Optimization of Drug Delivery by Tumor-Targeting Layer-by-Layer Nanoparticles Using Advanced Microscopic Technologies

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Continuing advances are being made in the development of novel therapies for cancer. However, the ability to target anti-cancer drugs directly to tumor tissue remains a significant unmet need. In addition, it is becoming increasingly clear that delivery of combinations of targeted agents in a defined temporal sequence, such as inhibitors of BRAF and MEK for the treatment of melanoma, is extremely important for the efficacy of these therapies. Tumor cells have unique physiochemical properties, including altered composition of their cell membranes, which provides an opportunity that can be exploited for drug delivery. We have been working to develop a unique drug delivery system, known as layer-by-layer (LbL) nanoparticles, that can both deliver drugs with high efficiency to cells with specific membrane characteristics, as well as deliver more than one drug with a defined temporal sequence. However, it is extremely difficult to characterize the delivery characteristics of the multiple layers of an LbL nanoparticle to tumors. Access to the imaging capabilities of the Harvard Center for Biological Imaging provides a unique opportunity to address these questions. We propose to package distinct fluorophores in the layers of LbL nanoparticles of diverse design and use advanced microscopic technologies to quantitate the delivery to tumor model systems. These experiments will have significant translational implications, and will provide insight into basic properties of cancer cell membranes. Based on the findings of these studies, we would plan to perform experiments in orthotopic model systems in animals, as a prelude to therapeutic clinical trials in patients.

A Microscopy-Based Platform For Rapid, At-will Antimicrobial Resistance Testing

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Antibiotic resistance is compromising our ability to treat bacterial infections. Clinical microbiology laboratories guide appropriate treatment through antimicrobial susceptibility testing (AST) of patient isolates. However, increasingly, pathogens are developing resistance to a broad range of antimicrobials, requiring AST of less commonly used or recently introduced agents for which no commercially available or FDA-cleared testing methods exist. Agar or broth dilution are gold standard methods for AST that can be used to test any antimicrobial; however, labor and technical complexity precludes their use in hospital-based clinical laboratories. Therefore, bacterial isolates often must be sent to a reference laboratory with a 4-6 day delay in results. Further, even standard methods require overnight incubation prior to readout. Therefore, there exists a significant AST testing gap in which current methodologies cannot adequately address the need for rapid results in the face of unpredictable susceptibility profiles. Our laboratory has recently verified inkjet, digital dispensing technology as a novel platform to facilitate perform reference AST for any antimicrobial at will. In this proposal, we aim to harness technical assets and expertise at HCBII/IDAC to leapfrog current technology through: (1) development of a method for microscopic imaging of bacterial replication in solid-phase 384-well microplate AST format, thereby determining susceptibility for any drug in <4 hours and (2) verification of the clinical performance of the new assay using well-characterized clinical