

Cryo EM-Based Structural Characterization of IMC-002, a Next-Generation Anti-CD47 Antibody with a Unique Binding Site and Biomarker Candidates, Supporting Evidence of Enhanced Safety and Efficacy

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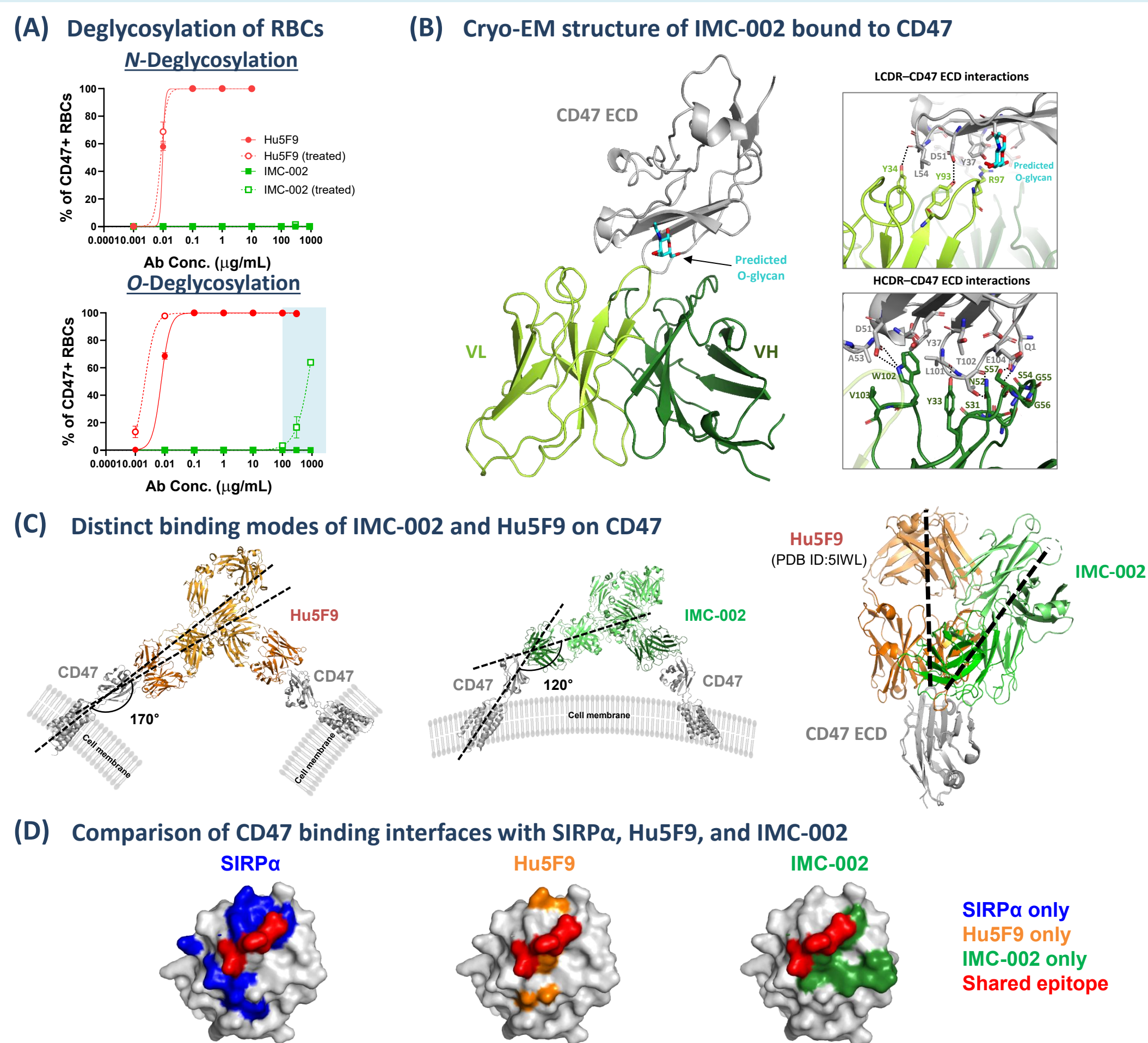
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BACKGROUND

- CD47 overexpression enables tumors to evade macrophage-mediated phagocytosis via interaction with SIRP α , but therapeutic targeting has been limited by toxicity from binding to normal cells.
- IMC-002 is a fully human IgG4 mAb targeting CD47, with optimized affinity to achieve tumor-selective binding while minimizing toxicity.
- Preclinical studies demonstrated favorable PK and no hematological toxicity in cynomolgus monkeys at doses up to 100 mg/kg.
- Here we present an updated Cryo-EM structural analysis of the IMC-002 binding site, preclinical efficacy data, and preliminary clinical biomarker findings from Phase 1b (NCT05276310)

RESULTS

Structural Basis of Tumor-Selective Binding

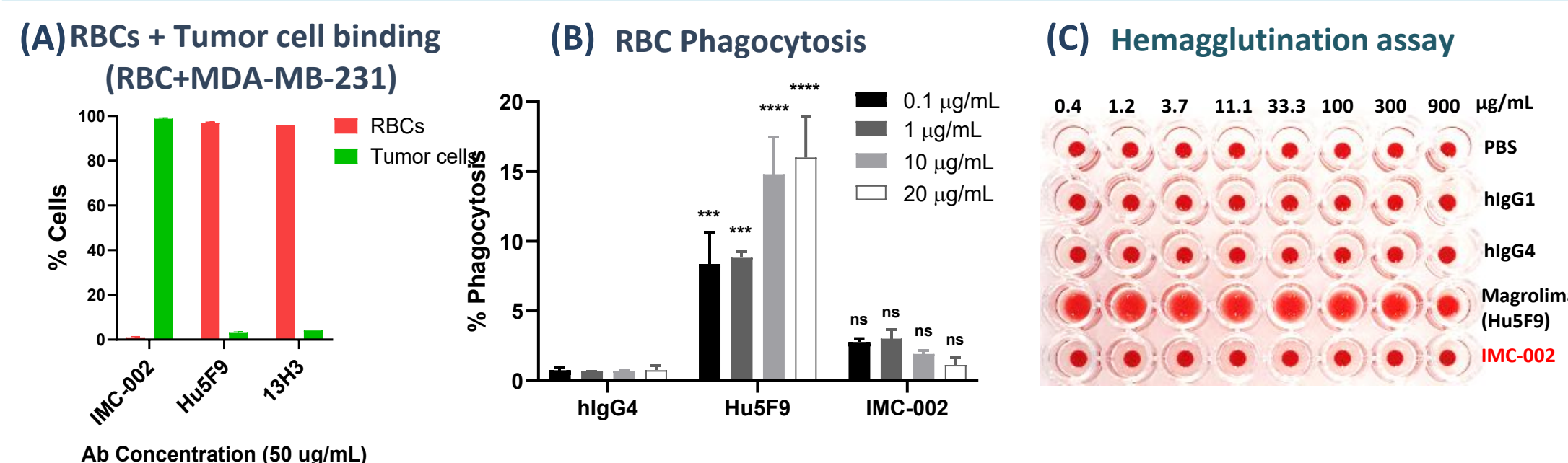


(A) IMC-002 binding to RBCs after O- or N-deglycosidase treatment. (B) Cryo-EM structure of the IMC-002 Fab-CD47 ECD complex. A predicted O-glycosylation site near the IMC-002 epitope is shown (left). Right panels show close-up views of the interaction interface; black dashed lines indicate polar interactions. Predicted O-glycan shown as sticks. (C) Structural comparison of IMC-002/CD47 and Hu5F9/CD47 complexes modeled on the full-length IgG4 antibody (PDB ID: 5DK3). (D) CD47-binding interface showing shared and antibody-specific epitopes for SIRP α , Hu5F9, and IMC-002.

SUMMARY

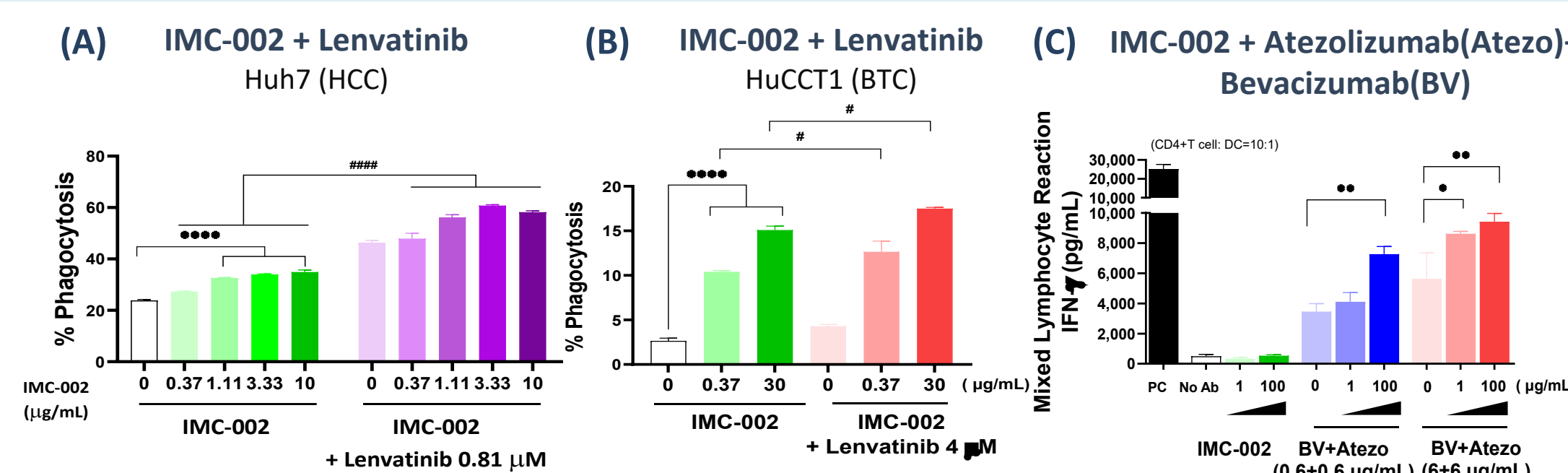
- IMC-002 demonstrates tumor-selective CD47 targeting that address the key safety limitations of existing CD47 therapies, on-target/off-tumor effects.
- Cryo-EM structural analysis identified a unique epitope near a predicted O-glycosylation site, providing a structural basis for its reduced hematologic toxicity.
- IMC-002 enhances macrophage-mediated phagocytosis and T-cell activation, with further potentiation observed in combination with SOC. These effects translated into robust anti-tumor activity without detectable toxicity.
- Collectively, these structural insights, together with robust preclinical efficacy and a favorable safety, support the continued clinical development of IMC-002 for solid tumors.

Tumor-Selective Binding and Improved Hematologic Safety



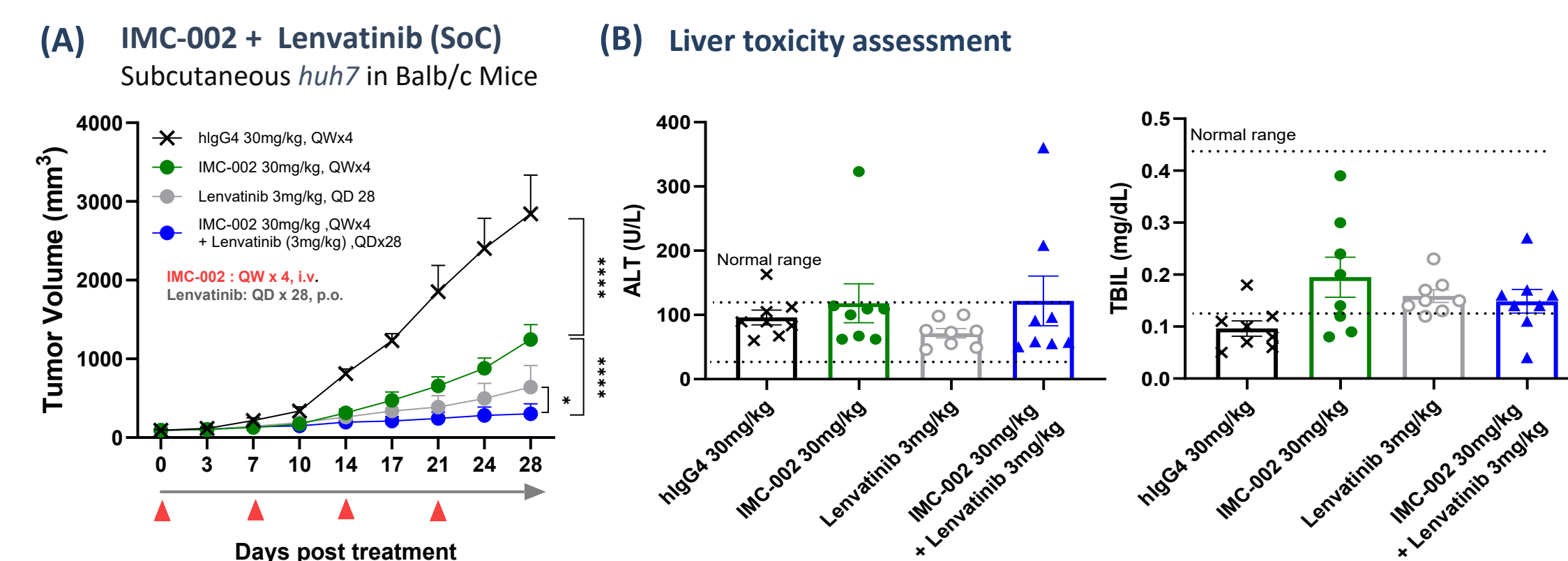
(A) IMC-002 selectively bound to CD47⁺ tumor cells with minimal binding to RBCs compared with Hu5F9 and 13H3 in a tumor-RBC co-culture system.
 (B) Unlike Hu5F9, IMC-002 dose not induce RBC phagocytosis, demonstrating selective targeting of tumor cells over normal cells.
 (C) Hemagglutination assay human RBCs. RBCs were incubated overnight at 37 °C with the indicated antibody concentrations. IMC-002 showed no hemagglutination.

SOC Combination Enhances Innate and Adaptive Immune Activation



(A-B) Enhanced Macrophage-Mediated Phagocytosis. Phagocytosis activity was assessed in human CD14⁺ monocyte-derived macrophages. IMC-002 was evaluated as a monotherapy and in combination with the standard-of-care (SoC) agents Lenvatinib (0.81 μM and 4 μM). One-way ANOVA. Compare with Isotype control (**** p <0.0001), compare with IMC-002 single (# p <0.05, ##### p <0.0001).
 (C) Synergistic T cell activation with Atezolizumab (Ate), Bevacizumab(BV) and IMC-002. T cell activation was assessed in a CD4⁺ T cell and Dendritic cell (DC) co-culture system (10:1 ratio). A fixed dose (1:1) combination of Ate and BV was evaluated with or without IMC-002. One-way ANOVA. Compare with atezolizumab and Bevacizumab combination only (* p <0.05 ** p <0.01).

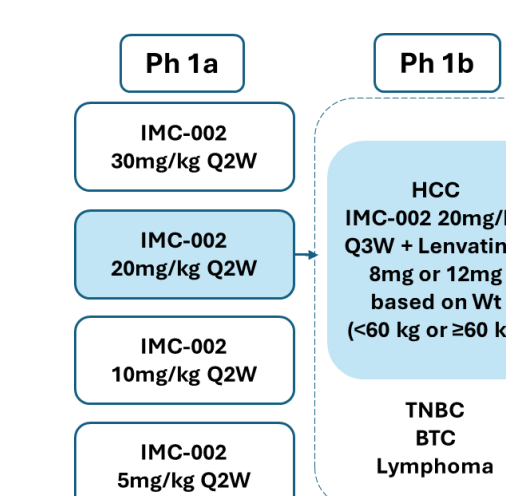
Potent Anti-Tumor Activity in Vivo without Hepatotoxicity



(A) In vivo efficacy of IMC-002 and Lenvatinib combination in subcutaneous Huh7 (HCC) xenograft models. Tumor-bearing nude mice were intravenously injected with hlgG4 or IMC-002 weekly, with or without daily oral Lenvatinib. Combination treatment with IMC-002 and Lenvatinib resulted in a statistically significant reduction in tumor growth compared with either IMC-002 of Lenvatinib alone. Two-way ANOVA (Dunnett's). * p <0.05, **** p <0.0001
 (B) Liver toxicity assessment. Serum liver injury markers were evaluated at study termination, showing no evidence of hepatotoxicity across treatment groups.

Clinical Biomarker Discovery

(A) Study design

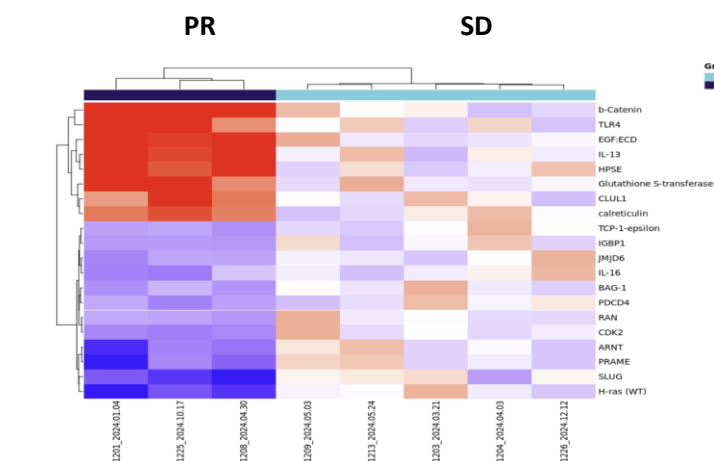


Clinical Response According to CD47 Expression

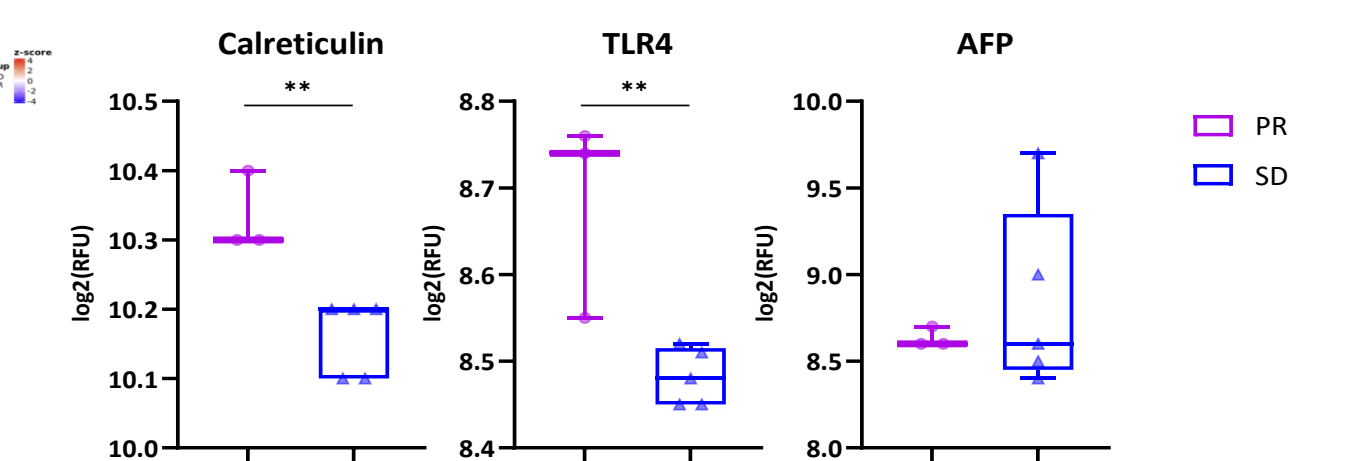
Group (n=12) CD47 expression	ORR	DCR
High	60% (3/5)	80% (4/5)
Low	0% (0/7)	43% (3/7)
P-value	0.018	0.198

- Membrane specificity = Membrane intensity / (Membrane intensity + Cytoplasm intensity + Nucleus intensity)
- Non-specific cell proportion = number of with (Mb intensity \geq 0.1 AND Mb specificity < 0.35) tumor cells / number of tumor cells
- High group: Non-specific cell proportion <15%
- Low group: Non-specific cell proportion \geq 15%

(B) Heat map



Univariate analysis of Calreticulin, TLR4 and AFP



(A) Study Design (left), AI-based CD47 IHC analysis (right). CD47 expression was analyzed using Lunit SCOPE uIHC, an AI-based platform that quantifies staining positivity and distinguishes cell types at the single cell level using the CD47 (clone EPR21794) antibody. A higher proportion of CD47⁺ membrane specific tumor cells was associated with better clinical response, whereas lower levels correlated with poor response.
 (B) Aptamer-based proteomic analysis. Heat map (left) showed the top analytes identified by differential expression analysis. SomaScan analysis (right) identified distinct profiles s between PR and SD groups. Univariate analysis demonstrated higher baseline expression of TLR4 and calreticulin in the PR group (t-test, p < 0.01).

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