Wednesday, April 24, 2024
4:00 P.M. By Zoom

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Biochemistry & Molecular Biophysics Seminar

Activation and Incorporation of Rare Sugars into Bacterial Surfaces

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Our planet is inhabited by trillions of bacteria that live inside and outside of humans. The "skin", or surface, of bacteria is called the cell envelope, which mediates infection of the host and protects bacteria from host immune defense tactics. While Gram-negative bacteria contain a protective outer membrane layer absent in most Gram-positives, almost all bacteria contain polymers composed of unique monosaccharides that extend from the cell surface. Gram-negative bacteria typically contain lipopolysaccharide (LPS) in the outer leaflet of the outer membrane with attached polysaccharides called O-antigens that help mediate interactions with the environment. O-antigens are composed of repeating oligosaccharides that define particular bacterial serotypes, which distinguishes bacterial strains within a single species. Foundational chemical biology work has contributed to our understanding of eukaryotic cell surface composition. However, we still lack a clear understanding of assembly of bacterial surface glycan polymers that contain prokaryote-specific or "rare" sugars. Here, we describe synthetic and chemoenzymatic methods to construct rare nucleotide sugars to study substrate recognition by bacterial glycosyltransferases that build O-antigens. We identify key regions in sugar substrates that are required for substrate binding and activity, and we use this knowledge to design chemical probes that will be used for the construction of synthetic O-antigens and small molecule inhibitors that will stall O-antigen synthesis. This work will expand our understanding of cellular mechanisms underlying bacterial polysaccharide synthesis, and will teach us about the roles that rare sugars play in bacterial cellular interactions.