A Novel Anti-BCMA ADC for the Development of an Effective Multiple Myeloma Therapy

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Abstract

B-cell maturation antigen (BCMA) expression is highly restricted to specific stages of B-cell development and it is not present on naive or long-lived memory B-cells. It is upregulated in multiple myeloma (MM) and has been shown to be a promising target for MM. Here we describe a novel anti-BCMA antibody, AVG-A11, isolated from AvantGen's yeast display human antibody libraries, that specifically recognizes human and cyno-BCMA and does not cross-react with the related protein receptors TACI or BAFFR. It is 4 to 6-fold more potent in blocking the BCMA-BAFF interaction and arresting BAFF-induced NF-κB activation, respectively, in a head-to-head comparison with J6M0, the humanized anti-BCMA antibody that has shown promising results in clinical trials as the antibody-drug conjugate platform. In a surrogate ADC format using a MMAF conjugated anti-human Fc Fab mixed with either AVG-A11 or J6M0 IgG, AVG-A11 was 3 to 5-fold more potent against H929, MM.1S and RPMI226 cells than J6M0 with EC50 values in the sub-nM range. Neither had a cytotoxic effect on B220-negative cells such as Flp (C57BL/6 Tg(human BCMA)) and BAFFR as a negative control. The maximum blood concentration of AVG-A11 in a non-human primate model was 3.7μg/ml and bound IgG detected with goat anti-human Fc -HRP. Curve fitting using Prism software showed that AVG-A11 had a longer half-life (t1/2) of 50 hours compared to 12 hours for J6M0.

In a competition assay, purified AVG-A11 blocked the BCMA-BAFF interaction and out-performed GSK-J6M0 in killing MM cell lines. In an ADC format, using a MMAF conjugate, AVG-A11 blocked B-cell maturation and induced apoptosis more effectively than J6M0. In an ADC format, AVG-A11-mcMMAF showed potent cytotoxic activity on BCMA-expressing MM cell lines as well as human bone marrow mononuclear cells (BMMCs) from MM patients. Together these data indicate that we have successfully isolated a potent, fully human anti-BCMA antibody directly from our yeast display antibody platform that has been further developed into a potent lead therapeutic ADC candidate for effective MM therapy.

AVG-A11 binds with high affinity to BCMA but not to the related proteins, TACI and BAFFR.

AVG-A11 blocks the BCMA-BAFF interaction and out-performs GSK-J6M0 in blocking BAFF-induced NF-κB activation.

AVG-A11 is more potent at triggering BCMA internalization than J6M0.

AVG-A11-mcMMAF is cytotoxic to MM cells but not to BCMA negative cells.

AVG-A11-mcMMAF exhibits cytotoxicity to BMMCs isolated from MM patients, but not BMMCs from a healthy individual.

AVG-A11 binds to native BCMA.

Figure 1. AvantGen's Human Antibody Libraries.

Figure 2. Binding anti-BCMA clones with antagonistic activity.

Figure 3. AVG-A11 as purified IgG recognizes native BCMA.

Figure 4. AVG-A11-mcMMAF can effectively kill MM cells present in BMMCs isolated from multiple myeloma patients.

Figure 5. AVG-A11 out-performs GSK-J6M0 in killing MM cells in an ADC format.

Figure 6. AVG-A11 induces more efficient BCMA internalization than J6M0 (performed by Photech in China).

Figure 7. AVG-A11 shows higher potency than J6M0 in an ADC format using unmodified antibody conjugated to human/Fc-Fab/CL-MMAF. Cytotoxic activity of AVG-A11 and J6M0 against the high BCMA-expressing MM cell line, H929, or the lower BCMA-expressing cell line, RPMI226, was determined by incubating cells in the presence of the indicated concentrations of primary antibodies, AVG-A11 or GSK-J6M0 (1.0 μM for H929 or 5 μM for RPMI226). Cell viability was determined using CellTiter-Glo. All experiments were performed in triplicate. Cytotoxicity was determined as the percentage of control treated wells and is expressed as mean ± standard deviation. (Experiments performed by CellTiter-Glo. Copyright 2021, Promega Corporation, Cat#G7771-25L, 45L, 450-000000 (human) and 45-000000 (cynomolgus) negative control cell line under these conditions (data not shown).