Dual Targeting of Tumor Cells and Tumor Neovasculature by Tissue Factor-Targeted Photodynamic Therapy

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Photodynamic therapy (PDT) is a treatment [1-5] that involves three components: a photoactivatable photosensitizer (PS), laser light, and tissue oxygen. The current applications of non-targeted PDT (ntPDT) involve intravenous injection or topical application of PS followed by irradiation of the diseased lesion with a laser light. Upon activation by laser light, PS converts intracellular oxygen to singlet oxygen ions, which then cause cellular necrosis and/or apoptosis [5]. PDT has clinical indications in the treatment of malignant tumors. However, a serious limitation of conventional ntPDT is the toxicity that results from internalization of the PS by normal cells [6].

To overcome the poor selectivity of PS, one of two targeting approaches has been used: (1) antibodies that recognize specific tumor antigens or ligands [7,8] or (2) peptides that bind receptors on neovascular endothelial cells [9]. However, these methods have a common limitation: each can target only one of the two desirable tumor compartments, the tumor angiogenic vascular endothelial cells or the actual tumor cells.

To overcome the poor selectivity of ntPDT and to improve the effect of current single tumor compartment-targeted PDT (stPDT), we proposed to simultaneously target both tumor compartments for development of dual tumor compartments-targeted PDT (dtPDT). The bottleneck of development of such dtPDT is to identify a common yet specific biomarker on both tumor compartments [10]. We [11-14] and several other groups [15,16] showed that tissue factor (TF) was selectively expressed by tumor angiogenic vascular endothelial cells and was also overexpressed by many types of cancer cells in melanoma, breast, lung and brain tumors. Thus we conclude that TF is a common yet specific biomarker and therapeutic target molecule for both the tumor cells and tumor neovascularulation [10-12,17,18]. By choosing the receptor TF as a target molecule and using its natural ligand, coagulation factor VII (FVII), as a targeting vehicle, we have successfully developed a novel dtPDT, namely FVII-targeted PDT (FVII-tPDT) using FVII-SnCe6 (activation wavelength at 635 nm) or FVII-VP (activation wavelength at 689 nm) conjugates, for treatment of human breast [12,17,18] and lung cancer [11] and wet macular degeneration [19] in preclinical studies. Our results showed that FVII-tPDT was selective and effective in vivo in killing angiogenic vascular endothelial cells and tumor cells that express TF as well as in vivo in treating breast and lung tumor xenografts in mouse models.

Since TF is expressed by tumor angiogenic vascular endothelial cells and by cancer cells of human solid cancers and leukemia [18], we believe that TF-targeted therapeutics by using FVII as targeting vehicle, including FVII-tPDT that we recently developed [10-12,17,18] and FVII-lgG1 Fc (IgG immunotherapy) that we previously developed [13,14,20,21] could have broad therapeutic potential for solid cancer and leukemia.

Acknowledgement

This work was supported by CT DPH Biomedical Research Grant (RFP#2009-0096), the Breast Cancer Alliance Exceptional Project Grant, the Susan Komen Award (BCTR0601204) and the Swebilius Translational Cancer Research Award from the Yale Cancer Center and partly by institutional support from the Yale Department of Obstetrics, Gynecology and Reproductive Sciences.

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Received July 26, 2012; Accepted July 27, 2012; Published August 06, 2012


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