# The future of monoclonal antibodies (mAbs) as therapeutics and concluding remarks

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Although monoclonal antibodies (mAbs) have had considerable success as therapeutics, the initial development of mAbs as therapeutics had several problems (Ezzell, 2001; Oldham & Dilman, 2008; Reichert, Rosensweig, Faden, & Dewitz, 2005). The original production of mAbs used fused mouse lymphocyte and myeloma cells resulting in the generation of murine mAbs (Kohler & Milstein, 2005; Milstein, 1999). When these murine mAbs were introduced into clinical studies in the early 1980s, there generally was a lack of efficacy and rapid clearance mainly due to the patients generating human anti-mouse antibodies. These problems were solved with the introduction of chimera mAbs where the fragment antigen-binding (Fab) region was murine with a human Fc construct (Boulianne, Hozumi, & Shulman, 1984; Morrison, Johnson, Herzenberg, & Oi, 1984). Eventually techniques were developed to produce humanized mAbs where the complementarity determining regions (CDRs) were still made up of murine residues but the rest of the mAb was a human sequence (Jones, Dear, Foote, Neuberger, & Winter, 1986). The production of humanized mAbs also required computer modeling to alter flanking sequences around the CDRs to maintain full activity (Presta et al., 1993). Fully human antibodies have also been produced using immortalization and hybridoma techniques to human cells (Cole, Campling, Atlaw, Kozbor, & Roder, 1984; Lakow, Valentine, Vaughan, Tsoukas, & Carson, 1984). Another problem with early development of mAbs was limitations on the amount of mAb that could be manufactured and processed. Many of the mAb doses were found to be quite high, thus requiring new technologies to meet the manufacturing requirements. Fortunately, the design of an efficient cell culture system with high titers, rapid and economical recovery, and purification steps has enabled manufacturing of large batches of mAbs. Thus, the generation of human and humanized versions of the mAbs, and improvements in process and manufacturing, have contributed largely to the success of these important biotherapeutics.

Recently, a major advance in mAb design is the creation of so-called "antibody drug conjugates" (ADCs) (Casi & Neri, 2012; Wakankar, 2010). The ADC approach uses mAbs as delivery systems that can deliver therapeutic agents directly to targeted cells. This has become an important new class of molecule for the treatment of cancer since standard chemotherapy results in toxic levels in the blood inhibiting the ability to achieve greater and more effective doses. Currently there are only two commercialized ADCs, Adcetris and Kadcyla (Mylotarg was the first ADC approved for market in 2001, but was withdrawn from the market in June 2010 due to safety issues and lack of efficacy). Nonetheless, there are now ~45 ADCs in clinical trials as summarized in a report from Roots Analysis Private Ltd. (Market-report, 2014). This class of molecule presents a new set of challenges for pharmaceutical development, but the details of the

**Monoclonal Antibodies.** http://dx.doi.org/10.1016/B978-0-08-100296-4.00010-5