ADG153-G1, a highly differentiated anti-CD47 IgG1 SAFEbody, demonstrates potent in vivo anti-tumor activities with enhanced ADCC/ADCP effects and significantly reduced RBC-related and antigen sink liabilities

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BACKGROUND AND SIGNIFICANCE

Anti-CD47 antibodies of the IgG4 isotype have shown promising activities in clinical trials for hematologic malignancies, mainly in the combination setting. To overcome the fundamental challenge of developing an anti-CD47 antibody of an active Fc isotype for strong anti-tumor activities without the safety (e.g., anemia) and pharmacokinetic (e.g., antigen sink) liabilities, we set out to design anti-CD47 antibodies of active isotypes that allow us to decouple efficacy from safety and PK liabilities. Our NEObody™ technology enables us first to identify an anti-CD47 antibody targeting a novel epitope on CD47. Next, our SAFEbody® technology for precision masking enables us to mask the CD47 binding sites to create the masked antibody in active IgG1 isotype called ADG153-G1 SAFEbody (now referred to as ADG153), which can be conditionally activated to bind and inhibit CD47 on tumor cells for potent tumor killing with much improved safety and PK profiles. Because of its effector function-dependent activities, we anticipate ADG153 to be effective in both hematologic and solid tumor indications.

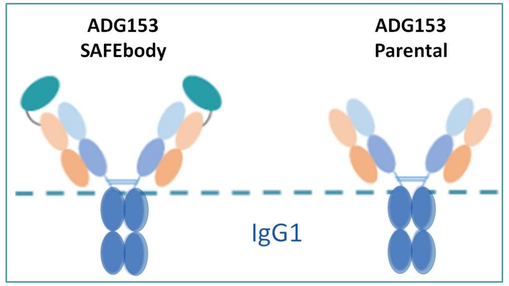

Fig 1. An Adagene SAFEbody, masked by covalently linked peptides, can be conditionally activated to bind its target. Shown is the ADG153 (anti-CD47) SAFEbody and its Parental forms in hIgG1 isotype.

RESULTS

The high masking efficiency of anti-CD47 SAFEbody in comparison with its parental, unmasked, and reference antibodies in binding to human CD47 *in vitro*

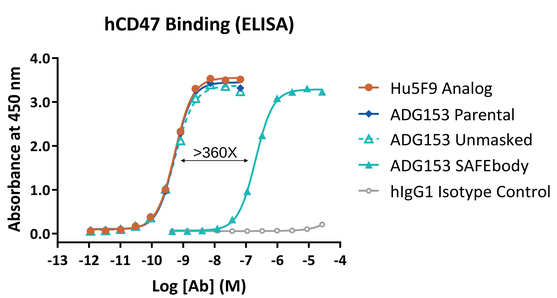

Fig 2. ADG153 Parental and Hu5F9 Analog showed overall comparable *in vitro* binding to hCD47 by ELISA. ADG153 SAFEbody demonstrated >360-fold masking efficiency for binding to hCD47; binding can be fully restored with *in vitro* MMP cleavage of the SAFEbody (Unmasked).

RESULTS

The high masking efficiency of anti-CD47 SAFEbody in comparison with its unmasked and reference antibodies in binding to Raji cells *in vitro*

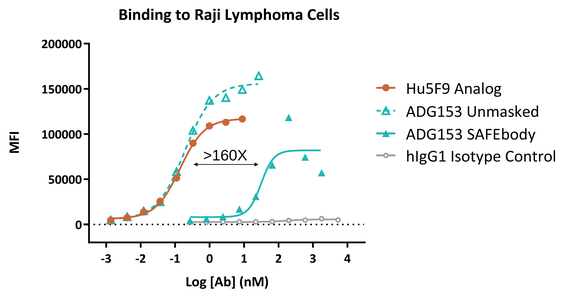

Fig 3. ADG153 SAFEbody demonstrated >160-fold masking efficiency for binding to Raji cells, compared with *in vitro* MMP cleaved ADG153 (Unmasked).

The high masking efficiency of anti-CD47 SAFEbody prevents its binding to human RBCs

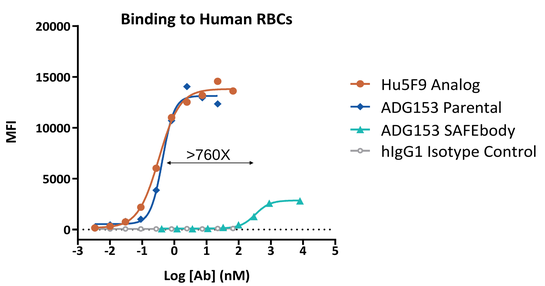

Fig 4. ADG153 Parental and Hu5F9 Analog showed comparable binding to human RBCs. ADG153 SAFEbody demonstrated >760-fold masking efficiency and dramatically reduced maximum for binding to human RBCs.

ADG153 targets a novel epitope and does not induce human RBC hemagglutination *in vitro*

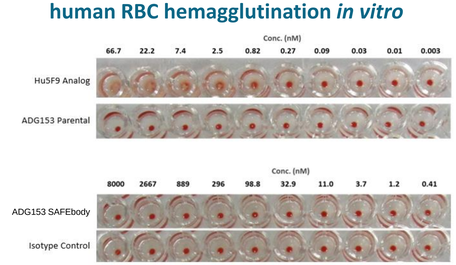

Fig 5. Hu5F9 Analog showed *in vitro* human RBC hemagglutination (HA) at concentrations ≥7.4 nM. ADG153 Parental and SAFEbody molecules did not induce HA. Results for 1 donor are shown; similar results were observed for a second donor (not shown).

Unmasked ADG153 induces stronger ADCP than reference antibody

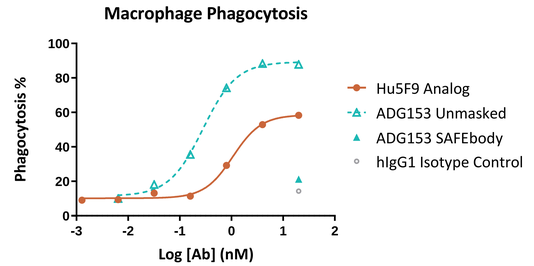

Fig 6. The ADG153 SAFEbody had no to minimal ADCP activity, while *in vitro* MMP cleaved ADG153 (Unmasked) demonstrated more potent and higher max induction of ADCP than the Hu5F9 Analog.

Unmasked ADG153, not the reference antibody, induces potent NK-mediated ADCC activity *in vitro*

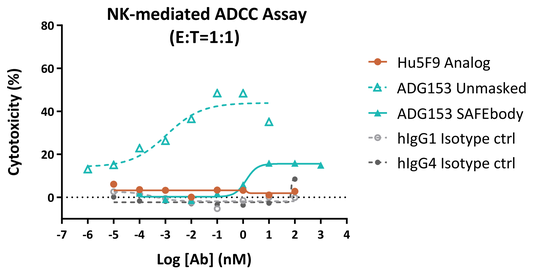

Fig 7. The ADG153 SAFEbody demonstrated minimal ADCC activity *in vitro*, and induction of NK-mediated ADCC activity can be fully restored with *in vitro* MMP cleavage (Unmasked). The Hu5F9 Analog did not have ADCC activity.

ADG153 SAFEbody shows strong in vivo anti-tumor activity in the Raji subcutaneous tumor model

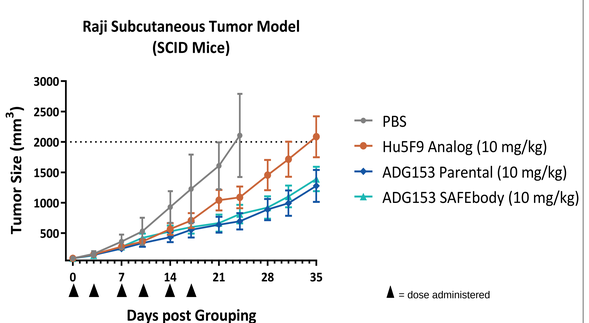

Fig 8. ADG153 Parental and SAFEbody molecules, both of which are of the IgG1 isotype, demonstrated better anti-tumor activities than Hu5F9 Analog in the Raji subcutaneous model in SCID mice that are known to have functional macrophages and NK cells.

ADG153 SAFEbody demonstrates significantly reduced RBC-related liabilities in cynomolgus monkeys

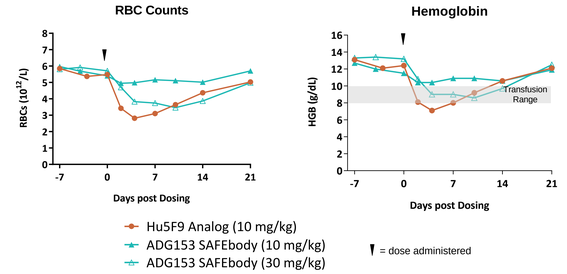

Fig 9. In exploratory toxicology studies in cynomolgus monkeys, the ADG153 SAFEbody showed less reduction than Hu5F9 Analog in RBC-related parameters such as RBC counts and hemoglobin level. Hu5F9 Analog at 10 mg/kg caused ~49% maximum decrease in RBCs at ~5X reduced AUC compared with ADG153, while the ADG153 SAFEbody at 10 and 30 mg/kg showed ~8 and ~40% maximum decrease in RBCs, respectively.

ADG153 SAFEbody demonstrates favorable PK properties with significantly less sink effect in cynomolgus monkeys

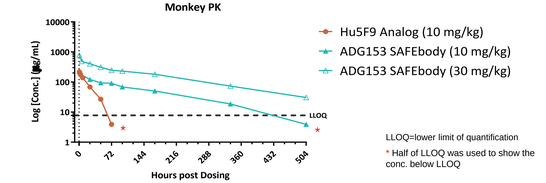

Fig 10. Pharmacokinetic (PK) studies of single intravenous dose of ADG153 SAFEbody compared with Hu5F9 Analog in monkeys demonstrated significantly less sink effect with ~8-fold longer apparent half-life and ~5-fold higher Area Under the Curve (AUC) at 10 mg/kg.

SUMMARY

- The anti-CD47 ADG153 IgG1 SAFEbody was developed using precision masking technology from the fully human anti-CD47 NEObody/Parental antibody targeting a novel epitope of CD47 with similar affinity against human and monkey CD47.
- ADG153 Parental and SAFEbody did not induce human RBC hemagglutination, unlike the reference anti-CD47 Hu5F9 IgG4 Analog.
- The ADG153 IgG1 SAFEbody had high *in vitro* masking efficiencies and was activated to bind strongly to CD47 protein, Raji lymphoma cells, and human RBCs. Unmasked ADG153 IgG1 induced stronger ADCP than the Hu5F9 IgG4 Analog and induced significant NK-mediated ADCC activity.
- The ADG153 IgG1 Parental and SAFEbody molecules demonstrated stronger anti-tumor activity in the Raji subcutaneous tumor model than the Hu5F9 IgG4 Analog.
- The ADG153 IgG1 SAFEbody, at 10 and 30 mg/kg, showed less RBC and hemoglobin decreases in monkeys compared to the Hu5F9 IgG4 Analog at 10 mg/kg, while still maintaining favorable PK properties in monkeys.
- The preclinical safety and efficacy profiles for the anti-CD47 ADG153 IgG1 SAFEbody provide a strong rationale for its advancement into clinical development for both hematologic and solid tumor indications.

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