Targeting pathogenic auto-reactive VH4-34 B cells with a rationally developed and highly specific anti-VH4-34 antibody offers a new therapeutic approach for VH4-34 autoimmune disorders

Shalini Paliwal, Dipti Thakkar, Wen Jie Chin, Warren Lee, Jie Ying Jacklyn Neo, Brendon Hanson, Konrad Paszkiewicz, Piers Ingram, Jerome Boyd-Kirkup

1Hummingbird Bioscience, Singapore

HMBD-011 binds selectively and with high affinity to the hydrophobic patch of VH4-34

(VH4-34+ BCR is a key target implicated in multiple B cell-associated disorders

- VH4-34 is an intrinsically autoreactive antibody heavy chain variable region with a germline-encoded hydrophobic patch in framework region (FR) 1 and is normally excluded from the mature B cell repertoire
- In multiple B cell-associated disorders, due to loss of tolerance, VH4-34+ B cells undergo expansion and affinity maturation to diverse self-antigens, contributing to disease pathology
- Self-antigens recognized by VH4-34+ antibodies include dsDNA, chromatin, and a lactosamine determinant of glycans displayed on red blood cells
- About 50% of systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE) patients have elevated levels of VH4-34+ IgG
- More than 85% of patients with primary chronic cold agglutinin disease (CAD) have VH4-34+ IgM

HMBD-011 clears VH4-34+ antibody and VH4-34+ B cells in circulation

- An effective anti-VH4-34 antibody must selectively bind to all VH4-34+ antibodies/BCRs over other VH antibodies/BCRs
- VH4-34 is similar to other VH genes, except for a small conformational hydrophobic patch
- The hydrophobic patch is not predicted to be highly immunogenic, and therefore, is challenging to target with traditional antibody discovery approaches
- Hummingbird Bio’s RAD platform (mAbHits) enabled focusing of the immune response to epitopes overlapping the conformational patch and generated antibodies specific for this patch

HMBD-011 mediates (4a) antibody-dependent cellular cytotoxicity (ADCC) of CHO cells engineered to express tabalumab (TABA; VH4-34+) determined by Jurkat-Lucia NFAT-CD16 reporter cells and (4b) OCI-Ly3 (B cells) with endogenous surface expression of VH4-34 and Pfeiffer (B cells with no endogenous expression of VH4-34).

HMBD-011 can deplete VH4-34+ autoantibodies and autoreactive B cells to address underlying disease pathology in lupus and CAD

Conclusion

- VH4-34+ antibodies (and BCRs) are intrinsically autoreactive as they possess a germline-encoded hydrophobic patch in FR1
- Expansion of VH4-34+ Abs and B cells has been associated with several pathologies including lupus (SLE and CLE) and CAD
- Developed through Hummingbird Bioscience’s proprietary Rational Antibody Discovery platform, HMBD-011 is a unique mAb, precisely targeting the hydrophobic patch of VH4-34+ Abs and BCRs
- HMBD-011 selectively binds, blocks and depletes VH4-34+ autoantibodies and autoreactive VH4-34+ BCR B cells
- The differentiated mechanism of action of HMBD-011 has the potential to selectively target disease pathogenesis in SLE/CLE and CAD versus a broad B cell depletion and inhibition approach that risks compromising normal immune functions
- HMBD-011 has demonstrated efficacy in preclinical models and is poised to enter the clinic in 18-24 months

References