

Characterisation of modified stilbenes for a new anticancer phototherapy, Type IV, using two-photon activation and imaging of combretastatins

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Stilbene-based combretastatins are a group of compounds, derived from a natural product, that inhibit tubulin function in cells. They act as vascular disrupting agents and have shown promise in treating solid tumours that depend on new blood vessel development for growth. They act as vascular disrupting agents and have shown promise in treating solid tumours that depend on new blood vessel development for growth and may also find potential application in other pathological states dependent on neovascularisation such as wet age-related macular degeneration (AMD). Clinical trials have demonstrated potential for these drugs in both cancer and AMD. However further use appears to be limited by systemic toxicity. We recently proposed a novel form of photodynamic therapy (PDT), Type IV, for vasculature-dependent diseases in which a trans-stilbene derivative is photoisomerized by two-photon absorption to the corresponding cis-stilbene, figure 1 [1]. The main advantage of the Type IV pathway over current PDT technique is that Type I, II, and III requires oxygen or the formation of reactive oxygen species whilst the tumour environment lacks oxygen (hypoxia).

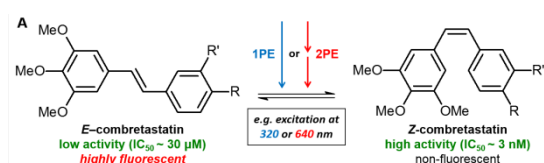


Fig 1: PE photoisomerisation Type IV PDT

The uptake of E-CA4, potential pro-drugs of the anticancer Z-isomers, into multicellular spheroids has been imaged by intrinsic fluorescence in three dimensions using two-photon excited fluorescence lifetime imaging with 625 nm ultrafast femtosecond laser pulses. The efficacy of new derivatives of CA4, CA4F and CA4CN in mammalian cell killing by imaging as well as their photophysics will be presented. The design and synthesis of CA4F and CA4CN aimed at creating molecules with strong charge transfer in the excited state and ultimately high 2-photon cross sections. Although CA4CN was found to have higher two-photon absorption cross section than CA4F, it also has a higher toxicity in the trans form than CA4F. The results show a clear effect of the combination of E-CA4 and CA4F together with light that is attributable to photoisomerisation of the trans isomer to the more potent cis isomer. This points the way to a new form of phototherapy dependent on only the prodrug activation. The use of two-photon excitation of the trans isomers allows access to deeper tissue regions than the usual one-photon method together with the molecular rearrangement offers a new form of phototherapy (Type IV) for diseases, including cancer and AMD that depend on neovascularization without the associated systemic cardiovascular toxicity when using the cis isomers.

[1] 4. KM Scherer, RH Bisby, SW Botchway, AW Parker 'New Approaches to Photodynamic Therapy from Type I, II and III to Type IV Using One or More Photons', *Anti-Cancer Agents in Medicinal Chemistry*, 17 (2), pp. 171-189(2016).