

Development of a Humanized Anti-CEA Antibody for the Near Infrared Optical Imaging of Cancer

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Abstract : Surgery for solid gastrointestinal (GI) cancers such as pancreatic, colorectal, and gastric adenocarcinoma remains the mainstay of curative therapy. Complete resection of the primary tumor with negative margins (R0 resection), its draining lymph nodes, and distant metastases offers the optimal surgical benefit. Real-time fluorescence guided surgery (FGS) promises to improve GI cancer outcomes and is rapidly advancing with tumor-specific antibody conjugated fluorophores that can be imaged using near infrared (NIR) technology. Carcinoembryonic Antigen (CEA) is a non-internalizing tumor antigen validated as a surface tumor marker expressed in >95% of colorectal, 80% of gastric, and 60% of pancreatic adenocarcinomas. Our humanized anti-CEA hT84.66-M5A (M5A) monoclonal antibody (mAb) was conjugated with the NHS-IRDye800CW fluorophore and shown it can rapidly and effectively NIR optical image orthotopically implanted human colon and pancreatic cancer in mouse models. A limitation observed is that these NIR-800 dye conjugated mAbs have a rapid clearance from the blood, leading to a narrow timeframe for FGS and requiring high doses for effective optical imaging. We developed a novel antibody-fluorophore conjugate by incorporating a PEGylated sidearm linker to shield or mask the IR800 dye's hydrophobicity which effectively extended the agent's blood circulation half-life leading to increased tumor sensitivity and lowered normal hepatic uptake. We hypothesized that our unique anti-CEA linked to the fluorophore, IR800 by PEGylated sidewinder, M5A-SW-IR800 will become the next generation optical imaging agent, safe, effective, and widely applicable for intraoperative image guided surgery in CEA expressing GI cancers.

Keywords : optical imaging, anti-CEA, cancer, fluorescence-guided surgery

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