SERVICE GUIDE

Target Enablement Research Service

Unlock your protein target and ligand series of interest for rigorous structure-based design

We're in the midst of a revolution in structural biology, with a proliferation of available structures across protein classes due to advances in cryo-EM, low sequence identity homology modeling, and machine learning technologies such as AlphaFold. However, significant protein structure refinement and accurate ligand placement is required to use these structures for accurate physics-based simulations, including free energy calculations with FEP+.

Free up your time and resources — let us prepare your protein-ligand system of interest for structure-based design. Whether you are starting from experimental X-ray structures, cryo-EM structures, AlphaFold predicted structures, or homology models, Schrödinger scientists will leverage our unique technologies and expertise to optimize and validate protein-ligand complexes for highly predictive structure-based design.

Best suited for companies and teams:

- Who want to accelerate hit-to-lead and lead optimization to achieve program milestones
- Who want to minimize time spent on preparing and validating structural models
- Who want to leverage Schrödinger's advanced physics-based methods and expertise

Best suited for projects:

- Where SAR data is available and location of the binding site is known, but structural data of the target is incomplete (cryo-EM, low resolution X-ray) or missing (homology model, AlphaFold model)
- Where the chemistry is evolving away from the original project hits or lead series and structural data is becoming suboptimal

Schrödinger

Propel your discovery program with unrivaled technologies and expertise

Create design-ready structures for your unique on-target or off-target

Schrödinger has successfully enabled use of FEP+ for a wide range of target classes, including GPCR, kinases, and more

Benefit from the full impact of Schrödinger technologies at scale

Service includes all computing, licensing, and service hours to perform comprehensive protein target assessment and build accurate structural models

Complement your unique target knowledge with our computational expertise

Schrödinger brings our years of expertise in enabling challenging targets for structure-based drug design with FEP+

Case Study I

Challenge:

Despite a ~3.2Å cryo-EM structure of the target in complex with a ligand from the series of interest, known SAR could not be explained and the program was, effectively, not structurally enabled.

Result:

Our ensemble trial-and-error approach allowed us to identify an alternate ligand binding mode, as well as small but important protein adjustments necessary for binding. Although the binding mode was flipped compared to the model proposed by the structural biology team, it also fit the experimental density and, importantly, was predictive of all known SAR available.

Case Study II

Challenge:

A series of small molecule inhibitors against a flexible protein target was reaching its limits due to the lack of structural insights to guide the design, as well as off-target activity on a homologue.

Result:

Schrödinger enabled accurate FEP+ predictions for the series of interest both on the target and the anti-target. Importantly, it revealed specific loop and side-chain motions that were necessary for the ligands to bind, and remarkably, the results were counterintuitive as they revealed different binding modes in the two proteins despite their high similarity.

Enable FEP+ starting from all levels of structural information

Whether you are starting with template-based homology and AlphaFold models or if you have incomplete cryo-EM or experimental X-ray structures, Schrödinger's team has the scientific expertise and computational resources needed to structurally enable your unique project.

Amount of structural information available

No available target structure

Low resolution structure(s) only

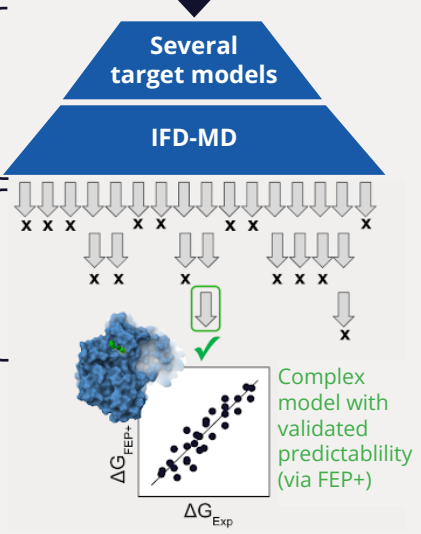
Atomic-resolution for relevant complex

Required inputs

- Target UNIPROT ID
- Binding site
- Ligand SAR

Target enablement workflow (Approx. 3-6 weeks)

1. Ensemble model generation
2. Stepwise model validation and optimization



Deliverables

- Top scoring predictive structural models, which enable prospective FEP+ by your team
- Knowledge transfer to equip your team to structurally enable future projects

Typical FEP+ enabled project

Scientifically-validated solutions for structure-based drug discovery

- Using AlphaFold and experimental structures for the prediction of the structure and binding affinities of GPCR complexes via induced fit docking and free energy perturbation. Coskun D, et al. *J. Chem. Theory Comput.* December 15, 2023.
- Benchmarking refined and unrefined AlphaFold2 structures for hit discovery. Zhang Y, et al. *J. Chem. Inf. Model.* 2023, 63, 6, 1656–1667.
- Induced-fit docking enables accurate free energy perturbation calculations in homology models. Xu T, et al. *J. Chem. Theory Comput.* 2022, 18, 9, 5710–5724.

Enabling digital technologies to drive discovery programs

FEP+

Digital assay for predicting protein-ligand binding across broad chemical space at an accuracy matching experimental methods

IFD-MD

Accurate ligand binding mode prediction for novel chemical matter, for on-targets and off-targets

Speak with an expert to structurally enable your program today

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