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Targeting isoprenoid biosynthesis pathway in *Staphylococcus lugdunensis*: Comparative docking and simulation studies of conventional and allosteric sites

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ABSTRACT

The current study establishes the use of *in silico* subtractive genomics approach, molecular docking and molecular dynamic (MD) simulation studies for identifying and inhibiting a potential therapeutic target protein involved in vital metabolic pathways and is therefore crucial for the survival of the human pathogen *Staphylococcus lugdunensis*. Filtering all the druggable target proteins based on cellular localization and functional annotation has led to the selection of farnesyl diphosphate synthase (Fds). Fds is the key enzyme involved in isoprenoid biosynthesis pathway. Homology model of the protein was generated *via* MODELLER and other web-based servers. Most reliable protein model selected on the basis of comparative analysis was used as an input for molecular docking studies performed using a total library of 374 compounds. Both conventional and allosteric binding sites were probed to assess the inhibitor binding potential. Among the studied compounds, non-bisphosphonate bisamidines, compound 160 (GOLD Score 79.8) and compound 193 (GOLD Score 87.84) were the top scoring compounds against the normal and allosteric binding pockets, respectively. MD simulations were applied further to explore the dynamic behaviour of both complexes in order to get an insight into structural and conformational changes induced upon ligand binding. MD simulation results revealed that the allosteric binding pocket was slightly more compact and stable when compared to the conventional binding pocket. Significant conformational changes including considerable side chain movements were observed in the binding site amino acid residues accompanied by rearrangement of the hydrogen bonding pattern in conventional and allosteric binding pockets.

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1. Introduction

The efficacy of antibiotics is widely endangered by the rapid emergence of resistant pathogen strains due to the frequent and prolonged use of these medications [1–3]. Since the discovery, antibiotics have aided in extending the expected life spans by killing bacterial pathogens. However, according to a current estimate, nearly 700,000 people die every year by antimicrobial resistance [4]. The antibiotic resistance crisis is posing a significant financial and clinical burden on the healthcare system worldwide [1]. Recent developments in the field of computational biology have generated numerous *in silico* drug design and discovery approaches that have played a crucial role in combating multiple drug-resistant pathogens while reducing the cost and time involved in traditional drug discovery [5,6]. Subtractive genomics is one such *in silico* method that helps in shortlisting the potential drug targets based on their essential role in the pathogen and absence in the host [7–9]. *In silico* subtractive genomics approach helps in identification of species-specific vital proteins accountable for the distinctive phenotype as well as for the virulent factors of the pathogen. Current study incorporates a similar approach to screen the proteome of *Staphylococcus lugdunensis* for the identification of potential druggable target proteins.

S. lugdunensis, an emerging human pathogen is known to be implicated in nosocomial and community-acquired infections. It is a habitual colonizer of human skin and is only pathogen accountable for 10% of skin and soft tissue cellulitis. In addition to these infections, it is reported to cause endocarditis with high mortality rate, abscesses, meningitis, ventriculoperitoneal shunt infection, spondylodiscitis, prosthetic joint infections, catheter-related bacteremia, septic arthritis, endophthalmitis, osteomyelitis, peritonitis and toxic shock syndrome [10–12]. It is a Gram-positive, coagulase-negative and catalase-positive bacterium which is clinically more identical to *Staphylococcus aureus* owing to its pathogenesis and virulence. *S. lugdunensis* was thought to be invariably

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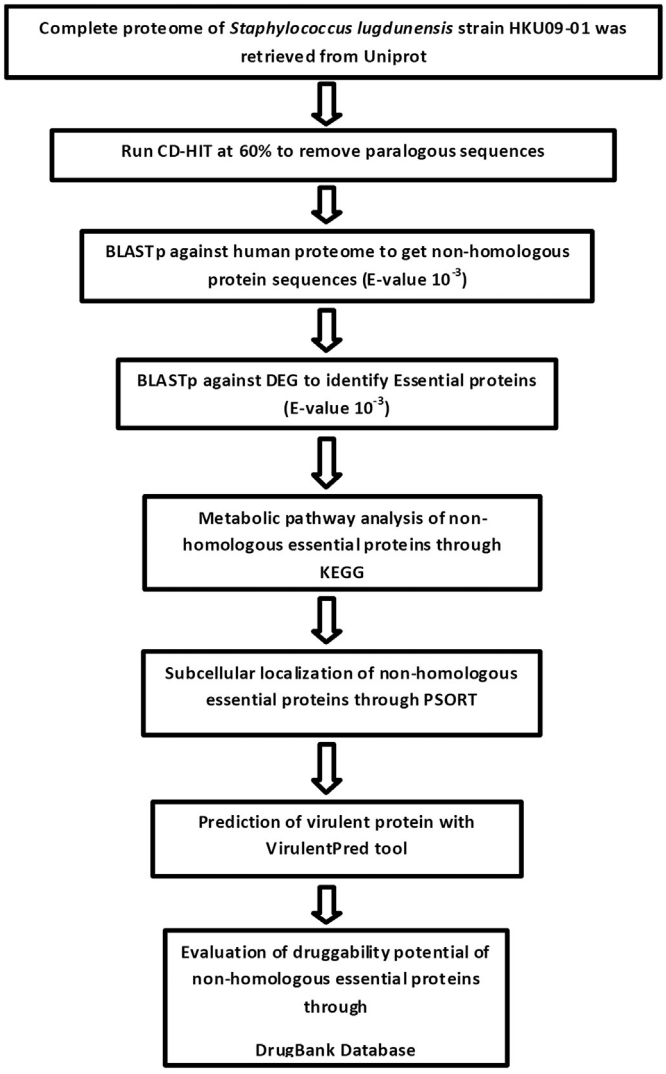

Fig. 1. Flow chart of systematic identification of novel targets in *S. lugdunensis* HKU09-01.

Table 1
Number of proteins followed at the end of each step of subtractive genomics approach.

Total number of proteins	2456
Paralogous removal by CD-HIT (>60% identical)	2428
Number of non-homologous proteins against *H. sapiens* using BLASTp (*E*-value 10^{-3})	2171
Essential proteins in DEG (E-value 10^{-3})	667
Essential proteins involved in unique bacterial pathways (KEGG)	132
Number of essential membrane proteins (PSORT-B)	24
Number of essential cytoplasmic proteins (PSORT-B)	97
Number of virulent essential proteins (VirulentPred tool)	41
Essential drug target proteins (DBD)	4

defenseless against antibiotics such as penicillin and cephalosporin. However, resistance of this bacterium, to the antibiotics penicillin, methicillin, tetracycline, erythromycin, cefoxitin, and clindamycin has been reported [12–17].

In the current study, molecular drug target identified against human pathogen *S. lugdunensis* is farnesyl diphosphate synthase (Fds) (EC 2.5.1.10). It is a critical enzyme involved in isoprenoid biosynthesis pathway. Fds enzyme belongs to the *E*-family of the prenyltransferases and mainly catalyzes the condensation of two molecules of dimethylallyl pyrophosphate (DMAPP) with its isomer isopentenyl pyrophosphate (IPP) to produce farnesyl diphosphate (FDP). FDP acts as a substrate to yield essential molecules such as ergosterol and cholesterol in both the mevalonate and non-mevalonate pathways [18]. Fds provides precursors for the synthesis of crucial isoprenoids including ubiquinones, sterols, withanolides and dolichols. Moreover, it participates in the biosynthesis of bacterial cell wall during early development and ubiquinones during cellular respiration. Aforementioned functions classify Fds as a key enzyme crucial for the survival of bacterial pathogen [18,19]. Farnesyl diphosphate synthase is Mg2+ dependent homodimeric enzyme composed of two subunits of substrate binding sites. It has an allylic binding site for DMAPP and a single homoallylic binding site for IPP in each subunit. Fds enzyme contains highly conserved aspartate-rich motifs involved in its catalytic activity. It is a major enzyme targeted in humans to treat various diseases including osteoporosis, Paget's disease, and hypercalcemia. Various research studies have proved Fds a key target protein for the drug development against several types of cancers and also towards the human pathogens (Dhar et al., 2013).

Following the identification of a potential therapeutic target Fds in *S. lugdunensis* molecular docking studies were conducted to

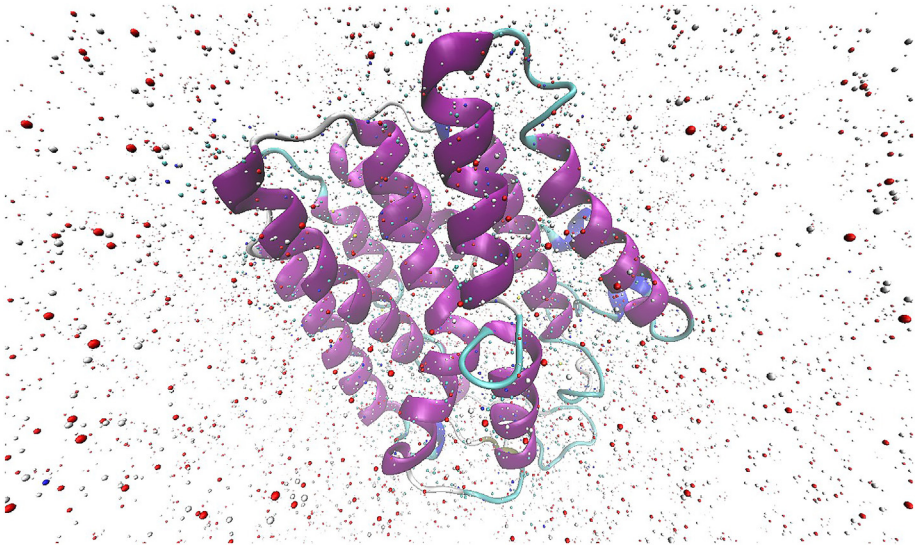

Fig. 2. 3D structure representation of Fds Protein inside TIP3P water box.

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