Discovery and Characterization Of ABT-122, An Anti-TNF/IL-17 DVD-Ig™ Molecule As a Potential Therapeutic Candidate For Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a serious autoimmune disease that significantly impacts patients' quality of life. Several approved biologic drugs targeting tumor necrosis factor (TNF) and other immune targets are efficacious treatments for RA, and newer drug candidates, including antibodies to interleukin-17 (IL-17), are at various stages of clinical development. Previous and current studies have demonstrated that in a preclinical mouse model of arthritis treatment with antibodies to TNF and IL-17 is significantly more efficacious than treatment with either antibody alone. We therefore generated a novel bispecific dual variable domain immunoglobulin (DVD-Ig™) molecule to both TNF and IL-17 as a potential drug candidate for RA.

Methods: An in vitro PROfusion™ mRNA display technology was used to screen for fully human antibodies against human IL-17. The identified IL-17 antibodies were further engineered to improve affinity. We inserted the variable domain of several affinity-matured IL-17 antibodies between an available anti-TNF variable domain and the human IgG1/κ constant region to obtain a panel of novel DVD-Ig™ molecules. These DVD-Ig™ molecules differ from each other in the anti-IL-17 variable domains and the peptide linkers (lengths and sequences) connecting the two variable domains. We characterized the DVD-Ig™ activities by ELISA, surface plasmon resonance, and cell-based potency assays. To demonstrate the activities of these DVD-Ig™ molecules in vivo, we studied the pharmacokinetic profiles of the top three candidates in rat. The in vivo pharmacologic activity was assessed in mouse models by inhibition of recombinant human TNF-Dgal-induced lethality and recombinant human IL-17-induced KC production.

Results: Fully human antibodies with sub-nM affinity to human IL-17 were selected from human antibody libraries. Their affinities were enhanced by molecular engineering to low pM range. The affinity-matured IL-17 antibodies were combined with an antibody to TNF into a panel of DVD-Ig™ molecules, and screened for optimal activities in antigen binding and neutralization assays. Three drug candidates with strong affinities and potencies (K_D and IC₅₀ in the low pM range) were selected for further characterization. In rat pharmacokinetic studies these DVD-Ig™ molecules had 9 to 13 day circulating half-lives upon intravenous injection. In acute mouse models in vivo, these DVD-Ig™ molecules also demonstrated potent inhibition of human TNF and IL-17 activity. The DVD-Ig™
molecule with the best affinity and potency, as well as the longest half-life in rat was designated ABT-122 for further development.

**Conclusion:** ABT-122 is a novel DVD-Ig™ molecule that is engineered to have high affinity and neutralizing potency to both human TNF and IL-17 cytokines. Based on the combined efficacy in a preclinical mouse arthritis model, the demonstrated efficacy of TNF-targeted therapy in RA patients, and encouraging response to IL-17 antibodies in RA clinical trials, we will be evaluating the efficacy and safety profile of the anti-TNF/IL-17 DVD-Ig™ molecule in human RA clinical trials.

**Disclosure:**

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