Background: BAFF and APRIL are TNF superfamily members that bind both TACI and BCMA on B cells; BAFF also binds BAFF-R. 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 provide safe and moderately effective T cell inhibition in many disease settings, and while B cell targeting therapies have demonstrated promising therapeutic potential, we postulate that improved, combined BAFF and APRIL inhibition, either alone or coupled 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 a panel of immunomodulatory molecules that block T cell costimulation and inhibit BAFF/ APRIL signaling in vitro in primary human lymphocytes, whereas in vivo in standard immunization models, and in the bm12-induced and NZB/NZW spontaneous mouse models of lupus.

Results: The novel engineered TACI vTD-Fc or BCMA vTD-Fc fusion proteins signified robust inhibition of BAFF- and APRIL-mediated signaling in vitro in TACI- and BCMA-expressing Jurkat cell lines. All fused immunomodulatory molecules attenuated T cell activation in primary human lymphocyte assays. When administered to mice, these molecules rapidly and potently reduced key B and T cell subsets, including plasma cells, follicular T helper cells, germinal center cells, & memory T cells. Treatment with TACI vTD-Fc or TACI/CTLA-4 vIgD-Fc proteins also significantly reduced titers of antigen-specific antibodies in immunized mice more so than abatacept or WT TACI-Fc, and potently suppressed anti-dsDNA autoantibodies, blood urea nitrogen levels, proteinuria, and renal immune complex deposition in the bm12 & NZB/W lupus models.

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 consistently demonstrated 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 provide safe and moderately effective T cell inhibition in many disease settings, particularly B cell-related diseases such as SLE, Sjogren’s syndrome, etc.
Results: NZB/W mice at 3 months and 6 months of age exhibit depressive-like disorder as assessed by SPT and TST (P <0.05 and <0.0001, respectively). Anxiety-like phenotype was evident in lupus-prone mice at both time points based on EPM test (Graph 1). Open-field test revealed decreased locomotor activity and rotarod (Graph 2) showed impaired motor coordination in 3 month-old and 6 month-old NZB/W mice (P<0.001 and <0.01, respectively). NZB/W mice exhibit cognitive dysfunction at 3 and 6 months of age based on NOR test (P<0.05). No differences in cognitive function was observed between the two groups (P=0.11). Prepulse inhibition test revealed decreased sensorimotor gating in 3 month-old NZB/W mice, a difference not reaching statistical significance (P=0.078). It was not possible to interpret correctly the PPI at second time point (6 months of age) due to age-related hearing loss in B6 at 6 month-old. NZB/W become more anxious over the course of the disease as assessed by EPM (3 mo. versus 6 mo. P<0.001, paired t-test, Graph 1).

Conclusion: The NZB/W lupus-prone strain exhibit depressive-like behavior, anxiety, cognitive impairment and motor disturbances both at early and late stages of the disease. This polygenic murine model may be more suitable for investigating the autoimmunity-mediated neuroinflammation in human SLE.

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SKIN PROTEOME INVESTIGATION IN CUTANEOUS LUPUS ERYTHEMATOSUS (CLE) REVEALS NOVEL UNIQUE DISEASE PATHWAYS

T. Niewold1, K. Popovic-Silverfeldt2, J. Lehman3, A. Meves4, C. Charlesworth5, B. Madden6, A. Hayry7, A. Antovic8, I. E. Lundberg9, M. Wahren-Herlenius9, E. Svennungsson9, V. Oke9, 1Colton Center for Autoimmunity, New York University, New York, United States of America; 2Karolinska Institutet, Institution for Clinical Sciences at Danderyd Hospital, Stockholm, Sweden; 3Mayo Clinic, Dermatology, Rochester, United States of America; 4Mayo Clinic, Rochester, United States of America; 5Mayo Clinic, Dermatology, Rochester, United States of America; 6Animal Sciences, Core, Rochester, United States of America; 7Karolinska Institutet, Dept of Medicine, Stockholm, Sweden

Background: Cutaneous lupus erythematosus (CLE) is an autoimmune disease. It can be limited to the skin or be one of manifestations of systemic LE (SLE). The typical histopathologic pattern in CLE/SLE is interface dermatitis, which can also be observed in dermatomyositis (DM). While DM most commonly affect muscles and skin, LE may affect any organ system, DM most commonly affect muscles and skin.

Objectives: The aim of this study was to investigate the whole proteome of skin inflammatory foci in the cohort of CLE and DM patients in a comparatory, hypothesis-free manner and identify disease-unique molecular mechanisms.

Methods: Open-field test revealed decreased locomotor activity and rotarod (Graph 2) showed impaired motor coordination in 3 month-old and 6 month-old NZB/W mice (P<0.001 and <0.01, respectively). NZB/W mice exhibit cognitive dysfunction at 3 and 6 months of age based on NOR test (P<0.05). No differences in cognitive function was observed between the two groups (P=0.11). Prepulse inhibition test revealed decreased sensorimotor gating in 3 month-old NZB/W mice, a difference not reaching statistical significance (P=0.078). It was not possible to interpret correctly the PPI at second time point (6 months of age) due to age-related hearing loss in B6 at 6 month-old. NZB/W become more anxious over the course of the disease as assessed by EPM (3 mo. versus 6 mo. P<0.001, paired t-test, Graph 1).

Conclusion: The NZB/W lupus-prone strain exhibit depressive-like behavior, anxiety, cognitive impairment and motor disturbances both at early and late stages of the disease. This polygenic murine model may be more suitable for investigating the autoimmunity-mediated neuroinflammation in human SLE.

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