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Preface

# Delivery of photosensitizers in photodynamic therapy

The benefit of sunlight in the treatment of skin diseases has been known for centuries. For example, vitiligo was treated with plants containing psoralens in combination with sun exposure in 1400 BC or earlier. At that time, mechanisms of selective delivery of photosensitizers were not identified. Later in the 1960s, psoralens began to be used against other skin diseases, e.g. psoriasis. Attempts to treat skin tumors date from 1903, when topical administration of eosin was used in combination with sunlight, and about half a century later a synthetic hematoporphyrin derivative (Photofrin®) appeared to show some selectivity in tumor accumulation. However, the latter first-generation photosensitizers suffered from several drawbacks, including pronounced skin accumulation, which caused prolonged skin photosensitivity lasting for up to 6–8 weeks. Second-generation photosensitizers showing improved photophysical properties have been developed since then, but enhancing tumor selectivity is still one of the major problems to be solved in photodynamic therapy (PDT).

Another challenge related to the use of photosensitizers is the fact that the most potent ones are hydrophobic, since these tend to localize in more photosensitive cellular compartments (e.g. membranes). In addition, hydrophobic photosensitizers are poorly water-soluble and therefore difficult to administer as such, and their tendency to aggregate has a strong negative effect on the photophysical properties. These problems (lack of tumor selectivity, poor water-solubility and aggregation propensity) call for the use of advanced delivery systems.

Several delivery strategies have been employed in PDT. They include the use of colloidal carrier systems such as (biodegradable) nanoparticles, liposomes, low-density lipoproteins (LDL), micelles and polymer-drug conjugates. These particles may accumulate passively in tumors through the leaky tumor vasculature, a phenomenon that is known as the enhanced permeation and retention effect. The use of active targeting ligands, either alone or in combination with colloidal carriers, is an important strategy to further improve the delivery at the site of action. This theme issue on "Delivery of photosensitizers in photodynamic therapy" highlights several recent developments in this field.

The first two chapters give overviews on the use of micelles and liposomes as carrier systems for the systemic or local delivery of photosensitizers. Several active targeting strategies are reviewed in the next chapter, while a special chapter is devoted to photosensitizer immunoconjugates, i.e. the use of antibodies to target photosensitizers. Topical delivery, as mentioned above being the oldest administration route of photosensitizers, has gained increasing interest in recent years by the use of 5-aminolevulinic acid (5-ALA) as a prodrug therapy. Therefore, a chapter is included about improving delivery of 5-ALA to the skin. The final chapter focuses on the use of photosensitizers to enhance the delivery of a variety of drugs and genes. This special form of PDT is called photochemical internalization (PCI) and should not be missed from this theme issue.

Most of the current research on PDT is focused on the treatment of cancer, being one of the leading causes of death and disease in the Western world, and this will be reflected in the contents of this issue. However, other PDT applications must not be neglected, including treatment of age related macular degeneration (the

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largest PDT market at present), atherosclerosis or autoimmune diseases, and killing of microorganisms. These applications often encounter similar delivery issues as cancer PDT, so the subject of this theme issue has a broad interest.

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