

4. Susan Lea

Towards a structural understanding of pathogenesis.

Knowledge of the way in which an invading pathogen interacts with its host at a molecular level is an essential aid to understanding the nature and extent of disease caused. My group aims to use a variety of techniques to probe the interactions that characterise different disease processes. Central to this approach is the use of X-ray crystallography to determine the structures of individual host or pathogen components, with a view in the longer term to examining the atomic structure of important host-pathogen complexes. The major targets are protein based but we are also involved in projects where folded RNAs provide the structural target. To aid understanding of biochemical and structural data we use a variety of other biophysical techniques (including surface plasmon resonance) to further characterise the biological systems under study. The main systems studied during 2004-2005 are summarised below.

Complement Regulation

Pietro Roversi, Rachel Abbott, Frank Cordes with the groups of Dr. C. Harris and Prof. P. Morgan (University of Cardiff), and Prof. P. Zipfel, Dr R. Wallich and Dr P. Kraiczy (Germany).

1. Harris, C.L., Abbott, R.J.M., Smith, R.A.G., Morgan, B.P. & **Lea, S.M.** (2005) Molecular dissection of interactions between components of the alternative pathway of complement and decay accelerating factor (CD55) **J. Biol. Chem.** 280, 2569-2578.

In this paper we use surface plasmon resonance to dissect the interactions between various complement regulators and the alternative pathway convertase.

2. White, J., Lukacik, P., Esser, D., Steward, M., Giddings, N., Bright, J., Fritchley, S.J., Morgan, B.P., **Lea, S.M.**, Smith, G.P. & Smith, R.A.G. (2004) Biological activity, membrane-targeting modification and crystallization of soluble human decay accelerating factor expressed in *E.coli*. **Prot. Sci.** 13, 2406-2415

This describes expression and refolding of a human complement regulator CD55 from a bacterial expression system.

3. Lukacik, P., Roversi, P., Smith, R.A.G. & **Lea, S.M.** (2005) From Structure to Function of a Complement Regulator: Decay Accelerating Factor (CD55) Chapter in **Structural Biology of the Complement System**, editor Lambris, J.D.

4. Cordes, F.S., Kraiczy, P., Roversi, P., Simon, M.M., Brade, V., Jahraus, O., Goodstadt, L., Ponting, C.P., Skerka, C., Zipfel, P.F., Wallich, R. & **Lea, S.M.** (2005) Structure-function mapping of BbCRASP-1, the key complement factor H and FHL-1 binding protein of *Borrelia burgdorferi*. **Int. J. Med. Microbiol.** *in the press*

5. Cordes, F.S.* , Roversi, P.* , Kraiczy, P., Simon, M.M., Brade, V., Jahraus, O., Wallis, R., Skerka, C., Zipfel, P., Wallich, R., & **Lea, S.M.** (2005) A novel fold for the factor H-binding protein BbCRASP-1 of *Borrelia burgdorferi*. **Nat. Struct. & Molec. Biol.** 12, 276-277

The preceding two papers describe our attempts to generate a molecular explanation of the way in which a pathogen hijacks human complement regulators to avoid destruction in the blood stream.

Shigella flexnerii Type Three Secretion System

Steven Johnson, Janet Deane & Frank Cordes with the groups of Dr. A. Blocker (Sir William Dunn School of Pathology) and Dr. W. Picking (University of Kansas)

6. Cordes, F.S., Daniell, S., Kenjale, R., Saurya, S., Picking, W.L., Picking, W., Booy, F., **Lea, S.M.** & Blocker, A.J. (2005) Helical packing of needles from functionally altered *Shigella* type III secretion systems **J. Mol. Biol.** *in the press*

7. Johnson, S., Deane J. & **Lea, S.M.** (2005) The type III needle and the damage done **Current Opinions in Structural Biology** *in the press*

Bacterial Adhesins

David Pettigrew & Pietro Roversi in collaboration with Dr S. Matthews (Imperial College)

8. Pettigrew, D.* , Anderson, K.L.* , Billington, J., Cota, E., Simpson, P., Urvil, P., Rabuzin, F., Roversi, P., Nowicki, B., du Merle, L., Le Bouguenec, C., Matthews, S.+ & **Lea, S.M.+** (2004) High resolution studies of the Afa/Dr adhesin DraE and its interaction with chloramphenicol **J. Biol. Chem.** 279, 46851-46857
9. Anderson, K.L.* , Billington, J.* , Pettigrew, D., Cota, E., Simpson, P., Roversi, P., Chen, H.A., Urvil, P., du Merle, L., Barlow, P.N., Medof, M.E., Smith, R.A.G., Nowicki, B., Le Bouguenec, C., **Lea, S.M.+** & Matthews, S.+ (2004) An Atomic Resolution Model for Assembly, Architecture, and Function of the Dr Adhesins **Molecular Cell** 15, 647-657
10. Das, M., Hart-Van Tassel, A., Urvil, P.T., **Lea, S.M.**, Pettigrew, D., Matthews, S., Nowicki, S., Popov, V., Goluszko, P. & Nowicki, B. (2005) Hydrophilic Domain II of *E. coli* Dr Fimbriae Facilitates Cell Invasion **Infection and Immunity** 73, 6119-6126

These papers describe our atomic structures for the Afa and Dr bacterial adhesins and functional studies which explain how chloramphenicol acts to prevent binding to the bacterial receptor the human complement regulator CD55.

Echoviruses

David Pettigrew groups of Dr. D. Evans (University of Glasgow) and Dr. D. Bhella (MRC Virology Unit, Glasgow)

11. Pettigrew, D., Williams, D., Kerrigan, D., Evans, D.J., Lea, S.M.+ & Bhella D.+ (2005) Decay accelerating factor binding by echoviruses: structural and functional insights **J. Biol. Chem.** in the press

Using cryoelectron microscopy and our atomic structure for both virus and receptor we generate an atomic model for the intact receptor binding to the virus which allows us to explain many prior observations concerning modes of attachment to receptors in the echovirus family.

RNA Structure

Antu Dey in collaboration with the groups of Dr. W. James (Sir William Dunn School of Pathology) and Prof. A. Lever (University of Cambridge)

12. Dey, A.K., Khati, M., Tang, M., Wyatt, R., **Lea, S.M.** & James, W. (2005) An aptamer that neutralizes R5 strains of HIV-1 blocks gp120-CCR5 interaction **J. Virol** 79, 13806-138210
13. Dey, A.K., Griffiths, C., **Lea, S.M.**, & James, W. (2005) Structural characterization of an anti-gp120 aptamer that neutralizes R5 strains of HIV-1 **RNA** 11, 873-84