De novo design of acyl-homoserine lactone synthase inhibitors

Anna Krzywdzinski, Jude Morgan, Heather L. Gordon, and Hongbin Yan
Department of Chemistry, Brock University, St. Catharines, ON, Canada L2S 3A1

Quorum sensing is a way for bacteria to communicate and form a biofilm that is resistant to antimicrobials and host immune systems. In *Pseudomonas aeruginosa*, quorum sensing involves the reaction (Figure 1) catalyzed by acyl-homoserine lactone (AHL) synthase LasI (Figure 2: PDB ID: 1RO5), which produces 3-oxo-C12-AHL from the substrates 3-oxo-C12-acyl-carrier protein (acyl-ACP) and S-adenosyl-L-methionine (SAM). In the absence of 3-oxo-C12-AHL, bacteria are unable to communicate and cannot form the resistant biofilm.

The overall objective of this research was to develop novel inhibitors of LasI, via a *de novo* design strategy. Since the coordinates of the substrates acyl-ACP and SAM in complex with LasI are unknown, the first goal was to locate their binding pockets by docking. Both ArgusLab and GOLD were used to dock the substrates into the crystal structure of LasI. Second, a fragment of the docked SAM was used as a seed to design LasI inhibitors for potential use as antibacterial agents. The program LigBuilder uses a genetic algorithm to grow the seed structure from predefined sites by extending into vacant cavities of the protein.

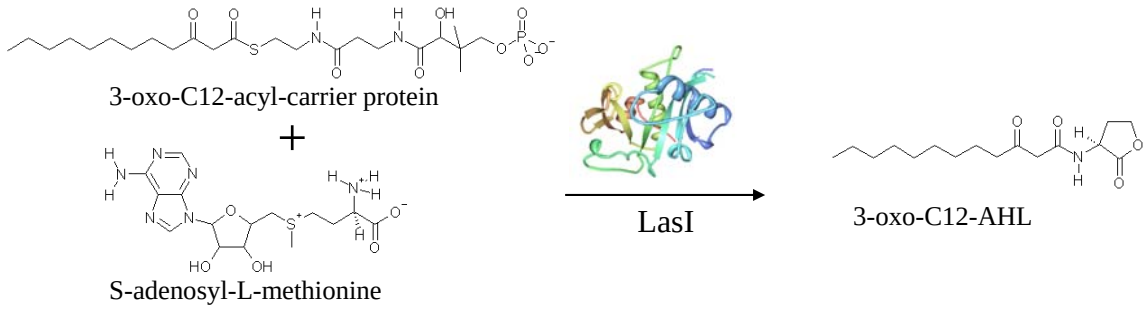

Figure 1: Schematic diagram illustrating the general AHL reaction.

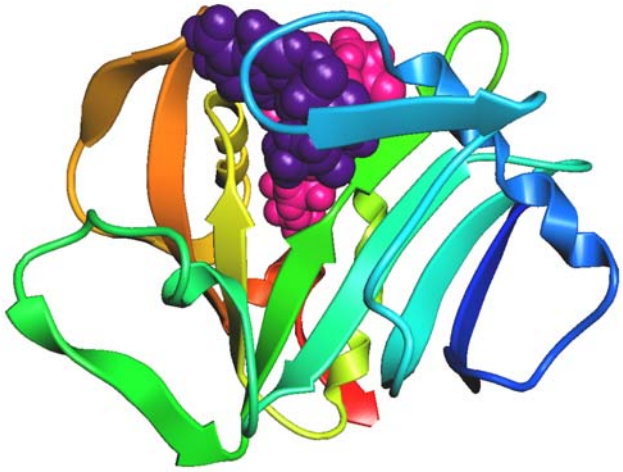

Figure 2: X-ray crystal structure of the AHL synthase LasI (PBD ID: 1RO5) with docked acyl-ACP (pink) and SAM (purple).