secretion achieved after a single IP implantation creates a viable alternative to traditional factor delivery or gene therapy with several important advantages. We aim to pursue first clinical studies in patients with Hemophilia A, and to develop therapeutics using Shielded Living Therapeutics™ for other serious bleeding disorders.

OC 60.5 | Development of a Formulation for Oral Delivery of FVIII via a Robotic Pill

G. Schrenk[1]; M. Hashim[2]; R. Korupolu[2]; A. Toledo[2]; V. Salgotra[2]; S. Sharma[2]; A. Garapathy[2]; A. Yamaguchi[2]; W. Hoellriegl[1]; M. Dockal[1]; M. Imram[2]; F. Scheiflinger[1]

[1]Baxalta Innovations GmbH Part of Takeda, Vienna, Austria, [2]Rani Therapeutics, San Jose, United States

Background: Hemophilia A, a bleeding disorder caused by a deficiency of functional coagulation factor VIII (FVIII), is commonly treated via intravenous replacement therapy 2-3 times weekly with plasma-derived or recombinant FVIII. Recently, a FVIII mimetic bispecific antibody for subcutaneous administration was approved in some geographies. Oral FVIII would substantially improve patients′ life by reducing the burden from intravenous or subcutaneous injections.

Aims: To develop a dry powder formulation suitable for oral administration for FVIII via a robotic pill. The key injectable element of the robotic pill is its drug payload (FVIII) formed as a solid microtablet of precise dose sealed inside a hollow, dissolvable microneedle.

Methods: The recombinant FVIII drug substance was formulated into a dry powder using GRAS injectable excipients suitable for making microtablets. Microtablets were made and then sealed inside microneedles. A qualified, sensitive and selective ELISA was used to measure FVIII activity during process steps.

Results: A dry powder formulation was successfully developed. Using a custom machine and an optimized process, the dry powder was used to create multiple batches of microtablets. In multiple, consecutive batches of microtablets and microneedles, FVIII activity was consistently retained (>90%) with little or minimal loss.

Conclusions: Results confirmed that FVIII could be successfully formulated into microtablets with no impact on activity, providing evidence for the concept of the FVIII as the drug payload in robotic pill. In-life proof-of-concept studies in appropriate animal models are in progress. Successful proof-of-concept studies will lead to an innovative concept for oral delivery of FVIII by using a robotic pill.

OC 62.1 | A Test of the GPIbα β-switch Hypothesis for Platelet-type von Willebrand Disease

A. Tischer; V. Machha; L. Moon-Tasson; M. Auton

Mayo Clinic Rochester, Hematology, Rochester, United States

Background: Von Willebrand Factor multimers mediate platelet adhesion through direct interactions between shear-flow exposed A1 domains and platelet GPIbα receptors. Mutations in the β-switch of GPIbα cause gain-of-function in the platelet-type pseudo-Von Willebrand Disease.

Aims: Crystals of free and A1 bound GPIbα suggest that the β-switch undergoes a conformational change from a random coil to a β-hairpin. Platelet-type VWD mutations have been proposed to stabilize the β-switch by shifting the equilibrium in favor of the β-hairpin conformation, a hypothesis predicated on the assumption that the co-crystal complex between A1 and GPIbα is the high-affinity state.

Methods: Hydrogen-deuterium exchange mass spectrometry is employed to test this hypothesis using common G233V, M239V and G233V/M239V disease variants of GPIbα. If true, the expected observation is that hydrogen-exchange in the β-switch would be quenched as result of hydrogen bonds newly formed between the β strands of the β-hairpin conformation.

Results: These experiments reveal that hydrogen exchange in the β-switch is enhanced rather than quenched indicating that the β-switch becomes more dynamic favoring the disordered loop conformation. Hydrogen-exchange is corroborated by differential scanning calorimetry which confirms that these mutations destabilize GPIbα resulting in a decreased unfolding enthalpy which indicates a dissociation of the β-switch from the Leucine Rich Repeat (LRR) domain in the native state. Furthermore, the stability of GPIbα and its A1 binding affinity, determined by surface plasmon resonance, are directly correlated to the extent of local disorder in the β-switch.

Conclusions: These studies demonstrate that GPIbα with a disordered loop is binding competent and support a mechanism by which disorder in the β-switch can dynamically expose the LRR domain of GPIbα. Taken in the context of the recently discovered local disorder of the A1 domain in Type 2B VWD, these results emphasize the role of protein chain disorder in establishing high-affinity interactions between platelets and VWF.