ASKG215β, An Fc-IL-15 Prodrug Fusion Molecule with Extended Half-life

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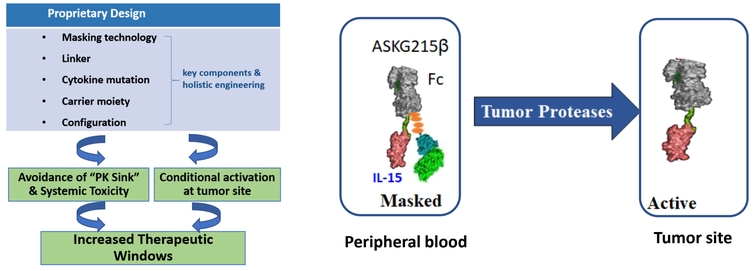
Abstract #1742

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.[1]
  - It was a challenge to develop a dosing strategy for cytokine molecules including antibody-cytokine fusion molecule.[2]
- "Homing" of or 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.

SmartKine® Prodrug Platform Technology

Enables Sustained PK and Reduced Systemic Toxicity

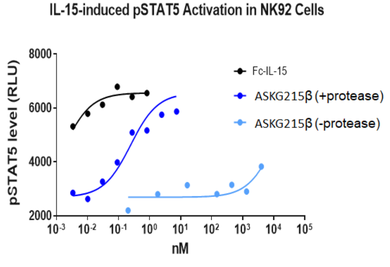


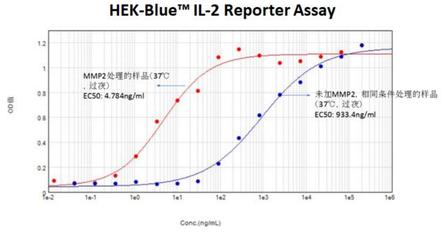
Methods

The *in vitro* activities of ASKG215β was evaluated in NK92 cell pSTAT5 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

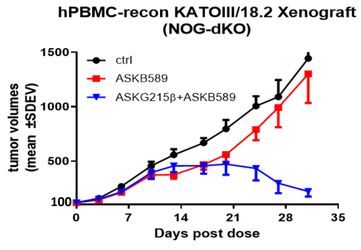


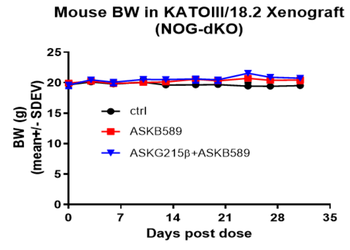


	Prior to activation	Post Activation
EC50 (ng/ml)	9.3	0.048

Anti-tumor Activity in Gastric Cancer CDX Model

ASKG215β Potentiated ADCC Effect without Introducing Additional Toxicity

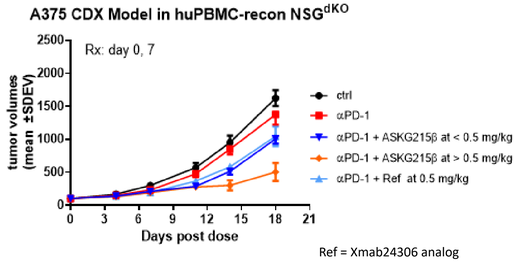




KATOIII cells were inoculated subcutaneously into the right lower flank of NOG-dKO mice. Animals were randomized upon reaching the size of 60-100 mm3 and followed by receiving fresh human PBMC intravenously. TA dosing started at the same day, was designated as Day=0 with n=10 animals in each treatment group. ASKB589 is an antibody against human Claudin 18.2.

Anti-tumor Activity in A375 CDX Model

ASKG215β Potentiated Anti-PD1 Effect with Better Safety Window than Ref



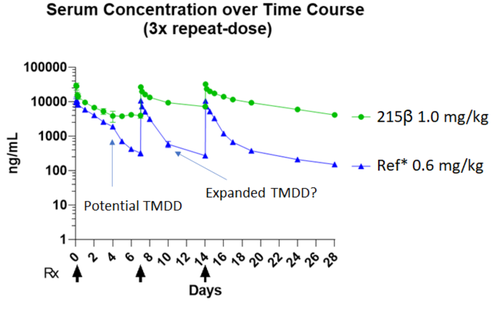
Ref = Xmab24306 analog

A375 cells were inoculated SC into the right lower flank of NSG-dKO mice. Animals were randomized into 10 animals in each treatment group upon reaching the size of 100±10mm^3, followed by fresh human PBMC injection intravenously. TA dosing started at the same day, was designated as Day=0, followed by a second dose at Day 7.

TAs	# of mice Death due to GvHD (D=18)
Ctrl	0/10
αPD-1	0/10
αPD-1 + ASKG215β (< 0.5 mg/kg)	0/10
αPD-1 + ASKG215β (> 0.5 mg/kg)	1/10
Ref at 0.5 mg/kg	3/10

Cyno Pharmacokinetic (PK) Study

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

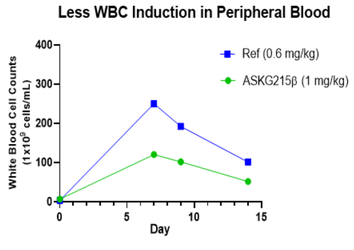


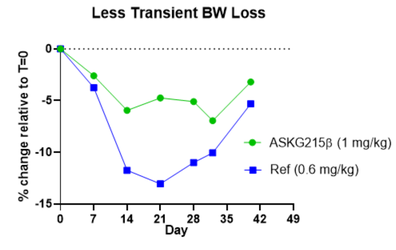
	ASKG215β n=2 (Female/Male)	Ref n=2 (Female/Male)
W1	1 mg/kg	0.6 mg/kg
W2	1 mg/kg	0.6 mg/kg
W3	1 mg/kg	0.6 mg/kg

* Ref = Xmab24306 analog
** ASKG215β & ref molecules evaluated had similar nM/kg dose

Peripheral Activity & BW Change Findings in NHPs

ASKG215β Showed Reduced Peripheral Activity & Lower Transient BW Loss with 6x Higher AUC





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Preliminary Results from Pilot Toxicology Study

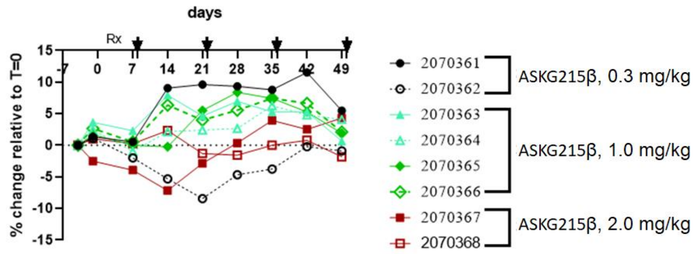
BW Data Indicated ASKG215β Was Well Tolerated at Biweekly Doses up to 2 mg/kg

Group No	Male	Female	Dose Level(mg/kg)
Group 1	1	1	0.3
Group 2	2	2	1
Group 3	1	1	2

Dosing schedule

Dose	Studying dose day
1	8
2	22
3	36
4	50

BW Change over Time Course



Conclusions

- ASKG215β demonstrated:
  - Protease-dependent conditional activation in vitro
  - Robust anti-tumor activities in huPBMC-reconstituted NSG-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 I/O antibody

References

1. Colon et al., Clin Cancer Res. 2019 Aug 15; 25(16): 4945–4954)
2. Grimm et al., PAGE 25 (2016) Abstr 5861 [www.page-meeting.org/?abstract=5861]).