



Supplementary Figure 1: The role of FVIII in the coagulation cascade. The coagulation cascade is dedicated to the formation of fibrin clots. It plays a role in blocking local hemorrhage after vascular breaches. The cascade is articulated around two pathways at the surface of the platelets: i) the intrinsic pathway, which is initiated by contact of the blood with components of the subendothelium, ii) the extrinsic pathway, which is initiated by the Tissue Factor (TF). After a first step of platelet adhesion to subendothelium components (e.g. $\alpha 2\beta 1$ integrin or glycoprotein (GP) VI to collagen, GPIIb-XI-V complex to von Willebrand Factor (VWF), platelets are activated and their aggregation leads to the thrombus formation. The activation of fibrinogen results in fibrin clots and enhances the platelet aggregation. The active form of FVIII (FVIIIa) acts as a cofactor in the tenase complex (factor IXa (FIXa)/FVIIIa) which allows the conversion of factor X (FX) to its active form, factor Xa (FXa), through the serine protease FIXa [5]. FXa contributes to prothrombinase complex with cofactor factor Va (FVa), which catalyzes the conversion of prothrombin into thrombin. *In fine*, formed thrombin (FIIa) induces the conversion of fibrinogen into fibrin, resulting in clotting. Thrombin is a pivotal actor of the coagulation cascade and is the main FVIII activator even if FXa can also induce the activation of FVIII to FVIIIa [6]. This activation is less efficient if FVIII is linked to von Willebrand Factor (VWF) [4]. Moreover, thrombin binds to Protease-Activated Receptor (PAR)-1 and -4 expressed at the platelets membrane and induced their activation and aggregation [7]. PL: phospholipids