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Engineering Bacterial Secretion Systems for Enhanced Tumor Imaging and Surgical Guidance

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Current imaging techniques suffer from a lack of specificity and resolution, leading to inaccurate tumor imaging and limited applicability of targeted contrast agents, as they require cancer-specific development. The need for enhanced contrast through improved tumor-to-background ratio (TBR) and the toxicity from repeated injections due to fading fluorescent signals further complicate the issue. Additionally, challenges in visualizing the entire 3D tumor with surface-stained contrast agents highlight the demand for advanced imaging solutions for more precise surgical guidance. A novel approach is proposed utilizing Streptavidin Associated *Salmonella* (SAS) as a contrast agent for image-guided surgeries. SAS selectively proliferates in cancerous tissues and secretes streptavidin upon induction, enabling the binding of subsequently injected biotin-conjugated fluorescent dyes. This approach enhances tumor visualization with a TBR of up to 15.3, far surpassing conventional agents (TBR ~ 2), while enabling prolonged 3-day imaging, deep tumor penetration, and precise invasive margin delineation with a single contrast agent injection. Furthermore, biosafety evaluations confirmed efficient bacterial clearance, absence of systemic toxicity, and stable physiological responses, supporting its potential for safe clinical translation. This innovative method offers substantial improvements over existing fluorescent contrast agents and holds promise for both diagnostic and therapeutic applications in cancer surgery.

1. Introduction

Cancer remains a leading cause of death, accounting for 9.7 million deaths in 2022.[1] Surgical resection is a primary treatment strategy for solid tumors; however, accurately distinguishing tumor margins from healthy tissue under white light remains difficult, often resulting in incomplete tumor removal or unnecessary excision of normal tissue.[2,3] Current surgeries rely on preoperative imaging (e.g., CT, MRI)[4,5] and intraoperative biopsies,[3] but these methods are limited in real-time accuracy. To improve precision, image-guided surgery using contrast agents that selectively highlight cancerous tissue is being explored. Although modalities such as MRI,[4,6] PET,[5,7] SPECT,[8] and CT[4,5,7,8] are used, their intraoperative application is hindered by bulky equipment, radiation exposure, and limited resolution at tumor margins.[6,9–12] Fluorescence-guided surgery (FGS) using optical contrast agents offers real-time, high-resolution imaging as a promising alternative.[13] However, current agents often require repeated

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