SYNTHOPLATE®: A PLATELET-INSPIRED HEMOSTATIC NANOTECHNOLOGY FOR TREATMENT OF BLEEDING COMPLICATIONS

Anirban Sen Gupta PhD, Case Western Reserve University, Department of Biomedical Engineering, USA
axs262@case.edu
Christa Pawlowski PhD, Case Western Reserve University, Department of Biomedical Engineering, USA
Ujjal D S Sekhon, Case Western Reserve University, Department of Biomedical Engineering, USA
Mitchell R Dyer, University of Pittsburgh, Department of Surgery and Critical Care Medicine, USA
Meenal Shukla PhD, The Cleveland Clinic Foundation, Department of Cellular and Molecular Medicine, USA
Venkaiah Betapudi PhD, The Cleveland Clinic Foundation, Department of Cellular and Molecular Medicine, USA
Matthew D Neal MD, University of Pittsburgh, Department of Surgery and Critical Care Medicine, USA
Keith McCrae MD, The Cleveland Clinic Foundation, Department of Cellular and Molecular Medicine, USA

Platelet transfusions are routinely used in the clinic to treat bleeding complications stemming from trauma, surgery, malignancy-related bone marrow dysfunctions, and congenital or drug-related defects platelet defects. These transfusions primarily use allogeneic platelet concentrates (PCs) that pose issues of limited availability and portability, high risk of bacterial contamination, very short shelf life (~3-5 days), need for antigen matching and several biologic side effects. While robust research is being directed at resolving some of these issues, there is in parallel a significant clinical interest in synthetic platelet substitutes that can render efficient hemostasis by leveraging and amplifying endogenous clotting mechanisms while avoiding the above issues. To this end, we have developed a unique platelet-inspired synthetic hemostat technology called the SynthoPlate® (US Patent 9107845). Since platelets promote primary hemostasis via adhesion to vWF and collagen at the injury site and concomitant aggregation via fibrinogen binding to integrin GPIIb-IIIa on active platelets, we have mimicked and integrated these key hemostatic mechanisms on the SynthoPlate® by heteromultivalent surface-engineering of a liposomal platform with vWF-binding peptides (VBP), collagen-binding peptides (CBP) and fibrinogen-mimetic peptides (FMP). These ~150nm diameter SynthoPlate® vesicles are sterilizable and can be stored as lyophilized powder for long periods of time. We demonstrated, in vitro, that this platelet-mimetic integrative design renders hemostatically relevant functions at levels significantly higher than designs that mimic platelet’s adhesion function only or aggregation function only. We further demonstrated in vitro that SynthoPlate®-mediated site-selective amplification of primary hemostatic mechanisms (active platelet recruitment and aggregation) in effect results in site-selective enhancement of secondary hemostatic function (fibrin generation). We also established that SynthoPlate® does not activate and aggregate resting platelets or trigger coagulation mechanisms in plasma, suggesting that this technology will not have systemic pro-thrombotic and coagulatory risks. The hemostatic efficacy of SynthoPlate® was tested in appropriate tail-transection and liver bleeding models in mice, as well as, pilot studies in arterial bleeding model in pigs. In tail-transection bleeding model in normal as well as thrombocytopenic mice, prophylactically administered SynthoPlate® was able to significantly reduce bleeding time by 60-70%. In laparotomy traumatic bleeding model in mice, prophylactically administered SynthoPlate® was able to reduce blood volume loss by ~30%, reduced hypotension effects and increased survival by >80%. In pilot pig models of arterial bleeding, emergency administration of SynthoPlate® has shown substantial reduction in blood volume loss. Immunohistological evaluation of tissues from various treated animals have shown marked co-localization of red fluorescent SynthoPlate® with green fluorescent platelets localized at the clot site. Biodistribution studies in animals indicate that SynthoPlate® is cleared primarily by liver and spleen, similar to clinically known liposomal technologies. We have also demonstrated that the platelet-mimetic heteromultivalent surface-decoration approach can be adapted to other biomedically relevant particle platforms. Altogether, our studies establish the promise of SynthoPlate® nanotechnology as a platelet-mimetic intravenous hemostat for treatment of bleeding complications in prophylactic and emergency scenarios. Ongoing studies are focused on evaluating this technology in clinically motivated large animal bleeding models, with a vision for translation.