INTRODUCTION

Masai cell heparrin proteoglycans (HEP-PG) inhibit collagen- and von Willebrand factor (VWF)-mediated platelet thrombosis maintaining platelet adhesion. APAC, platelet and fibrin inhibiting HEP-PG mimic, is developed for antithrombotic management of vascular interventions.

Previous work shows that APAC:

- inhibits arterial thrombosis (Fohts and AV-shunt model) and reduces fibrin formation in baboons (A and B)
- reduces ischemic reperfusion injury in acute kidney injury model in rats (C)
- decreases platelet and fibrin deposition and procoagulant activity under VWF-dependent high shear rate conditions (D) in human blood in vitro

AIMS

to assess the role of APAC in:

- platelet aggregation in human blood and PRP
- global blood coagulation (ROTEM)
- targeting to injured porcine vascular sites
- collagen-induced thrombosis in mouse

CONCLUSIONS

APAC unlike UFH:

- inhibits collagen- and ristocetin-induced platelet aggregation both in blood and PRP
- is a broader anticoagulant
- targets injured vascular sites: co-localizes with VWF and laminin – not the intact endothelium
- reduces collagen-dependent platelet thrombus formation in mouse - without bleeds

RESULTS

LOCAL APAC TARGETS VASCULAR INJURY SITES IN PORCINE AVF AND BALLOONED ARTERY MODEL

APAC co-localizes with VWF, laminin

no co-localization with PECAM

MCC

APAC binds to AVF

APAC IV INHIBITS COLLAGEN-INDUCED THROMBOSIS IN MOUSE

Inverted epigastric artery inserted to carotid artery lumen

Localized APAC (0.5 mg/kg IV) reduced platelet (green) accumulation (< 0.05) at thrombogenic challenge vs. control (n=6; representative images) – courtesy of Dr. Brian Cooley

APAC IV HAS A WIDE SAFETY MARGIN IN VIVO

RATS

- Single dose: NOAEL was 20 mg/kg
- Repeated 3-day dosing: MTD was not reached with the highest dose of 7.5 mg/kg

PRIMATES

- Single dose: MTD was 10 mg/kg
- Repeated 7-day dosing: NOAEL was 3 mg/kg