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Tumor-Targeted Contrast Agents for Image-Guided Cancer Surgery

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Two fundamental and unsolved problems facing bioimaging and nanomedicine are nonspecific uptake of intravenously administered diagnostic and/or therapeutic agents by normal tissues and organs, and incomplete elimination of unbound targeted agents from the body. These problems make image-guided cancer surgery extremely difficult because tissue background is high, and therefore the tumor-to-background ratio (TBR) is low. To solve these problems, we have synthesized a series of indocyanine near-infrared (NIR) fluorophores that varied systematically in net charge, conformational shape, hydrophilicity/lipophilicity, and charge distribution. Using 3D molecular modeling and optical fluorescence imaging, we have defined the relationship among the key independent variables that dictate biodistribution and tumor-specific targeting using nanoparticles in human prostate cancers (*Nat Nanotechnol*. 2010), small molecules in human melanomas (*Nat Biotechnol*. 2013), and micelles in human breast cancers (*Nat Nanotechnol*. 2014).

Recently, we have developed new pharmacophore design strategy "structure-inherent targeting," where tissue- and/or organ-specific targeting is engineered directly into the non-resonant structure of an NIR fluorophore, thus creating the most compact possible optical contrast agent for bioimaging and nanomedicine (*Nat Med*. 2015). The biodistribution and targeting of these compounds vary with dependence on their unique physicochemical descriptors and cellular receptors, which permit 1) selective binding to the target tissue/organ, 2) visualization of the target specifically and selectively, and 3) provide curing options such as image-guided surgery or photo dynamic therapy. Our study solves two fundamental problems associated with fluorescence image-guided surgery and lays the foundation for clinically available tumor-targeted agents with optimal optical and *in vivo* performance.

KEY WORDS: Nanotechnology; Optical imaging; Diagnostic imaging; Tumor targeting; Near-infrared fluorophore; Biodistribution; Clearance; Image-guided surgery