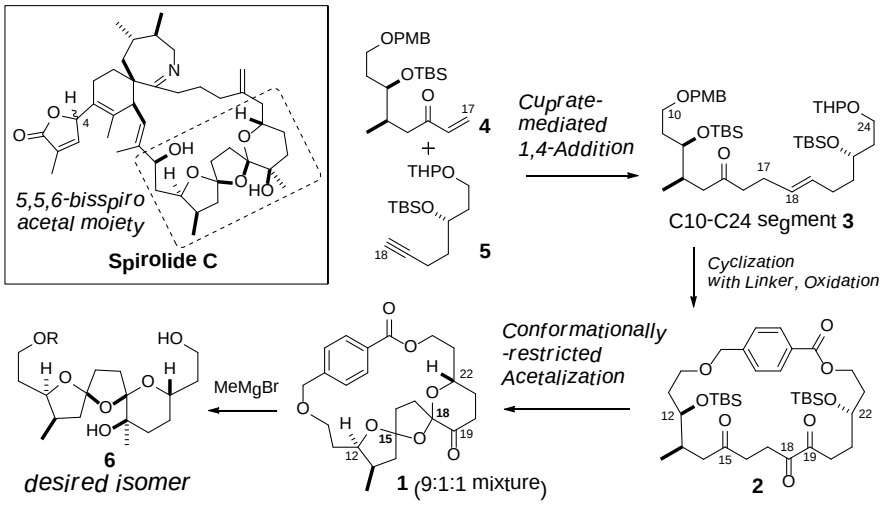
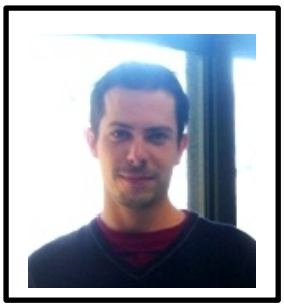
Keywords: stereoselective, synthesis, spiroacetal, spirolide

ABSTRACT:
The 5,5,6-bis-spiroacetal moiety is an important fragment for the total synthesis of spirolide C. However, its stereoselective synthesis has not been established due to its intrinsic difficulties; an anomeric stabilization of 5,5-spirocenter cannot be expected, and the undesired configuration of 5,5-spirocenter seems to be more thermodynamically favorable.
In this study, we examined its stereoselective construction via the conformationally-restricted spirocyclization of the benzoate-linked macrocyclic triketone **2**. Our strategy is based on the hypothesis that if C-12 and C-22 substituents are linked together with an appropriate tether, the desired diastereomer of **1** could be more thermodynamically stable than the undesired diastereomer.
The cyclization precursor **2** with a benzoate linker was efficiently synthesized via the C10-C24 segment **3** which was obtained by cuprate-mediated 1,4-addition of alkyne **5** to enone **4** as a key step. The complete deprotection of two secondary alcohols and the following critical spirocyclization of **2** proceeded smoothly by treatment with an excess amount of HF·pyridine to furnish a mixture of three bis-spiroacetal products in 9:1:1 ratio in 60% yield. After the conversion of the main isomer to triol **6**, its stereostructure was unambiguously determined to be a desired one by the NOE experiment. This result strongly suggested that the key bis-spirocyclization of cyclic triketone **2** should occur in a stereoselective manner as we expected.





Sébastien LETHU, Ph.D
Postdoctoral Researcher

Received his Ph.D in Organic Chemistry at the Institut de Chimie des Substances Naturelles (ICSN), Gif-sur-Yvette, France under the supervision of Dr. J. Dubois in December 2009. Did a first postdoctoral fellowship in the laboratory of Dr. H. Alper at the University of Ottawa, Canada (Jan 2010-Mar 2011) and then started a second postdocdoctoral position under the supervision of Pr. M. Murata at Osaka University, Japan (Apr 2011-present).

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Design and Synthesis of Labeled Compounds for Conformation Analysis of Fatty Acids Bound to Proteins

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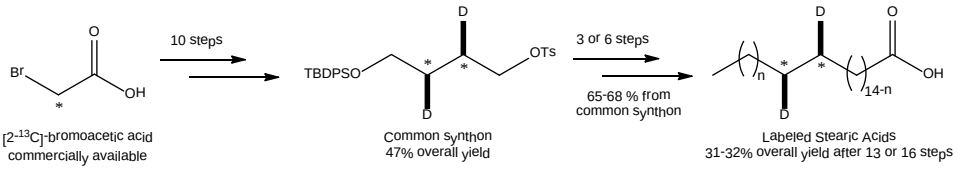
Keywords: labeled fatty acids, alkyl-alkyl coupling

ABSTRACT:

In our lab, we are studying the impact of protein-lipid interactions on the lipid alkyl chain conformation. To fulfill our needs, spectroscopic methods to evaluate alkyl chain conformation have been developed by vibration spectroscopy and NMR with isotopically labeled samples. Indeed, incorporation of isotopes is required for improvement of experiments sensitivity. Particularly in solid-state NMR, site-selective labeled compounds with an isotope-cluster containing ^{13}C and D allow efficient background suppression and provide interatomic distance restraints which define the conformation.[1] The minimum structure for defining an alkyl chain conformation by NMR is a butylene-type unit C-^{13}CHD-^{13}CHD-C with defined configuration at C2 and C3.

Here, we aim to introduce a new highly efficient route to access stearic acids bearing this labeled moiety.
To prepare those compounds, we first developed a strategy to synthesize a common synthon that would afford stearic acids with the labeled moiety in any position of the aliphatic chain. After the common precursor was obtained in a very efficient way, the desired fatty acids were provided following a strategy involving one or two powerful copper-catalyzed Kumada-Corriu C_{sp^3}-C_{sp^3} couplings.[2] Thanks to this route, several labeled fatty acids were synthesized in excellent overall yields after 13 to 16 steps.



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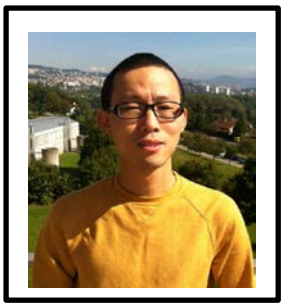

Bo Yao, Ph.D

Postdoc researcher

Graduated at Institute of Chemistry, Chinese Academy of Sciences and received Ph.D in organic chemistry in 2010. Postdoc at Institute of Chemical Science and Engineering, Ecole Polytechnique Fédérale de Lausanne from 2010.

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Pd(II)-Catalyzed Domino Reactions of Alkynes Under Aerobic Conditions: Facile Access to Potentially Bioactive Heterocycles

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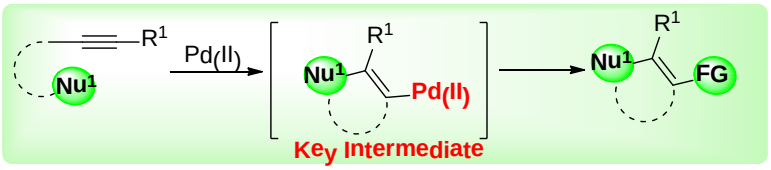
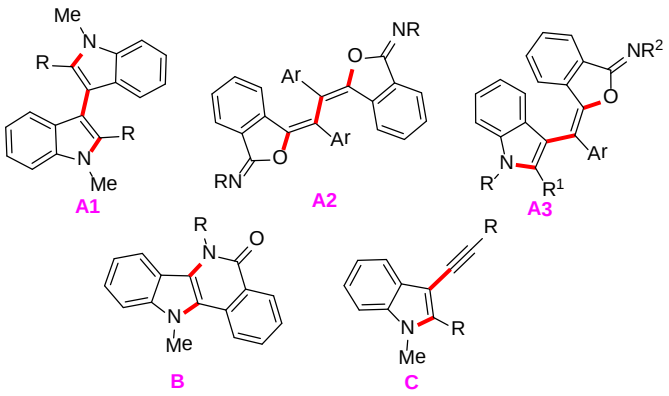
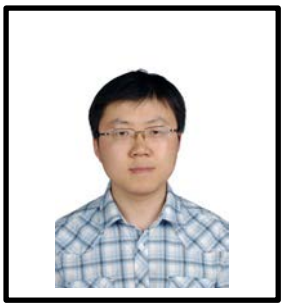
Keywords: homogeneous catalysis, alkynes, heterocycles, indoles,

ABSTRACT:

Heterocycles, such as indoles, isoindolinones, isoquinolinones, isocoumarines and their derivatives show diverse biological activities, such as anticancer, antiallergic and antimicrobial, immunomodulatory, cytotoxic, antifungal, anti-inflammatory, antiangiogenic, antimalarial, antimuscarinic, antiviral, antiplasmodial, antihypoglycemic, and PARP-inhibiting activities. Using $Pd(OAc)_2$ as a powerful catalyst, we developed a series of domino reactions involving an unusual double nucleophilic addition across the triple bond for the construction of diverse heterocycles with potential biological activities.







Zhengren XU, Ph.D
Postdoctoral Researcher

Graduated at School of Pharmaceutical Sciences, Peking University and received Ph.D in chemical biology at the State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University. Now work as a postdoctoral researcher at the Laboratory of Synthesis and Natural Products (LSPN) in EPFL.

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My research interests focus on the design of novel strategies for the efficient synthesis of natural products, especially total synthesis of indole alkaloids with unique skeletons. On the other hand, we are also interested in the development of new methodologies for the fast construction of molecular complexity, which will greatly facilitate the total synthesis of natural products.

Total Synthesis of (±)-Goniomitine

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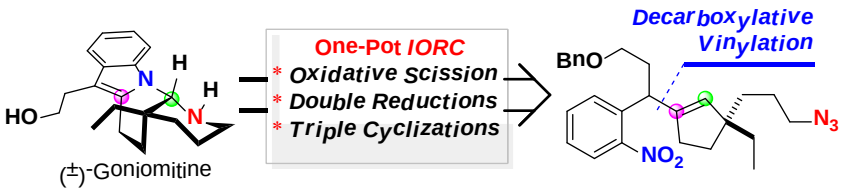
Laboratory of Synthesis and Natural Products
EPFL-SB-ISIC-LSPN, CH-1015 Lausanne, Switzerland

Keywords: goniomitine, monoterpene indole alkaloids, decarboxylative coupling.

ABSTRACT:

The class of monoterpene indole alkaloids, comprising nowadays over 2000 members with broad skeleton diversity and important bioactivities, has fascinated scientists for over a century. Goniomitine, a unique member of the *Aspidosperma* family, was isolated from the root bark of *Gonioma malagasy* by Husson and co-workers in 1987. Its unprecedented octahydroindolo[1,2-*a*][1,8]naphthyridine skeleton, resulted from the oxidative rearrangement of vincadifformine, has attracted widespread interest from the synthetic community. Five total syntheses have been achieved so far.



We here present our recent seven-step total synthesis of (±)-goniomitine, featuring two key steps: 1) A novel palladium-catalyzed decarboxylative coupling reaction between potassium nitrophenyl acetates and vinyl triflates for the rapid construction of the functionalized cyclopentene that incorporates all the atoms required for the natural product. 2) A one-pot *I*ntergrated *O*xidation/*R*eduction/*C*yclization (*IORC*) process for converting the substituted cyclopenetene into the tetracyclic skeleton of goniomitine. In this process, the oxidative scission of a double bond, the chemoselective reduction of an azido and a nitro group, and the concurrent formation of three C-N bonds and three rings took place with high regio-, chemo- and diastereoselectivity.

Reto FREI, Ph.D

Laboratory of Catalysis and Organic Synthesis

Post-doctoral Marie Curie Fellow in the group of Prof. Jérôme Waser at the EPFL.

Received a Ph.D in chemistry in 2011 under the supervision of Prof. Helen E. Blackwell at the University of Wisconsin-Madison, United States.

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Total Synthesis and Biological Evaluation of Jerantinine E

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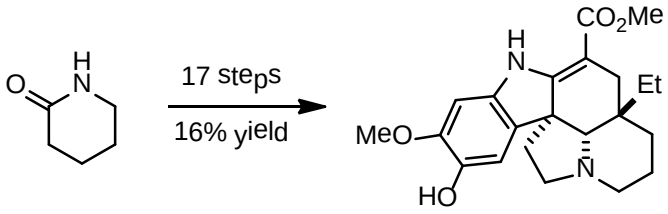
Keywords: natural product, total synthesis, anticancer, tubulin disruption

ABSTRACT:
Heterocyclic scaffolds occupy a privileged position among natural and synthetic drugs. Consequently, the discovery and implementation of cyclization reactions to efficiently access such cyclic structures are highly sought after in organic chemistry. In this context, our laboratory developed the first catalytic formal homo-Nazarov cyclization of vinyligous cyclopropyl ketones for the synthesis of polycyclic hetero and non-hetero cyclohexenone derivatives.[1] The effectiveness of the developed mild and highly regio-selective reaction for the cyclization of acyl indole substituted aminocyclopropanes has been demonstrated by the efficient formal total synthesis of aspidospermidine and the total synthesis of goniomitine.[2] Herein we report the broad applicability of the developed formal homo-Nazarov cyclization by employing it as key transformation during the first total synthesis of the highly electron-rich aspidosperma type alkaloid jerantinine E.[3] This synthetic feat allowed in addition for an in depth evaluation of the biological profile of jerantinine E. As such, the cytotoxic activity of the natural product was determined in several human-derived breast and lung cancer cell lines. Investigations into the mode of action suggested that jerantinine E acts *via* disruption of the microtubule network, as indicated by its potent inhibitory activity displayed in tubulin polymerization.



Jerantinine E
Potent Tubulin Disruptor

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[2] F. De Simone, J. Gertsch, J. Waser, *Angew. Chem. Int. Ed.* **2010**, *49*, 5767-5770.
[3] R. Frei, D. Staedler, A. Raja, R. Franke, F. Sasse, S. Gerber-Lemaire, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *ASAP* (DOI: 10.1002/anie.201305533).

Inmaculada RENTERO REBOLLO

Ph.D. student

Graduated in Biotechnology at Autonomous University of Barcelona. Currently pursuing Ph.D. studies in Chemical Biology at Swiss Federal Institute of Technology, Lausanne, Switzerland.

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My work focuses on the development of new antibiotics based on bicyclic peptides. In addition to the sortase, we are currently working with other targets such as penicillin-binding proteins (PBPs) and metallo beta lactamases (MBLs).

Bicyclic peptide inhibitors of SrtA from *Staphylococcus aureus*

Inmaculada RENTERO REBOLLO[1], Christian HEINIS[1],
[1]Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland

Keywords: peptide, inhibitor, phage display, sortase, antimicrobial

ABSTRACT:

There is a constant need of new antibacterial compounds to combat the inevitable emergence of antibiotic resistance. In spite of huge screening efforts by pharmaceutical companies, only a few new antibiotics have reached the clinic in the last decades. Besides, the majority of them are derivatives of previously approved ones.

Bicyclic peptides constitute new and promising architectures to explore for antibacterial agents. Many natural antibiotics are based on constrained peptidic structures, and bicyclic peptides offer a richer three dimensional complexity and can reach higher affinities than linear or monocyclic peptides. For example, we have developed potent and selective inhibitors of sortase A (SrtA) of *S. aureus*, a transpeptidase that anchors virulence factors and adhesins to the peptidoglycan cell wall of the bacterium, playing a critical role in pathogenesis. A bicyclic peptide inhibitor of SrtA could become an alternative drug for the treatment of infections, including multi-drug resistant strains.

Shiyu CHEN, Ph.D

Graduated as a chemist from the Shanghai Institute of Materia Medica (SIMM). Ph.D from the Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL).

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I have a broad interest in chemical biology. In my PhD, I have developed new formats of bicyclic peptides.

Bicyclic peptide ligands pulled out of cysteine-rich peptide libraries

Shiyu CHEN[1], Inmaculada Rentero Rebollo[1], Sergey A. Buth[2], Julia Morales-Sanfrutos[1], Jeremy Touati[1], Petr G. Leiman[2], and Christian Heinis*[1],
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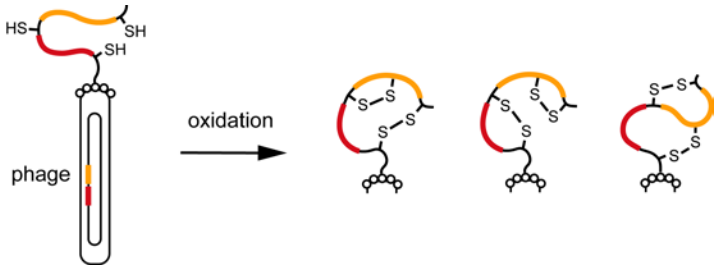
[2]Institute of Physics and Biological Systems, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Keywords: peptide macrocycle, peptide ligand, bicyclic peptide, peptide therapeutics, phage display

ABSTRACT:
Bicyclic peptide ligands were found to have good binding affinity and target specificity. However, the method applied to generate bicyclic ligands based on phage-peptide alkylation is technically complex and limits its application to specialized laboratories. On my poster, I show a method that involves a simpler and more robust procedure that additionally allows screening of structurally more diverse bicyclic peptide libraries. In brief, phage-encoded combinatorial peptide libraries of the format $X_mCX_nCX_oCX_p$ are oxidized to connect two pairs of cysteines (C). (Figure) This allows the generation of 3×(m+n+o+p) different peptide topologies because the fourth cysteine can appear in any of the (m+n+o+p) randomized amino acid positions (X). Panning of such libraries enriched strongly peptides with four cysteines and yielded tight binders to protein targets. X-ray structure analysis revealed an important structural role of the disulfide bridges. In summary, the presented approach offers facile access to bicyclic peptide ligands with good binding affinities.



Kenichi MURAI, Ph.D
Assistant Professor

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http://www.phs.osaka-u.ac.jp/homepage/b005/

Kenichi Murai was born in 1980 in Hiroshima, Japan. He studied chemistry at the Graduate School of Pharmaceutical Sciences, Osaka University (1999-2008) and obtained his Ph. D under the guidance of Professor Yasuyuki Kita. After he obtained Ph.D, he worked as a researcher at Ritsumeikan University with Professor Yasuyuki Kita and at Osaka University with Associate Professor Hiromichi Fujioka. In 2008, he got a position of assistant professor at the research group of Professor Hiromichi Fujioka.

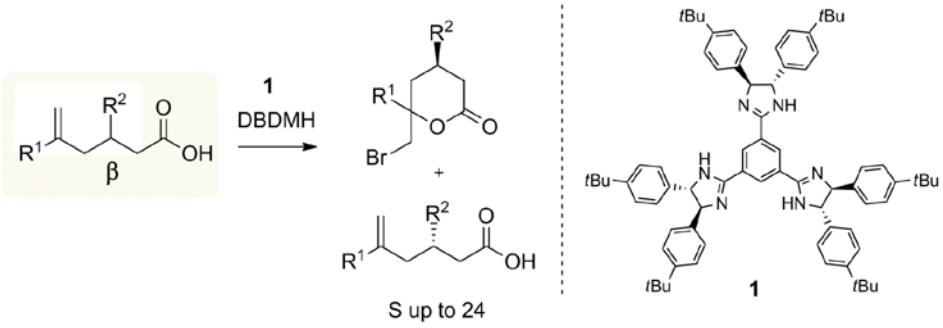
Asymmetric bromolactonization based kinetic resolution of β-substituted olefinic carboxylic acids

Kenichi Murai, * Tomoyo Matsushita, Norimichi Hyogo, Akira Nakamura, Junki Nakajima, Hiromichi Fujioka *
Graduate School of Pharmaceutical Sciences, Osaka University

Keywords: Organocatalyst, asymmetric reaction, halolactonization

Kinetic resolution of racemic carboxylic acids is an important process in organic synthesis. As a result, significant efforts have been devoted to develop efficient non-enzymatic chemical methods with artificial molecules. The direct kinetic resolutions of α-substituted carboxylic acids, relying on the use of chiral acyl transfer catalysts, have been successfully developed by several groups. In contrast, techniques for kinetic resolutions of β-substituted carboxylic acids have been less well explored and a new strategy should be developed. In this presentation, we will report our effort on the development of kinetic resolution of β-substituted carboxylic acids, which is featured by the utilization of the asymmetric bromolactonization reaction.

We have recently developed the asymmetric bromolactonization reaction catalyzed by the trisimidazoline catalyst, which produces 6-membered lactones from 5-hexenoic acid derivatives in highly enantioselective manner.[1] As part of a program aimed at broadening the perspective of this process, we explored the feasibility of the bromolactonization reaction to a novel strategy for a kinetic resolution of β-substituted olefinic carboxylic acids, and found that the new trisimidazoline catalyst **1** (4-*t*BuPh-tris) achieved this task with 1,3-dibromo dimethyl hydantoin (DBDMH) as a bromine source in a moderate to good selectivity (S factor up to 24).[2] The cyclization stage, which provides δ-lactone, is proposed to be operative for discrimination of each enantiomer of carboxylic acids. The readily regeneration of the starting carboxylic acids from the lactone products is an important component of this resolution method: The reductive cleavage process is available for transformation of the bromolactone to the starting olefinic carboxylic acids.



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Selective Transformations of Carbonyl Functions Using in situ Protection Methodology

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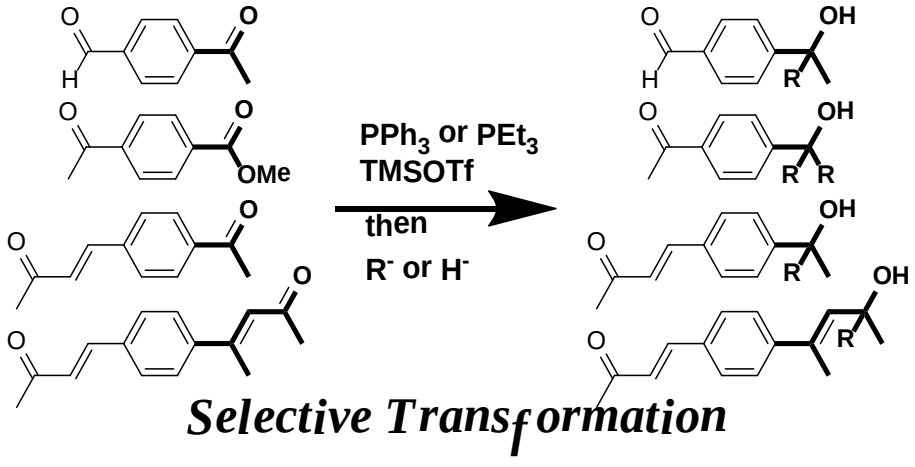
Keywords: Chemoselectivity, Carbonyl Group, One-pot Reaction

The methodology for selective transformations of carbonyl groups has been developed. Functional groups have inherent reactivity each other. While the reactivity enables selective transformations of the most reactive groups in polyfunctionalized compounds, it necessitates intrusive multi step operations using protective group when we seek to transform less reactive functions in the presence of more reactive ones.

Carbonyl groups are one of the most important functional groups in synthetic organic chemistry. It is well known that the reactivity of carbonyl groups towards nucleophiles falls in the following order: aldehydes > ketones ~ enones > esters > amides. We found the combination of TMSOTf and PPh_3 (or PEt_3) enabled to reverse reactivity of aldehydes, ketones, esters, and amides by forming phosphonium salts, which are stable to reduction and alkylation conditions, from aldehydes (or ketones). Namely, the pre-addition of TMSOTf and PPh_3 prior to the addition of nucleophile permits the selective transformations of ketones, esters, and amides in the presence of aldehydes. And the replacement of PPh_3 with PEt_3 makes the selective conversion of esters and amides possible in the presence of ketones. Furthermore, we accomplished the discrimination between ketones and enones and moreover β mono- and di-substituted enones, of which reactivities are remarkably similar.



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Dioxygen Activation by Bio-Inspired Trinuclear Copper Complexes with a Cage Ligand

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Keywords: Metalloenzyme, Cryptand, Bio-insired

ABSTRACT:

The copper-mediated activation of dioxygen plays a vital role in biological and synthetic oxidative catalyses. In biological systems, the $4e^-$ reduction of dioxygen is accomplished by copper-containing enzymes, called as Cytchrome c Oxidase (CcO) and Multi Copper Oxidase (MCO). The latter enzyme, containing three copper ions in the active site (Figure 1), has an intermediate $2e^-$ reduced form of dioxygen in the catalytic cycle. Based on the spectroscopic and computational studies, the intermediate has been considered as three copper ions bridged by a peroxo ion ($O\text{-}O^{2-}$) in the active site. In order to obtain details about the peroxo intermediate of MCO, we synthesized biomimetic model compounds having three copper atoms and investigated the reaction with dioxygen.

The trinuclear complexes, $[\mathbf{L_{NH}}Cu^{II}_3(OH)_2(H_2O)](ClO_4)_4$ (**1**) and $[\mathbf{L_{NH}}Cu^{I}_3Cl_3]$ (**2**) were synthesized by reactions of copper salts with a novel cage-type ligand $\mathbf{L_{NH}}$ (Figure 2). These complexes were fully characterized by x-ray structure analysyses and spectroscopic methods. The reaction of **1** with H_2O_2 and the reaction of **2** with O_2 resulted in the peroxo species, respectively. These peroxo compounds were detected by UV-Vis, rRaman, ESR, and ESI-MS spectra. The oxygenated product from the reaction of **1** with H_2O_2 at low temperature exhibited a remarkable increase of absorption bands around 347 nm (ε = 2000 $M^{-1}cm^{-1}$) in the UV-Vis spectra. The product in the reaction of **2** with O_2 also showed an analogous absorption spectral change at 377 nm (ε = 2700 $M^{-1}cm^{-1}$). The rR study indicated that corresponding peroxo-intermediate species formed in these systems. We discuss about spectroscopic data of two different types of peroxo-intermediates formed by oxygenation of **1** and **2** with O_2 and H_2O_2, respectively.

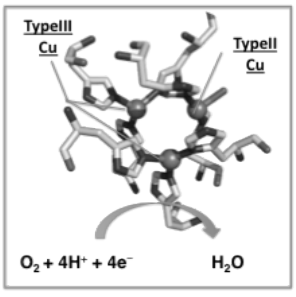

Fig. 1. MCO active site

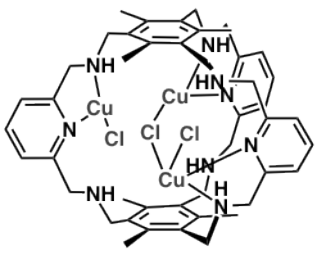

Fig. 2. Structure of $[\mathbf{L_{NH}}Cu_3Cl_3]$

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