ASKG915 – An Anti-PD1 Antibody-IL-15 Prodrug Fusion Molecule With Enhanced Therapeutic Potential

Kurt Shanebeck[1], Chunxiao Yu[1], Shiguang Yu[1], Jiye Sun*, Donfang Wang*, Jeanine Ruiz, Ming Li, Ray Chuang, Jing Chen, Samantha Ruiz, Lynwel Cunanan, Stone D.-H. Shi, Matt Hsu, Yong Wen*, Jeff Lu, Yuefeng Lu.

AskGene Pharma Inc., Camarillo, CA; *Aosaikang Biotherapeutics Co Ltd, Nanjing, China; [1]These authors made equal contributions to this presentation.

SITC2022
Abstract #1183

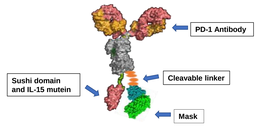
Background

AskGene has established a proprietary cytokine prodrug platform (Smartkine®) to achieve its overarching objective of modulating immune reactions at a disease site in a selective and controlled manner. Cytokines are potent molecules, yet their broad application as therapeutics has been hampered due to short PK, severe systemic toxicity, and narrow therapeutic window. To improve the therapeutic potential of cytokines, AskGene has developed several antibody-cytokine prodrug fusion molecules using its proprietary Smartkine® platform.

Methods

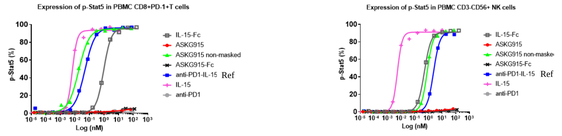
The in vitro activities of ASKG915 were evaluated using PBMC-based assays. Peripheral immune activation was evaluated in a GvHD model with human PBMC-engrafted NSG mice. Anti-tumor activities were tested in a human PBMC engrafted tumor xenograft model, and a syngeneic tumor model. The PK/PD properties and safety profiles of ASKG915 were assessed in non-human primates (NHPs) following three IV injections every two weeks.

ASKG915 Is Designed to Avoid "Cytokine Sink" and Be Truly Bifunctional



ASKG915 is designed to be truly bifunctional:
- **Cleavable linker a family of proteases overexpressed in tumor**
- **High enough dosage so that the PD-1 antibody is fully functional as the PD-1 blockage**
- **Tumor protease activation, PD-1 targeting, and Cis-activation enhance tumor-selective immune stimulation**

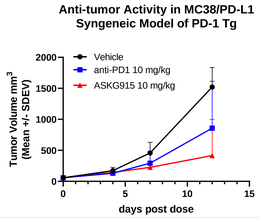
Activated ASKG915 Selectively Stimulates PD-1+ T Cells



	CD8+PD1+ T Cells	NK Cells
ASKG915 non-masked	0.018 nM	0.80 nM
Anti-PD1-IL1-15 Ref (not a prodrug)	0.048 nM	2.4 nM
IL-15-Fc (ASKG315 non-masked)	0.93 nM	0.5 nM

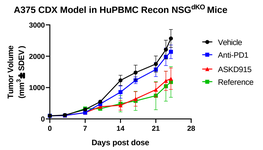
- **Selective stimulation of PD-1+ T cells, 40X lower EC50 than stimulating NK cells**
- **Cis-activation boosted the potency by ~50X:**
  Activated ASKG915 is 50X stronger than the same molecule without the PD-1 binding domain

ASKG915 Demonstrates Augmented Anti-Tumor Activity

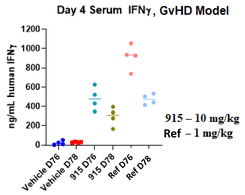


ASKG915 shows enhanced anti-tumor activity in a syngeneic mouse model using human PD1 transgenic mice compared to anti-PD1 alone.

Significantly Expanded Therapeutic Window

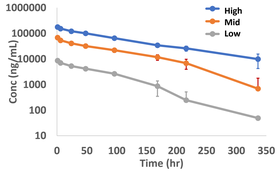


Test Articles	# of Death due to GvHD (up to Day 24)
Control	0/10
αPD-1	0/10
ASKG915	0/10
Ref	3/10



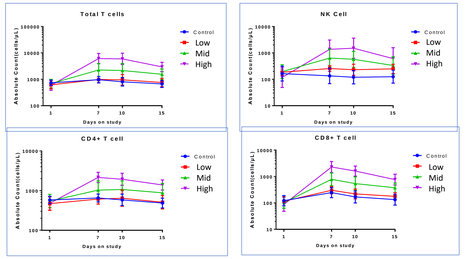
- **Lower peripheral activation (>10X) and similar anti-tumor efficacy suggest strong tumor-selective immune stimulation**
- **Demonstrated expanded therapeutic window**

ASKG915 TK in Cyno Monkeys

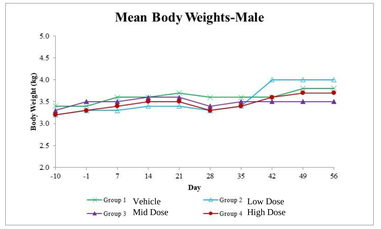


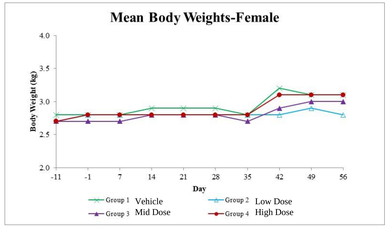
- **Linear PK from Low to High Dosages**
- **Significantly prolonged T1/2 of ~5 days**
- **Low level of non-specific activation in the circulation**

ASKG915 Stimulates Significant and Sustained Expansion of T and NK Cells in Cyno Monkeys without Causing Severe Toxicity



Monkey GLP Toxicology Study – General Findings





- **ASKG915 was well tolerated**
- **No mortality or moribundity**
- **No cytokine release (IFN-γ, TNF-α, IL-6, or IL-8)**
- **The Low Dose is identified as NOEAL**
- **The High Dose is identified as the highest non severe toxicity dose (HNSTD)**

Results

ASKG915 showed minimal activity prior to protease-dependent activation and significantly enhanced activity after protease-dependent activation in vitro. Specifically, it has significantly higher activities stimulating PD-1$^+$ immune cells, presumably through "cis-activation". In in vivo efficacy studies, it showed similar potency as a reference anti-PD1-IL-15 fusion molecule (not masked) while having a better safety profile. In addition, in a GvHD study, ASKG915 at 10 mg/Kg i.p. induced lower interferon gamma levels in the periphery compared to the reference molecule at 1 mg/Kg. These results showed that, compared to the reference molecule, ASKG915 had comparable immune stimulation in the tumor while having significantly reduced immune stimulation in the periphery. In NHPs, ASKG915 demonstrated prolonged and antibody-like PK profiles. More importantly, ASKG915 was well tolerated at the highest dosage tested in NHP, with no cytokine release syndrome (CRS) and minimal immune reaction at injection sites.

	ASKG915	Reference
Avoid "cytokine sink"	Y	N
PK – T1/2 in cyno	5 Days	?
Targeting PD-1+ T cells in TME	Y	?
Tumor-selective immune stimulation	Y	N
Full PD-1 blockage functionality	Y	N
Therapeutic window	ASKG915 may have more expanded therapeutic window vs Ref	

Conclusions

- Activated ASKG915 shows selective stimulation for PD1+ immune cells in in vitro PBMC assays.
- ASKG915 in vivo shows tumor-selective activation compared to a reference molecule.
- ASKG915 has extended antibody-like PK in NHPs and was well tolerated at the highest dosage tested in the GLP PK/PD study.
- ASKG915 shows a significantly expanded therapeutic window.

An IND filing is planned in Q4 2022. To our knowledge, ASKG915 is the first anti-PD1 antibody-IL-15 prodrug fusion molecule moving into clinical development.