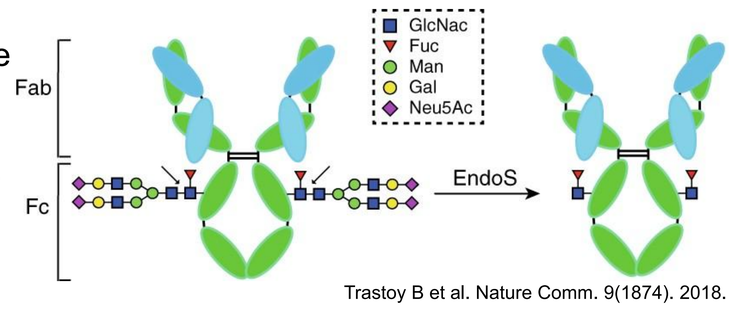
Design of a deimmunized EndoS for IgG-mediated diseases using the ADAx platform

A. Ta, J. Knauer, P. Srinivas, M. Tomison, S. Lashbrook, F. Vermersch, K. Lam, M. Koslen, V. Lieuw, M. Corpuz, R. Orcutt, C. Tran, H. Pugh, J. Wang, D. Plouffe, G. Gabrelow, J. Shoda, M. Amour, A. Miller, M. Numa, R. Morse, S. DePorter, D. Aivazian

ADAXION Therapeutics, San Diego, CA, United States

Background

- EndoS is a bacterial enzyme that deglycosylates IgG, eliminating FcγR-mediated ADCC and ADCP, and C1q-mediated CDC.

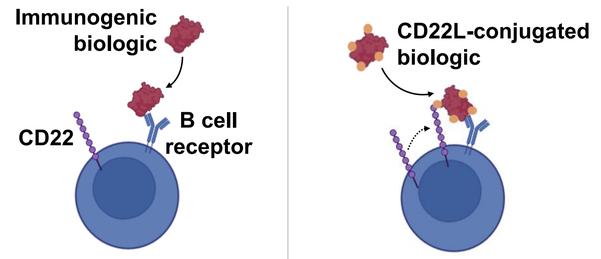


Trastoy B et al. Nature Comm. 9(1874). 2018.

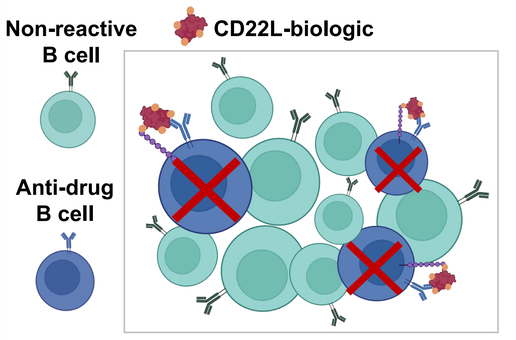
- EndoS has promising therapeutic potential for antibody-driven autoimmune diseases.
- Being a foreign bacterial enzyme, EndoS is expected to be highly immunogenic in humans, potentially limiting dosing, efficacy and safety.
- A half-life extended EndoS was engineered with cysteine mutations for site-specific conjugation of CD22 ligands (CD22L) to inhibit drug-specific B-cell responses and prevent anti-drug antibody (ADA) formation.

ADAx Platform

CD22L mediated B cell inhibition



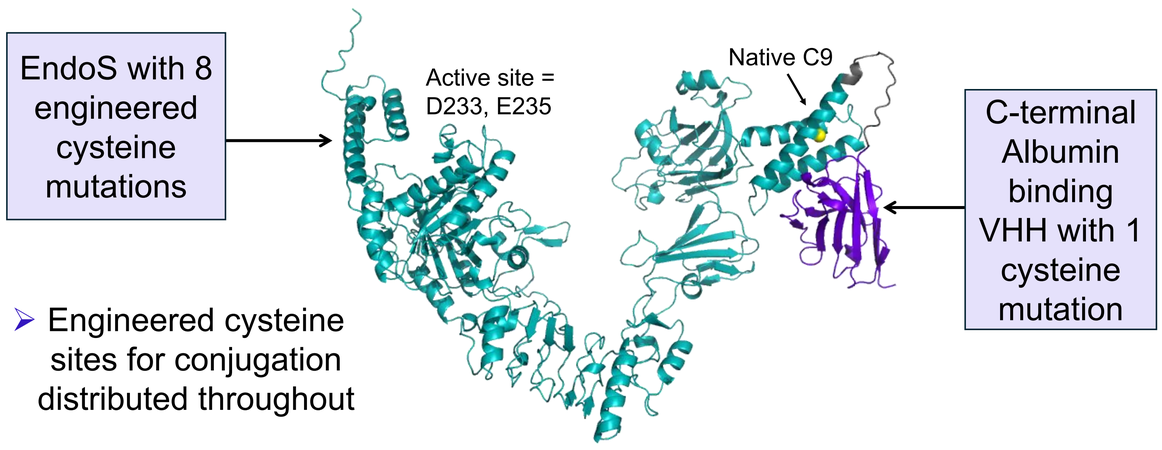
Drug-specific B cell suppression



CD22L conjugation to an immunogenic biologic drug aims to eliminate or prevent the proliferation of drug-reactive B cells.

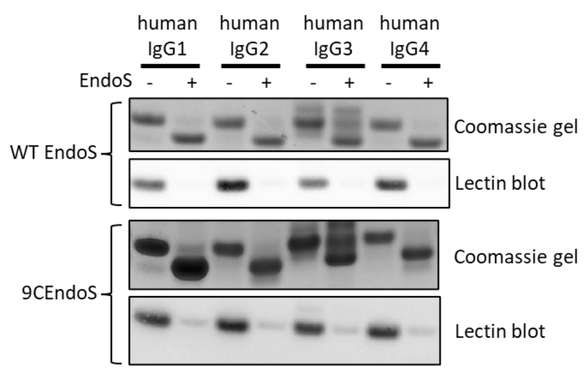
Results

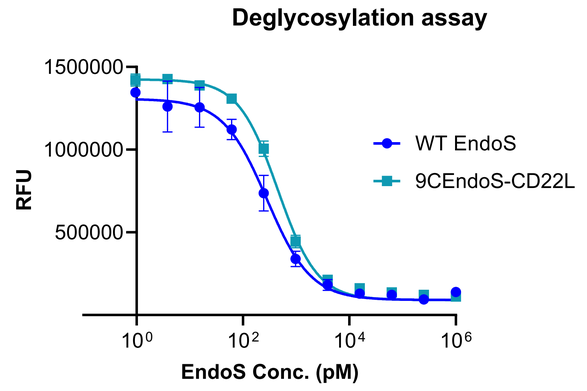
9CEndoS-VHH-CD22L: A half-life extended, site-specific conjugated EndoS



- Engineered cysteine sites for conjugation distributed throughout

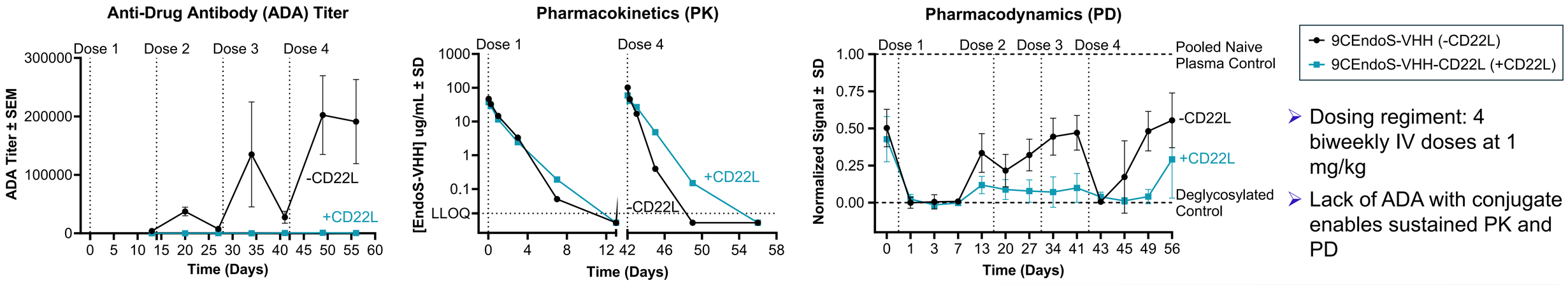
Engineered 9CEndoS maintains WT activity





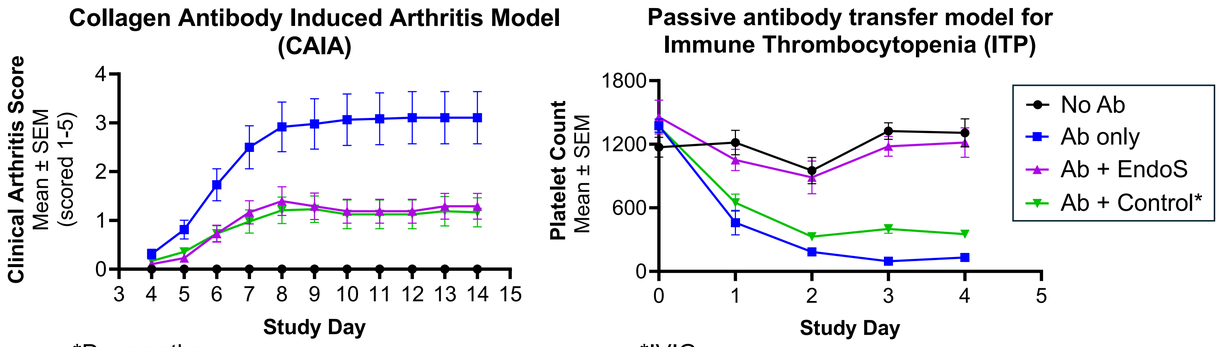
- Addition of cysteine mutations and conjugation of CD22 ligands does not perturb the deglycosylation activity as measured by WB and ELISA

9CEndoS-VHH-CD22L effectively suppresses ADA response in C57BL/6 hFcRn KI mice



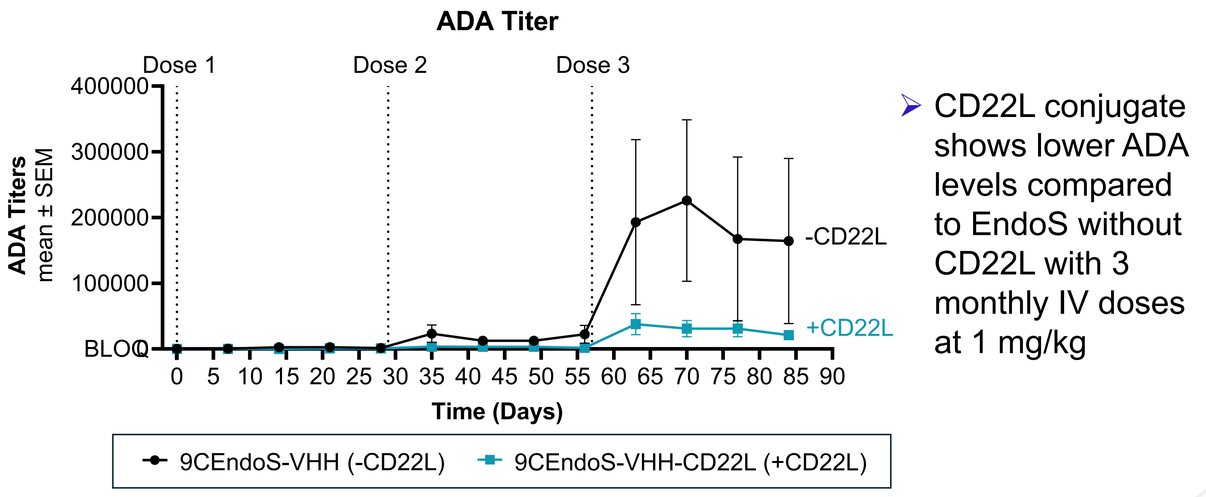
- Dosing regiment: 4 biweekly IV doses at 1 mg/kg
- Lack of ADA with conjugate enables sustained PK and PD

9CEndoS-VHH-CD22L shows efficacy in CAIA and ITP mouse models



- EndoS inhibited arthritis development similar to dex positive treatment control in CAIA model and rescued platelets better than IVIG control in ITP model

9CEndoS-VHH-CD22L has reduced immunogenicity in Cynomolgus monkeys



- CD22L conjugate shows lower ADA levels compared to EndoS without CD22L with 3 monthly IV doses at 1 mg/kg

Conclusion

- Using the ADAx platform, 9CEndoS-VHH conjugated with proprietary CD22Ls is less immunogenic in mice and non-human primates with reduced anti-drug antibody formation, prolonged exposure, and more sustained IgG inactivation
- IgG deglycosylation with 9CEndoS-VHH-CD22L effectively disables pathogenic autoantibodies in arthritis and ITP mouse models, showing potential in IgG driven autoimmune diseases
- Further lead optimization in progress

ADAXION THERAPEUTICS

Poster Number: A01