FIBROBLAST ACTivating PROTEIN (FAP)-TARGETING IL-12 (ANTI-FAP/IL-12) TMEKINE™ POTentiATES ANTI-CANCer EFFECTS IN PRECLINICAL CANCER MODELS

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Background Although cancer immunotherapy showed promising results in hematologic malignancies, it has come up with relatively low tumor response for many solid tumors partly due to immune-suppressive tumor microenvironment (TME). Because of the immune-suppressive nature of TME, TME has been an active area of research and therapeutic target for restoring immune system and subsequent tumor growth inhibition. Among the many components in TME, cancer-associated fibroblasts (CAFs) are one of the key cell components of TME where one of the promising solid-tumor TME marker, fibroblasts (CAFs) are one of the key cell components of TME. Restoring immune system and subsequent tumor growth inhibition results in hematological malignancies, it has come up with the anti-FAP/IL-12 TMEkine™ platform containing anti-FAP and IL-12. Our TMEkine™ (anti-FAP-IL-12) molecule induced strong anti-cancer effects in preclinical solid tumor models by immune-modulation.

Methods IL-12 cytokine was mutated in TMEkine™ (anti-FAP-IL-12) to reduce systemic toxicity and its binding affinity was tested to FAP and IL-12 receptor. The anti-tumor activity of anti-FAP-IL-12 was investigated on CT26 (murine colorectal cancer) syngeneic mouse models with/without NIH-3T3 (murine fibroblast). Additionally, mice showing complete response after anti-FAP-IL-12 administration were re-injected CT26 with/without 4T1 cells for re-challenge study to monitor long-term durable response generated from the initial immune activation.

Results We showed that TMEkine™ (anti-FAP-IL-12) interacts with FAP and IL-12 receptor. IL-12 activity was attenuated by our IL-12 mutants. We also showed that TMEkine™ (anti-FAP-IL-12) induced IFN-γ from primary human T cells and NK cells. TMEkine™ (anti-FAP-IL-12) administration resulted in significant reduction of the tumor burden in both CT26 + NIH-3T3/FAP+ and CT26/FAP+ models. In the re-challenge experiments, CT26 tumor growth was inhibited significantly compared to 4T1 tumor suggesting memory immune response was generated in TMEkine™ (anti-FAP-IL-12) treated mice.

Conclusions These findings provide evidences that the treatment of anti-FAP-IL-12 TMEkine™ induced anti-cancer effects without serious adverse effects. Anti-FAP-IL-12 has a strong potential to provide a therapeutic option for cancer-specific immunomodulator and cancer cell eradication.

A NOVEL HUMAN ANTI-PD1/IL15 BI-FUNCTIONAL PROTEIN WITH ROBUST ANTI-TUMOR ACTIVITY AND LOW SYSTEMIC TOXICITY

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Background IL-15 is a key cytokine promoting CD8+ T, NK, and NKT cell proliferation and has demonstrated clinical activity in cancer patients without evidence of any Treg stimulation.1 2 However, its short half-life and systemic toxicity limit its clinical utility. Kadmon has established an IL-15 fusion protein platform to extend the IL-15 serum half-life and direct its action to the tumor microenvironment.3 A major asset of this platform is anti-PD1/IL15 bifunctional protein. To test the bifunctionality hypothesis of this fusion protein in murine models, four different formats of the surrogate bi-functional proteins were engineered by fusing mouse IL-15 to a mouse-human chimeric anti-mouse PD1 antibody (m3A7). We presented earlier that the single IL-15 N-terminal fusion to anti-PD1 antibody (1N-IL-15/m3A7) showed significantly stronger anti-tumor activity in vivo mainly due to the cis-presentation to the PD1 and IL2Rβγ co-expressed on TILs. The cis-presentation potentially maximizes the bi-functionalility of PD1 blockade and IL-15 stimulation.4 Here, the therapeutic single IL-15 N-terminal fusion antibodies containing a novel human PD1 antagonist antibody (38B2) and either wild-type IL15 (1N-IL-15/38B2) or mutated 65S-IL15 (65S-1N-IL-15/38B2) have been constructed; their anti-PD1 functions, IL15 stimulation and anti-tumor activities were evaluated.

Methods Purified 1N-IL-15/38B2 and 65S-1N-IL-15/38B2 were generated and characterized in vitro. The anti-tumor activities were examined in the human-PD-1/PD-L1 transgenic BALB/c mice subcutaneously transplanted with the human-PD-L1 positive CT26 colon carcinoma. The treatment was started when tumors reached 100 mm³ (IP, QW).

Results All 1N-IL-15/anti-PD1 fusions showed similar potencies in binding to the soluble and cell expressed human PD1 and blocking the hPD1-L1 binding to hPD1. Comparing to wild-type 1N-IL-15/38B2, mutated 65S-1N-IL-15/38B2 showed lower stimulation (>150 folds) in the M07e, CTLL2, mouse spleen cells and hPBMC (mainly CD8+ T cell) proliferation. When we treated hPD1-CT26 tumor transplanted hPD1-L1 transgenic mice with 65S-1N-IL-15/38B2 at 6 mg/kg, 80% of tumor growth inhibition (TGI) was achieved with no body-weight loss. Although wild-type 1N-IL-15/38B2 at 3 mg/kg demonstrated similar efficacy, a significant mouse body-weight loss was observed and 1/3 mice died after second injection. No anti-tumor activity was observed for 65S-1N-IL-15 non-target fusion in 6 mg/kg.

Conclusions The previous observation of robust anti-tumor activity of surrogate 1N-IL-15/m3A7 in PD1 resistant LL2 model was replicated with the therapeutic bifunctional protein in this study. We also found that lower stimulation 65S-1N-IL-15/38B2 showed strong anti-tumor activity with significant low systemic toxicity; suggesting that the 65S mutation increased the therapeutic window of this bi-functional protein.

REFERENCES


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