Structure Determination of Outer Surface Protein BBA57 From the Lyme Disease Pathogen Support the Structure-Based Design of Needed Therapeutics

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Advances in structural biology technologies support the structure-based design of drugs against infectious diseases. To support novel drug development against Lyme disease, here we review structural biology efforts for the tick-borne pathogen and spirochete bacterium Borrelia burgdorferi. Annually, Lyme disease infects over 400,000 Americans. Many are unaware that they have been infected due to problematic diagnoses and to undetected symptoms that are variable and non-specific. Some 10-20% of those infected suffer from lifelong, untreatable, and debilitating symptoms of Lyme arthritis, heart inflammation (Lyme carditis), and neurological complications (Lyme neuroborreliosis). B. burgdorferi accomplishes pathogenesis and invasion of various human tissues by the action of over a hundred outer membrane lipoproteins that are unique to the genus Borrelia and that are upregulated only upon mammalian infection. To date, there are no published reports of the application of X-ray free electron lasers or cryo-electron microscopy to any spirochetal pathogen. Existing reports of atomic-resolution structures of the outer membrane proteins of B. burgdorferi were accomplished using synchrotron X-ray crystallography and, importantly, relied on recombinantly expressed protein that was not directed to the bacterial cell membranes. Our group recently pioneered the membrane-translocated recombinant expression of outer membrane proteins from B. burgdorferi, in which we identified the novel result that the arthritogenic BBA57 outer membrane lipoprotein forms an oligomeric (homo-multimeric), alpha-helical pore that crosses the outer surface of the Lyme disease pathogen. This pore is analogous to those previously identified by X-ray crystallography in the outer surface of pathogenic Proteobacteria and that function in the formation of biofilms and toxins, adhesion to tissues, evasion of the immune system, secretion of biomolecules, and active drug export. Our efforts are expected to reveal the first atomic-resolution structure of a membrane-translocated outer membrane protein from B. burgdorferi. These structures will enable the structure-based design of anti-arthritic drugs and anti-infectives that will prevent Lyme disease and aid patients who suffer from persistent symptoms.