Poster Th193
FOCIS 2025 Annual Meeting
June 26, 2025

Application of HiFiBiO Drug Intelligence Science (DIS®) translational platform to guide the clinical development of HFB200604, a Phase I BTLA agonist monoclonal antibody

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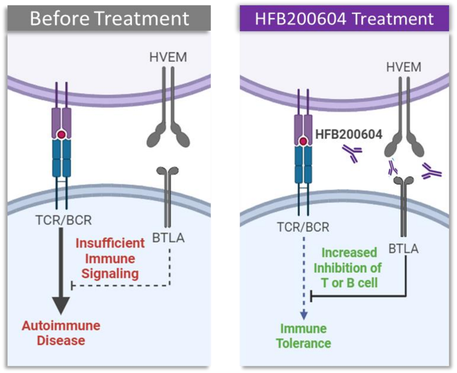
BACKGROUND

BTLA (B and T lymphocyte attenuator) is a co-inhibitory immune checkpoint expressed on B, T and dendritic cells. In contrast to blockade of individual cytokines, BTLA agonism has the potential to restore tolerance by impacting multiple pathogenic cell types and inflammatory cytokines. To date, BTLA agonistic antibodies have failed to demonstrate the expected outcomes in patients with lupus and atopic dermatitis. Different factors might account for this, including inadequate antibody pharmacological profile and/or the selection of appropriate indications. Combining single cell technology and AI/ML algorithms, we applied our unique Drug Intelligence Science (DIS®) platform to discover and develop a best-in-class antibody, HFB200604, and to identify appropriate indications to address these challenges.

HFB200604 is a differentiated BTLA agonist with optimized Fc-mediated agonism that significantly suppresses B cell proliferation, production of IFNγ, TNFα, and IL-17, and T cell activation and proliferation, both in vitro and in vivo. HFB200604 clinical evaluation is guided by DIS® single immune cell profiling of autoimmune diseases and focused on indications with reduced HVEM expression and BTLA signaling, where deregulated BTLA function can be restored through BTLA agonism. Based on the enrichment of a BTLA activation signature, we have prioritized autoimmune diseases where B and T cells exhibit lower levels of pathway activation.

In conclusion, DIS® interrogation of patient datasets supports HFB200604 as a promising therapy to treat autoimmune diseases where BTLA suppressive functions are not fully engaged.



RESULTS: Target analysis

Single cell analysis of BTLA in HiFiBiO Disease Cell Atlas (Cellect™)

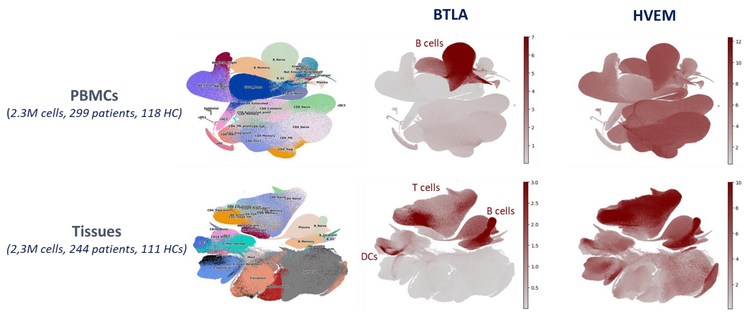


Figure 1. Cellect™ ScRNA-seq analysis of PBMCs and tissue samples from I&I patients and healthy control (HC) reveals that BTLA expression is restricted to B, T and dendritic cells, while HVEM expression is broad

RESULTS: Antibody characterization

In vitro functions of HFB200604

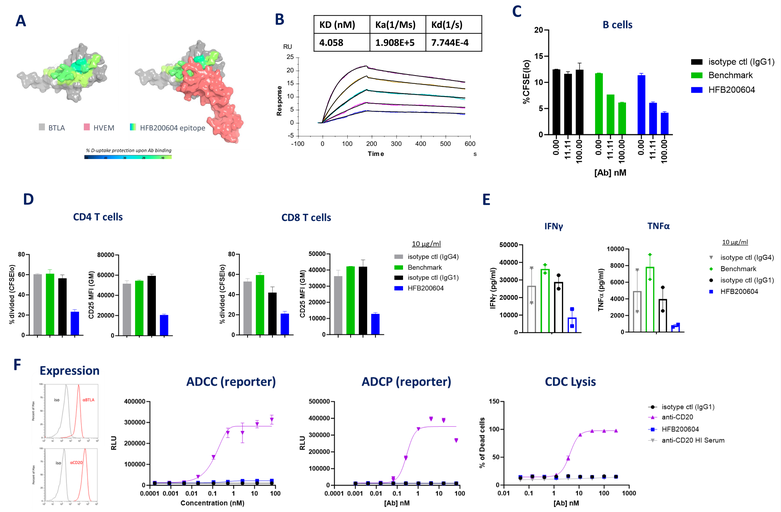


Figure 2 (A) HFB200604 epitope on BTLA identified by HDX-MS. BTLA in gray; HVEM in pink; HFB200604 epitope on BTLA in green-blue. By comparing the Deuterium labeling with or without HFB200604, the epitope region (blue or green based on the relative labeling difference) can be mapped on BTLA structure. **(B)** KD values of HFB200604 antibody binding to rhBTLA-His. **(C)** HFB200604 inhibits anti-IgM induced proliferation of human B cells in a dose-dependent manner as measured by CSFE dilution. **(D)** HFB200604 at 10µg/ml inhibits anti-CD3/CD28-induced proliferation and activation of CD4 and CD8 T cells in human PBMCs as measured by CSFE dilution and CD25 level. **(E)** HFB200604 at 10µg/ml inhibits anti-CD3/CD28-induced IFNγ and TNFα production in human PBMCs. **(F)** HFB200604 minimally engages CD16, CD32a and does not induce complement lysis of Ramos.2G6.4C10 cells. HI Serum: heat-inactivated human serum

In vivo efficacy of HFB200604 in acute GvHD model

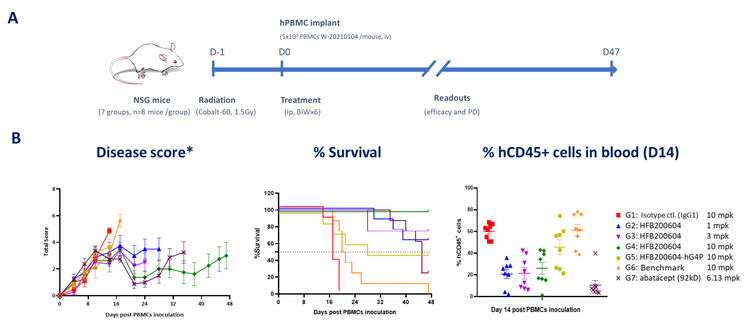


Figure 3 (A) acute graft-vs-host disease (GvHD) model study design. Irradiated NSG mice implanted with human PBMCs, dosed with HFB200604 or controls (ip, BIWx6) starting on the implantation day and monitored for 47 days. **(B)** HFB200604 shows greater disease control and survival benefit than its IgG4 version, benchmark and abatacept consistent with a reduction in the expansion of human CD45+ cells. (* Mean values and standard error are not reported for a given treatment group from the timepoint where an animal is sacrificed in that group.)

Evaluation of HFB200604 in NHPs

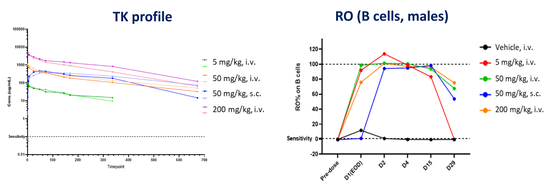


Figure 4 Toxicokinetics (TK) profile and receptor occupancy (RO) of HFB200604 in a Non-GLP NHP SAD Safety Assessment. Four-week study with single administration of vehicle or HFB200604 at 5, 50, 200 mg/kg iv and 50 mg/kg sc into 1 male and 1 female monkey/group. HFB200604 is well tolerated at all doses with no local injection reactions, sustained exposures increasing with dose, sc bioavailability, no ADA and 100% RO for >15d.

In one-month GLP repeated dose toxicity study, HFB200604 was well tolerated in all animals and NOAEL was determined at 150 mg/kg

RESULTS: Translational analysis

Ex vivo study of HFB200604 with I&I patient PBMCs

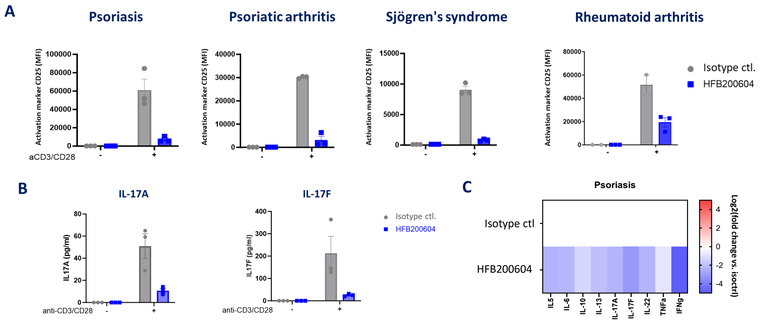


Figure 5 (A) Activation of peripheral CD4+ T cells from patients with psoriasis, psoriatic arthritis, Sjogren's syndrome and rheumatoid arthritis is inhibited by HFB200604 as measured by flow cytometry. **(B)** HFB200604 inhibits the production of IL-17A and IL-17F by stimulated PBMCs from psoriasis patients as measured by Legendplex. **(C)** Heat map view of the multiple Th cytokines downregulated by HFB200604 treatment using stimulated psoriasis patient PBMCs.

Drug Intelligence Science (DIS®) guided indication selection

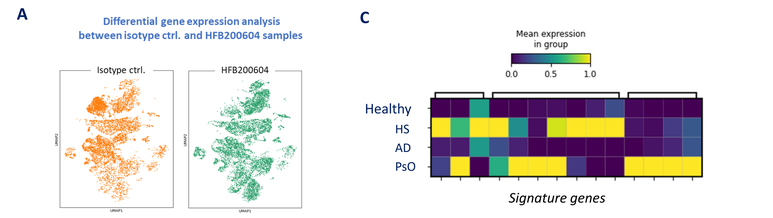


Figure 6 (A) Indication selection based on HFB200604 regulated gene signature in T cells. PBMCs were stimulated with anti-CD3/CD28 in the presence of isotype control antibody or HFB200604. HiFiBiO DIS® ScRNA-seq analysis identified an HFB200604 regulated gene signature in T cells. **(B)** BTLA/HFB200604 gene signature is elevated in all CD4 and CD8 T cell subsets upon stimulation with anti-CD3/CD28 and decreased or normalized by HFB200604 treatment. **(C)** I&I indications from public datasets are ranked based on signature gene expression. The heatmap includes HFB200604-regulated genes expressed in Hidradenitis Suppurativa (HS) & Psoriasis (PsO), but not in Atopic Dermatitis (AD) and healthy subjects.

Conclusion

We are developing a BTLA agonist antibody, HFB200604 with best-in-class potential. We aim to stimulate BTLA-mediated immunosuppressive signals in B and T cells to restore immune tolerance in autoimmune diseases with reduced HVEM expression or insufficient BTLA signaling. Highlights of HFB200604:

- *A humanized anti-BTLA hIgG1 mAb with strong agonism and minimal ADCC/ADCP or CDC activity*
- *Exhibit potent suppression of B and T cell activation in vitro*
- *Superior in vivo efficacy in acute GvHD model than benchmark Ab or positive control compound*
- *Favorable pharmacological, pharmacokinetic, safety and developability profiles*
- *Innovative translational strategy applying HiFiBiO's Drug Intelligence Science (DIS®) single-cell immune profiling platform for indication selection*
- *HFB200604 IND application cleared by the FDA*

For additional information, please email contact@hifibio.com or visit Hifibio.com