Controlling Photosensitizer Efficiency through Photoinduced Electron Transfer for ALDH1A1-Activated Photodynamic Therapy

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Cancer cells that express elevated levels of the enzyme Aldehyde Dehydrogenase isoform 1A1 (ALDH1A1), such as cancer stem cells, are key drivers of tumor aggressiveness, metastasis, and resistance to conventional therapies. These cells often play an outsized role in generating treatment-resistant secondary tumors that ultimately prove fatal to patients across many different cancer types. Targeting these cells represents a significant challenge in cancer therapy. Here, we present a novel class of activatable photodynamic therapy (PDT) agents specifically designed to target high ALDH1A1-expressing cells using a differential donor photoinduced electron transfer (d-PeT) mechanism. This design allows precise control over the photosensitizer's active and inactive states, minimizing off-target effects commonly seen with traditional chemotherapeutics and non-selective PDT agents. Prior to activation by ALDH1A1, these photosensitizers generate minimal singlet oxygen under irradiation. Upon ALDH1A1 activation, singlet oxygen production is enhanced up to three-fold, optimizing therapeutic efficacy. The selective activation in high ALDH1A1-expressing cells reduces collateral damage to surrounding healthy tissue compared to non-targeted approaches. *In vitro* studies using the lead compound, AAP, confirm ALDH1A1-dependent, light-mediated cytotoxicity in lung cancer cells. We challenged AAP to ablate tumors *in vivo* with an A549 xenograft model in Nu/J mice. Tumors that were treated with AAP alone and irradiated showed significantly reduced tumor burden compared to those tumors treated with a vehicle control or co-treated with AAP and an inhibitor of ALDH1A1, showcasing the necessity of enzyme activation to establish potency. AAP was also applied to metastatic models of lung cancer to highlight its utility in these often difficult-to-treat secondary tumors.