OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Biothreats & Biodefense

October 15-17, 2012 DoubleTree by Hilton Chicago-North Shore, USA

FDTS enzyme as a target for infectious diseases and biowarfare agents

Irimpan I. Mathews
SLAC, Stanford University, USA

Thymidylate synthesis is the terminal step in the sole de novo synthetic pathway to deoxythymidine monophosphate (dTMP), a nucleotide essential for the synthesis of DNA. Thymidylate synthase (TS) catalyzes this crucial reaction. TS inhibition stops DNA production, arresting the cell cycle and eventually leading to "thymineless" cell death. Flavin-dependent Thymidylate synthase (FDTS) are encoded by the thy1/thyX gene and are not homologous to classical TS encoded by thyA and thyB genes. FDTSs are essential for cell survival of many pathogenic organisms (*Treponema pallidum* (syphilis), *Bacillus anthracis* (anthrax), *Mycobacterium tuberculosis* (tuberculosis), *Mycobacterium leprae* (leprosy), *Borrelia burgdorferi* (Lyme disease), *Helicobacter pilori* (gastric ulcer), *Clostridium botulinum* (botulism), *Rickettsia prowazekii* (epidemic typhus), and *Chlamydia pneumoniae* (pneumonia) are FDTS family members). FDTSs provide a unique alternative for the development of antimicrobials capable of simultaneously targeting a wide range of organisms with potential use as biological weapons. Thymidylate synthases use N^5,N^{10}-methylene-5,6,7,8-tetrahydrofolate (CH_2H_4folate) to reductively methylate 2'-deoxyuridine-5'-monophosphate (dUMP) producing dTMP. In contrast to classical TSase where the cofactor CH_2H_4folate provides both the H- and methylene, in the FDTS reaction the H- is provided by the $FADH_2$ and CH_2H_4folate is used only as a source for the methylene moiety. The absence of homology between FDTS and classical thymidylate synthase offers the possibility of developing specific inhibitors for many pathogenic microbes including various biowarfare agents. We have identified the folate binding site of the FDTS enzyme that will enable the design of inhibitors for use as antimicrobial compounds against deadly microbes.

Biography

Irimpan Mathews works at SLAC, Stanford University as a Staff Scientist. He has around 20 years of experience in structural biology including pharmaceutical industry. Main focus of his research is the mechanistic study of enzymatic reactions with an emphasis on structure-based drug design. He has published more than 45 papers in reputed journals.

iimathew@slac.stanford.edu, iimathew@stanford.edu