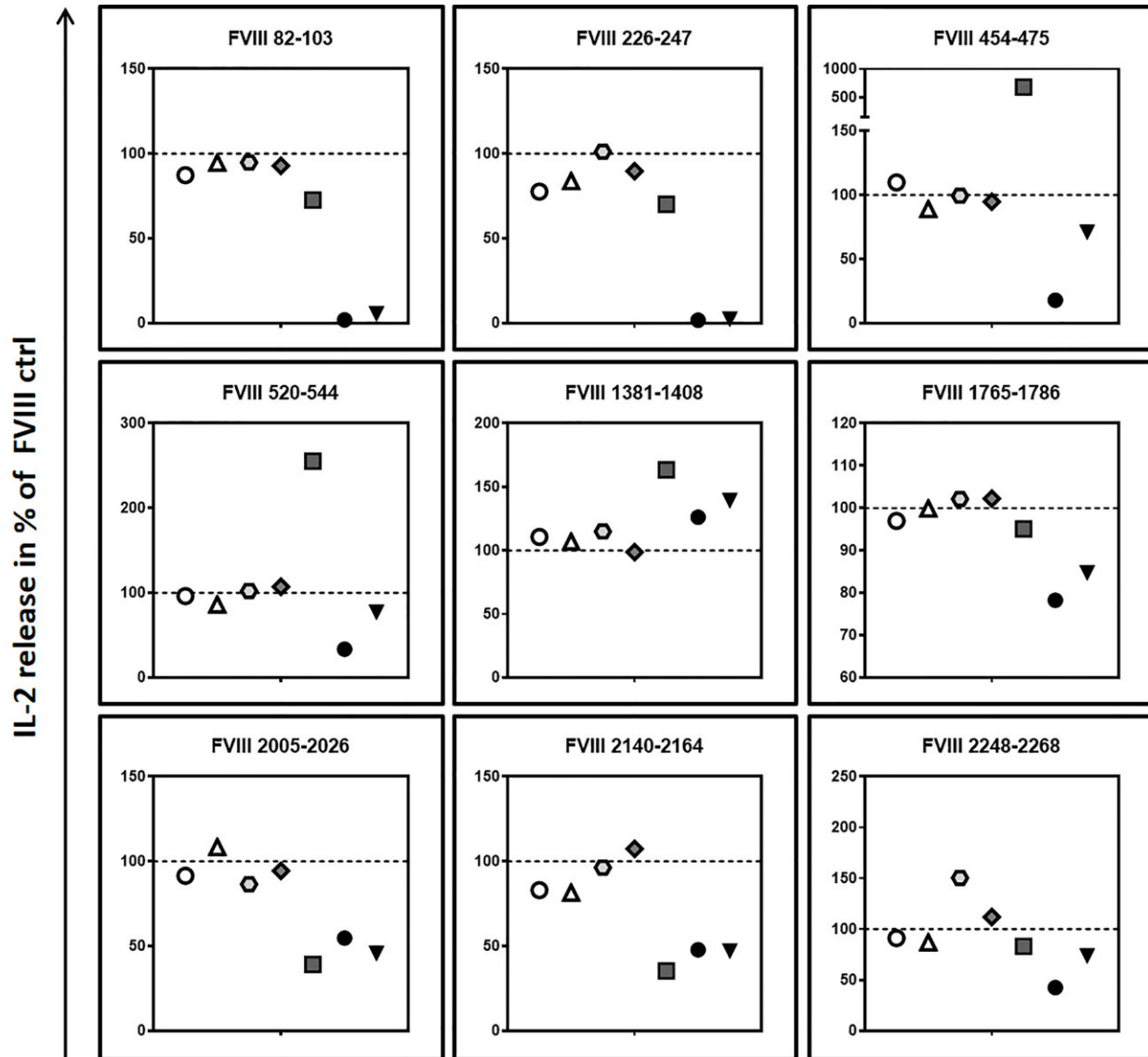


New hemophilia insights could minimize or eliminate side effects in the future

November 22 2022



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| <p>10U FVIII +</p> <ul style="list-style-type: none"> ○ 10µg/mL aMR antibody △ 2mg/ml Mannan ⬡ 14,4 µg/mL LRPAP1 ◇ 5,5mM Galactose ■ 100µg/mL Heparin ● 5mM EDTA ▼ 1,25mM EDTA | <p>Endocytosis receptors</p> <ul style="list-style-type: none"> Mannose receptor LRP/LDLR/vLLDR ASGPR HSGPR Ion-dependent receptors |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Blocking endocytosis receptors during preincubation of APCs modulates presentation of FVIII-derived peptides and subsequent stimulation of FVIII

peptide-specific CD4⁺ T cells hybridoma clones. APCs were preincubated with specific blocking agents for endocytosis receptors which are associated with the endocytosis of FVIII: 5mM Galactose to block the asialoglycoprotein receptors (ASGPR); 100µg/mL Heparin to block heparan sulfate proteoglycans (HSGP), 2mg/mL Mannan or 10µg/mL of a specific monoclonal antibody to block the Mannose Receptor, 14.4 µg/mL recombinant mouse LRPAP1 to block the low-density lipoprotein receptor–related protein-1 (LRP1), 1.25mM and 5mM EDTA to inhibit the function of bivalent ion-dependent receptors. After 3hrs incubation, APCs were washed and subsequently cocultured with FVIII specific CD4⁺ T cell hybridoma clones covering the 9 CD4 T-cell epitopes recognized by the hybridoma library. Relative IL-2 release as an indicator for the activation of hybridoma clones in relation to the normal FVIII control (100%) is presented. Depicted is the mean value derived from 2 independent experiments done in triplicates (n=6). Credit: *Frontiers in Immunology* (2022). DOI: 10.3389/fimmu.2022.975680

Immune responses against Factor VIII, which is used to treat hemophilia A (bleeding disorder), are influenced by the microenvironment of antigen presenting cells. This is the result of a scientific study conducted in cooperation between the Institute Krems Bioanalytics of IMC University of Applied Sciences Krems and the international pharmaceutical company Takeda, which was recently published in the journal *Frontiers in Immunology*.

In this study, a cell culture model was used to investigate the impact of the microenvironment on factor VIII uptake and processing in antigen presenting cells. The observed alterations in protein processing might have profound effects on immune responses to FVIII. The novel data provide the basis for the development of future FVIII therapies that elicit minimal immune responses in patients.

Hemophilia A is a hereditary bleeding disorder caused by absence or

deficiency of active clotting factor VIII (FVIII) in the blood. Patients are therefore treated with FVIII replacement therapy.

A major complication of this therapy is the development of a neutralizing immune reaction in 30% of the patients, thereby rendering the administered FVIII ineffective. Why such a complication occurs in some people while others are spared is not yet clear—and it is precisely this issue that the research group from Takeda and IMC Krems led by Dr. Christian Lubich set out to address.

Adverse immune response

"The experimental design of our cell culture study," Dr. Lubich stated, "was aimed at taking a closer look at the response of different immune cells in the context of FVIII administration and thereby gaining better insight into the underlying processes."

And indeed, the study data suggest a crucial link between the specific microenvironment during FVIII uptake by specific immune cells—so-called antigen-presenting cells (APCs)—and the FVIII proteins (antigens) presented by these cells on their [cell surface](#). Depending on the microenvironment, the composition of these surface proteins differs and thus also influences the specificity of the subsequently activated CD4+T [cells](#), partly resulting in the undesired neutralizing [immune response](#).

New technology

To verify the relevance of the data in vivo as well, it would now be useful to conduct a follow-up study in humans. Dr. Lubich and his team at the Institute of Krems Bioanalytics already have an idea for this, based on a [promising new technology](#): "Immunopetidomics is a pioneering

method for investigation of the composition and dynamics of proteins presented by [antigen-presenting cells](#) with the aid of mass spectrometry."

"This method can be used, for example, to determine peptides of a pathogen, a tumor cell or, as in this case, a biotherapeutic agent that elicit an immune response. This platform will therefore not only help to better understand adverse reactions of the immune system to biotherapeutics, but will also enable the identification of important antigens for the development of immunotherapies."

More information: Christian Lubich et al, Modulating the microenvironment during FVIII uptake influences the nature of FVIII-peptides presented by antigen-presenting cells, *Frontiers in Immunology* (2022). [DOI: 10.3389/fimmu.2022.975680](https://doi.org/10.3389/fimmu.2022.975680)

Provided by IMC Krems

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