Anthraquinone Photoclick Chemistry to Probe the Intracellular Fate of Cell-Penetrating Peptides

Cell-penetrating peptides (CPPs) are powerful molecular vectors capable of transporting cargos across biological membranes and enabling intracellular delivery of therapeutic agents, probes, and biomolecules. Despite their broad potential in drug delivery, or as chemical biology tools, the molecular mechanisms governing their internalization remain incompletely understood. Key questions persist regarding the roles of peptide sequence, membrane interactions, conformational dynamics, molecular partners involved in uptake pathways and intracellular fate after internalization.

Progress in this field is currently limited by the lack of chemical tools capable of simultaneously reporting on localization, environment, and molecular interactions in living systems. Existing strategies rely mainly on fluorophores or photoreactive units such as benzophenone, which often require lengthy syntheses, provide limited modularity, and can perturb peptide structure and function.

This project proposes to develop a new generation of CPP probes based on anthraquinone chemistry enabled by a recently developed photoclick strategy allowing selective tagging of primary amines and thiols. These anthraquinone tags display large Stokes shifts, visible-light absorption, near-infrared emission, and tunable photochemical reactivity depending on the targeted nucleophile. Additionally, they could be used as photocrosslinking labels to capture CPP interaction partners.

Anthraquinone tags are thus versatile tools, that will be used as dual labels to provide mechanistic insight into CPP internalization mechanisms, with a specific focus on two aspects: intracellular partners after internalization, and light-activated penetration enabling spatio-temporal control of internalization. This project will provide a new chemical toolbox based on anthraquinone chemistry for downstream biological and mechanistic studies.

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