OP0039

ALPN-303, an Enhanced, Potent Dual BAFF/APRIL Antagonist Engineered by Directed Evolution for the Treatment of Systemic Lupus Erythematosus (SLE) and Other B Cell-Related Autoimmune Diseases

Stacey Dillon, Ph.D.

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- Presenter is an employee and shareholder of Alpine Immune Sciences, Inc.

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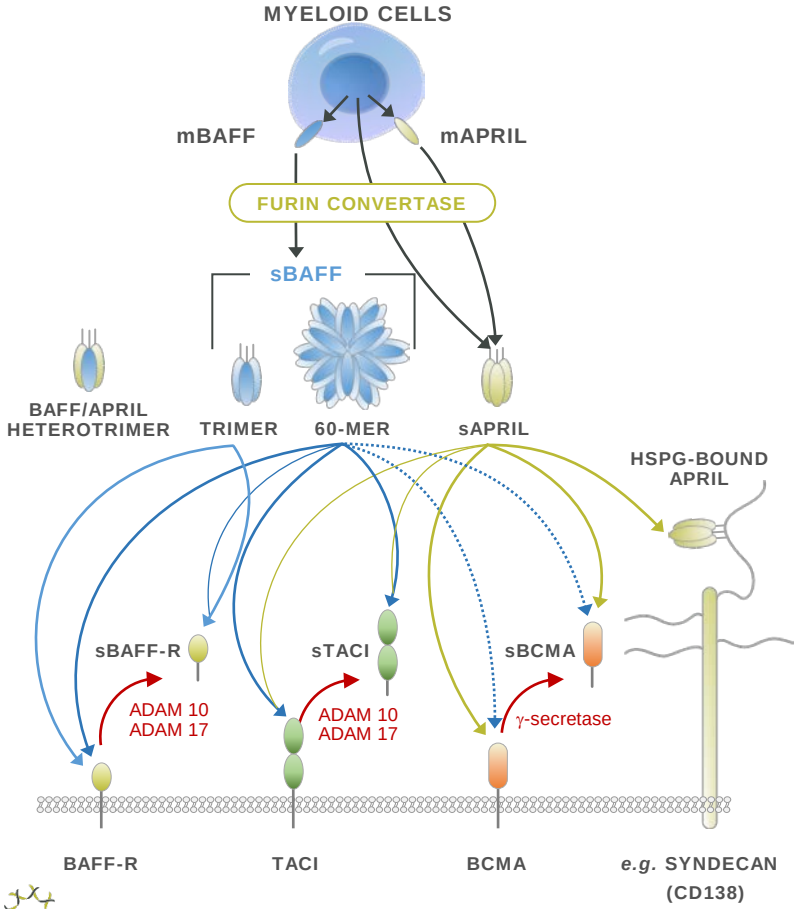
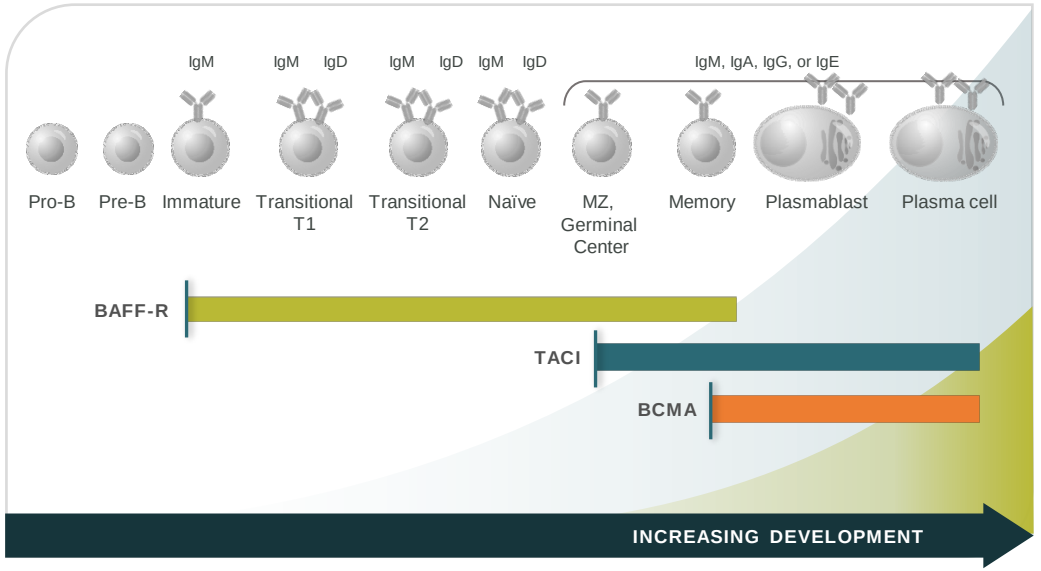
Picture taking is ALLOWED during my presentation (including presented slides)

BAFF and APRIL play key roles in B cell development and function



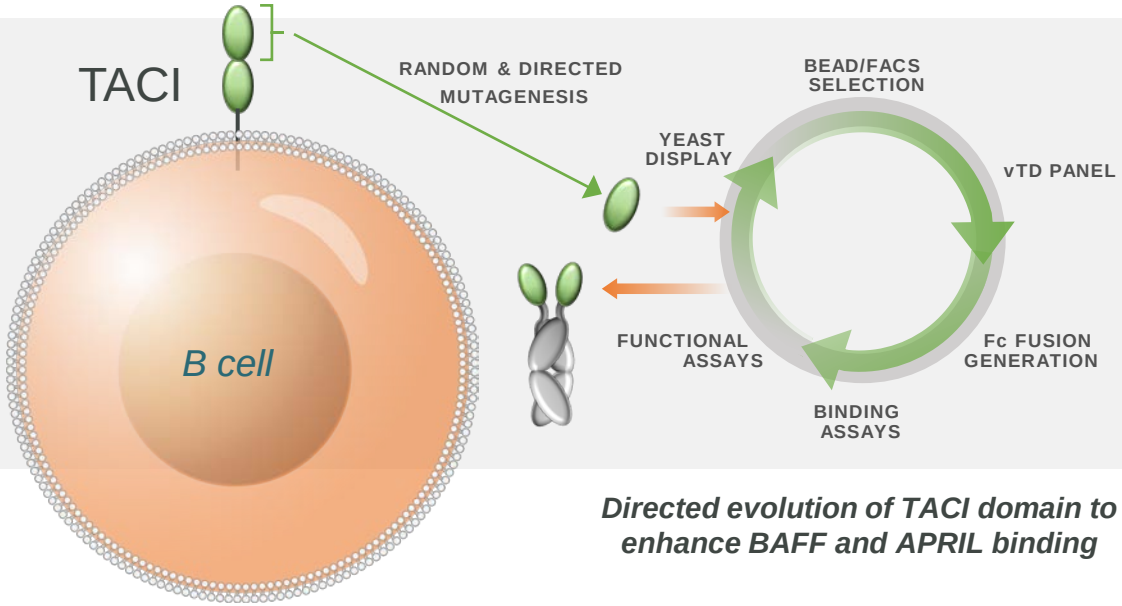


Adapted from Sakai J, et al. (2017) Clin Microbiol Rev. 30:991

Dual BAFF/APRIL inhibition provides deeper and more sustained B cell suppression than anti-BAFF or anti-APRIL therapy

- BAFF and APRIL antagonism with wild-type (WT) TACI-Fc (atacicept, telitacicept) shows encouraging clinical potential in systemic lupus erythematosus (SLE) and IgA nephropathy
  - Most reported responses are partial
- In nonclinical models, BAFF or APRIL inhibition alone mediates modest effects
  - Co-neutralization dramatically reduces B cell function, including antibody production
- ALPN-303 (TACI vTD-Fc) was engineered to have optimal BAFF and APRIL inhibition to provide superior efficacy and clinical benefit compared to WT TACI-Fc and BAFF- or APRIL-specific mAbs

ALPN-303 is a modified TACI-Fc fusion protein generated via directed evolution that mediates enhanced BAFF and APRIL inhibition vs. WT TACI-Fc

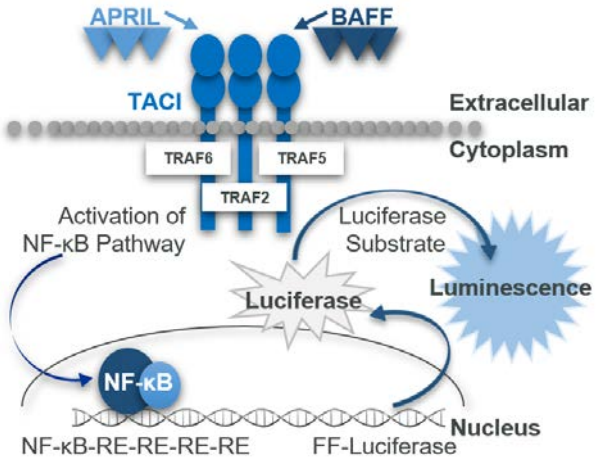


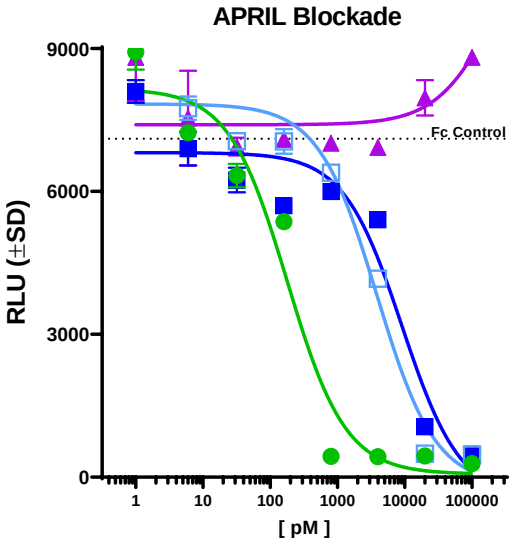
Directed evolution of TACI domain to enhance BAFF and APRIL binding

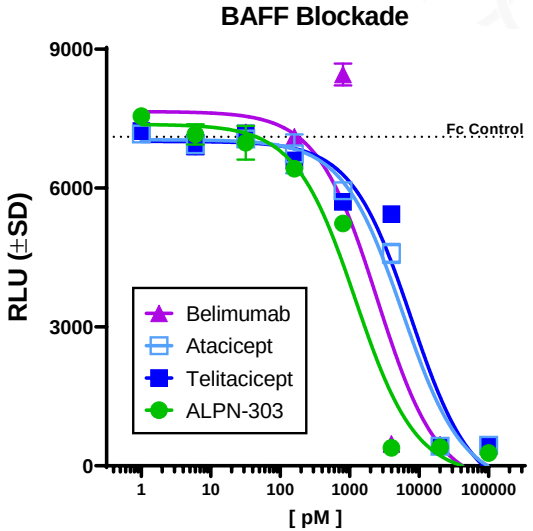
ALPN-303
(TACI vTD-Fc)

ALPN-303 neutralizes APRIL and BAFF activity more potently than WT TACI-Fc in a cell-based reporter assay

TACI-Jurkat Functional Assay:







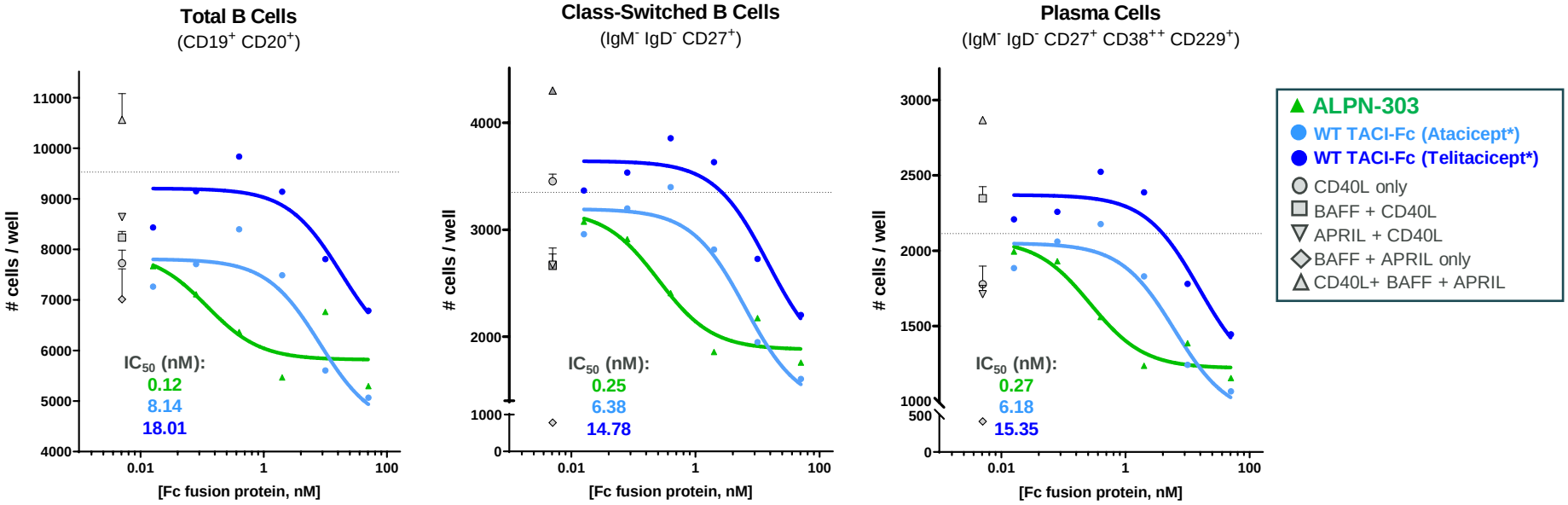
Generated at Alpine based on published sequences:
Belimumab : PDB ID 5Y9K
Atacicept : US Patent 8,815,238 B2 SEQ ID NO: 54
Telitacicept : US Patent 8,193,315 SEQ ID NO: 3

IC_{50} Values:

Test Article	Human		Mouse	
	APRIL	BAFF	APRIL	BAFF
*Belimumab	–	2496	–	1725
*Atacicept	3849	5771	270	1322
*Telitacicept	9103	7699	380	2445
ALPN-303	**179**	**1216**	**16**	**255**

ALPN-303 inhibits B cell survival more potently than WT TACI-Fc in primary human B cell assays

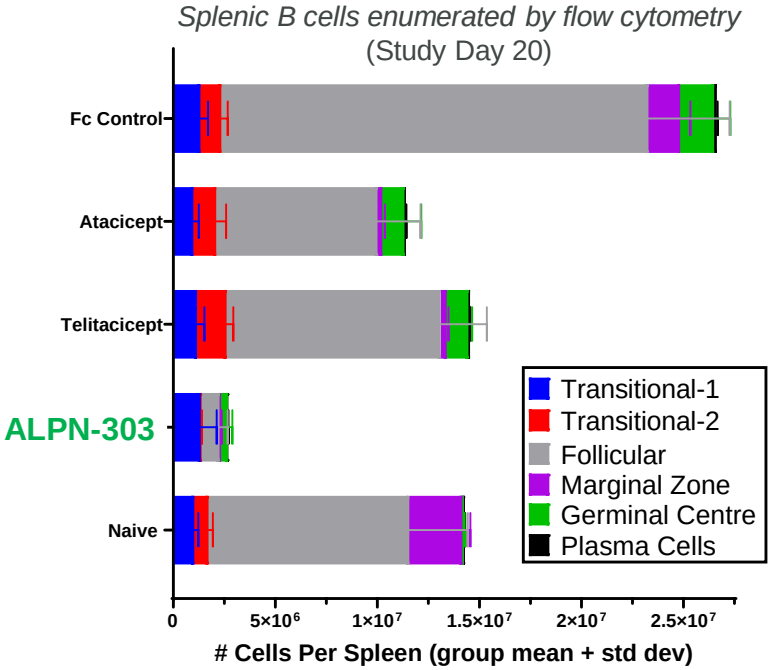
Primary B cell survival assay

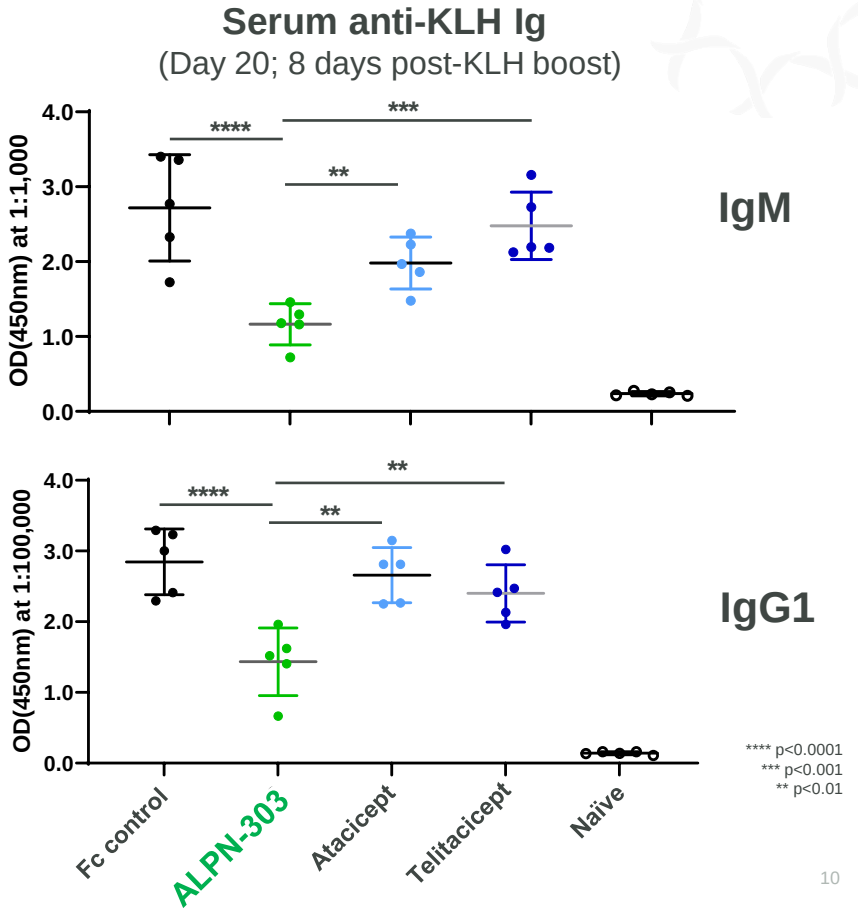


Purified hu memory B cells @40,000/well
2 nM BAFF + 0.2 nM APRIL + 0.1 nM CD40L, 4 days

*Generated at Alpine based on published patent sequences

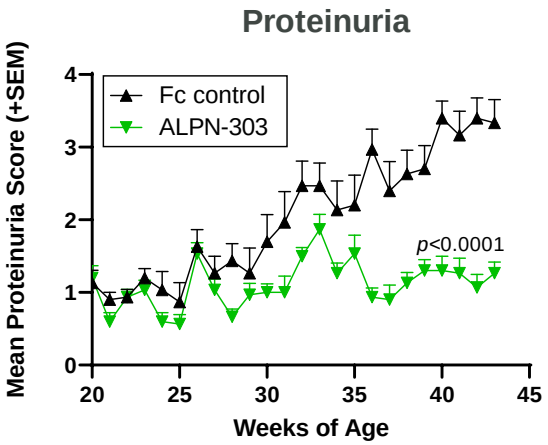
ALPN-303 inhibits T cell-dependent antibody formation more potently than WT TACI-Fc in KLH-immunized mice

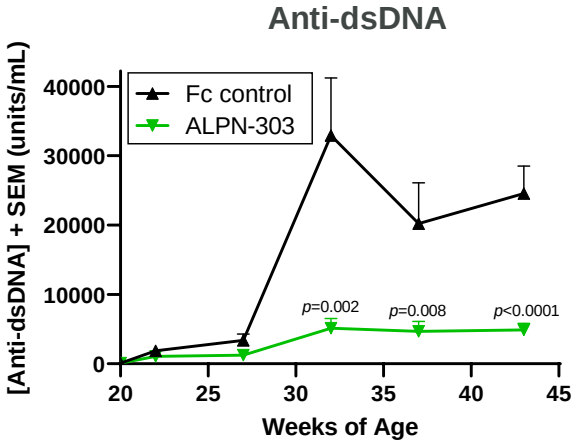


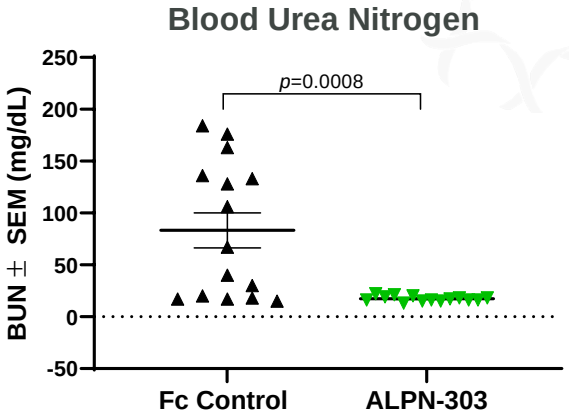


- Female C57BL/6 mice injected IP with 250 µg KLH in PBS w/o adjuvant on Days 0 & 12
- Test articles were molar matched to 15 mg/kg ALPN-303 and administered IP on Days 4 & 11 (5 mice/group)

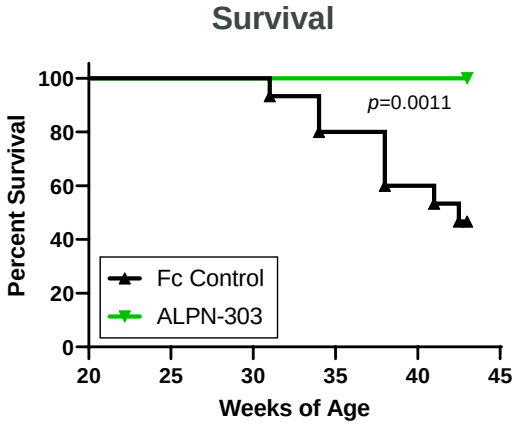
ALPN-303 suppresses disease in the (NZBxNZW)F_1 spontaneous lupus model

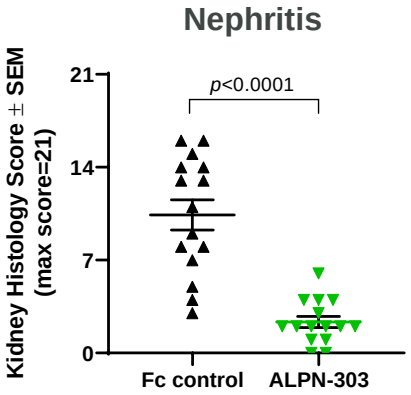


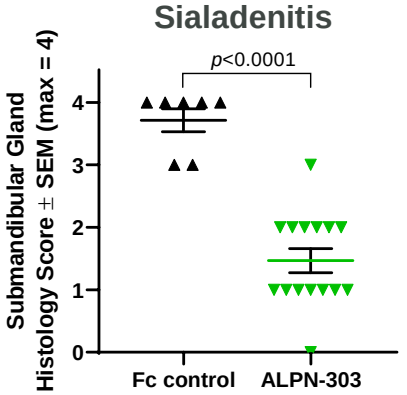




Dosed 17 mg/kg IP 2x/week from 22-42 wks of age



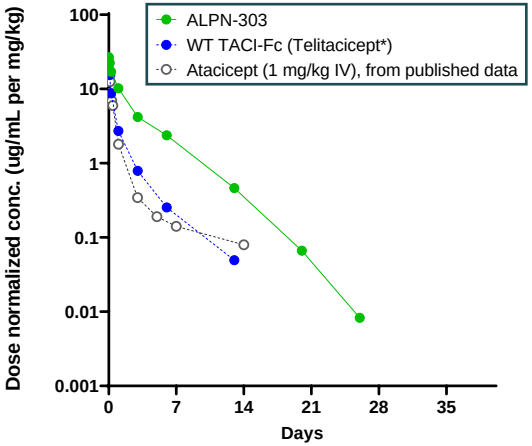




Following a single dose, ALPN-303 exhibits increased exposure and enhanced Ig suppression vs. WT TACI-Fc in non-human primates

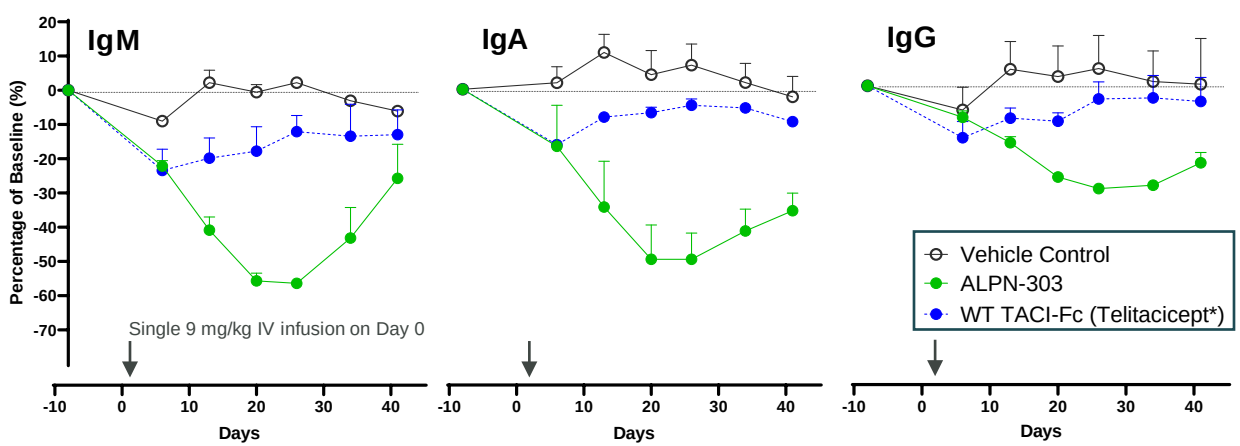
- N=2 female cynomolgus monkeys/group
- Single dose, 9 mg/kg, 30 min IV infusion
- Serum Ig baseline collected on Day -8

Serum Concentration



	C_{max}/Dose (µg/mL per mg/kg)	AUC/Dose (µg*hr/mL per mg/kg)
ALPN-303	27	1167
WT TACI-Fc*	21	314
Atacicept	23	215

Serum Immunoglobulins



Generated at Alpine based on published patent sequences

Atacicept PK data: Carbonatto et al. (2008) *Toxicol Sci* 105: 200–210

Summary

- ALPN-303 is a potent BAFF/APRIL antagonist derived from our directed evolution platform
- ALPN-303 demonstrates encouraging immunomodulatory activity and efficacy *in vitro* and *in vivo*, superior in preclinical studies to WT TACI-Fc
- ALPN-303 exhibits favorable preliminary developability characteristics
  - Higher serum exposures and more potent immunomodulatory activities may enable improved efficacy, lower clinical doses, and/or longer dosing intervals compared to WT TACI-Fc therapeutics
- ALPN-303 is an attractive development candidate for the treatment of multiple autoimmune and inflammatory diseases
  - Focus on B cell-related disorders including SLE, Sjögren's syndrome, and other connective tissue diseases
- Preclinical development has been initiated to enable clinical trials

Acknowledgements

ALPN-303 Project Team

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