Oral factor VIII (FVIII) bispecific molecule for haemophilia A

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Disclosures

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Rising clinical interest in oral administration of proteins and peptides

Oral treatment is one of the most attractive modes of drug administration due to ease and safety, also potentially increasing patient adherence

Extensive research focusing on novel technologies for oral administration of proteins and peptides has been conducted, increasing knowledge, with the number of publications increasing exponentially since 1995

Many historical efforts targeting oral administration of proteins and peptides, starting from the discovery of insulin in 1921, have failed due to challenges in facilitating oral absorption

Commercial products of oral proteins and peptides are therefore very limited (e.g., cyclosporin A and semaglutide)

Zhu et al. Acta Pharmaceutica Sinica B 2021;11(8):2416-48.

Why have previous oral administration attempts failed?

There are many challenging factors for effective oral administration

Large molecular size and variation in structure of biologics

- Smaller molecular weight is associated with enhanced absorption and improved bioavailability

Instability in the GI

- Proteins only stable within a narrow pH range (6.7–7.0), and GI pH fluctuates significantly by various factors (e.g., food intake, age, gender, pathological conditions, etc.)

High hydrophilicity of biologics

- The hydrophilicity of proteins and peptides hinders their ability to permeate hydrophobic membrane barriers

These factors lead to poor transmembrane permeability across intestinal epithelia and difficulty in formulation

GI, gastrointestinal tract.

Zhu et al. Acta Pharmaceutica Sinica B 2021;11(8)2416-48; Liu et al. Expert Opin Drug Deliv 2018;15:223-33; Durán-Lobato et al. Adv Mater 2020;32:e1901935; Smart et al. Expert Opin Drug Deliv 2014;11:1323-35.

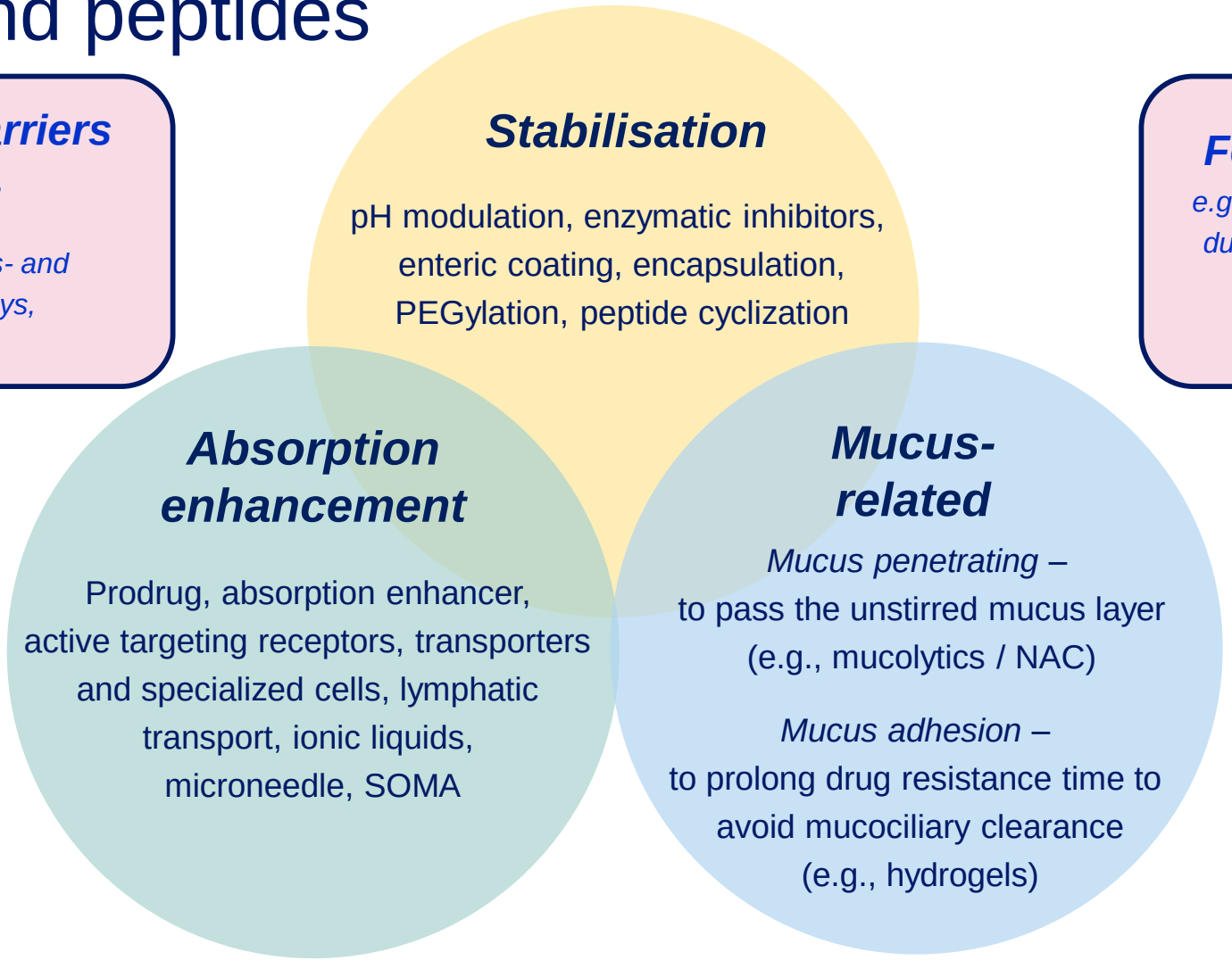
Strategies to manage the barriers for oral delivery of proteins and peptides

Physiological barriers

e.g., pH gradient, enzymes, mucus, epithelial cells for trans- and paracellular pathways, gut motility

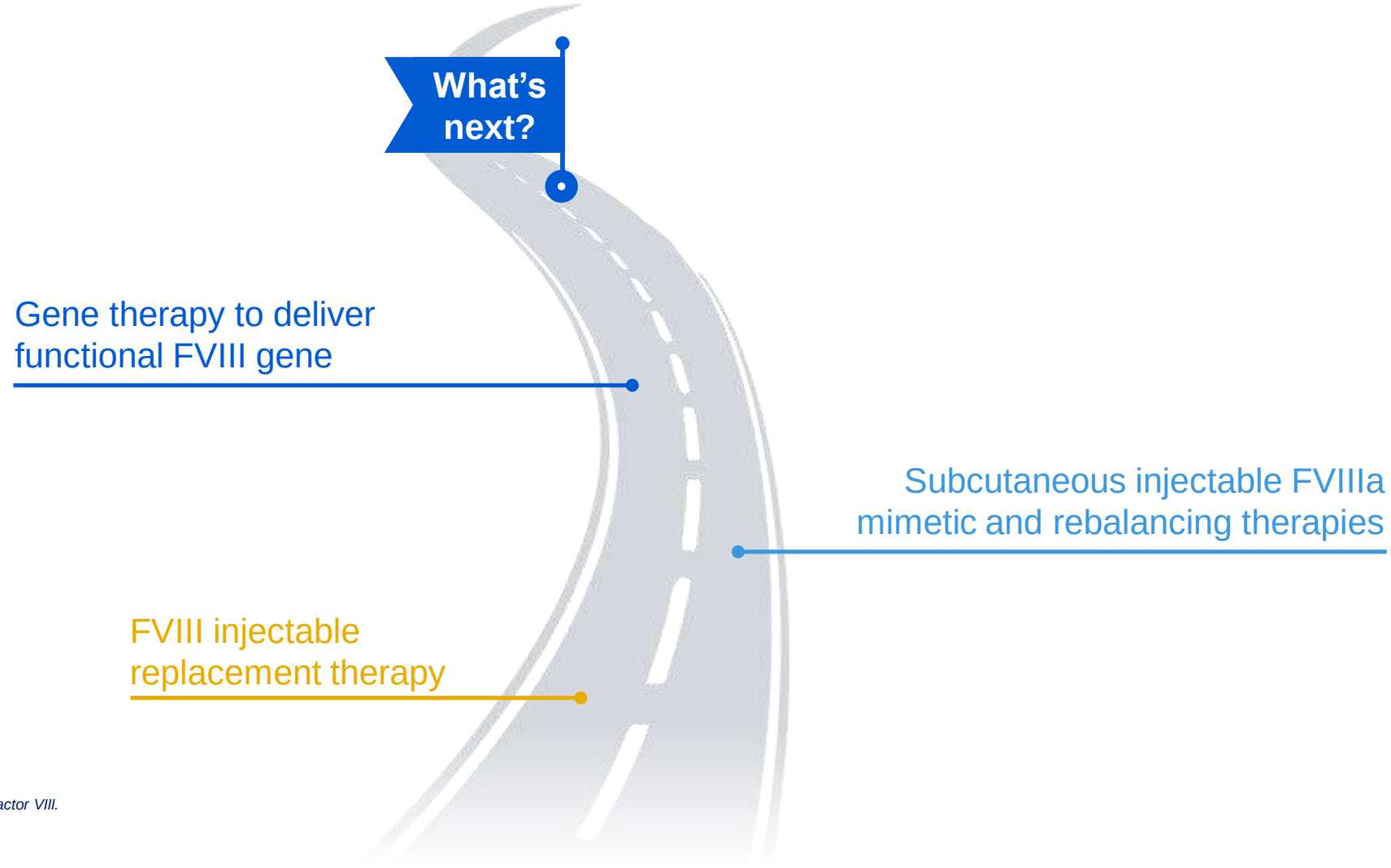
Formulation barriers

e.g., chemical and physical stability during the manufacturing process, transportation, storage and administration



Modified from Zhu et al. Acta Pharmaceutica Sinica B 2021;11(8)2416-48. NAC, N-acetylcysteine; PEG, polyethylene glycol; SOMA, self-orienting millimetre-scale applicator.

Oral treatment of haemophilia A as a next treatment frontier?



FVIII, factor VIII; FVIIIa, activated factor VIII.

Previous non-factor-based attempts for oral treatment in haemophilia

2007

- **AV513** was a select fucoidan, a sulfated polysaccharide of botanical origin that inhibited TFPI activity and accelerated clotting of human haemophilia A and B plasma[1]
  - AV513 was well tolerated by the dogs without any adverse events

2020

- **PTC124** for nonsense-mutation-caused haemophilia
  - Chemical compound to induce ribosomal readout beyond nonsense mutation
  - Study was terminated early due to sponsor decision and not reflective of adverse safety findings[2]

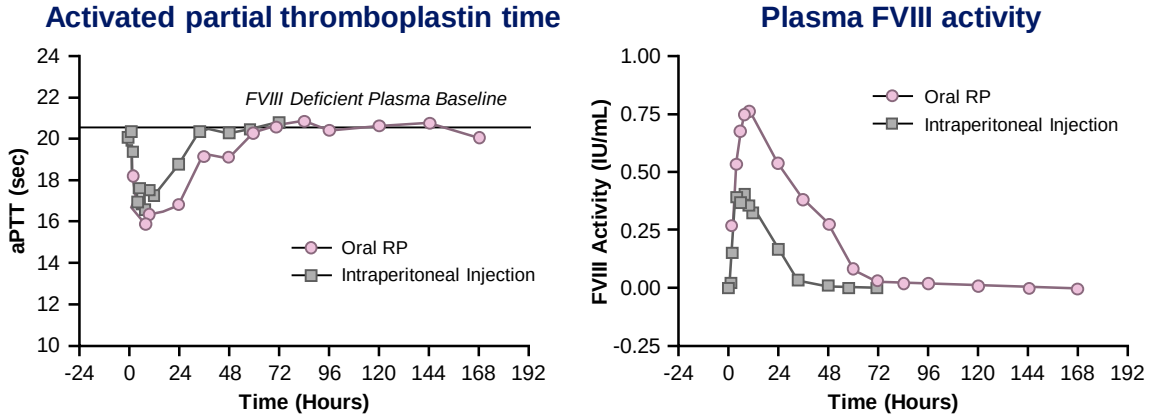
TFPI, tissue factor pathway inhibitor.
1. Prasad et al. Blood 2007;111(2):672-9; 2. NCT00947193 ClinicalTrials.gov.

Previous factor-based attempt for oral treatment in haemophilia

2019–2021

- A **dry powder formulation** suitable for oral administration for FVIII via a robotic pill was successfully developed
  - The key injectable element of the robotic pill was its drug payload (FVIII) formed as a solid microtablet of precise dose sealed inside a hollow, dissolvable microneedle[1]
  - In-life proof-of-concept studies in haemophilia A models in dogs showed similar PK/PD results to intraperitoneal injection of FVIII and no adverse events were noted through the study[2]

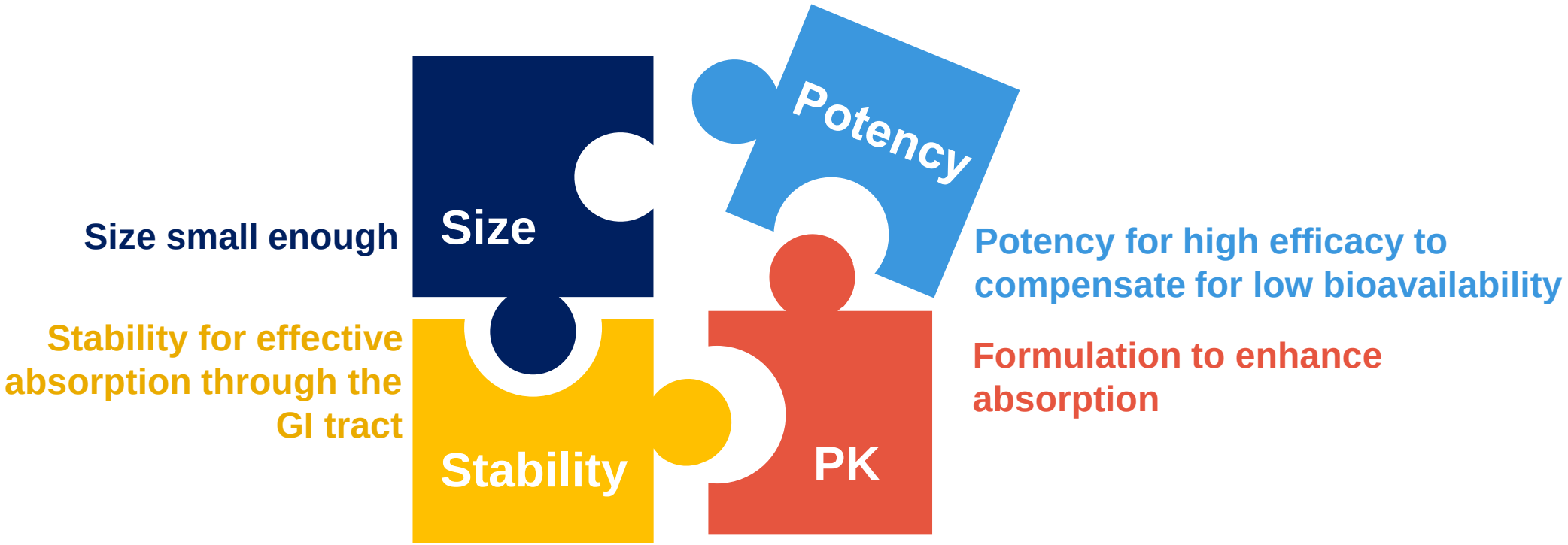
Time-course in two dogs with haemophilia A following oral robotic pill administration (Dog 1) *vs.* direct intraperitoneal injection of FVIII (Dog 2; ~150 IU/kg)



aPTT, activated partial thromboplastin time; FVIII, factor VIII; FVIIIa, activated factor VIII; PD, pharmacodynamic; PK; pharmacokinetic; RP, robotic pill.

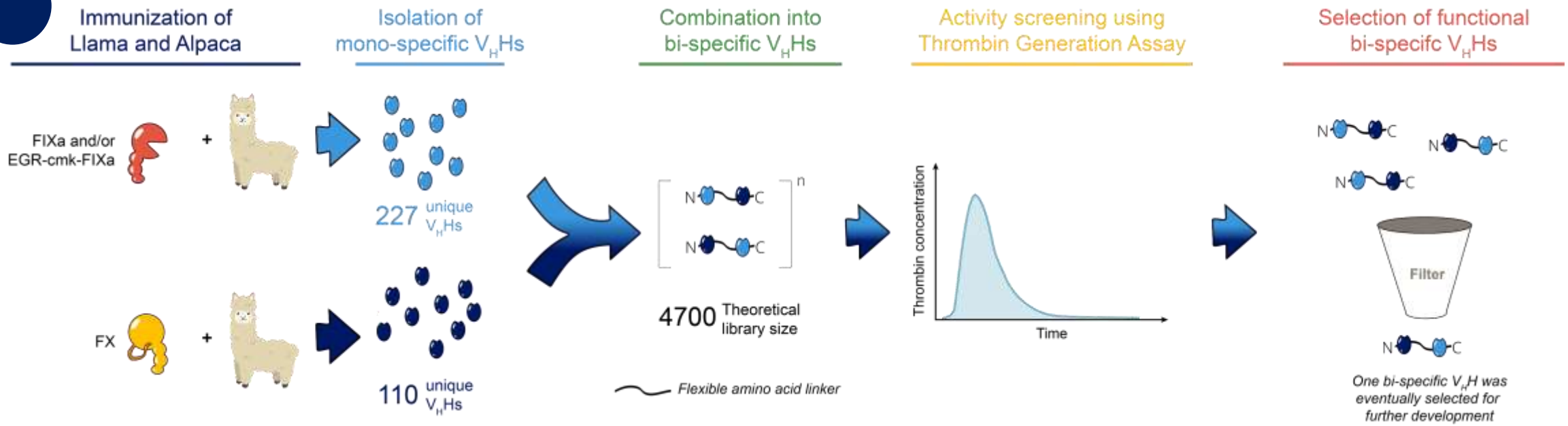
1. Schenk et al. ISTH 2019, OC60.5; 2. Hashim et al. ISTH 2021, OC48.4.

Could a FVIIIa mimetic bi-specific binder fulfil the criteria for an oral haemophilia drug?



Size

The development of a novel FVIIIa mimetic molecule based on camelid V_HH domains



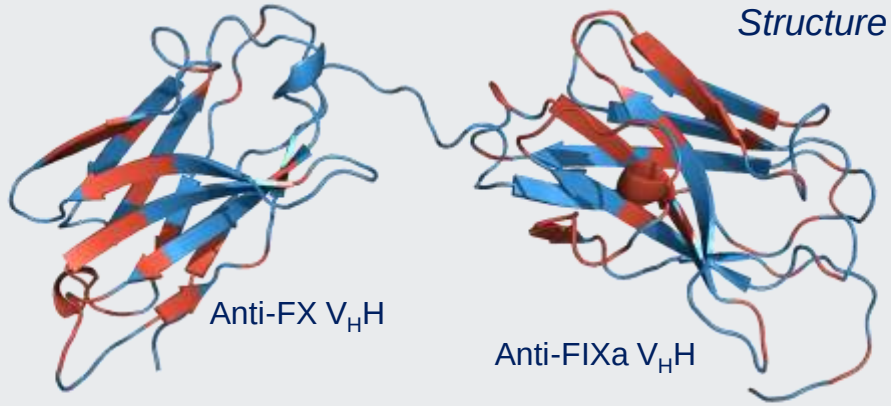
I. Unique anti-FIXa and anti-FX mono-specific V_HH domains were identified
II. Selected V_HH domains were used to make several libraries with bi-specific V_HHs
III. Bi-specific V_HHs were screened for activity (FX-activation rate and thrombin generation assay)
IV. 6 unique, bi-specific V_HHs were selected for initial optimisation
V. One molecule was selected for further optimisation and development

Lund et al. Res Pract Thromb Haemost 2024;8(Suppl 2):e102503.

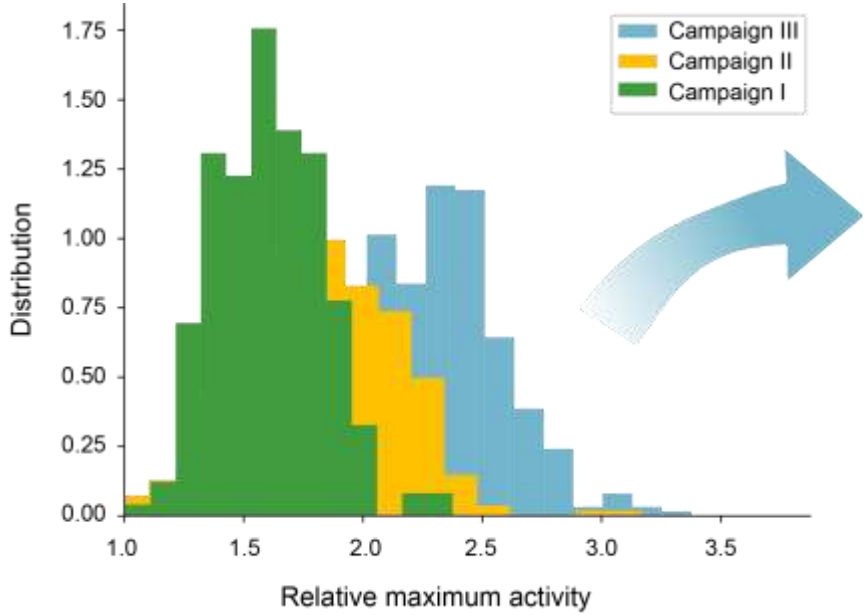
Size

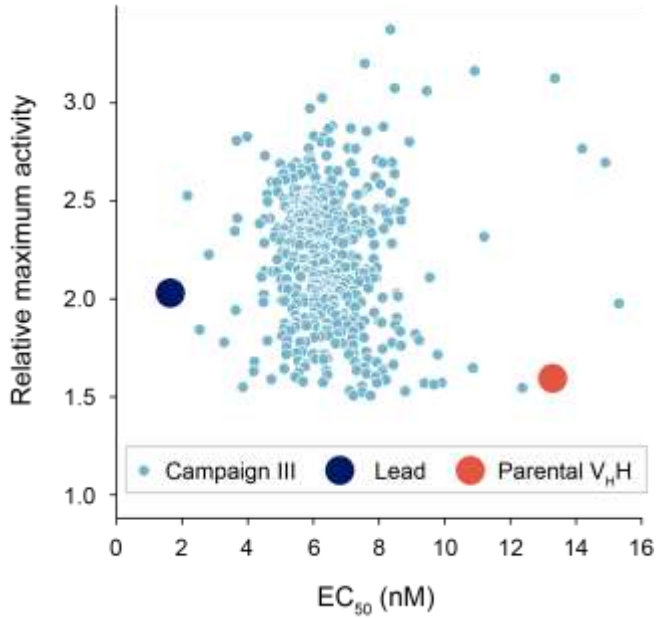
Molecular optimisation of bi-specific V_HHs by mutagenesis aimed for high potency

Structure model of bi-specific V_HH



Red residues: Positions investigated during mutagenesis optimisation

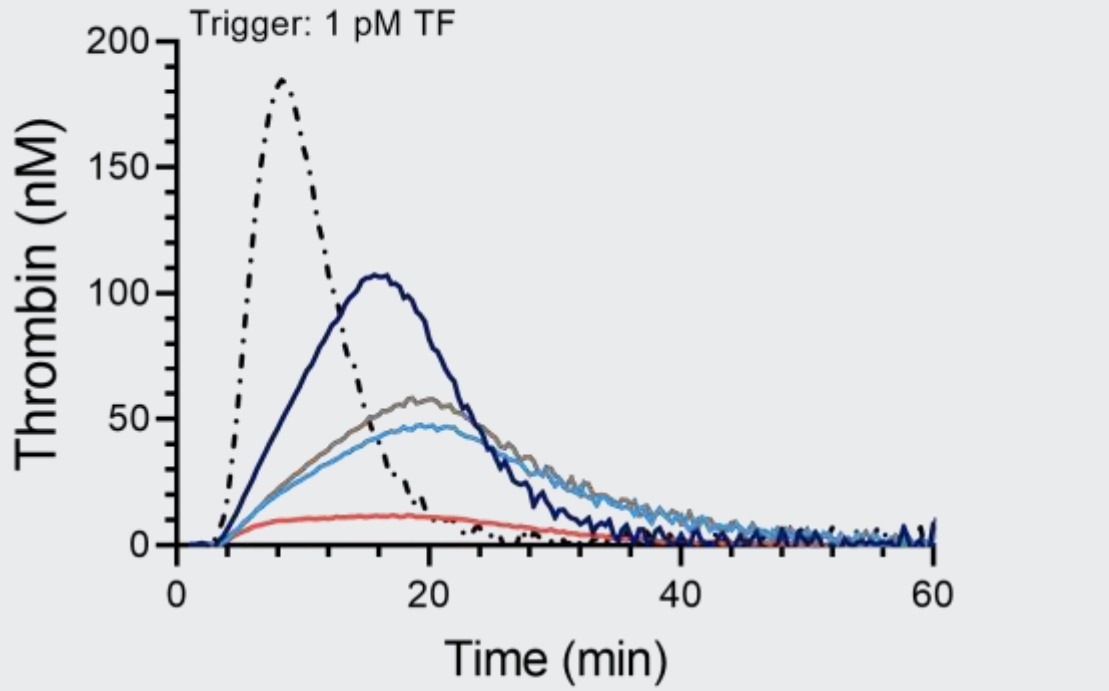


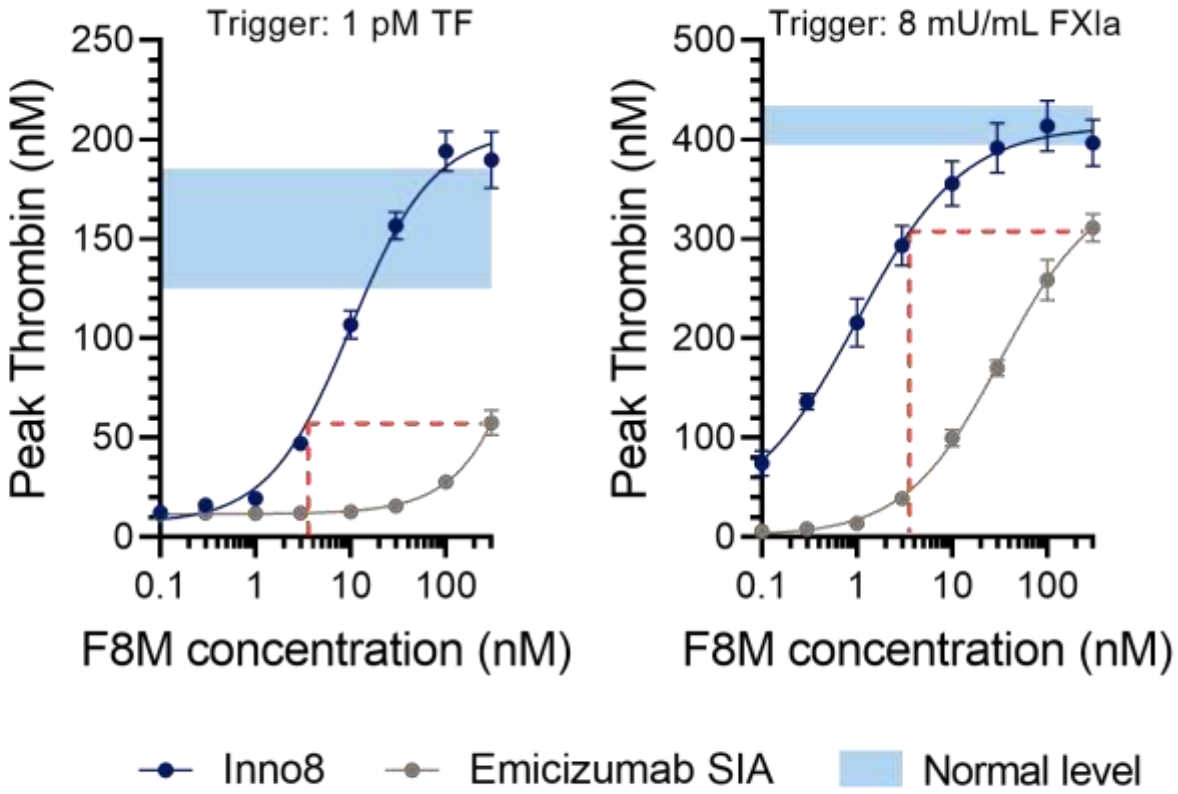


*Bi-specific V_HH screening based on **high throughput Thrombin Generation Assay** with 1 pM Tissue Factor trigger. Potency estimated from 8-point dilution series.*

Potency

Inno8 achieved similar *in vitro* effect as emicizumab SIA at ~90 fold lower molar concentrations





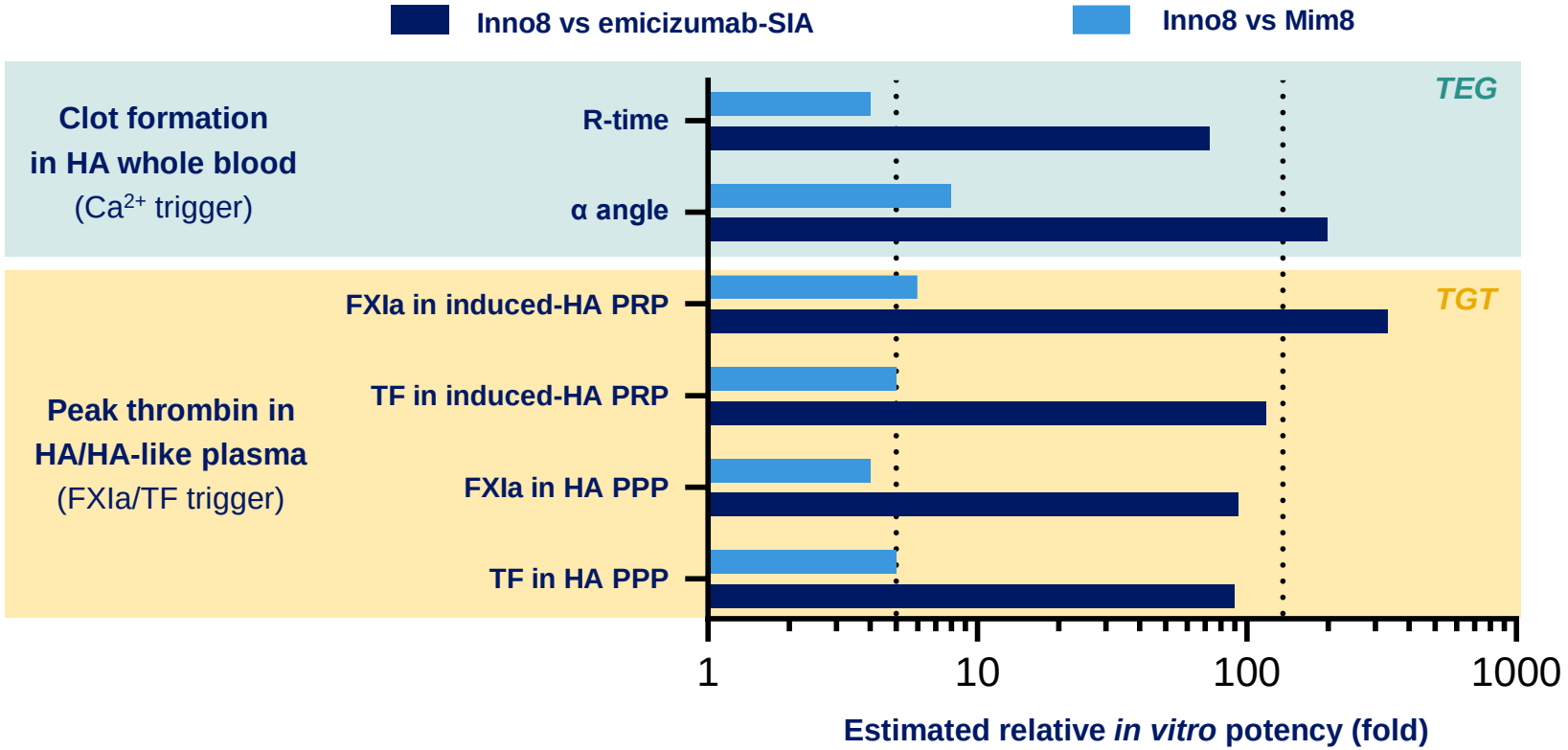
The effect of FVIIIa mimetics on in vitro thrombin generation does not necessarily translate directly to clinical efficacy.
F8M, FVIIIa mimetic; HA, haemophilia A; SIA, sequence identical analogue; SD, standard deviation.

Potency

Inno8 showed high *in vitro* potency enabling oral formulation

- Despite differences in observed EC_{50} values obtained with the different assay conditions, the potency comparison between FVIIIa-mimetic compounds appeared consistent across assays
- Inno8 was found to be more potent compared with:
  - Emicizumab SIA by 89.7–117.6 fold
  - Mim8 by 5.0–5.5 fold

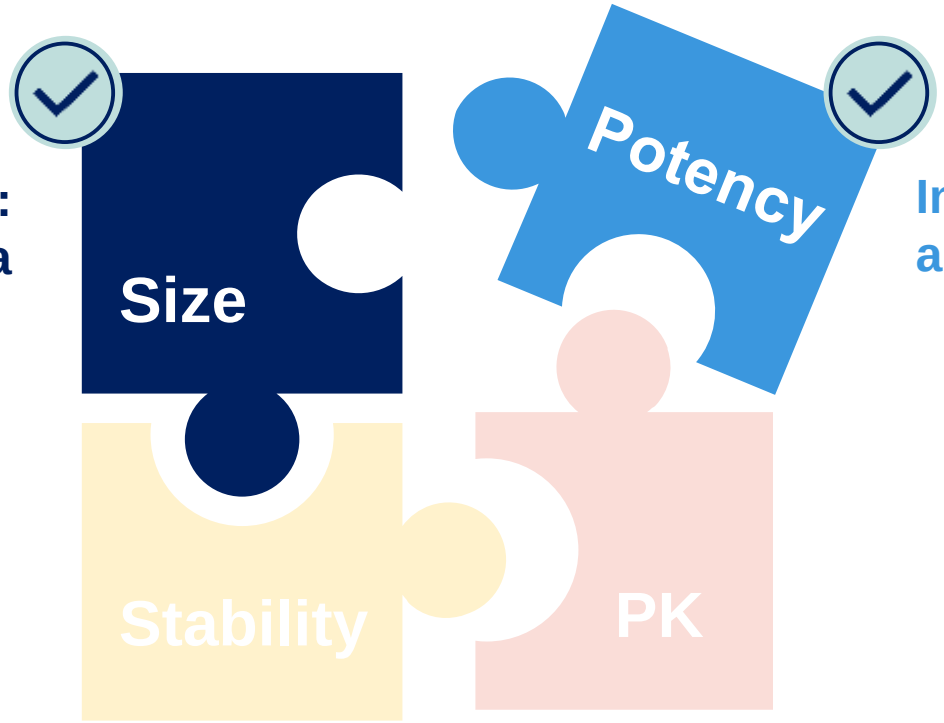
TF-triggered assays



R-time is defined as time to 2 mm amplitude of the TEG-trace. EC_{50}, half maximal effective concentration; FVIIIa, activated factor VIII; FXIa, activated factor XI; PPP, platelet-poor plasma; PRP, platelet-rich plasma; SIA, sequence-identical analogue; TEG, thromboelastography; TF, tissue factor; TGT, thrombin generation test.

Inno8 – A novel FVIIIa mimetic bi-specific binder

Molecular size of Inno8: approx. 30 kDa

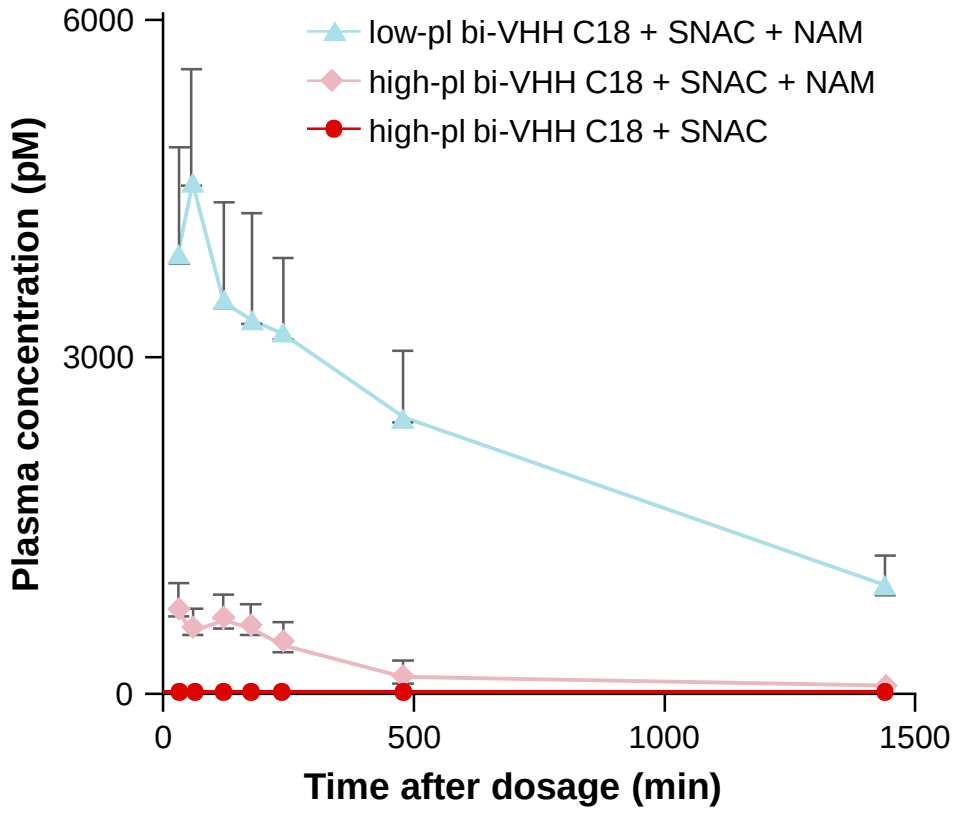


Inno8 is more potent than Mim8 and emicizumab

Stability of Inno8 was achieved by adapting the isoelectric point (pI)

- Oral bioavailability studies showed distinct exposure levels for bi-VHH variants
  - pI lowered by changing surface-exposed amino acids
  - A low-pI variant demonstrated significantly higher exposure than high-pI variants (SNAC and Niacinamide enhances solubility)

➡ With low-pI, Inno8 is less likely to unfold or degrade before absorption

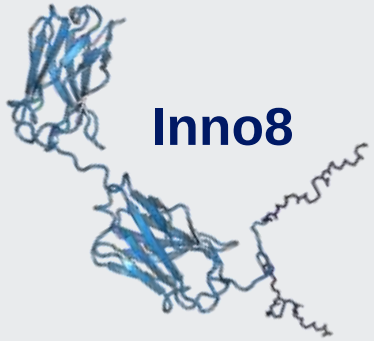


Graph depicts mean ± standard error (n=6). NAM, Niacinamide; pI, isolectric point; SNAC, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate; VHH, variable heavy domain of heavy chain.

Stability

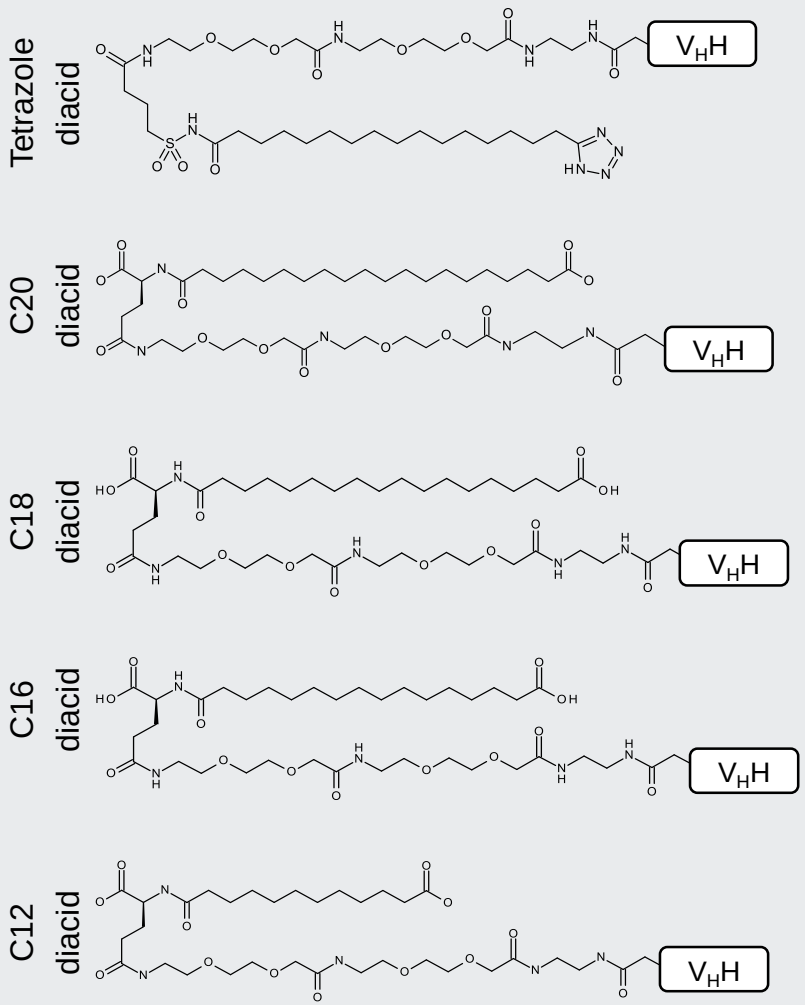
Inno8 – A novel FVIIIa mimetic bi-specific binder

Optimisation of the plasma half-life through well-established protraction technology promoting albumin binding

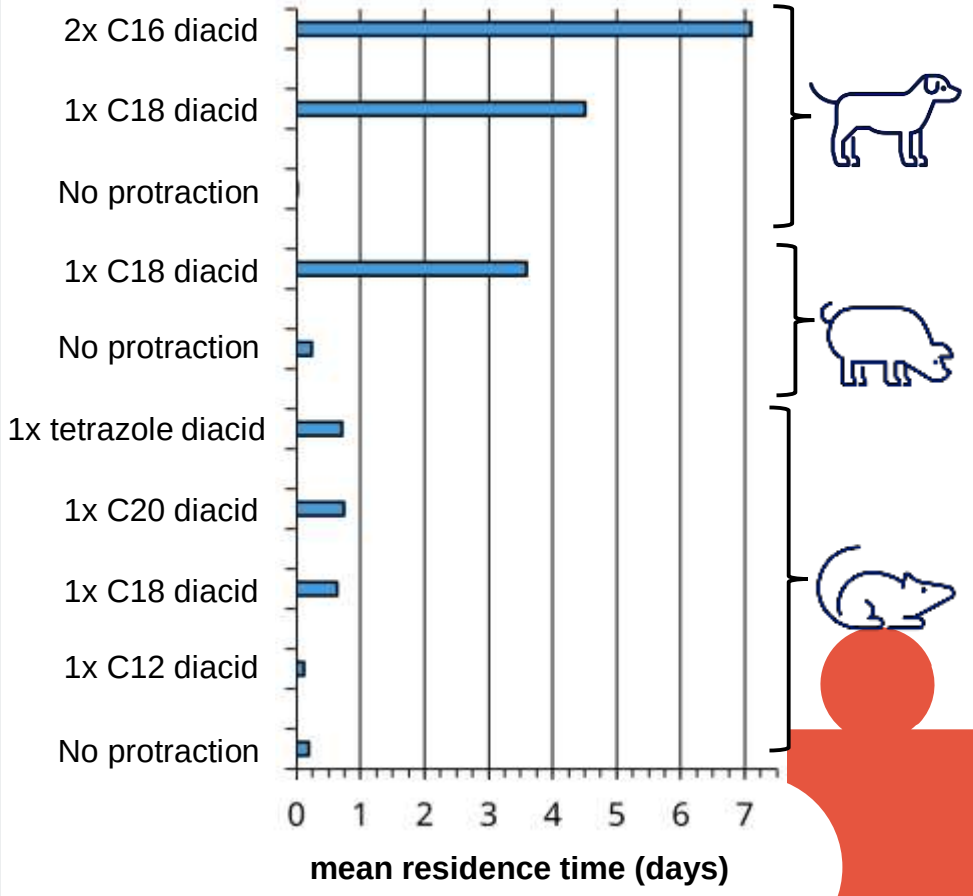


Inno8

Protraction technology that promotes albumin binding was required for Inno8 as the molecule does not have an Fc domain, making the half-life short



Plasma half-life following i.v. injection

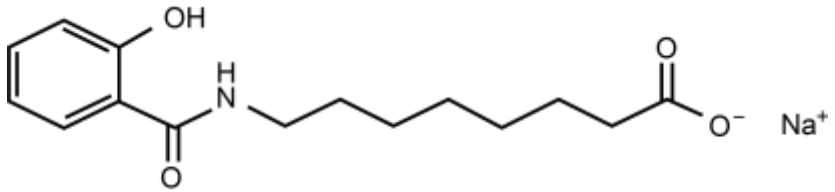


PK optimisation screening to select the optimal fatty acid linker to promote albumin binding and prolonged plasma half-life. Fc, fragment crystallisable region; i.v., intravenous.

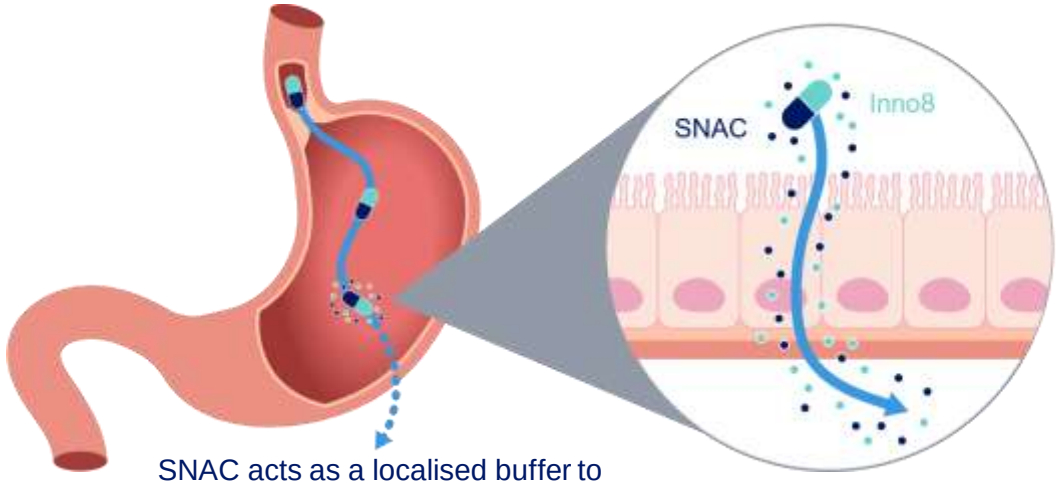
PK

Oral delivery of peptides can be achieved using the SNAC absorption enhancer

SNAC Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate[1]



- SNAC, a small fatty acid derivative, is an absorption enhancer
- Mechanism of action have been studied using semaglutide[2]
- The available data for other peptides co-formulated with SNAC support that **absorption takes place in the stomach** in a localised buffered environment
- The effect is strictly time-dependent and occurs primarily **via transcellular route**



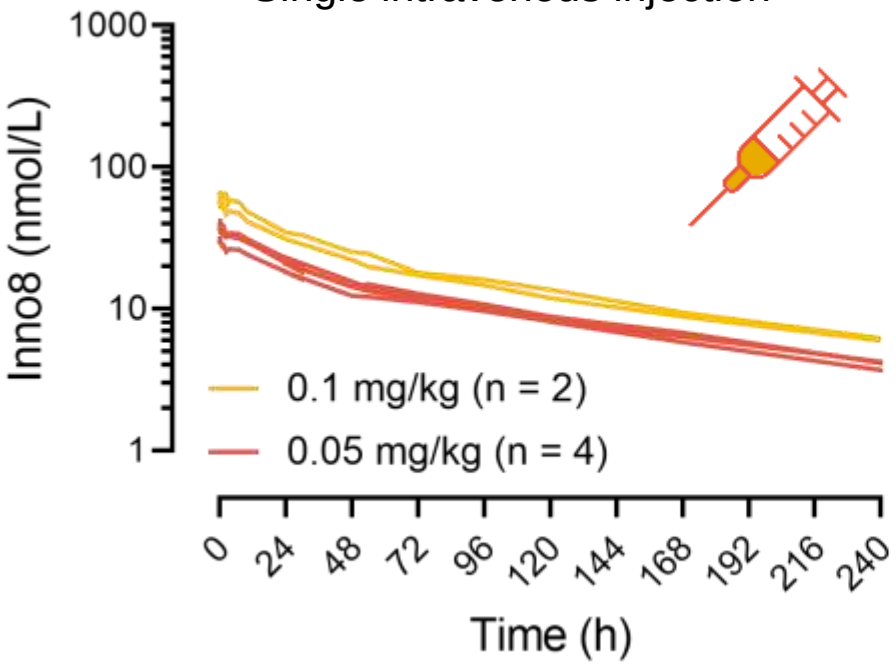
SNAC acts as a localised buffer to neutralise the pH around the drug, stabilising and protecting it from degradation by gastric enzymes

PK

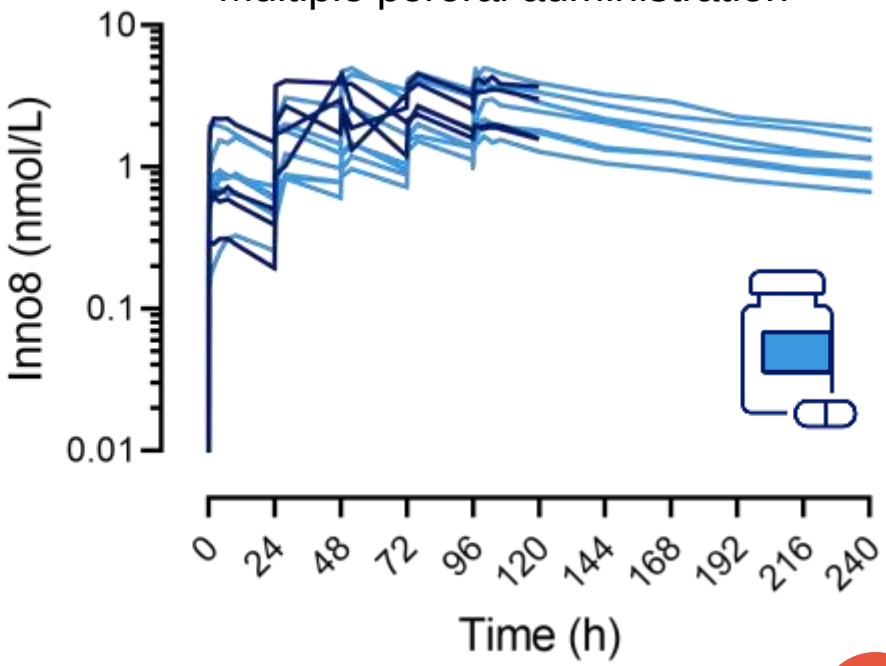
PK, pharmacokinetic; SNAC, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.
1. Buckley et al. Science Translational Medicine 2018; 10(467): eaar7047. 2. Lund et al. RPTH 2024. 22–26 June (OC 21.1).

Inno8 has a long terminal plasma half-life and can be administred orally using SNAC co-formulation

Single intravenous injection



Multiple peroral administration



Inno8 had a 115 h terminal half-life in beagle dogs (based on intravenous dosing study)

Repeated daily oral dosing of Inno8 reduced the exposure variability in beagle dogs

Variation in $AUC_{0\text{-}24h}$

After 1st dose: 62.1 CV%

After 5th dose: 37.4 CV%

PK

AUC, area under the curve; CV, coefficient of variation; SNAC, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.

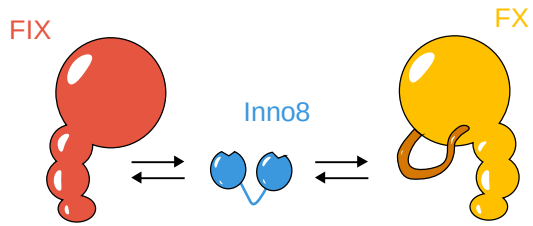
Inno8 – A novel FVIIIa mimetic bi-specific binder

- ✓ **SNAC absorption enhancer for oral bioavailability**
- ✓ **Albumin binding for long terminal plasma half-life**

Inno8 – Mechanism of action

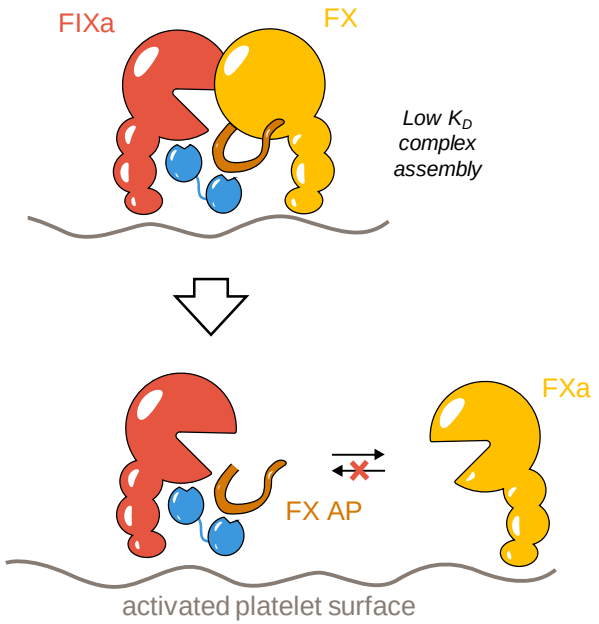
In solution

Minimal interaction with FIX and FX



On procoagulant phospholipid surface

Efficient assembly of FIXa and FX on the surface of activated platelets, stimulation of FIXa procoagulant activity and immediate release of FXa



FIXa, activated factor IX; FVIIIa, activated factor VIII; FX, factor X; FXa, activated factor X.
Lund et al. Res Pract Thromb Haemost 2024;8(Suppl 2):e102503.

Conclusion

- Extensive research focusing on novel technologies for oral administration of proteins and peptides has been conducted over the last decade
- For oral treatment to be viable and effective, several drug aspects need to be considered and balanced including size, stability, potency, adsorption and mucus-related properties
- Oral treatment of haemophilia seems feasible using both factor and non-factor-based approaches, but several issues remain to be addressed
- Inno8, a novel FVIIIa mimetic bi-specific binder, seems to balance the required aspects for an oral haemophilia drug – currently being evaluated in phase 1 clinical studies for the management of haemophilia A with and without inhibitors

Thank you for your attention

- *The data on Inno8 was kindly provided by Novo Nordisk A/S, Bagsværd, Denmark and discussed with Jacob Lund and Damaris Bausch-Fluck*
- *Medical writing support was provided by Ashfield MedComms GmbH (Mannheim, Germany), an Inizio company*