"New chemical probe technologies: applications to cancer imaging and drug discovery "

Guest Speaker:
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Abstract: Proteases are enzymes that often play pathogenic roles in many common human diseases such as cancer, asthma, arthritis, atherosclerosis and infection by pathogens. Therefore tools that can be used to dynamically monitor their activity can be used as diagnostic agents, as imaging contrast agents for intraoperative image guidance and for the identification of novel classes of protease-targeted drugs. In the first part of this presentation, I will describe our efforts to design and synthesize small molecule probes that produce a fluorescent signal upon binding to a protease target. We have identified probes that show tumor-specific retention, fast activation kinetics, and rapid systemic distribution making them useful for real-time fluorescence guided tumor resection and other diagnostic imaging applications. In the second half of the presentation, I will present our recent advances using chemical probes to target a protease in the bacterial pathogen *Clostridium difficile* toxin proteins. *Clostridium difficile* infection (CDI) is worldwide health threat that is typically triggered by the use of broad-spectrum antibiotics, which disrupt the natural gut microbiota and allow this Gram-positive anaerobic pathogen to thrive. The increased incidence and severity of the disease coupled with decreased response, high recurrence rates, and emergence of multiple antibiotic resistant strains have created an urgent need for new therapies. Through a targeted screen using one of our protease probes, we identified a number of potent inhibitors against a toxin derived cysteine protease. Importantly, one bioactive compound is currently in human clinical trials for a clinically unrelated indication. This drug showed activity in cell based assays and treatment in a mouse model of CDI that closely resembles the human infection confirmed a significant therapeutic benefit in the form of reduced disease pathology. Taken together, this presentation will highlight multiple applications for chemical probes and present examples in which our efforts have led to near-term clinical applications.

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