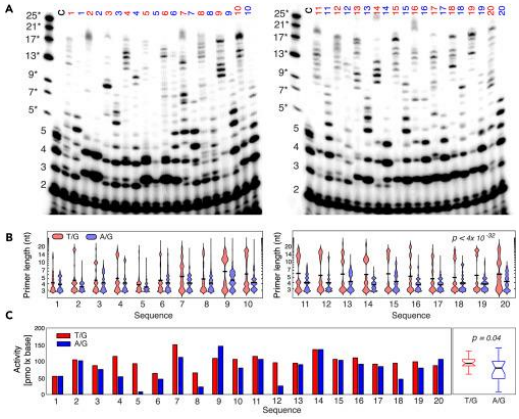
Fragment-Based Virtual Screening for the Detection of New Anti-Infective Drugs

Too few antibiotics are in the pipeline to tackle the global crisis of drug resistance, which is responsible for the rise of hardly treatable infections around the world as the World Health Organization (WHO) warns. Among the multi-drug resistant bacterial diseases that are increasing and spreading at an alarming pace is Mycobacterium tuberculosis (Mtb), which requires a treatment of between 9 and 24 months. There are 250,000 deaths per year from drug-resistant Mtb and only 52% of patients globally are successfully treated. Yet, only 2 new Mtb antibiotics have reached the market in 70 years. The major challenges in developing effective new antibiotics are the long and expensive drug discovery processes. With the increasing numbers of multi resistant bacterial strains novel, shorter and more precise drug discovery processes are needed in order to overcome the threat of lack of appropriate treatment.

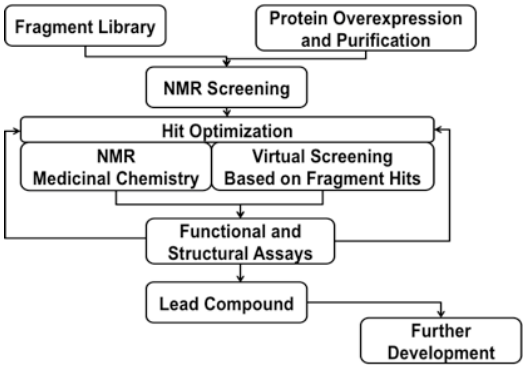
The Technology

We have used Mycobacterium tuberculosis as our first target for new and effective anti-infective compounds. Combining fragment-based screening with NMR and virtual screening (FBVS) we developed a novel approach to select new small molecules that target the bacterial DNaG primase. We used the T7 primase, as our first proof- of- concept target for the screening of new compounds to be followed by the development of additional anti-tuberculosis compounds using our new approach. This same methodology can be used for the discovery of compounds to many other diseases including cancer. Up to date with this methodology we have identified and isolated several compounds that inhibited DnaG primase within the Mtb replisome, leading to the inhibition of bacterial growth.



Advantages

- ✓ Our fragment based virtual screening (FBVS) approach combines tools from different disciplines in drug development that by passes many of the limitations of current drug discovery high-throughput screening in terms of costs and time.
- ✓ FBVS enable the isolation of inhibitors against targeted pathways that cannot be adapted for high-throughput screening and therefore are considered as “undruggable” targets.
- ✓ This platform serves as the basis for the development of inhibitors targeting **any biochemical pathway.**



Scheme 1: Basic principles of the novel combined fragment-based screening and virtual screening technique.

Patent Status

Patent pending

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