BIOGRAPHICAL SKETCH

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NAME: Tsuchikama, Kyoji

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Assistant Professor (Tenure Track)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Waseda University, Tokyo, Japan	B.S.	03/2005	Chemistry
Waseda University, Tokyo, Japan	M.S.	03/2007	Organic Chemistry
Waseda University, Tokyo, Japan	Ph.D.	03/2010	Organic Chemistry
The Scripps Research Institute, La Jolla, CA	Postdoctoral	06/2014	Organic Chemistry, Chemical Biology

A. Personal Statement

I have considerable skills and expertise in organic chemistry and chemical biology necessary to successfully implement the proposed research project. Throughout my careers, I gained experience in *organic synthesis, peptide synthesis, chemical protein modification including antibody-drug conjugation, structure–activity relationship study, analysis of physicochemical properties of bioactive compounds, chemoproteomic analysis for target protein identification, cell-based assays, in vivo pharmacokinetic analysis, and treatment experiments using xenograft mouse models.* In my graduate work, I was committed to the development of new chemical reactions using transition metal catalysts for obtaining useful synthetic building blocks. Subsequently, I began postdoctoral work at the interface of chemistry and biology to better understand biomolecular mechanisms of bacterial physiology and to discover therapeutic targets for bacterial infection. I also developed chemical probes for identifying unrecognized target proteins of the signaling molecule. Since I started my independent career at UTHealth, I have been committed to the development of novel chemical linkers towards next-generation antibody-drug conjugates (ADCs). Our laboratory is capable of performing not only chemical synthesis of ADC linkers and ADCs, but also in vitro/in vivo evaluation.

B. Positions and Honors

Positions and Employment

2014-present Assistant Professor (tenure track), Texas Therapeutics Institute, The Brown Foundation Institute of Molecular Medicine, The University of Texas Health Science Center at Houston, Houston, TX

Other Experience and Professional Memberships

2015-present Member, American Chemical Society

Teaching Appointments

2016-present Associate Member, The University of Texas Graduate School of Biomedical Sciences at Houston

Honors and Awards

2001-2004 Waseda University Alumni Association Fellowship, Waseda University, Tokyo, Japan
2005 Presentation Award for the Best Bachelor's Research, Department of Chemistry, School of Science and Engineering, Waseda University, Tokyo, Japan
2005-2006 Waseda University Sokichi Tsuda Fellowship, Waseda University, Tokyo, Japan
2007-2010 Research Fellowship for Young Scientists, The Japan Society for the Promotion of Science (JSPS)
2010 Excellent Doctoral Thesis Award, Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Tokyo, Japan
2010 CSJ Student Presentation Award 2010, The Chemical Society of Japan
2010-2012 Postdoctoral Fellowship for Research Abroad, JSPS
2013 Scripps California Society of Fellows Travel Award, The Scripps Research Institute, La Jolla, CA

Invited Lectures

Nanyang Technological University, Singapore, April 2013
CPRIT Antibody Therapeutic Core Annual Symposium, UTHealth, Houston, TX, December 2016
Texas A&M University Health Science Center, Houston, TX, February 2017
CPRIT Antibody Therapeutic Core Annual Symposium, UTHealth, Houston, TX, December 2017
138th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, Japan, March 2018
University of Tokyo, Tokyo, Japan, March 2018
Waseda University, Tokyo, Japan, March 2018

C. Contribution to Science

1. Development of Carbon-Hydrogen Bond Activation Using Cationic Iridium Catalysts (Graduate Work)

The direct functionalization of unactivated C-H bonds is an atom-economical transformation and has attracted considerable attention both in academia and industry. To develop highly active catalysts for C-H functionalization, I focused on the potential of "cationic" metal catalysts, which had yet to be fully investigated at the outset of this project. I discovered that cationic iridium catalysts exerted high catalytic activity not only in direct sp^2 C-H alkenylation but also in challenging sp^3 C-H alkenylation. Furthermore, these new catalysts turned out to promote unique cascade processes, enabling the concise synthesis of benzofulvenes and C4-substituted benzoheteroles. My work provided new insights into design of highly active catalysts for direct C-H activation as well as new chemical conversions of simple materials into useful synthetic building blocks.

a. **Tsuchikama, K.**, Kuwata, Y., & Shibata, T. (2006). Highly Enantioselective Construction of a chiral Spirocyclic Structure by the [2 + 2 + 2] Cycloaddition of Diynes and *exo*-Methylene Cyclic Compounds. Journal of the American Chemical Society, 128(42), 13686-13687.
b. **Tsuchikama, K.**, Kasagawa, M., Endo, K. & Shibata, T. (2009). Cationic Ir(I)-Catalyzed sp^3 C-H Bond Alkenylation of Amides with Alkynes. Organic Letters, 11(8), 1821-1823.
c. **Tsuchikama, K.**, Hashimoto, Y., Endo, K. & Shibata, T. (2010). Iridium-Catalyzed Selective Synthesis of 4-Substituted Benzofurans and Indoles *via* Directed Cyclodehydration. Advanced Synthesis and Catalysis. 351(17), 2850-2854.
d. **Tsuchikama, K.**, Kasagawa, M., Endo, K., Shibata, T. (2010). Sequential Catalytic Reactions for the Synthesis of Benzofulvenes Using an Iridium Complex with Dual Function. Synlett, 2010(1), 97-100.

2. Synthesis and Biological Evaluation of Chemical Analogues of the AI-2 Quorum Sensing Signal (Postdoc Work)

Bacteria have developed a unique cell-to-cell communication system termed quorum sensing (QS), which allows for gene expression in a cell population-dependent manner. QS is required for gene expression that causes pathogenic events such as biofilm formation and virulence factor production. Thus, chemical modulators and probes are crucial tools to better understand this system and to seek for new antibacterial strategies. I designed, synthesized, and evaluated a panel of structurally locked analogues of AI-2, one of the natural QS ligands. One of the analogues exerted greater potency than AI-2, which is the first example of a synthetic agonist surpassing the natural QS ligand. In addition, I developed chemical probes enabling selective chemical labeling for proteomic analysis, which revealed unrecognized proteins that could be modulated by AI-2.

Collectively, my work provided clear insights into the signal-receptor interactions making up AI-2-based QS as well as a strategy for designing effective QS modulators.

a. **Tsuchikama, K.**, Lowery, C. A. & Janda, K. D. (2011) Probing Autoinducer-2 Based Quorum Sensing: The Biological Consequences of Molecules Unable To Traverse Equilibrium States. The Journal of Organic Chemistry. 76(17), 6981-7294. ***Selected as a Featured Article and featured on the front cover of Volume 76, Issue 17.***
b. **Tsuchikama, K.**, Zhu, J., Lowery, C. A., Kaufmann, G. F. & Janda, K. D. (2012) C4-Alkoxy-HPD: A Potent Class of Synthetic Modulators Surpassing Nature in AI-2 Quorum Sensing. Journal of the American Chemical Society, 134(33), 13562-13564.
c. Collins, K. C., **Tsuchikama, K.**, Lowery, C. A., Zhu, J., Janda, K. D. (2016) Dissecting AI-2-mediated quorum sensing through C5-analogue synthesis and biochemical analysis. Tetrahedron, 72(25), 3593-3598.
d. **Tsuchikama, K.**, Gooyit, M., Harris, T. L., Zhu, J., Globisch, D., Kaufmann, G. F., & Janda, K. D. (2016) Glycation Reactivity of a Quorum-Sensing Signaling Molecule. Angewandte Chemie International Edition, 55(12), 4002-4006. ***Selected as a Very Important Paper.***

3. Truncated Autoinducing Peptides as a Selective Delivery Vehicle for Antibacterial Agents (Current Work)

The accessory gene regulator (*agr*) of *Staphylococcus aureus* coordinates various pathogenic events and is recognized as a promising therapeutic target for virulence control. *S. aureus* utilizes autoinducing peptides (AIPs), cyclic-peptide signaling molecules, to mediate the *agr* system. Despite the high potency of synthetic AIP analogues in *agr* inhibition, the potential of AIP molecules as a delivery vehicle for antibacterial agents remains unexplored. We have found that truncated AIP scaffolds can be fused with fluorophore and cytotoxic photosensitizer molecules without compromising their high *agr* inhibitory activity, binding affinity to the receptor AgrC, or cell specificity. Strikingly, a photosensitizer-AIP conjugate exhibited 16-fold greater efficacy in a *S. aureus* cell-killing assay than a non-targeting analogue. These findings highlight the potential of truncated AIP conjugates as useful chemical tools for in-depth biological studies and as effective anti-*S. aureus* agents. Role: PI

a. **Tsuchikama, K.***, Shimamoto, Y., Anami, Y. (2017) Truncated Autoinducing Peptide Conjugates Selectively Recognize and Kill *Staphylococcus aureus*. ACS Infectious Diseases, 3(6), 406–410.

4. Novel ADC Linkers for Constructing Efficacious ADCs (Current Work)

Antibody–drug conjugates (ADCs) are emerging therapeutic agents in treatment of cancer, and various conjugation strategies and chemical linkers have been developed to efficiently construct ADCs. Despite previous extensive efforts for improving conjugation efficiency and ADC homogeneity, most ADC linkers developed to date load only single payloads. It is logical to envisage that a multi-loading linkers will allow for increase in drug-to-antibody ratio (DAR) with less chemical or enzymatic modification to the antibody structure compared to traditional linear linkers, leading to enhanced ADC efficacy. We reported that the branched linkers we designed could be quantitatively installed on an anti-HER2 monoclonal antibody by microbial transglutaminase (MTGase)-mediated conjugation without impairing its antigen binding affinity, enabling modular installation of payload molecules and construction of homogeneous ADCs with increased DARs (4 or 8). An anti-HER2 antibody–monomethyl auristatin F conjugate constructed using the branched linker showed greater in vitro cytotoxicity against HER2-positive breast cancer cell lines than that consisting of conventional linear linkers, demonstrating the effectiveness of the branched linker-based payload delivery. Very recently, we found a novel acidic tripeptide linker could significantly enhance the in vivo stability and therapeutic activity of ADCs in mouse models compared to traditional valine-citrulline linkers. This new linker technology will minimize failure rates in preclinical studies caused by in vivo linker instability and poor efficacy. Role: PI

a. **Tsuchikama, K.***, An, Z. (2018) Antibody-drug conjugates: recent advances in conjugation and linker chemistries, Protein & Cell, 9, 33–46.
b. Anami, Y., Xiong, W., Gui, X., Deng, M., Zhang, C. C., Zhang, N., An, Z., **Tsuchikama, K.*** (2017) Enzymatic Conjugation Using Branched Linkers for Constructing Homogeneous Antibody–Drug Conjugates with High Potency. Organic & Biomolecular Chemistry, 15, 5635–5642.

c. Anami, Y., Yamazaki, C. M., Xiong, W., Gui, X., Zhang, N., An, Z., **Tsuchikama, K.*** (2018) Glutamic acid–valine–citrulline linkers ensure stability and efficacy of antibody–drug conjugates in mice. Nature Communications, accepted.
DOI: 10.1038/s41467-018-04982-3

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40675838/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

BC170897 (PI: Tsuchikama) DOD/BCRP 02/01/2018-01/31/2021
Dual-Loading ADCs for Combating Cancer Drug Resistance and Heterogeneity
We will prepare and evaluate anti-HER2 ADCs incorporating two antitumor drugs or drug/cancer-specific ligand through dual-loading linkers.
Role: PI

Startup Package, University of Texas HSC Houston 07/07/2014-current
This fund is used for a new laboratory to purchase equipment and consumables and to hire researchers.
Role: PI

Previous Research Support

Regents' Health Research Scholars Award, University of Texas System 07/07/2014-03/31/2017
This award is conferred to the most potential tenure-track faculty who is newly employed by an institution participating in the University of Texas System. This fund can be used only for equipment, renovation, and construction.
Role: PI

E. Patents

1. Linkers for Antibody Drug Conjugates (PCT/US2018/034363 filed)