2024 Annual Scientific Meeting
PODIUM TO PRACTICE®
Advancing Allergy/ Immunology Discovery
OCT. 24-28 ■ BOSTON, MA

ePoster ID: **R058**

Briquilimab Potently Inhibits Stem Cell Factor (SCF)/c-Kit Signaling and Mast Cell (MC) Degranulation and Survival

Hind Bouzid[1], Cheryl Kwan[1*], Chikako Yanagiba[1], Song Eun Lee[1], Minyoung Youn[1], Mang Yu[1], Hye-Sook Kwon[1], Wendy W. Pang[1].
[1]*Jasper Therapeutics Inc., Redwood City, CA, USA*
**Presenting Author*

BACKGROUND

- Stem Cell Factor (SCF) signaling through c-Kit (CD117) plays a key role in mast cell (MC) differentiation, activation, and survival
- SCF/c-Kit signaling is essential for IgE-dependent and -independent MC activation/degranulation leading to release of mediators including inflammatory cytokines and chemokines
- Briquilimab, a humanized aglycosylated monoclonal antibody targeting c-Kit, blocks SCF binding to c-Kit and inhibits SCF/c-Kit signaling
- Inhibition of the SCF/c-Kit pathway has the potential to treat mast cell-related disorders

METHODS

- Human primary MCs were differentiated from mobilized peripheral blood CD34$^+$ cells. c-Kit$^+$ FcεRI$^+$ mature MCs were used to evaluate MC degranulation, cytokine release, and survival
- For degranulation and cytokine release assays, MC were incubated with Ab/TKI for 90 min prior to IgE/α-IgE stimulation. Degranulation was assessed ~1 hour after IgE/α-IgE stimulation. Cytokine release was assessed 16-20 hours after IgE/α-IgE stimulation. For MC survival assays, MC numbers were calculated as live c-Kit$^+$ FcεRI$^+$ cells after 6 days of culture
- Briquilimab's effect on MC was compared to JSP084, a comparative reagent that blocks c-Kit dimerization, and Imatinib, a small molecule inhibitor of multiple tyrosine kinases including c-Kit
- Antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity were evaluated using M-07e cells

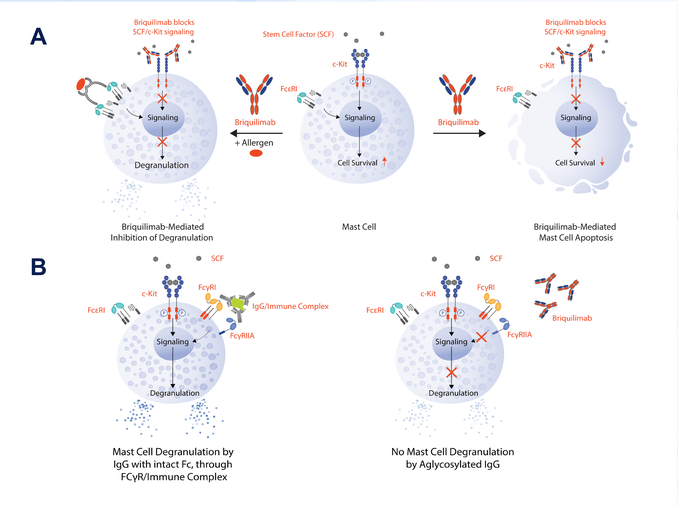

Figure 1. (A) The SCF/c-Kit pathway is essential for mast cell activation/degranulation and survival. Inhibiting SCF/c-Kit signaling by briquilimab prevents MC degranulation and induces mast cell apoptosis. (B) The engagement of MCs by immunoglobulins with intact Fc through FcγRs induces MC degranulation. Aglycosylated briquilimab (N297Q) cannot bind to FcγRs and thus does not induce FcγR/IgG immune complex-mediated MC degranulation.

RESULTS

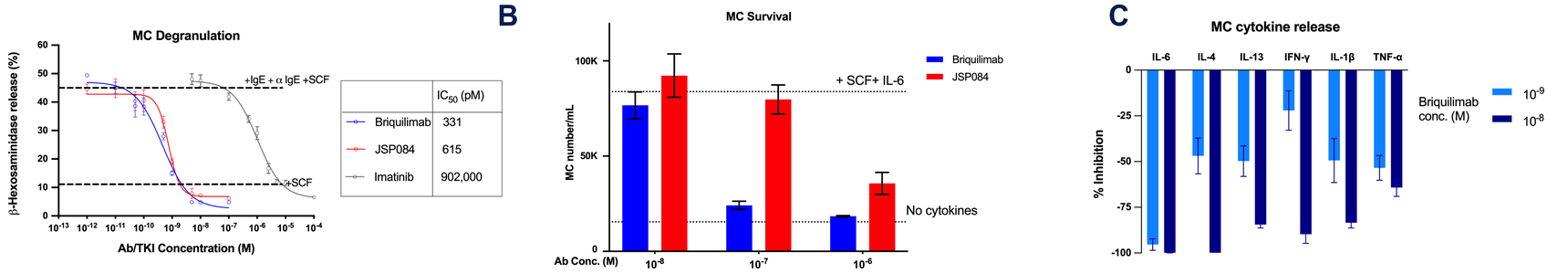

Figure 2. In cultured human MCs, briquilimab inhibits (A) IgE/α-IgE mediated MC degranulation more potently than JSP084 and Imatinib, and (B) MC survival more potently than JSP084. 10-7 M briquilimab inhibited MC survival, whereas the same concentration of JSP084 did not significantly decrease MC survival. Even at briquilimab concentrations that did not inhibit MC survival (10-8 and 10-9 M), briquilimab at these concentrations inhibited (A) MC degranulation and (C) MC cytokine release following IgE/α-IgE stimulation. The representative data are shown as mean ± SD from two to three independent experiments.

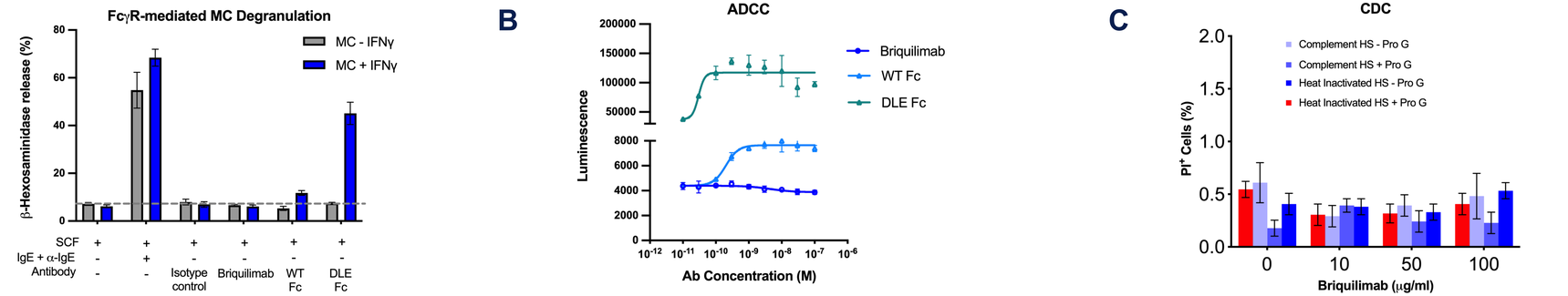

Figure 3. Briquilimab does not induce (A) FcγR-mediated degranulation of MCs, (B) ADCC, or (C) CDC. In contrast, WT Fc (identical to briquilimab except with wild-type N297 Fc) and DLE Fc (identical to briquilimab except with N297 and S239D/A330L/I332E leading to increased affinity to FcgR) exhibited (A) FcγR-mediated degranulation of MC, and (B) ADCC activity. The representative data are shown as mean ± SD from two to three independent experiments.

CONCLUSION AND FUTURE DIRECTIONS

- Briquilimab via direct blocking of SCF binding to c-Kit, inhibits MC degranulation and survival more potently than JSP084, which blocks c-Kit dimerization
- Briquilimab, through the N297Q modification, does not induce FcγR mediated MC degranulation, ADCC, and CDC
- Jasper is actively enrolling in a phase 1b/2a trial evaluating briquilimab in participants with chronic spontaneous urticaria, (BEACON trial, NCT06162728) and a phase 1b/2a in participants with chronic inducible urticaria (SPOTLIGHT trial, NCT06353971) and will commence enrolling participants for the proof-of-concept Phase 1b/2a asthma challenge study evaluating briquilimab in asthma