Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, Suppresses Disease in a Mouse Model of Autoimmune Encephalitis

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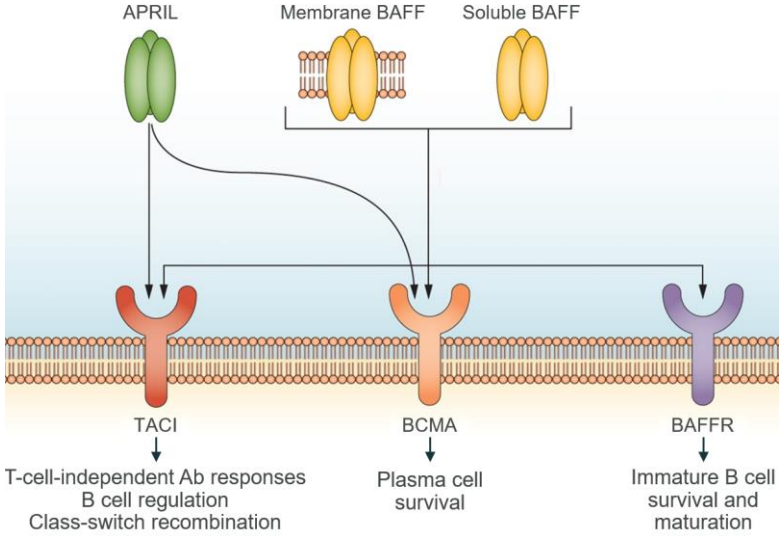
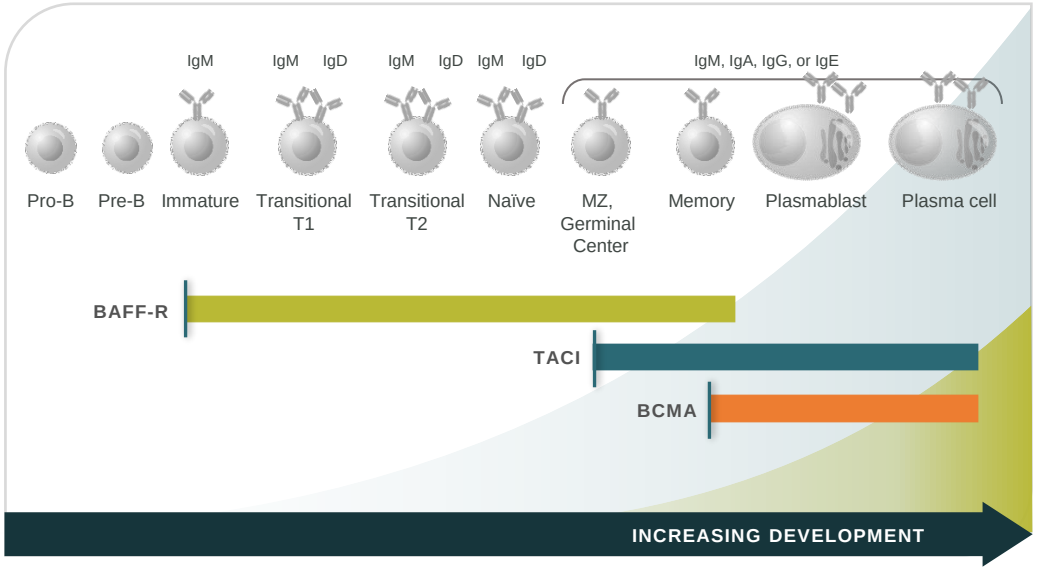
Disclosures:

Katherine E. Lewis is an employee and shareholder of Alpine Immune Sciences.

BAFF and APRIL: Critical regulators of multiple immune cells, especially B cells

BAFF/APRIL can also promote pathogenic T cells and innate immune cells





BAFF: B Cell Activating Factor

APRIL: A Proliferation-Inducing Ligand

TACI: Transmembrane Activator and CAML Interactor

BCMA: B Cell Maturation Antigen

Sources: *Nat Rev Rheumatol* 10:365, 2014; *Nat Rev Rheumatol* 9:705, 2013; *Nat Rev Neurol* 8:613, 2012; *Clin Microbiol Rev.* 30:991, 2017.

Autoimmune encephalitis (AIE)

- Uncommon disease of unknown etiology but characterized by anti-neuronal autoimmune response.
  - Anti-NMDAR (N-methyl-D-aspartate receptor), as well as non-NMDAR AIE.
- Treatment often includes immunosuppressive agents, such as steroids and IVIg, as well as tumor removal if applicable.
- No approved therapies but experience with rituximab (anti-CD20) suggests that B cells play a key role in disease pathogenesis.
- Targeting BAFF/APRIL may be advantageous over CD20 depletion by better addressing antibody-secreting cells.
- Furthermore, BAFF and APRIL concentrations are higher in CSF of anti-NMDAR AIE patients and are associated with worse outcomes*, further supporting a BAFF/APRIL targeted approach in the treatment of AIE.

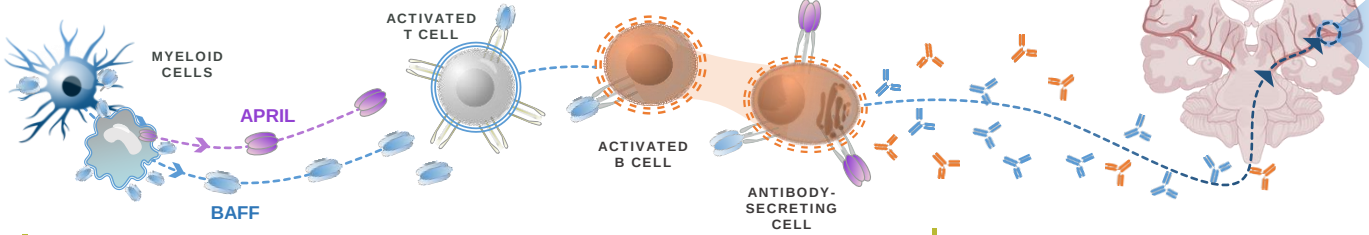
*Deng et al. (2017) *J. Neuroimmunol.*

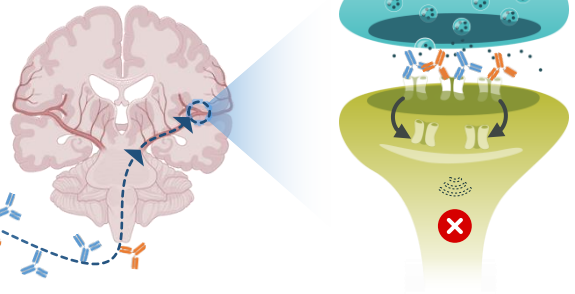
Povetacicept potently modulates B cells and pathogenic autoantibodies

Autoimmune Encephalitis

BAFF and APRIL play key roles in the activity of many disease-related immune cells

BAFF/APRIL can also promote pathogenic T cells and innate immune cells





BAFF/APRIL promote autoantibody-producing B cells, including development of anti-neuronal autoantibodies

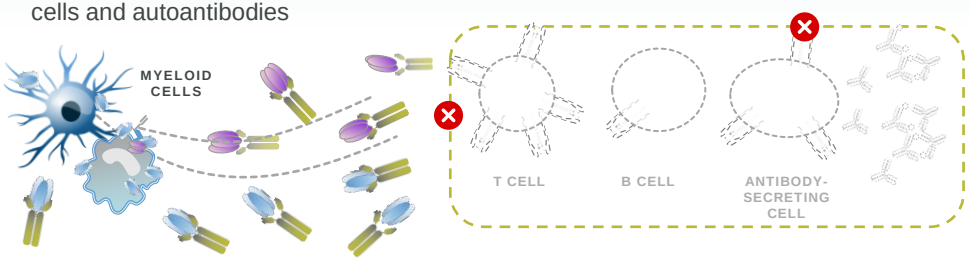
Anti-neuronal autoantibodies, e.g., anti-NMDAR, can damage neurons, leading to dysfunctional receptors and neuronal hypoactivity.

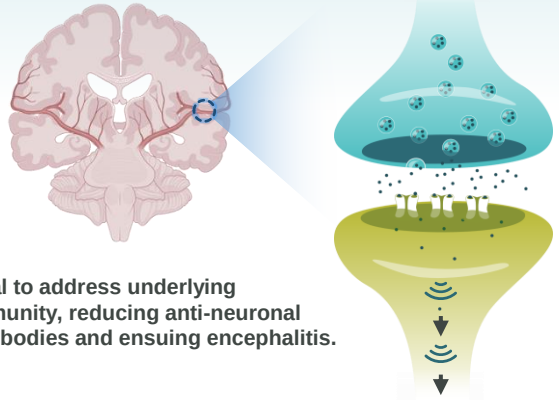
ANTI-NMDAR AUTOANTIBODIES

NON-ANTI-NMDAR AUTOANTIBODIES

Povetacicept: Dual BAFF/APRIL Inhibitor

Designed to suppress the formation and/or promotion of autoimmune cells and autoantibodies





Potential to address underlying autoimmunity, reducing anti-neuronal autoantibodies and ensuing encephalitis.

Evaluation of povetacicept in a mouse model of anti-NMDAR autoimmune encephalitis

Compared to FcRn inhibition and B cell depletion

C57BL/6NJ (F) Mice

Stage mice by anti-GluN1 IgG Abs at week 4

*Dosing (IP)

Cognitive Testing

Week 0 1 2 3 4 5 6 7 8 9 10

GluN1pep/ CFA (SC)

GluN1pep/ IFA (SC)

GluN1pep/ IFA (SC)

Pertussis Toxin (IP)

End of Study: Blood and Tissue Collection

***Treatments evaluated:**

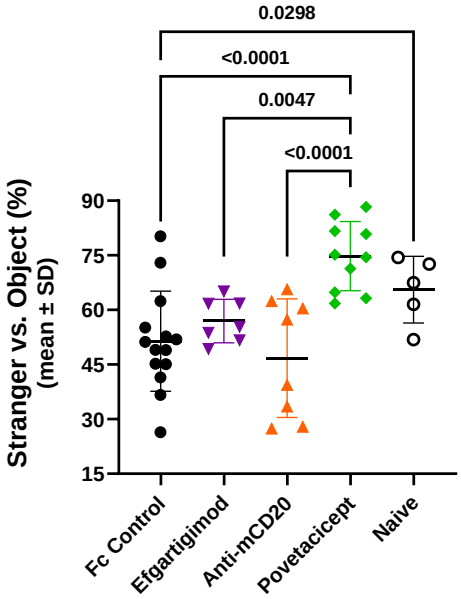
1. **Povetacicept**
2. **Matched Fc control**
3. **Efgartigimod (FcRn blocker)**
4. **Anti-CD20 (B cell depleter; weekly)**

Modified from Ding et al (2021) *J. Neuroinflammation* 18:53

Povetacicept treatment significantly protects mice from cognitive deficits associated with autoimmune encephalitis

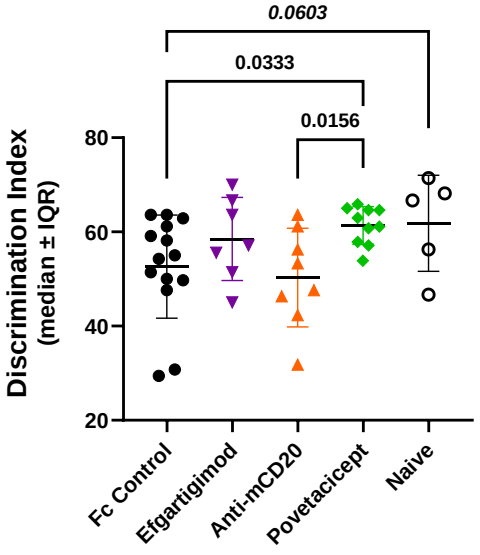
Three Chamber Test

sociability and novel object recognition



Novel Object Recognition Test

learning and recognition memory

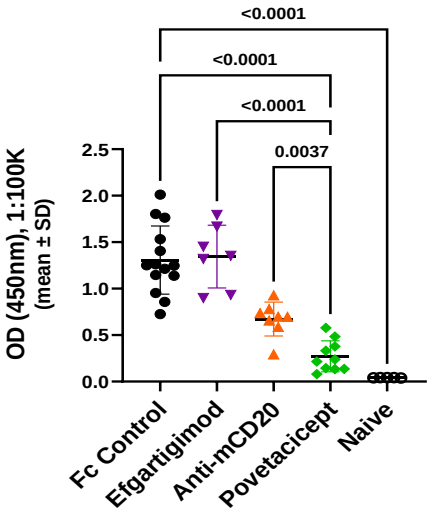


Significant differences (p<0.05) vs. the povetacicept group, or Fc control vs. naïve group, are shown, determined by one-way ANOVA (left) or the Kruskal-Wallis test (right).

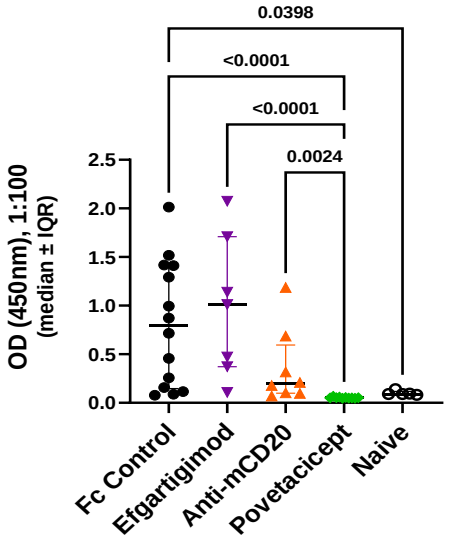
Povetacicept significantly reduces serum anti-GluN1 antibodies and total Ig isotypes more than all evaluated comparators in the anti-NMDAR AIE model

Anti-GluN1 Antibodies

IgG

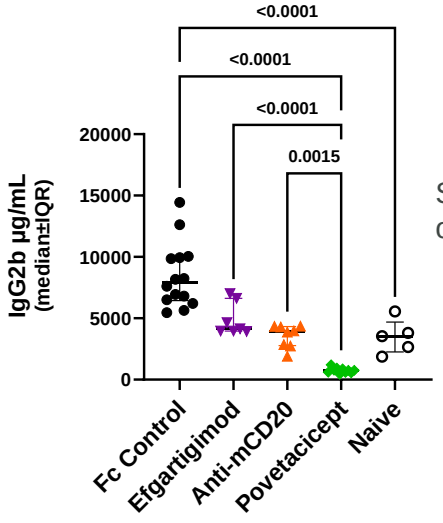


IgM



Total IgG2b

IgG2b

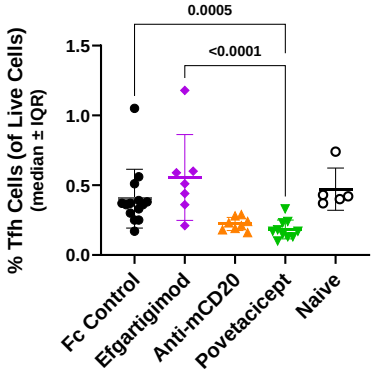


Similar results for other IgG isotypes

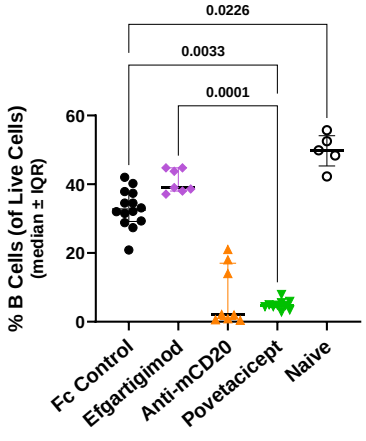
Significant differences (p<0.05) vs. the povetacicept group, or Fc control vs. naïve group, are shown, determined by one-way ANOVA (IgG) or the Kruskal-Wallis test (IgM; IgG2b).

Povetacicept treatment in the AIE model significantly reduces frequencies of splenic T and B cell subsets that play key roles in Ab/autoAb development

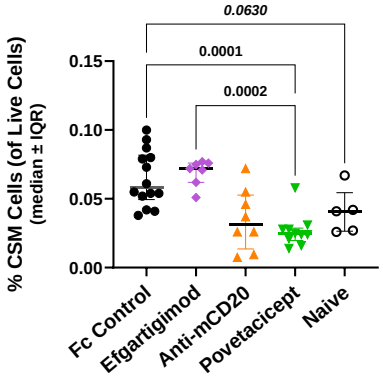
T Follicular Helper (Tfh) Cells



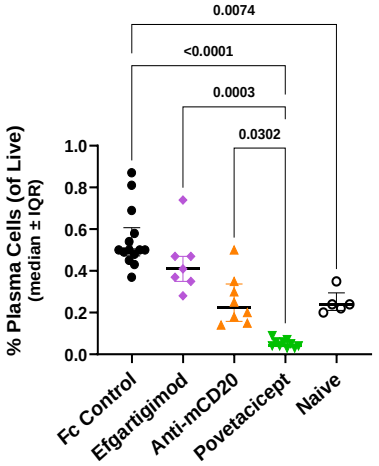
Total B Cells



Class-Switched Memory (CSM) B Cells



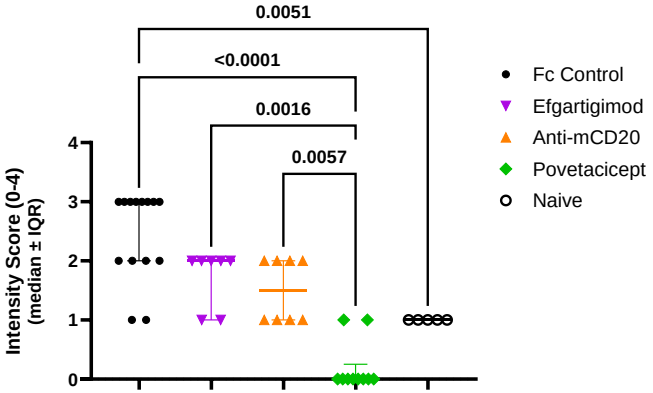
Plasma Cells



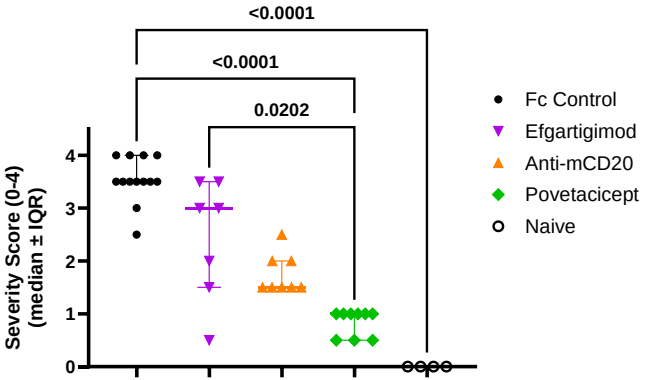
Significant differences (p<0.05) vs. the povetacicept group, or Fc control vs. naïve group, are shown, determined by the Kruskal-Wallis test.

Povetacicept significantly reduces cerebral IgG deposition and neuronal damage in anti-NMDAR autoimmune encephalitis model

IgG (IHC)



Neuronal Damage (H&E)



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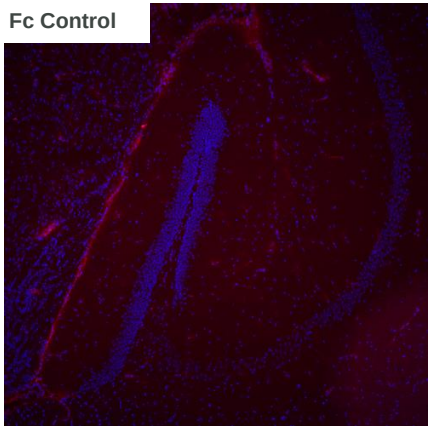

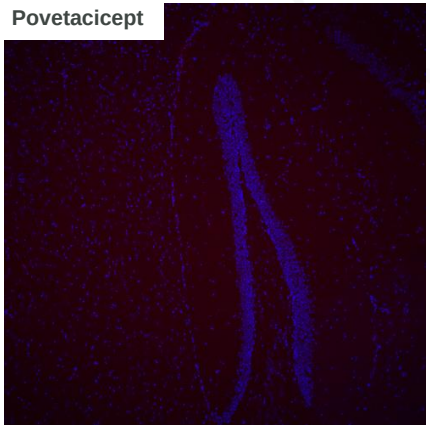

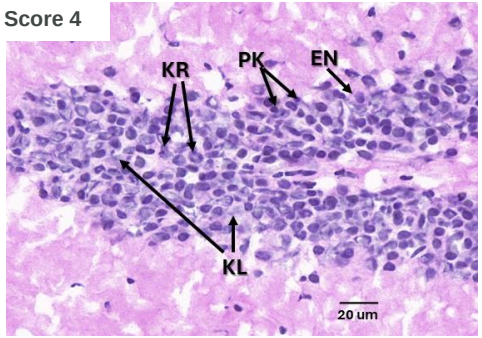

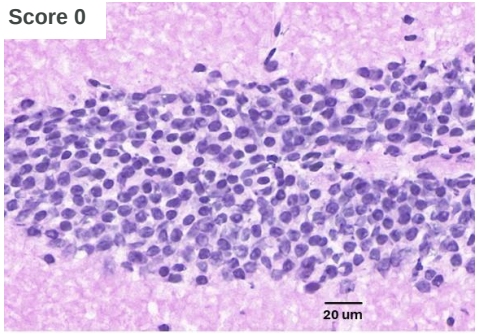

KR = Karyorrhexis; PK = Pyknotic nuclei;
EN = Eccentrically displaced nucleus; KL = Karyolysis

Povetacicept shows greater biodistribution to brains and lymph nodes of healthy C57BL/6 mice following a single IV dose

This may contribute to the enhanced efficacy of povetacicept in AIE

Tissue	% Fc-Positive (Mean ± SEM)			Fold Increase	
	Povetacicept	Efgartigimod	Anti-CD20	Povetacicept vs. Efgartigimod	Povetacicept vs. Anti-CD20
Brain	0.10 ± 0.03	0.03 ± 0.01	0.02 ± 0.01	**3.3**	**5.0**
Lymph Nodes	1.40 ± 0.03	0.02 ± 0.01	0.31 ± 0.06	**7.0**	**4.5**

- Povetacicept (12 mg/kg) or a molar-matched dose of efgartigimod or anti-CD20 was administered IV to healthy female C57BL/6 mice.
- Tissues were collected ~18 hours later and evaluated by quantitative immunohistochemistry for human Fc or rat Fc staining.

Study conducted at Hooke Laboratories (Lawrence, MA)

Summary/Conclusions

- Povetacicept is a high affinity dual antagonist of BAFF and APRIL, key cytokines in B cell survival/differentiation, as well as pathogenic T cell and innate immune cell development.
- In the anti-NMDAR mouse model of AIE, therapeutic povetacicept treatment was highly effective at reducing disease, to a greater extent than FcRn blockade and conventional (anti-CD20) B cell depletion.
- Povetacicept-mediated improvements in cognitive readouts were associated with significant changes at the tissue and cellular level:
  - Lower levels of anti-GluN1 IgG, IgM, and IgA antibodies and total Ig isotypes in serum
  - Lower splenic T and B cell subsets important in antibody production, including antibody-secreting plasma cells
  - Reductions in cerebral IgG deposition and neuronal damage
  - Greater biodistribution to brains and lymph nodes of healthy mice
- These studies suggest that dual inhibition of BAFF and APRIL with potent therapeutics like povetacicept may confer significantly improved clinical outcomes in AIE.