1. Investigator Information

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How did you hear about us?

LinkedIn

- I am eligible for the award
-
- I agree to the terms and conditions

2. Project Information

Research Area

Infectious Diseases

Disease or Condition of Interest

Antibiotics

Protein Target of Interest

Mur Ligase

What is the role or significance of the protein target in the disease?

Many of the most effective antibiotics target fundamental pathways such as, bacterial cell wall biosynthesis, DNA replication and protein biosynthesis.

Mur ligase are a set of four Mur ubiquitin ligase enzymes: MurC, MurD, MurE, MurF which catalyze the addition of a short polypeptide to UDP-D-acetylmuramic acid in the process of bacterial cell wall buildup from peptidoglycans. The four enzymes, MurC, MurD, MurE, and MurF catalyze sequential ATP-dependent ligations to the growing peptide chain of the developing peptidoglycan unit. More details here https://github.com/opensourceantibiotics/murligase/wiki/Overview

What is the purpose or potential impact of a small molecule intervention?

A Mur Ligase inhibitor would be a potential novel antibiotic

3. Protein Information

Uniprot ID:

P14900

Is an experimental structure (e.g. X-ray crystal structure, NMR, cryo-EM) available for the protein?

Yes

PDB ID or Link:

3UAG

Provide information about the location of the binding site if known (domain or residues).

Fragment screening has identified several potential binding sites however comparison with substrate binding sets suggests only a limited number of the binding sites will have enzyme inhibition activity.

Comments or additional guidance

Fragment screens on both MurD and MurE have been undertaken, the results are fully disclosed on the Open Source Antibiotics wiki MurD https://github.com/opensourceantibiotics/murligase/wiki/MurD-fragment-screen and MurE https://github.com/opensourceantibiotics/murligase/wiki/MurE-fragment-screen
The crystal structures for all these fragments bound to the enzyme are available.

4. Small Molecule Information

Are there known ligands that bind to the target protein?

Yes

If there are any known ligands, please list them here.

The Open Source Antibiotics wiki contains a description of published ligands https://github.com/opensourceantibiotics/murligase/wiki/Overview most (all?) suffer from poor cell penetration.

If there are any specific properties of the small molecule that are desired, please describe them here.

The published ligands have poor cell penetration, possibly due to the number of potential hydrogen bonding interactions and high TPSA. Reducing this would be attractive. Lower molecular weight starting points would also be attractive.

Comments or additional guidance

We would be happy to discuss this in more detail, and would encourage someone from Atomwise to sign up on the Open Source Antibiotics site.

5. Assay Information

Will you test the molecules in an assay that quantifies the protein-ligand interaction (i.e. KD, Ki, IC50)?

Yes

Tell us about your assay(s) that you would use to test the compounds. Please be specific and as detailed as possible.

The first screen would be a crystallographic screen carried out at XChem at Diamond, under the direction of Frank von Delft https://www.diamond.ac.uk/Instruments/Mx/I04-1/Staff/von-Delft.html. More details are available on the website. https://www.diamond.ac.uk/Instruments/Mx/Fragment-Screening.html

Interesting compounds would then be evaluated in Prof Chris Dowson's Lab https://warwick.ac.uk/fac/sci/lifesci/people/cdowson/

Comments or additional guidance

The Open Source Antibiotic project aims to use an open source model with all the results being in the public domain and no associated intellectual property.

More information can be found here https://github.com/opensourceantibiotics

Our aim is that in the future additional molecular targets will be developed under the Open Source Antibiotics Project.