SB/FT/LS400/2012-DST YOUNG SCIENTIST

Salient features

Synthetic circuits are being used for controlling the emergence of infectious diseases. One of the many applications of synthetic biology is to reengineer the existing biological networks. Sphingolipids play an important role in controlling the infectivity and viability of parasite 'Leishmania'. To reduce the sphingolipid content with a purpose of rewiring the sphingolipid metabolism of the parasite, a tristable genetic circuit was constructed. Time course behavior of the system favored the production of a target protein 'SLS4' which is present in trypanosomes. SLS4 protein is capable of converting the IPC to sphingomyelin. With an increased and sustained production of SLS4 it is expected that such synthetic circuit would be able to target the parasite proliferation within the macrophages of the host.

The *in silico* circuit design has been submitted and curated by the **Biomodel database [MODEL150170000]** for a reproducible circuitry dynamics and the said model is available in public domain. (https://www.ebi.ac.uk/biomodels-main/BIOMD0000000584)

BT/PR6037/GBD/27/372/2012-DBT RGYI

Salient features

Systems biology aims to develop mathematical models of biological systems by integrating experimental and theoretical techniques by leveraging on the genome wide data to unravel the complexity of gene regulation. Despite the availability of effective chemotherapy, leishmaniasis continues to be one of the major parasitic infections to affect the human population worldwide. Currently, little is known of the structural biology of the parasites that are responsible for the disease and few attempts have been made to develop second generation drugs, which may become essential if multi-drug resistance arises. Multiscale modeling and simulation techniques permit us to study the spatial and temporal properties of large systems to be simulated using atomic-detail structures. The estimation of kinetic parameters for the mathematical modeling provides a basis for iterative manipulation of biochemical pathways. In particular, the focus is laid onto the evaluation of the model by emphasizing on the prediction behaviors of gene regulatory network and also whether it represents the true structure of the system. Quantitative stochastic models of molecular interaction networks help understand the behavior of complex systems of *L.major*. These techniques are carried out upon treating a biological process as a system of equations, represented by their rate constants and other parameters and simulating their interactions through numerical techniques. The numerical simulations capture the effects of genes and their expression level through the time-course of evolution at molecular concentration. Combining the mathematical modeling with homology modeling via protein

docking based techniques would further unravel structural insights into the deeper understanding of designing inhibitors for chemotherapeutic intervention.

Through this systems biology project, we identified

- Crucial enzymes (IPCS, SPT, SPL and ISCL) which were essential in the lipid metabolism of the parasite.
- Developed inhibitors against these enzymes.

We tested these inhibitors for anti-leishmanial properties, both *in vitro* and *in vivo*.

In nutshell, we can say that the project has led to the identification of a new lead compound which may be further explored for laying a mechanistic insight into the action of the drug and thereby its effect on leishmaniasis**.**

Media Coverage: 1) THE HINDU, leading national newspaper (31.10.2016)

2) Science Media Centre, IISc Bangalore

3) Deccan Herald

The citations have been uploaded separately as an attachment file in citation file document endorsed by the nominator.

Our lab is focused on Systems biology and Synthetic biology for aiding precision biotherapeutics.