ASKG215β, AnFc-IL-15 Prodrug Fusion Molecule with Extended Half-life
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Abstract #1742

Background

- IL-15 is a potent molecule. It stimulates the proliferation of immune cells including NK cells, CD8+T cells, and γδ T cells.
- IL-15 molecules in development typically have very short half-lives in vivo due to “cytokine sink”, leading to limited exposure and poor efficacy yet dose-dependent systemic toxicities.
- Cytokines often run into target-mediated drug disposition (TMDD) when dosed systemically.
- TMDD expanded during repeated dosing or continued dosing. The serum concentration of IL-15 decreased almost linearly and for a total of over 10 times during a 10-day continuous infusion. It was a challenge to develop a dosing strategy for cytokine molecules including antibody-cytokine fusion molecules.2
- “Homing” of delivering cytokines to the disease sites is often challenging even when the cytokines were fused to disease specific targeting antibodies, because the cytokine molecules dominantly control the destinations of the fusion molecules.
- To fully harness the therapeutic potentials of cytokine molecules, AskGene created a novel cytokine prodrug platform (SmartKine®), wherein cytokine molecules can avoid the “cytokine sink” at systemic level and be activated at a disease site.
- ASKG215β is the first project from the prodrug platform.

Anti-tumor activity in Gastric Cancer CDX Model

ASKG215β Potentiated ADCC Effect without Introducing Additional Toxicity

Peripheral Activity & BW Change Findings in NHPs

ASKG215β showed reduced peripheral activity & lower transient BW loss with 6x higher AUC and be activated at a disease site. ASKG215β is the first project from the prodrug platform.

Methods

The in vitro activities of ASKG215β was evaluated in N92 cell iPSCs assay and HEK-Blue IL-2 reporter assay. The PK/PD properties and safety profiles of ASKG215β were assessed in non-human primates (NHPs) following three weekly IV injections at 1 mg/kg for ASKG215β. The anti-tumor activities were tested in human PBMC engrafted tumor xenograft models.

In Vitro Activation by Protease

ASKG215β Prodrug Activity Was Restored in the Presence of Protease

Cyno Pharmacokinetic (PK) Study

ASKG215β Demonstrated Sustained PK with AUC 6x Greater than Ref at the Same nm/kg Dose

Conclusions

- ASKG215β demonstrated:
  - Protease-dependent conditional activation in vitro
  - Robust anti-tumor activities in hEPSC-reconstituted N92-KATOIII/18.2 and A375 CDX models
  - Extended PK & improved safety with reduced peripheral activity in NHPs
  - No obvious signs of immunogenicity in NHPs with three consecutive weekly IV doses
  - Well tolerated at biweekly dose up to 2 mg/kg in NHPs (pilot tox study)

We established a novel cytokine prodrug platform technology SmartKine®. The first PoC molecule ASKG215β showed antibody-like PK in NHPs with acceptable safety profiles. This is the first report showing that an IL-15 fusion molecule was able to avoid the “cytokine sink” usually associated IL-15 molecules. This would enable the targeted delivery of a cytokine molecule to a disease site via a tumor-targeting antibody or an iO/antibody.

References