

# **BLOOD** **TRANSFUSION**

since 1956

**Official journal of**

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**Associazione Italiana dei Centri Emofilia - AICE**

**Hrvatsko Društvo za Transfuzijsku Medicinu - HDTM**

**Sociedad Española de Transfusión Sanguínea y Terapia Celular - SETS**

**Società Italiana per lo Studio dell'Emostasi e della Trombosi - Siset**

## **ABSTRACT BOOK**

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PLENARY SESSION 2

OC007

**THE CARBOXYL-TERMINAL REGION OF HUMAN COAGULATION FACTOR X AS A NOVEL NATURALLY-OCCURRING LINKER FOR FUSION STRATEGIES**

Ferrarese M.<sup>(1)</sup>, Pignani S.<sup>(2)</sup>, Lombardi S.<sup>(2)</sup>, Balestra D.<sup>(2)</sup>, Bernardi F.<sup>(2)</sup>, Pinotti M.<sup>(2)</sup>, Branchini A.<sup>(2)</sup>

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**Background.** Fusion with human serum albumin (HSA) represents a well-established technique to extend half-life of therapeutic proteins used to treat bleeding disorders. A key issue to be addressed is the fusion strategy, which mainly involves intervening linker sequences ensuring proper spatial separation and biological activity. Here, we explored direct fusion to coagulation factor X (FX) carboxyl-terminal region, previously demonstrated by us to be dispensable for secretion/function, as a natural linker suitable for fusion with HSA. We also produced, as comparators, fusion proteins exploiting flexible (glycine/serine; FX-GS-HSA) or cleavable (incorporating the FX activation site; FX-CL-HSA) linkers, mimicking the long-acting recombinant activated factor FVII (rFVIIa)-HSA and factor IX (FIX)-HSA, respectively.

**Methods.** Proteins were stably expressed in human embryonic kidney 293 cells and characterized for secretion (ELISA), activation (Western blotting, time-course amidolytic assays) and activity (thrombin generation, PT-based assays). Concentrated proteins were tail-vein injected into wild-type C57/BL6 mice to evaluate half-life.

**Results.** All chimeras were efficiently secreted and possessed remarkable activity, with FX-HSA and FX-CL-HSA displaying comparable functional features both in thrombin generation and PT-based assays. The two chimeras were able to shorten coagulation times in a dose-dependent manner, with virtually normal pro-coagulant activity for FX-HSA (88.7±6.0% of FX) and FX-CL-HSA (98.0±16.2%). Conversely, the FX-GS-HSA variant showed a reduced efficiency in both assays, with a coagulant activity of 55.8±5.4% of FX. Upon incubation with activators, FX-HSA and FX-CL-HSA displayed a correct activation profile while the FX-GS-HSA activation was slightly defective. In fluorogenic-based assays, the FX-HSA showed normal activity over time and a specific amidolytic activity (1.0±0.12) comparable to that of FX. Moreover, FX-HSA showed prolonged plasma persistence in mice (the fusion protein was detectable by ELISA at 36 hours post-injection whereas FX alone disappeared at 16 hours). Overall, the FX-HSA features indicate that the FX carboxyl-terminus represents an intrinsic sequence allowing tandem fusion.

**Conclusions.** Our results provide the first experimental evidence for i) a coagulation factor fusion protein with features independent from artificial linkers, ii) the suitability of FX carboxyl-terminal region as a novel naturally-occurring linker for fusion purposes, and iii) the suitability of FX as a versatile platform for protein engineering, with potential therapeutic

meaning for patients. Interestingly, we can try to speculate that the absence of an artificial sequence joining FX with HSA, as well as with other potential fusion partners, could have a low association with the risk of triggering an immune response.

OC008

**THE CHAPERONE-LIKE COMPOUND SODIUM PHENYLBUTYRATE IMPROVES INTRACELLULAR TRAFFICKING, SECRETION AND COAGULANT ACTIVITY OF FACTOR IX IMPAIRED BY THE FREQUENT P.R294Q MUTATION**

Pignani S.<sup>(1)</sup>, Todaro A.<sup>(2)</sup>, Ferrarese M.<sup>(2)</sup>, Marchi S.<sup>(3)</sup>, Lombardi S.<sup>(2)</sup>, Balestra D.<sup>(2)</sup>, Pinton P.<sup>(3)</sup>, Bernardi F.<sup>(2)</sup>, Pinotti M.<sup>(2)</sup>, Branchini A.<sup>(2)</sup>

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**Background.** Amino acid substitutions caused by missense mutations, representing the most frequent cause of human disease, exert the most detrimental effect by impairing protein folding and intracellular processing, which can be improved by small molecules exhibiting chaperone-like activity. However, despite the potential of these compounds, only very few attempts have been made in coagulopathies, where even modest increases of functional levels could have therapeutic implications.

**Methods.** Cellular models mimicking severe HB were created to perform expression studies and evaluation of intracellular trafficking (immunofluorescence), protein (ELISA, Western blotting), and activity (coagulant assays) levels of recombinant (r)FIX variants before and after treatment of cells with chaperone-like compounds.

**Results.** As model we chose the most frequent HB mutation (p.R294Q, ~100 patients), compared with other recurrent mutations (p.Y115C, n=9; p.Y161C, n=5; p.Y305C, n=9) associated with severe/moderate type I HB. Mutations were characterized by expression of rFIX variants in HEK293 cells and investigations at the extracellular and intracellular level. In transient expression studies, all missense mutations resulted in impaired rFIX secretion (<1% of wild-type rFIX), in agreement with coagulation phenotypes in HB patients. At the intracellular level, immunofluorescence studies revealed that, at variance from wild-type rFIX, missense variants mainly co-localized in the ER and scarcely with Golgi, thus indicating impaired intracellular trafficking, in line with the observed defective secretion. The chaperone-like compound sodium phenylbutyrate (NaPBA) promoted secretion (from 0.26±0.06% to 1.5±0.3%) only of the rFIX-294Q variant in a dose-dependent manner, as also indicated by the appreciable and quantitatively improved trafficking to Golgi. Importantly, the shortening of coagulation times (from 80±0.1 to 62±3 seconds) corresponded to a concurrent increase in activity levels (from 0.5±0.04% to 3.0±0.9%) that, if achieved in patients, would ameliorate the bleeding phenotype. Noticeably, the rFIX-294Q variant displayed a specific coagulant activity that was higher (~2.0) than that of wild-type rFIX at all treatment conditions, a feature that magnifies the functional impact of the NaPBA-mediated rescue.