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S298 CS585 IS A FIRST-IN-CLASS COMPOUND TARGETING THE IP RECEPTOR FOR PREVENTION OF THROMBOSIS WITHOUT INCREASED RISK OF BLEEDING

Topic: 34. Thrombosis and vascular biology - Biology & Translational Research

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Background: Uncontrolled platelet activation leads to the formation of occlusive thrombi resulting in myocardial infarction, stroke, VTE and critical limb ischemia. There is an unmet need for more efficacious anti-thrombotics with less bleeding in this area. Our group recently identify a novel oxidized lipid in the blood that potently and selectively inhibits platelet activation through activation of the prostacyclin receptor.

Aims: Develop a first-in-class antiplatelet drug, CS585, that potently and selectively inhibits platelet reactivity and thrombosis without altering hemostasis and bleeding risk.

Methods: We developed a mimetic of the oxidized lipid shown to selectively bind to and activate the prostacyclin receptor. Using human platelets, we assessed the ability of CS585 to inhibit platelet activation by assessing 1)aggregometry, 2)adhesion under arterial flow, and 3) granule secretion and integrin activation using flow cytometry. We additionally assessed thrombosis in vivo in 2 different mouse models as well as bleeding. Finally, we assessed potential off-target effects using thromboelastography (TEG).

Results: CS585 potently inhibited both collagen and thrombin-induced platelet aggregation. This inhibition was confirmed by measuring inhibition of αIIbβ3 activation, α-granule secretion, and dense-granule secretion by flow cytometry. Selectivity was confirmed in human platelets by demonstrating a full reversal of inhibition when the IP receptor was pharmacologically blocked or genetically eliminated in IP receptor knockout mice. In vivo inhibition of injury-induced thrombosis in the small (laser-induced cremaster thrombosis model) and large ($FeCl_3$-induced carotid artery thrombosis model) vessels by CS585 was demonstrated and no increased risk for bleeding was observed using the tail vein bleeding model. Finally, TEG experiments in human blood spiked with CS585 demonstrated no delay or decrease in clot strength confirming the tail vein bleeding assay experiments in the mouse.

Summary/Conclusion: We have shown for the first time that CS585, a first-in-class analog of an oxidized lipid in the blood potently and selectively activates the prostacyclin receptor resulting in inhibition of human and mouse platelet activation and thrombosis without an increased risk of bleeding. This discovery represents a new class of inhibitors for prevention of platelet activation and thrombosis and protection from myocardial infarction, stroke, VTE, and critical limb ischemia.