Efficacy and Toxicity Evaluation of Anti-human CD47 and SIRPa Antibodies in Genetically Humanized B-hSIRPa/hCD47 Mice

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ABSTRACT

CD47 and SIRPa (CD172a) are two transmembrane proteins that are expressed on all cells in the human body. CD47 is a ligand for the SIRPa receptor, and SIRPa has been shown to enhance the phagocytic function of macrophages. Anti-CD47 and anti-SIRPa antibodies that interfere with the CD47-SIRPa interaction have demonstrated promise in clinical trials as new class immunotherapies. To accelerate direct efficacy and toxicity testing of anti-human CD47 and SIRPa antibodies, Biocytogen has generated the double humanized mice, B-SIRPa/hCD47, in which the human extracellular domains of SIRPa and CD47 replace their respective murine counterparts. Homozygous B-hSIRPa/hCD47 mice express humanized but not the wild type mouse CD47 and SIRPa. In this study, we aimed to establish a series of double, triple (2), and quadruple humanized CD47/SIRPa mouse models, and we evaluated their efficacy and toxicity in tumor models of the engineered MC38-hCD47 cell line that expresses human CD47 in MC38 cells. Anti-human CD47 and anti-human SIRPa antibodies alone (A) and in combination (B) showed significant anti-tumor efficacy against human MC38 tumors. Anti-human CD47 and anti-human SIRPa antibodies alone (A) and in combination (B) showed significant anti-tumor efficacy against human MC38 tumors. Furthermore, we also created a quadruple humanized mouse strain, B-hPD-1/hPD-L1/hSIRPa/hCD47, which was characterized for efficacy and toxicity in tumor models. The results showed that these B-hSIRPa/hCD47 humanized mice are useful tools for in vivo antibody efficacy tests and toxicity assessment.

RESULTS

1. Biocytogen has generated a series of double, triple (2), and quadruple humanized CD47/SIRPa mouse models in combination with hPD-1 and h-PD-L1 humanization.

2. Anti-human PD-1 and anti-human CD47 antibodies showed single agent and combination anti-tumor effect in B-hPD1/hSIRPa/hCD47 mice. So did a bispecific anti-human PD-1/PD-L1 antibody in the B-hPD-L1/hSIRPa/hCD47 strain. A quadruple humanized strain, B-hPD-1/hPD-L1/hSIRPa/hCD47, is being characterized.

3. Blood counts, RBC morphology, and blood chemistry also show comparable values between the B-hSIRPa/hCD47 and C57BL/6 mice. The body weight loss of the B-hSIRPa/hCD47 mice was comparable to that of the C57BL/6 mice. However, body weight loss was more severe in the anti-human CD47 antibody group and the combination group compared to the control group.

4. Efficacy and Toxicity Evaluation of Anti-human CD47 and SIRPa Antibodies in Genetically Humanized B-hSIRPa/hCD47 Mice

SUMMARY

1. Biocytogen has generated a series of double, triple (2), and quadruple humanized CD47/SIRPa mouse models in combination with hPD-1 and h-PD-L1 humanization.

2. Anti-human CD47 and anti-human SIRPa antibodies alone (A) and in combination (B) showed significant anti-tumor efficacy against human MC38 tumors.

3. Further enhanced human CD47 antibodies showed signs of human toxicity in terms of RBC counts and blood chemistry changes in humanized mouse models.

4. Our results demonstrated that these B-hSIRPa/hCD47 humanized mice are useful tools for in vivo antibody efficacy tests and toxicity assessment.

REFERENCES


