Finding the lock for a key - Identification of the targets of screening hit molecules

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When molecules from phenotypic screens have been identified as hits the main question is: What are the targets of these hit molecules? Targets could be primary target molecules that are affected directly by the hit molecule or secondary targets associated with side effects or polypharmacology. Knowing the targets and potential binding sites of a hit molecule can provide the basis for further optimization of the initial hit, e. g. by structure-based design. But, how can targets and binding sites be identified?

We developed a target identification procedure that is based on hit molecule fragmentation and binding site analogy search using structures from the Protein Data Bank [1], the Credo Database [2], and models of *Mycobacterium tuberculosis* (Mtb) proteins from the Chopin Database [3]. The initial system was developed for Mtb, because tuberculosis is still a wide-spread disease today [4] and a number of drug design efforts have been initiated in recent years in order to fight this disease [5]. The target identification procedure was implemented into a database-based web platform that can be easily handled by medicinal chemists. Furthermore, the database of protein structures can be extended to proteins of other organisms, so that in the future target identification beyond *M. tuberculosis* proteins will be possible. We therefore believe that the developed platform will largely facilitate target identification for phenotypic screening hit molecules.

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[2] Adrian M. Schreyer and Tom L. Blundell. CREDO: a structural interactomics database for drug discovery, *Database*, **2013**, doi:10.1093/database/bat049.
[3] B. Ochoa-Montaño, N. Mohan, T. L. Blundell, CHOPIN - a web resource for the structural and functional proteome of Mycobacterium tuberculosis, *Database*, **2015**, doi: 10.1093/database/bav026.
[4] URL: http://www.who.int/gho/tb/epidemic/cases_deaths/en
[5] E. S. Zuniga, J. Early, T. Parish, The future for early-stage tuberculosis drug discovery, *Future Microbiol.*, **2015**, *2*, 217–229.