IDENTIFICATION OF PUTATIVE ORTHOSTERIC AND ALLOSTERIC BINDING SITES OF INTERLEUKIN-33 USING EXTENSIVE MOLECULAR DYNAMICS SIMULATIONS

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Introduction

Interleukin (IL)-33 plays a pivotal role in inflammatory and autoimmune diseases through its protein-protein interaction (PPI) with the ST2 receptor. Targeting this interaction holds promise for disease management. Although the IL-33/ST2 complex crystal structure has been resolved for nearly a decade, no comprehensive investigations into the druggability of IL-33 have been conducted. Furthermore, while several IL-33 inhibitors have been reported, their binding mechanisms have predominantly relied on rudimentary molecular docking approaches.

Objective

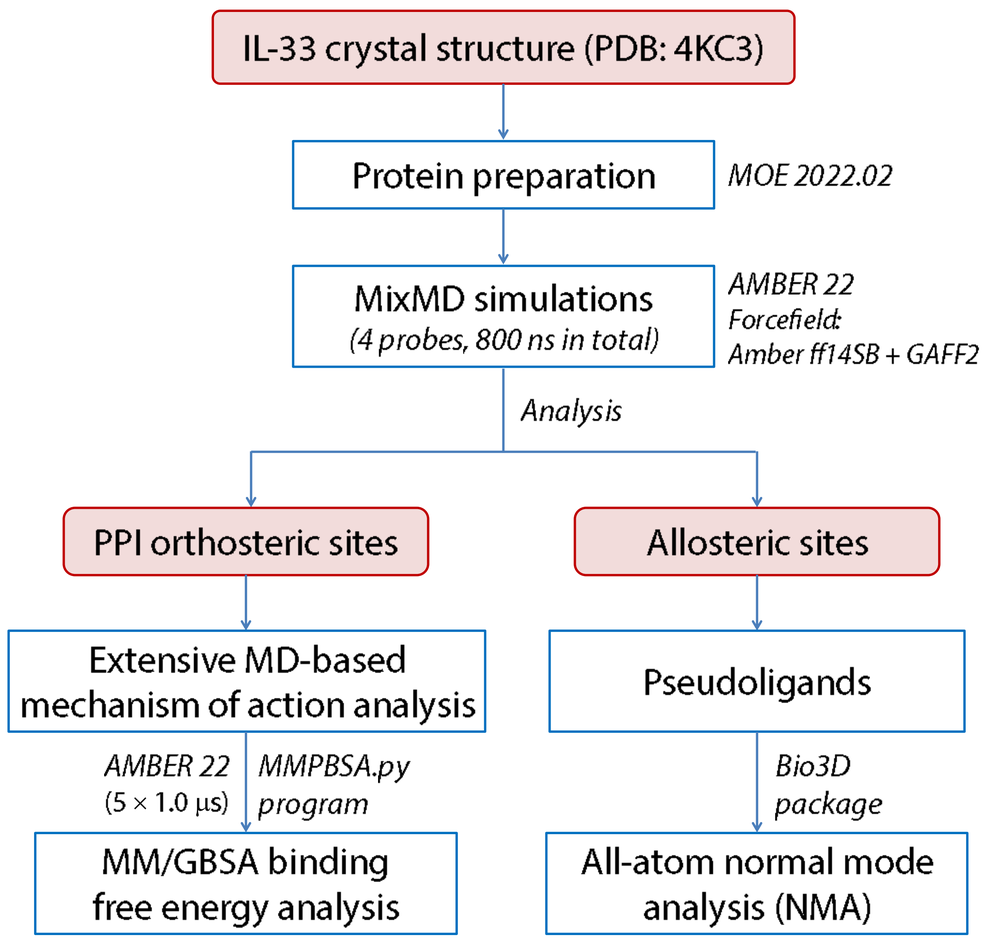
To identify possible druggable sites on the IL-33 surface using mixed-solvent molecular dynamics (MixMD) simulations and propose the possible mechanism of action of a reported IL-33 inhibitor using extensive-MD simulations.

MD analysis programs: cpptraj, MixMD probeview, PyMOL, MMPBSA.py, Bio3D

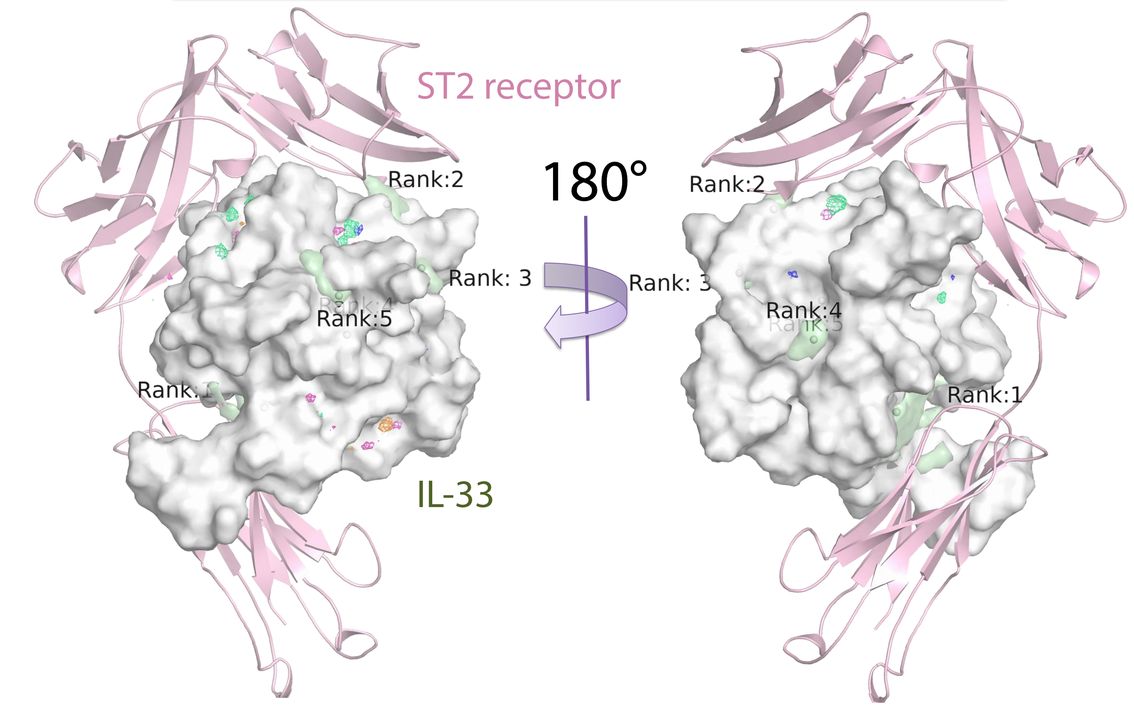
***B*-factor calculation:** $B = \frac{8\pi^2}{3}\langle\mu^2\rangle$

where μ is the mean-squared displacement of protein residues from 10-nonredundant NMA

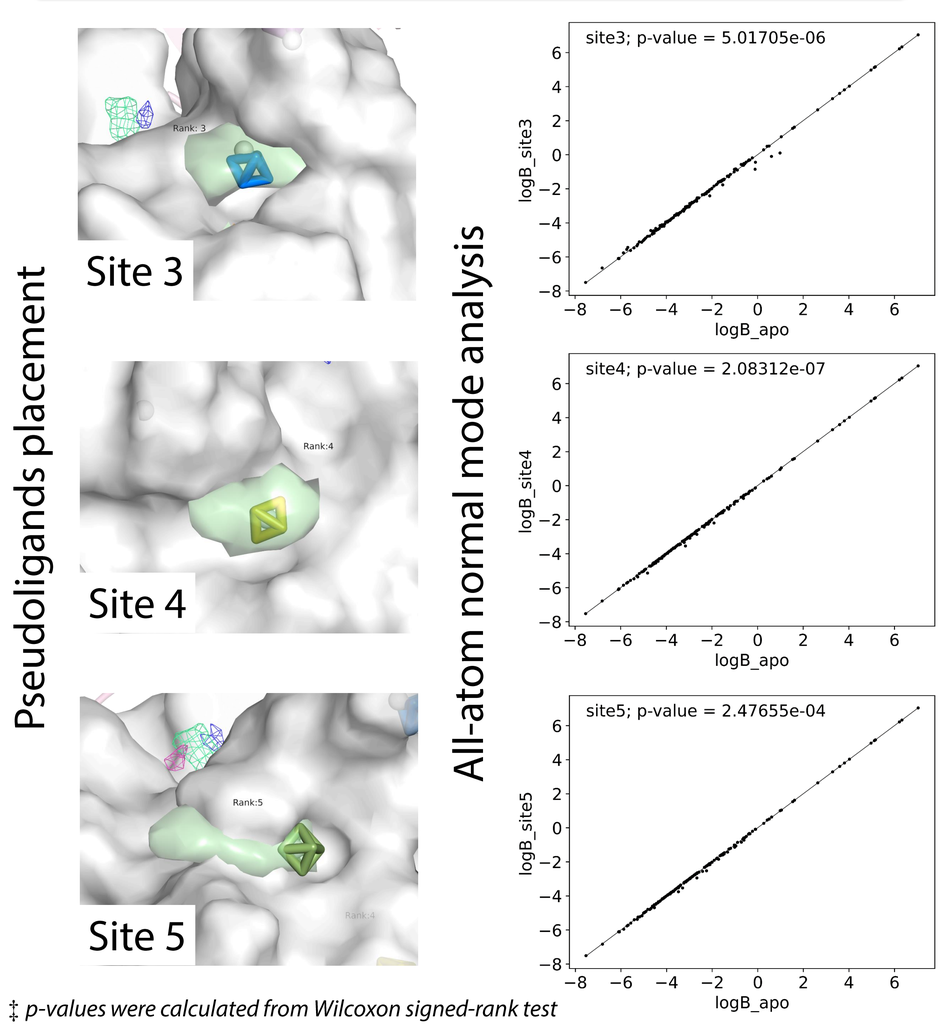
Methods



MixMD sites identification

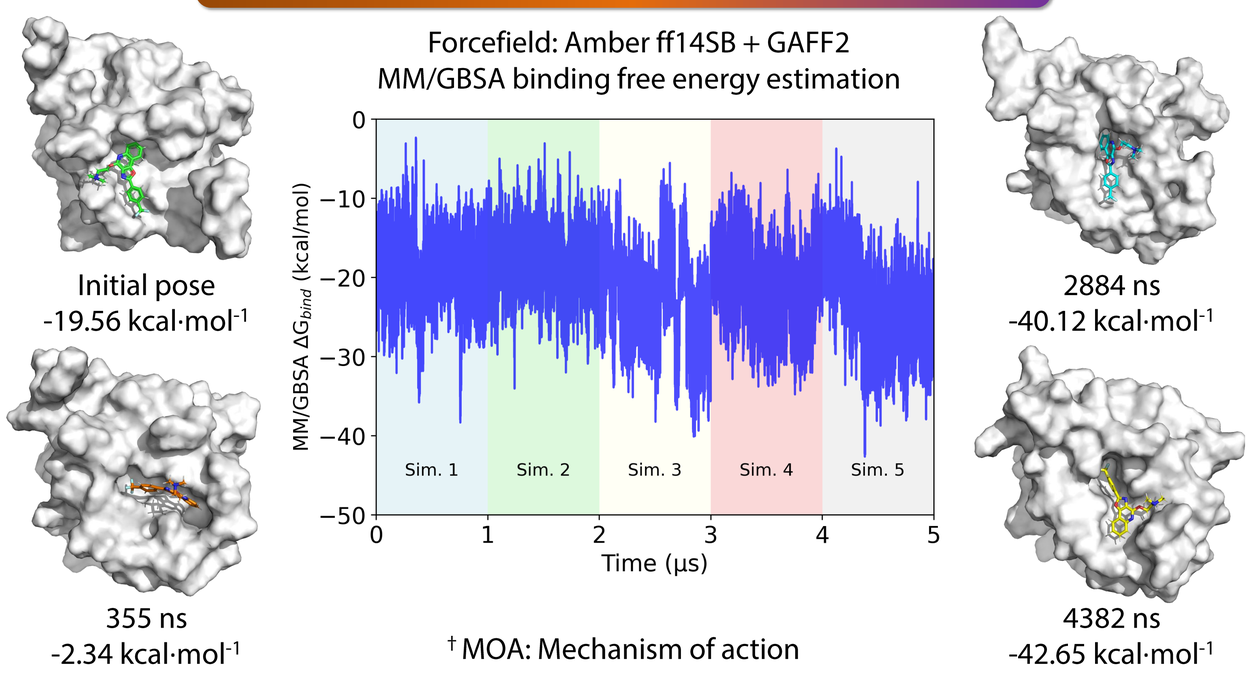


Allosteric modulation prediction



‡ *p-values were calculated from Wilcoxon signed-rank test*

Orthosteric MoA prediction†



† MOA: Mechanism of action

Conclusion

MixMD has facilitated the identification of potential binding sites on IL-33, laying the groundwork for future research endeavors focused on modulating the PPI of IL-33/ST2 using both orthosteric and allosteric strategies.

Conflicts of Interest: The authors declare no conflict of interest.
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