Pitfalls of Target Validation for Novel Antibacterial Strategies

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Target validation is the process of demonstrating a target is critically involved in the disease process and modulation will have the desired therapeutic effect. Consequently, robust target validation is an essential process in drug discovery and issues with target validation will substantially compromise achieving the therapeutic goals of a drug discovery program. This presentation will focus on the potential pitfalls in target validation in the antibacterial therapeutic area and draw from our experience of progressing >50 different novel targets. One theme will be to highlight the importance of avoiding assumptions based on the essentiality of a target in other species or the essentiality of other steps in an attractive pathway. Furthermore, although bacterial genomes provide a powerful source of information to assess and initiate target validation studies this information only provides the genetic make up of the single strain sequenced and may not be representative of the entire species. For example bioinformatic analysis of the novel antibacterial target methionyl tRNA synthetase (MRS) showed the target to be a promising broad spectrum antibacterial target. However, it will be shown how the discovery of a second MRS in *S. pneumoniae* resulted in the termination of a promising lead optimization program against this target. Furthermore, the presence of this second MRS was not revealed in the *S. pneumoniae* genomes available at that time and thus introduces the need for target validation beyond the genome. The implications of this scenario and other examples of target validation pitfalls will be discussed.