

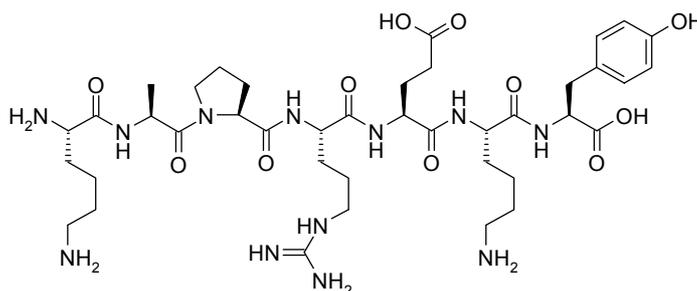
## CONFORMATIONALLY CONSTRAINED ANALOGUES OF THE hFcεRIα STALK PEPTIDE KAPREKY

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The signaling of mast cells and basophils is triggered by the binding of IgE to the  $\alpha$ -chain (Fc $\epsilon$ RI $\alpha$ ) of the high-affinity IgE-receptor followed by cross-linking with polyvalent antigen.[1] It was shown previously that the anti-human Fc $\epsilon$ RI $\alpha$ -monoclonal antibody 5H5F8 which recognizes the membrane-proximal epitope <sup>171</sup>KAPREKY<sup>177</sup> inhibits the signaling of mast cells without affecting the binding of IgE to the same receptor.[2] This epitope thus represents a novel molecular target for the modulation of Fc $\epsilon$ RI $\alpha$ -mediated cell activation.

Goal of the project described here is the generation and characterization of conformationally constrained KAPREKY analogues which mimic the secondary structure given in the corresponding part of the Fc $\epsilon$ RI $\alpha$ . These conformationally constrained KAPREKY-analogues are intended to serve as tools for studying the interaction of potential LMW binders to the KAPREKY sequence.



The poster presentation describes the design, modeling studies and the synthesis of constrained analogues of the KAPREKY peptide. Basis for the design of these mimics is an X-ray structure of the 5H5F8-Fab fragment in complex with the KAPREKY peptide. Our approach covers the introduction of modified peptide-backbones as well as the replacement of stabilizing hydrogen bonds between side chains by covalent bonds.

[1] Nadler, M.J.; Matthews, S.A.; Turner, H.; Kinet, J.-P. Signal Transduction by the High-Affinity Immunoglobulin E Receptor Fc $\epsilon$ RI: Coupling Form to Function. *Adv. Immunol.* **76**, 325 – 355, (2000).

[2] Nechansky, A.; Robertson, M. W.; Albrecht, B. A.; Apgar, J. R.; Krichek, F. Inhibition of antigen-induced mediator release from IgE-sensitized cells by a monoclonal anti-Fc $\epsilon$ RI  $\alpha$ -chain receptor antibody: implications for the involvement of the membrane-proximal  $\alpha$ -chain region in Fc $\epsilon$ RI-mediated cell activation. *J. Immunol.* **166**, 5979-5990, (2001).