Glycoengineering of Therapeutic Antibodies

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Antibody dependent cellular cytotoxicity (ADCC) is the process of lysis of (tumor) target cells by immune effector cells. It requires the simultaneous binding of an antibody to a cell surface receptor on the target cell and via the Fc region of the antibody to the FcγRIIa receptor on immune effector cells such as NK cells or macrophages/monocytes. Binding of the antibody to target and immune effector cells results in the cross-linking of FcγRIIa with subsequent activation of FcγRIIa signaling and release of proteins mediating the killing of the target cells such as perforin and of proteases such as granzymes. ADCC has been established as an important mode of action of therapeutic antibodies such as rituximab/MabThera (targeting CD20), cetuximab/Erbilux (targeting EGFR) and trastuzumab/Herceptin (targeting HER2) which are approved for the treatment of various cancers. Translational research on rituximab and cetuximab has established that the response to therapeutic antibodies in patients can be influenced by the FcγRIIa-158V/F polymorphism. This polymorphism results in the expression of a high affinity FcγRIIa receptor (158V) and a low affinity FcγRIIa receptor (158F) on immune effector cells and impacts the capability of antibodies to mediate ADCC [1 – 7]. We have recently developed a so-called GlycoMab technology that enhances the affinity of therapeutic antibodies for both the high and low affinity FcγRIIa receptors through the introduction of a bi- secting N-acetyl-glucosamine residue in the carbohydrate chain of the Fc region of the antibodies. The introduction of this bi- secting N-acetyl-glucosamine moiety in the carbohydrate chain results in a steric interference with core fucosylation of the carbohydrate. This process and other approaches resulting in the afucosylation of therapeutic antibodies are known as “antibody glycoengineering”. We and others have demonstrated that glycoengineering and lack of the core fucose residue results in an up to 50-fold enhanced affinity of human lgG1 antibodies for the human FcγRIIa receptors, and this subsequently results in an up to 100-fold enhanced ADCC induction (potency). Recently, we have demonstrated that glycoengineering and lack of the core fucose residue results in an up to 50-fold enhanced affinity of human lgG1 antibodies for the human FcγRIIa receptors, and this subsequently results in an up to 100-fold enhanced ADCC induction (potency). Recently, we have demonstrated that glycoengineering and lack of the core fucose residue results in an up to 50-fold enhanced affinity of human lgG1 antibodies for the human FcγRIIa receptors, and this subsequently results in an up to 100-fold enhanced ADCC induction (potency).

Conflicts of Interest: The author is employed by Roche Glycart AG.

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