Engineering Models and Developing Therapies for the CNS

Following central nervous system (CNS) injury, there are limited options to promote neuroprotection and repair. Our lab has spent many years developing delivery systems for the eye for neuroprotection and regeneration. We have also been developing hemostatic nanoparticles to control bleeding and deliver drugs after brain injury. In recent years, we have been exploring building 3D models of the neurovascular niche to better understand the impact of trauma and disease on the CNS and to help screen for therapies post injury.

We have begun to look at active delivery systems using nanocapsules that are triggered by ultrasound to deliver controlled and repeatable amounts of drug. We synthesized nanocapsules encapsulating acriflavine, a HIF-1alpha inhibitor. Release studies demonstrated delivery of fluorescein or acriflavine over several weeks. Application of either an ultrasonic probe or a clinical grade, ultrasound imaging system used for assessing the retina led to release of a fraction of drug that could be tailored by the energy applied to the nanocapsules, and multiple pulses of release could be triggered over time with at least 10 separate release events triggered for each formulation. Being able to tailor the on-demand release over multiple cycles has the potential to fundamentally change how we can approach delivery of drugs for a variety of applications. This system has the potential to treat angiogenesis in wet age-related macular degeneration, and in our first model, in collaboration with Dr. Budd Tucker, we see neuroprotection of the retina. We have been able to leverage these nanocapsules as the basis for hemostatic nanocapsules so that we can address bleeding and deliver drugs in models of CNS trauma.

One of the challenges with developing therapies is being able to screen them efficiently. To that end, we are developing an approach to rapid fabrication of tissue models including the neural stem cell niche. 3D printing has revolutionized making tissue models, but the instruments are often quite expensive, and the approach can involve heat and/or shear forces that can damage cells, particularly neural stem cells. As a complement to more traditional 3D printing approaches, we have developed a screen-printing approach, leveraging the 2000 year old technique that is also used in the electronics industry. We are able to screen print hydrogels as well as induced pluripotent stem cell derived endothelial cells and neural stem cells to build models of the neural stem cell niche in defined patterns. This provides a foundation for building models for high throughput screening applications.