Luciferase-induced photoreductive uncaging of small-molecule effectors

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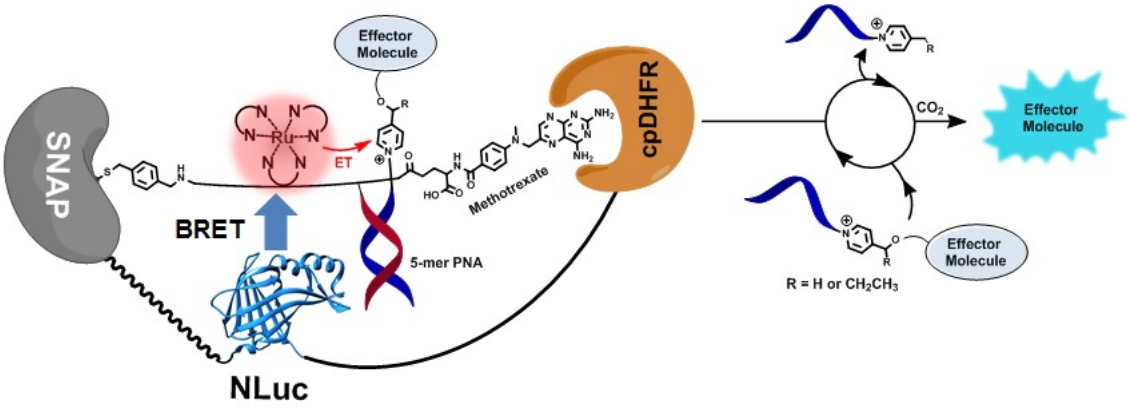
Bioluminescence resonance energy transfer (BRET) is extensively used to study dynamic systems and has been utilized in sensors for studying protein proximity, metabolites, and drug concentrations [1, 2, 3]. We demonstrate that BRET can activate a ruthenium-based photocatalyst which performs bioorthogonal reactions. BRET from luciferase to the ruthenium photocatalyst was used to uncage effector molecules with up to 64 turnovers of the catalyst, achieving concentrations > 0.6 μM effector with 10 nM luciferase construct. Using a BRET sensor, we further demonstrate that the catalysis can be modulated in response to an analyte, analogous to allosterically controlled enzymes. The BRET-induced reaction was used to uncage small-molecule drugs (ibrutinib and duocarmycin) at biologically effective concentrations *in cellulo*.



[1] S. J. A. Aper, P. Dierickx, M. Merkx, *ACS Chem. Biol*., **2016**, *11*, 2854-2864.
[2] A. Dragulescu-Andrasi, C. T. Chan, A. De, T. F. Massoud, S. S. Gambhir, *Proc. Nat. Acad. Sci*., **2011**, *108*, 12060-12065.
[3] F. X. Schaub, *et al*., *Cancer Res*., **2015**, *75*, 5023-5033.