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Engineering responsive nanoscale systems for precision medicine

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Tumors are host to complex, dynamic microenvironments that pose fundamental challenges in diagnosis and treatment. Engineered micro- and nanosystems may serve as powerful tools in addressing these challenges, but strategies are required to control them in the body or focus their action at the site of disease. To address this need, my laboratory develops micro- and nanosystems that respond to disease-specific biochemical cues or noninvasive external stimuli like magnetic fields. In this talk, I describe some of the systems we are developing to diagnose and therapeutically target tumor tissues.

In a first example, we address the need to capture information about the molecular activity of individual tumors *in vivo* to pinpoint which interventions may maximize a patient's therapeutic response. Protease-activated agents are an emerging class of therapies that may improve the therapeutic windows of numerous drugs. Matrix metalloproteinases (MMPs) drive multiple tumorigenic pathways, and their enzymatic activity can be measured using engineered peptide substrates as protease-specific probes. We designed a protease-activity based sensor for use in local sampling of tumor microenvironments. These activity-probing nanosensors can be remotely activated at the disease site via an alternating magnetic field (AMF), and enable minimally-invasive signal detection in the urine.

In another example, we designed tumor-selective contrast agents with the potential to aid in cancer diagnosis via magnetic resonance imaging (MRI). Several peptides have been identified as useful tumor-targeting agents in cancer diagnostics. Rather than synthesizing magnetic nanoparticles and coupling peptides of interest to them, we instead exploited iron oxide nanoparticles of biogenic origin. A type of aquatic bacteria synthesizes these particles, also called magnetosomes, to help themselves navigate. We genetically modified these magnetotactic bacteria to display the pH low insertion peptide (pHLIP), a long peptide intended to enhance MRI contrast by binding to cell membranes in response to the acidic environment present in tumors. After separating these particles from the bacteria, and applying them both *in vitro* and *in vivo,* we found enhanced binding and tumor imaging contrast. Our experiments indicate that these tailored magnetosomes retain their magnetic properties, making them well-suited as T2 contrast agents, while exhibiting increased binding compared to wild-type magnetosomes.

Once a tumor's location is known, bacteria themselves may prove useful as living magnetic "materials" to enhance drug accumulation and penetration, a possibility we explored in a separate approach.

Nanoparticles (NPs) have emerged as an advantageous drug delivery platform for the treatment of cancer, however, their efficacy in shuttling materials to diseased tissue is hampered by a number of physiological barriers. One hurdle is transport out of the blood vessels, compounded by difficulties in subsequent penetration into the target tissue. We employed magnetotactic bacteria power by rotating magnetic fields to exceed diffusion-limited transport of nanosized drug carriers by enhancing local fluid convection. By exploiting ferrohydrodynamics, these bacterial swarms become a directable “living ferrofluid”. With this strategy, we showed wirelessly driven convective transport and enhanced accumulation of nanoparticles as potential drug carriers in tissue models.