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Poster abstract submission

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Poster title

Orthology- and mutational constraint-guided drug repurposing efficiently identifies narrow-spectrum inhibitor of M. tuberculosis acting through a new target

Poster abstract

The principal challenge of modern antibacterial drug discovery is to discover new small molecules which, without host toxicity, circumvent prevalent resistance mechanisms. One way to meet this challenge is to discover antibacterial molecules acting through new targets. Known antibacterial drugs act through only a handful of the hundreds of essential gene products, indicating a largely untouched antibacterial target space. In contrast, drugs that were not developed to treat bacterial infections (i.e., non-antibiotics) have demonstrated widespread antibacterial activity through mechanisms orthogonal to known antibacterial drugs. Thus, non-antibiotics represent a chemical space enriched in new, albeit mainly unknown, targets.

We discovered that orthology of non-antibiotics' targets to essential proteins in bacteria explained the surprising widespread antibacterial activity of non-antibiotics against Escherichia coli and gut bacteria. Furthermore, we found that mutational constraint of human targets correlated with cytotoxicity. Therefore, we developed a Repurposing by orthology (RepOrt) approach, where we curated ~200 inhibitors whose canonical targets were (i) under low evolutionary constraint, (ii) orthologous to essential proteins in E. coli, K. pneumoniae, S. aureus, and M. tuberculosis, and (iii) not conserved across all bacterial species (i.e. potentially narrow spectrum). We then screened them for growth inhibition of these species. Because each hit molecule was already annotated with a hypothetical target, we could rapidly validate mechanism of action in these pathogens using metabolite complementation or chemical-genetic interactions.

Using RepOrt, we discovered a potent, narrow-spectrum, nontoxic inhibitor of M. tuberculosis that inhibits a previously undrugged target in this pathogen, confirmed using metabolite complementation, chemical-genetics, resistance evolution, and X-ray crystallography. Now, we are testing for microbiome sparing and pharmacokinetics of this inhibitor, and testing other prioritized compounds. Thus, RepOrt retrospectively explains the widespread antibacterial activity of non-antibiotics, and prospectively enables efficient discovery and validation of whole-cell active inhibitors of new targets in pathogenic bacteria.

Research topic

Small molecule therapeutics

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