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The ability of the surgeon to accurately visualize tumor margins and identify metastases is necessary for accurate staging and the success of any cancer operation. Fluorescence imaging, because of its high sensitivity, low cost, portability, and real-time capabilities has great potential to improve surgical outcomes. In our laboratory, we have developed a variety of tumor specific antibodies and nanobodies conjugated to near infrared dyes to label GI cancers including pancreatic, colon, and gastric cancers in mouse models of cancer. While most of the studies are pre-clinical in nature, several antibodies and small peptides are now in human clinical trials for fluorescence guided surgery (FGS). In addition to labelling tumors for accurate and complete resection, it is also vital to preserve nearby anatomical structures, such as nerves, to decrease the morbidity of surgery and reduce complications. In this presentation, I will review preclinical studies that have led to the current technology for fluorescence imaging that is now available in the operating room. I will also discuss several current clinical trials of novel probes for FGS for GI tumors and for labeling of nerves during thyroidectomy and neck dissection. Lastly, I will discuss future directions in this rapidly evolving and exciting field.