HCB101: A SAFE AND EFFECTIVE LIGAND TRAP THERAPEUTIC TARGETING THE CD47-SIRPA SIGNALING PATHWAY FOR CANCER TREATMENT

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Background Macrophages patrol intercellular spaces mainly through their receptor SIRPa, which interacts with CD47 on target cells. Such interaction elicits a ‘do not eat’ signal and spares the target cell from being phagocytosed. Many cancers take advantage of this mechanism via overexpressing CD47 to evade immune surveillance. Therefore, blocking SIRPa-CD47 interaction represents a promising approach for anti-cancer therapy. Numerous anti-CD47 antibodies and SIRPa fusion proteins have been developed with therapeutic potential, but their clinical progress was hindered by either severe side effects or lack of appreciable efficacy. To overcome this deficiency, we aim to produce a SIRPa-fusion biologic that exhibits superior efficacy against multiple hematological and solid malignancies while maintaining good safety profiles and protein stability.

Methods Using display technology combined with structure-guided protein engineering, we identified several SIRPa mutants that exhibited significant CD47-blocking activities and phagocytosis against tumor cells while minimizing side effects on CD47-expressing normal cells. To assess the impact of CD47 blockade on macrophages within the tumor microenvironment, these novel mutants were evaluated in multiple human tumor xenograft mouse models and compared with selected anti-CD47 monoclonal antibodies and/or SIRPa fusion proteins currently being investigated in clinical trials. The leading candidates were further analyzed for their respective CMC profiles to ensure good protein stability and straightforward manufacturability.

Results In comparison with prominent clinical candidates targeting the CD47 pathway (Magrolimmab, TTI-622, ALX148, TJC4, IMM01), HCB101 demonstrated superior or compatible CD47-blocking activities; meanwhile, it triggered strong phagocytosis against tumor cells but not red blood cells. In all 7 human tumor xenograft NOD/SCID mouse models that we investigated, HCB101 consistently showed excellent efficacy against hematological and solid tumors as monotherapy, with tumor growth inhibition index (TGI) ranging from 60-100% at the dose of 0.5-10mg/kg over placebo. We observed an increase in the M1/M2 macrophage ratio and a reduction of CD24 expression in certain cases after the treatment with HCB101. This could partially account for its superior antitumor efficacy. There was no apparent adverse reaction observed during the exploratory cynomolgus monkey toxicology studies, suggesting a good safety profile of HCB101.

Conclusions Compared to relevant clinical candidates, HCB101 exhibits superior efficacy in 7 different CDX models of hematological and solid malignancies while maintaining good safety profiles. A highly effective blockade of the CD47-SIRPa pathway by HCB101 leads to robust pre-clinical results. Moreover, it exhibits outstanding protein stability and manufacturing characteristics for large-scale production. Clinical development of HCB101 is currently underway both as monotherapy and in combination.