# Comparison between homology-based and experimentally determined structures on prostanoid GPCR receptor

Camille Lescanne*,[1], Maud Jusot*,[2], Anita Rayar[1], Brice Hoffmann[2], France de Malglaive[1], Sophie Saunier[3], Jean-Philippe Annereau§,[1], Luis Briseño-Roa§,[1]

*(1) Medetia Pharmaceuticals (75015 Paris, France), (2) Iktos (75017 Paris, France), (3) Institut Imagine (75015 Paris France); * co-authors; §corresponding: contact@medetia.com*

**Summary.** Available high-quality models have historically been a limiting step in computer guided drug discovery. Here we compare the results of separate dockings into two 3D structures of the same protein: a experimentally obtained and homology-based model. In short, though our results show some differences in the poses of the co-crystalised ligands, the enrichment factors were consistently higher with our homology-derived model. **Figures. (A)** Summarizes our process to generate and select the best models of human prostanoid receptor 2 (EP2); templates seeds included known structures of homologues EP3 (pdb codes 6AK3, 6M9T) and EP4 (5YWY). **(C)** Figure from Quo et al. 2021 comparing binding pocket within PGE2-EP2 and PGE2-EP3 (PDB ID: 6AK3) complex structures. PGE2 was shown in fushia or pink, respectively. **(D – E)** Comparison between binding poses obtained in the co-crystalised structure and the final selected homology model fot both PGE2 and the taprenepag. Structural differences shaded in pink. **(F – G)** Overview of binding interactions with structure and the RMSD obtained. To compare the performance of the two models for a screen of molecules, we docked in both models Medetia's curated **(B)** database of molecules with known activities of the EP. **(H)** Enrichment factors obtained after docking, **(I – J)** along with proportion and the respective classification of docked molecules with both models.

**About Medetia.** The project to create the Medetia was initiated in January 2019 by two former R&D executives from the pharmaceutical industry. Jean-Philippe Annereau (CEO) and Luis Briseño-Roa (CPO), whom had the opportunity to develop and promote new therapeutic proposals in the field of ciliopathies. Medetia's lab is located at the Imagine Institute, a research and medical center of excellence in ciliopathies and rare diseases at large. In that context, Medetia and IKTOS worked together in a first collaboration to create, characterized, and use homology models that served as targets to test Medetia's proprietary annotated compounds datasets.

## A Workflow of generation and selection of the homology-based model

**900 generated models:** 6 seeds x 30 models x 5 templates (Modeller)

**Docking** 3 ligands : ONO-AE_208, PGE2, Misoprostol

**Selection** DOPE score, Molpdf score

**29 models:** 15 from EP3, 7 EP4, 6 from EP3/EP4 mix

**Docking** 5 ligands : PGE2 + 4 specific agonists

**Selection** RMSD, Docking score

**11 models:** 5 from EP3, 5 EP4, 1 from EP3/EP4 mix

**Docking** 639 + 13 000 ligands : EP_non_binders + Decoys

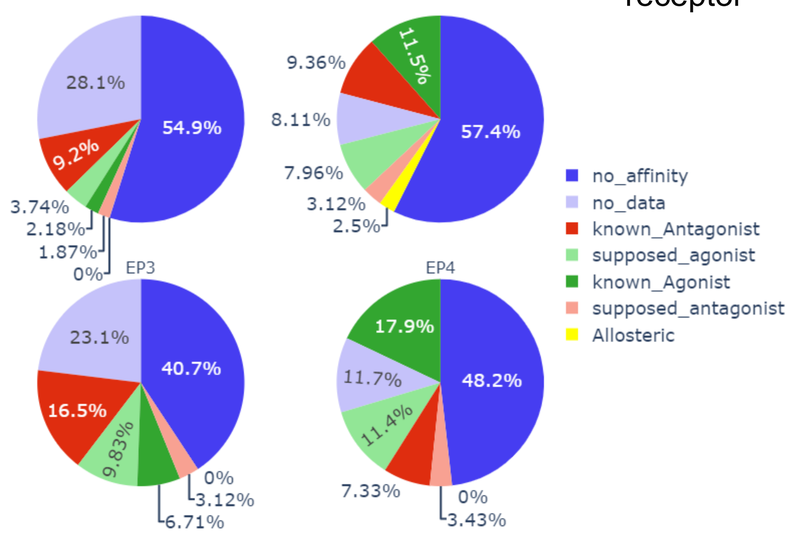
**Selection** Enrichment factors on : Continuous score, Contact score

**1 model from EP3 Template**

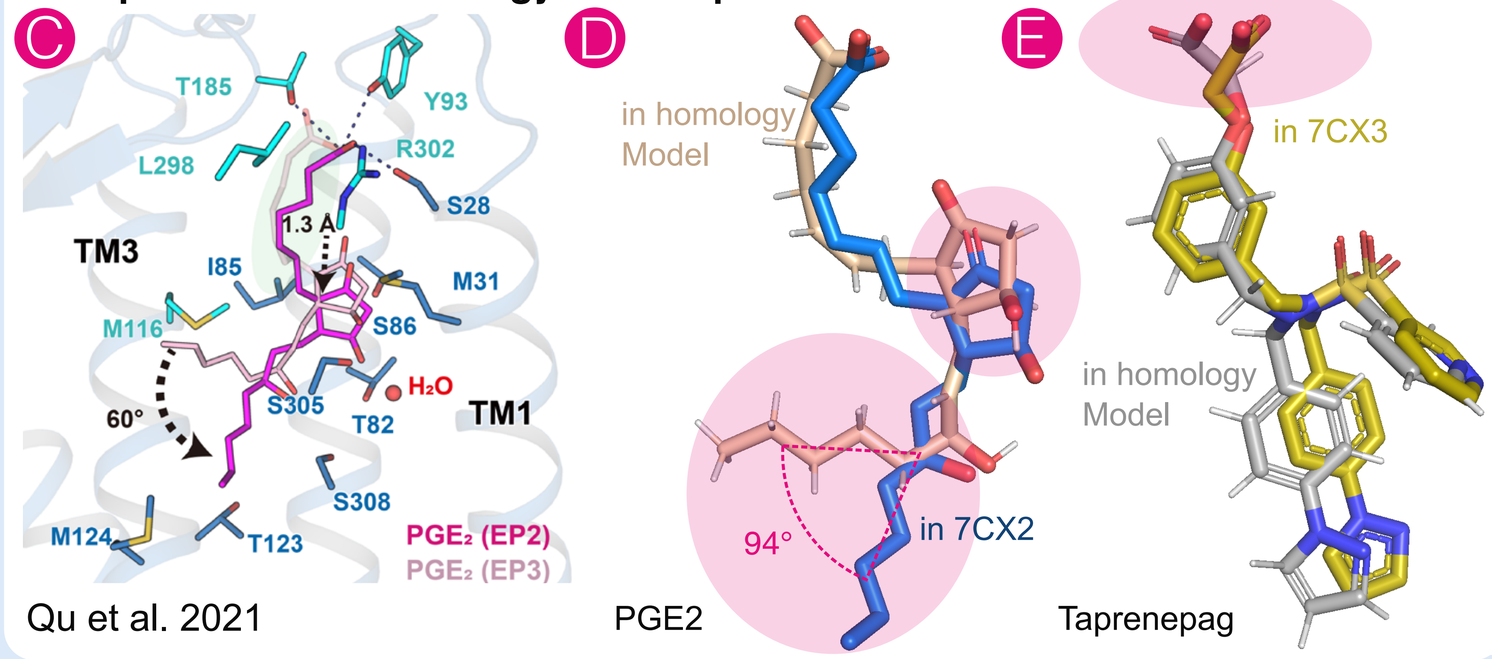
**Use:**
- Study of ligands interactions to EP2
- Custom contact score for this model
- Molecules screening for the discovery of good EP2 agonists

## Database: curated EP ligands

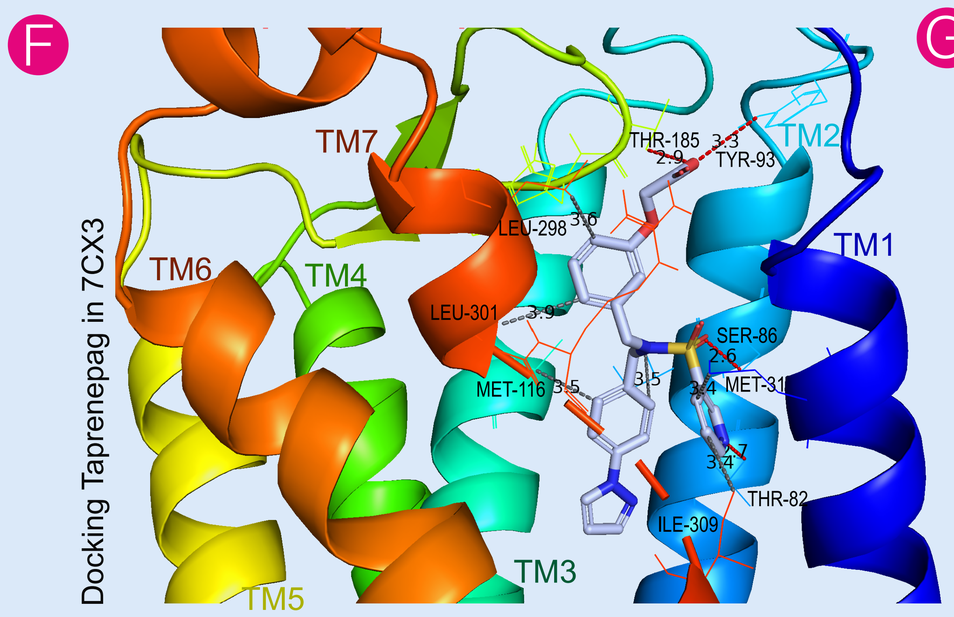
B Proportions of each type of molecules for each receptor

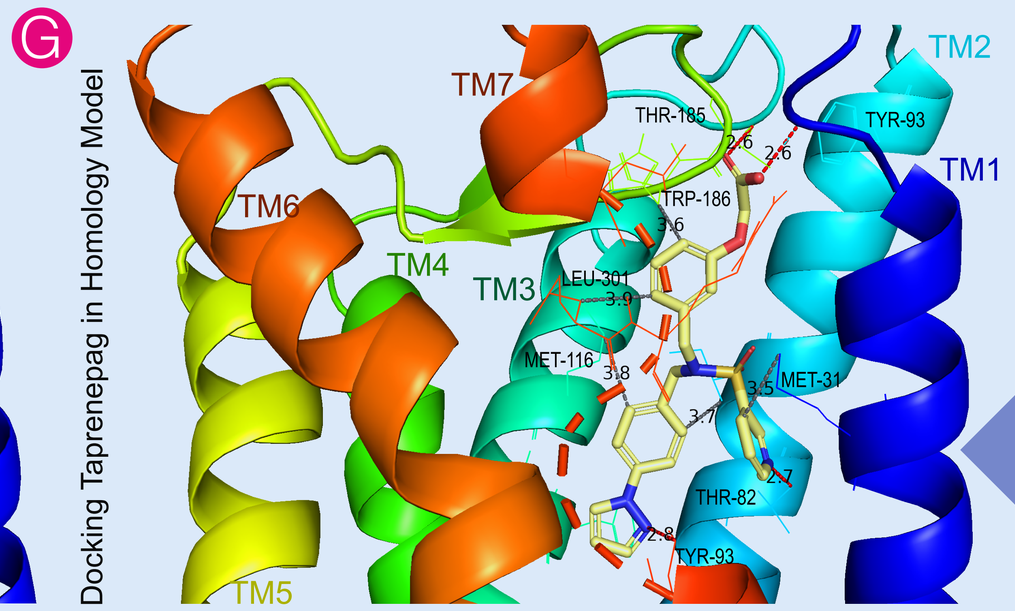



## Experimental & Homology models poses




## Co-crystallised interactions within models



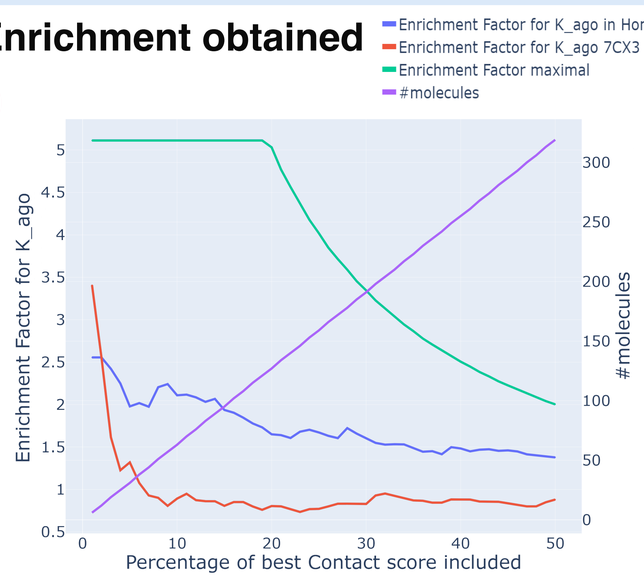




Structures RMSD : 2.698 over 256 residues

Ligands RMSD :
PGE2 : 3.139 (56 to 56 atoms)
Taprenepag : 7.214 (55 to 55 atoms)

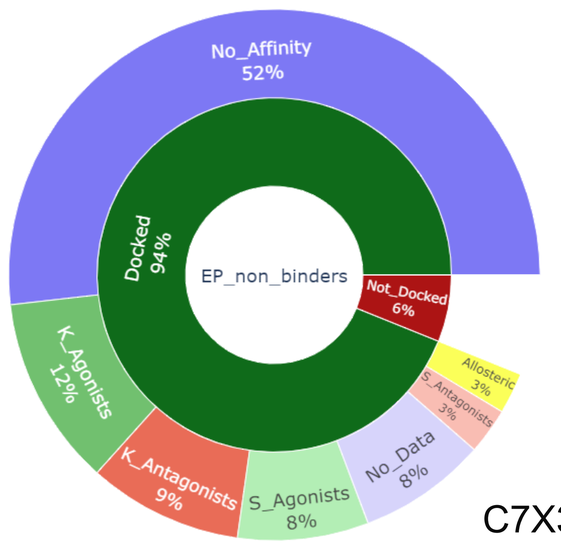
## Enrichment obtained

H

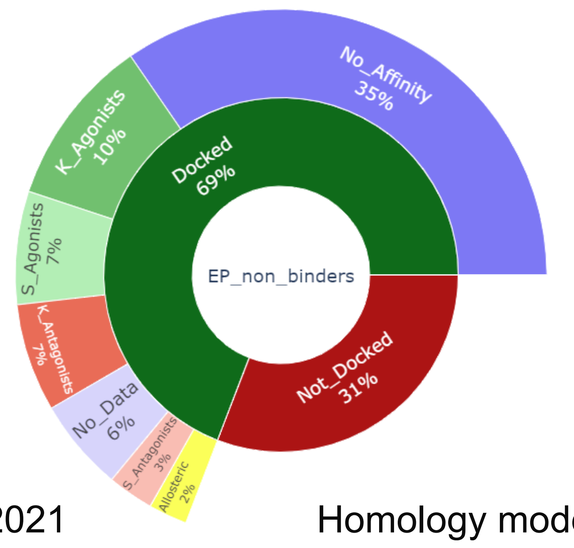



## Proportion of docked molecules

I




J




**References**. Tautermann, C. S.. Methods Mol. Biol. 1705, 115–131 (2018).Qu, C. et al. Sci. Adv. 7, 1–12 (2021). Morimoto, K. et al. Nat. Chem. Biol. 15, 8–10 (2019). Toyoda, Y. et al. Nat. Chem. Biol. 15, 18–26 (2019). Audet, M.et al. Nat Chem Biol. 47, (2019).