APAC, A DUAL ANTIPLATELET AND ANTICOAGULANT HEPARIN PROTEOGLYCAN MIMETIC, INTEGRATES WITH EXTRAVASCULAR MATRIX DURING VASCULAR INJURY

K. Barreiro, Msc; A. Jouppila, Msc; R. Tulamo, MD, PhD; A. Albäck MD, PhD; and R. Lassila, MD, PhD, Prof 1, 2

1 Institute for Molecular Medicine Finland FIMM, University of Helsinki, Finland; 2 Helsinki University Hospital Research Institute; 3 Vascular Surgery, University of Helsinki and Helsinki University Hospital; 4 Coagulation Disorders Unit, University of Helsinki and Departments of Hematology and Clinical Chemistry (HUSLAB Laboratory Services), Comprehensive Cancer Center, Helsinki University Hospital; 5 Aplagon Oy, Helsinki, Finland

**Aims**

- APAC's binding and localization to denuded iliac, carotid and femoral artery after local exposure in vitro and in vivo in a pig model.
- APAC co-localization with Von Willebrand factor (VWF), laminin, podocalyxin, and PECAM.

**Methods**

In vivo we locally, intraluminally applied biotinylated APAC (0.5 mg/mL) on vascular injury site, allowed 2 min exposure and released blood flow. In vitro APAC-Biotin was incubated with a scraped artery injury models.

- Mast cell heparin proteoglycans (HEP-PG) inhibit collagen-induced and Von Willebrand (VWF)-mediated platelet thrombosis, but preserve adhesion.
- APAC as a HEP-PG mimic contains conjugate of unfractionated heparins (UFH) with a core protein is designed to be used in association with vascular interventions.
- APAC shows dual antiplatelet and anticoagulant activity, inhibits arterial thrombosis.
- Mast cell heparin proteoglycans (HEP-PG) inhibit collagen-induced and Von Willebrand (VWF)-mediated platelet thrombosis, but preserve adhesion.
- APAC as a HEP-PG mimic contains conjugate of unfractionated heparins (UFH) with a core protein is designed to be used in association with vascular interventions.
- APAC shows dual antiplatelet and anticoagulant activity, inhibits arterial thrombosis (Folts and AV-shunt model in baboons) and reduces fibrin formation and protects from ischemic reperfusion injury in acute kidney injury model.

**Results**

1. APAC binds to *in vitro* denuded arteries

2. APAC binds to *in vivo* denuded arteries

3. APAC binds to *in vivo* arteriovenous fistula wall

4. APAC co-localizes *in vivo* with VWF in both balloon injury and AVF

5. APAC co-localizes *in vivo* with Laminin in both balloon injury and AVF

6. APAC shows limited co-localization with PECAM

7. APAC binding is reduced in presence of Podocalyxin

8. Manders' co-localization coefficients quantified the vascular co-localization of APAC

**Conclusions**

- APAC, developed as a local antithrombotic therapy to be used in association with vascular intervention shows multiple binding sites on vascular injuries.
- APAC adheres to vascular injury site of arteries and AVF and co-localizes with VWF and Laminin.
- APAC binding and colocalization are strongly reduced in presence of PECAM or Podocalyxin.
- APAC, a dual antiplatelet and anticoagulant, binds to site of vascular damage and offers local antithrombotic action.

**Abbreviations**

* Lumen; Arrowheads: Internal elastic lamina; FV: femoral vein; An: anastomosis; FA: femoral artery; scale bar: 20 µm


**Acknowledgments**

Balloon denudation

Arterio-venous fistula wall

VWF

APAC

Laminin

PECAM

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst

APAC

Merga

Hoechst