New polymethine dyes for photodynamic therapy

Nadia Barbero[a], Sonja Visentin[b], Claudia Barolo[a], Roberto Buscaino[a], Guido Viscardi[a]

[a] University of Torino, Department of Chemistry and NIS Interdepartmental Centre, Via P. Giuria 7, 10125 Torino, Italy; [b] University of Torino, Department of Molecular Biotechnology and Health Sciences, via Quarello 15A, 10135 Torino, Italy.

Photodynamic therapy (PDT) (1) is an emerging non-invasive technique for the treatment of cancer. It involves the systemic or topic administration of a photosensitizer (PS) that, after its excitation with light at a specific wavelength, is able to produce reactive oxygen species (ROS), causing damage to targeted cancer cells. An ideal PS should fulfil specific, clinically relevant requirements: i) sharp, intense absorption in the biological tissues' transparency window (600-900 nm), ii) good solubility in the biological environment, iii) low dark toxicity but strong photo-cytotoxicity and iv) a high ROS sensitization quantum yield. Moreover, an ideal PS should possess a high specificity for cancer tissues and be easily and rapidly removed from the body post-treatment.

Even if some important developments have been achieved and some porphyrin-based PSs are already commercially available and clinically used (2), some problems still exist. Haematoporphyrin derivative-mediated PDT has several clinical disadvantages, including prolonged skin photosensitivity (4 weeks), relatively low quantum yield of singlet oxygen, and a limited depth of associated tissue damage of 2-5 mm. Consequently, there has been extensive research into the design of improved alternative PSs aimed at overcoming these drawbacks. Polymethine dyes (3) deserve to be counted among the innovative potential PS classes for PDT for their strong absorption in the tissue transparency window (600-800 nm).

In this work we designed and synthesised a new series of near infra-red (NIR) absorbing polymethine dyes with different substitution groups in order to investigate how the structure may influence the capacity of these molecules to produce $^1O_2$. The oxygen-generation ability of the new dyes was accessed *in vitro* by the 1,3-diphenylbenzofuran (DPBF) quenching method (4), envisioning their potential use as sensitizers for PDT. On the most promising PSs, ROS generation, cytotoxicity, cell death and DNA damage analyses were performed after the photodynamic treatment. Here we present the results obtained along with a structure-activity relationship discussion of these new potential photosensitizers for PDT. In particular, two of these squaraine dyes showed very interesting PDT performances as well as co-localization in mitochondria (5).

References: 1. A.M. Rkein, D.M. Ozog. Dermatol. Clin. 32 (2014) 415–425. 2. R.R. Allison, C.H. Sibata. Photodiagn. Photodyn. Ther. 7 (2010) 61–75. 3. R.R. Avirah, D.T. Jayaram, N. Adarsh, D. Ramaiah. Org. Biomol. Chem. 10 (2012) 911–920. 4. Y. Prostota, O.D. Kachkovsky, L.V. Reis, P.F. Santos. Dyes Pigment 96 (2013) 554-562. 5. L. Serpe, S. Ellena, N. Barbero, F. Foglietta, F. Prandini, M. P. Gallo, R. Levi, C. Barolo, R. Canaparo, S. Visentin. Eur. J. Med. Chem. (2016), 113, 187-197.