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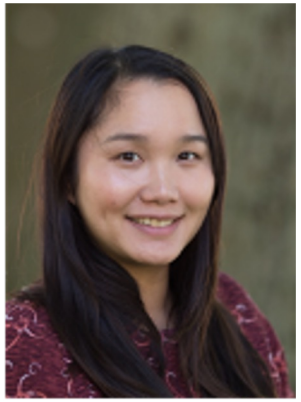
THERAPEUTICS

Cerberus Therapeutics: Overview

- A platform company exploiting an alpaca-derived single domain antibody fragment ("VHH") to create novel therapeutics for immune modulation
- Founded by Dr. Novalia Pishesha, Prof. Hidde Ploegh, & Prof. Harvey Lodish
- Product concept is a VHH-antigen/drug conjugates in a pure protein formulation to induce antigen-specific immune tolerance
- Preclinical mouse models of autoimmune diseases demonstrate not only long-lasting protection prophylactically, but also therapeutic benefits to halt and ameliorate disease progression
- Foundational paper on tolerance induction has been published in Nature Biomedical Engineering in June 2021(PMID: 34127819)
- Patent application covering these technologies was filed in February 2021 and CerberusTx has signed an exclusive licensing agreement with the Boston Children's Hospital for this IP

2

The Team



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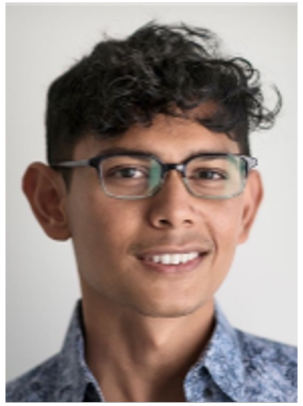

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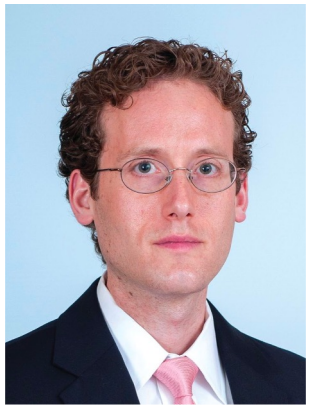

Michael Dougan, M. D. , Ph.D.
Scientific Advisor

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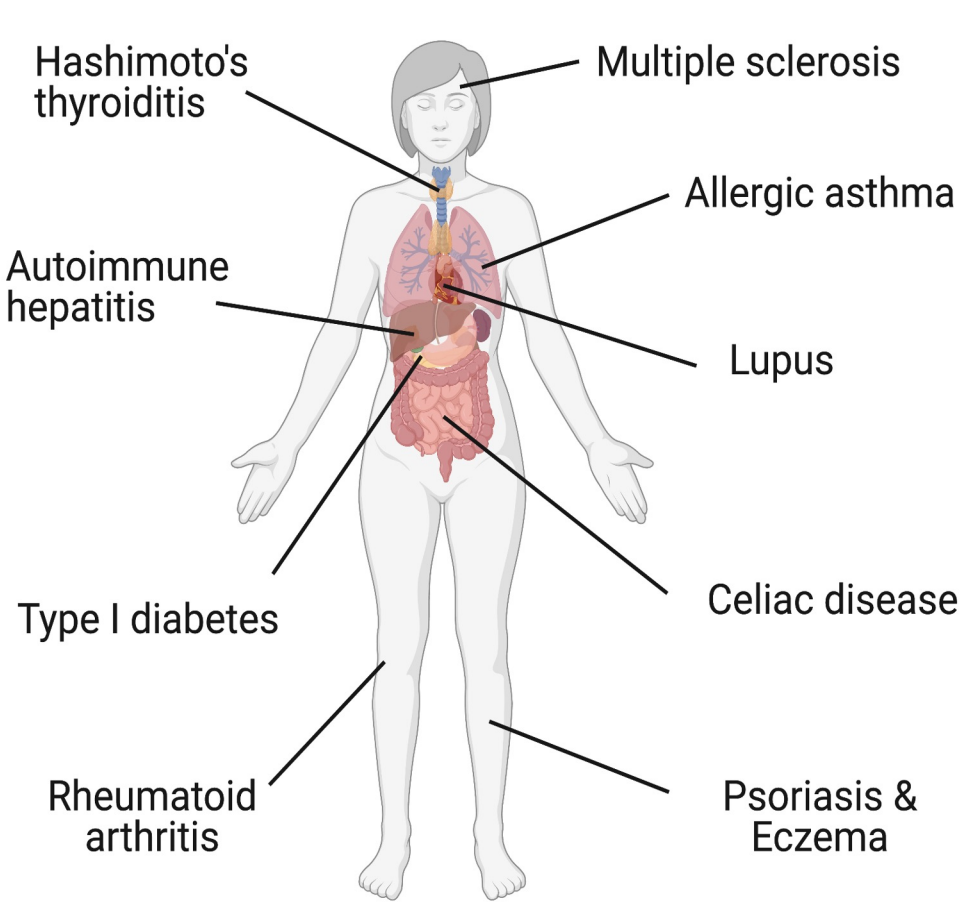
Cerberus Therapeutics: Overview

- A platform company exploiting an alpaca-derived single domain antibody fragment ("VHH") that binds to Major Histocompatibility Complex Class II (MHCII) to create novel therapeutics for immune modulation
- Product concept is a VHH_{MHCII}-antigen-corticosteroid conjugates in a pure protein formulation to induce antigen-specific immune tolerance
- A highly modular platform able to address various autoimmune diseases with a single dose administration

Autoimmune Diseases



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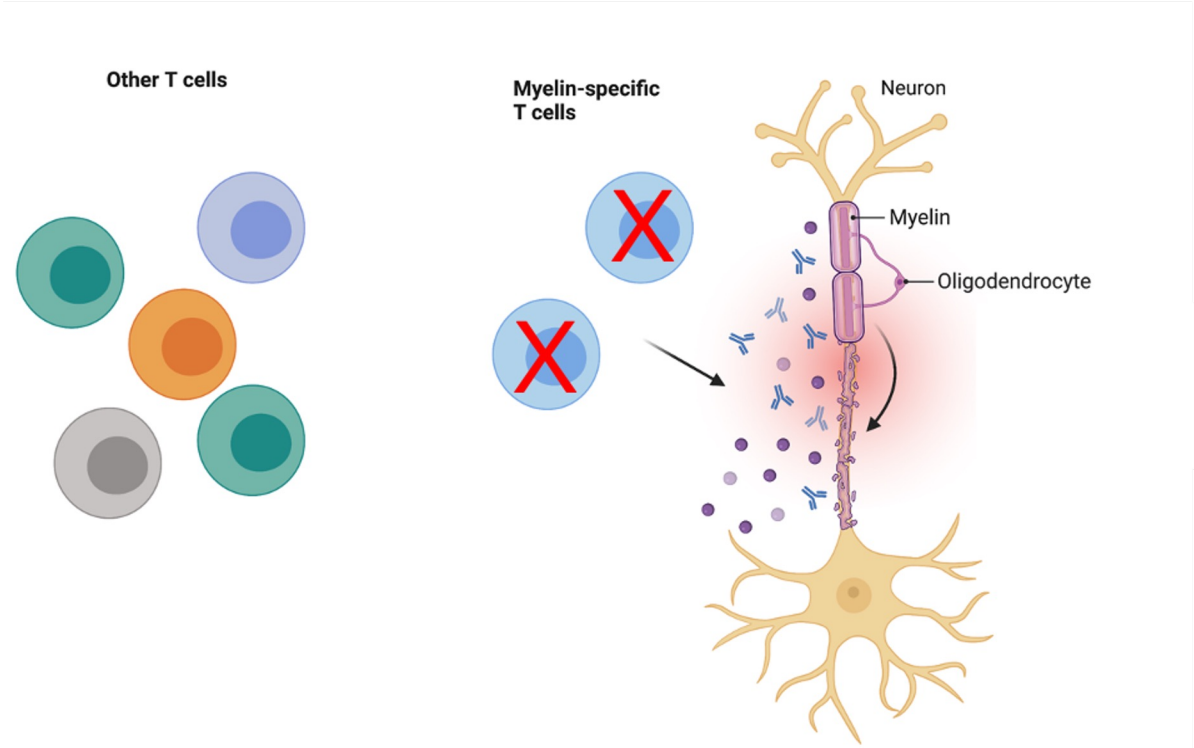
The strategy: deleting the specific immune response to cure autoimmunity

An Example: Multiple Sclerosis



A therapy with the following characteristics:

Easy to Scale Up

Easy to Distribute

A Single Dose

Lifetime protection

Addresses multiple diseases

Work across MHC allotypes/immune genetic background

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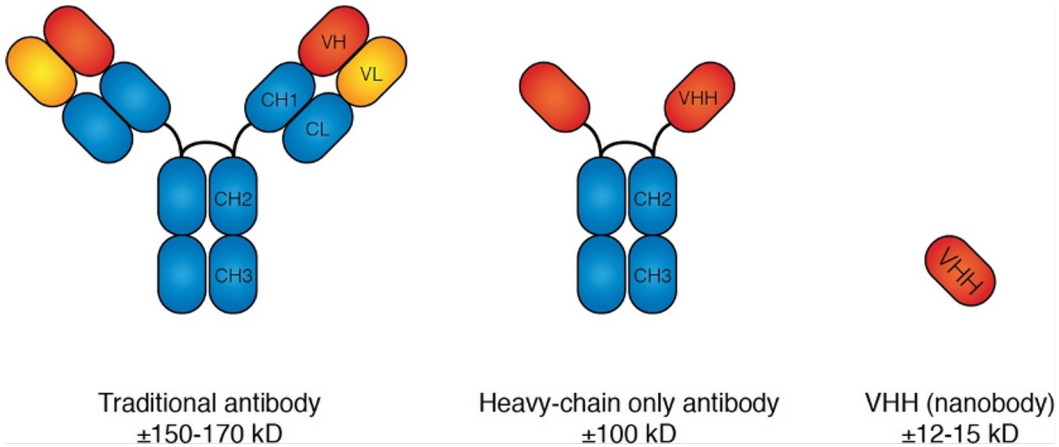
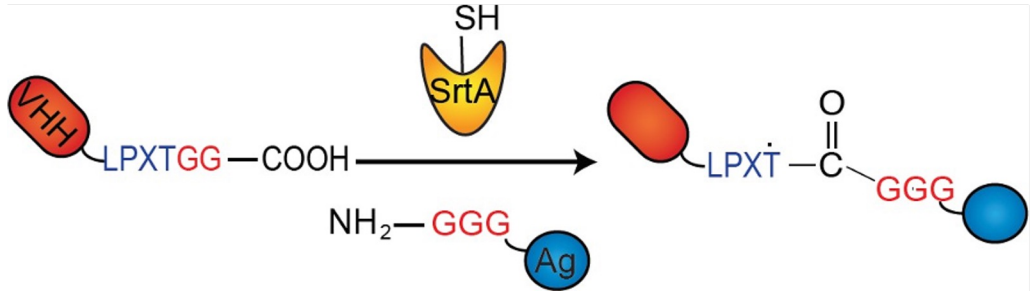
Advantages of VHHs as therapeutics; it is small but mighty

VHHs are the smallest naturally-derived antibody fragments with antigen binding affinities comparable to those of conventional antibodies



- Superior biochemical and biophysical properties
- Much shorter circulatory half-life – minimizing systemic exposure to toxic compounds
- Excellent targeting properties – ensuring that once on site, self-immolating linkers will release the payload predominantly at the intended site
- Easily produced by recombinant expression in *E. coli cells* at kilogram levels

Sortase allows covalent conjugation of VHHs with a wide array of peptides, proteins, drugs, and other types of molecules



- Mix-and-match VHHs with antigens of natural or synthetic origins to treat specific autoimmune diseases
- Co-delivery of immune modulators (e.g. cytokines or other drugs) => Covalent conjugation allows specific targeting, enhanced efficacy
- VHH manipulability => Small size and easy manufacturing in bacterial cells, capability to link VHHs to proteins with post-translational modifications or non-genetic payloads. Whole protein delivery eliminates the need to isolate specific peptide epitopes

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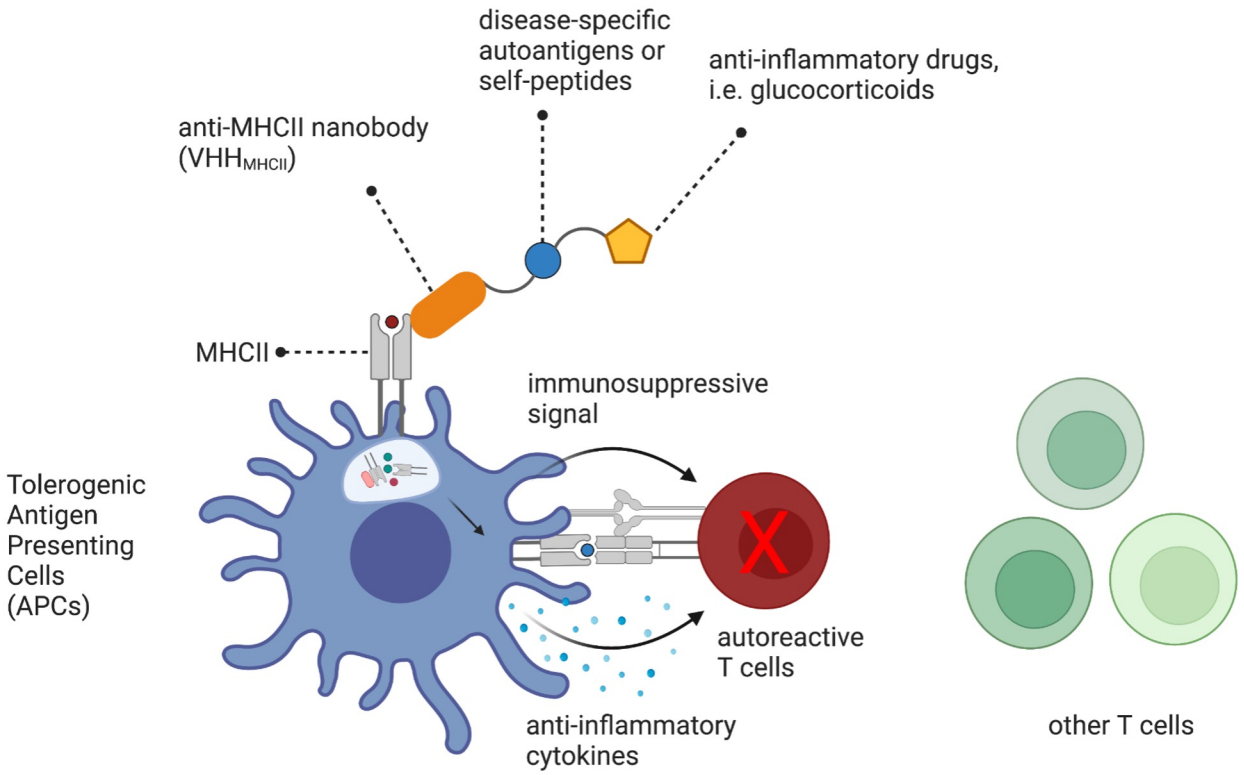
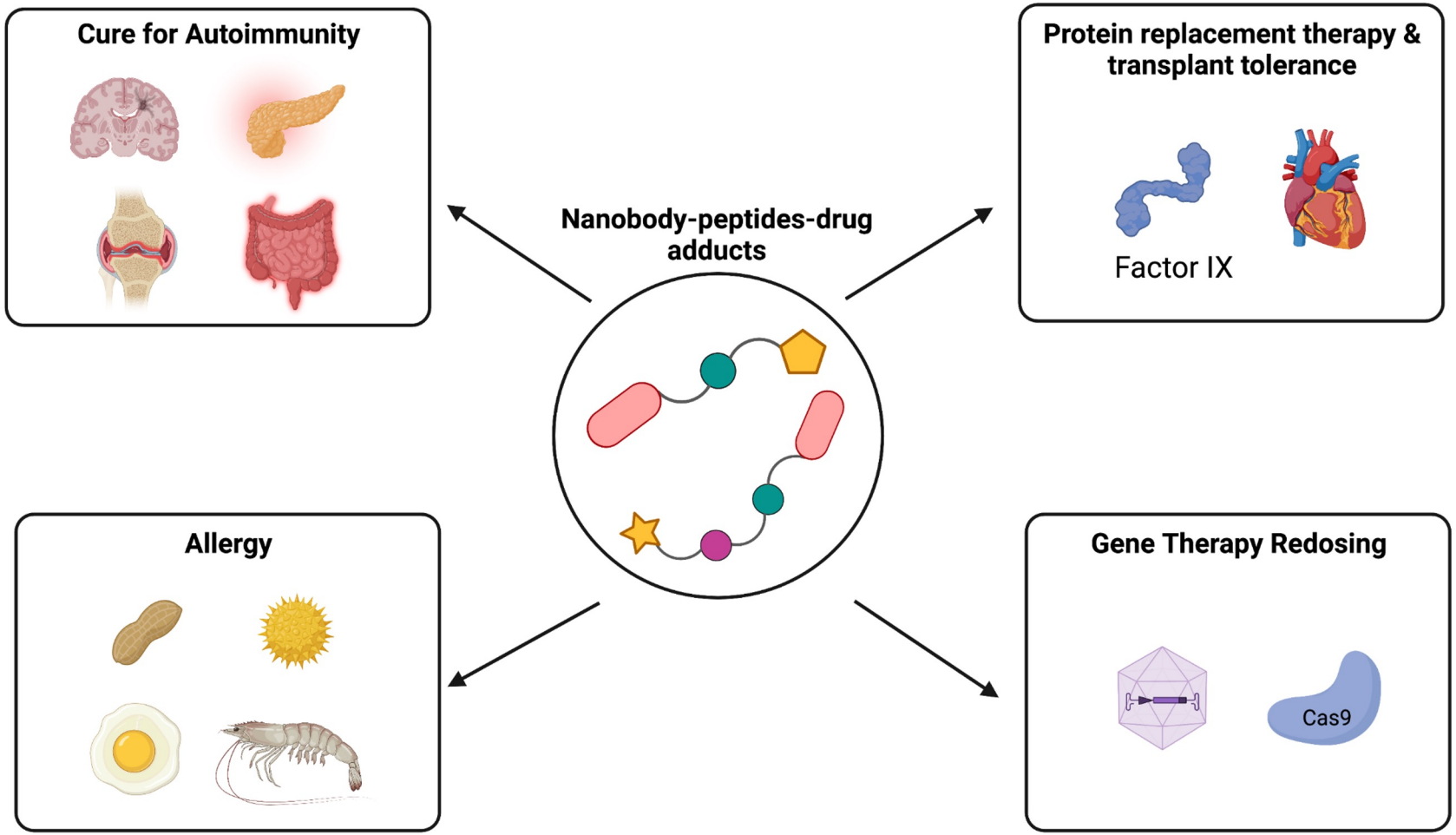
CerberusTx's adducts effectively eliminate only the unwanted immune response



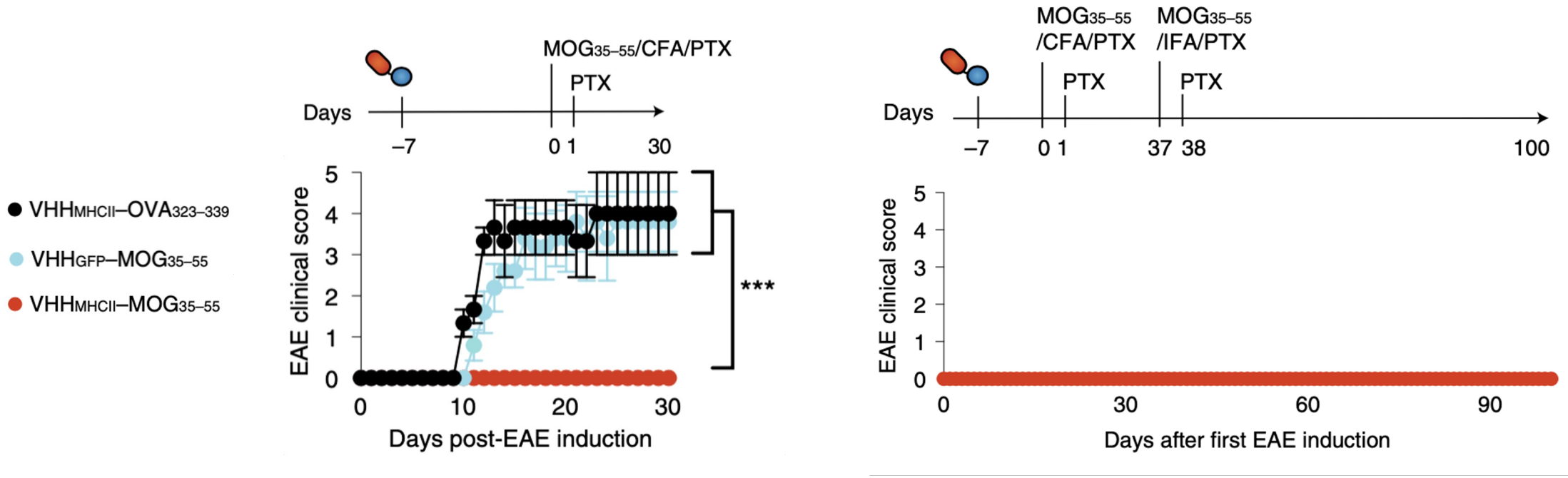
- VHH$_{MHCII}$ recognizes the major histocompatibility complex II (MHCII) on the APC cell surface.
- To induce tolerance to an antigen of interest, we conjugate the antigen to VHH$_{MHCII}$ using sortase to yield a VHH$_{MHCII}$-antigen adducts.
- Delivery of the VHH$_{MHCII}$-antigen adduct under non-inflammatory conditions (to steady state APCs or co-delivery of VHH$_{MHCII}$-drug adducts) leads to antigen uptake, processing, and antigen presentation by tolerogenic APCs.
- When autoreactive T cells specific for the antigen "see" these APCs, they will become anergic, undergo deletion, or differentiate into regulatory T cells, resulting in antigen-specific tolerance.

CerberusTx employs nanobody-based adducts to selectively mute immune responses



A single dose of provides durable protection in an MS model

A single dose of VHH_{MHCII}-MOG_{35-55} provides durable protection against induction of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, and in a rechallenge model



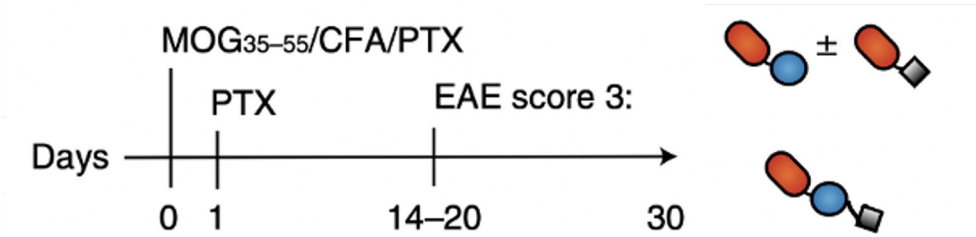
MOG = Myelin Oligodendrocyte Glycoprotein
CFA = Complete Freund's Adjuvant
PTX = Pertussis Toxin

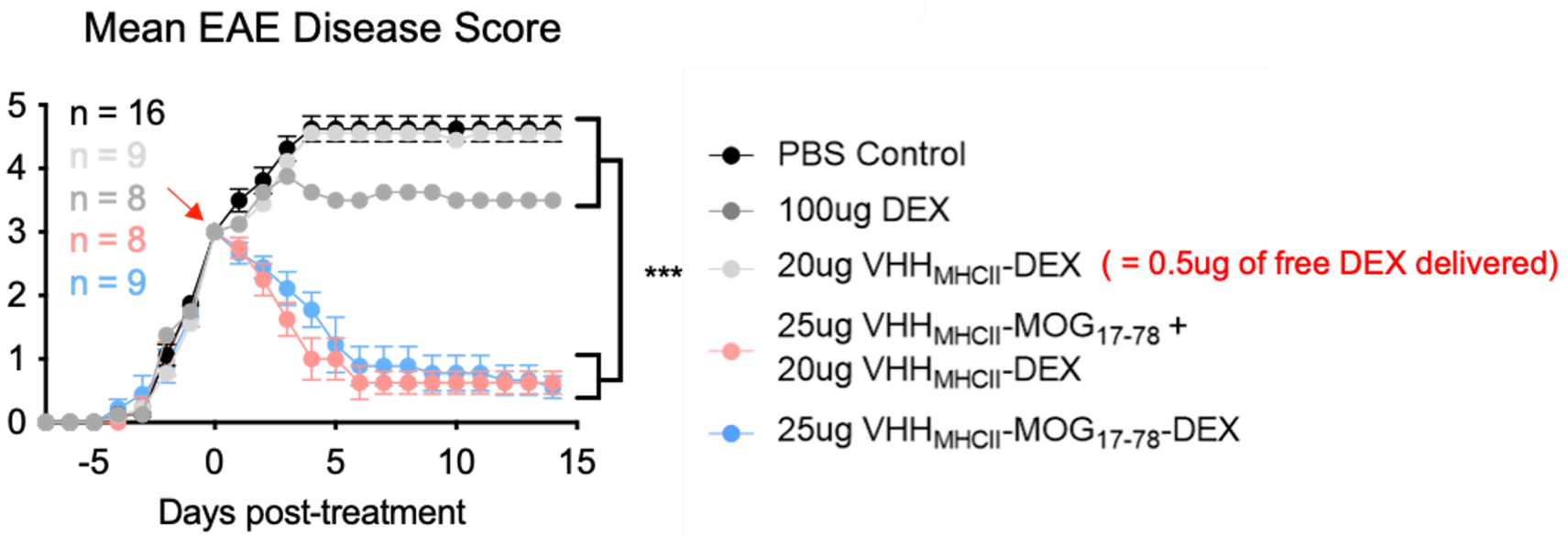
Clinical scores:
1 - limp tail
2 - partial hind leg paralysis
3 - complete hind leg paralysis
4 - complete hind and partial front leg paralysis
5 - moribund

Pishesha, Harmand, et al, *Nat Biomed Eng*, 2021

10

A single dose bestows immediate therapeutic benefit in an MS model





We need both antigen and dexamethasone for optimal effect

A single dose bestows immediate therapeutic benefit in an EAE model

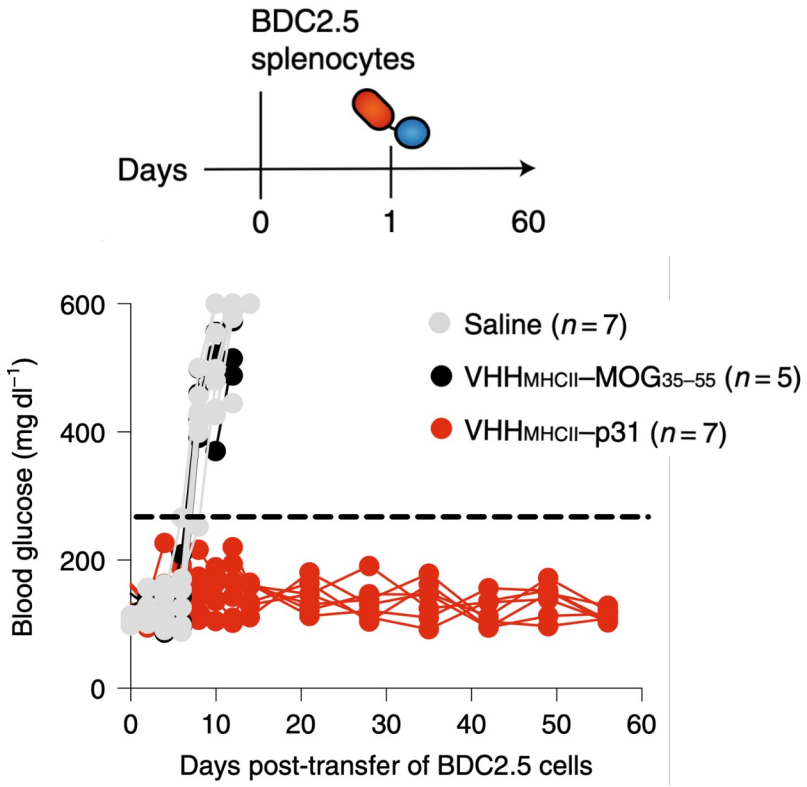
EAE mouse at clinical score 3 (complete hindlimb paralysis)

24h after a single dose of VHH_{MHCII}-MOG_{17-78}-DEX

4 days after a single dose of VHH_{MHCII}-MOG_{17-78}-DEX

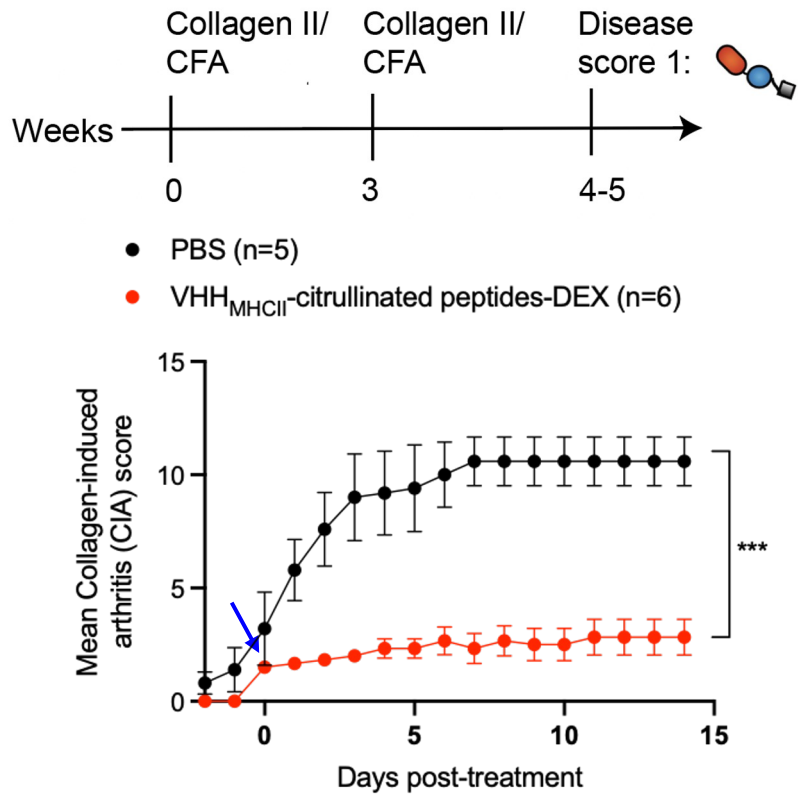
A single dose provides durable protection in a T1D and RA model

T1D (Type 1 Diabetes)



BDC2.5 cells recognize p31 peptide

RA (Rheumatoid Arthritis)



Higher disease score indicates higher degree of joint inflammation, i.e. swollen toes and paws

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