Hyper-glycosylated Antibodies with Selective Fc Receptor Binding

Summary
This technology is a set of hyper-glycosylated antibodies that have been modified in the Fc domain of the antibody to either enhance or reduce the affinity of the Fc region to the Fc γ Receptors (FcγRs) that are expressed on the surface of immune cells. The FcγR interactions with immune complexes trigger a wide range of pro-inflammatory or anti-inflammatory immune responses. Acquiring the ability to tightly regulate the immune response is important for the treatment of numerous diseases. In humans, the activating receptors are FcγRIIA and FcγRIIIA, while the sole inhibitory receptor is FcγRIIB.

Market
Targeted immunotherapy is one the most recent advances in modern healthcare with monoclonal antibodies (mAbs) accounting for 40% of the biotech market. The ability to modulate the Fc region of mAbs would offer an additional level of specificity to existing therapies or be used as a novel therapy on its own. In 2011, there was approximately 28 monoclonal antibodies approved in the US and EU and currently, 10 of them have already achieved blockbuster status. Global sales of therapeutic antibodies exceed $50 billion a year with Abbott's top selling Humira garnering $9.3 billion in 2012.

Key Investigator
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Field
Immunology

Technology
Hyper-glycosylated antibodies with improved effector function

Advantages
Reduced binding to inhibitory FcγR
Increased binding to activating FcγRs

Status
Available for licensing
Available for sponsored research

Patent Status
US 15/037,185; EU 14 862 317.6

UMB Docket Reference
ES-2013-128

Technology
Previous attempts to engineer the Fc region have been met with limited success due to the high sequence and structural similarities of the FcγRs. In addition, antibody interactions with the receptors often interact with both the activating and inhibitory domains causing opposing actions and it is this balance of actions that will dictate the overall immune response. Current industry approaches focus mainly on the activation of the FcγRs, with very little attention to the countering inhibitory actions. This technology addresses these challenges through site-specific hyper-glycosylation (i.e., incorporating *N*-linked glycosylation sites in addition to that of the naturally occurring site at Asn297, which is required for FcγR binding) and amino acid mutations. The result is a series of therapeutic antibodies that can alter the balance of activating versus inhibitory FcγR-mediated responses. Exploitation of the antibody-Fcγ receptor interactions allow for the use of naturally occurring immune cell functions for therapeutic potential in diseases such as autoimmune, neurodegenerative and infectious diseases, as well as for cancer. This manipulation of the relative binding affinities for inhibitory versus activating FcγRs results in the de-repression of antibody-mediated effector functions, as measured by a relative increase in antibody-dependent cellular cytotoxicity. The ability to manipulate with engineered antibodies holds great therapeutic promise.

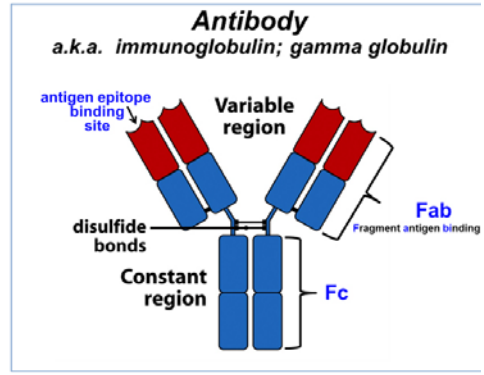

Fig 1: Antibodies contain two regions, the Fab region which recognizes antigen (self or foreign) and the Fc region which binds to FcγR on immune cells. Source: Janeway's Immunobiology

Technology Status
The inventors have produced several hyper-glycosylated IgG1 Fc variants in which a single additional N-linked glycosylation site was generated adjacent to the Fc-FcγR binding interface. The current lead antibody, an IgG variant that incorporates hyper-glycosylation sites at positions 226 and 290, as well as a serine to alanine mutation at position 298 (Fc-226hg/290hg/S298A), has been optimized with 60-fold reduced binding to inhibitory FcγRIIB, while exhibiting only 6x and 10x reduced affinity for activating receptors FcγRIIIA and FcγRIIA, respectively.

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