Photocatalytic proximity labelling of ligand-binding proteins utilizing single-electron transfer mediate radical reaction

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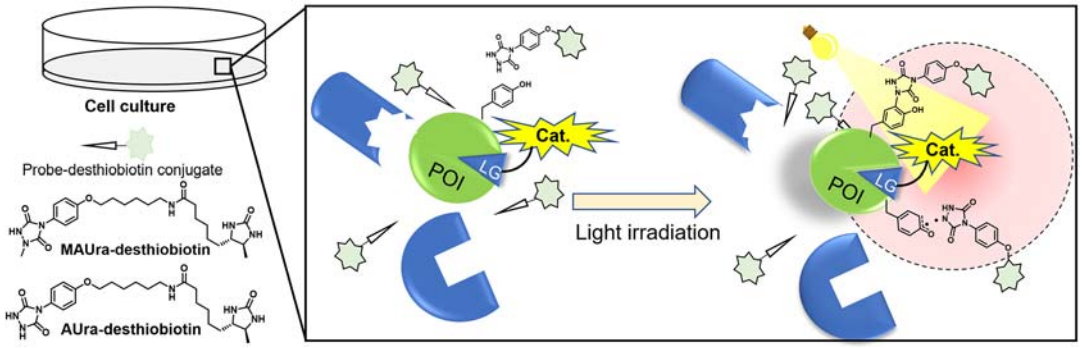
Small molecule target identification traditionally relies on *in vitro* affinity-based purification analysis. To study endogenous proteins in the cellular environment, serval chemical labelling and profiling methods utilizing affinity-guided catalyst chemistry have been developed.[1,2] However, few such techniques are capable of endogenous protein labelling. We recently reported a ruthenium photocatalyst-directed chemical labelling method with radical sensitive probes.[3] However, it has been limited to *in vitro* due to its low membrane permeability and high cytotoxicity. To overcome this difficulty, we set out to search for a combination of organic photocatalyst and radical sensitive probes for endogenous application of ligand-directed proximity labelling platform.

Based on the previously reported *in vitro* proximity labelling system of urazole probe, 1-methyl-4-arylurazole (MAUra),[3] and $Ru(bpy)_3$ complex, different urazole derivatives probes were screened for intracellular proximity labelling ability. Interestingly, urazole probes' labelling capability differs significantly from *in vitro* to intracellular conditions. Although MAUra was found to be the superior labelling probe for *in vitro* system, 4-arylurazole (AUra) was discovered to be a better candidate for intracellular radical proximity labelling reactions. Further organic photosensitizer screening with both MAUra and AUra probes for the labelling platform optimization will be presented.



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