Symposium | Asian International Symposium：Asian International Symposium - Natural Products Chemistry, Chemical Biology / Biofunctional Chemistry and Biotechnology / Medicinal Chemistry -

Thu. Mar 27, 2025 1:00 PM - 3:40 PM JST | Thu. Mar 27, 2025 4:00 AM - 6:40 AM UTC
[A]D302(D302, Bldg. 4, Area 3 [3F])

# [[A]D302-2pm] Asian International Symposium - Natural Products Chemistry, Chemical Biology / Biofunctional Chemistry and Biotechnology / Medicinal Chemistry -

Chair, Symposium organizer: Hirokazu Tamamura, Shigeki Kiyonaka, Shinya Tsukiji, Tasuku Hirayama, Masafumi Minoshima, Hirokazu Arimoto

English Invited Lecture
1:00 PM - 1:20 PM JST | 4:00 AM - 4:20 AM UTC
[[A]D302-2pm-01]
Drug discovery research based on strategic chemistry approaches
○Yukihiro Itoh[1] (1. Osaka University)

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English Keynote Lecture
1:20 PM - 1:50 PM JST | 4:20 AM - 4:50 AM UTC
[[A]D302-2pm-02]
How to tackle the challenge of selective ligand discovery in target protein degradation strategies
○Jun-Seok Lee[1] (1. Korea University)

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English Invited Lecture
1:50 PM - 2:10 PM JST | 4:50 AM - 5:10 AM UTC
[[A]D302-2pm-03]
Exploration of Binders and Degraders targeting Biomolecules
○Haruo Aikawa[1] (1. The University of Tokyo)

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2:10 PM - 2:15 PM JST | 5:10 AM - 5:15 AM UTC
Break

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English Asia Special Lecture
2:15 PM - 2:45 PM JST | 5:15 AM - 5:45 AM UTC
[[A]D302-2pm-04]
New Aldehyde Chemistry for Peptide Modification
○Gong Chen[1] (1. Nankai University)

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English Invited Lecture
2:45 PM - 3:05 PM JST | 5:45 AM - 6:05 AM UTC
[[A]D302-2pm-05]
Natural Product Synthesis Based on Regioselective Functionalization of Cross-Conjugated Dienones
○Minami Odagi[1] (1. Tokyo Univ. of Agri.)

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English Keynote Lecture
3:05 PM - 3:35 PM JST | 6:05 AM - 6:35 AM UTC
[[A]D302-2pm-06]
Organic Synthesis of Complex Natural Products to Facilitate Chemical Biology Studies

〇Tuoping Luo[1] (1. Peking University)

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3:35 PM - 3:40 PM JST | 6:35 AM - 6:40 AM UTC

### Closing Remarks

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# Drug discovery research based on strategic chemistry approaches

([1]*SANKEN, Osaka University*) ○Yukihiro Itoh[1]

**Keywords**: Enzyme inhibition kinetics, Histone deacetylase, Targeted protein degradation

In conventional drug discovery research, receptor agonists/antagonists and enzyme inhibitors are common drug candidates. Medicinal chemists aim to discover such molecules by combining chemical library screening with structure-based drug design (SBDD), which focuses on the structure of the target protein, and ligand-based drug design (LBDD), which optimizes compounds based on their own structures. These methods have undoubtedly led to the identification of many promising receptor agonists/antagonists and enzyme inhibitors. However, conventional drug discovery research faces various challenges. For example, numerous disease-related proteins remain undruggable. In addition, the efficiency and reliability of the conventional drug methodologies are still insufficient due to factors such as the limited diversity and quality of chemical libraries, the structural flexibility of target proteins in SBDD, and the inefficiency of LBDD, which often relies on heuristics and trial-and-error approaches. In other words, the field of medicinal chemistry is still unestablished. Therefore, it is essential to not only rely on the conventional modalities and methods but also continually incorporate innovative ideas to advance drug discovery.

Based on these backgrounds, we have been performing drug discovery research that consistently emphasizes "chemistry." By integrating concepts from organic chemistry into library construction, molecular design, and drug modalities, we aim to drive innovate. The representative examples of our work include drug discovery leveraging target protein degradation,[1] enzyme inhibition kinetics,[2] *in situ* click chemistry,[3] and the theoretical design of inhibitors based on the chemical reactions catalyzed by target enzymes.[4] We believe that harnessing "chemistry" to discover bioactive compounds offers a new paradigm in drug discovery. In this presentation, we will discuss our drug discovery research based on strategic chemistry approaches.

1) a) J. Chotitumnavee, Y. Yamashita, Y. Takahashi, Y. Takada, T. Iida, M. Oba, Y. Itoh, T. Suzuki, *Chem. Commun.* **2022**, *68*, 4635. b) T. Iida, Y. Itoh, Y. Takahashi, Y. Yamashita, T. Kurohara, Y. Miyake, M. Oba, T. Suzuki, *ChemMedChem* **2021**, *16*, 1609. c) Y. Itoh, M. Ishikawa, M. Naito, Y. Hashimoto, *J. Am. Chem. Soc.* **2010**, *132*, 5820. 2) Y. Itoh, P. Zhan, T. Tojo, P. Jaikhan, Y. Ota, M. Suzuki, Y. Li, Z. Hui, Y. Moriyama, Y. Takada, Y. Yamashita, M. Oba, S. Uchida, M. Masuda, S. Ito, Y. Sowa, T. Sakai, T. Suzuki, *J. Med. Chem.* **2023**, *66*, 15171. 3) Y. Miyake, Y. Itoh, Y. Suzuma, H. Kodama, S. Uchida, T. Suzuki, *ACS Catal*. **2020**, *10*, 5383. 4) a) Y. Ota, Y. Itoh, A. Kaise, K. Ohta, Y. Endo, M. Masuda, Y. Sowa, T. Sakai, T. Suzuki, *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 16115. b) D. Ogasawara, Y. Itoh, H. Tsumoto, T. Kakizawa, K. Mino, K. Fukuhara, H. Nakagawa, M. Hasegawa, R. Sasaki, T. Mizukami, N. Miyata, T. Suzuki, *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 8620.

# How to tackle the challenge of selective ligand discovery in target protein degradation strategies

Jun-Seok Lee[1]*

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Target protein degradation (TPD) has emerged as a transformative approach in drug discovery, enabling the selective degradation of proteins that were previously considered undruggable. By hijacking the cellular degradation machinery, TPD technologies such as PROTACs have demonstrated immense potential for therapeutic applications. These strategies rely on the recruitment of E3 ubiquitin ligases to target proteins, facilitating their ubiquitination and subsequent proteasomal degradation. The appeal of TPD lies in its catalytic mechanism, which can achieve significant pharmacological effects with minimal drug dosage. Over the years, diverse TPD platforms, including molecular glues and lysosomal-targeting chimeras (LYTACs), have expanded the scope of this field.

Despite these advancements, the discovery of target protein-specific ligands remains a significant bottleneck. Many proteins lack well-defined ligand-binding pockets, limiting the ability to engage them with small molecules. Additionally, current TPD strategies often require complex synthetic processes to couple ligands with degradation-inducing components. This complexity increases development time and costs, presenting a barrier to wider adoption.

To address these challenges, we propose a simplified and versatile platform for TPD development leveraging aptamers utilizing Aptamer N-degron PNA emsemble (AptaGron) system. This approach eliminates the reliance on small molecule ligands and simplifies the design process, offering a promising alternative for expanding the range of targetable proteins.

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Jun-Seok Lee (이준석).
B.S. 2005 POSTECH
Ph.D. 2009, New York University
Research Fellow, National University of Singapore 2007-2009
Research Scientist, KIST 2010-2012
Senior Research Scientist, KIST 2013-present
Associate Professor, KIST-School 2015-present
Research Interest: Chemical Proteomics, fluorescence probe, photo-crosslinker

# Exploration of Binders and Degraders targeting Biomolecules

(*Graduate School of Science, The University of Tokyo*) ○Haruo AIKAWA

**Keywords**: binder, degrader, screening, RNA, RiboTAC

To control the function of biomolecules, we need molecules which bind to the target to alter/stabilize the structure or inhibit/enhance the interaction with other biomolecules. Studies of the three-dimensional structure of the target make it possible to design binders, and recent remarkable advances in cryo-electron microscopy (EM) and computational simulations such as the AlphaFold program are accelerating this approach. On the other hand, chemical library screening and *in vitro* selection methodologies could yield binders without the structural information of the target.

As a target biomolecule, RNA including mRNA and micro-RNA (miRNA), etc., has recently attracted more attention. Although the design of RNA binders[1] is still difficult, the integration of studies on RNA-binding small molecules enables the development of molecules that control RNA functions. In the first part, the development of RNA binders targeting the precursor of the onco-miRNA (pre-miR-21) will be presented.[2] A benzimidazole-type binding motif targeting two bulge structures on pre-miR-21 was designed based on the database named inforna.[3] A dimer molecule consisting of two benzimidazoles with peptoid linker was synthesized by SPPS. The in vitro binding assay of the molecule targeting pre-miR-21 was performed by MST, to show a $K_d$ of about 1 μM, which is 18 times stronger binder than the corresponding monomer. The bioactivity of the molecule was evaluated using MDA-MB-231 cells to show alteration of the abundance of miR-21 and pre-miR-21 upon treatment with the molecule. The methodology was also successfully applied to develop a binder targeting FTD/ALS-related RNA, $(G_4C_2)^{exp}$.[4]

Binders only show their bioactivity when they bind to the functional binding pocket on the target. In addition, a stoichiometric amount of the molecule is required. If a molecule not only binds to the target, but also degrades it, since the molecule doesn't necessarily bind to the functional site, it is easier to find catalytically bioactive molecules. Inspired by the success of PROTACs, we next have developed ribonuclease-targeting chimera (RiboTAC).[2] RNase L was chosen as the ribonuclease, and a heterocyclic small-molecule-type recruiter was explored by the *in vitro* cleavage assay. The conversion of a binder into a degrader by linking the RNA binder to the RNase L recruiter increased its bioactivity in inhibiting miR-21 maturation by approximately 20-fold using MDA-MB-231 cells. In addition, the RiboTAC molecule inhibited metastasis of triple-negative breast cancer (TNBC) in vivo using mice. Binders and degraders for other biomolecule targets will also be presented.

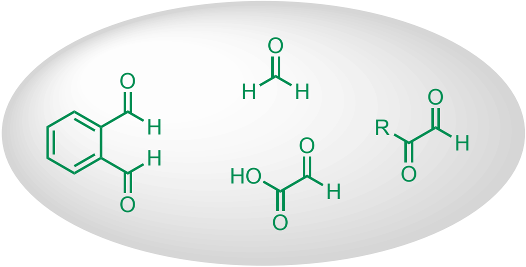
1) K. Nakatani, M. Toda, H. He, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 558. 2) M.G. Costales, H. Aikawa, Y. Li, *et al.*, *Proc. Natl. Acad. Sci. USA*. **2020**, *117*, 2406. 3) S.P. Velagapudi, S.M. Gallo, M.D. Disney, *Nat. Chem. Biol.* **2014**, *10*, 291. 4) J.A. Bush, H. Aikawa, R. Fuest, *et al.*, *Sci. Transl. Med.* **2021**, *13*, eabd5991.

# New Aldehyde Chemistry for Peptide Modification

*State Key Lab of Elemento-Organic Chemistry, Nankai University*, Gong Chen

**Keywords**: Peptide stapling; peptide conjugation; formaldehyde; lysine modification

Selective biomolecule modification techniques are crucial to advancing modern biopharmaceuticals. As the field rapidly evolves, the demand for new crosslinking methods that offer greater precision, flexibility, and practicality has become paramount. Crosslinking biomolecules via their native endogenous functional groups, as opposed to post-introduced exogenous reaction handles, provides significant advantages in simplicity and accessibility. However, practical methods of this kind have been largely limited to those based on thiol groups, which, despite their distinct reactivity and specificity, are naturally scarce. To expand this native modification toolkit, leveraging other common functional groups within biomolecules and bioactive compounds, particularly the ubiquitous amino groups is vital. In this lecture, I will discuss our recent exploration of modifying native peptides and proteins through amino handles with simple aldehyde reagents such as formaldehyde, *ortho*-phthalaldehyde, alpha-ketoaldehydes, and glyoxylic acid under mild conditions.



1) Bo Li, Hong Tang, Aneta Turlik, Zhao Wan, Xiao-Song Xue, Li Li, Xiaoxiao Yang, Jiuyuan Li, Gang He, K.N. Houk, and Gong Chen *Angew. Chem., Int. Ed.* **2021**, *60, 6646-6652*. 2) Bo Li, Zhao Wan, Hanliang Zheng, Shaokun Cai, Hanwen Tian, Hong Tang, Xin Chu, Gang He, Dong-Sheng Guo, Xiao-Song Xue, and Gong Chen. *J. Am. Chem. Soc.* **2022**, *144,* 10088-10090. 3) Li, B.; Wang, L.; Chen, X.; Chu, X.; Tang, H.; Zhang, J.; He, G.; Li, Li.; Chen, G. *Nat. Commun.* **2022**, *13,* 311. 4) Shaokun Cai, Hong Tang, Bo Li, Yingbo Shao, Danqi Zhang, Hanliang Zheng, Tianjiao Qiao, Xin Chu, Gang He, Xiao-Song Xue, and Gong Chen. *J. Am. Chem. Soc.* **2024**, *146,* 5952-5963. 4) Pan Guo, Xin Chu, Chengjin Wu, Tianjiao Qiao, Wenli Guan, Chuanzheng Zhou, Tao Wang, Changlin Tian, Gang He, and Gong Chen. *Angew. Chem. Int. Ed.* **2024**, e202318893.

# Natural Product Synthesis Based on Regioselective Functionalization of Cross-Conjugated Dienes

([1]*Faculty of Life Sciences, Tokyo University of Agriculture,*) ○Minami Odagi[1]

**Keywords**: Natural Product Synthesis; Dearomatization; Cross-Conjugated Dienones

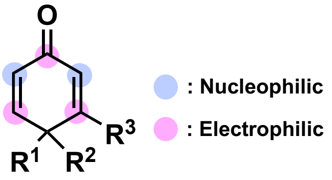


**Figure 1.** Properties of unsymmetrical cross-conjugated dienones

Highly functionalized and sterically complex frameworks are prevalent in natural products, and developing efficient synthetic strategies for constructing these intricate skeletons remains a significant challenge in synthetic chemistry. To address this issue, we have focused on cross-conjugated dienone frameworks as versatile intermediates for natural product synthesis.[1] Particularly, unsymmetrical cross-conjugated dienones allow for the electronic or steric differentiation of all carbon atoms, enabling regioselective functionalization (Figure 1). Moreover, these compounds can be readily synthesized *via* the oxidative dearomatization of phenol derivatives. Subsequent regioselective transformations, including intramolecular aza-Michael reactions, facilitate rapid access to highly functionalized polycyclic compounds (Figure 2). In this study, we present the synthetic studies of hasubanan alkaloids based on the regioselective functionalization of cross-conjugated dienones as a key strategy.[2,3]

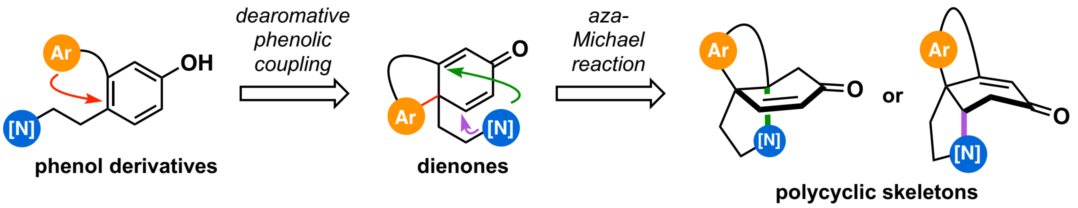


**Figure 2.** Our synthetic strategy of polyalicyclic skeletons based on regioselective functionalization of dienones

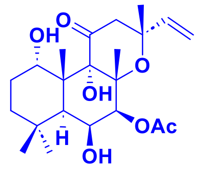
1) M. Odagi, K. Nagasawa *Synlett* **2023**, *34*, 1087. 2) M. Odagi, K. Nagasawa et al. *J. Am. Chem. Soc.* **2021**, *143*, 2699-2704. 3) M. Odagi, K. Nagasawa et al. *J. Org. Chem.* **2022**, *87*, 1065-1073.

# Organic Synthesis of Complex Natural Products to Facilitate Chemical Biology Studies

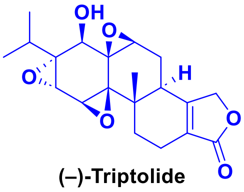
([1]*College of Chemistry and Molecular Engineering, Peking University*, [2]*Center for Life Sciences, Peking University*) ○Tuoping Luo,[1,2]

**Keywords**: Total Synthesis; Natural Product; Synthetic Strategy; Overbred Intermediate; Rearrangement **【5 words at most】**

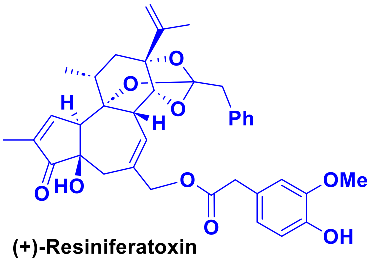
Small-molecule natural products offer advantageous starting points for developing tool compounds and probes to specifically modulate target proteins. Despite their limited abundance in nature and the challenges associated with isolation, purification, and modification, as well as the identification of mechanism-of-action, organic synthesis has proven to be a powerful technology for advancing chemical biology studies in this realm. Our group has dedicated efforts to investigate unique natural products, including anti-inflammatory diterpenoids, agonists of opioid and neurotransmitter receptors, and modulators of ion channels. Our endeavors have not only contributed to the development of efficient synthetic strategies, but also led to novel insights into organic transformations and new advancement of the synthetic methodology. More importantly, expediently accessing the underexplored chemical space would yield valuable tool and lead compounds for drug discovery. These efforts underscore the critical role of organic synthesis in leveraging the biological functions of natural products, serving as a crucial element in navigating untapped molecular diversities and facilitating chemical biology research. **【ref. This body consists of 160 words.】**



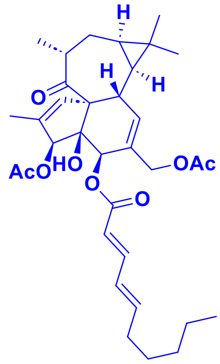
**(–)-Forskolin**



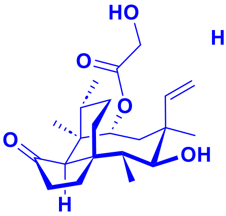
**(–)-Triptolide**



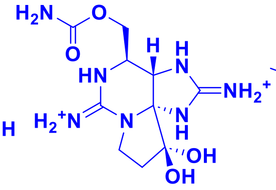
**(+)-Resiniferatoxin**



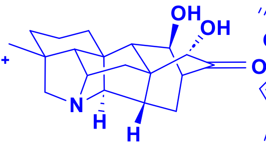
**Euphorstranoid B**



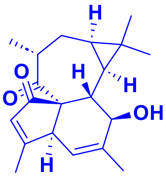
**(+)-Pleuromutilin**



**(+)-Saxitoxin**



**(+)-Kobusine**



**Pepluanol A**

1) a) X. Yu, L. Xiao, Z. Wang, T. Luo, *J. Am. Chem. Soc.* **2019**, *141*, 3440. b) Y. Zhu,† L. Wang,† J. Li,† Y. Zhao, X. Yu, P. Liu, X. Deng, J. Liu, F. Yang, Y. Zhang, J. Yu, L. Lai, C. Wang, Z. Li, L. Wang, T. Luo, *Cell Chem. Biol.* **2024**, *31*, 452. (†co-first author) c) X. Yu, L. Xiao, T. Luo, *J. Org. Chem.* **2024**, *89*, 1709. 2) S.-C. Chen, Q. Zhu, Y. Cao, C. Li, Y. Guo, L. Kong, J. Che, Z. Guo, H. Chen, N. Zhang, X. Fang, J.-T. Lu, T. Luo, *J. Am. Chem. Soc.* **2021**, *143*, 14046. 3) X. Fang, N. Zhang, S.-C. Chen, T. Luo, *J. Am. Chem. Soc.* **2022**, *144*, 2218. 4) H. Chen, Z. Li, P. Shao, H. Yuan, S.-C. Chen, T. Luo, *J. Am. Chem. Soc.* **2022**, *144*, 15462.