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Deorphaning anti-tuberculosis compounds using chemogenomic approaches and data from the ChEMBL database

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Background: The emergence of drug resistant strains of *Mycobacterium tuberculosis* (*Mtb*), the causative agent of tuberculosis (TB), calls for an urgent need for new drugs that have distinct mechanisms of action. To date, several thousands of active compounds against tuberculosis have been identified through high throughput screening (HTS). The challenge then rests identifying the molecular targets and characterising the mechanism of action of these actives.

Methods & Materials: We have embarked on applying computational chemogenomics to facilitate identification of potential new TB drug targets. Such methods involve identification of potential targets for new bioactive compounds using chemical space for bioactive ligands and biological space for their targets [1]. This has been made possible by use of ChEMBL, which comprises the largest, freely accessible, primary bioactivity database. The current release, ChEMBL_17, contains approximately 1.3 million diverse small molecules along with their biological measurements against more than 9,000 annotated targets [2]. Specifically, we analyzed more than 600,000 target-ligand pairs retrieved from the database. Multi-category Naïve Bayesian classifier models were trained using randomly selected 80% of the target-pairs from the dataset. The remaining 20% of the pairs were used to validate the models. The models were then employed to predict targets for 25 clinically used TB drugs, 13 drugs under clinical development, and 773 orphan anti-TB hits.

Results: The models correctly assigned several validated *Mtb* targets to their respective ligands, e.g. fluoroquinolones were predicted to interact with the protein DNA gyrase and also with a novel potential target, Isocitrate lyase. 419 highly ranked target-ligand pairs contained *Mtb* proteins and ~33%, 13%, 5%, of compounds were assigned kinases, hydrolases, and phosphatases, respectively, as their potential *Mtb* targets.

Percentage of compounds assigned to different Mtb protein families

Conclusion: We have predicted potential targets for the current TB drugs and for anti-tuberculosis hits. The results could go a long way in facilitating reduction of drug resistance and help alleviate the health burden caused by tuberculosis. Follow-up biological experiments will be carried out in order to validate the predicted targets.

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Effectivity of Daptomycin therapy in patients with febrile neutropenia

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Background: Daptomycin (DAP) has the most potent in vitro and bactericidal activity against Gram-positive (G+) pathogens in comparison to other anti-MRSA agents (vancomycin teicoplanin, linezolid and tigecycline). Clinical data for DAP in the treatment of neutropenic patients are limited. The aim of this study was to evaluate the efficacy of DAP in febrile neutropenic patients.

Methods & Materials: We evaluated data of neutropenic patients who treated with DAP at Adult Hematology Unit of our hospital between Jan 2011 and April 2013. Neutropenia was classified based on the neutrophil count as severe (<100/mm3), moderate (101-499/mm3), and mild (500-100/mm3). Clinical outcomes included cure, improved, failed and nonevaluable response. Clinical success described patients with an outcome of cure or improved.

Results: In the study period, 43 neutropenic patients (55.8% male, median age 50. 8 ± 13.7 min: 19 max: 75) who used DAP were idantified. All patients had hematological malignancies and 21 (48.8%) patients had severe neutropenia. 40 (93%) patients received antibiotics prior to DAP therapy, including teikoplanin (63%), imipenem (49%), piperacillin-tazobactam (40%), others (9%). Skin and soft tissue infections (%75) was the most common diagnosis. G+ organisms were identified only in 12 patients (27.9%). Enterococcus feacium was the most common G+ pathogen (7/12). The initial dose of DAP was 6 mg/kg in all patients and the median duration of therapy was 15.5 days (range 2-45). Overall clinical success was 82.5% (33/40). Clinical success rates were 84%, 72%, 90% in severe, moderate and mild neutropenic patients, respectively. The success rates in patients receiving daptomycin as first-line therapy was 100% (12/12) compared with 75% (21/28) success rate in patients who received daptomycin as second-line therapy. Success rates were 83% for bacteraemia and 81% for skin and soft tissue infection in patients with neutropenia. Daptomycin was well tolerated. No advers event related to DAP was reported.

Conclusion: Daptomycin was highly effective and safe in the treatment G+ infections in neutropenic patients with hematological malignancies.

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