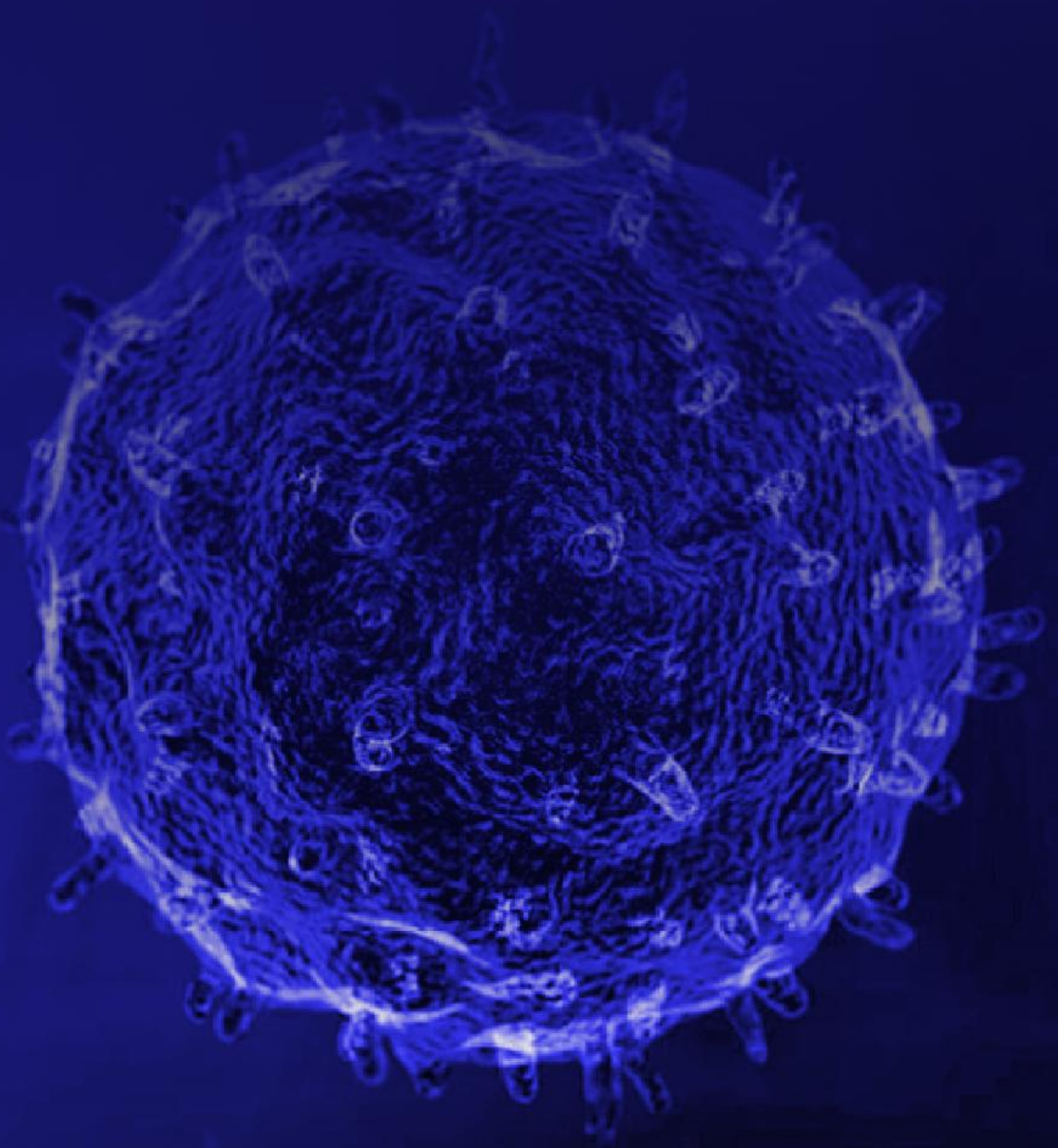
ADAXION THERAPEUTICS

# ADAx
## A novel platform for overcoming immunogenicity in biologics

Sandra DePorter, PhD
Senior Director-Discovery Biology

Antibody Engineering & Therapeutics 2025
Conference presentation



# What if …

We could design and dose any protein biologic without worrying about generating an ADA response

# The ADAx platform is focused on deimmunizing biologics

**The Challenge:** **The human immune system's natural response against foreign proteins and biotherapeutics**

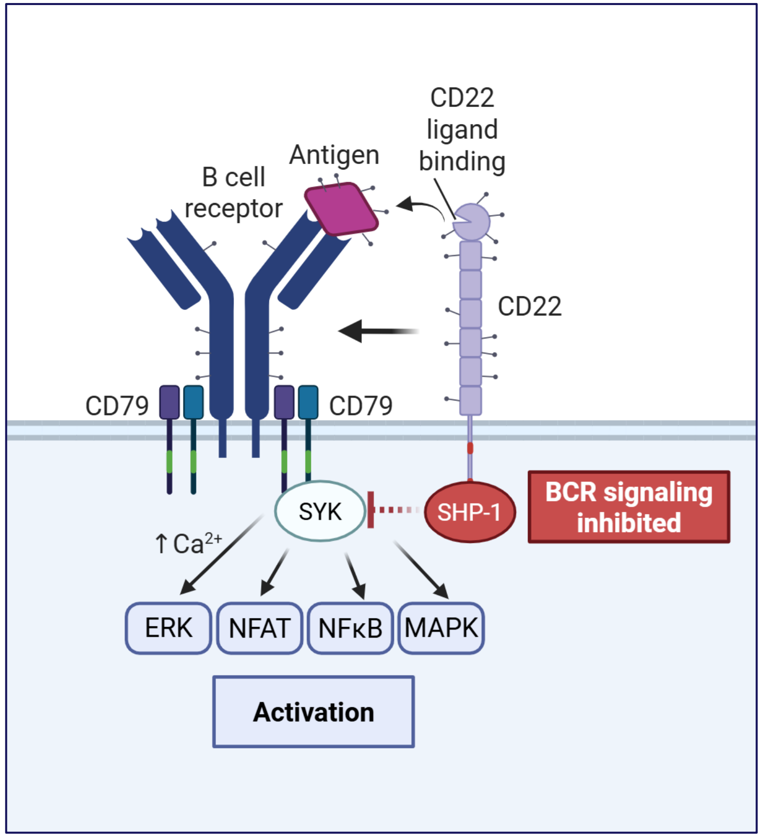
This response produces anti-drug antibodies (**ADAs**) that can reduce efficacy by:

- Limiting the length of therapeutic exposure
- Blocking therapeutic activity
- Triggering unintended immune reactions

**Our Solution:** **The ADAx platform enables best-in-class deimmunized biologics**

- Utilizing novel CD22 ligands conjugated to highly immunogenic biotherapeutics (e.g., immunogenic bispecifics, foreign enzymes)
- CD22 ligand bioconjugates silence biologic-specific B-cells, resulting in reduced or eliminated ADAs

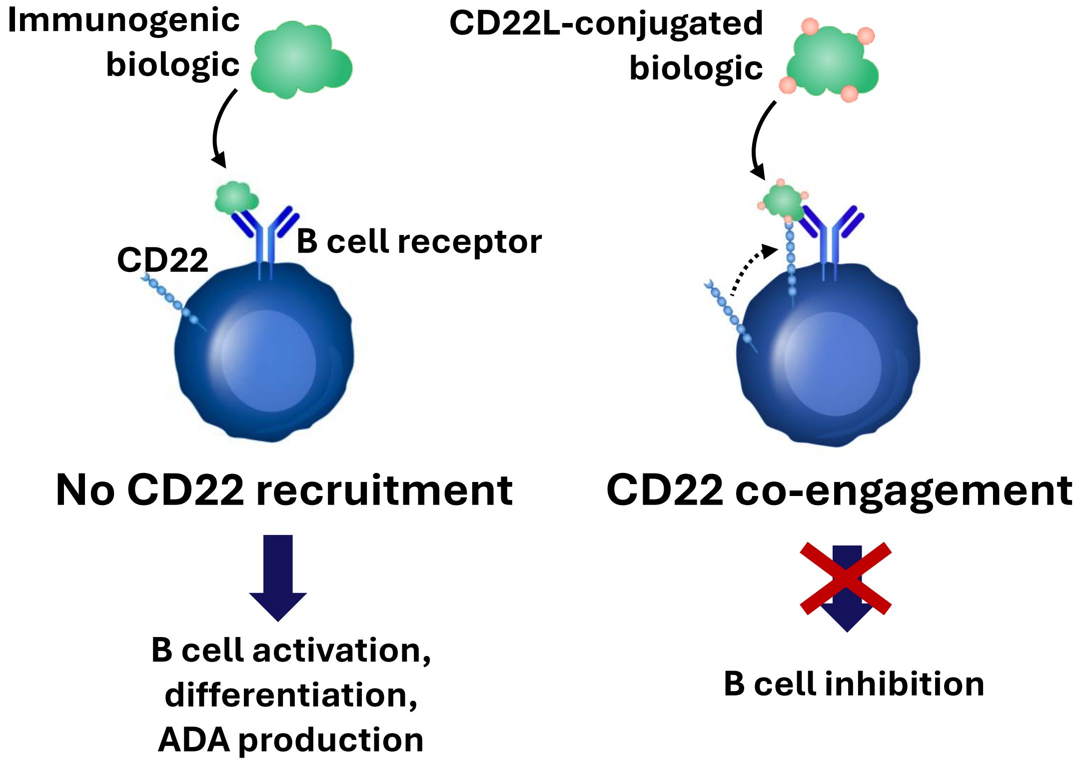
**CD22L acts as an inhibitory BCR co-receptor to enforce B cell tolerance to self**



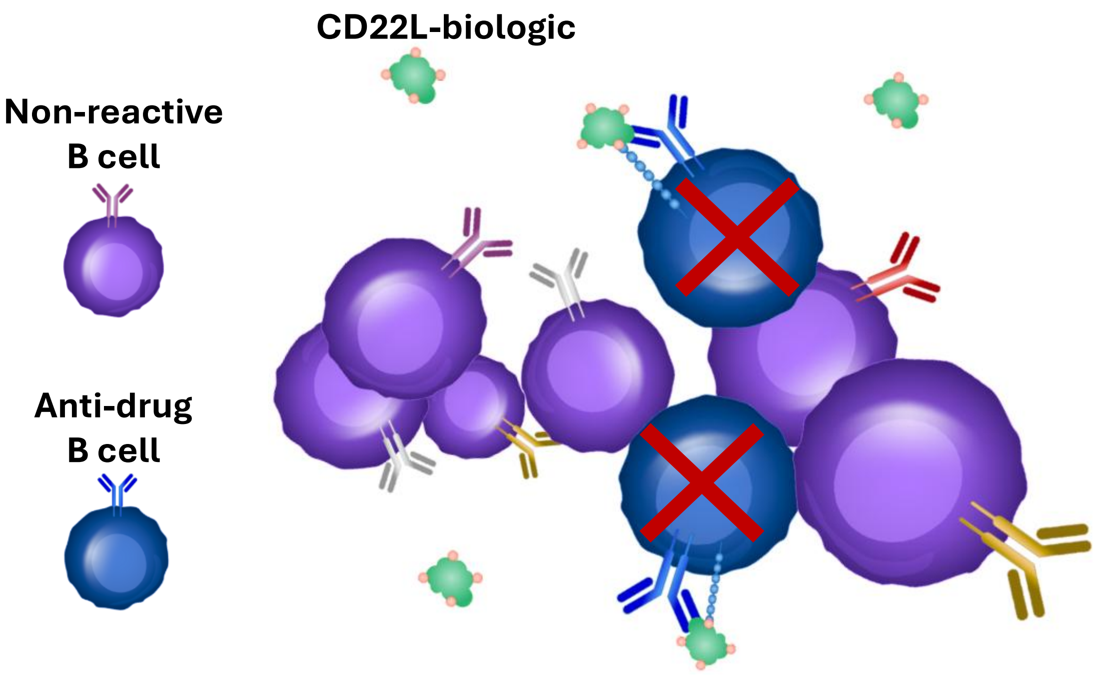

ADAXION THERAPEUTICS

# ADAx utilizes novel CD22 ligands incorporated on biologics to inhibit B cell activation and ADA development

## CD22 ligand (CD22L) is conjugated directly to drug to silence antigen-specific B cells




## Effect is specific to anti-drug reactive B cells




**Only anti-drug reactive B cells are eliminated**

ADAXION THERAPEUTICS

# Immunogenic biologics are directly conjugated to CD22 ligands to suppress ADA production

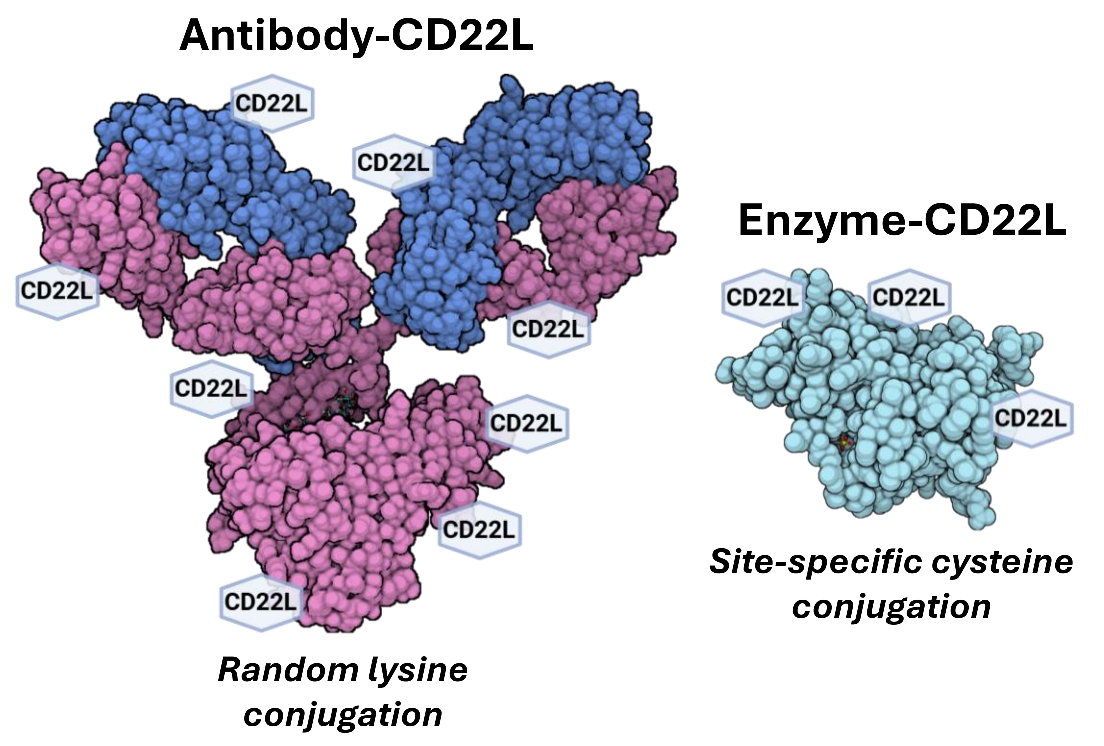
### Our approach conjugates proprietary synthetic CD22 ligands (CD22L) to protein therapeutics

- CD22Ls are 1 kDa hydrophilic compounds that are tuned for affinity and specificity
- Conjugates are optimized for Ligand-to-Drug Ratio (LDR)
- Conjugates retain full pharmacological activity

### Technology reduces immunogenicity driven by:

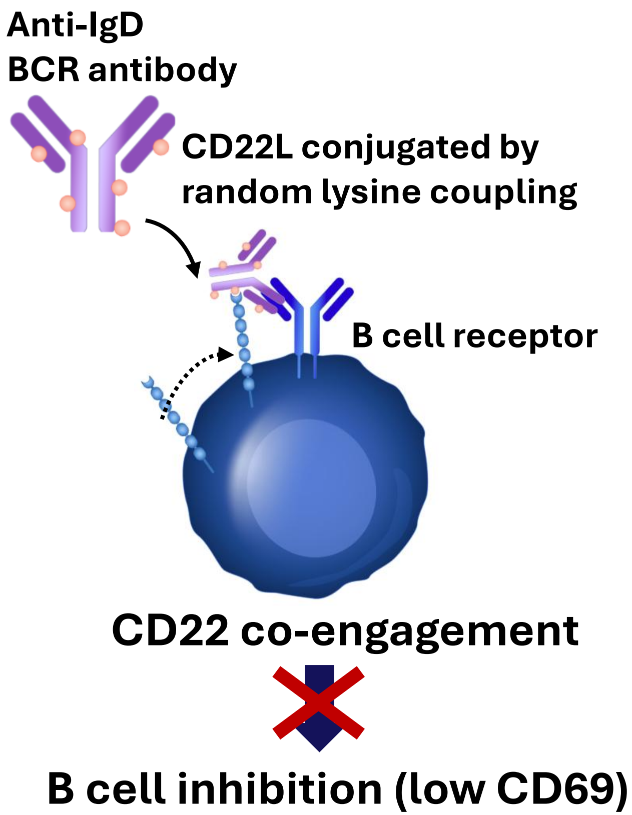
1) Drug pharmacology (e.g., TNFα & TL1A complexation)
2) Structural foreignness (e.g., bacterial protein in humans)

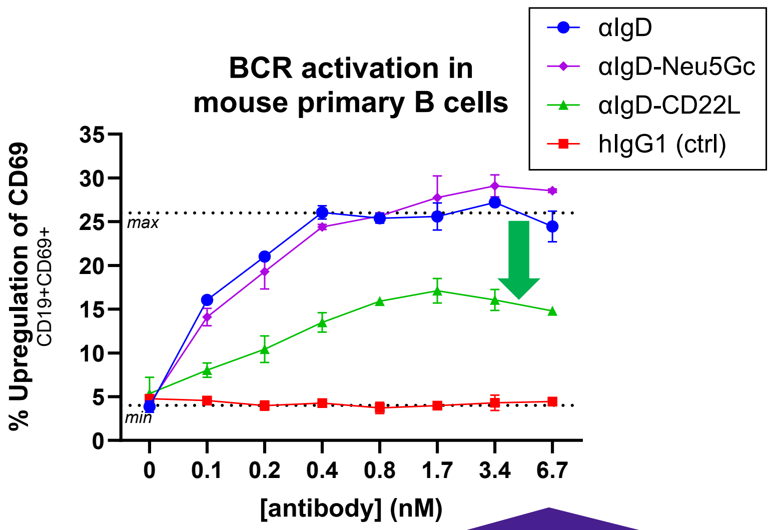
**Immunogenic biologics are conjugated to CD22L to suppress ADA**



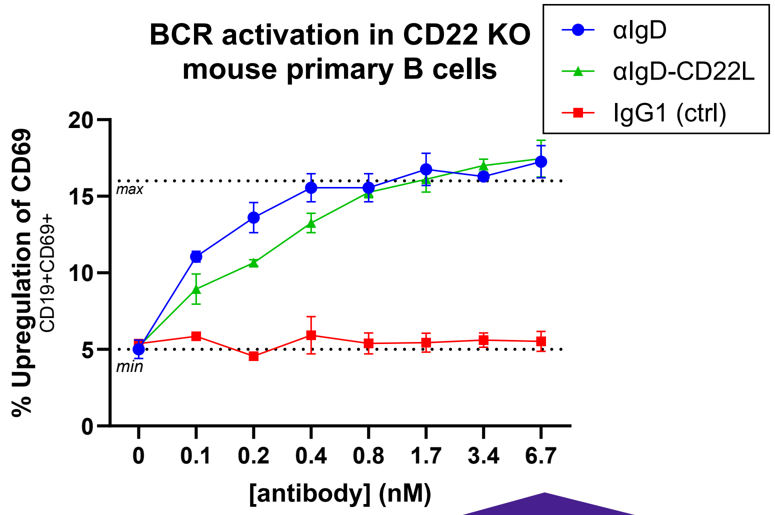
# Suppression of BCR activation is CD22L-dependent in mouse B cell assays

## *In vitro* model for B cell suppression



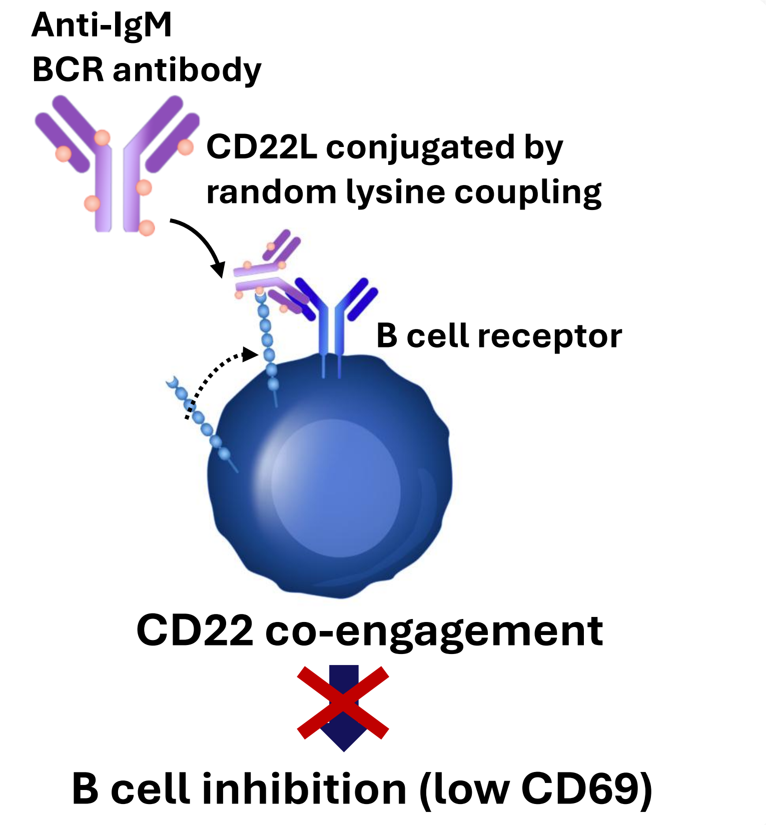

- ✓ CD22L conjugate suppresses BCR activation by anti-BCR antibody in mouse B cells

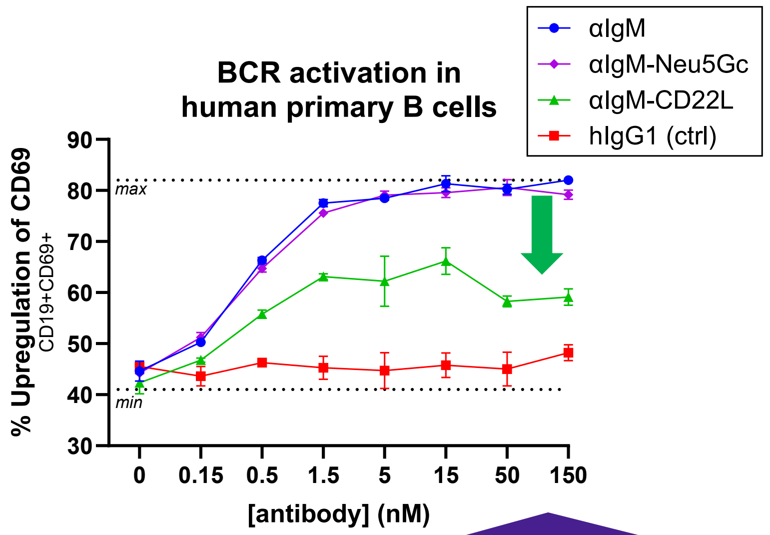



- ✓ CD22 KO mice demonstrate CD22 dependency of conjugate mechanism

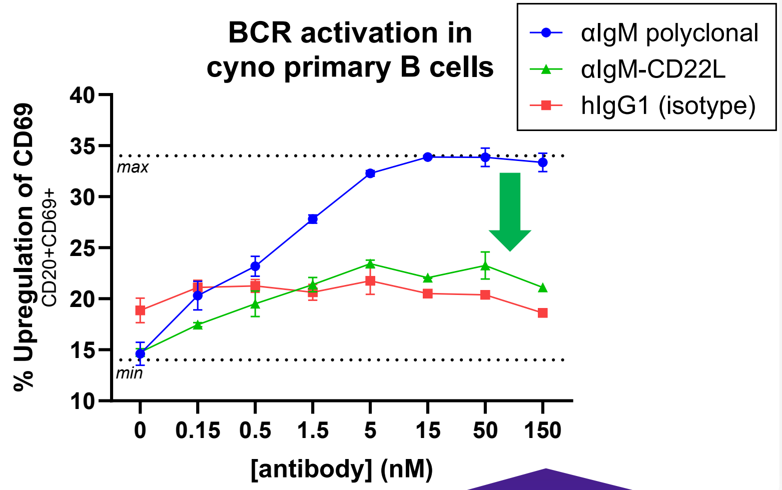
# *In vitro* suppression of BCR activation is achieved with anti-BCR CD22L conjugates in human & cyno PBMCs

## *In vitro* model for B cell suppression




- ✓ CD22L suppresses BCR activation in human B cells
- ✓ Effect not observed with Neu5Gc native glycan



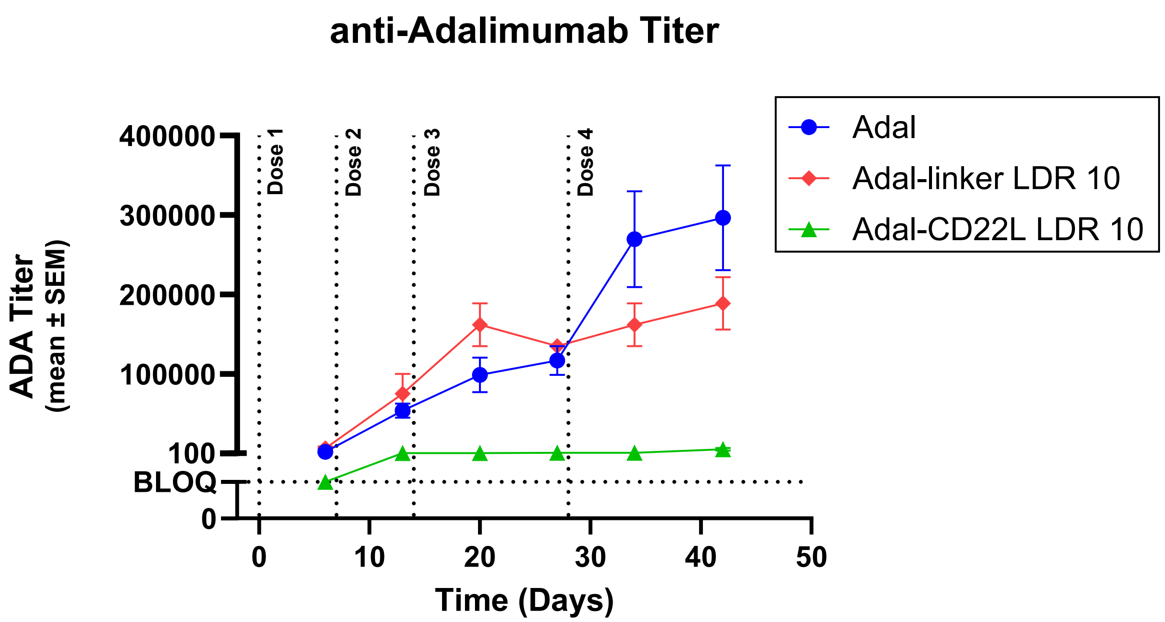

- ✓ CD22L binds and suppresses BCR activation on cyno PBMCs
- ✓ Mechanism is functional across mouse, human and cyno B cells

➢ ***Key finding:*** Native glycan not sufficient for suppression of BCR activation, affinity must be increased >100-fold

ADAXION THERAPEUTICS

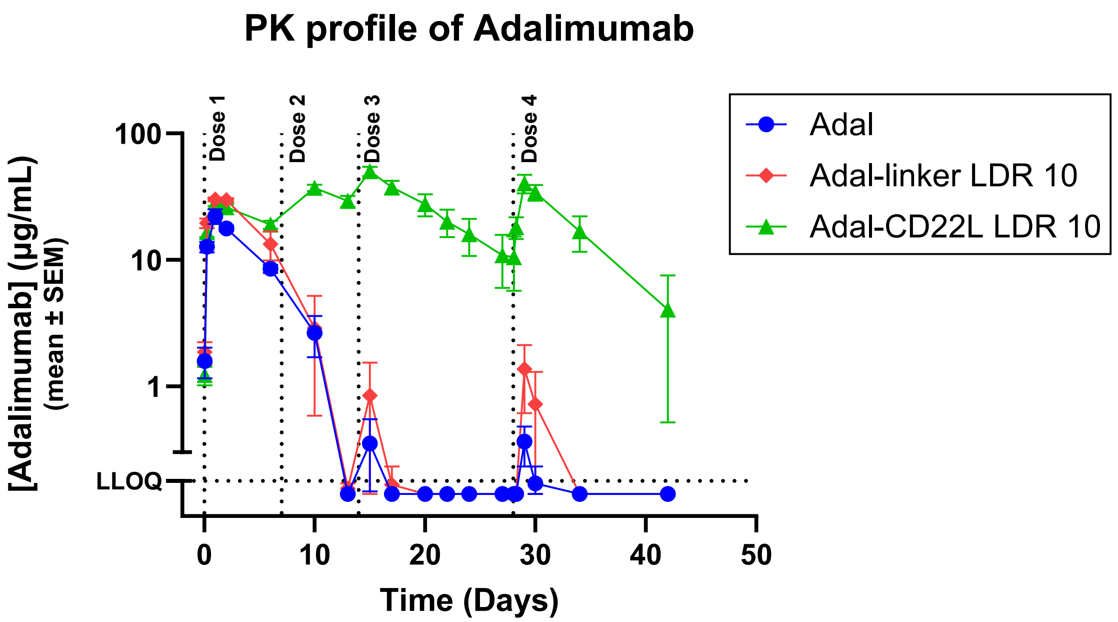
# Anti-TNFα conjugated with CD22L suppresses ADA and rescues PK exposure in rodents

## CD22L conjugated Adalimumab suppressed ADA titers after repeat dosing in Bl/6 Mice




**Dose: 4 mg/kg**
**SC: D0, D7, D14, D28**
**N=5 per group**

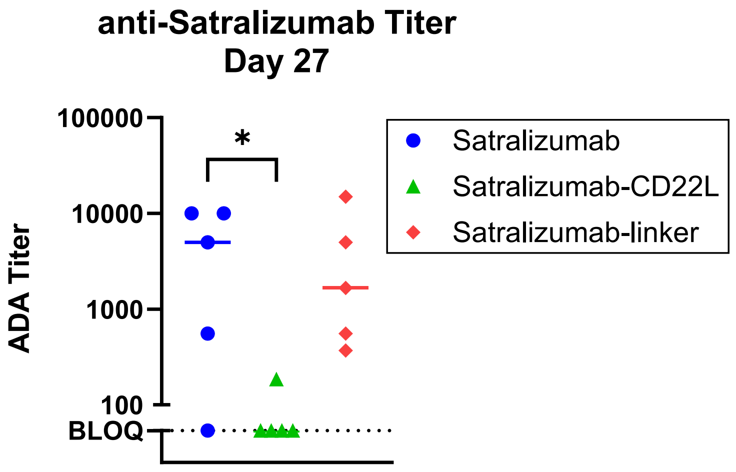
## Exposure is rescued for Adalimumab-CD22L conjugate




Adal= Adalimumab

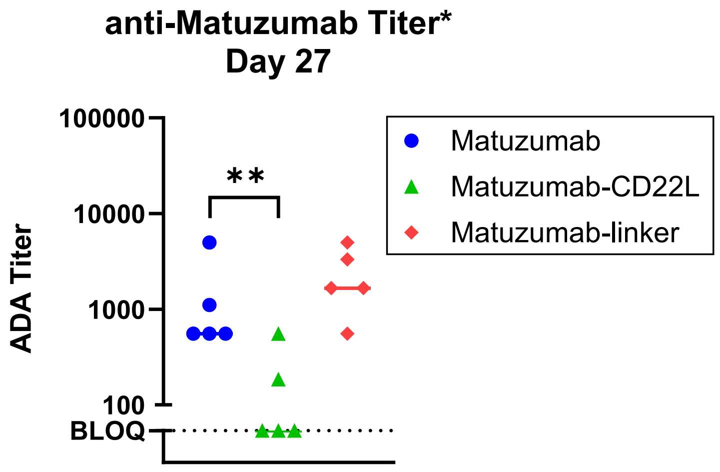
ADAXION THERAPEUTICS

# ADAx platform enables ADA suppression across antibody and bispecific formats in mice



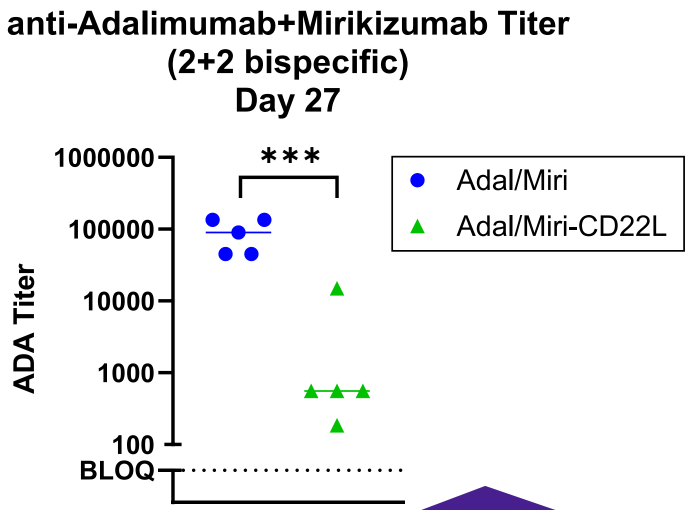

- ✓ Anti-IL6R antibody
- ✓ IV dosing weekly
- ✓ PEG conjugate demonstrates epitope masking not contributing to ADA suppression

**Dose: 5 mg/kg, 4 total doses**
**N=5 per group**




- ✓ Anti-EGFR antibody
- ✓ SC dosing weekly
- ✓ Suppression in presence of adjuvant

**Dose: 5 mg/kg, 4 total doses**
**N=5 per group**
***Adjuvant added to all samples**

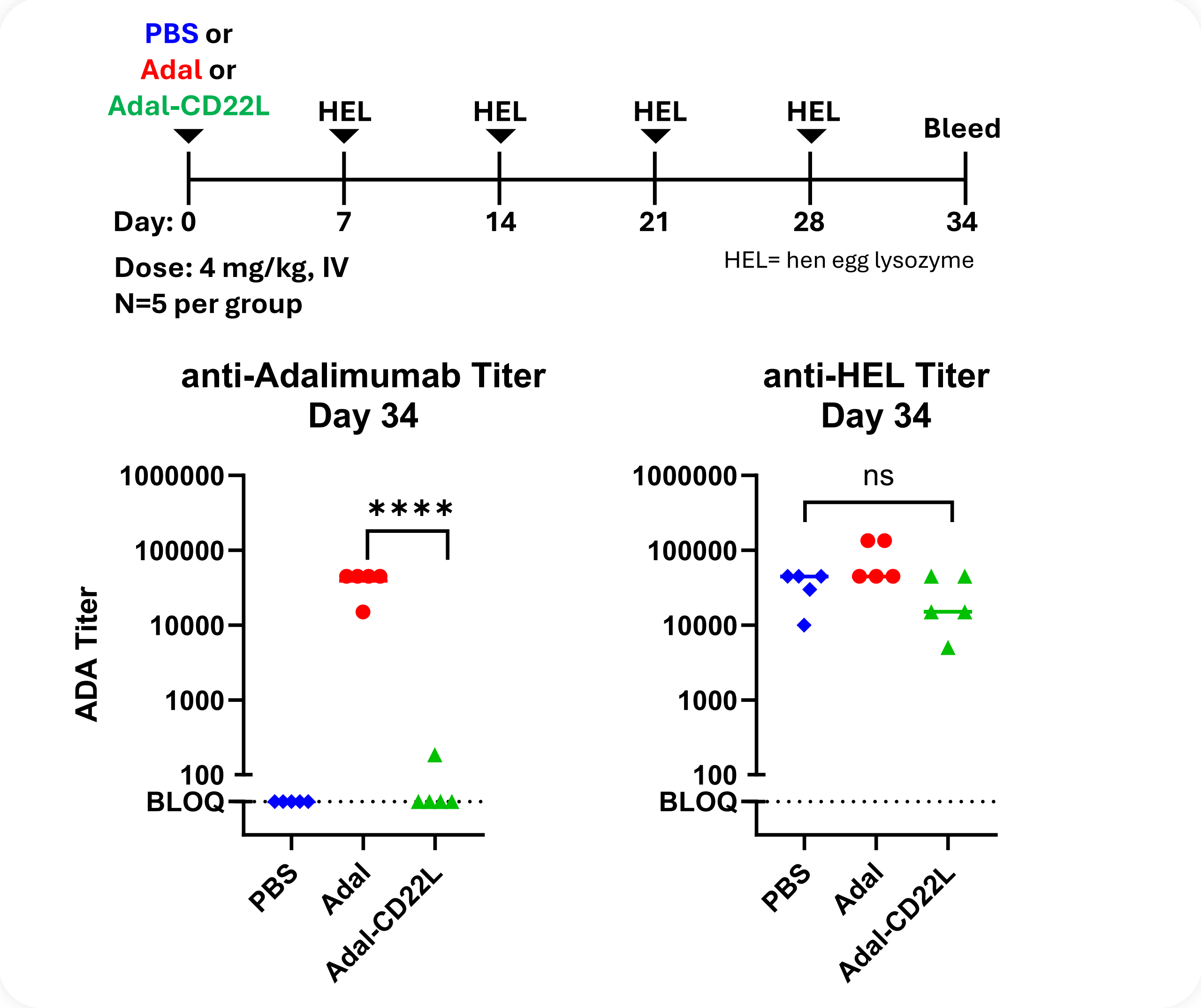



- ✓ Anti-TNFα/IL-23 bispecific
- ✓ Suppression of ADA associated with 2+2 bispecific
- ✓ SC dosing weekly

**Dose: 2 mg/kg, 4 total doses**
**N=5 per group**

ADAXION THERAPEUTICS

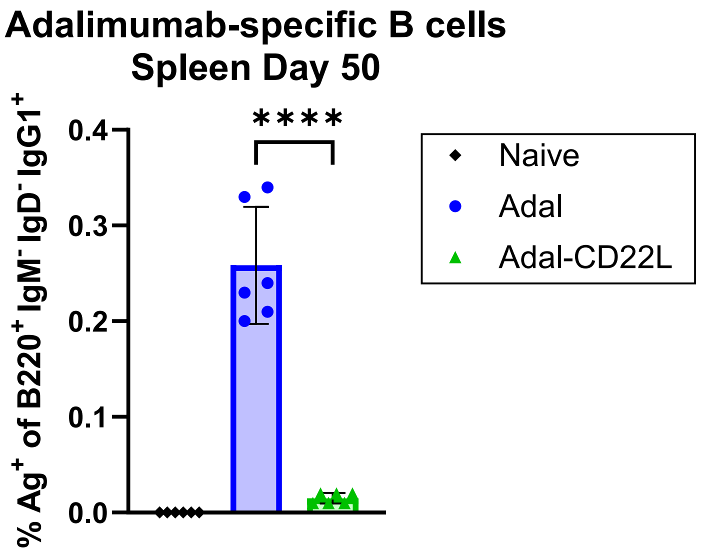
# CD22L conjugate does not alter B cell response to other non-conjugated antigens




- Conjugated Adal-CD22L demonstrates strong anti-Adalimumab ADA suppression
- Adalimumab-CD22L conjugate does not affect the ADA response to the non-conjugated HEL challenge
- ***Key finding:*** Mechanism is not broadly immuno-suppressive, CD22L administration does not affect the B cell response to other antigens

# Adalimumab-specific B cells are absent after Adal-CD22L treatment, while global B cell populations are unchanged

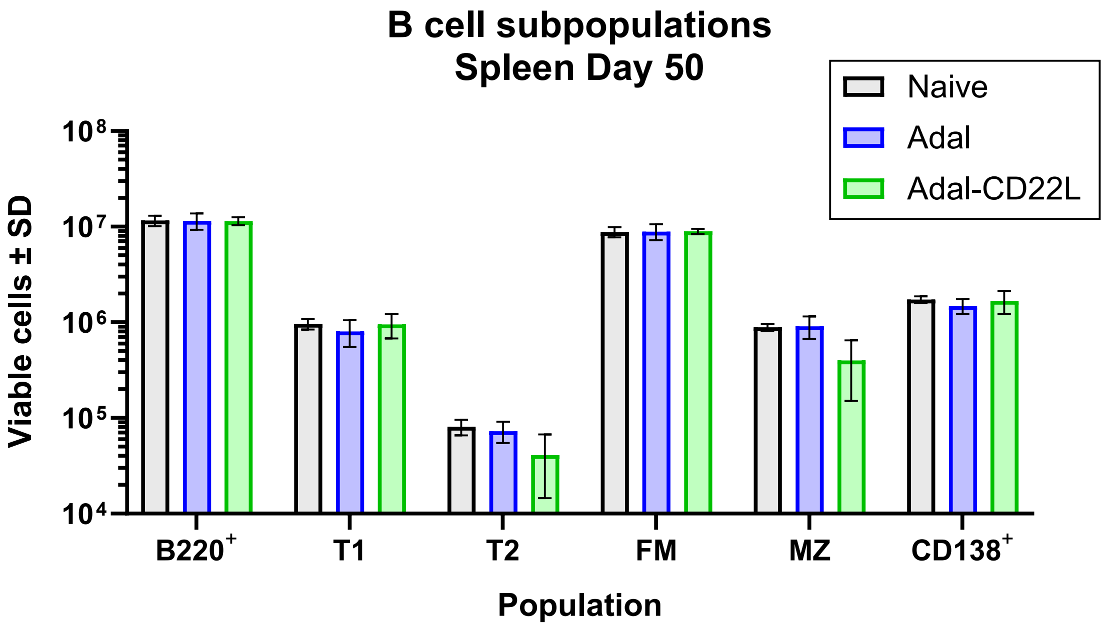
## Adalimumab-specific B cells are absent in Adal-CD22L group




**Antigen-specific B cells analyzed with Adal-AF488**

**Dose: 4 mg/kg, SC: 4 weekly doses**

## No significant global B cell changes observed with Adal-CD22L

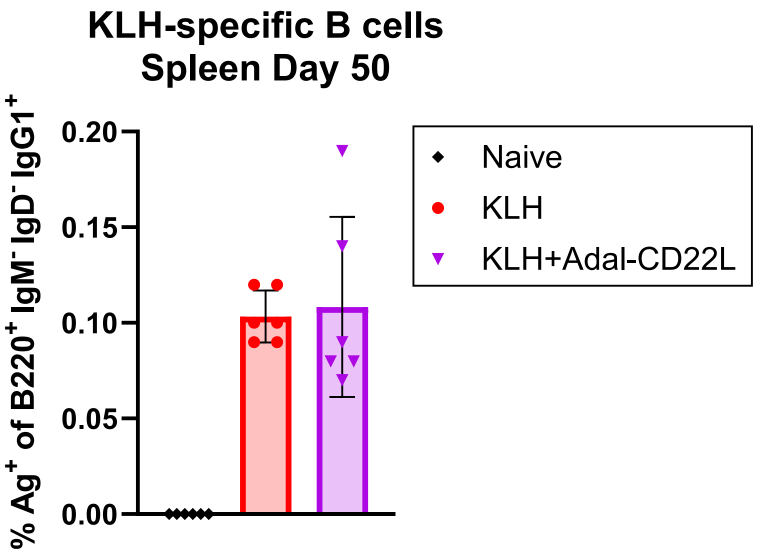



T1, T2= Transitional B cells
FM=Follicular mature B cells
MZ= Marginal Zone B cells
CD138+= plasma cells

**Dose: 4 mg/kg, SC: 4 weekly doses**

# B cell population is maintained to non-conjugated KLH antigen when co-dosed with Adal-CD22L

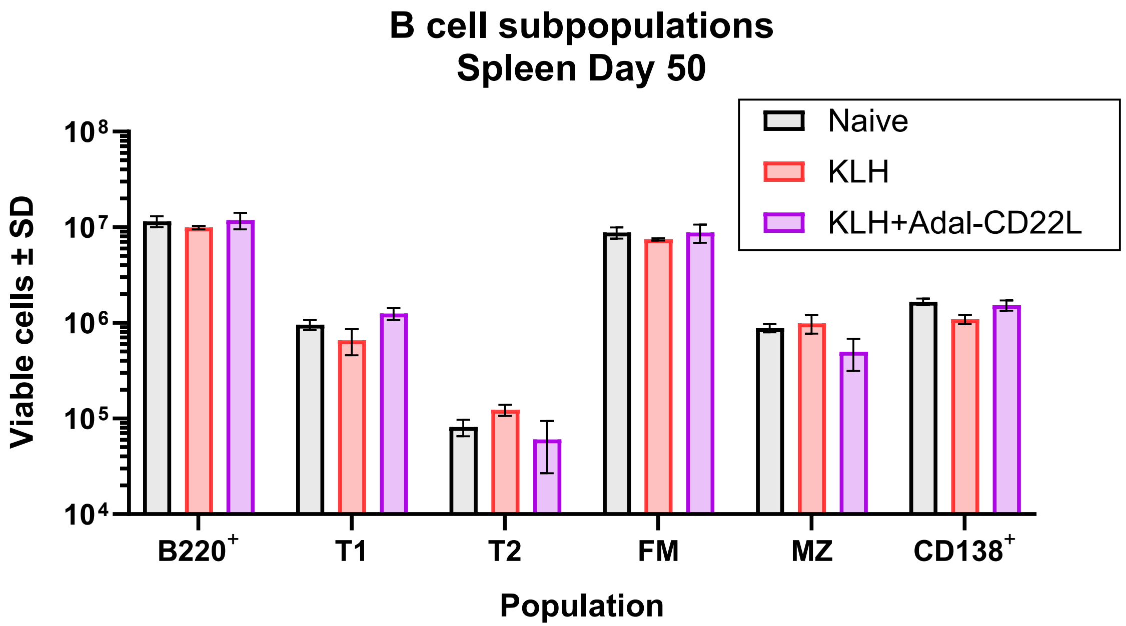
## Co-dosing KLH and Adal-CD22L did not affect KLH response




**Antigen-specific B cells analyzed with KLH-AF488**

**4 weekly doses:**
**KLH: 1 mg/kg + adjuvant, IP**
**Adal-CD22L: 4 mg/kg, SC**

## No significant global B cell changes observed with co-dosing Adal-CD22L

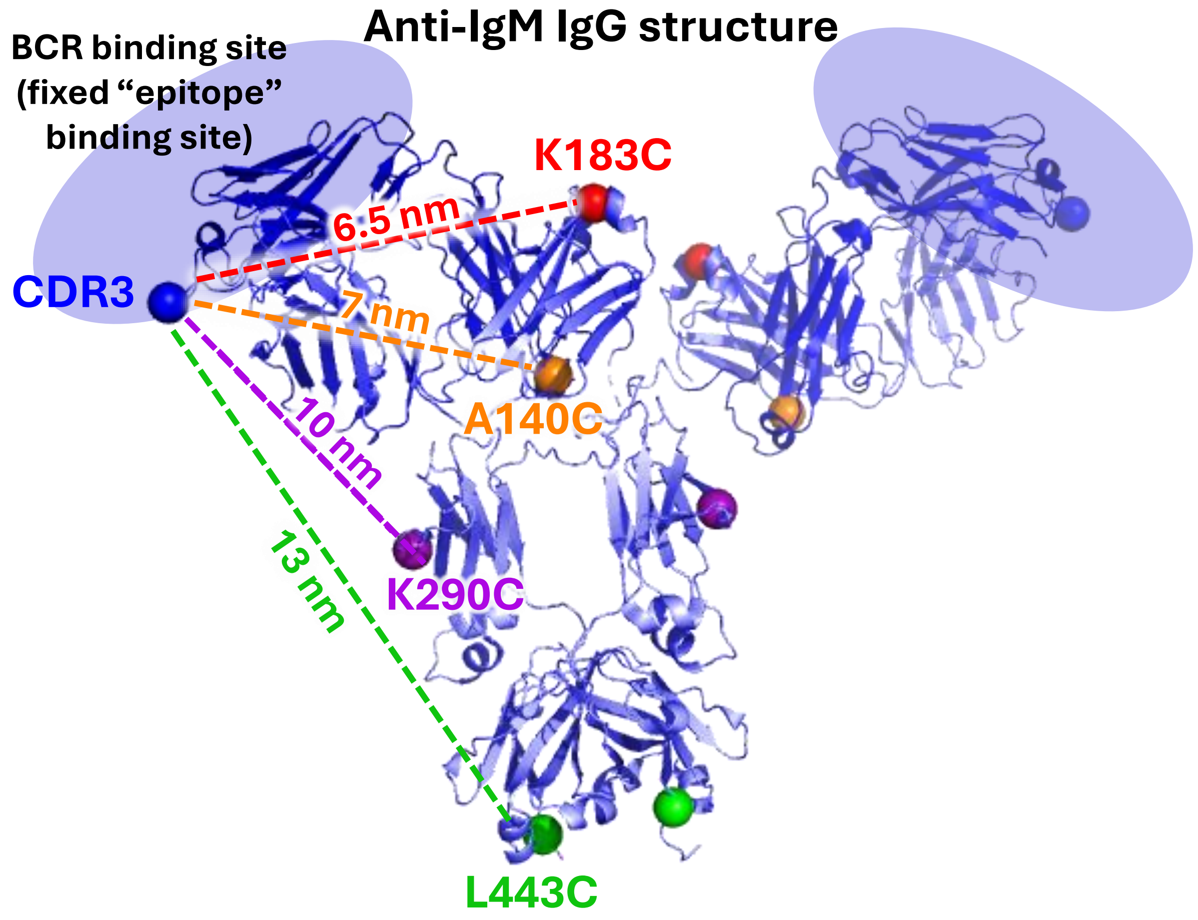


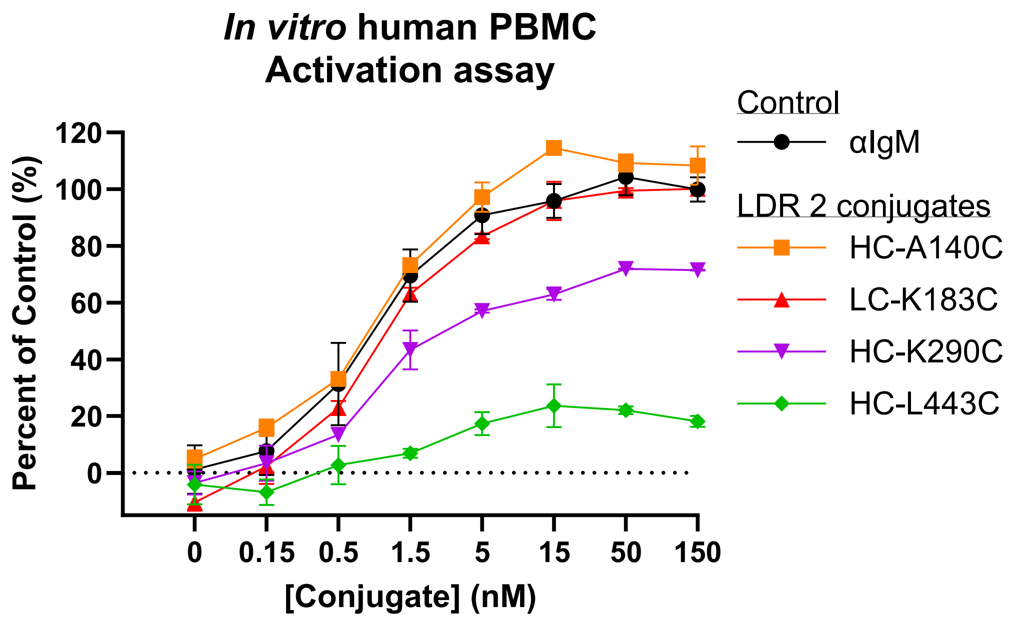

T1, T2= Transitional B cells
FM=Follicular mature B cells
MZ= Marginal Zone B cells
CD138+= plasma cells

**4 weekly doses:**
**KLH: 1 mg/kg + adjuvant, IP**
**Adal-CD22L: 4 mg/kg, SC**

ADAXION THERAPEUTICS

# Co-engagement of BCR and CD22L is distance dependent in controlled B cell activation assay

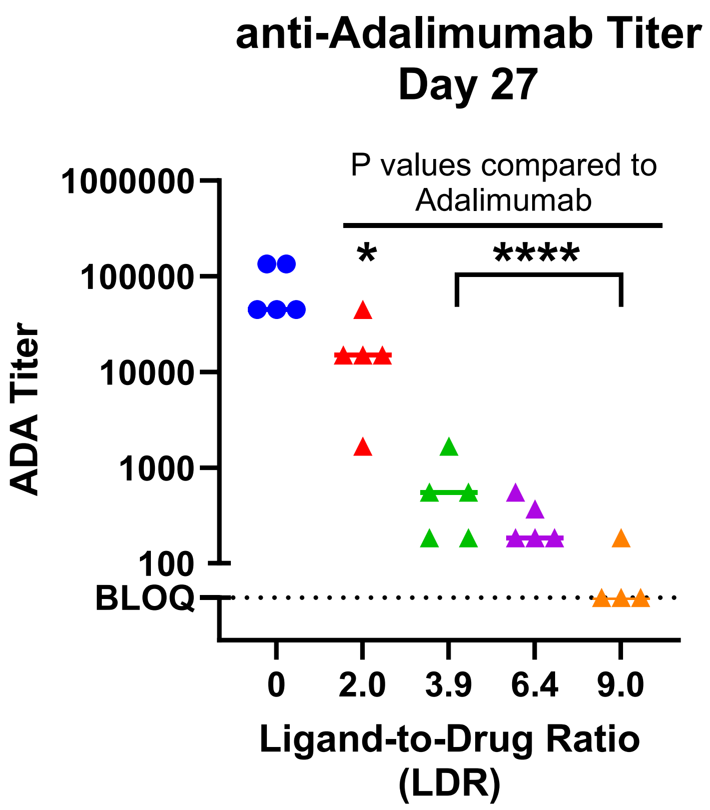



- BCR "epitope" engagement is fixed at CDRs with anti-IgM antibody
- Cysteine conjugation of CD22L allows precise control of CDR to CD22L distance
- ***Key finding:*** Suppression of BCR activation increases as CD22L is moved further from the CDR3 ("epitope" binding site)

ADAXION THERAPEUTICS

# Higher Ligand-to-Drug Ratio (LDR) results in better ADA suppression in mice



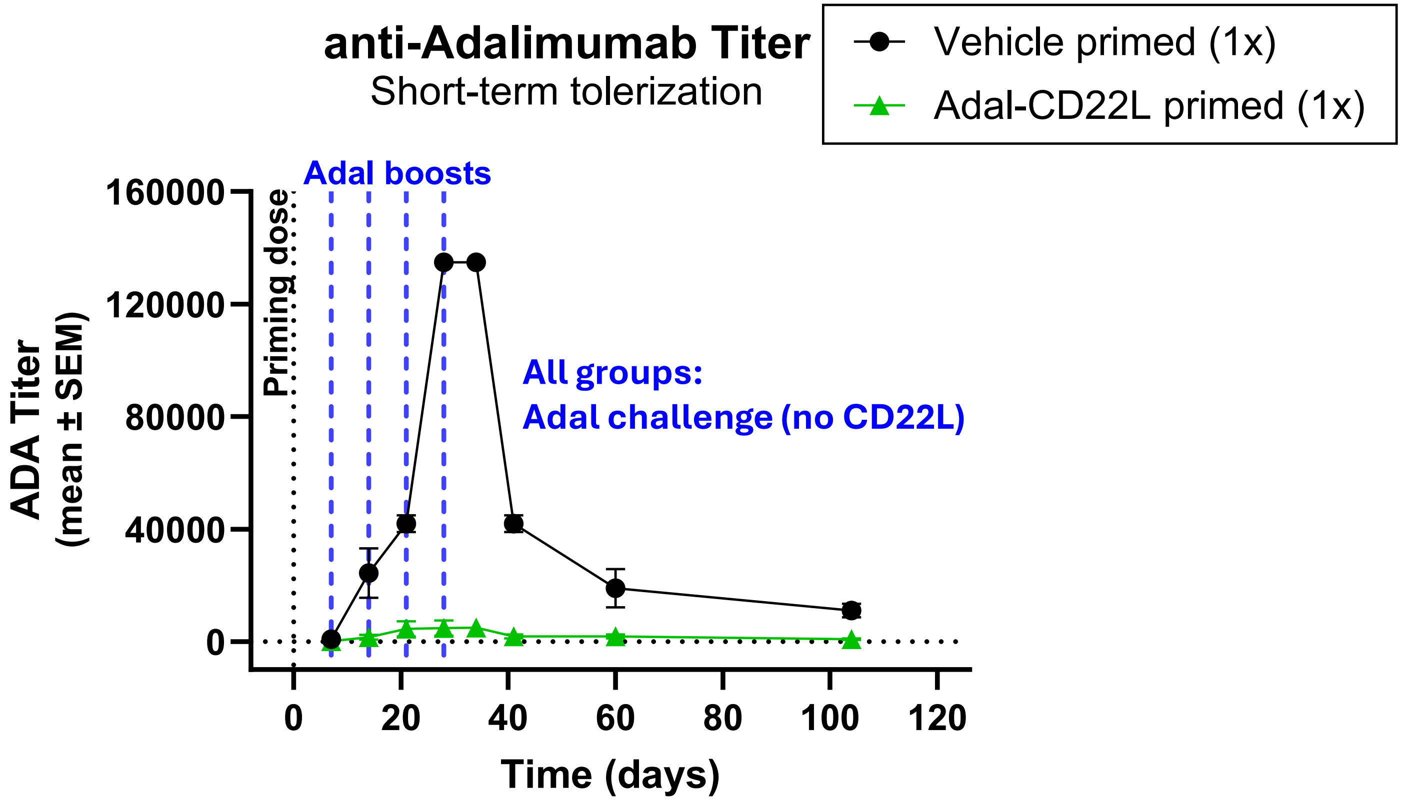

**Dose: 4 mg/kg, SC, weekly, 4 total doses**
**N=5 per group**

- Examined variable LDRs via random lysine conjugation for ADA suppression in mice after 4 weekly injections
- ADA suppression increased as LDR increased
- Previous study showed no epitope masking at LDR ≥ 11, indicating trend is CD22L dependent
- ***Key finding:*** Can increase ADA suppression with higher LDR conjugates

# Single priming dose of Adalimumab-CD22L rapidly tolerizes mice to Adalimumab

- Primed mice with single dose of Adal-CD22L or vehicle and rechallenged all groups with non-conjugated Adalimumab 7 days later
- Mice primed with Adal-CD22L demonstrate ADA suppression even after 4 weekly challenge doses of Adalimumab
- ***Key finding:*** CD22L tolerization mechanism is rapid

## Single dose of Adal-CD22L tolerizes mice to Adal challenge beginning 7 days later

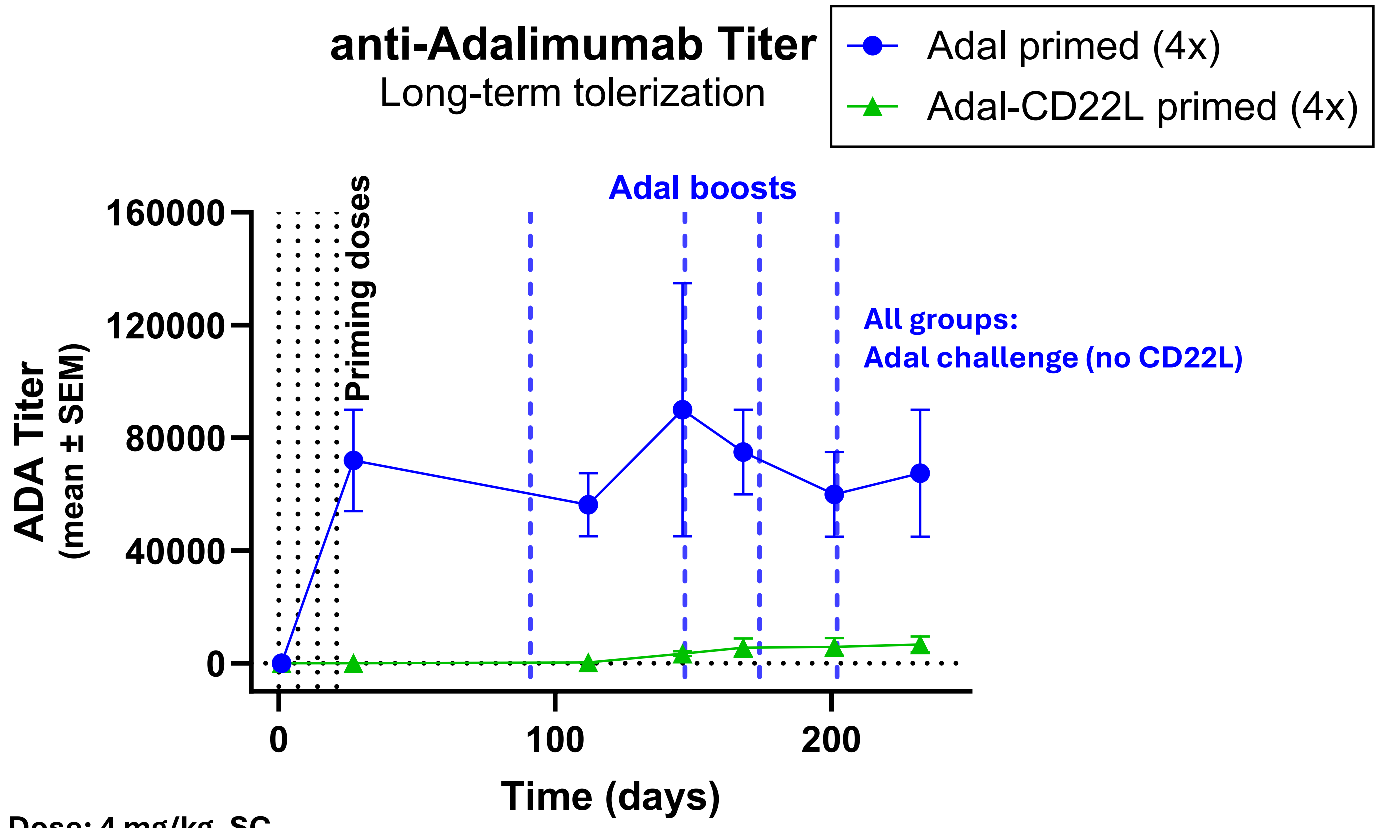



Dose: 4 mg/kg, SC
N=5 per group

# Prophylactic treatment with Adalimumab-CD22L enables durable tolerization to subsequent non-conjugated Adalimumab

- Primed mice with 4 weekly doses of Adalimumab or Adal-CD22L
- All groups were challenged with non-conjugated Adalimumab beginning at day 91
- Mice primed with Adal-CD22L demonstrate ADA suppression out to 200 days
- ***Key finding:*** CD22L conjugate tolerization is durable long-term

## Durable Adal tolerization out to 200 days with only 4 priming doses of Adal-CD22L

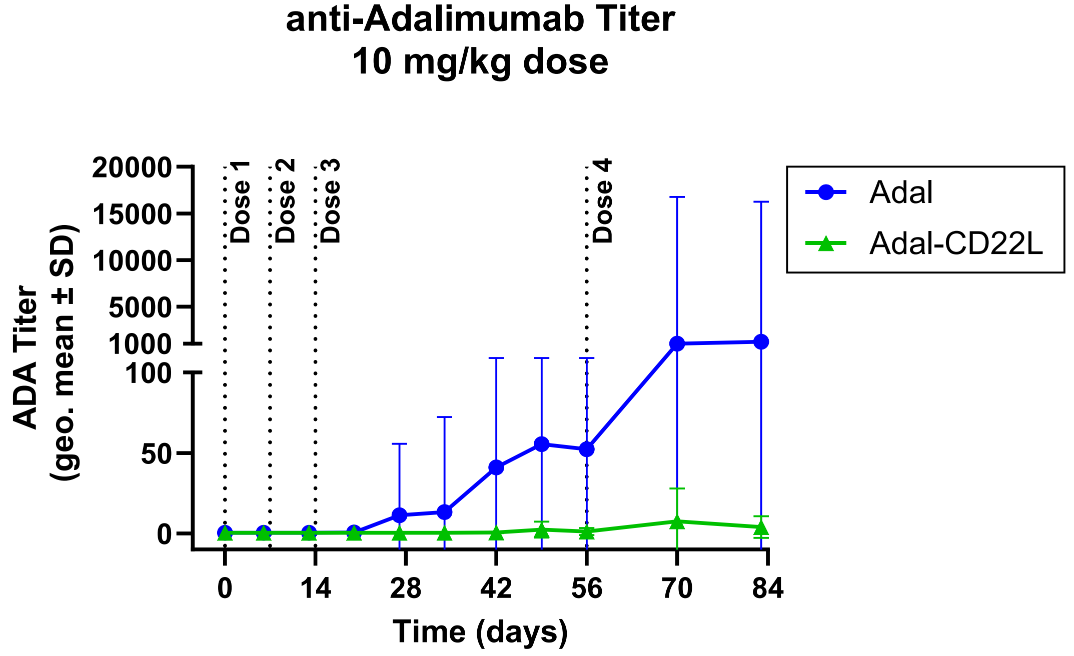



Dose: 4 mg/kg, SC
N=5 per group

ADAXION THERAPEUTICS

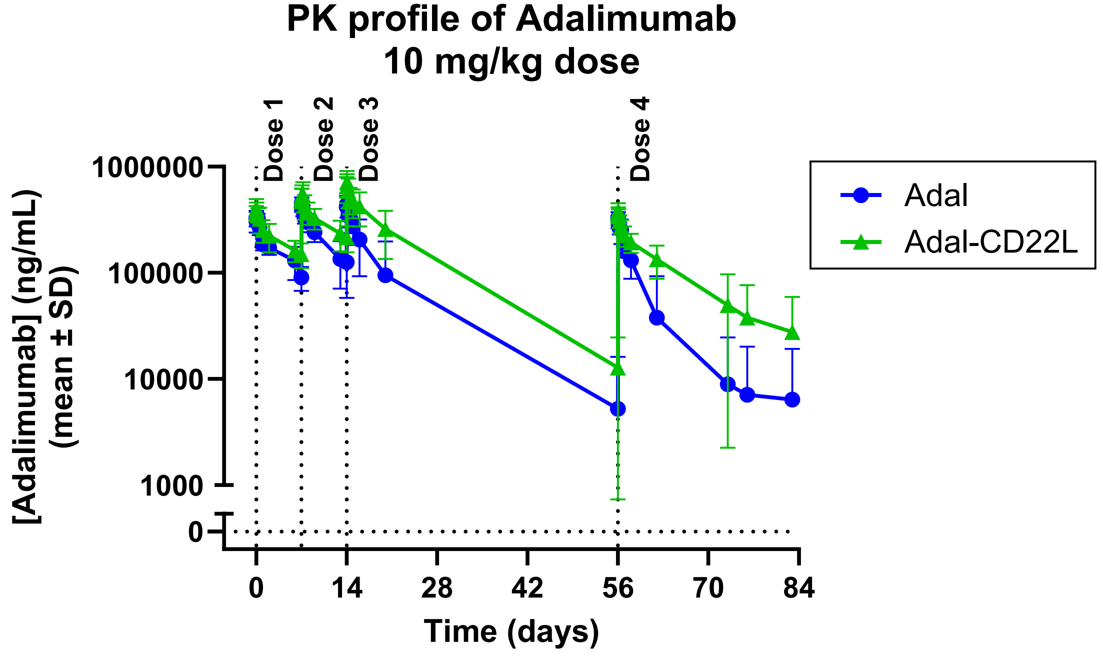
# Adalimumab conjugated with CD22L potently and durably suppresses ADA in primates

## Adal-CD22L suppresses ADA development in cynos




IV: D0, D7, D14, D56
N=5 per group

## Exposure is improved with Adal-CD22L in comparison to non-conjugated Adal




*adal: Adalimumab; SigL: CD22L*

ADAXION THERAPEUTICS

# ADAXION's pipeline of CD22L conjugated therapeutics

| Programs | Indications | Discovery | Lead Optimization | IND Enabling | Phase 1 |
|---|---|---|---|---|---|
| ADX-001<br>Bifunctional antibody, targeting TNFα & IL-23 | Ulcerative colitis, Crohn's disease, psoriatic arthritis | | | | |
| ADX-002<br>Uricase enzyme | Refractory Gout | | | | |
| ADX-003<br>EndoS enzyme Therapy for rapid IgG neutralization | Transplant rejection, immune thrombocytopenia | | | | |
| ADX-004<br>Bifunctional antibody, targeting TL1A & IL-23 | Ulcerative colitis, Crohn's disease | | | | |
| IDE<br>IgG degrading enzyme | Autoimmune diseases | | | | |

**Check out our bispecifics poster #86 on ADX-001!**

ADAXION THERAPEUTICS