

## Transition Metal-Free, Tryptophan-Selective Bioconjugation of Proteins

○ Kounosuke OISAKI<sup>1</sup>, Yohei SEKI<sup>1</sup>, Takashi ISHIYAMA<sup>1</sup>, Daisuke SASAKI<sup>1,2</sup>, Junpei ABE<sup>1</sup>, Yohei SOHMA<sup>1,2</sup>, Motomu KANAI<sup>1,2</sup>

<sup>1</sup>Graduate School of Pharmaceutical Sciences, The University of Tokyo,

<sup>2</sup>JST, ERATO Kanai Life Science Catalysis Project

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Chemical modifications of native proteins can facilitate production of supernatural protein functions that are not easily accessible by complementary methods relying on genetic manipulations. Even though precise control over the chemo-, site, and modification-number selectivity in protein chemical conjugates with maintained structural integrity and homogeneity is highly important, it still represents a major challenge. The available toolbox of native protein conjugations does not contain satisfactory solutions to this challenge at present. In many cases, the conjugation sites are located at the side chains of lysine and cysteine residues. Despite recent improvements, these methods often afford unsatisfactory levels of selectivity with disintegrated higher-order structures.

We report a transition metal-free method for tryptophan-selective bioconjugation of proteins that is based on an organoradical and operates under ambient conditions. This method exhibits low levels of cross-reactivity and leaves higher-order structures of the protein and various functional groups therein unaffected. The strategy to target less abundant amino acids contributes to the formation of structurally homogeneous conjugates, which may even be suitable for protein crystallography. The absence of toxic metals and biochemically incompatible conditions may thus easily find therapeutic applications.