AIMS research plan

Identification of small molecule inhibitors of Mur Ligase

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Project ID	A19-229

Target evaluation

Disease indication	Antibiotics
Purpose	Inhibit Mur Ligase with a small molecule for generation of novel antibiotics
Target UniProt Accession Number	P14900
Target structure type	X-ray

Primary target
Site 1

PDB ID	3UAG
Target site selection criteria	Bound Ligand
Target site residues/chains	Residues: T16 S71 P72 G73 D94 I95 G111 S112 N113 K115 S116 G137 N138 E157 L158 S159 S160 F161 Q162 T165 D182 H183 S318 K319 A320 T321 N322 S325 L342 L343 G344 G345 D346 K348 Y367 C368 F369 G370 Q386 T387 E388 T389 M390 E391 Q392 A393 M394 L397 L408 L409 S410 P411 A412 C413 A414 S415 L416 D417 F419 N421 F422 R425 E428 F429 L432 I11 G12 L13 G14 L15 T16 G17 M34 D35 T36 R37 L57 S71 P72 G73 I74 D94 I95 G111 S112 N113 G114 K115 S116 T117 V118 G137 N138 I139 G140 L141 P142 A143 E157 S159 F161 Q162 L177 N178 D182 H183 R186 H267 N268 T270 N271 L299 R302 F303 D317 K319 A320 T321 G324 S325 A328 A329 K348 L416 F422 I11 G12 L13 G14 L15 T16 G17 M34 D35 T36 R37 L57 S71 P72 G73 I74 D94 G111 S112 N113 G114 K115 S116 T117 G137

	N138 I139 G140 L141 P142 E157 S159 F161 Q162 N178 D182 H183 H267 N268 T270 N271 L299 R302 F303 D317 K319 A320 T321 G324 S325 A328 K348 L416 F422
Residue numbering	PDB

Assessment and recommendations

Site 1 on the primary target Mur Ligase recommended for screening since a high-resolution crystal structure (3UAG) is available with an appropriate target site for screening as evidenced from the crystal structure with bound UMA.

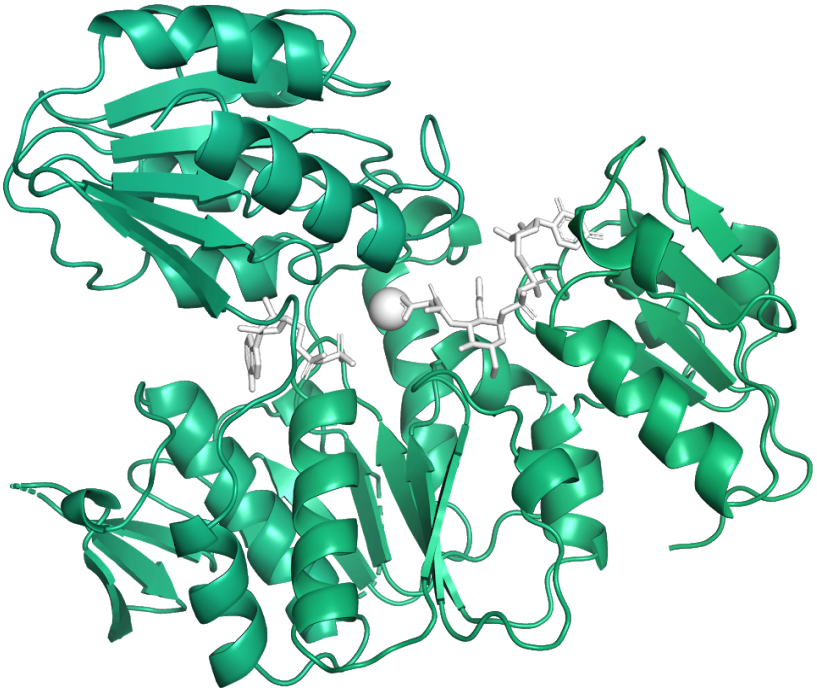
Virtual Screen

Atomwise will screen a molecular library of several million compounds at the selected target Site 1, (Target Evaluation and Figure 1) using AtomNet®, its proprietary technology. AtomNet® is the first deep learning neural network for structure-based drug design and discovery, and its speed and accuracy make it the most advanced technology for small molecule binding affinity prediction. Top scoring compounds will be clustered and filtered to arrive at a final subset of approximately 72 deliverable compounds.

Caveats

This project is experimental in nature. The selected target site may not be relevant to the biological function of the protein, and any model may not represent the relevant biological conformation of the target.

A)



B)

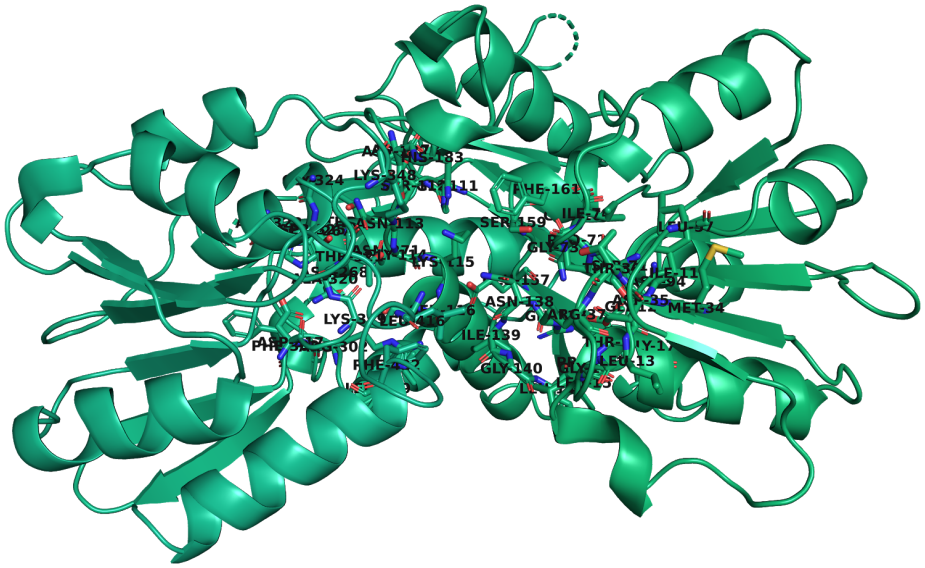


Figure 1. The virtual screening sites on Mur Ligase: A) Site 1 (PDBID: 3UAG) B) Possible Pocket Residues