CS585 IS A NOVEL ORALLY AVAILABLE PROSTACYCLIN RECEPTOR AGONIST WITH SUSTAINED IN VIVO INHIBITION OF PLATELETS AND THROMBOSIS FORMATION IN MOUSE WITHOUT INCREASED RISK OF BLEEDING

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BACKGROUND

Attenuation or inhibition of Platelets represent the first line therapy in mainly secondary prevention of myocardial infarction (MI) and stroke. While current antiplatelet therapy has been effective, bleeding is still a problem. Targeting the prostacyclin receptor (IP) with our recently developed first-in-class orally available prostacyclin receptor agonist (CS585) represents a novel and effective approach for prevention of thrombosis, MI, and stroke without any observed increase in bleeding.

METHODS

Human blood was assessed either as platelet rich plasma or washed platelets for determination of effectiveness of CS585 in preventing platelet activation ex vivo; including platelet aggregometry following stimulation with thrombin or collagen. Samples were also assessed by flow cytometry looking at activation of integrin and granule secretion. Mice were administered CS585 by oral gavage or IV for assessment of CS585 effectiveness and persistence of effect in vivo. This included cremaster and carotid artery thrombosis assays as well as the tail bleeding assay.

RESULTS

CS585 was found to be selective to the IP receptor. IP receptor activation on human platelets can be detected by VASP phosphorylation at 10 pM CS585 with an effective IC_{50} of 5 nM. Effectiveness was confirmed in vivo in the mouse thrombosis assays with full inhibition occurring at 1-3 mg/kg dosing. Further, the effect of CS585 in the blood persisted for more than 18 hours post-IV administration. Oral administration of CS585 was highly effective in preventing injury induced thrombotic clot formation in the vessel. Finally, CS585 demonstrated no increased bleeding risk compared to control conditions.

CONCLUSION

CS585 represents a first-in-class approach for inhibiting platelet activation and thrombosis without altering hemostasis or increasing the risk for bleeding. Additionally, CS585 is an effective orally available drug with persistent efficacy in the blood and represents an effective new target for treating patients at risk for an occlusive thrombotic event (e.g., MI and stroke).

CS585 is an orally available, selective, prostacyclin receptor.

IV or oral administration of **CS585** prevents injury-induced thrombus formation without increasing bleeding risk.

CS585 is effective in vivo between 1-3 mg/kg and is stable in the blood for a more than 4 hours.

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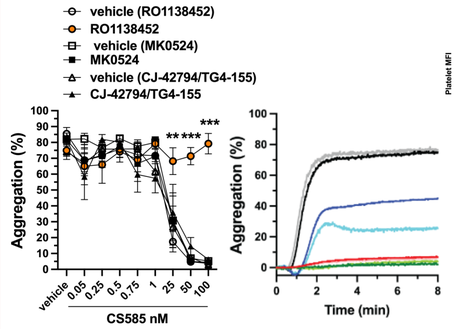
DISCUSSION

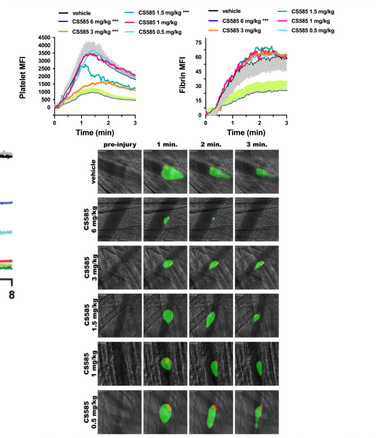
The platelet remains a primary target for regulation of hemostasis and thrombosis. There has been a paucity of successful targeting of platelet reactivity beyond targeting COX-1 and the $P2Y_{12}$ receptor. Here, we demonstrate for the first time, a novel lipid analogue known as CS585. CS585 is shown to selectively target the prostacyclin receptor for prevention of thrombosis. CS585 does not increase the risk for bleeding. Hence, CS585 may represent a new approach for prevention of thrombosis while maintaining normal hemostasis.

FIGURE 1



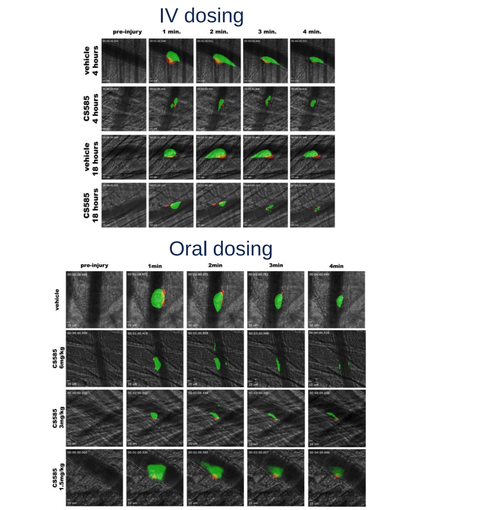
CS585 inhibits platelet aggregation at low nM dosing. Platelet inhibition is prevented when IP receptor is selectively blocked. Inhibition of DP1, EP2, or EP4 receptors do not alter CS585-induced inhibition of platelet function.

FIGURE 2



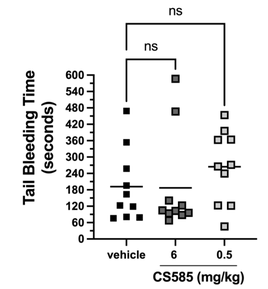
In vivo laser-induced cremaster intravital thrombosis assay: Platelet accumulation at site of injury (green) is dose-dependently inhibited by CS585 while fibrin formation is unaltered.

FIGURE 3



CS585 inhibits thrombus formation in both IV and oral routes of administration for at least 4-18 hours.

FIGURE 4



CS585 does not alter bleeding diathesis even at high (6 mg/kg) doses of drug

DISCLOSURE INFORMATION

Michael Holinstat: equity holder and serves on the scientific advisory board for Veralox Therapeutics. Michael Holinstat is also an equity holder and consultant for Cereno Scientific and received research funding from Cereno Scientific for this project. Michael Holinstat is an inventor for CS585 with associated patents US11,236,044 and US11,498,905. Bjorn Dahlof: CMO for Cereno Scientific.