PROTHAP: PROTEIN THERAPEUTICS: DEVELOPMENTS FOR LABELLED ANTIBODIES TO ENABLE NEUTRON STRUCTURAL STUDIES FOR IMMUNOLOGY

Leading beneficiary: ILL

Partners: ILL, Synthelis (http://www.synthelis.fr/), ISIS, AstraZeneca UK, FRM-II/TUM, Keele University

Estimated budget (in person months, other direct cost) and tentative distribution per partner

ILL: 372 Synthelis: 36, ISIS: 36, AZ: 36, TUM: 36

(assuming 3 yr project – otherwise multiples of 48)

the following points)

Neutron structural biology techniques can provide powerful information about biological systems if the right samples are made available. The ability to deuterium label macromolecules or particular parts thereof has provided major impetus for the application of neutrons in the life sciences over the last 8 years or so. A key aspect of this has been the pursuit of method developments (with EU support, initially under an RTD and then as part of NMI3) that have progressively widened the range of systems from relative simple ones to progressively more complex ones. In this JRA we seek to bring neutron scattering (in particular SANS) directly into one of the most exciting and rapidly growing areas of development - protein therapeutics. Specifically we seek to make provision for the production of deuterated antibodies – something that is not currently accessible. A successful outcome to this would allow the study of an extensive range of structural studies of front-line relevance to numerous 1st, 2nd and 3rd world diseases.

These developments will be challenging but we have a clear strategy marked out and have identified the right combination of partners that will collectively enable the success. Recombinant proteins must mimic as closely as possible natural human proteins, in terms of amino-acid sequence and post-translational glycosylation. We will have two lines of work with specific tasks in each shared out amongst the partners who between them have expertise in molecular biology, purification, neutron scattering and NMR. The first will be the development of deuteration methods for mammalian cells such as CHO or HEK. The second will be development of other organisms such as *Dictyostelium discoideum* which offers a promising alternative expression system for eukaryotic proteins especially where both human-like post-translation glycosylation, complex folding (as for multi-domain proteins) and isotope-labelling including high level deuteration is needed. To drive the development we will focus on a number of key immune system factors for structural studies, in each case making a interdisciplinary approach wherein neutron scattering and solution NMR are used together to study the same samples on a scale that has never previously bee accessible.

The benefits to the user community are obvious – like previous EU-funded developments for deuteration, we anticipate user impact during the timescale of the JRA.