Engineering Materials for Non-Compressible Torso Hemorrhage and Internal Bleeding

by
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Non-compressible torso hemorrhage (NCTH) and internal bleeding results in a significant number of preventable casualties worldwide among civilians and in the field. In particular, internal bleeding can only be diagnosed through changes in vital signs and then through imaging modalities that may only be available in a hospital setting. Over the past few decades, researchers in the field have sought to address these needs by developing hemostats that can rapidly expand, bind, or seal an exposed wound, or interact with wound-specific components when delivered intravenously to enhance preexisting hemostatic processes.

The first part of this thesis investigates the effect of hemostatic nanoparticle size on their interactions with platelets. Small nanoparticles were observed to result in an increased percentage of specifically-bound single platelets under flow and intermediate nanoparticles were observed to result in the greatest degree of platelet recruitment to a platelet-collagen surface. Large nanoparticles were observed to result in the most nanoparticle mass bound to a surface, the shortest circulation time and retention, and the highest pulmonary accumulation. Ultimately, intermediate nanoparticles were shown to result in the most significant increase in survival relative to the saline control in a lethal inferior vena cava (IVC) injury model (84.6% vs 26.7%), as well as the greatest accumulation at the injured IVC relative to uninjured vessel controls.

Subsequently, the intermediate nanoparticles from the prior study were functionalized with bio-orthogonal click-crosslinkable azide groups to achieve targeted crosslinking behavior. Commercial multiarm PEG functionalized with the corresponding clickable moiety, dibenzylcyclooctyne (DBCO), and DBCO-PEG-b-PLGA nanoparticles were delivered as the second part of this two-component system. This system was demonstrated to increase platelet recruitment and decrease fibrin loss during plasminolysis *in vitro*. When challenged in a mouse liver resection model, the two-component system resulted in significantly increased survival relative to the nanoparticle-only system and higher accumulation in the remnant liver.

Finally, a charge-inverting polymer was synthesized through controlled radical polymerization. The material was demonstrated to undergo rapid charge inversion when exposed to physiological pH, resulting in the near-complete lift-off within a minute of a layer-by-layer drug film into the dermis when coated on microneedles. Potential uses of this versatile release platform may include its inclusion in wound dressings to facilitate the release of therapeutics, or other applications involving charged films. Overall, this thesis has investigated several new materials and assays for the treatment of traumatic hemorrhage, opening potential avenues for the development of more effective hemostats.

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