Systemic Administration of Acazicolcept (ALPN-101), a Dual ICOS/CD28 Antagonist, Suppresses Ocular Inflammation in Rat Experimental Autoimmune Uveitis

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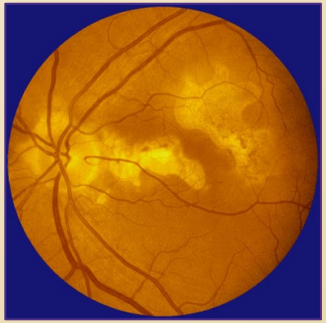
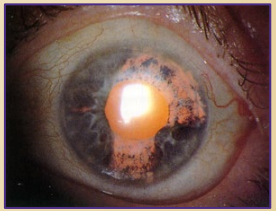
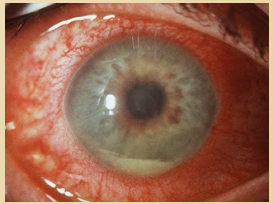
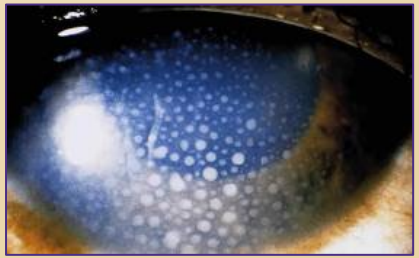
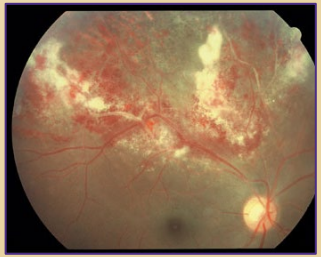
Uveitis is a blinding eye disease











Broad term including any inflammatory disease of the eye

Caused by infection or immune dysfunction (autoimmunity)

Impacts 300,000-400,000 patients in the US[1,2]

~10% blindness in the US[3]

1. *Ophthalmol.* 2004;111(3):491-500.

2. *JAMA Ophthalmol.* 2016;134(11):1237-1245.

3. *Br J Ophthalmol*. 1996;80(9):844-848.

Treatment failures indicate new therapies are needed

First line agents:

Local and systemic corticosteroids

Conventional immunosuppression[1]:

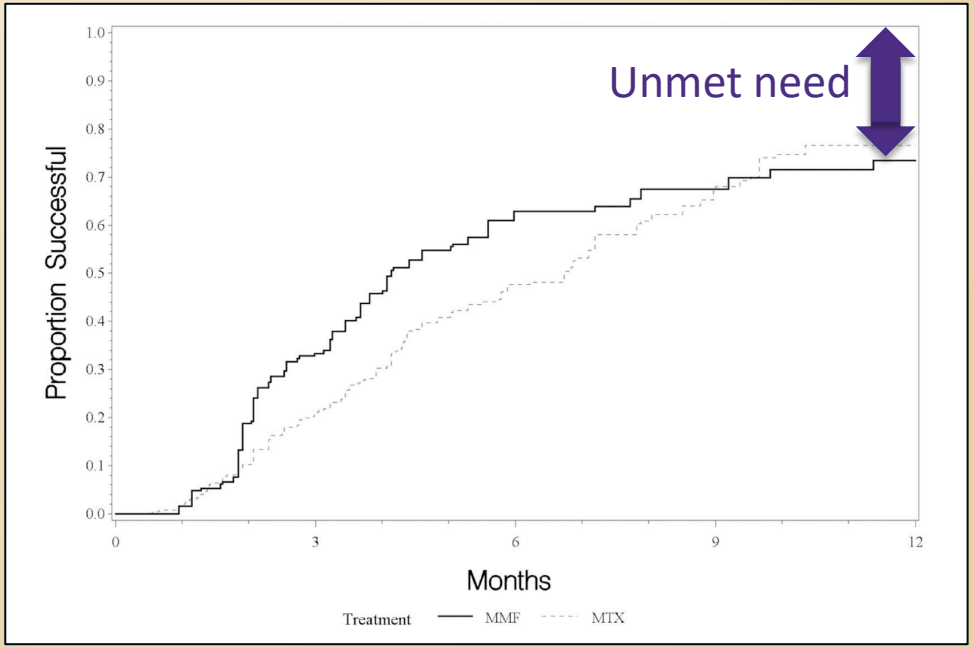
Methotrexate, Mycophenolate, Azathioprine

Cyclosporine, tacrolimus

Cyclophosphamide or chlorambucil

Immunosuppression with biologics

Adalimumab and Infliximab[2]



Gangaputra et al., AJO 2019

1. Jabs et al., Am J Ophthal. 2000

2. Levy-Clarke et al., Ophthalmology 2004

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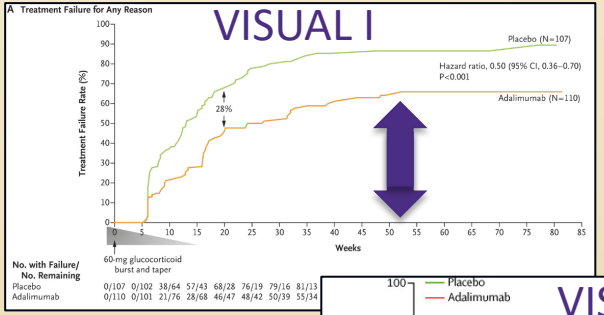
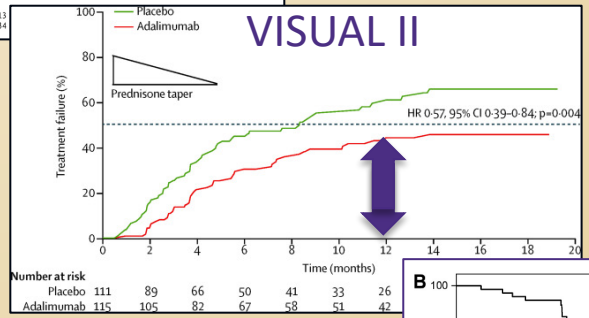
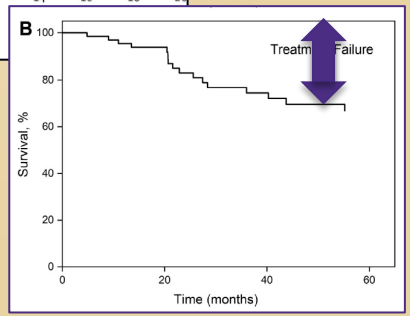


Jaffe et al., NEJM 2016



Nguyen et al., Lancet 2016



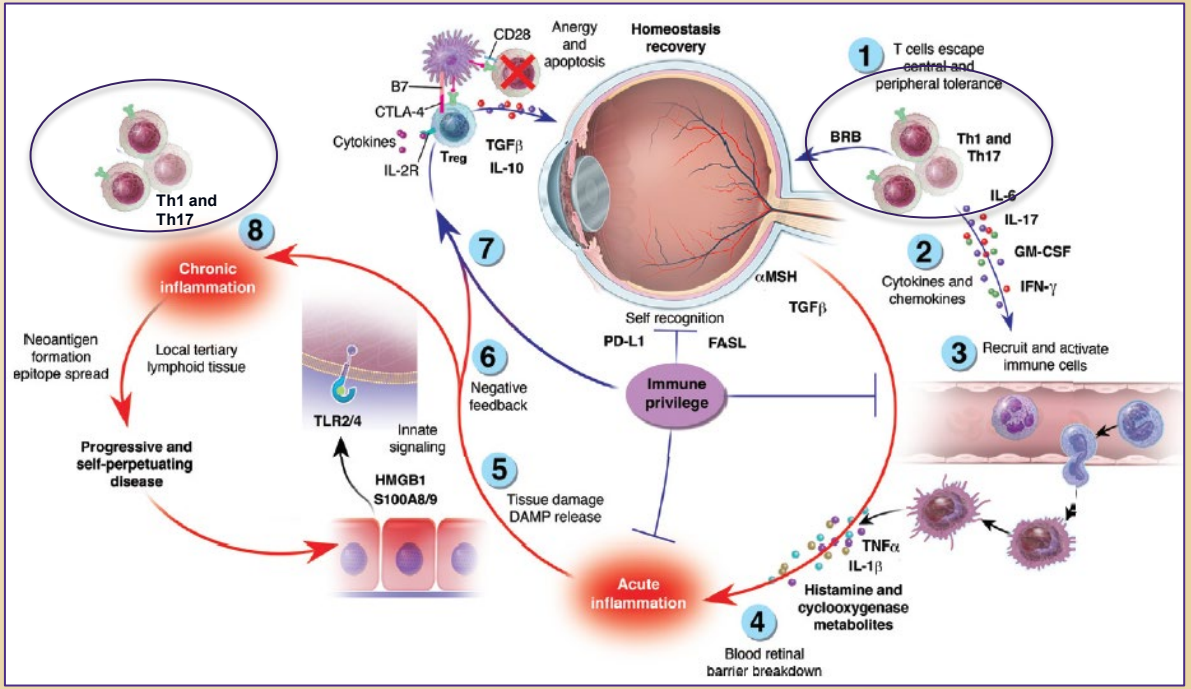
Al-Janabi et al., Ophthalmology 2020

1. Jabs et al., Am J Ophthal. 2000
2. Levy-Clarke et al., Ophthalmology 2004

Non-infectious autoimmune uveitis is T cell-mediated

Experimental Autoimmune Uveitis (EAU)

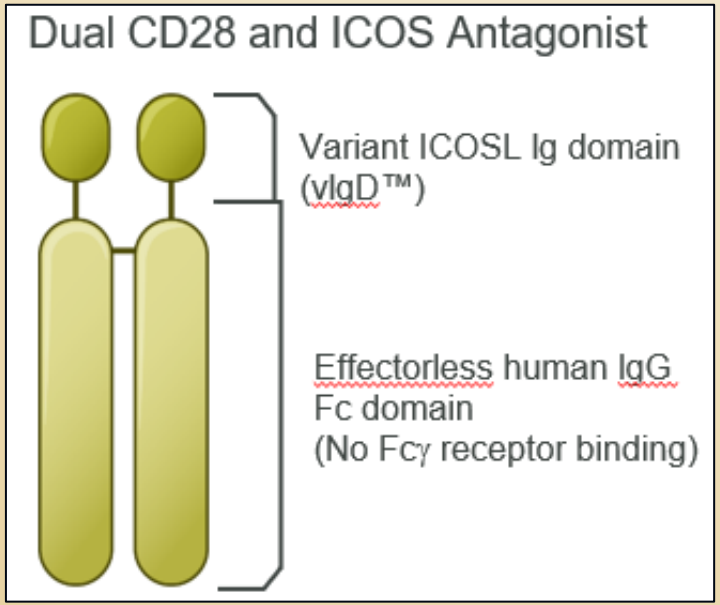
- Th1 and Th17 responses mediate inflammation and ocular damage.[1]
- T reg cells contribute to disease resolution and maintenance of homeostasis



Adapted from Tummala and Pepple, Ch. 28 Ryan's Retina v7

1. Chen et al. Curr. Mol. Medicine 2015

Acazicolcept (ALPN-101)



Previous efficacy demonstrated in animal models of systemic sclerosis and graft versus host disease

Cauvet et al., Arthritis Res Ther. 2022

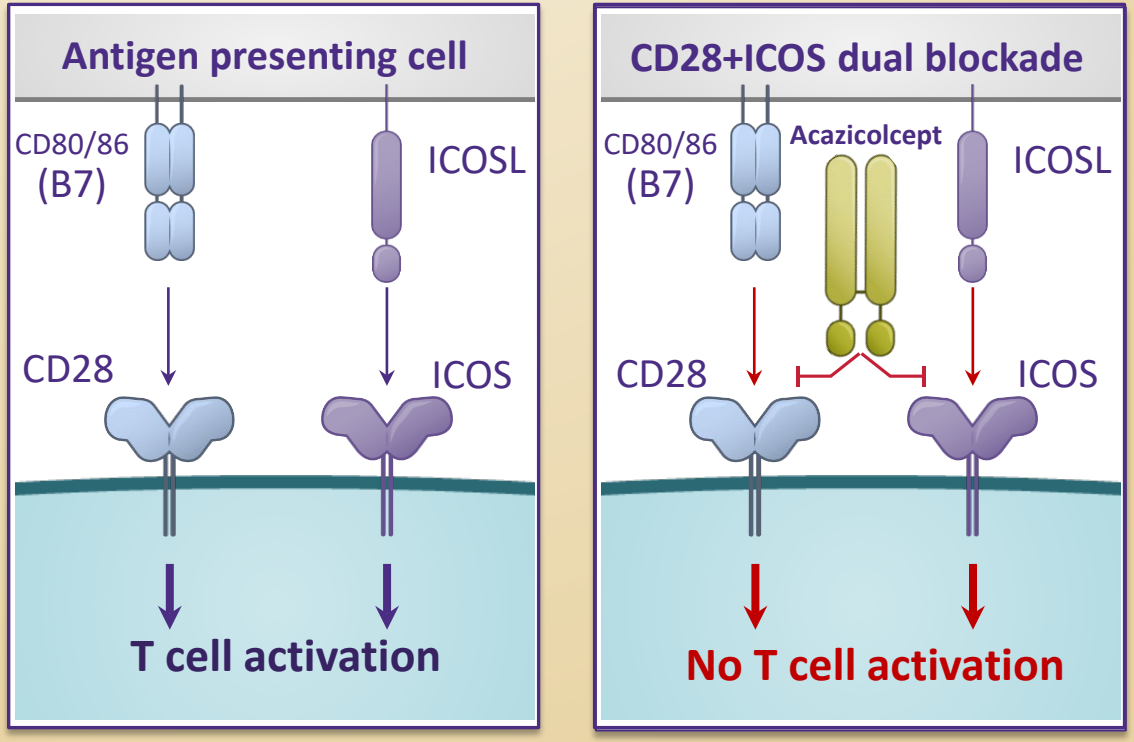
Yang et al., Clin Transl Sci. 2021

Adom et al., Sci Trans Med. 2020

Acazicolcept (ALPN-101) is a dual CD28 and ICOS antagonist

CD28 is central to naïve T cell co-stimulation

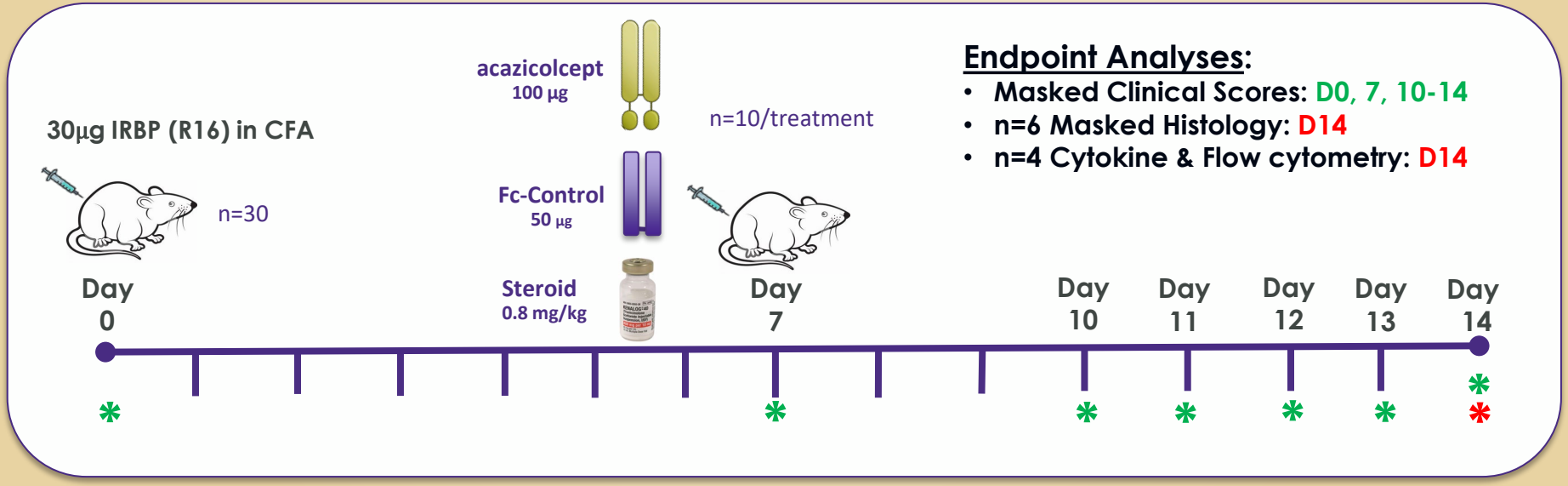
ICOS is important in effector T helper cell function (Th1, Th2, Th17) and follicular helper T cell development



Chen et al., Nature Reviews Immunology 2013

Study design

Systemic acazicolcept for treatment in rat Experimental Autoimmune Uveitis (EAU)

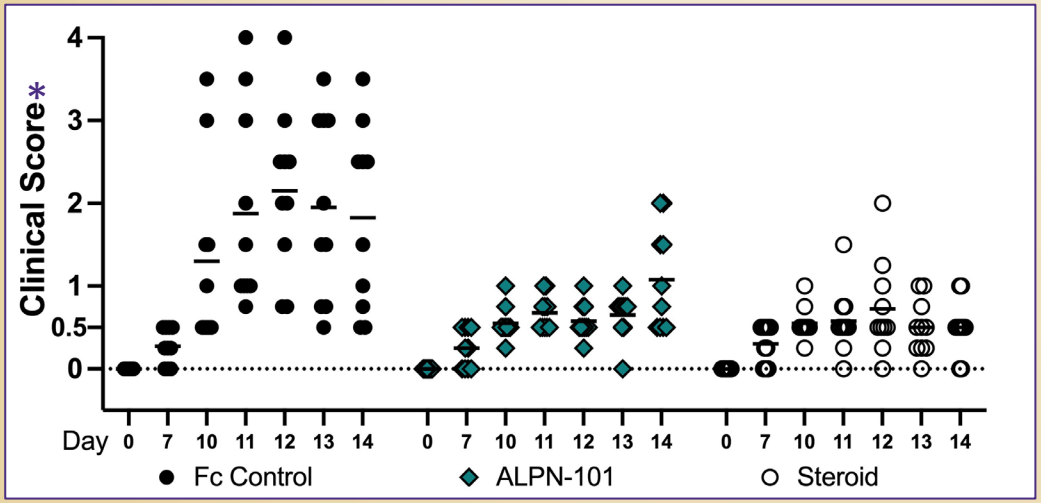


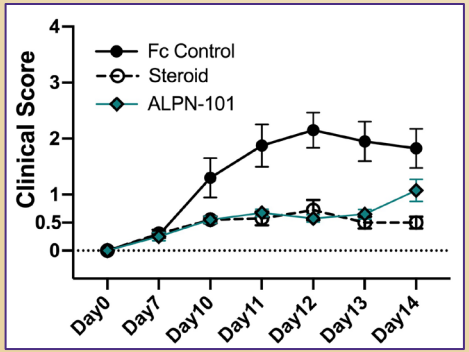
Endpoint Analyses:

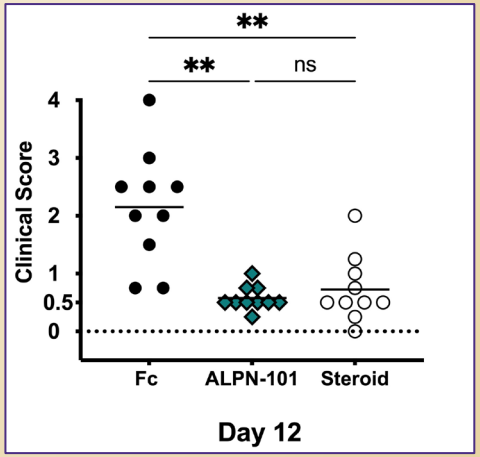
- Masked Clinical Scores: D0, 7, 10-14
- n=6 Masked Histology: D14
- n=4 Cytokine & Flow cytometry: D14

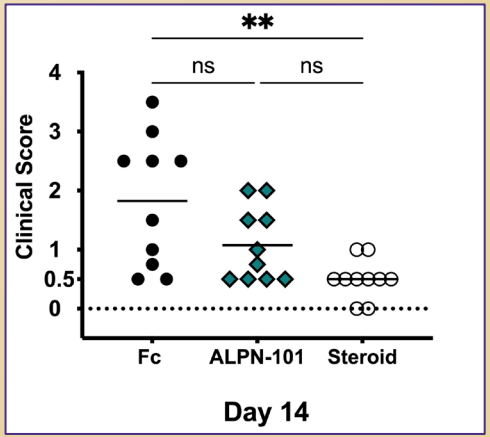
IRBP = Interphotoreceptor Retinoid-Binding Protein
CFA = Complete Freund's Adjuvant

Acazicolcept (ALPN-101) prevents clinical signs of EAU





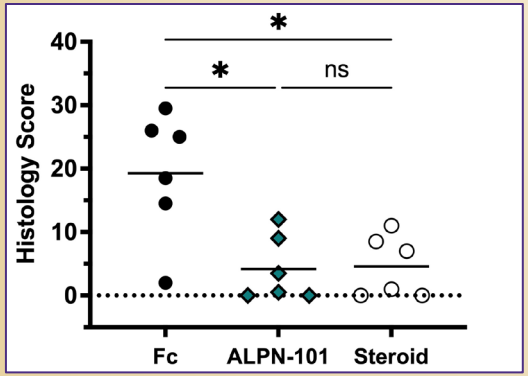


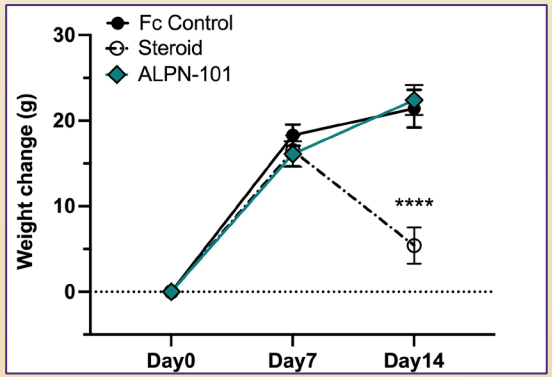


Agarwal et al., 2012
Methods Mol. Bio.

** $p < 0.01$ by Kruskal-Wallis with Dunn's test.

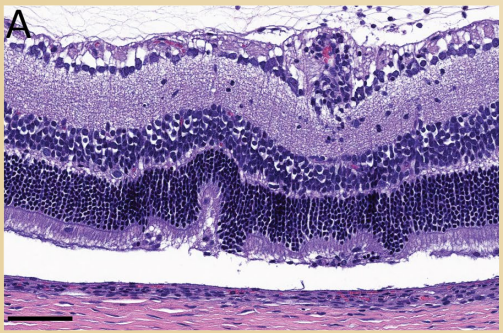
Acazicolcept (ALPN-101) preserves retinal histology

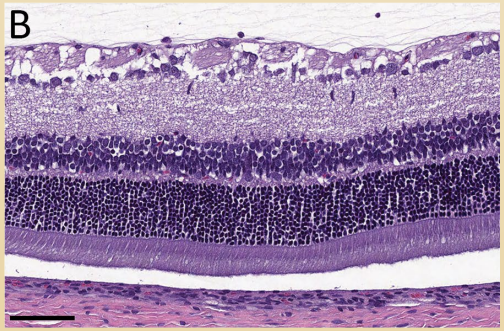


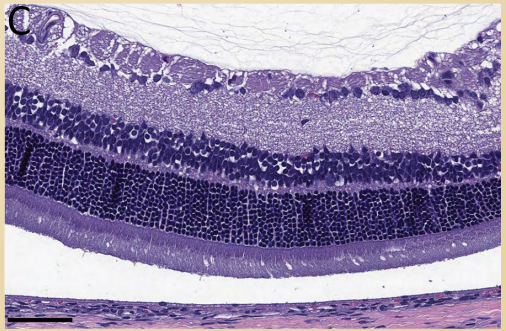


Steroid treatment leads to significant weight loss.

Acazicolcept treatment effect is not associated with weight loss.







Fc **Steroid** **ALPN-101**

*$p < 0.05$, **** $p < 0.001$ by Kruskal-Wallis with Dunn's test. ns = not significant

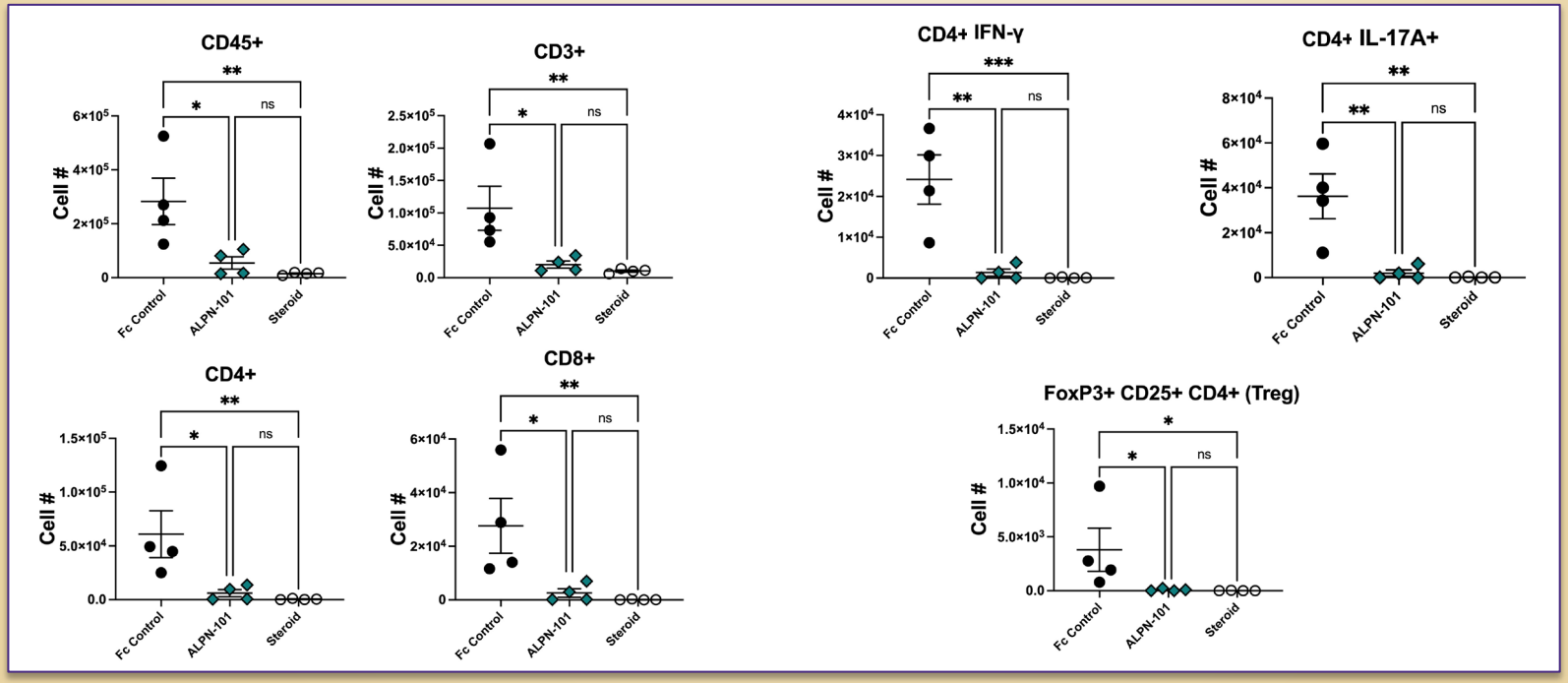
Histology score: Dick et al., 1994 Eye.

Acazicolcept (ALPN-101) suppresses ocular T cell number

Ocular flow analysis

Th1

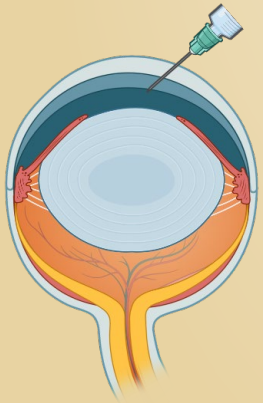
Th17



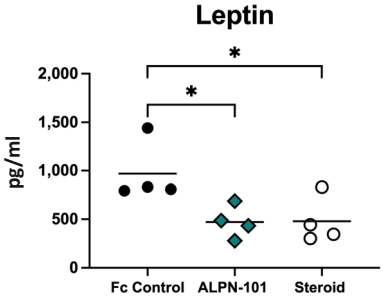
* $p < 0.05$; ** $p < 0.01$ by 1-way ANOVA.
ns = not significant

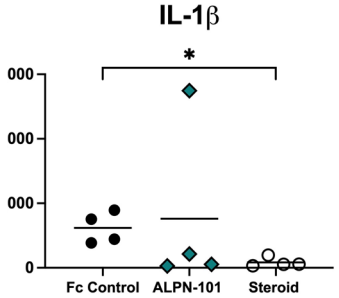
Treg

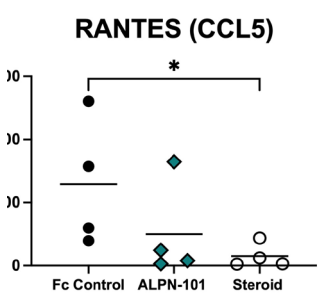
Treatment significantly decreased some aqueous cytokines



Samples collected from the same eyes analyzed by flow

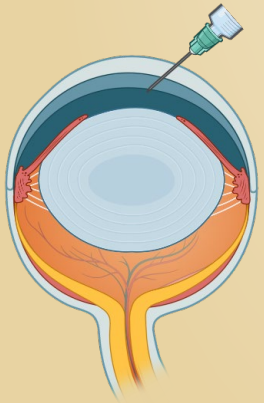






Kruskal-Wallis with Dunn's test.
*$p<0.05$, ns = not significant

Many indicate a trend towards decreased concentrations



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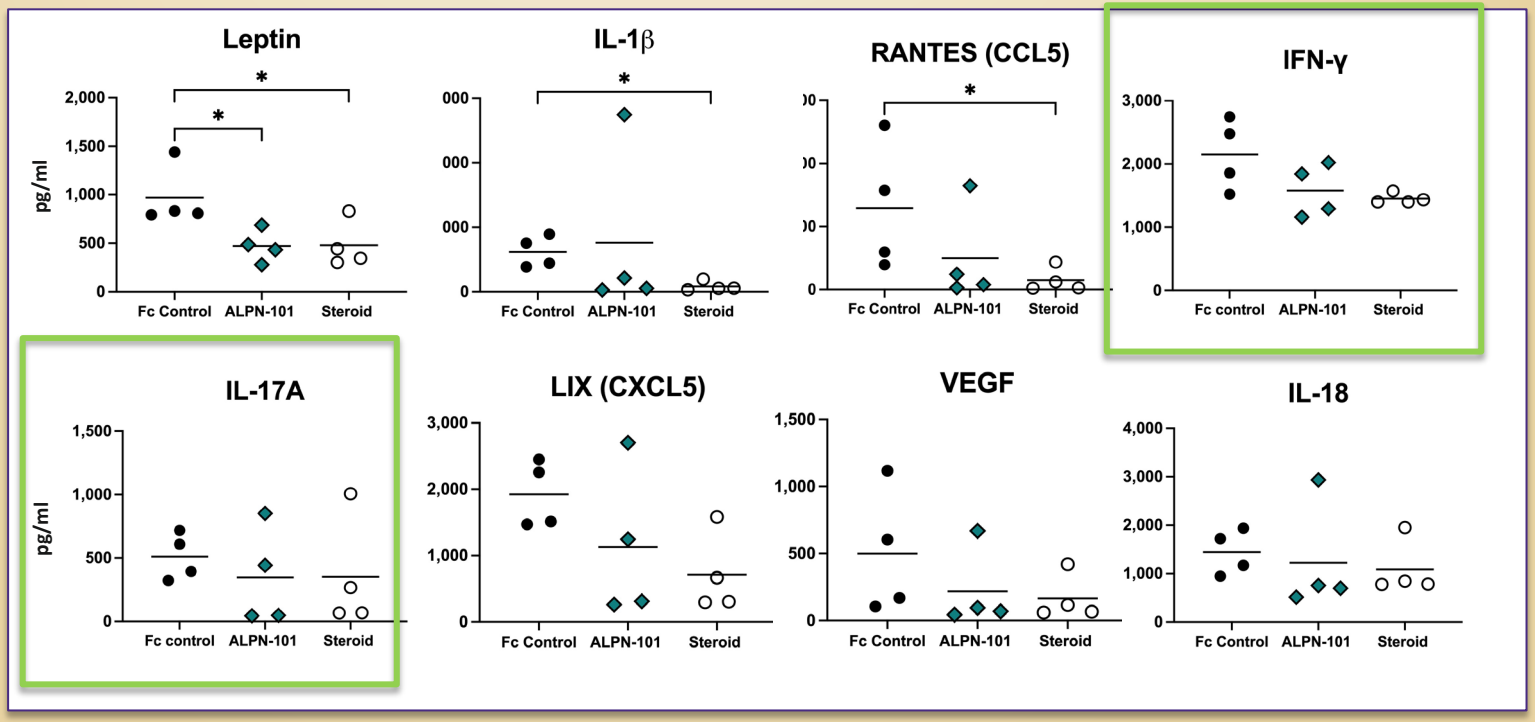
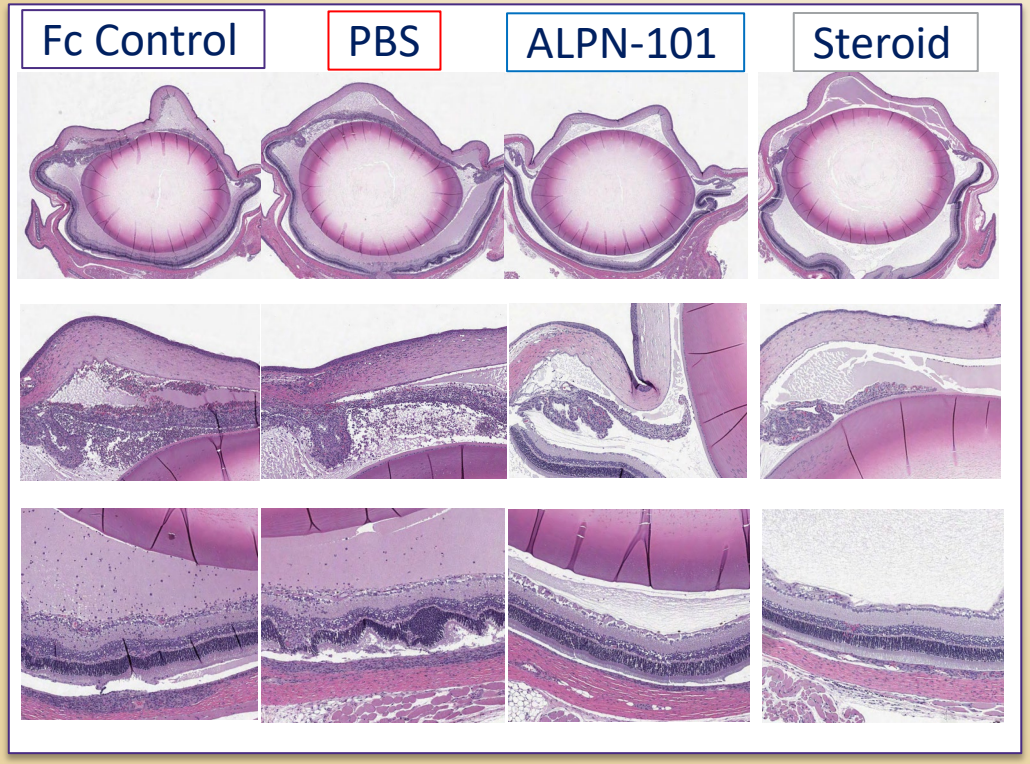


Kruskal-Wallis with Dunn's test.
*p<0.05, ns = not significant

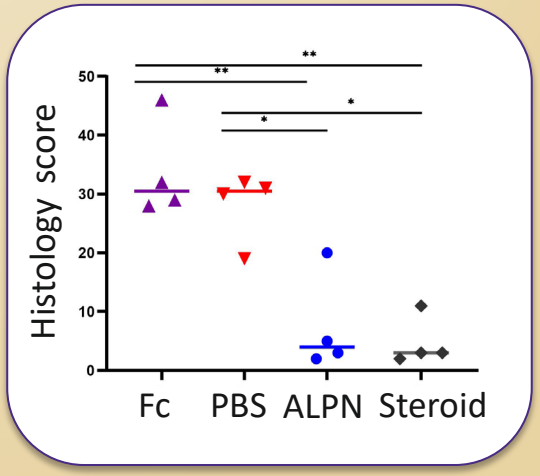
SUMMARY AND CONCLUSIONS

- Systemic inhibition of CD28 and ICOS with acazicolcept (ALPN-101) significantly suppresses EAU in rats.
- Both Th1 and Th17 cell # and cytokines were suppressed to a similar degree as with steroid treatment.
- Acazicolcept provided uveitis control without the weight loss (toxicity) caused by steroid treatment.
- Acazicolcept could be explored as a potential therapeutic option for patients with non-infectious uveitis.

Local therapy with acazicolcept (ALPN-101) protects from EAU inflammation



Injected on day 8 and day 10



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RPB Unrestricted Departmental Award

Latham Innovation in Vision Science Award

Alcon Research Institute Young Investigators Award

UNIVERSITY of WASHINGTON

National Eye Institute
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RPB Research to Prevent Blindness
Preserving vision and restoring sight through research.

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