

D3R Grand Challenge2 2016

Wilma/SIE Stage1 prediction results

**Hervé Hogues
Purísima Lab**

**D3R webinar
March 27, 2017**



Purissima Lab

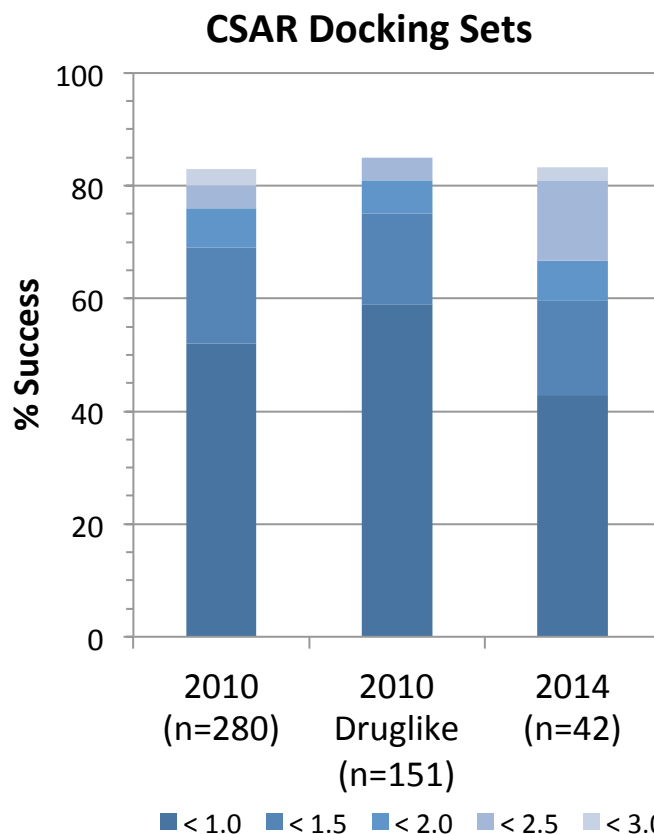
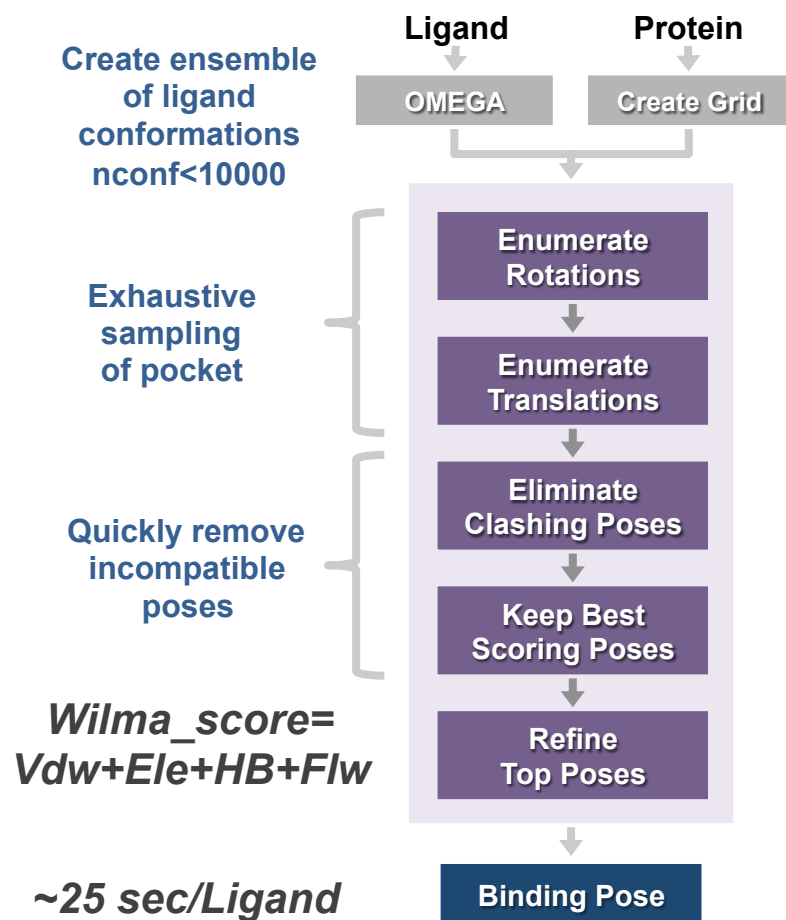
Molecular Modeling Team :

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Christopher Corbeil
Francis Gaudreault

Christophe Deprez
Hervé Hogues
Enrico Purissima

| Challenge | Scope | System | Reference |
|--------------|----------------------------------|----------------------------|--|
| SAMPL-1 | Solvation | Many | JPCB 2009, 113:4511 |
| SAMPL-2 | Solvation | Many | JCAMD 2010, 24:373 |
| CSAR-2010 | Affinity | Many | JCIM 2011, 51:2066 |
| SAMPL-3 | Solvation, Docking, Affinity, VS | Trypsin, Host-guest, PCBDs | JCAMD 2012, 26:617 JCAMD 2012, 26:661 |
| SAMPL-4 | Docking, Affinity, VS | HIV-I, Host-guest | JCAMD 2014, 28:417 |
| CSAR-2013/14 | Docking, Affinity | Steroid-BP, FXA, Syk, TrmD | JCIM 2016, 56:955 |

WILMA: Docking Tool for Virtual Screening *Developed @NRC*



1. Sulea, T. et al. *J. Comp. Aided. Mol. Des.* **2012**, 26, 617–633.
2. Purisima, E. O. et al. *J. Phys. Chem. B* **2012**, 116, 6872–6879.
3. Hogues, H. et al. *J. Comp. Aided. Mol. Des.* **2014**, 28, 417–427.

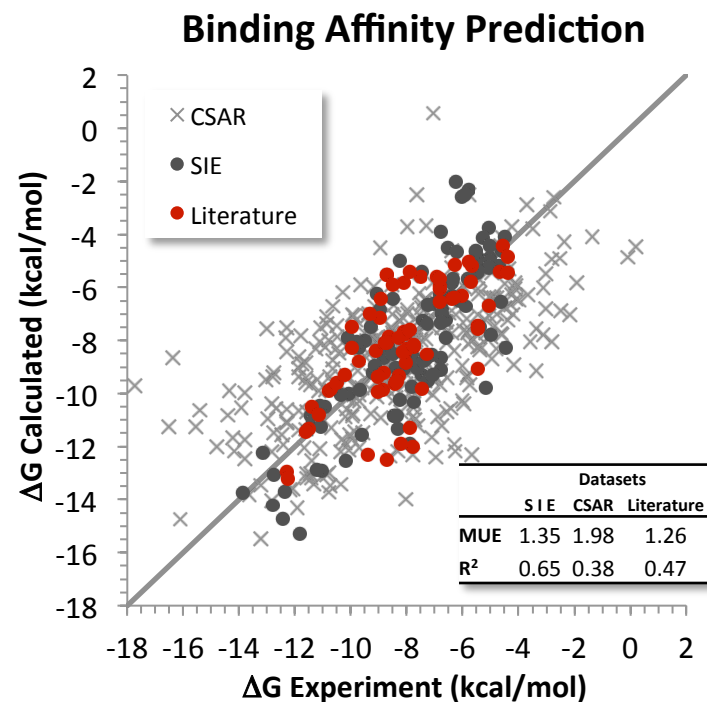
SIE: Scoring function for binding affinity *Developed @NRC*

- Few terms, increased transferability

$$\Delta G = \alpha (E_{\text{VdW}} + \beta E_{\text{Elec}} + \beta E_{\text{RF}} + \gamma \Delta \text{SA}) + C$$

Amber FF BEM Surface
Interaction Solvation Area

- Trained on 99 protein:ligand complexes, 11 proteins
- **19 independent predictions, 72 validated ligands**
>150 non-NRC citations
- Identify Ab residues for affinity maturation



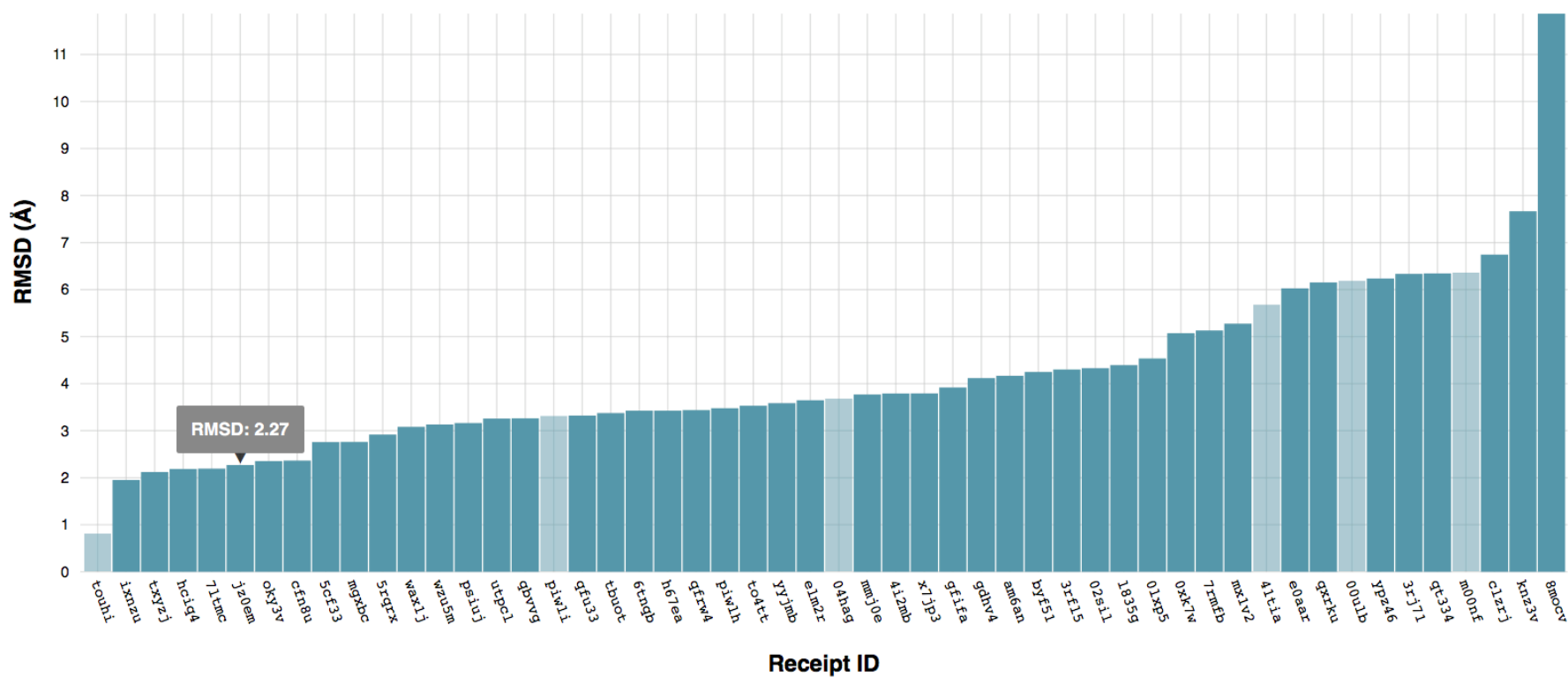
1. Sulea, T. *et al.* *J. Chem. Inf. Model.*, **2011**, 51(9), 2066–2081.
2. Naïm, M. *et al.* *J. Chem Inf Model.*, **2007**, 47 (1), 122-133.

D3R Stage1: Pose Prediction

Grand Challenge 2

Pose - RMSD - Compound: AVG - Pose 1

Compound:



D3R Stage1: Pose1 Prediction - jz0em

| Ligand | Class | RMSD | Rank | #Success |
|--------|---------------|------|------|----------|
| FXR_18 | Misc | 9.66 | 47 | 0 |
| FXR_23 | Isoxazole | 7.82 | 40 | 0 |
| FXR_2 | Misc | 7.38 | 32 | 0 |
| FXR_4 | Isoxazole | 6.35 | 28 | 3 |
| FXR_1 | Sulfonamide | 5.95 | 23 | 0 |
| FXR_3 | Misc | 5.90 | 22 | 5 |
| FXR_11 | Spiro | 3.06 | 7 | 6 |
| FXR_12 | Spiro | 3.05 | 21 | 20 |
| FXR_34 | Steroid | 3.04 | 6 | 5 |
| FXR_10 | Spiro | 2.73 | 10 | 10 |
| FXR_32 | Benzimidazole | 2.24 | 25 | 30 |
| FXR_22 | Benzimidazole | 2.18 | 28 | 32 |
| FXR_13 | Benzimidazole | 1.77 | 17 | 17 |
| FXR_31 | Benzimidazole | 1.73 | 31 | 42 |
| FXR_30 | Benzimidazole | 1.71 | 15 | 36 |
| FXR_15 | Sulfonamide | 1.66 | 2 | 3 |
| FXR_16 | Sulfonamide | 1.46 | 5 | 15 |

| Ligand | Class | RMSD | Rank | #Success |
|--------|---------------|-------|------|----------|
| FXR_17 | Sulfonamide | 1.390 | 4 | 25 |
| FXR_14 | Benzimidazole | 0.908 | 38 | 38 |
| FXR_27 | Benzimidazole | 0.879 | 19 | 43 |
| FXR_28 | Benzimidazole | 0.828 | 14 | 40 |
| FXR_35 | Benzimidazole | 0.798 | 13 | 36 |
| FXR_7 | Benzimidazole | 0.746 | 8 | 34 |
| FXR_25 | Benzimidazole | 0.715 | 17 | 38 |
| FXR_21 | Benzimidazole | 0.698 | 18 | 35 |
| FXR_20 | Benzimidazole | 0.688 | 10 | 28 |
| FXR_24 | Benzimidazole | 0.680 | 3 | 39 |
| FXR_5 | Indole | 0.600 | 10 | 33 |
| FXR_8 | Benzimidazole | 0.486 | 7 | 27 |
| FXR_26 | Benzimidazole | 0.448 | 5 | 34 |
| FXR_9 | Benzimidazole | 0.424 | 8 | 29 |
| FXR_36 | Benzimidazole | 0.413 | 1 | 34 |
| FXR_19 | Benzimidazole | 0.389 | 6 | 38 |
| FXR_29 | Benzimidazole | 0.385 | 1 | 40 |

D3R Stage1: FXR Structure Selection

- **Steroids:**

1OSV 1OT7 3BEJ 4QE6

- **Isoxazoles:**

3DCT 3DCU 3FXV 3GD2 3HC5 3HC6
3P88 3P89 3RUT 3RUU 3RVF

- **Indoles:**

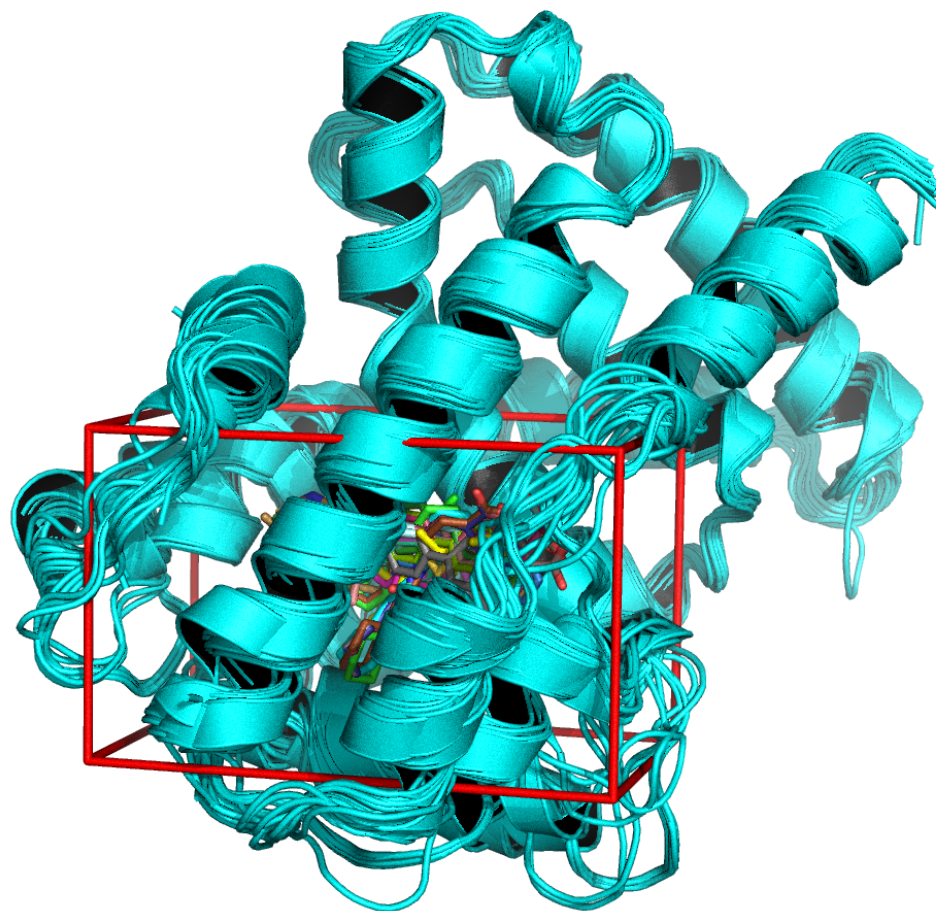
3FLI 3L1B

- **Benzimidazoles:**

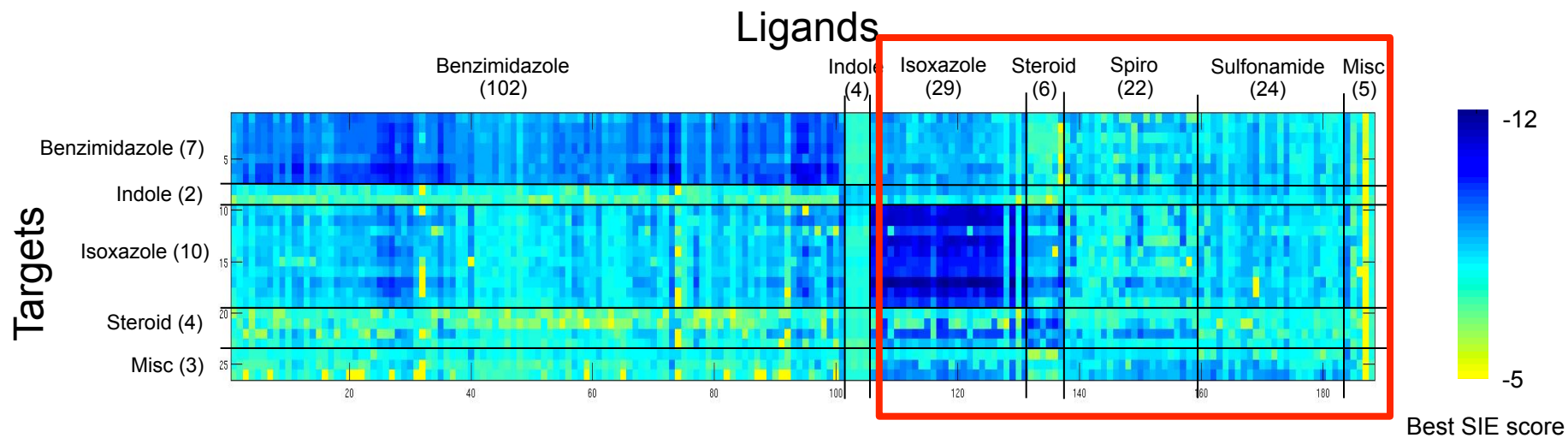
3OKH 3OKI 3OLF 3OMK 3OMM
3OOF 3OOK

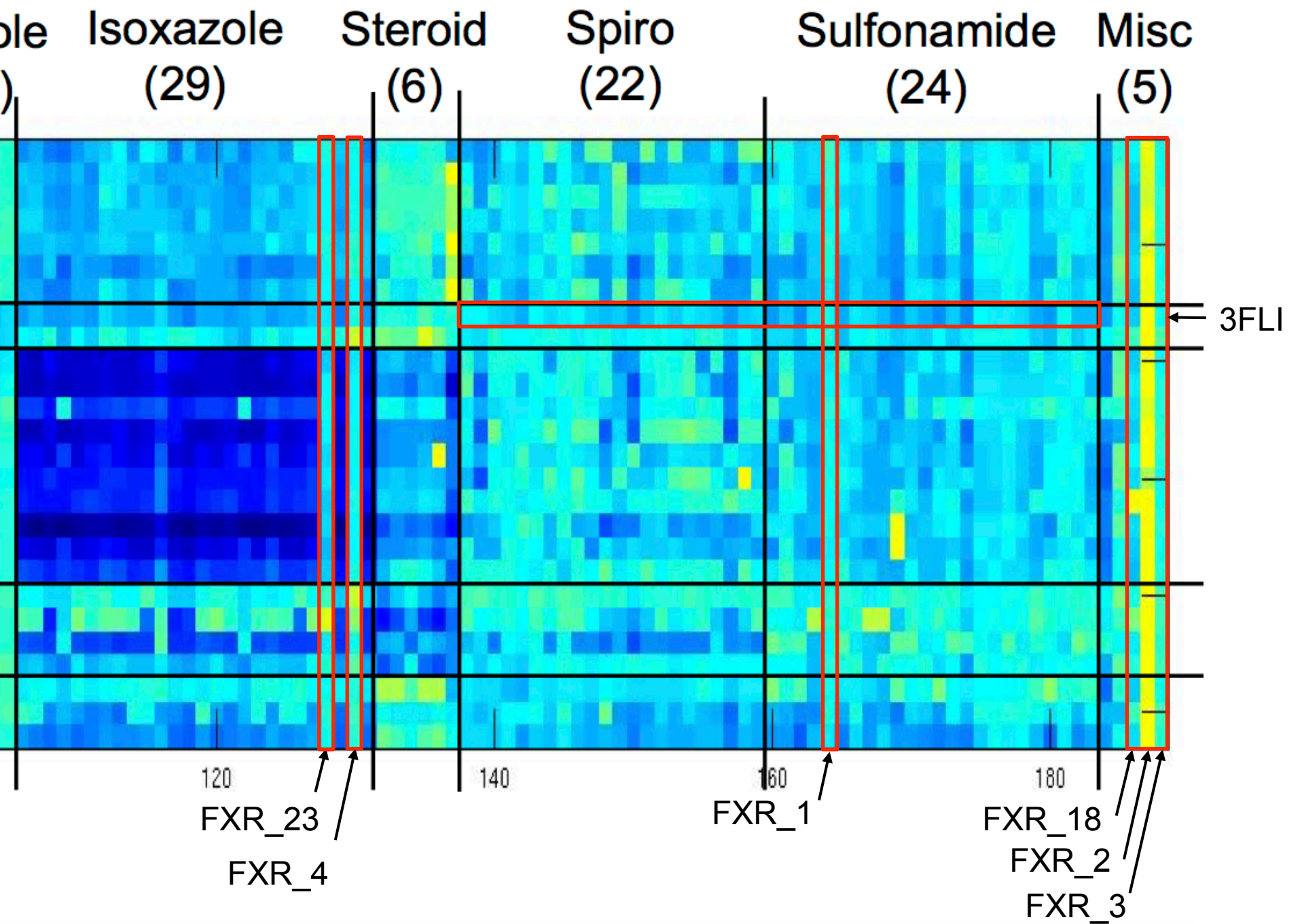
- **Other:**

4QE8 1OSH FXR_APO

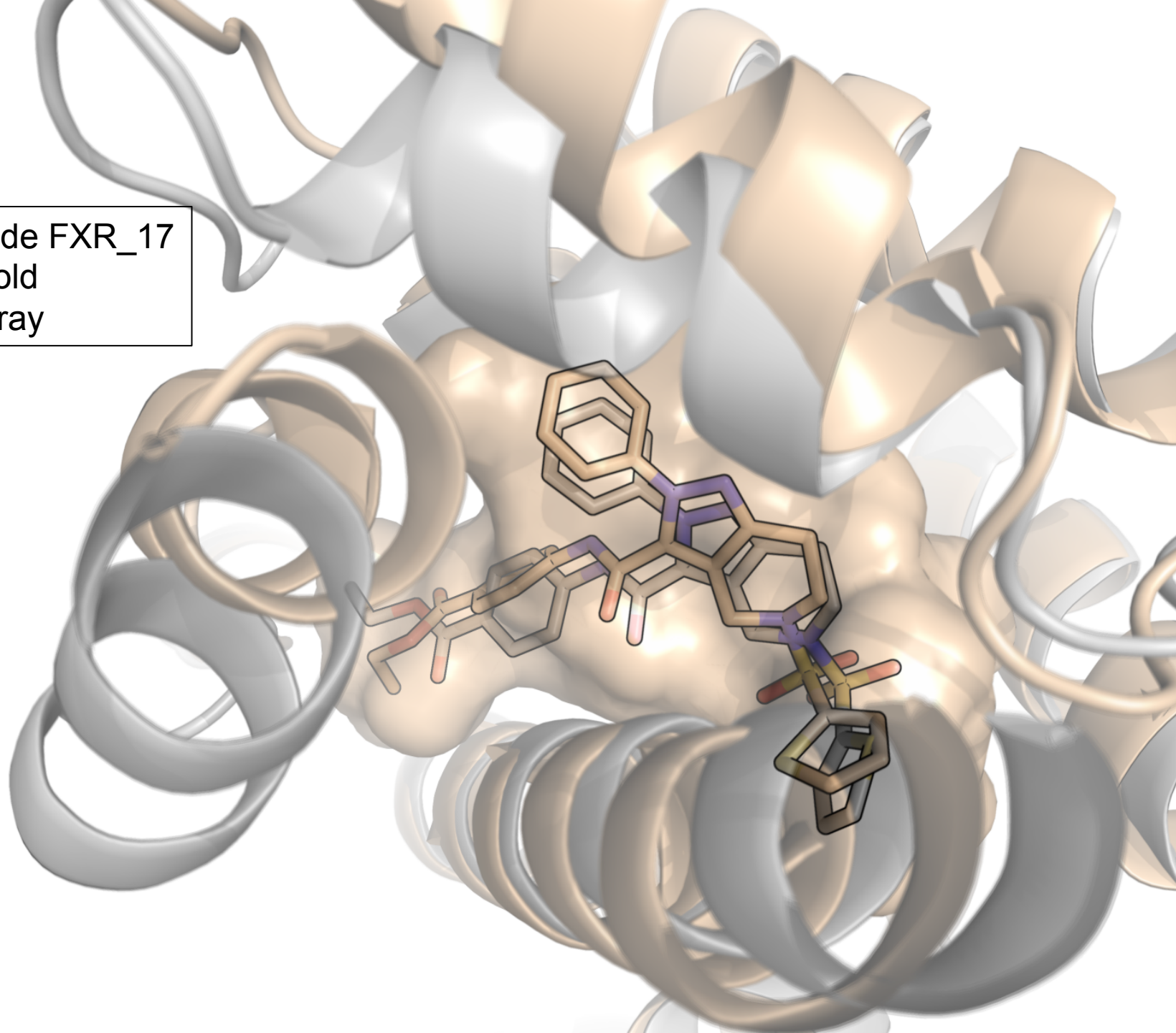


D3R Stage1: Pose Selection

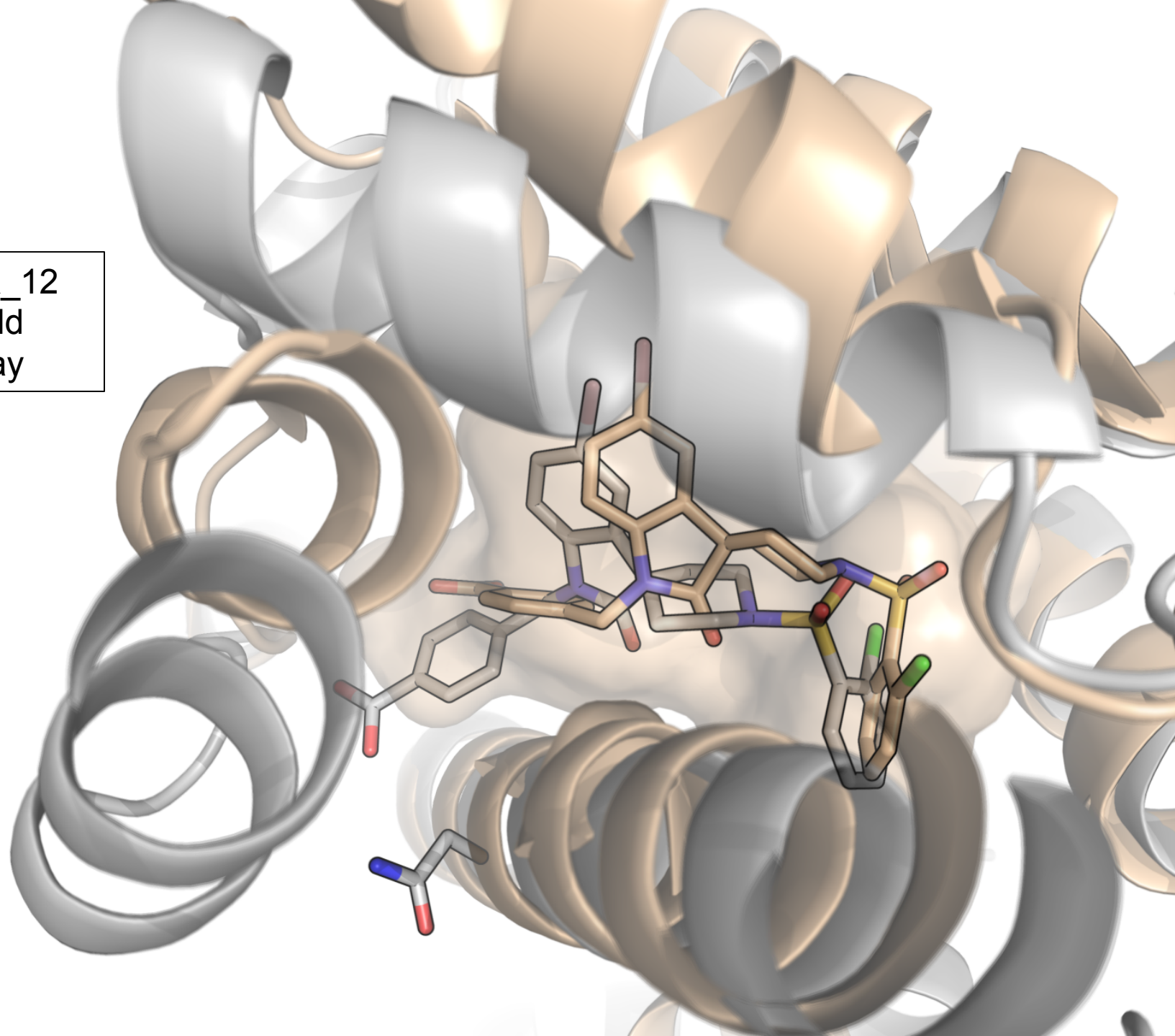




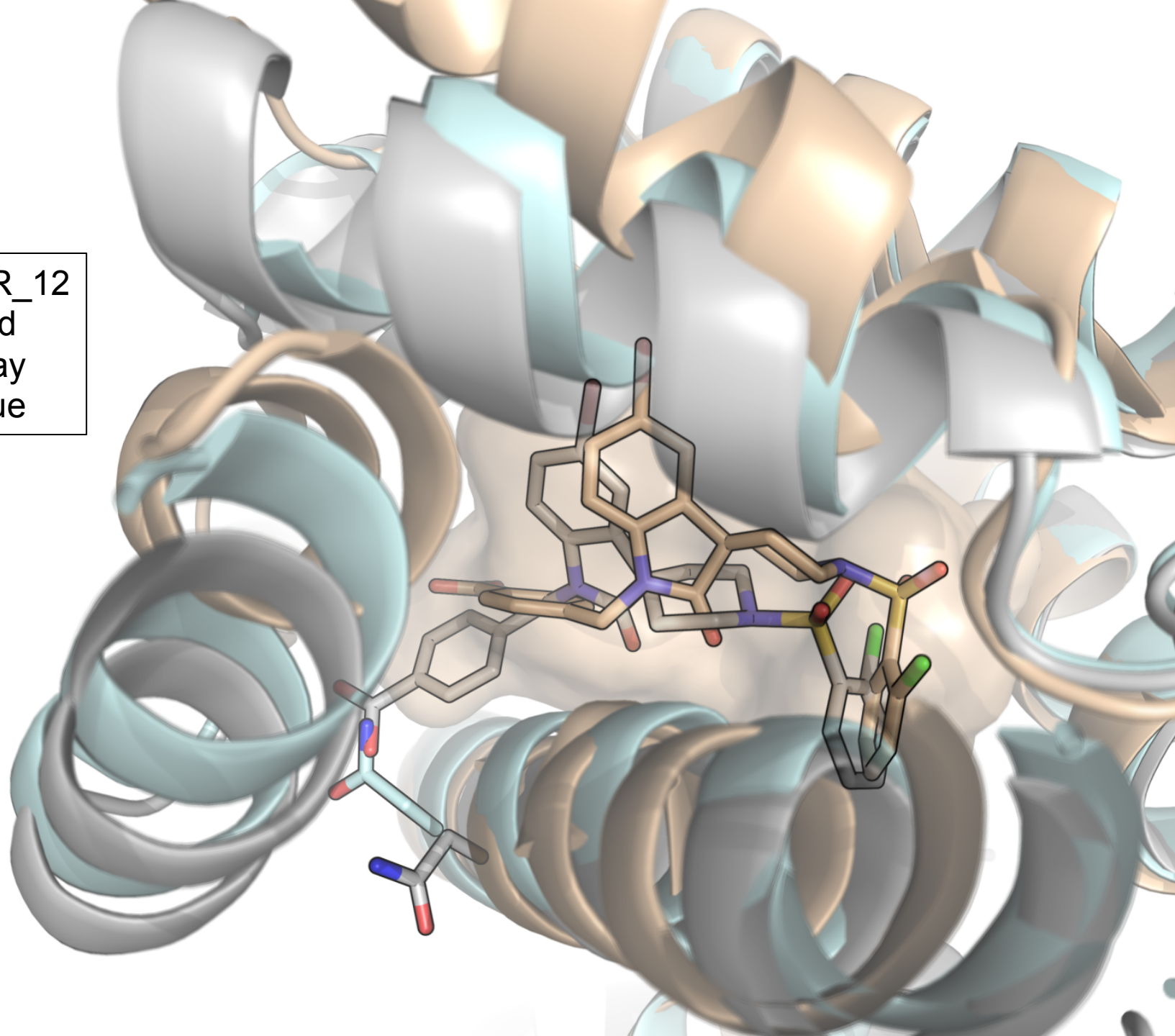
Sulfonamide FXR_17
3FLI : gold
HQMF: gray



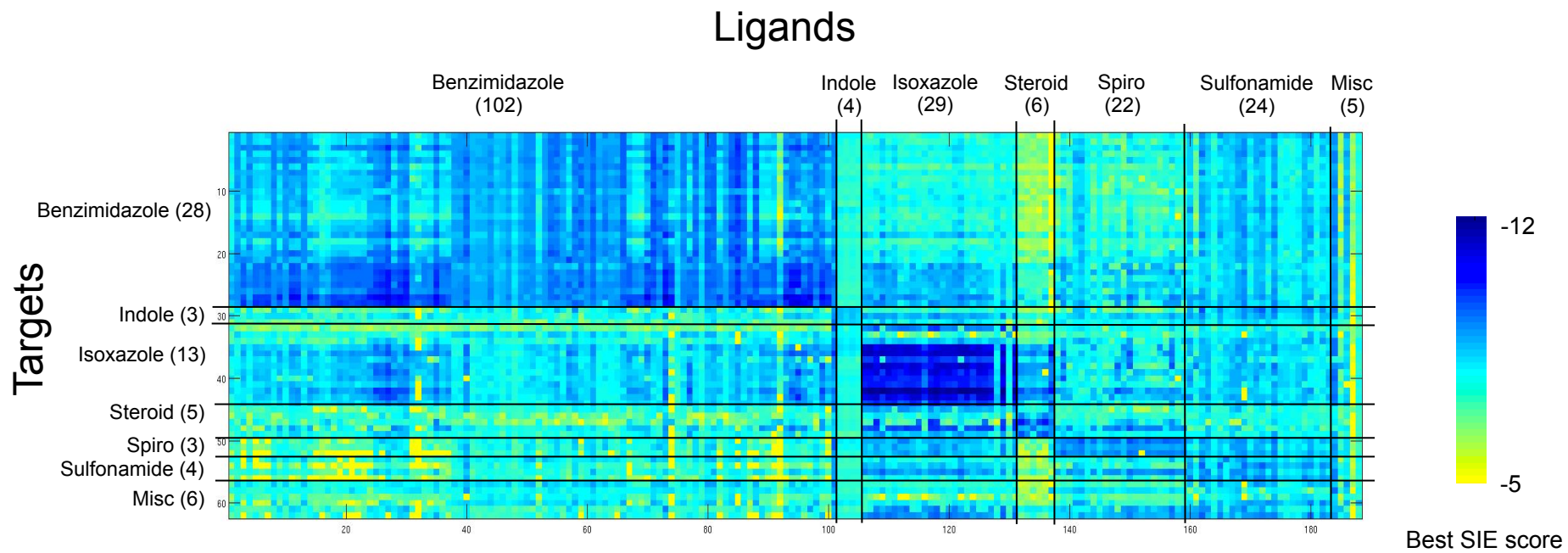
Spiro FXR_12
3FLI : gold
KJYP: gray



Spiro FXR_12
3FLI : gold
KJYP: gray
4QE8: blue



FXR Structure Selection



D3R Stage1: Pose1 Prediction - jz0em

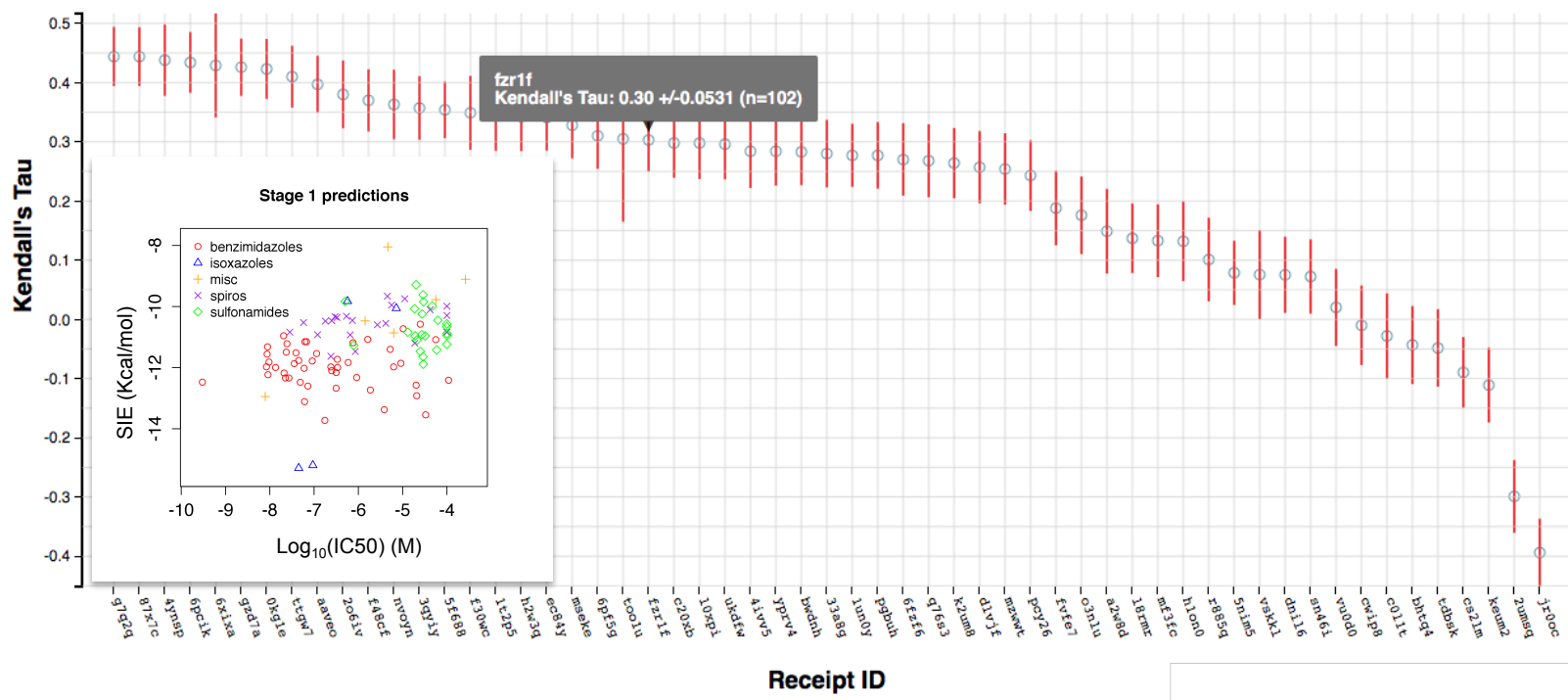
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D3R Stage1: structure base affinity prediction

Grand Challenge 2

Structure-Based Scoring (Stage 1) - Kendall's Tau **



Lessons learned and future improvements

- Docking is easier than Scoring
- Any single FXR structure leads to multiple false negatives
- Sidechain sampling should improve docking accuracy

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