Pascoe et al., 2007). Similar differences in ADCC efficacy might pertain *in vivo* since more favorable responses were reported for patients, diagnosed with systemic lupus erythematosus or leukemia and homozygous for FcγRIIIa-158V when exposed to Rituxan than for homozygous FcγRIIIa-158F patients (Cartron et al., 2002; Pascoe et al., 2007). Similarly, FcγRIIIa polymorphisms were shown to influence the response of Crohn's disease patients to infliximab (99) and red blood cell clearance by anti-D antibody (Miescher et al., 2004).

All FcγR are transmembrane molecules, with the exception of FcγRIIIb which is glycosylphosphatidylinositol (GPI)-anchored within the membrane of neutrophils. FcγRI and FcγRIIIa are members of the multichain immune recognition receptor (MIRR) family and are present in the membrane as heterooligomeric complexes comprised of an α and a γ chain: an IgG/antigen complex binds the α chain to initiate signaling through the γ chain; the FcγRIIIa α chain of NK cells is also associated with a signaling ζ chain. FcγRIIa and FcγRIIb molecules are composed of an α chain only (Gillis et al., 2014; Lux et al., 2013; van de Winkel, 2010). The FcγR α chains show a high degree of sequence homology in their extracellular domains (70%–98%) but differ significantly in their cytoplasmic domains. The cytoplasmic domains of γ chains and the FcγRIIa α chain express the immunoreceptor tyrosine-based activation motif (ITAM) that is involved in the early stages of intracellular signal generation. By contrast, the FcγRIIb receptor α chain expresses an immunoreceptor tyrosine-based inhibition motif (ITIM) (Deisenhofer, 1981; Gillis et al., 2014; Jefferis, 2012; Lux et al., 2013; Stanfield and Wilson, 2014). Cellular activation may be dependent on the balance between the relative levels of expression of these two isoforms and hence the balance of signals generated through the ITAM and ITIM motifs (Gillis et al., 2014; Lux et al., 2013).

4.23 CONCLUDING COMMENTS

The challenge to develop biosimilar therapeutics is being met. There seems to be no issues relating to antigen-binding specificity and affinity; given that the sequence is determined by that of the innovator molecule. However, the unique structure of the paratope is principally responsible for immunogenicity and the development of ADA regardless of whether the antibody is a chimeric, humanized, or fully human molecule. A further immunogenicity issue is evident for Erbitux, produced in Sp2/0 cells, since the glycosylation sequon present at asparagine 88 of the heavy chain results in the addition of a complex array of oligosaccharides, including the allergenic gal α(1–3)gal residue. Consequently, biosimilars of this antibody are being developed with production in CHO cells that add familiar diantennary oligosaccharide structures. The focus of interest rests with the structure/conformation of the IgG-Fc region that is a composite of the protein and oligosaccharide moieties.

There remains unresolved understanding of the finesse of structural changes induced by the presence or absence of a fucose and/or bisecting *N*-acetylglucosamine sugar residue, the functional activity of the human IgG-Fc and consequently, presumably, on the MoA. While the glycoform is identified as a CQA, it is in fact the conformation of the IgG-Fc that determines interactions with effector ligands. It is