ADG206, an anti-CD137 agonistic POWERbody™ with tailor-made efficacy and safety profiles by strong crosslinking and tumor selective activation for single agent and combinational cancer immunotherapy

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BACKGROUND AND SIGNIFICANCE

Therapies targeting CD137 by agonistic antibodies face various challenges in the clinic. Urelumab shows potent efficacy but severe dose-dependent liver toxicity, although utomilumab appears safe but little efficacy. By targeting a unique, highly conserved epitope of CD137, differentiated from both urelumab and utomilumab, we developed ADG106 with robust clinical safety but limited efficacy. Here we describe a new anti-CD137 ADG206 POWERbody™ by combining our SAFEbody® technology for precision masking to secure the safety with the Fc-engineered cross-linking on top of ADG106 in order to achieve improved safety and efficacy profiles. Masking CD137 antigen binding interfaces of ADG206 using a covalently linked designer peptide can limit on-target off-tumor toxicities in normal tissues, whereas the masked antibody can be activated to selectively bind CD137 in the tumor microenvironment (TME). Furthermore, Fc-engineered IgG1 of ADG206 increases FcγR-mediated crosslinking, resulting in enhanced T cell responses and antitumor activity (Fig1) .

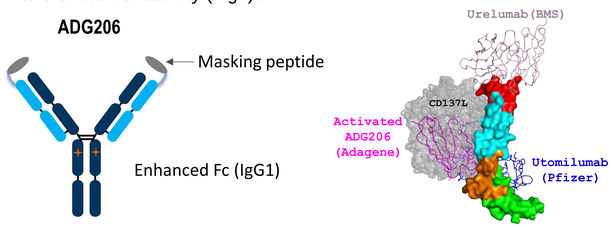

Fig 1. ADG206, an Adagene POWERbody, *i.e.,* an Fc-engineered IgG1 SAFEbody. The efficacy is powered by Fc-engineered IgG1 to enhance the cross-linking with FcγRs, FcγRIIB in particular. The safety is secured using covalently linked masking peptides which can be conditionally activated to bind its target in TME. The activated ADG206 binds to a unique epitope on CD137, different from that of urelumab and utomilumab.

RESULTS

ADG206 exhibits broad species reactivity and high masking efficiency as a masked anti-CD137 antibody

Antigen	Test antibody	KD (nM)
Human CD137	ADG206	> 1000
	Unmasked ADG206	3.19
Cynomolgus monkey CD137	ADG206	> 1000
	Unmasked ADG206	4.23
Mouse CD137	ADG206	> 1000
	Unmasked ADG206	27.54
Rat CD137	ADG206	> 1000
	Unmasked ADG206	42.37

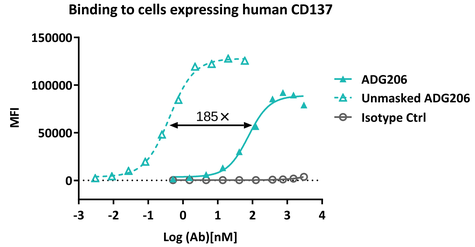

Fig 2. Binding affinities, as determined by SPR, of ADG206 and its unmasked form to recombinant CD137 from different species (table). Unmasked ADG206, but not the masked ADG206, binds with high affinity to CD137 from different species. Binding to cell surface expressed CD137, as determined by flow cytometry (graph), also confirmed the high masking efficiency of ADG206 for CD137 binding.

RESULTS

Unmasked ADG206 binds to activated T cells

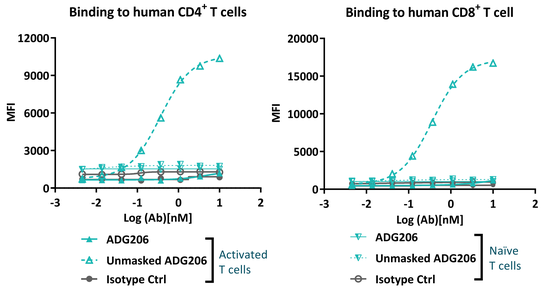

Fig 3. Unmasked ADG206, but not the masked form, binds to activated CD4+ and CD8+ T cells at high affinity, but not the unstimulated naïve T cells, as determined by flow cytometry. Human T cells were stimulated in vitro with anti-CD3/anti-CD28.

Unmasked ADG206 is a potent ligand-blocking CD137 agonist

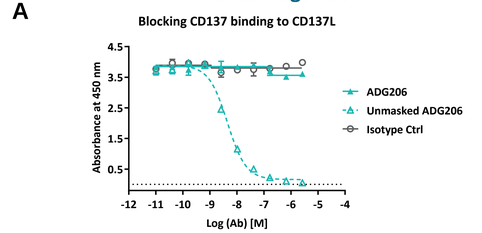

Fig 4. (A) Unmasked ADG206 can block CD137 binding to its ligand in a dose-dependent manner, as determined by ELISA. (B) Activation of CD137 signaling by different anti-CD137 antibodies in the presence (upper) or absence (lower) of hFcγRIIB-expressing CHO-K1 cells as crosslinker. Unmasked ADG206 exhibited strongest activation of CD137, which is dependent on hFcγR-mediated crosslinking, in contrast to FcγR-independent stimulation of CD137 by clinical reference antibody urelumab. * benchmark antibody produced in-house.

Potent co-stimulation of human T cells by unmasked ADG206 *in vitro*

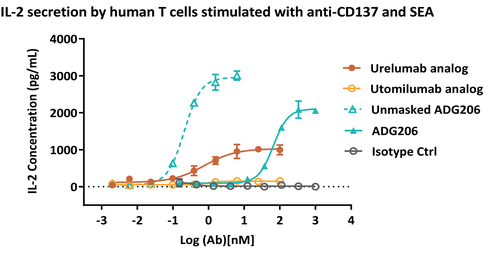

Fig 5. Activation of human T cells *in vitro* by various anti-CD137 antibodies. Human PBMCs were stimulated with different anti-CD137 antibodies in the presence of SEA. IL-2 levels in supernatant were determined by ELISA as a readout for T cell activation. Representative results for 1 donor are shown, the unmasked ADG206 exhibited the strongest activity to enhance T cell activation *in vitro*.

ADG206 exhibits robust anti-tumor activity in mouse tumor models

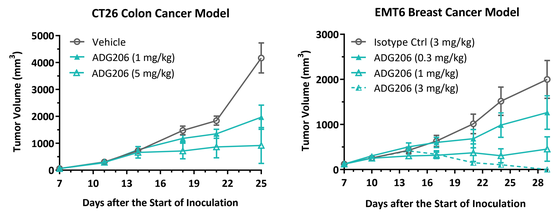

Fig 6. Dose-dependent single agent anti-tumor activity of ADG206 in mouse syngeneic tumor models. Antibodies were *i.p.* dosed, BIW × 2 wks; n=8/group.

Combination of ADG206 with checkpoint inhibitors shows enhanced *in vivo* antitumor activity

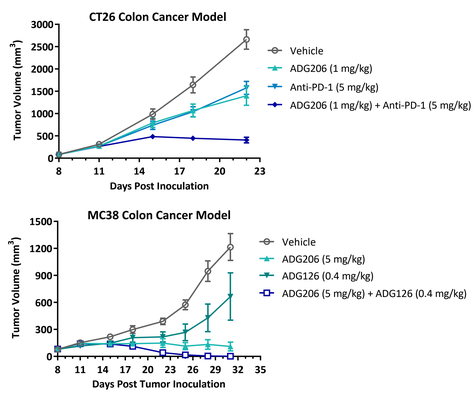

Fig 7. Enhanced anti-tumor activity was observed with ADG206 in combination with anti-PD-1, or anti-CTLA-4 SAFEbody ADG126, in mouse syngeneic tumor models.

ADG206 demonstrates normal systemic PK properties and minimal accumulation after repeat dosing in cynomolgus monkeys

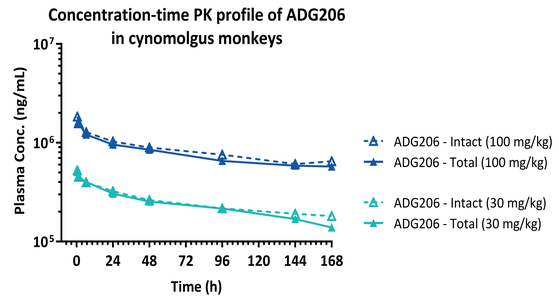

Fig 8. Pharmacokinetic (PK) studies of intravenous administration of ADG206 in monkeys. The plasma concentrations of both intact and total ADG206 were measured by ELISA-based assays. The results demonstrated that ADG206 was maintained predominantly as the intact form, *i.e.*, the masked inactive form, in systemic circulation. ADG206 was well-tolerated (up to 100 mg/kg) in both rats and cynomolgus monkeys in toxicology studies.

SUMMARY

- ADG206, a masked Fc-enhanced anti-CD137 agonistic POWERbody, was developed using the precision masking technology targeting a novel epitope of CD137 with broad species cross-reactivity.
- ADG206 exhibited high masking efficiency and was conditionally activated to bind strongly to CD137 co-stimulatory receptor on activated T cells.
- Unmasked ADG206 exhibited stronger FcγR-dependent anti-CD137 agonistic activity than urelumab for T cell activation in the presence of a primary stimulatory signal, but little activity for masked ADG206.
- ADG206 demonstrated robust anti-tumor activity as a single agent and enhanced anti-tumor activity in combination with other immune checkpoint inhibitors including anti-PD-1 or anti-CTLA-4.
- ADG206 is well-tolerated in rats and cynomolgus monkeys in nonclinical toxicology studies, with normal pharmacokinetic properties and minimal activation in circulation.
- The preclinical safety and efficacy profiles support advancing the masked anti-CD137 ADG206 POWERbody into clinical development.

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