Project description

Project Title: Anti-Glycan Nanobodies for the Diagnosis and Treatment of Parasitic Infections

Research Group: Biomolecular Systems
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Project Description:

In the1980`s it was discovered that the Camelidae family produce special IgG3 antibodies lacking the light chain. The antigen-binding sites in each of these unusual heavy chain antibodies (hcAbs) are formed only by a single domain (VHH or "Nanobody" (Nb)). Several structural characteristics make Nb`s different and superior compared to conventional antibodies. Nb`s penetrate and bind unique epitopes that are simply inaccessible to classical antibodies with reported affinities as low as 100 pM.
Similar to any other recombinant proteins, Nb`s can be easily expressed in bacteria, yeasts, plants or human cells systems. Compared with mAb`s expression in human or hybrid cells, high scale expression of Nb`s is significantly cheaper and shorter.
Since Nb's are small monomeric proteins, the molecular engineering tools to functionalize and modify multivalency, specificity and/or effector molecules, are already well-established.
Nb`s can be expressed as monomers, dimers or higher oligomers to form several binding entities simultaneously ("chain of beads"). Fused Nb`s can have different specificities as part of a single multispecific chain. The multispecific chain is then able to simultaneously bind multiple antigens or different epitopes on a single antigen. NBs are stable. Having shaped by evolution as a "stand alone" single chain binding unit, Nb`s are highly soluble and in general can withstand harsh conditions. Nb`s can be administrated via multiple routes. Due to their size and stability, Nb`s can be administered efficiently by inhalation.
Nb`s are approximately 4 nm in length compared to 10-15 nm of conventional mAb`s. As a result, fluorescent labeled Nb`s are widely used for fluorescent imaging super resolution microscopy. The fluorescent dye is conjugated directly to the Nb and brought as close as 2-4 nm to the binding epitope. This is a dramatic improvement compared to 25-30 nm proximity of conventional primary and secondary antibody complexes. The close proximity to target domains enables ultra-high resolution staining that is broadly used for imaging in vivo and in vitro.

While hundreds of Nb`s target different proteins, none target glycans. The automated glycan assembly technology developed at the Max Planck Institute of Colloids and Interfaces, provides the basis to develop Nb`s that recognize glycans ("Glycobodies").
Nb`s are easy to produce small functionalized binding units that can be used for a broad range of applications ranging from stabilizing agents in crystallography, to cell imaging and drug delivery. The possibility to multimerize Nb`s is particularly suitable when targeting glycans, notoriously known molecules for their dense and heterogeneous cell membrane dispersion.

Targeting Glycosyl-inositol-phosphotidyl(GPI) Molecules on Parasitic Infections with Nanobodies

Malaria is a devastating parasitic disease that threatens 40% of the world's population and claims more than 600.000 lives each year. The cell surface of *P. falciparum* expresses abundant amounts of GPIs, in both the protein-linked and protein-free forms. GPI constitutes more than 95% of the total carbohydrate modification of *P. falciparum* parasite and reflects the virtual absence of N- and O-linked glycosylation in these parasites.
Synthetic *P. falciparum* GPI of different length were used to determine the minimal epitope required to raise an immune response in mice that resulted in the protection from malaria. Monoclonal antibodies against the cell-surface GPI glycans have been produced as a means to study the role of glycans during infection and for passive vaccination to protect from malarial disease