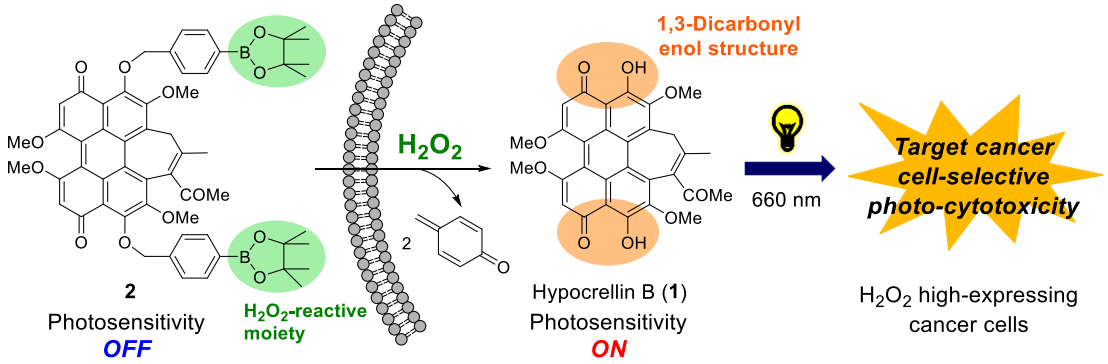
Creation of H_2O_2-Activatable Photosensitizer based on Hypocrellin B

(*Faculty of Science and Technology, Keio University*) ○Takashi Kitamura, Hirotaka Nakata, Daisuke Takahashi, Kazunobu Toshima

Keywords: Stimuli Activatable Photosensitizer; Hypocrellin B; Hydrogen Peroxide; Boronic Acid; Photocytotoxicity

Stimuli activatable photosensitizers, which can turn on their photosensitizing ability by reacting with a specific biomarker expressed in the target tissues, have great potential for minimizing non-specific photodamage to healthy tissues during and after photodynamic therapy (PDT). In this context, we focused on a natural perylenequinone dye hypocrellin B (**1**) as a core structure of an activatable photosensitizer, because **1** is a potent PDT agent with absorption at long-wavelength visible region,[1] and has a 1,3-dicarbonyl enol structure, which we recently found as a responsive substructure of photosensitizer to control its photosensitivity.[2] Herein, we report a molecular design, chemical synthesis, and biological evaluation of a tumor-related biomarker, H_2O_2-activatable photosensitizer based on **1**.

Firstly, H_2O_2-activatable photosensitizer **2** consisting of **1** and H_2O_2-reactive boronic ester moieties conjugated to the hydroxyl group of **1** through a benzyl ether link, was designed. After chemical synthesis of **2**, its singlet oxygen ($^1O_2$) generating ability was evaluated under 660 nm light irradiation. The results showed that the $^1O_2$ generating ability of **2** significantly decreased in comparison with that of **1**. Next, the reactivity of **2** against H_2O_2 was evaluated, indicating that **2** reacted with H_2O_2, and released **1**. Finally, the cytotoxicity of **2** against normal human-lung fibroblast WI-38 cells and mouse melanoma B16F10 cells, which express H_2O_2 at a higher concentration, was examined with or without photo-irradiation. As the results, it was found that **2** showed significant and selective cytotoxicity against targeted B16F10 cells only with photo-irradiation.



1) G. G. Miller, K. Brown, Å. M. Ballangrud, O. Barajas, Z. Xiao, J. Tulip, J. W. Lown, J. M. Leithoff, M. J. Allalunis-Turner, R. D. Mehta, R. B. Moore, *Photochem. Photobiol.* **1997**, *65*, 714.
2) T. Kitamura, S. Shiroshita, D. Takahashi, K. Toshima, *Chem. Eur. J.* **2020**, *26*, 14351.