Background: BAFF and APRIL are TNF superfamily members that bind both TACI and BCMA on B cells; BAFF also binds BFFR. Together, BAFF and APRIL support B cell development, differentiation, and survival. Their co-neutralization dramatically reduces B cell function, including antibody production, whereas inhibition of either BAFF or APRIL alone mediates relatively modest effects.

Objectives: While, CTLA-4-based therapeutics that block T cell costimulation dramatically reduces B cell function, including antibody production, whereas inhibition of either BAFF or APRIL alone mediates relatively modest effects. For this reason, we postulate that improved, combined BAFF and APRIL inhibition, either alone or with inhibition of T cell costimulation, will provide more effective and durable relief from severe B cell-related autoimmune diseases like SLE.

Methods: We used our directed evolution platform to identify variant domains of the TNF family receptors TACI or BCMA that exhibit enhanced affinity for BAFF and APRIL as compared to their wild-type (WT) counterparts. These variant TACI or BCMA domains (vTDs), alone or together with platform-derived CTLA-4 domains (vIgDs), were fused to a modified human IgG1 Fc lacking effector function, yielding BAFF and APRIL receptor domains (vTDs) with or without fusion to CTLA-4 domains (vIgDs). These novel immunomodulators were characterized in standard immunization models, in vivo; and in vivo in standard immunization models, and in the bm12 and NZB/NZW spontaneous mouse models of lupus.

Results: The novel engineered TACI vTD-Fc or BCMA vTD-Fc fusion proteins showed significantly inhibited BAFF- and APRIL-mediated signaling in vitro in TACI−/−/− and BCMA−/−/− transgenic mouse models. These novel immunomodulators consistently demonstrate potent immunosuppressive activity and efficacy in vitro and in vivo, appearing superior to existing and/or approved immunomodulators like belimumab, abatacept, or atacicept. Such biologics may therefore be attractive candidates for the treatment of serious autoimmune diseases, particularly B cell-related diseases such as SLE, Sjogren syndrome, etc.

Conclusion: Directed evolution of TNFR and IgSF domains has successfully facilitated the development of Fc fusion proteins containing TACI or BCMA vTDs, with or without fusion to CTLA-4 vIgDs. These novel immunomodulators are currently in clinical development in collaboration with leading biopharmaceutical companies, and we expect to see clinical proof of concept in the near future.