HST-2011, a Potent, Selective IRF5 Small Molecule Inhibitor, Enables Coordinated Inhibition of Innate and Adaptive Immune Responses in SLE

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INTRODUCTION

Transcription factor with essential role in immune regulation

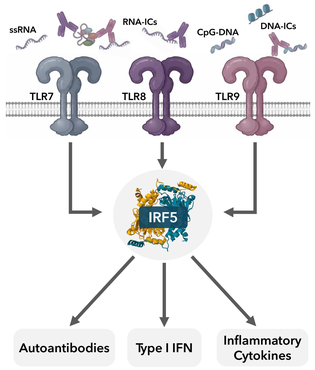
- IRF5 is a transcription factor downstream of Toll-like receptors 7, 8, and 9
- Primarily expressed in dendritic cells, B cells, monocytes, and macrophages
- Critical role in autoantibody production, type I interferon, and proinflammatory cytokines

Preclinical validation

- IRF5-deficient and heterozygous mice exhibited strong disease protection in several models of SLE with reductions in type I interferon levels and autoantibodies

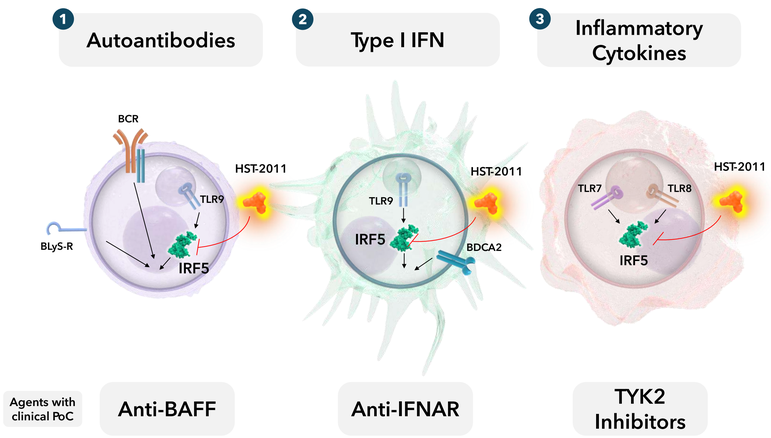
Genetic validation

- Genetic polymorphisms in IRF5 are associated with increased risk of SLE, Sjögren's disease, and other autoimmune diseases



HST-2011 is a potent, selective, small molecule IRF5 inhibitor; here, we assess its effects on innate and adaptive immune pathways implicated in SLE.

IRF5: Master Transcriptional Regulator Impacting Three Clinically-Validated Pathways in Autoimmunity



METHODS

IN VITRO ASSAYS

- Primary B cells were induced to undergo plasmablast differentiation and IgG production using sCD40L + IL-21 + RNA-containing immune complexes.
- RNA immune complexes or small molecule TLR agonists were used to induce IFNβ production in healthy whole blood or SLE PBMCs.
- Proinflammatory cytokines including TNF and IL-1β were assessed after stimulation of healthy or SLE PBMCs with a TLR agonist.

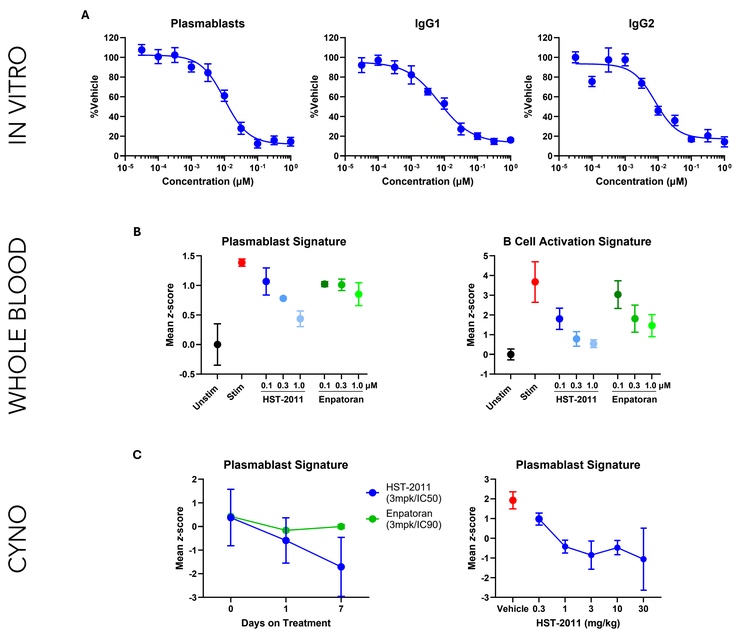
WHOLE BLOOD RNA SEQUENCING

- 90% human whole blood treated with HST-2011 or enpatoran was stimulated with a TLR agonist and mRNAseq was performed at 4h or 24h post-stimulation.
- Plasmablast, B cell activation, and interferon gene signature scores were assessed.

ORAL DOSING IN CYNO WITH EX VIVO TLR AGONISM

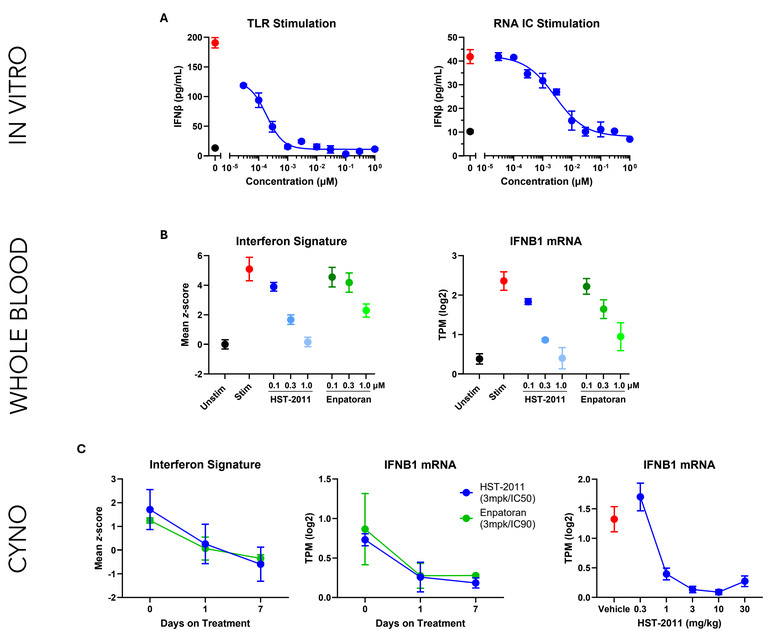
- Cynomolgus monkeys were dosed orally with HST-2011 (IC50 coverage) or enpatoran (IC90 coverage). Whole blood was isolated and mRNAseq was performed following 4h stimulation with a TLR agonist.

AUTOANTIBODIES: HST-2011 Blocks B Cell Activation, Plasmablast Differentiation, and IgG Production



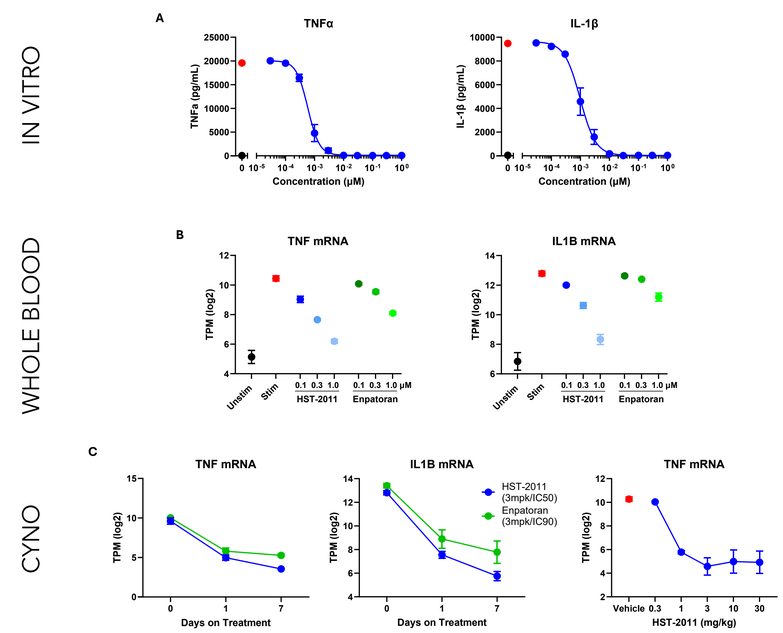
(A) Human B cells were cultured with sCD40L + IL-21 + RNA immune complexes to induce plasmablast differentiation and IgG production in the presence of increasing amounts of HST-2011. Plasmablasts ($CD27^+$ $CD38^+$) were measured by flow cytometry and IgG production was measured by LEGENDplex. (B) 90% human whole blood was stimulated with a TLR agonist in the presence of HST-2011 or enpatoran. mRNAseq was performed and gene signature scores are shown for both plasmablasts and B cell activation. (C) Cynos were orally dosed with HST-2011 or enpatoran. Whole blood was taken 1h post-dose and stimulated ex vivo with a TLR agonist. mRNAseq was performed and the plasmablast gene signature is shown.

TYPE I IFN: HST-2011 Blocks Type I IFN Production and Interferon Gene Signature



(A) SLE PBMCs or human whole blood was stimulated with a TLR agonist or RNA immune complexes in the presence of HST-2011 and IFNβ cytokine levels were measured by MSD. (B) 90% human whole blood was stimulated with a TLR agonist in the presence of HST-2011 or enpatoran. mRNAseq was performed and gene signature scores are shown for type I interferon and log2 TPM for IFNB1 mRNA. (C) Cynos were orally dosed with HST-2011 or enpatoran. Whole blood was taken 1h post-dose and stimulated ex vivo with a TLR agonist. mRNAseq was performed and the type I interferon gene signature and IFNB1 mRNA levels are shown.

INFLAMMATORY CYTOKINES: HST-2011 Blocks Proinflammatory Cytokine Production



(A) SLE PBMCs or human whole blood were stimulated with a TLR agonist in the presence of HST-2011 and TNF and IL-1β cytokine levels were measured by MSD. (B) 90% human whole blood was stimulated with a TLR agonist in the presence of HST-2011 or enpatoran. mRNAseq was performed. TNF and IL1B mRNA levels are shown. (C) Cynos were orally dosed with HST-2011 or enpatoran. Whole blood was taken 1h post-dose and stimulated ex vivo with a TLR agonist. mRNAseq was performed and TNF and IL1B mRNA levels are shown.

CONCLUSIONS

- HST-2011 is a potent, selective IRF5 small molecule inhibitor advancing towards clinical development
- HST-2011 blocks B cell activation, plasmablast differentiation, and IgG production
- HST-2011 suppresses type I interferon production and its gene signature
- HST-2011 potently inhibits proinflammatory cytokine production
- These data support targeting IRF5 to address both innate and adaptive immune responses in SLE