Peptide Targeting of Photosensitisers for Photodynamic Therapy and Drug Delivery

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The conjugation of tetrapyrroles and related photosensitisers with proteins or targeting peptides is now a well-established approach for enhancing the solubility and tissue selectivity of such molecules in the photodynamic therapy (PDT) of cancer. We are interested in developing chemical strategies for the generation of novel porphyrin-related molecules for targeted PDT, and also porphyrin-based systems whose structures are tailored for use in the light-triggered delivery of therapeutic agents by photochemical internalisation (PCI) [1]. PCI is a light-based approach that exploits the technique of PDT to enhance the delivery of nano-sized biotherapeutics that would normally be prevented from reaching their intended intracellular targets due to sequestration in certain sub-units or organelles within the cell. Effective PCI requires the use of photosensitisers that have the appropriate physical properties to localize in the membranes of the organelles (endosomes or lysosomes) where a therapeutic agent may be trapped. Upon irradiation, reactive oxygen species that are generated may then induce a highly selective damaging effect and cause partial rupture of the organelles, allowing entrapped molecules to escape to their targets within the cell. In this communication, we will describe some of our studies on the synthesis and biological evaluation of porphyrin and chlorin derivatives that are targeted with cationic cell-penetrating peptides (CPPs) via biorthogonal ligation chemistries [1, 2], and the application of these conjugates for PCI of saporin, a nano-sized protein toxin. We will also describe the extension of this principle to the CPP-targeting of liposomal nanocarriers [3] to produce molecular assemblies that allow the codelivery of a porphyrin photosensitizer and a macromolecular therapeutic in order to produce an optimal PCI effect.

[1] R. Dondi, E. Yaghini, K. M. Tewari, L. Wang, F. Giuntini, M. Loizidou, A. J. MacRobert and I. M. Eggleston, *Org. Biomol. Chem.* 2016, **14**, 11488-11501.

[2] E. Yaghini, R. Dondi, K. M. Tewari, M. Loizidou, I. M. Eggleston and A. J. MacRobert, *Sci. Rep.* 2017, **7**, 6059.

[3] E. Yaghini, R. Dondi, K. J. Edler, M. Loizidou, A. J. MacRobert and I. M. Eggleston, *Nanoscale* 2108, **10**, 20366-20376.