Transient gene therapy to decrease the stability of thrombi for coagulopathy and thrombosis

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Thrombotic disorders are prevalent and dangerous. Thrombosis involves the formation of unwanted blood clots inside blood vessels, which can impair blood flow and lead to severe cardiovascular events, such as heart attack, stroke, and pulmonary embolism. Current therapies for thrombosis are unsatisfactory in that they require frequent re-administration, and are associated with a significant bleeding risk, a consequence of inhibiting the coagulation cascade upstream of fibrin generation. Coagulation factor XIII (FXIII) acts to stabilize clots, downstream of fibrin generation and polymerization. Though this makes it an ideal target to reduce the burden of thrombosis while maintaining hemostasis, inhibitors suitable for clinical use have not been identified. We have recently published that lipid nanoparticles can be used to deliver siRNA to knock-down FXIII-B subunit and achieve depletion of the enzymatic A-subunit from circulation in mice and rabbits (Strilchuk, et al. Blood. 2020). In the current abstract, we discuss the findings that FXIII-A depletion causes less antiplasmin to be crosslinked to clots, resulting in clots that are more susceptible to fibrinolysis. Further, showing that while clots are weaker and easier to clear with thrombolytic therapy, bleeding is not enhanced in mice or rabbits after minor or major injury. In the short term, these novel RNA agents will be valuable tools in investigating the biology of thrombotic disorders. The ultimate goal is to develop this agent into a precise and long-acting prophylactic therapy for thrombotic disorders, that is safer and more effective than current standards of care.