In-silico desing of drug and vaccine for Leptospirosis

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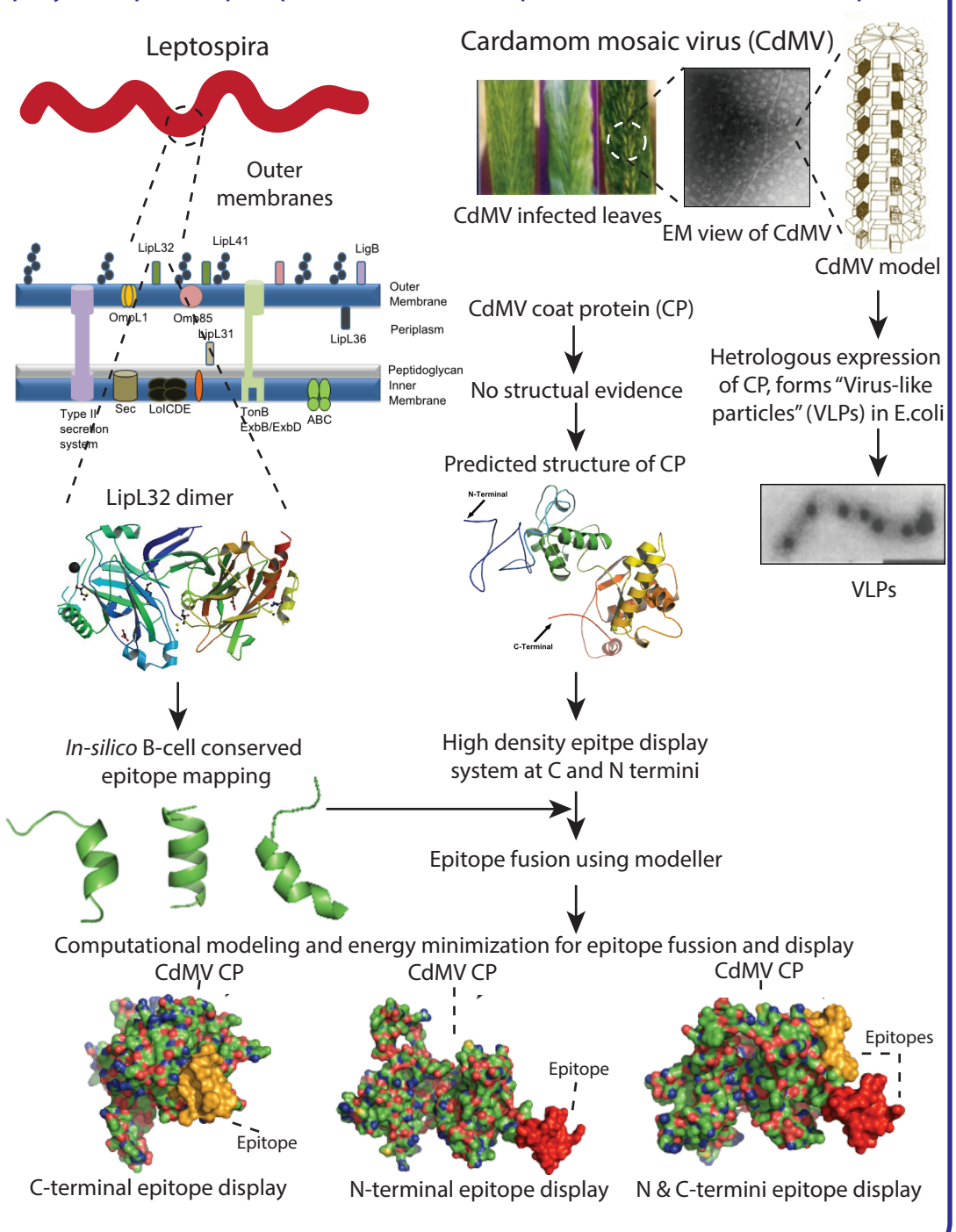
Abstract

Leptospirosis is a global zoonotic disease caused by the spirochete *Leptospira*. The pathogen enters the human body through cuts, wounds, sodden skin or abrasion, initiates an infection and caused multiple organ disorder. During the invasion, *Leptospira* secretes extra cellular collagenase and other proteases to dissolve the extracellular matrix of the host cells and attaches itself to the host surface through various surface associated proteins LipL21, LipL32, LipL36, LipL41, and LipL48. Hence, we targeted LipL32 as vaccine candidate and predicted chemical inhibitors against Leptospira collagenase structure as drugs.

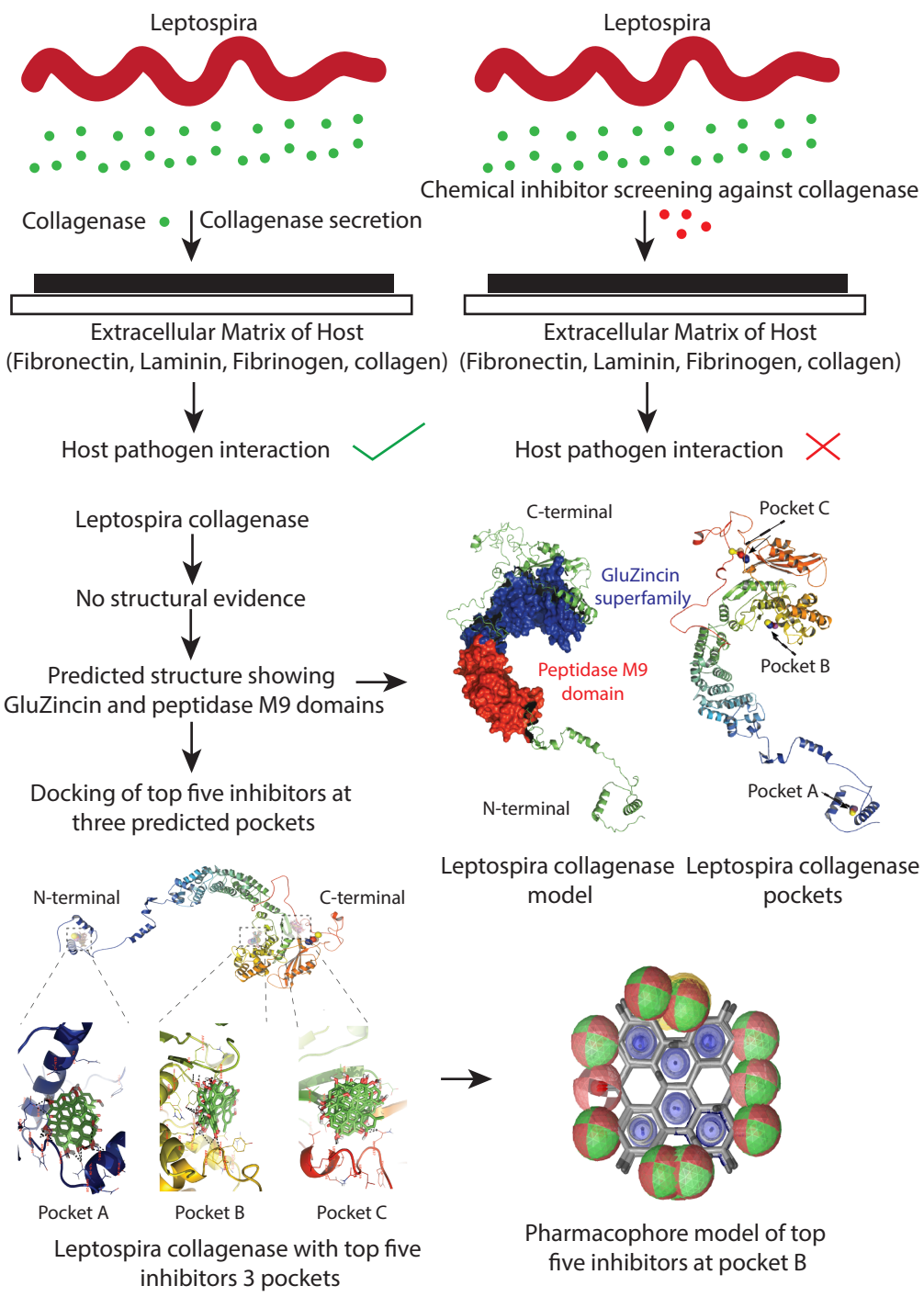
LipL32 is an abundant surface, surface exposed, conserved, highly antigenic lipoprotein and found to be biomarker for Leptospirosis. Due to lack of proper LipL32 epitope presentation, the present recombinant vaccines did not show a good immune response. Therefore, In this study, we used coat protein (CP) of *Cardamom masaic virus* (CdMV) as a epitope display system for displaying and enhance immune response of *in-silico* mapped potential B-cell epitope of LipL32.

Comparative genome and transcriptome analysis has shown the collagenase gene is only expressed in pathogenic strains of *Leptospira* and its expression increases 49 fold during host adaption. Therefore, we predicted its collagenase structure, screened inhibitors, and docked at three potential pockets as drug.

Display of LipL32 epitope on CdMV coat protein for vaccine develpment



Protohypericin: A potential inhibitor for Leptospiral collagenase



Results and Conclusion

Six sequential and conformational B-cell epitopes of LipL32 from its monomeric crystal structure were predicted by using IEDB Elipro, ABCpred, BCPRED, and Vaxi-Jen servers. These epitopes were modeled at N, C and both the termini of CdMV CP and checked for display. Our result showed that epitopes 4 (EP4) amino acids sequence (IPNPPKSFDDLKNIDTKKL) displayed at N-terminal of CdMV CP is a promising candidate for vaccine development. Based on the type of amino acids, length, surface accessibility, and docking energy with CdMV CP model, the order of antigenicity of the LipL32 epitopes was found to be EP4 > EP3 > EP2 > EP6. Order of quality of epitope displayed on CdMV CP models is found to be CdMV CP-EP4 > CdMV CP-EP3 > CdMV CPEP2 > CdMV CP-EP6. Thus, CdMV CP with epitope 4 can be used as a high-density epitope display system for vaccine development.

Bioinformatics analysis of collagenase of *Leptospira interrogans Icterohaemorrhagiae serovar copenhageni* (Fiocruz L1 – 130) revealed that it belongs to peptidase M9 of gluzincins family and is conserved among 32 different strains of *Leptospira interrogans*. It is predicted to be an extracellular protein with N-terminal signal sequence. The sequence alignment of collagenases has shown that it contains motifs of Zinc metallo protease. The model of Leptopsira collagenase was built by threading method with the crystal structure of collagenase G and further refined by SPDB viewer and 3Drefine. Three ligand binding sites at N- terminus, catalytic site and C-terminus were predicted by Metapocket server. Among sixty seven inhibitors from the ChEBI and Zinc databases, Protohypericin binds at the catalytic site was predicted as the best inhibitor (-9.7 kCal/mol) for Leptospiral collagenase.

References

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