

SAR650984: A Potent Anti-CD38 Therapeutic Antibody with Three Mechanisms of Action (Apoptosis, ADCC, CDC) for Hematological Malignancies

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Introduction

CD38 is a promising target for antibody therapeutics for the treatment of various hematological malignancies, including multiple myeloma as well as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. CD38 is a type II transmembrane glycoprotein with ectozyme activity that has been implicated in Ca²⁺ mobilization. CD38 expression correlates with the poor disease prognosis in some hematological malignancies. It has been proposed that rituximab, a well-established anti-CD20 antibody for the treatment of non-Hodgkin's lymphoma, works by several mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. A panel of murine anti-CD38 antibodies was first screened for their ability to induce apoptosis, as measured by Annexin-V staining, in various lymphoma, leukemia, and multiple myeloma cell lines. Chimeric human IgG1 versions of the selected murine antibodies with potent apoptotic activity were then produced and screened for ADCC and CDC activities. Among the screened antibodies, a chimeric version of SAR650984, a humanized anti-CD38 antibody, had the best overall activity. SAR650984 induced potent apoptosis in Daudi, Raji, Ramos, and SU-DHL-8 lymphoma cells, as well as MOP-8 multiple myeloma (MM) cells and DND-41 acute T lymphocytic leukemia (T-ALL) cells, which like most, if not all, MM and T-ALL cells, express CD38, but not CD20. SAR650984 also induced potent ADCC and CDC in these tumor cells. When the activities of SAR650984 and rituximab were directly compared in Daudi and Raji lymphoma cells that express similar levels of CD38 and CD20, SAR650984 had similar ADCC and CDC activities as rituximab, and, in addition, SAR650984 induced a greater percentage of lymphoma cells to undergo apoptosis when compared with rituximab.

Figure 1 Pro-apoptotic activity of murine anti-CD38 antibodies

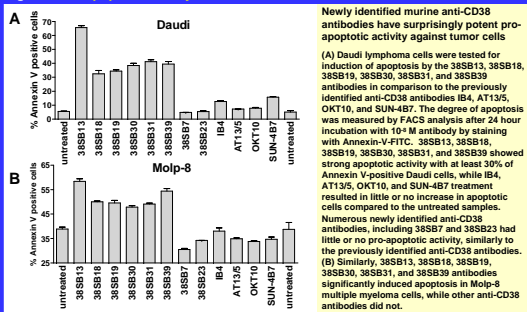


Figure 2 Binding affinity of the humanized antibody SAR650984

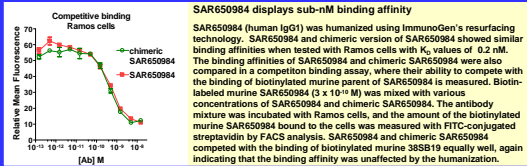


Figure 3 Pro-apoptotic activity of SAR650984

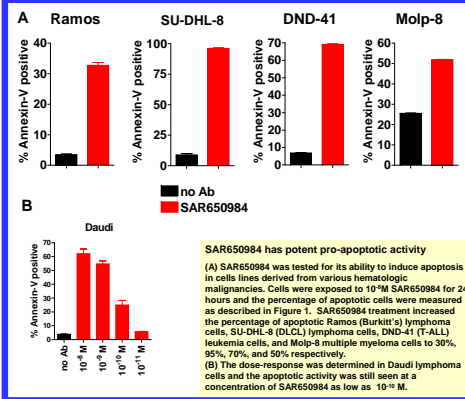


Figure 4 CDC and ADCC activities of SAR650984

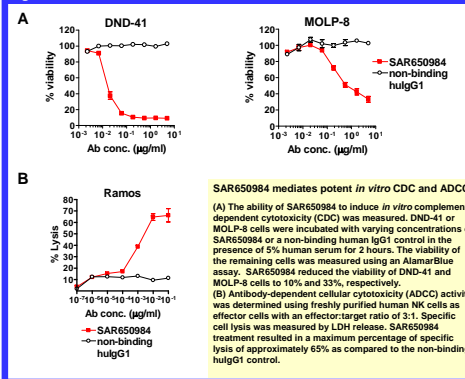


Figure 5 *In vitro* activities of SAR650984 in comparison to rituximab

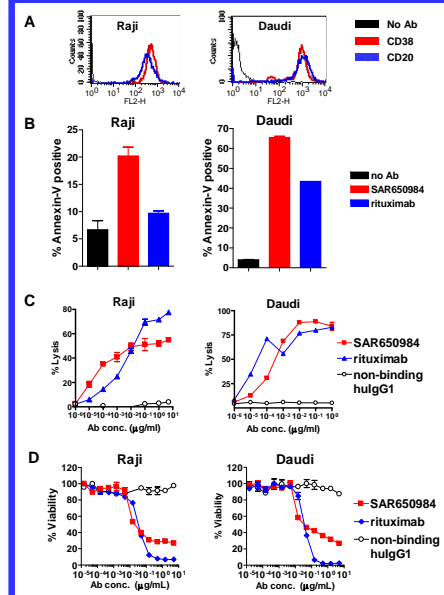
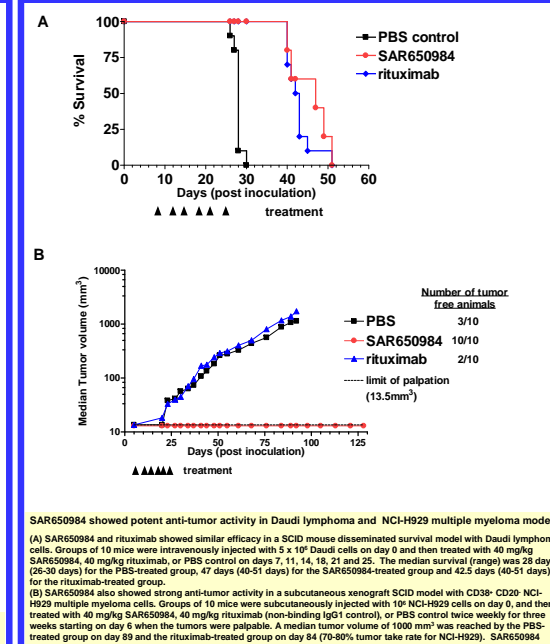


Figure 6 *In vivo* activity of SAR650984 in comparison to rituximab



Conclusions

In summary, the humanized anti-CD38 antibody, SAR650984, has potent ADCC, CDC, and apoptotic activities *in vitro* and anti-tumor activity *in vivo*. In a direct comparison with rituximab using Raji and Daudi cells, SAR650984 demonstrated superior direct pro-apoptotic activity, while showing similar CDC and ADCC activities as rituximab. *In vivo*, SAR650984 was as active as rituximab in a Daudi lymphoma model. In addition, it showed strong efficacy in a NCI-H929 model, a xenograft model for multiple myeloma, in which rituximab was not active due to the lack of CD20 expression. SAR650984 is a promising therapeutic antibody candidate for a number of hematologic malignancies.