

Towards a rational design of Interleukin-15 inhibitors through various molecular modelling approaches

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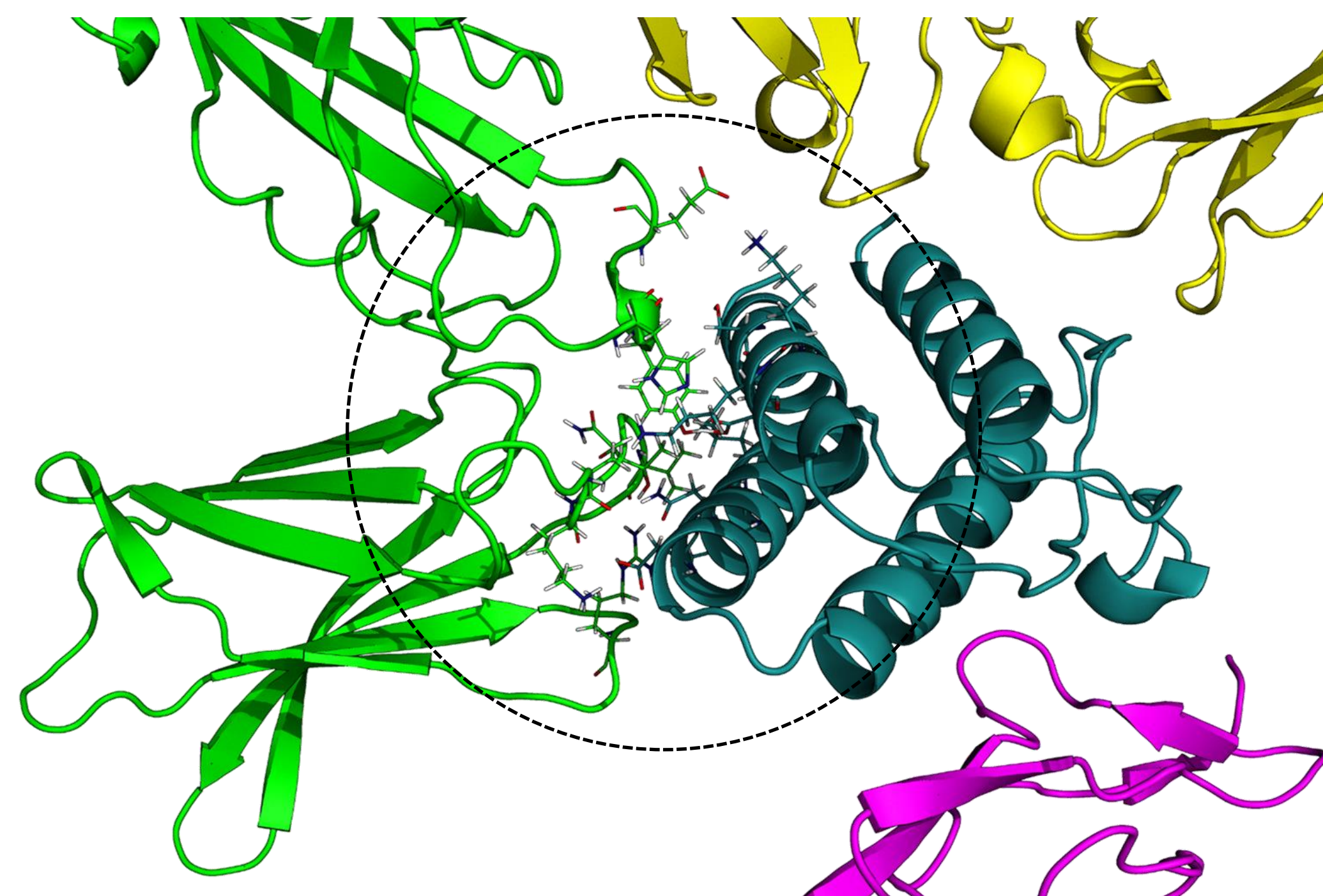
Introduction

- Interleukin 15 (**IL-15**): a tightly regulated pleiotropic cytokine involved in a plethora of different cellular functions. (1)
- IL15 structure**: based on a quaternary complex between **IL-15** and its α (**IL-15R α**), β (**IL-15R β**) and γ (**IL-15R γ**) receptors. (2, 3)

The design of ligands targeting IL-15 interfaces requires a deep knowledge of their structure and behavior

Objectives

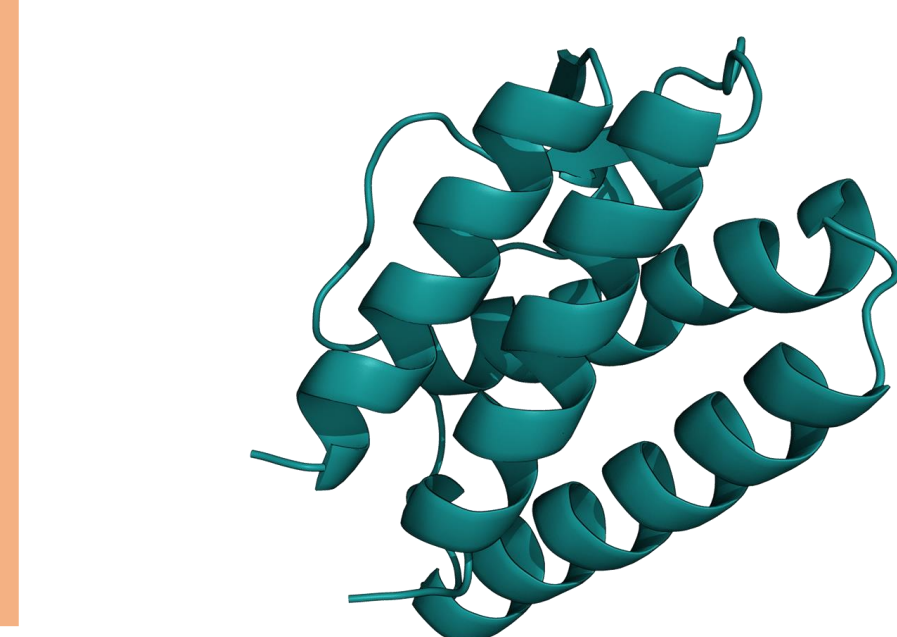
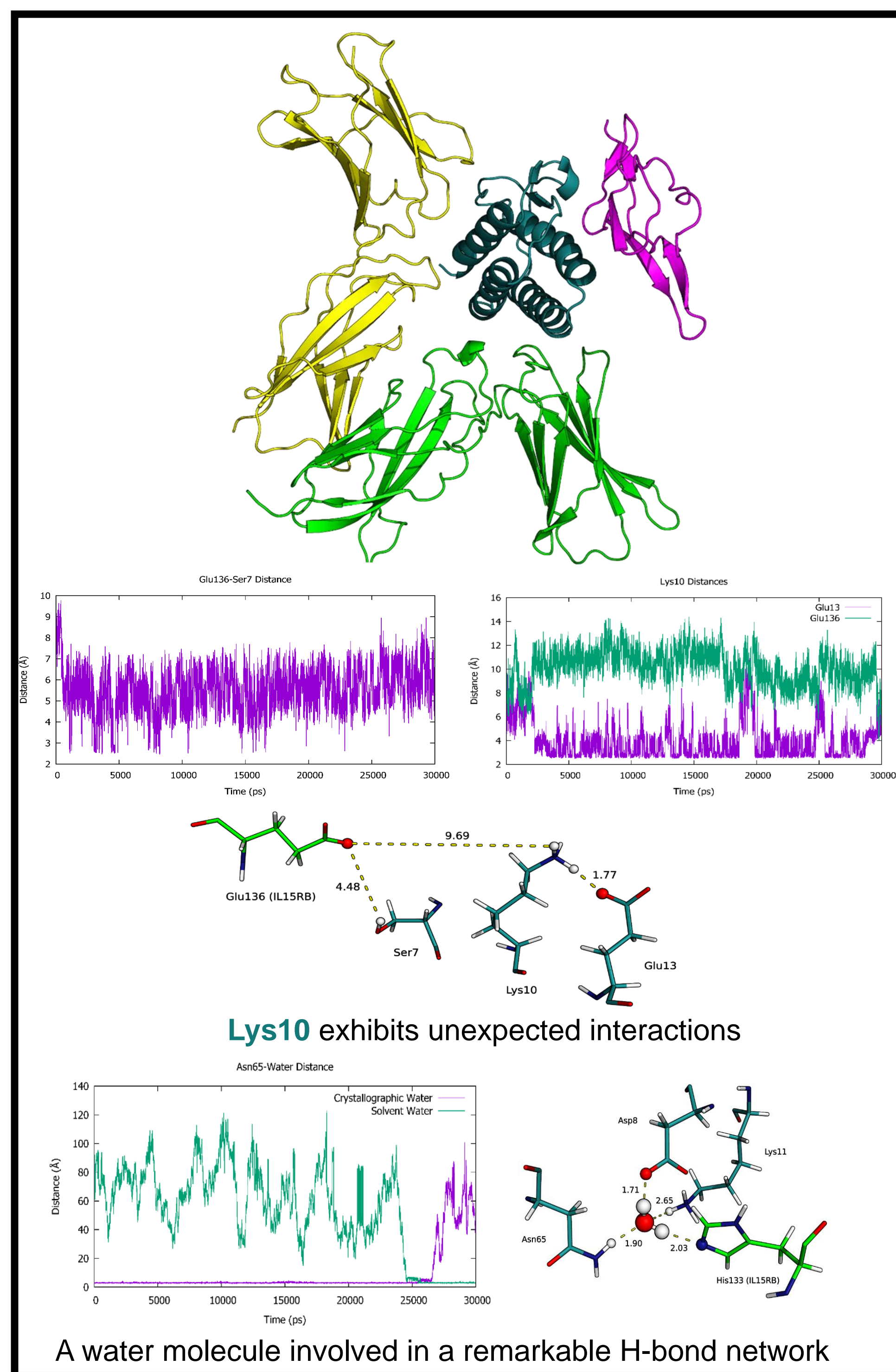
- Investigate the time related behavior of the **IL-15/IL-15R β** interface through MD simulations
- Determine the **key amino acid components** of the interface and their **interactions**.



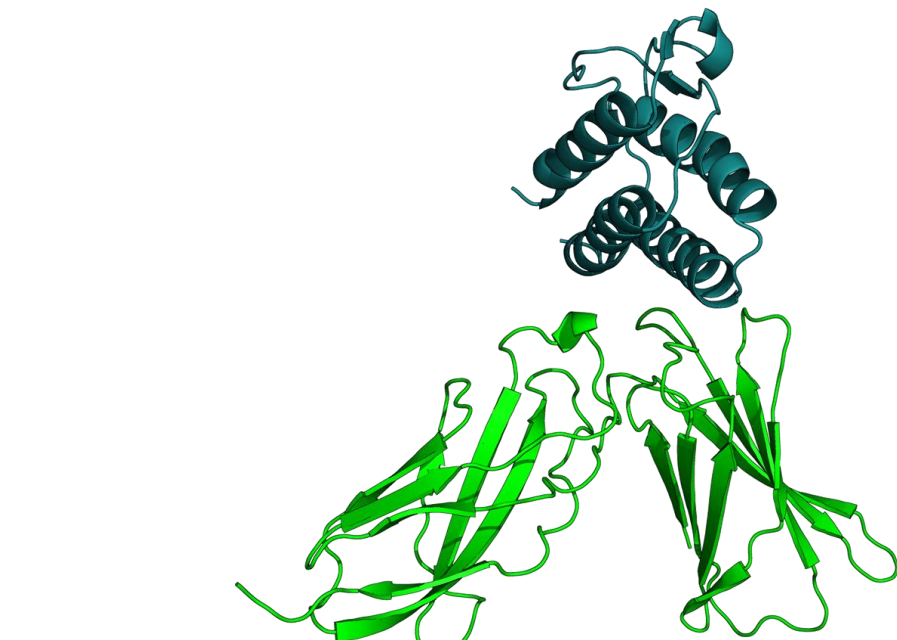
Methods

- MD simulations – NAMD (CHARMM3)
- 200 ps equilibration (NVT) followed by 30 ns production (NPT), on the different multimeric models

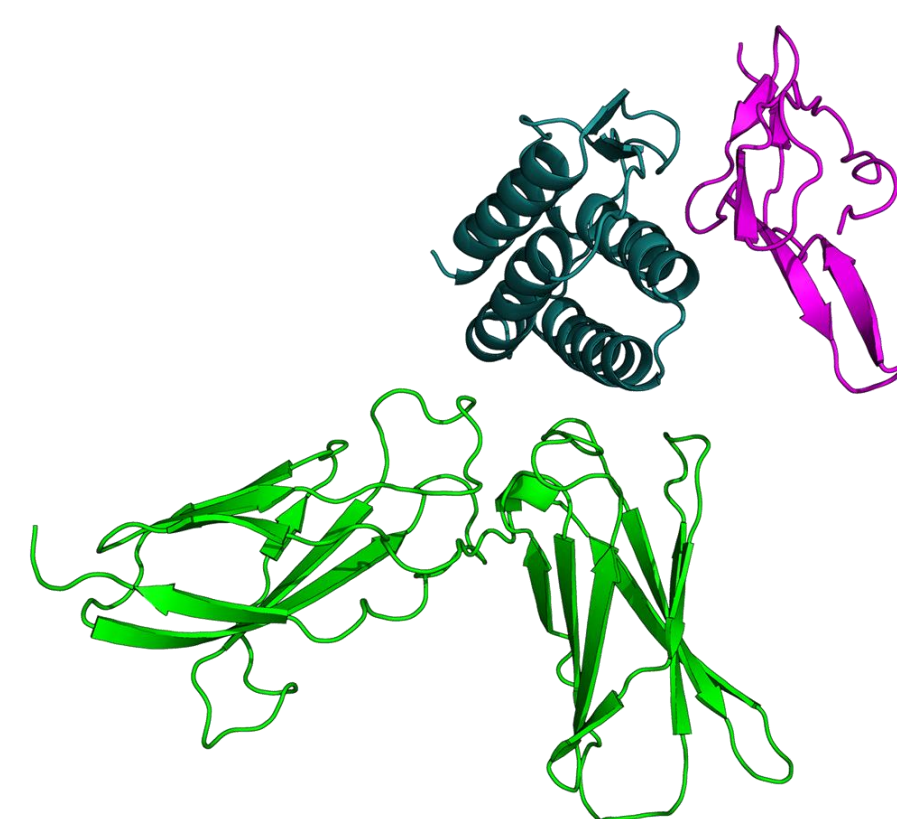
Results



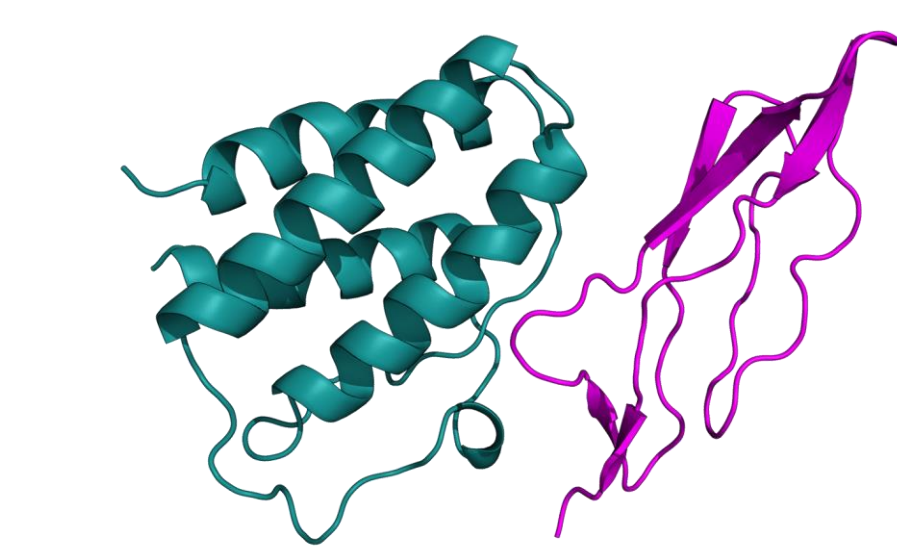
IL-15



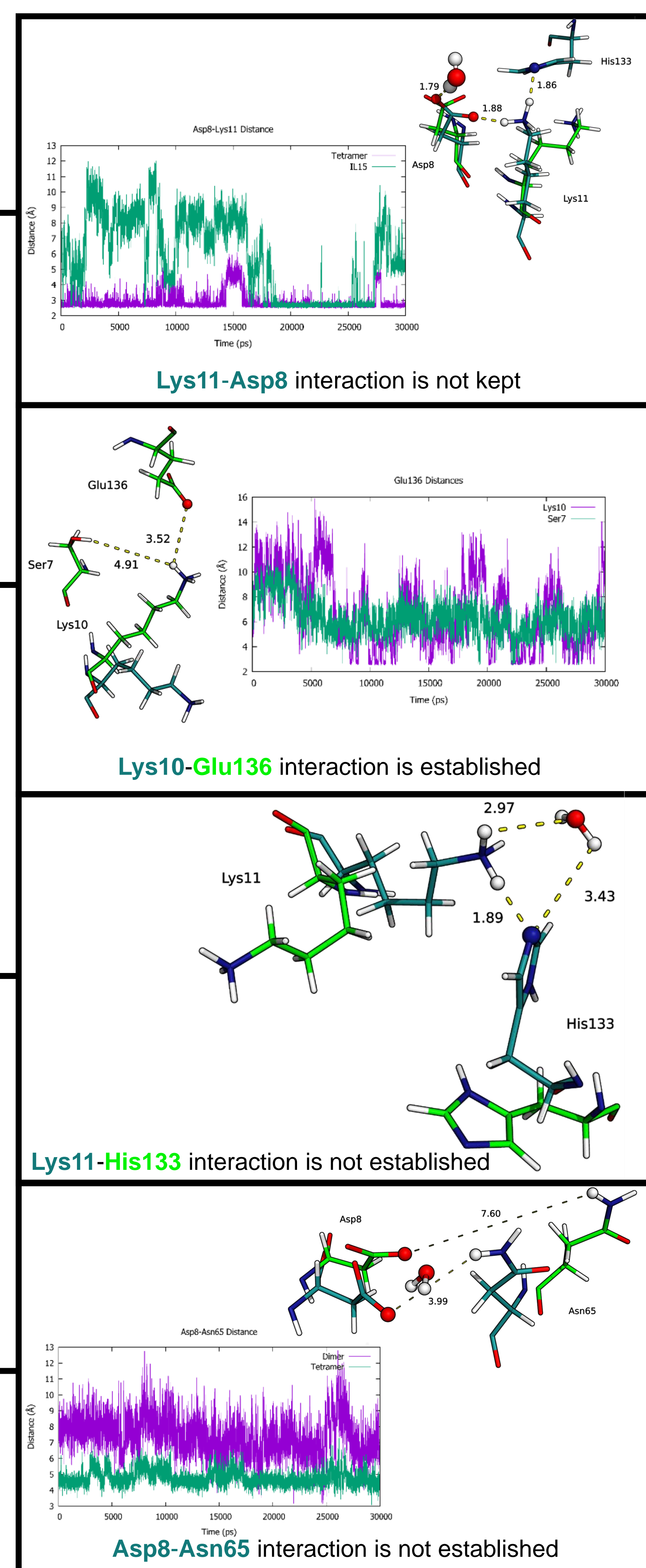
IL-15/IL-15R β



IL-15/IL-15R α /IL-15R β



IL-15/IL-15R α



Conclusions

- MD simulations allow the identification of key features not previously observed.
- The presence/absence of receptor chains directly or indirectly influences the structural features of the **IL-15/IL-15R β** interface.

Work in progress

- Analyses of the other IL-15/receptor interfaces.
- Study of relevant mutants to probe the influence of key residues in the features of the different interfaces.

References

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