

4. Susan Lea

Structural Studies of Host-Pathogen Interactions

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Disease resulting from infection of a host by any organism, be it viral, bacterial or fungal, must, *a priori*, involve formation of complexes between proteins derived from the invading organism and the host. We are using a variety of methods to look at the constraints that formation of these complexes places on the evolution of both the pathogenic agent and the host and, in the long-term, hope to exploit structural information about such complexes to develop therapeutic agents.

This year we have determined novel structures for several pathogen and host derived proteins. A long-standing interest in the essential interactions between viruses and their receptor molecules (e.g. Lea & Stuart 1995, Lea et al 1998 & Fry et al 1999) has this year been focused on studies of Echoviruses 11 and 12 (EV11, EV12), human picornaviruses. Most infections with these viruses are symptomless but in neonates, and occasionally in adults, infection with EV11 can lead to meningitis and cardiac myopathies. In collaboration with David Brown and others at the University of Cambridge we have solved the structure of an EV11 derived from a clinical sample at 2.9Å (Stuart et al 2002). This EV11 uses Decay Accelerating Factor (DAF, CD55) as a receptor and the structure provides a framework for understanding of a series of mutant viruses which demonstrate that simple changes in the amino acid composition of the coat proteins allow this virus to become independent of CD55 in its infection process. Our recent structure of its receptor, the complement regulator CD55 (Lukacik et al 2004) and of CD55 in complex with EV12 (Bhella et al 2004) have begun to extend our understanding of many aspects of this multifaceted protein.

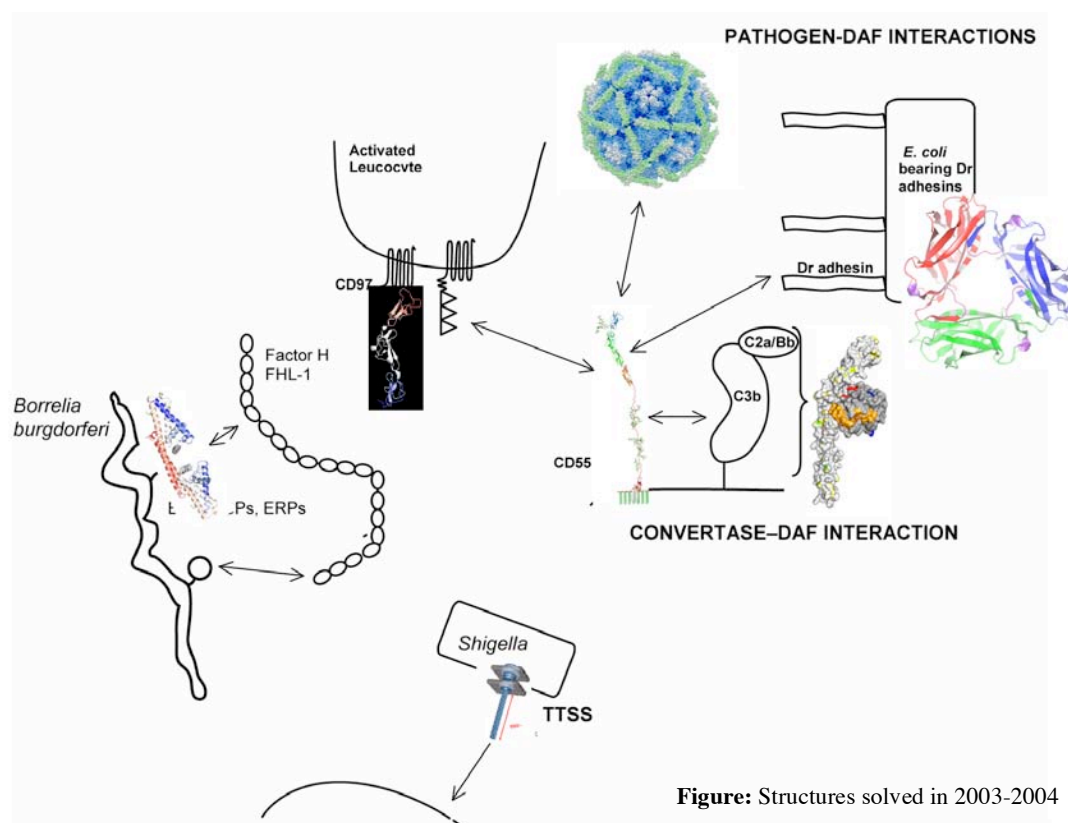


Figure: Structures solved in 2003-2004

More recently we have begun to study bacterial systems relevant to pathogenesis with atomic structures solved this year for two bacterial adhesions (Anderson et al, 2004 & Pettigrew et al 2004), for a Borrelial protein critical for the chronic forms of the disease (Cordes et al, submitted) and a low resolution structure for the Shigella needle (Cordes et al 2003). This work has moved forward rapidly with our collaboration with Dr. A. Blocker leading to the first structural evidence of multiple helical states for the needle being linked to the functional state of the needle (Cordes et al, submitted) and with the production of crystals for the needle subunit and for one of the components of the translocon.

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