BiophysTO Lunchtime Seminar Series

Date
Thursday Sept 12, 2019
12 - 1 pm

Location
McLennan Physical Laboratories, Rm MP606
60 St. George Street

Pizza and refreshments will be provided

Dr. Walid A. Houry

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Development of Novel Antibiotics that Dysregulate the ClpP Protease

There has been an alarming increase in the number of reported cases of antibacterial resistance especially in hospital settings. Despite the introduction of some new compounds in recent years, most of these are derivatives of pre-existing classes of antibiotics and, hence, are prone to the current multi-drug resistant mechanisms employed by bacteria. To avoid cross-resistance, the development of novel antibiotics with new mechanisms of action are needed to tackle the growing crisis. The discovery of a novel antibacterial target, the caseinolytic protease P (ClpP), has been the subject of recent studies. In targeting ClpP for antibiotic development, several inhibitors have been developed. More recently, compounds that dysregulate ClpP have also been identified. Our efforts have concentrated on the development of ClpP dysregulators (also termed activators) for Gram-negative bacteria. In this study, we describe the generation and characterization of a large number of analogues of ClpP dysregulators. We concentrated our efforts on targeting *Neisseria meningitides* ClpP (NmClpP) and *Escherichia coli* ClpP (EcClpP). Several compounds showed potent activities against the bacteria. X-ray cocrystal structures of ClpP with compounds were also obtained. Based on these structures and on mutational analyses, we propose a novel mechanism by which these compounds activate ClpP.

Host: Dr. Sidhartha Goyal

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