



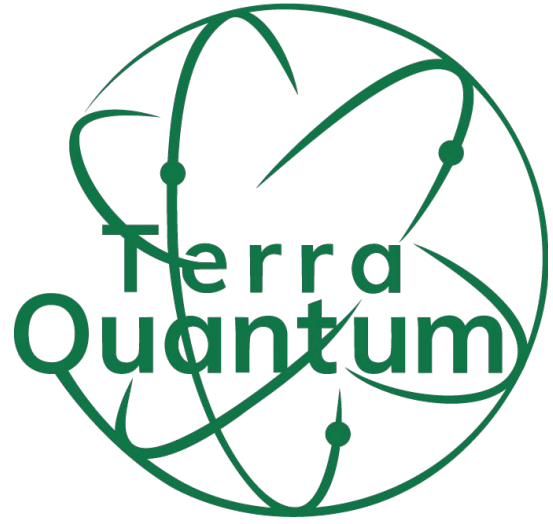
Physics-Based AI Virtual Screening of Non-Canonical Cyclic Peptides via Tensor Networks

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Physics-Based AI Virtual Screening of Non-Canonical Cyclic Peptides via Tensor Networks



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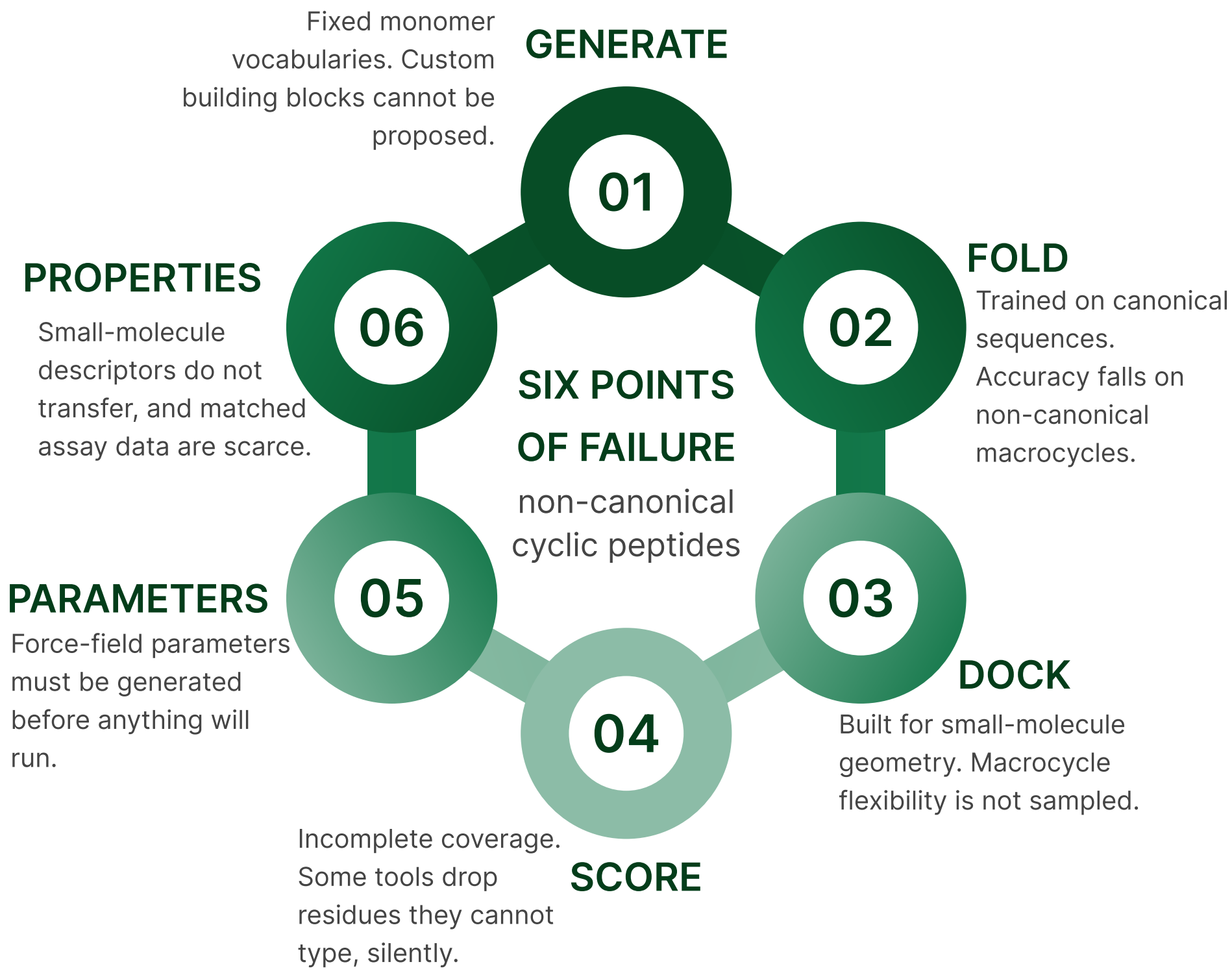
ABSTRACT

The properties of **cyclic peptides** are governed by **conformational ensembles** rather than by single structures, and the non-canonical residues that make this modality useful are poorly handled by existing tools. Generative methods are restricted to fixed monomer vocabularies, folding methods trained on canonical sequences lose accuracy on non-canonical macrocycles, and scoring functions correlate only weakly with measured affinity while covering this chemistry incompletely. A virtual screening workflow was therefore developed in which **tensor-train representations** sample ligand torsions, backbone flexibility and side-chain dihedrals together, **giving induced fit for highly flexible protein-peptide systems** without combinatorial explosion and integrating with existing AI workflows.

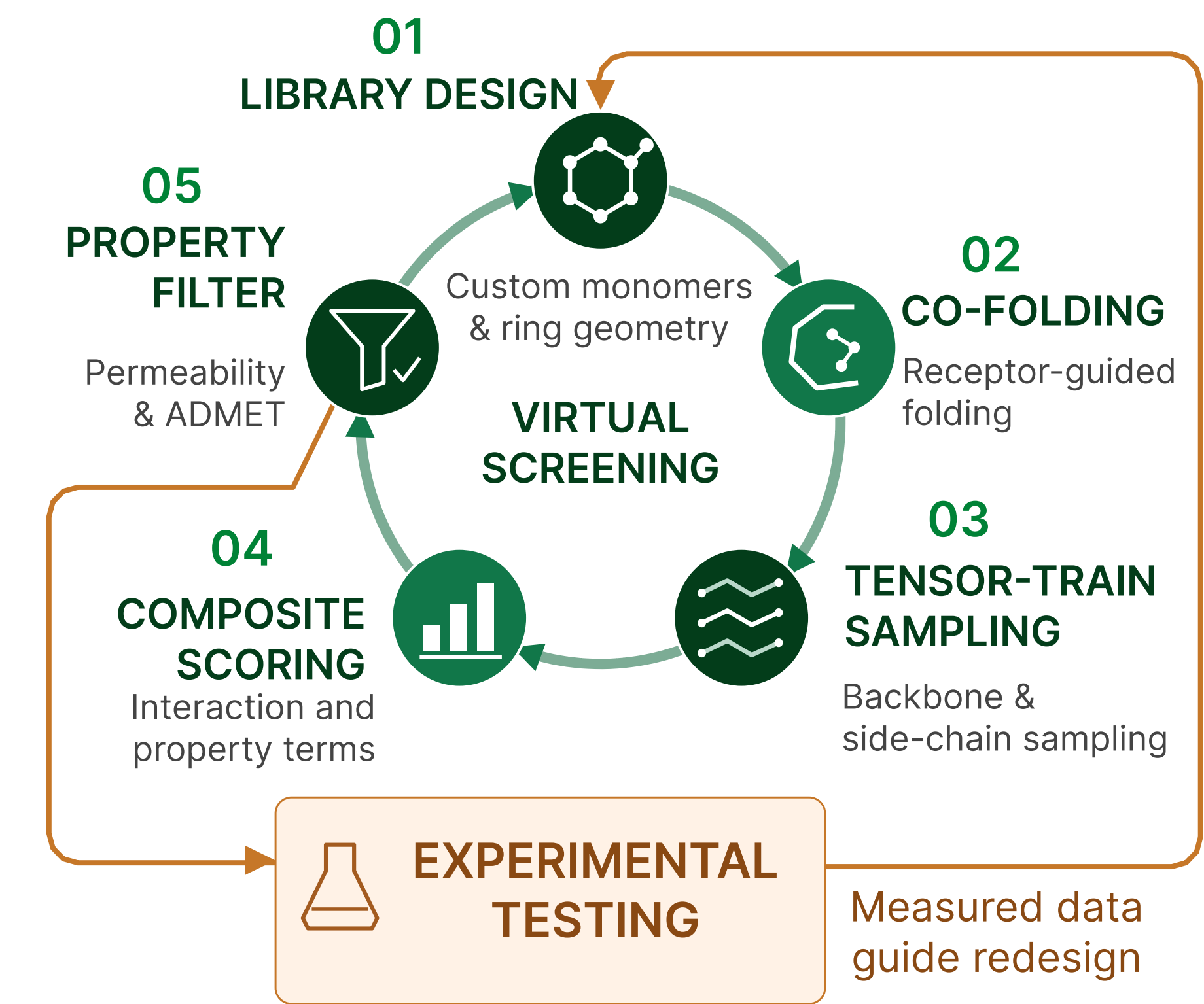
Custom non-canonical building blocks are supported, and libraries are generated either *de novo* or by optimization of existing leads. **Permeability models** for the same chemistry were benchmarked against the reproducibility of the underlying assay and tested separately for transfer to new chemistry and to new assay conditions. Performance is retained across chemistry and degrades across protocols, so models are **recalibrated on partner data** before use. The workflow was applied to a class A receptor whose active and inactive states were characterized by microsecond simulations. **Boltz2 was adapted for peptide macrocycles containing non-canonical amino acids** and used to co-fold a combinatorial library spanning four chemical dimensions with the receptor. The resulting complexes underwent **physics-based docking with an optimized force field and a customized scorer**. Ensemble-based ranking recovered established receptor contacts and highlighted recently reported interactions that were uncommon in well-known leads but consistently maintained across the designed ligands' poses.

THE PROBLEMS & OUR SOLUTION

Pain Points: *in silico* design of Cyclic Peptides



Customized Virtual Screening for Cyclic Peptides



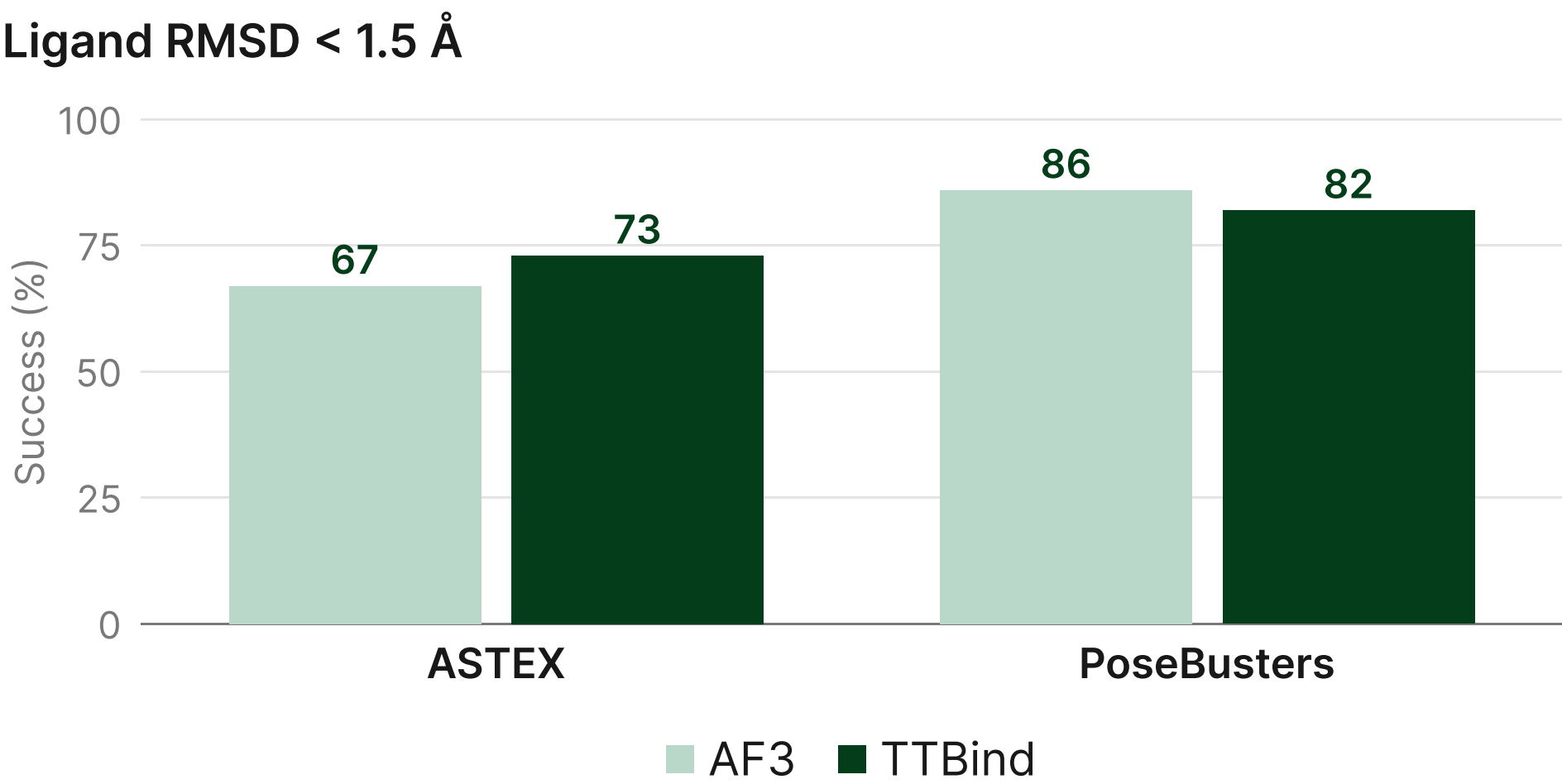
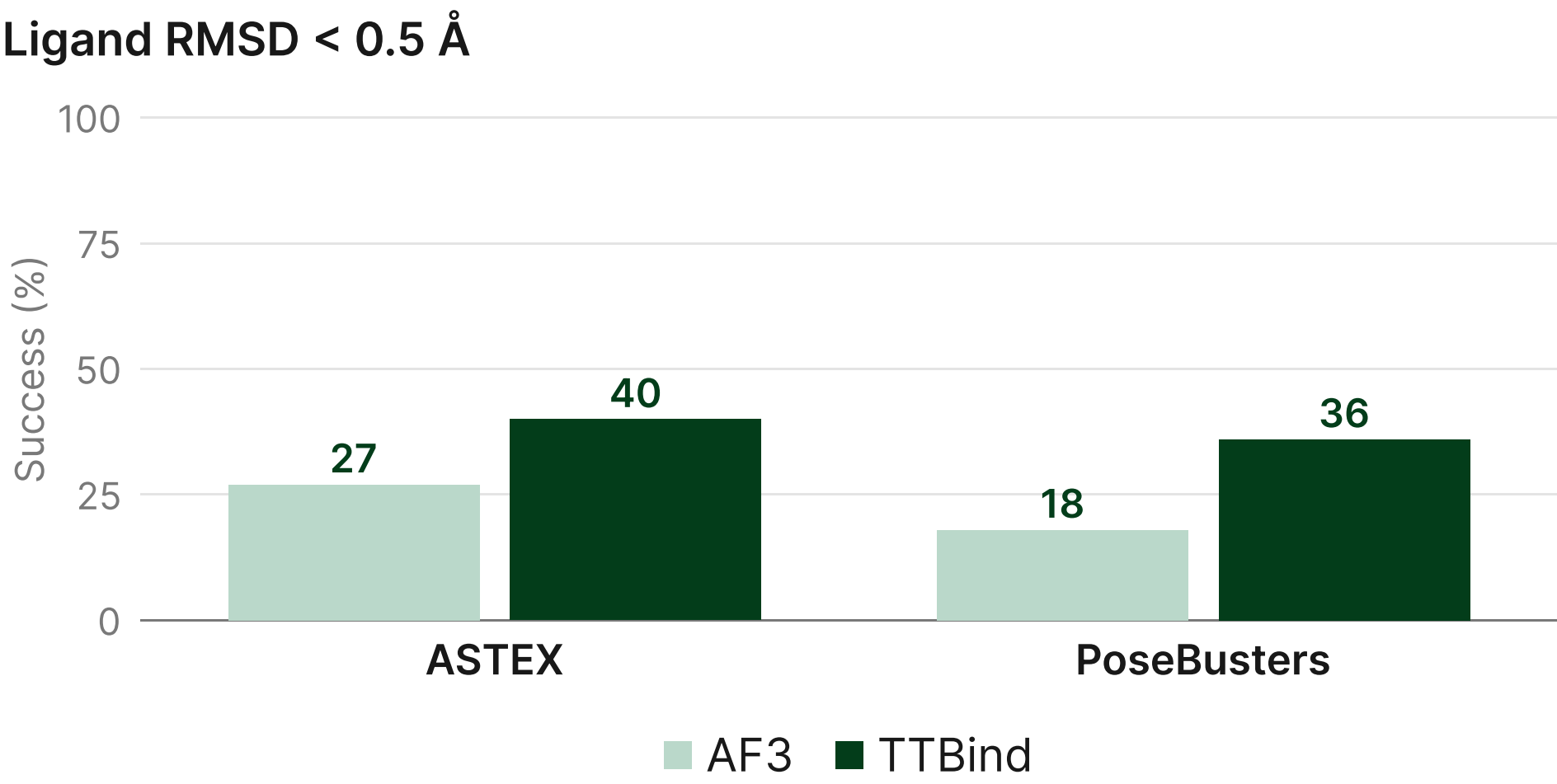
OUR TECHNOLOGY

Tensor Train-based Protein-Ligand Binding

The bound state is represented as a tensor train, with one core per set of degrees of freedom. Ligand position and orientation, ligand torsions and the side chains lining the site are optimized jointly, so induced fit is obtained without enumerating the product space.



TTBind Refinement Compared with Gold Standard Folding Algorithm^[1,2]



AF3 starting pose against TTBind refinement. ASTEX n = 15, PoseBusters n = 22. Median ligand RMSD 0.672 to 0.634 Å (ASTEX) and 0.787 to 0.623 Å (PoseBusters).

Refinement improves strict-threshold success and lowers median RMSD; at 1.5 Å the methods are comparable.

- Morehead, A., Giri, N., Liu, J. et al. Nat Mach Intell 8, 32–41 (2026)
- Abramson, J., Adler, J., Dunger, J. et al. Nature 630, 493–500 (2024).

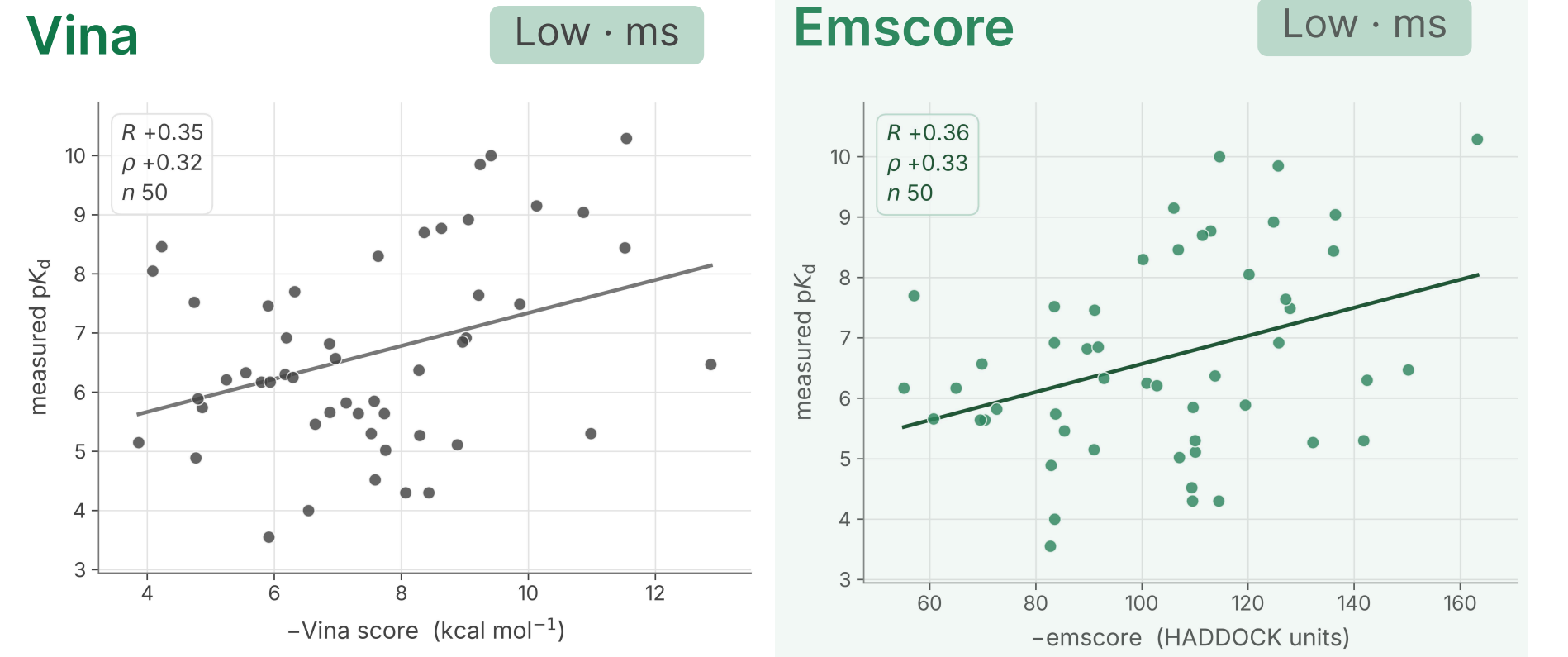
SCORING BENCHMARK

High Throughput Scoring Accuracy

13 methods, four datasets: two affinity sets and two pose-ranking sets. Intervals resample receptor clusters, not individual complexes or targets.

Method	Cost	Scoring p	Docking AUC	Best observed
AA-Score	ms	0.43	0.71	p = 0.43
Vinardo	ms	0.35	0.67	vs measured affinity
Emscore	ms	0.33	0.65	Most pairwise differences remain unresolved at these sample sizes.
Vina	ms	0.32	0.67	With non-canonical residues, coverage falls below 1 in 3 structures.
PyRosetta	s	0.30	0.67	Scores alone cannot guide selection.
MM-GBSA	min	0.27	0.72	

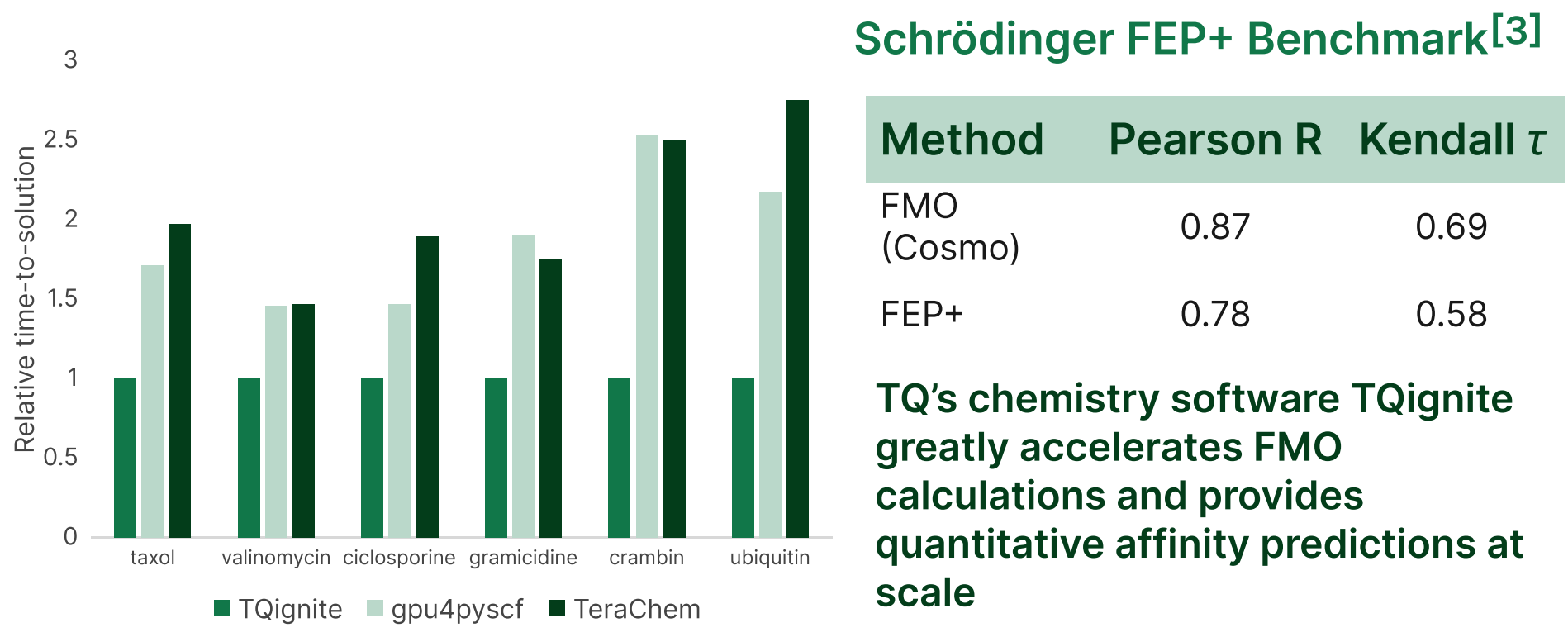
Full benchmark
Affinity: 134 complexes / 63 clusters
Pose ranking: 90 targets / 43 clusters



Two methods on same data: 50 complexes / 21 receptor clusters

FMO & FEP: Quantitative Binding Affinities

Fragment Molecular Orbital (FMO) calculations and Free Energy Perturbation (FEP) provide quantitative predictions in ≈1 kcal/mol accuracy at high compute resources (hours to days)^[3]

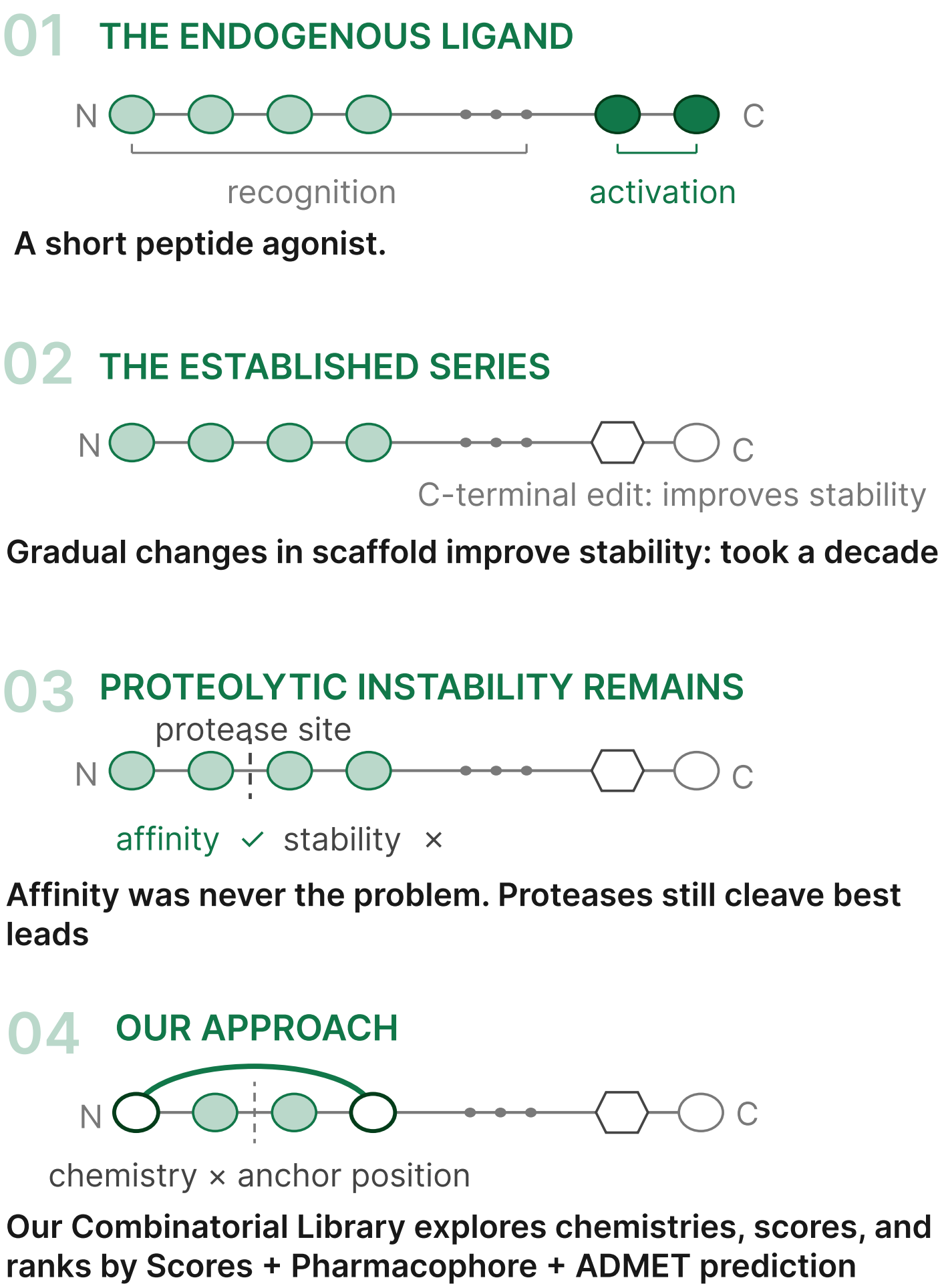


RESULTS

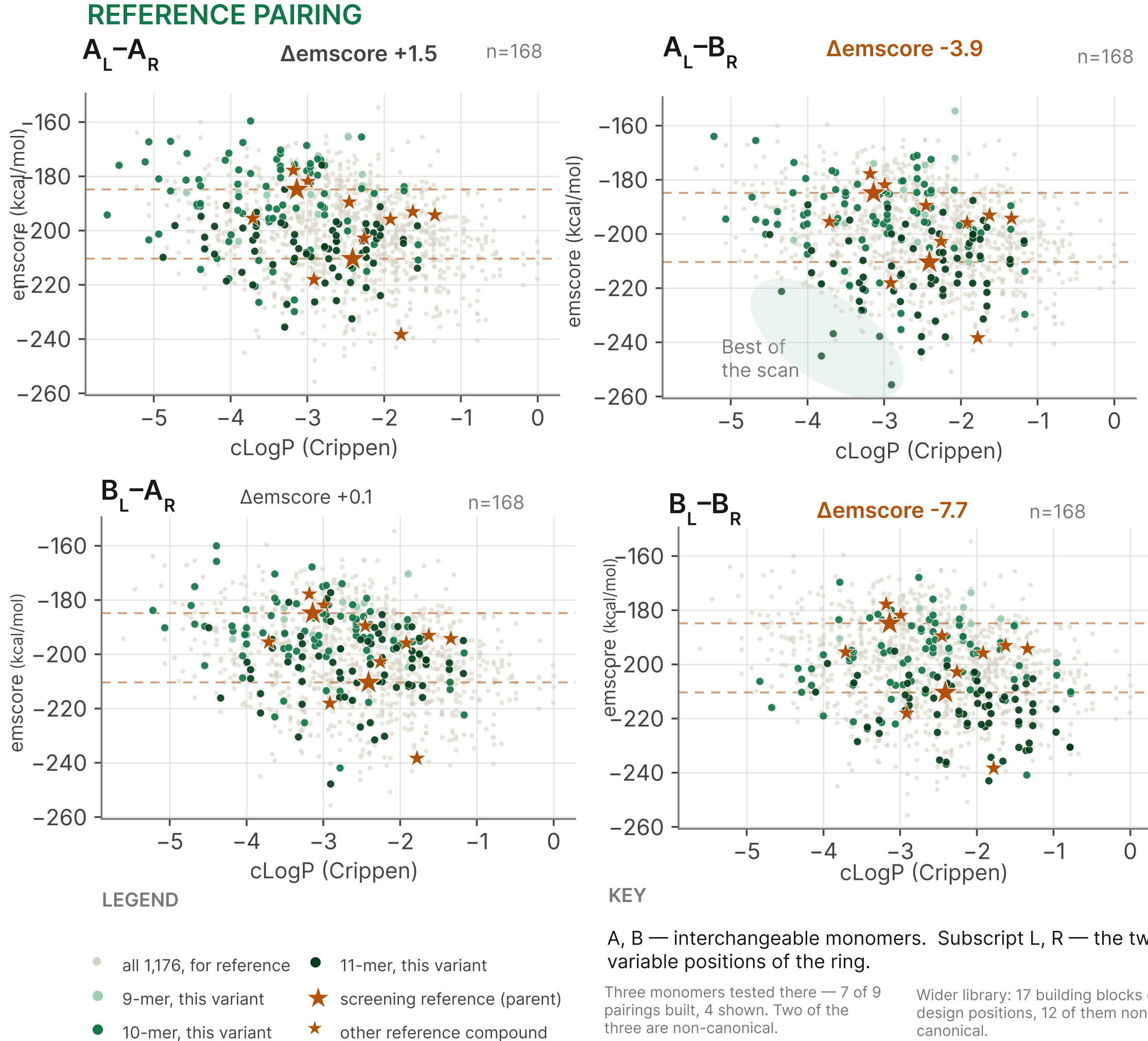
Case Study: An Undisclosed Class A Receptor

Active and inactive states were characterized by 1 μs molecular dynamics each and remain separated along the cytoplasmic opening coordinate, so every design is scored against a defined receptor state. A library of 1,176 candidates was built from a reference scaffold across four chemical dimensions. Ranking across ensembles reproduced the orthosteric contacts reported from structural work on this receptor family, and several designs score above the reference set on a size-normalized basis.

Design Exploration from existing Reference



Score: ADMET Outcomes: Chemical Explorations



Collective Analysis: Chemical Explorations

Reference parents:		uncapped, emscore −184.9		capped, emscore −210.4		
		= better kcal/mol, vs own parent		no good direction vs own parent		+ = longer % vs library mean +
		Δ emscore		Δ cLogP		library 57.2% emscore
Ring size	Ring 1	n=150	+1.4	+1.25	+0%	44.0%
	Ring 2	n=918	−3.2	+0.65	−0%	59.4%
Monomer pairing	A-A	n=60	+0.9	+0.07	−12%	43.3%
	A-B	n=168	−2.4	+0.39	−30%	53.6%
	B-A	n=168	+1.0	+0.39	−16%	48.8%
	B-B	n=168	−6.5	+0.78	−25%	72.6%
	A-C	n=168	−4.8	+0.78	+31%	61.9%
	C-A	n=168	+0.7	+0.78	+11%	45.2%
	C-C	n=168	−4.5	+1.56	+61%	66.1%
N-terminal scaffold	No cap	n=534	−5.3	+0.74	+17%	68.9%
	Cap	n=534	+0.2	+0.74	−14%	45.5%

Δ emscore (− better), Δ half-life (+ better)

Δ cLogP

worse

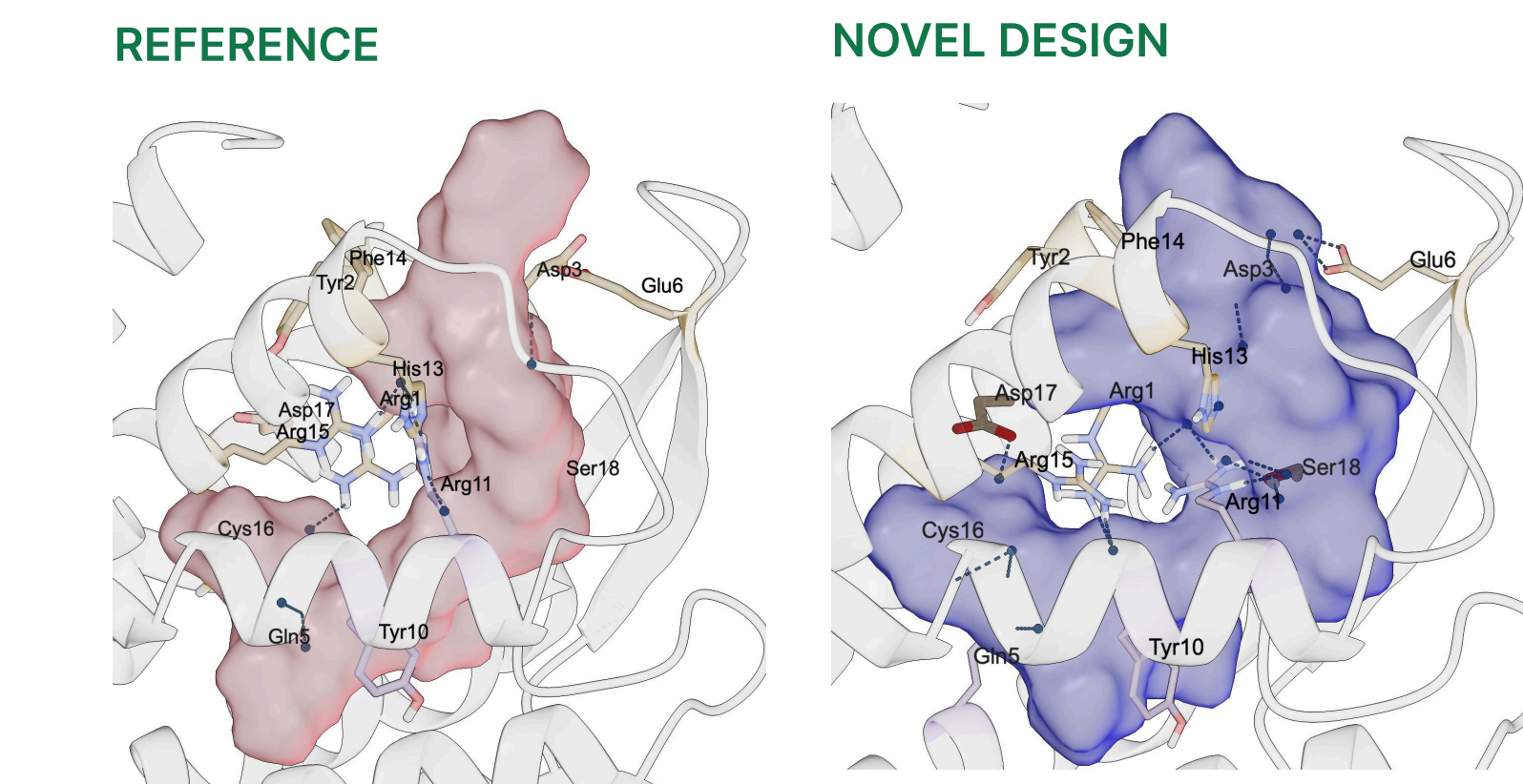
better

less lipophilic

more lipophilic

Comparison of Reference & Novel Design: Docked Poses

Novel design shows more interactions compared to reference. Core pharmacophores retained.



Next: higher-accuracy affinity by FMO with continuum solvation and free-energy perturbation; further design iterations; additional targets.

Benchmarking of scoring functions and of permeability models was carried out with colleagues on the Terra Quantum Chemistry team.