MS13-P8 Crystal structure of a human Fab in complex with a dominant antigen from *Neisseria meningitidis*.

Jacinto Lopez Sagaseta[1]

1. GSK Vaccines

email: jlopez.sagaseta@gmail.com

López-Sagaseta J.[a] Bottomley M.J.[a]

[a] *GlaxoSmithKline Vaccines S.r.l., Via Fiorentina 1, 53100 Siena, Italy. jacinto.x.lopez-sagaseta@gsk.com*

Anchored yet exposed to the outside moiety of the bacterial shell, Factor H binding protein (fHbp) is one of the main antigenic components of *Neisseria meningitidis*, one of the causative agents of meningitis, an infectious disease that can cause a fatal outcome or permanent disability within 24 hours of infection. Though there have been described up to three different variants of fHbp, it is fHbp variant 1 (fHbp-1), the subclass showing the highest prevalence amongst MenB strains, and also, one of the actual components of Bexsero, the current licensed vaccine against serogroup B Meningococci (MenB). In order to define the structural basis that underlie the recognition of this highly immunogenic antigen and the broad strain coverage offered by Bexsero, we have determined the crystal structure of a complex between a human Fab and fHbp-1 at a resolution of 2.2 Å. The Fab has been originated from an immunization study that included a recombinant form of fHbp-1, and importantly, it is cross-reactive against all of them. The cross-reactive epitope spans along the c-terminal beta barrel of fHbp and encompasses residues that are highly conserved across the different fHbp variants. The hypervariable CDR3 loop of the heavy chain dominates the recognition of the antigen. This crystal structure represents the first evidence, at the atomic level, of the recognition of *Neisseria meningitidis* fHbp by a human Fab raised in an individual upon vaccination, and provides the basis behind the broad strain coverage of the current vaccine against MenB. In addition, the information gathered from this structure will be of high value for future structure-based antigen design.

Keywords: STRUCTURAL BASIS; MENINGITIS; VACCINATION; IMMUNE RESPONSE.

MS13-P9 Unexpected Active Site in *Trypanosoma brucei* Flap Endonuclease

Faizah AlMalki[1,2], Sarah Oates[3], Svetana Sedelnikova[1], Jon Sayers[3], Peter Artymiuk[1]

1. University of Sheffield, MBB Department, UK
2. Taif University, Biology & Biotechnology Department, Saudi Arabia
3. University of Sheffield, Medical School, UK

email: faalmalki459@gmail.com

Flap endonuclease (FEN) and 5'---3' exonucleases form a class of nucleolytic enzymes that are metalloenzymes using two metal ions in their activity. The primary function of these enzymes is as a 5' exo- and endonucleases that is required during the DNA replication procedure. According to the recent studies, FEN proteins are involved in multiple DNA metabolism and repair pathways which make them a new drug targets. *Trypanosoma brucei* (Tb) parasitic is the causative agent of sleeping sickness and its flap endonuclease enzyme shares more than 50% sequence identity with the human flap endonuclease (FEN-1). The crystal structure of TbFEN enzyme has been solved for the first time in our lab using X-ray crystallography and computational techniques. It has the same architecture as the other FEN family members which is composed of four main parts: the N-terminal region, the C-terminal region, a helical arch that is disordered in our structure and the active site. The structure has been complexed with calcium ions present in the crystallization buffer. According to the electron density map, there are two calcium ions separated by less than 4 Å and coordinated with four acidic residues for each ion are present in M1 and M2 sites in the active site. Another calcium ion 3.8 Å apart from the one in M1 sit has been observed in a new place underneath of the arch and coordinated with two amino acids from the same molecule and other two glutamic residues from neighbouring molecule to create unexpected before active site. This active site is presented and reported in FEN family members for the first time. The number and placement of metal ions is still a topic of hot debate in FEN family enzymes.This work will enable us to compare the Trypanosomal FEN structure with the human FEN one in the hope of designing molecules that will inhibit the former but not the later. The aim of this is to provide potential lead molecules for anti-protozoan drug design avoiding the toxicity and drug resistance that may occur from using current drugs.

Keywords: Flap endonuclease, Trypanosoma brucei, DNA replication and repair