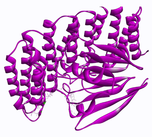
RECEPTOR·AI

AI-ACCELERATED WORKFLOW FOR MOLECULAR GLUE DESIGN

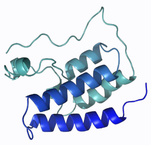
The workflow starts from predicting the structure of the complex of two proteins, which are supposed to be glued together by a small molecule.

Two parallel strategies are used for this:

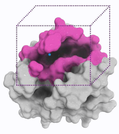
PROTEIN A



PROTEIN B

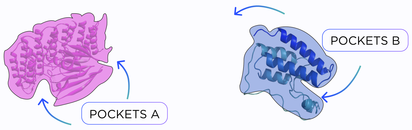


First strategy is based on the identification of small molecules, which bind independently to both of the target proteins. Matching the spatial arrangements of involved pockets from both proteins and aligning them according to the ligand binding poses allows to predict a protein-protein binding interface (PPI).

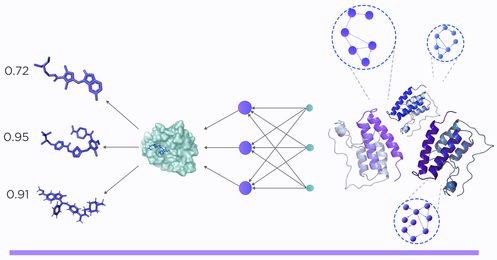


AI-BASED POCKET AND PPI PREDICTION

To find such dual binders we perform an AI pocket prediction for both proteins and run a virtual screening against all identified tentative binding pockets.

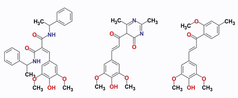


AI virtual screening of stock space or fragment library

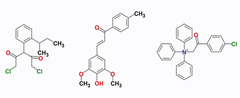


The stock chemical spaces or readily available fragment libraries are used at this stage. The molecules, which are predicted to bind to both protein partners are selected and their binding poses and the corresponding pockets are analyzed.

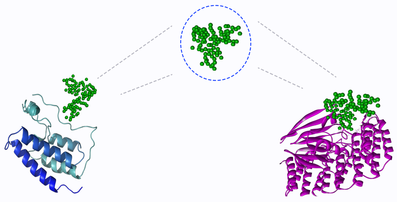
COMPOUNDS FOR POCKET A



COMPOUNDS FOR POCKET B



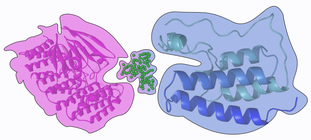
DUAL BINDERS



Pocket matching and spatial arrangement

The second strategy involves direct prediction of the PPI by means of dedicated AI models and the protein-protein docking. Obtained structures of the protein-protein complexes are compared with the predictions of the first approach and the consensus structural model of the PPI is derived as well as the tentative sites for the glues.

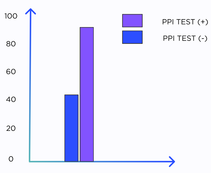
DIRECT PPI PREDICTION (AI + PP DOCKING)



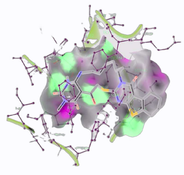
Predicted PPI

The production virtual screening using the full power of the Receptor.AI platform is then performed against the tentative glue locations on the PPI and the candidate compounds are selected from the large and diverse combinatorial chemical space.

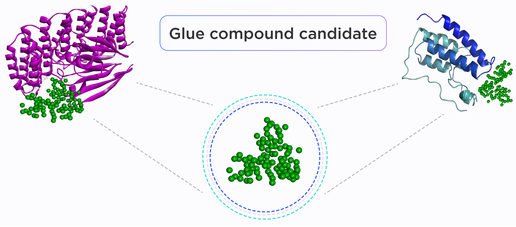
PPI stability assessment (MD)



Production screening



The complexes of the best compounds with the proteins are subject to the stability assessment by means of MD simulations.

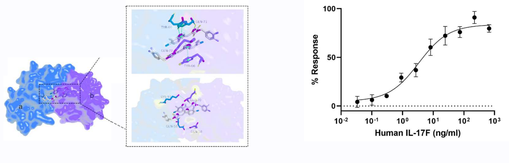


Glue compound candidate

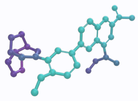
Those compounds, which effectively stabilize the complex are designated as the glue compound candidates. In the next stage the glue candidate compounds' biological activity is evaluated. The complexes with the most active compounds are subject to structure determination by means of CryoEM to confirm their structure and location of the glues.

BIOLOGICAL VALIDATION OF ACTIVITY

STRUCTURE DETERMINATION CryoEM



The compounds, which pass this stage, are designated as confirmed glues and are subject to subsequent lead discovery and lead optimization stages using the standard Receptor.AI workflow.



CONFIRMED GLUE COMPOUNDS