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 FcgRIIIa 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 FcgRIIIa with subsequent activation of FcgRIIIa 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/Erbitux (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 FcgRIIIa-158V/F polymorphism. This polymorphism results in the expression of a high affinity FcgRIIIa receptor (158 V) and a low affinity FcgRIIIa 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 FcgRIIIa receptors through the introduction of a bisecting N-acetyl-glucosamine residue in the carbohydrate chain of the Fc region of the antibodies. The introduction of this bisecting 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 IgG1 antibodies for the human FcgRIIIa receptors, and this subsequently results in an up to 100-fold enhanced ADCC induction (potency). Recently, we have demonstrated the structural basis of the enhanced affinity of afucosylated Fc regions for FcgRIIIa by X-ray crystallography. These studies provide a structural explanation for the high affinity and FcgRIIIa specificity of glycoengineering as opposed to other technologies used for Fc-engineering such as the introduction of mutations in the Fc region that also affect binding to other FcgRs [8–15]. Roche is currently investigating three therapeutic glycoengineered antibodies with optimized immune effector function targeting CD20, EGFR and HER3 in different phases of clinical trials. Obinutuzumab (GA101, RG7159) is a type II, anti-CD20 GlycoMab monoclonal antibody that was designed to mediate enhanced direct and immune effector cell-mediated cell killing as compared to rituximab. In addition to enhanced ADCC, due to its type II characteristics, GA101 exhibits enhanced direct cell death induction with a concomitant reduction of CDC. In NHL animal models GA101 demonstrated a superior efficacy in terms of tumor growth inhibition and survival compared to type I CD20 antibodies such as rituximab and ofatumumab, including the induction of complete tumor remission. In non-human primates GA101 induces superior and profound B cell depletion in lymphoid tissues compared to rituximab. In Phase I/II clinical trials GA101 showed promising activity in heavily pretreated NHL patients. GA101 is currently being investigated in pivotal clinical trials in B-CLL, iNHL and DLBCL in combination with chemotherapy, head-to-head with rituximab-based regimens and in Rituximab-refractory iNHL as well as in various Phase II clinical trials. GA101 was the first glyco- and Fc-engineered antibody to enter clinical trials and is now the most advanced glyco- and Fc-engineered antibody in clinical trials in the world [16–24].

GA201 (RG7160) is a second anti-EGFR GlycoMab monoclonal antibody that is currently being investigated in Phase II clinical trials. It was designed to combine potent EGFR signaling inhibition with enhanced ADCC induction. In xenograft models GA201 demonstrated superior activity compared to cetuximab and panitumumab. Hence, GA201 has the potential to show clinical activity in patients with solid tumors. Phase I clinical testing in heavily pretreated patients with advanced solid tumors demonstrated a manageable toxicity profile. Evidence of anti-tumor activity was also seen, especially in patients with colorectal cancer, including a number of patients who had previously received cetuximab and/or panitumumab (1 CR, 2 PR). Interestingly, one of the partial responses was reported in a tumor-harboring a k-ras mutation. GA201 is currently undergoing Phase II clinical trials in CRC and NSCLC in combination with chemotherapy as well as a neo-adjuvant biomarker study in HNSCC [25].

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

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