ASK AN EXPERT

Health Science Inquiry

DR. STEFANIE NOVAKOWSKI is a recent PhD graduate from the Kastrup Lab at the University of British Columbia, where she developed tools for modifying platelets. The Kastrup lab uses biochemistry and biochemical engineering to solve problems related to hemostasis and hemorrhage. They investigate, utilize, and mimic the biochemistry and biophysical dynamics of blood coagulation to create innovative materials that perform new functions inside blood vessels.

DR. CHRISTIAN KASTRUP is an Associate Professor in the Michael Smith Laboratories and Department of Biochemistry & Molecular Biology. He is a recipient of the Sir Major Banting Award from the True Patriot Love Foundation, and a founder of CoMotion Drug Delivery Systems, Inc., which is currently working to develop a hemostatic agent for treating severe combat and surgical hemorrhage.

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What New Technologies are Needed to Halt Bleeding in the Most Severe Cases of Hemorrhage? Can This be Achieved by Enhancing Delivery of Therapeutics to the Wound?

Uncontrolled bleeding is a leading cause of death across all socioeconomic backgrounds, and can arise from diverse scenarios, including trauma, surgery, and childbirth [1]. Current strategies for treating hemorrhage include transfusing blood products, such as platelets, as well as delivering hemostatic and anti-fibrinolytic agents designed to stop the flow of blood or prevent clot lysis. The early control of hemorrhage drastically improves the outcome for patients; however, challenges still exist for managing severe, intractable hemorrhage, which is characterized by platelet dysfunction, increased clot lysis, and poor clot adhesion. Furthermore, escaping blood pushes externally applied hemostatics away from the wound, preventing delivery of the therapeutic to the site of injury.

Platelets seal vascular damage by adhering to blood vessel walls, releasing molecules which promote platelet activation and clot formation, and contracting the clot to narrow the wound. A promising strategy for the management of intractable hemorrhage is to increase the responsiveness, adhesion, and hemostatic efficacy of platelets specifically at sites of vascular damage. This has been achieved in part by use of refrigerated platelets. Compared to platelets stored at room temperature, which is the standard temperature for platelet storage, refrigerated platelets show higher efficacy when used to treat acute bleeding [2]. However, refrigerated platelets only circulate for a short time before they are cleared by the reticuloendothelial system, limiting the ability of refrigerated platelets to prevent bleeding when used prophylactically.

There is evidence that genetic modification can be used to enhance the hemostatic efficacy of platelets. In animal models, genetically engineered platelets were shown to improve hemophilia by releasing coagulation factor VIII [3]. These platelets are generated by modifying platelet precursor cells. While platelets can be generated from cultured precursor

cells, this technology has just reached the stage where it is possible to generate large numbers of platelets. Platelets generated from cultured cells need pre-clinical and clinical testing before they can be used in the clinic [4]. Therefore, a method for directly modifying donor-derived platelets to enhance their hemostatic abilities may be useful for treating severe bleeding.

Using small lipid nanoparticles to deliver nucleic acids and proteins to isolated platelets is an innovative approach to tackling this challenge [5, 6]. Using this technology, platelets are loaded with thrombin, a potent activator of clotting and platelets [5]. The nanoparticles shield the platelets from the thrombin during delivery, preventing the platelets from becoming activated until they are treated with additional platelet agonists. These thrombin-loaded platelets form clots faster than regular platelets, and produce stronger clots, even in plasma from patients with defective clotting. The next step would be to determine whether they maintain their enhanced clotting abilities in animal models, by using lipid nanoparticles to deliver mRNA to platelets [6]. While the platelets cannot yet translate the mRNA after endocytosing the nanoparticle, this approach could be used to genetically engineer platelets to produce additional pro-coagulant or anti-fibrinolytic proteins. A delivery vehicle for mRNA would not have to be optimized for each mRNA, providing an advantage over delivering different proteins to the platelets.

Beyond the enhancement of platelets, there are alternative approaches to enhance the delivery of hemostatic agents into wounds. CounterFlow is a novel wound-penetrating drug delivery vehicle composed of calcium carbonate and tranexamic acid [7, 8]. Tranexamic acid is a clot stabilizing anti-fibrinolytic agent, improving the efficacy of this delivery system. Various proteins, including thrombin, can be loaded onto CounterFlow, and upon contact with blood are propelled deep into the wound. In pig and sheep animals of trauma and surgery, respectively, CounterFlow reduced bleeding and improved survival compared to the current standard-of-care. This approach has potential for use in combat casualty care, due to its relative stability, portability, and ease-of-use.

Coagulation is controlled by a complex network of reactions that was first described over 50 years ago. Understanding blood coagulation has led to numerous therapies to control bleeding, yet intractable hemorrhage remains a problem. To treat severe hemorrhage, it is necessary to use innovative approaches to deliver therapeutics to the sites of wounds, and to re-think what aspects of coagulation should be targeted to enhance hemostasis.

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