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Leveraging a Humanized SLE Mouse Model to Evaluate Next-Generation Immune-Cell-Targeted Therapeutics

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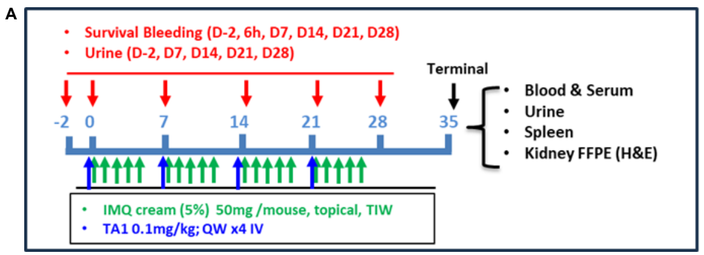
ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by aberrant B-cell activation, autoantibody production, and systemic inflammation. However, preclinical development of effective therapies remains challenging due to species-specific immune differences and the limited translational relevance of conventional mouse models. To overcome these limitations, we developed a novel humanized SLE mouse model designed specifically to enable robust screening of advanced therapeutics, including cell therapies and bi-/tri-specific antibodies.

This model is established by inducing disease with imiquimod (IMQ), a Toll-like receptor 7 (TLR7) agonist, in CD34⁺ humanized mice. IMQ stimulation activates human immune components, resulting in an SLE-like phenotype that more closely recapitulates human disease biology. Leveraging this platform, we evaluate the efficacy of next-generation modalities such as tri-specific T-cell engagers and in vivo CAR-T therapies targeting pathogenic B cells.

To support these studies, we have built a comprehensive analytical panel encompassing pharmacokinetics, biodistribution, immune activation, cytokine profiling, immunogenicity, and efficacy biomarkers (e.g., anti-dsDNA antibodies and urinary lipocalin-2). Together, this integrated platform enables reliable efficacy screening and mechanistic insights, providing a highly translational tool to accelerate the development of innovative SLE therapies.

CD34+ hu-NSG-SGM3 Humanized SLE Model Study Design



B

Grouping:
- hCD45 engraftment check by flow cytometry in D-2 blood samples
- Randomization (based on hCD45%)

In vivo live monitoring:
- BW and general health (Three times/week).
- Urine Protein Test (Once/week)
- Collect urine sample (weekly) for mouse Lipocalin-2/NGAL ELISA

Survival bleed:
- IL-6 cytokine assay, anti-dsDNA antibodies assay, anti-Nuclear Antibody (Direct ELISA) ELISA
- flow cytometry assay (D14, D28) (hCD45/hCD3/hCD19/hCD20/hCD14/LD/mCD45)

In vivo terminal:
- Photo of spleen, measure and record the weight
- Left Kidney tissue: FFPE (H&E, PAS)
- Terminal serum
- Urine

In vitro assay:
- anti-dsDNA antibodies assay
- IL-6 cytokine assay
- mouse Lipocalin-2/NGAL ELISA
- anti-Nuclear Antibody (Direct ELISA) ELISA

Fig 1. Study Design for Establishing a CD34⁺ hu-NSG-SGM3 Humanized SLE Model. (A) Schematic diagram of the study design. (B) Key study readouts for evaluating TA efficacy

SLE mouse model body weight and Proteinuria

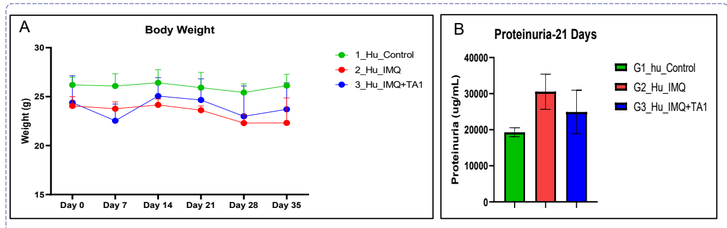


Fig 2. SLE mouse model body weight and Proteinuria. (A) Mouse Boday weight during the study. (B) Urinary protein concentration on Day 21

Flow cytometry analysis

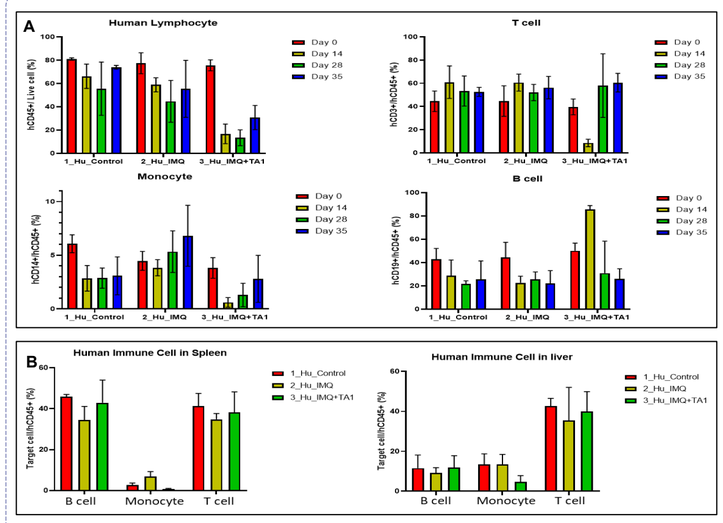


Fig 3. Immune Cell Population Analysis by Flow cytometry (A) Immune cell analysis in SLE mouse blood sample. (B) Immune cell analysis in SLE mouse spleen and liver samples.

Anti-dsDNA Antibody and Anti-nuclear Antibody (ANA)

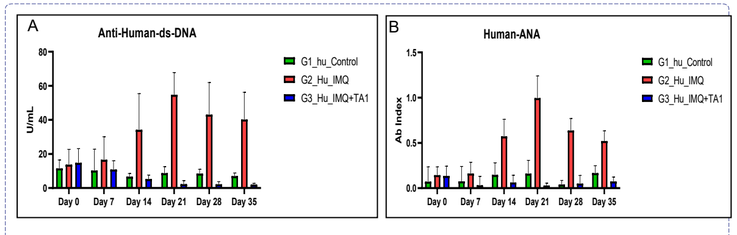


Fig 4. Anti-dsDNA Antibody and Anti-nuclear Antibody (ANA) ELISA assay (A) Anti-dsDNA Antibody (human IgG) ELISA assay (B) Anti-nuclear Antibody (human IgG) ELISA assay

Spleen Size, Human IL6 and Kidney Histology

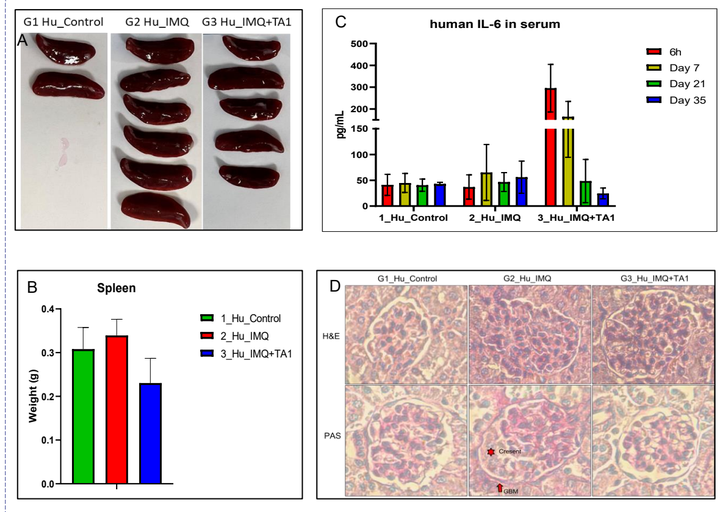


Fig 5. Spleen Size, Human IL6 and Kidney Histology (A) The photo of the spleen in SLE mouse model. (B) The spleen weight result of SLE mouse model. (C) The human IL6 concentration in SLE mouse serum. (D) The kidney histology of SLE mouse.

SUMMARY & ACKNOWLEDGEMENT

- We successfully established an SLE model in human CD34⁺ NSG-SGM3 mice that recapitulates key clinical features of the disease.
- Biomarkers in this model—including immune cell profiling, anti-dsDNA antibodies, anti-nuclear antibodies, and kidney histology—demonstrate strong translational relevance to clinical biomarkers.
- This humanized SLE model provides a reliable platform for evaluating the efficacy of various therapeutic modalities, particularly CAR-T cell therapies and bi-/tri-specific T cell engagers..
- As a trusted CRO partner, we offer flexible, customized solutions to accelerate therapeutic development from discovery through preclinical evaluation.
- The authors acknowledge the valuable contributions of the dedicated team at Medicilon US Corp. for their support of this work.

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