Poster Presentation

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Structural characterization of a potent humanized anti-CD38 antibody in phase I

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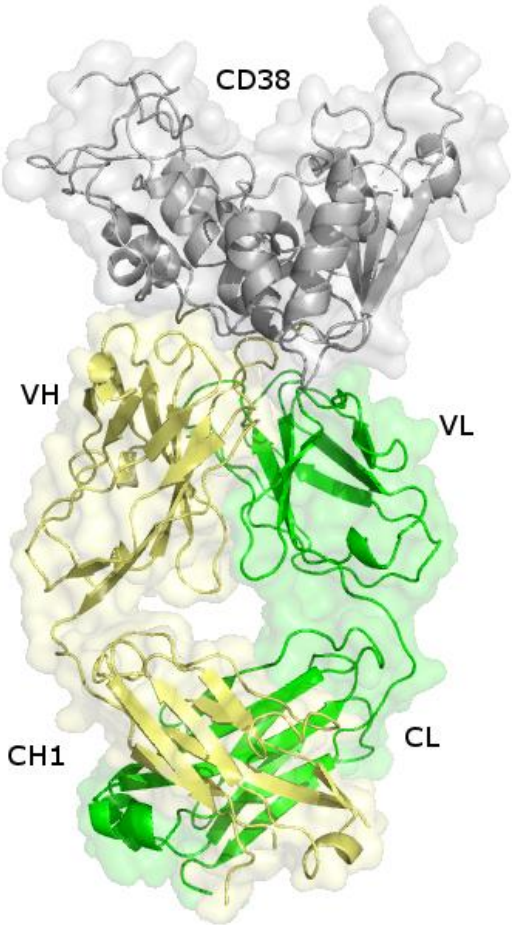
CD38 is a type II transmembrane glycoprotein with both ADP-rybosyl cyclase and glycohydrolase activities. CD38 is highly expressed at the surface of malignant plasma cells of multiple myeloma. SAR650984 is a humanized IgG1 antibody targeting CD38 in early clinical developement that is acting through several potential mechanisms including ADCC, CDC and pro-apoptotic activity. Here we report further preclinical characterization of SAR650984 with a high resolution structure of Fab-SAR650984 in complex with CD38 allowing an epitope mapping. The crystal structure of SAR650984-Fab/huCD38 complex shows that SAR650984 neither blocks the access nor alters the configuration of the ADPRC catalytic site of CD38 although in vitro assays have demonstrated that SAR650984 behaves as a strong inhibitor of the ADPRC activity of CD38. These results suggest that SAR650984 is likely an allosteric antagonist of CD38 that alters the dynamics of enzyme upon binding.

[1] *Deckert et al (July 1, 2014), Clinical Cancer Research 10.1158/1078-0432.CCR-14-0695,* ***[2]*** *Wetzel et al; AACR2013 #4736,* ***[3]*** *Wetzel et al; IMW2013 #P228*



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