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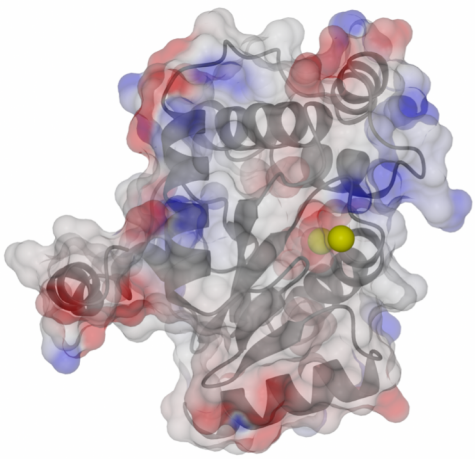
metals.bbsrcnibb@durham.ac.uk @METALSBBSRCNIBB https://mib-nibb.webspace.durham.ac.uk

Exploiting a copper-dependent chaperone system to improve bioprocessing of therapeutic antibodies

"NIBB meetings have brought me into contact with a range of industrial contacts. This BIV sparked a new project with Diosynth Biotechnologies to investigate the potential of bacterial copper-tolerance machinery to facilitate assembly of protein targets of biotechnological importance." Mark Shepherd, University of Kent

Mark Shepherd, University of Kent; Christopher Lennon, FujiFilm Diosynth Biotechnologies



Structure of ScsC, a thioredoxin-like protein of Salmonella with a potential role in disulphide folding of therapeutic proteins. Negative and positive surface charge are shown in red and blue, respectively. Sulphur atoms of active site cysteines are shown as yellow spheres.

This project explored the impact of copper and the Salmonella Scs proteins upon the assembly of Herceptin and Lucentis, therapeutic antibodies used to treat breast cancer and macular degeneration respectively. First we developed systems for expression of Herceptin and Lucentis in *E. coli*. After this we used state-of-the-art mass spectrometry approaches to perform quantitative proteomics measurements on *E. coli* strains grown in the presence and absence of copper to assess total protein and antibody abundance. We showed that copper elevates protein levels in *E. coli*. Copper diminished the expression of Herceptin, an effect that was reversed by expression of ScsABCD. We also showed that the native disulphide-folding machinery in *E. coli* is essential for Herceptin production.

INITIAL AIMS: The production of biotherapeutics has a total market value of around £100 billion per year. As well as therapeutic uses, antibodies have applications as research tools, in diagnostics and in consumer healthcare products. We have previously investigated the potential of copper-dependent protein folding catalysts (Scs proteins) to improve the production of antibody fragments of Herceptin (Trastuzumab) in *E. coli (*BIVMiB014). This project expands the repertoire of that system; we will build upon work done so far with Herceptin and also study Lucentis (Ranibizumab).

- Future studies may focus on the effects of copper and ScsABCD on Lucentis yield