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

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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.