Transforming Patients' Lives Through Precision Immunoengineering in Autoimmune Disease

November 2025

CUE® BIOPHARMA

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This presentation contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

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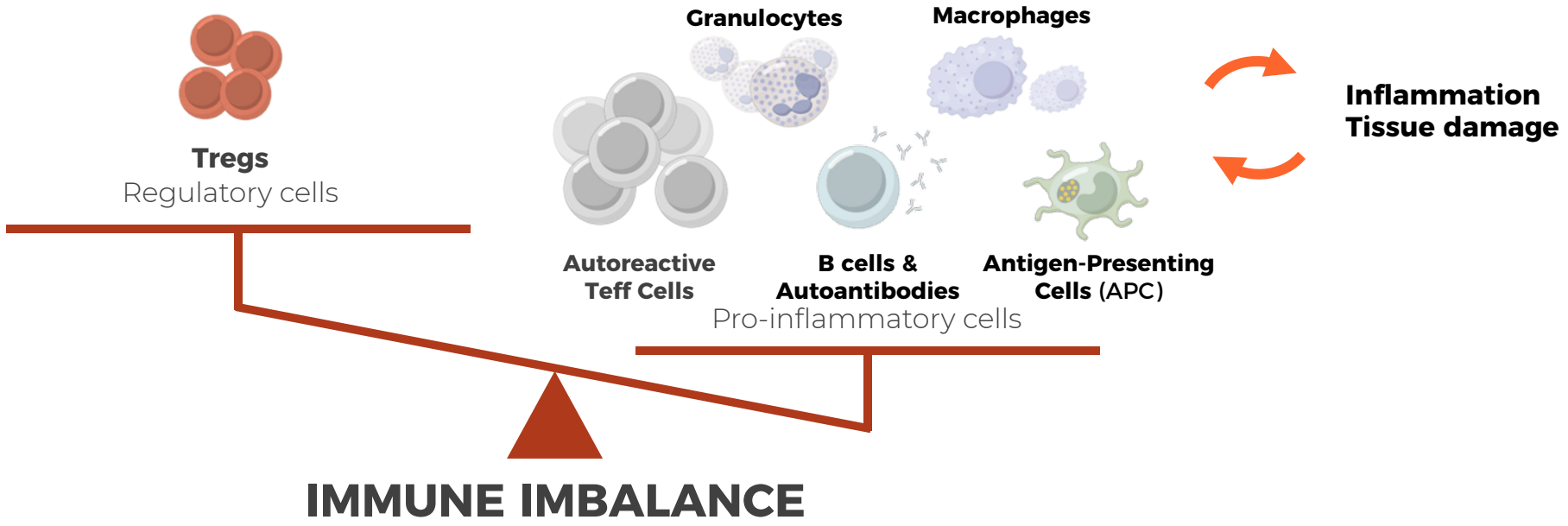
The Problem: Immune Imbalance Underlies Autoimmunity

Regulation is Dominated and Suppressed by Inflammatory Players

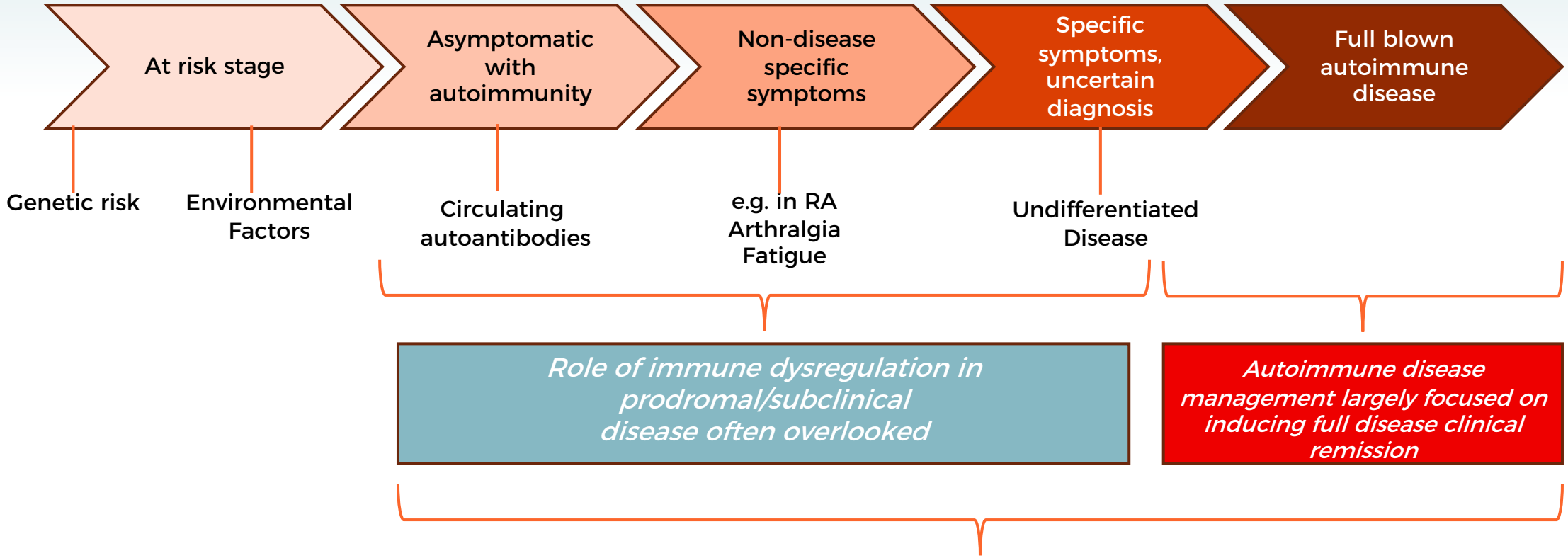
Deficient Regulatory Cells
- ↓ IL-2
- ↓ Treg frequency
- ↓ Treg function
- ↓ Anti-inflammatory/cytokines (e.g. TGFβ and IL-10)

Dominant Pro-Inflammatory Cells
- ↑ Autoreactive Teffs
- ↑ B cells/Autoantibodies
- ↑ Proinflammatory innate immune cells
- ↑ Proinflammatory cytokines (e.g. IL-17 and IL-4/13)



Stages of Autoimmune Disease

Distinct Immunological Characterization of Prodromal Disease Documented for over Three Decades in Major Autoimmune Disorders*



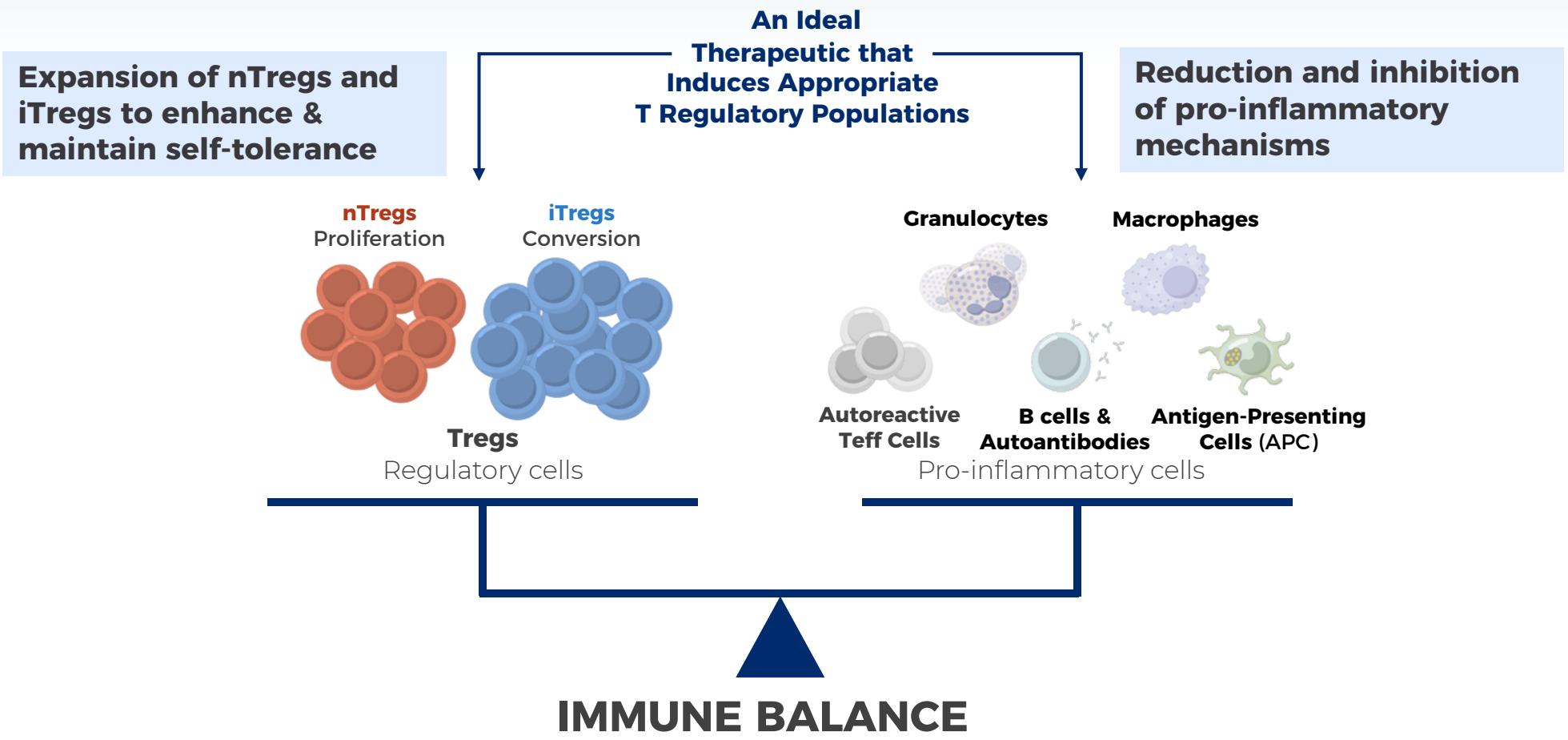
The ideal autoimmune therapeutic can aid in:

1. Controlling Inflammation
2. Resetting the Immune System
3. Homeostasis & Tissue Repair

* Lu. R et al. Journal of Immunity, June 2016, 1-12
Scherer, H.U. Nature Reviews Rheumatology. Vol 18 July 2022

A ‘Master Switch’ of Immune Balance?

Restoring Long-Term Tolerance by Re-Establishing Balance via T Regulatory Cells



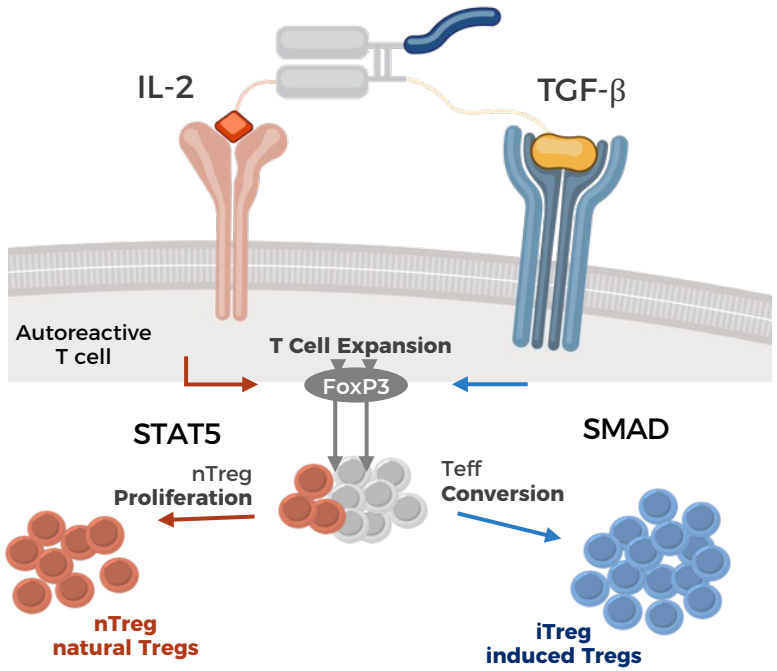
Nobel Prize Confirms the Role of IL-2 and TGFβ in Treg Induction

Critical Signaling Agents to Produce Induced T-regulatory Cells via FOXP3 Gene Upregulation

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

Scientific background 2025

Immune tolerance
The identification of regulatory T cells and FOXP3



TGF-β provides the "GO" signal to turn on the FOXP3 gene

- Primary cytokine that activates the SMAD pathway and directs FoxP3 transcription, protein activation, and conversion of Teff cells to Treg cells
- Contextual Differentiation – steers T cells away from inflammatory lineages towards regulatory lineages

IL-2 provides the "STAY" signal to keep the FOXP3 gene on, expand the Treg cell population, and make the phenotype functional and durable

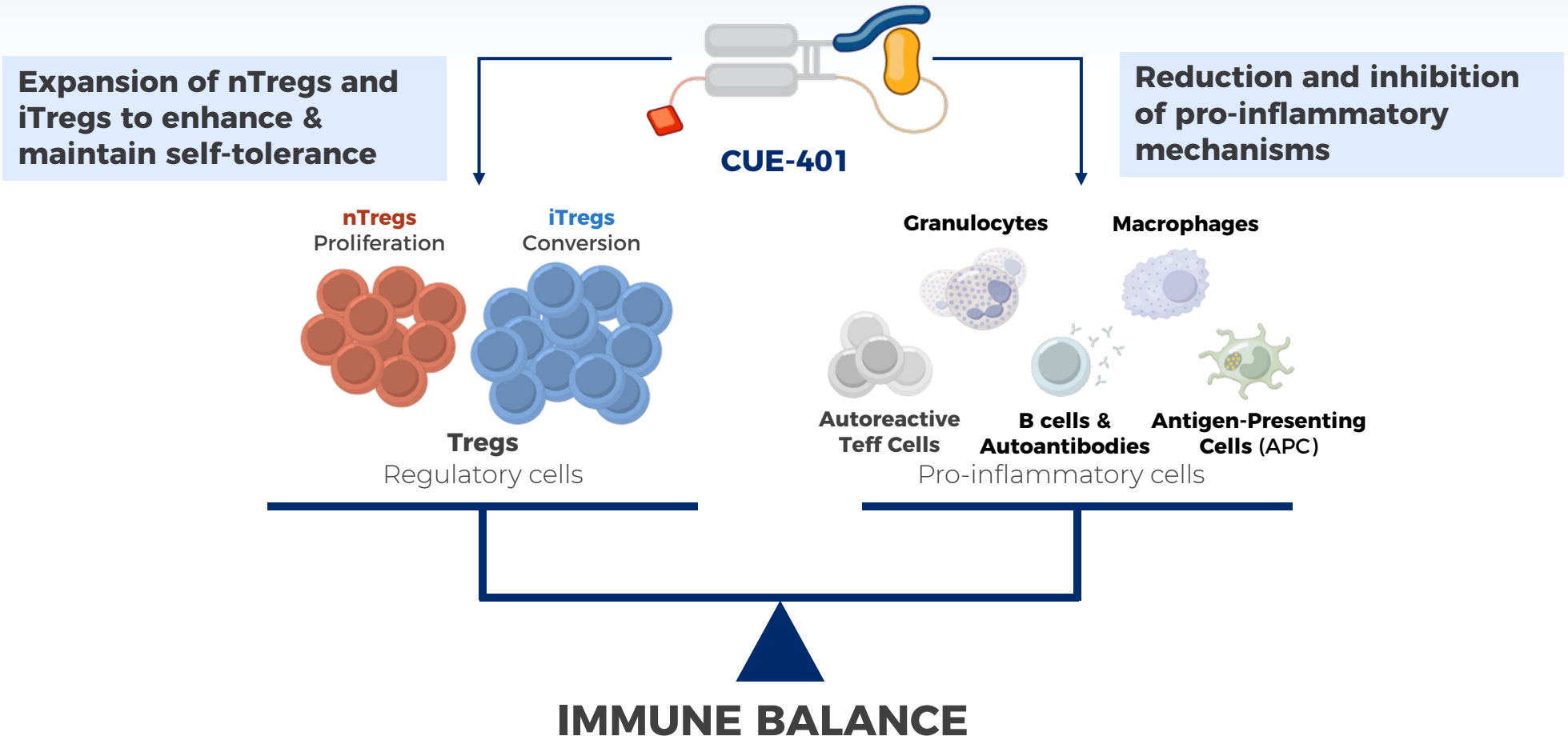
- FoxP3 Stabilization and Maintenance – IL-2 activated STAT5 pathway and TGF-β activated SMAD pathways co-operate to cause stable and high-level expression of FoxP3
- Survival and Expansion – IL-2 acts as a T cell growth factor

FOXP3 – Forkhead Box P3
STAT5 - Signal transducer and activator of transcription 5
SMAD - Suppressor of mothers against decapentaplegic

https://www.nobelprize.org/uploads/2025/10/advanced-medicineprize2025.pdf

CUE 401 - A ‘Master Switch’ of Immune Balance

Restoring Long-Term Tolerance by Re-Establishing Balance via T regulatory cells



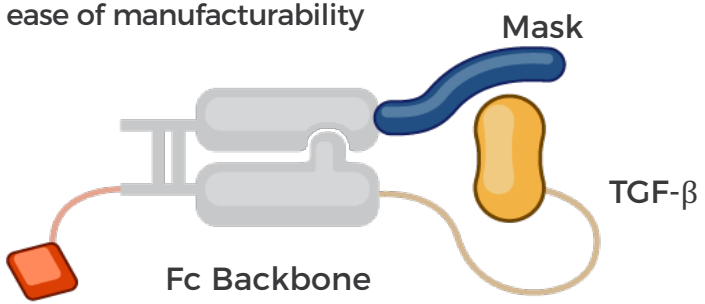
CUE-401: First in Class, Bifunctional Tolerogenic Mechanism

Transformative first-in-class molecule incorporating attenuated components of TGF-β and IL-2

Pipeline in a Product	• Unique next generation mechanism tolerizes multiple cell types involved in autoimmunity • Pre-clinical activity shown in multiple disease models suggests broad application in the autoimmune space
Components* Clinically Derisked	• Incorporates IL-2* and parts of Fc from CUE-100 Series programs already validated in the clinic • Tolerability demonstrated in 3 species (non-GLP)
Defined Path to Clinic	• Manufacturing and IND enabling studies underway
Near-term Value Inflection	• Projected FIH initiation in Q2 2026 and clinical PoC in 2H 2027

Fc Backbone

Allows for simultaneous delivery of both IL-2 and TFG-β, along with ease of manufacturability



TGF-β Variant

Affinity attenuated; improved safety and manufacturability

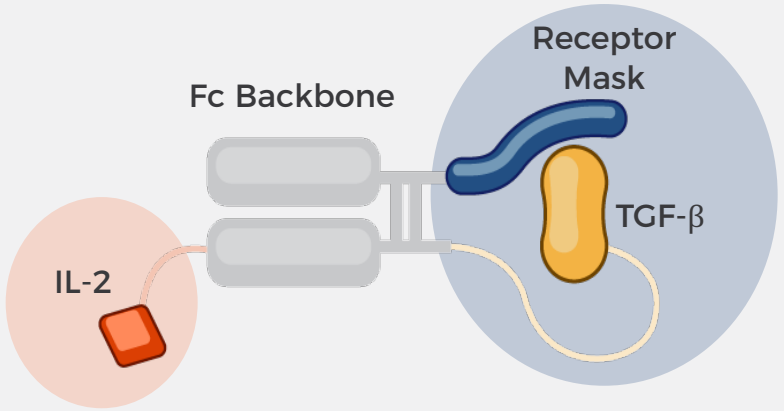
IL-2 Variant

Affinity attenuated; same as in CUE-100 series

CUE-401 Masked Tolerogenic Bifunctional

CUE-401: A "Master Switch" of Immune Balance

Designed with Goal of Restoring Long-Term Tolerance via Re-Establishing Balance



Proprietary IL-2 Mutein

Clinically derisked in close to 150 patients via CUE-100 series

Novel Attenuated TGF-β Mutein

'Breathing Mask' design enables attenuated TGF-β function and clinical-scale manufacturing

Protein design solves classic challenges of TGF-β

- Engineered mask **improves stability and enables clinical scale manufacturing**
- Targeted point mutations reduce affinity of each cytokine and **enhance therapeutic window**
- Fusion protein design **enables co-delivery** of both cytokines to a target cell

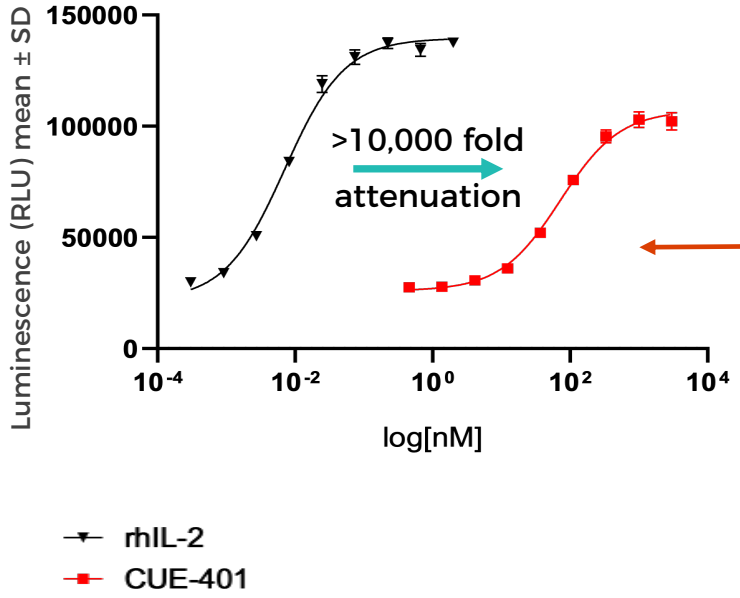
CUE-401 harnesses complementary mechanisms of immunoregulation

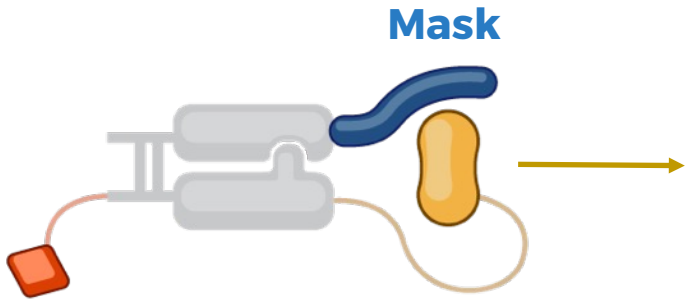
- **Conversion** of autoreactive T effector cells to stable iTregs
- **Expansion** of nTregs without increase in T effector cells
- Potential for **direct regulatory effects** on T effector cells, NK cells, B cells, and dendritic cells via TGF-β

Optimizing Biological Activity via Protein Engineering

Attenuating Cytokine Affinities Retains Key Biologic Functions and Reduces Potential for Effects on Non-Immune Cells

IL-2 Induced Reporter

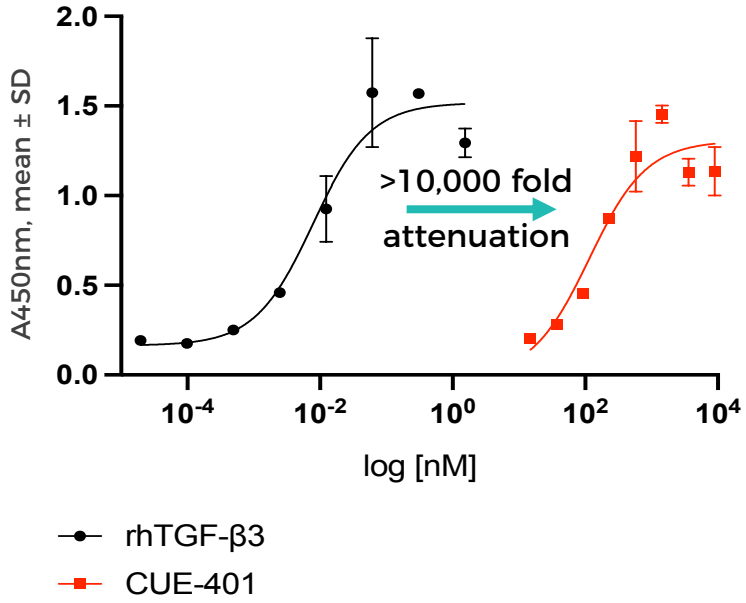




IL-2 Variant
Affinity attenuated; same as in CUE-100 series

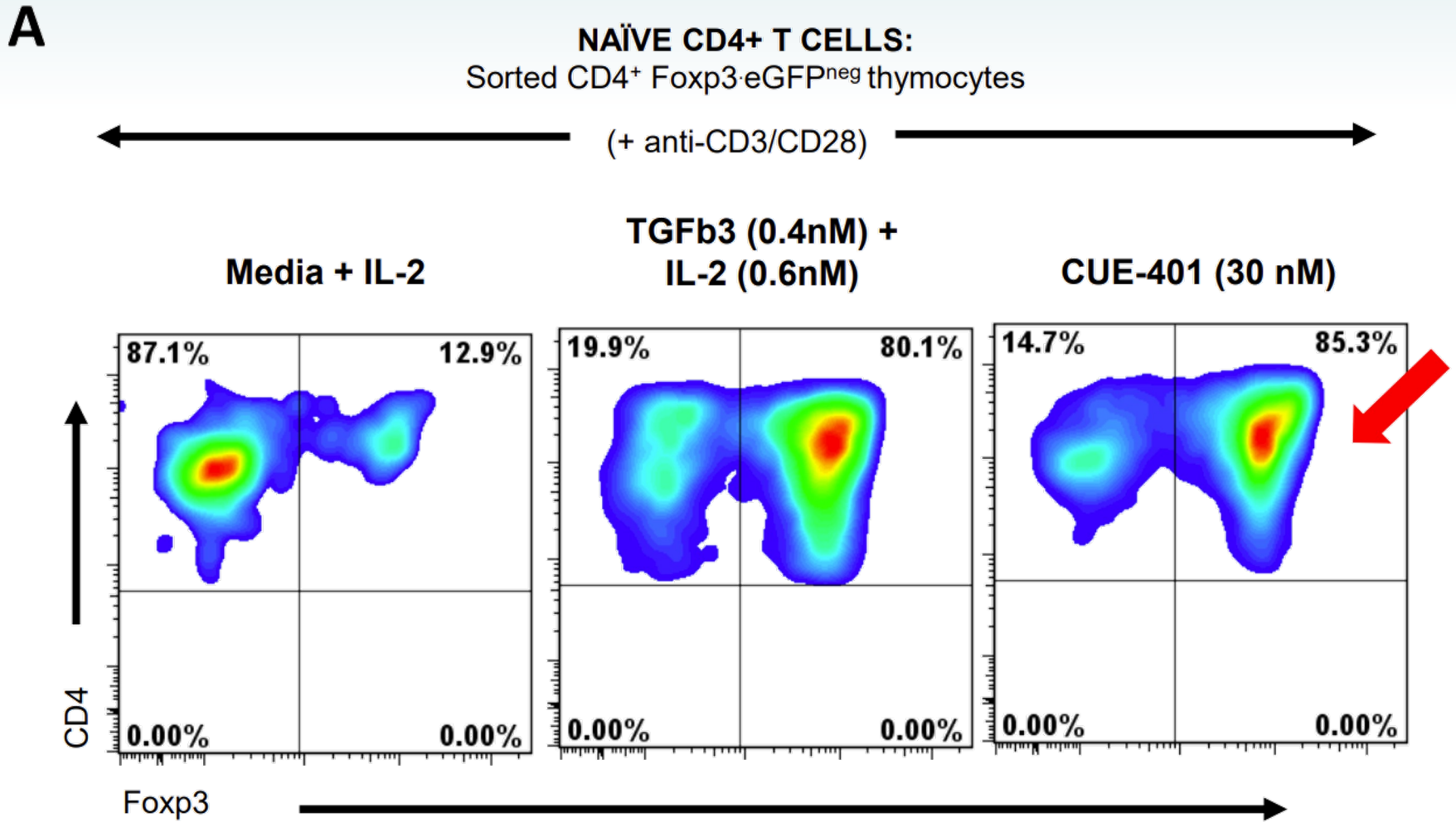
TGF-β Variant
Affinity attenuated; improved safety and manufacturability

TGF-β-Induced Signaling



CUE-401 Induced FOXP3+ Suppressive iTregs From Naïve Murine CD4+ T Cells

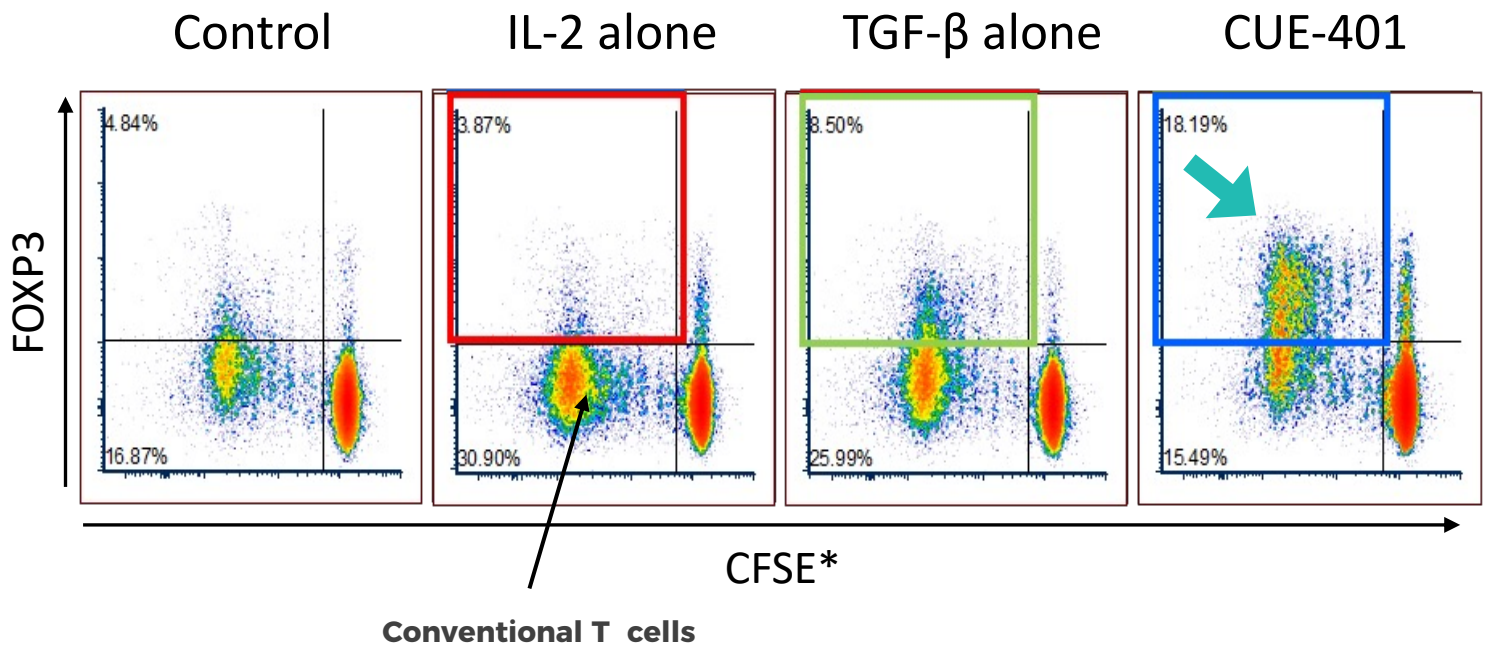
IL-2 and TGF-β are Both Critically Required Cytokines to Produce Sufficient iTregs



Source: Sponsored Research Collaboration with Dr. Richard DiPaolo, St. Louis University

CUE-401 Harnesses Multiple Signals to Induce iTregs

Provides Both IL-2 and TGF-β activating Signals that are Necessary for iTreg Differentiation



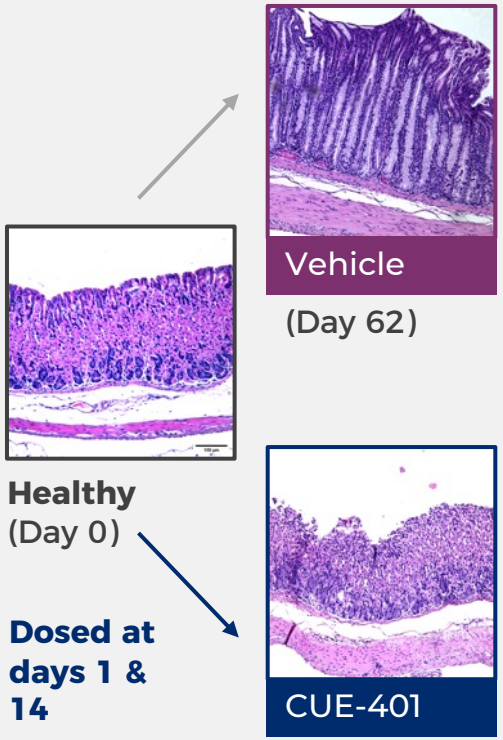
*carboxyfluorescein succinimidyl ester

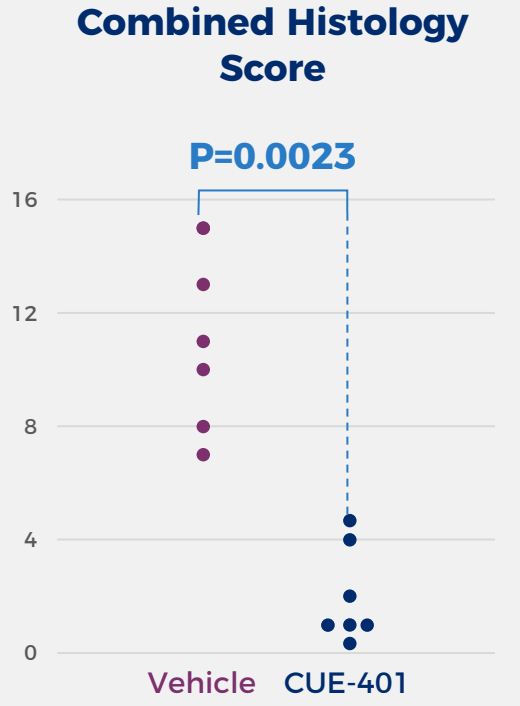
CUE-401: Durable Efficacy in Preclinical Model of Autoimmune Gastritis

Normalizes Histopathologic Gastritis Scores While Markedly Reducing Pathologic Autoimmune Effector T Cells in Tissue

Prevention of Autoimmune Gastritis

In vivo gastritis histology scores (7 weeks post-dose)

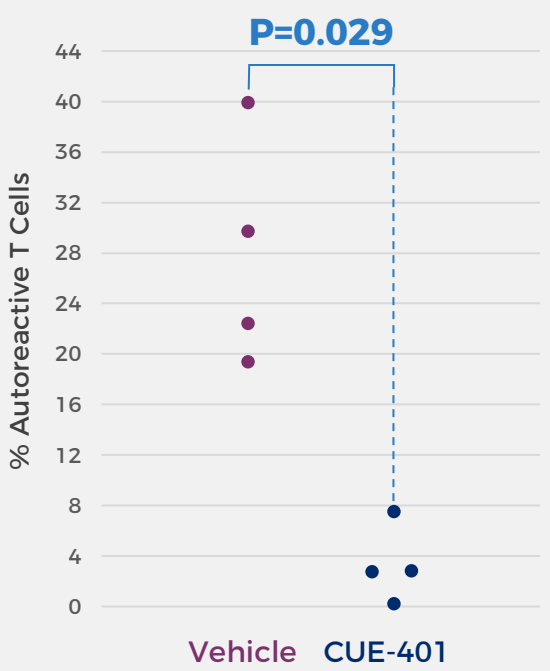


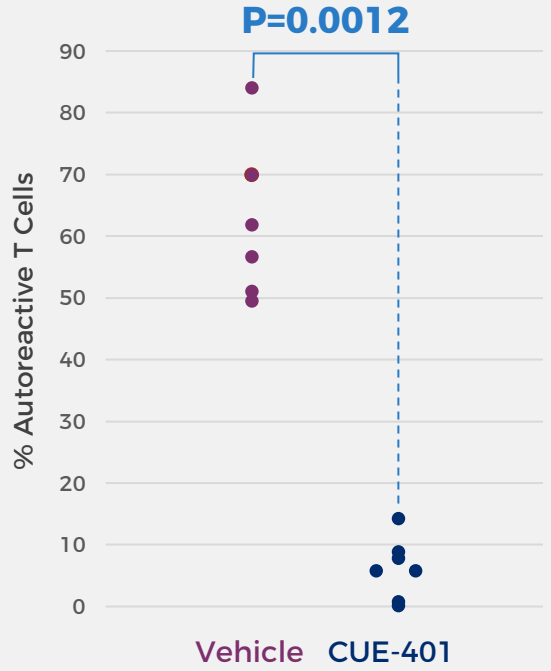


Source: Sponsored Research Collaboration with Dr. Richard DiPaolo, St. Louis University

Frequency of Self-Reactive Effector T Cells in Tissue

Day 62

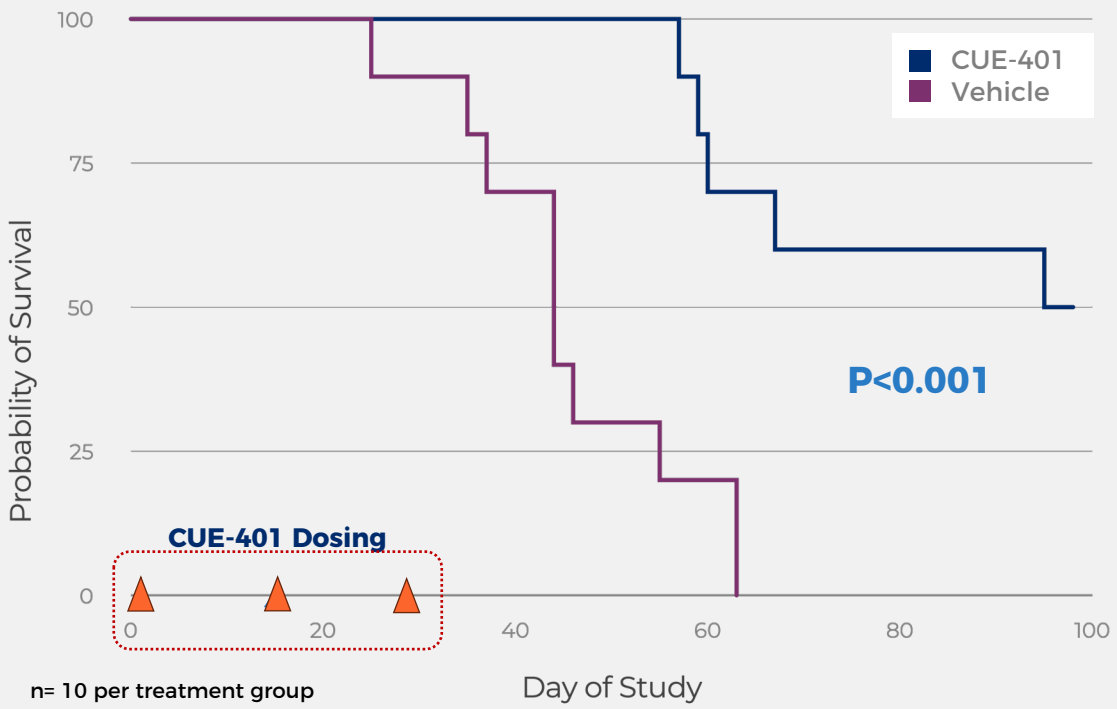




CUE-401: Durable Benefit in Model of Acute GVHD

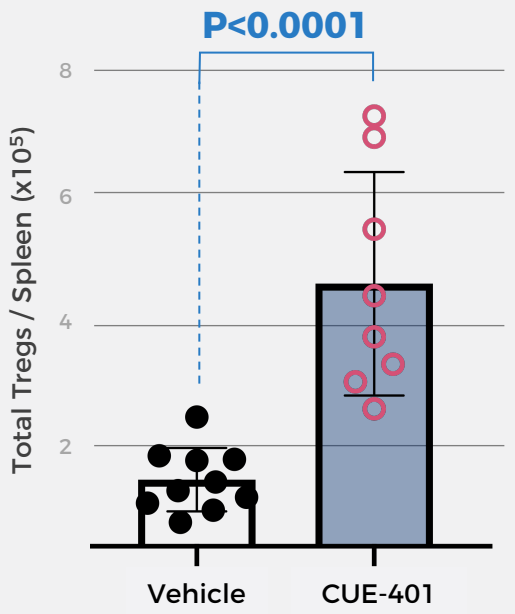
Increased Tissue Tregs and Maintenance of Graft 9+ Weeks Post-Treatment after 3 Doses

Delayed GVHD & Increased Overall Survival

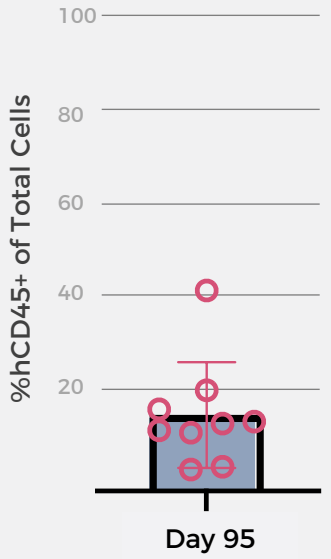


n= 10 per treatment group

Increased Treg Numbers in GVHD Target Tissue



Persistence of Human T Cell Graft Provides Evidence of Tolerance

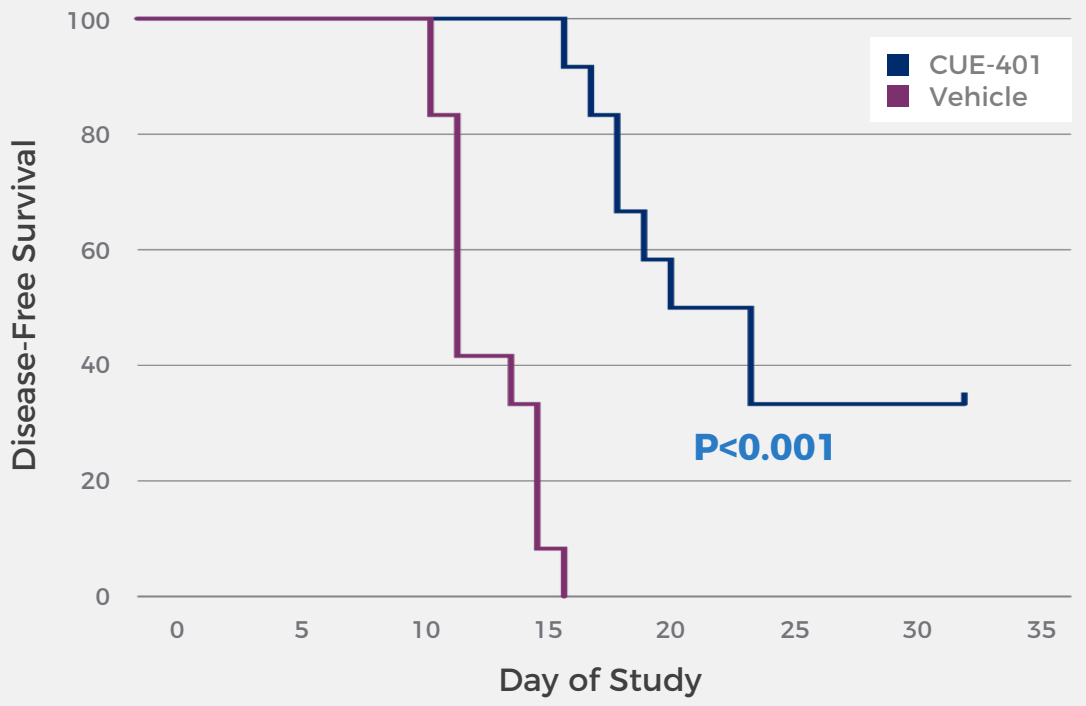


CUE-401: Suppression of Inflammation in Diverse Models of Disease

Functional Suppression of Inflammation in Multiple Disease Models Supports Broad Applicability in the Clinic

EAE Model of Multiple Sclerosis

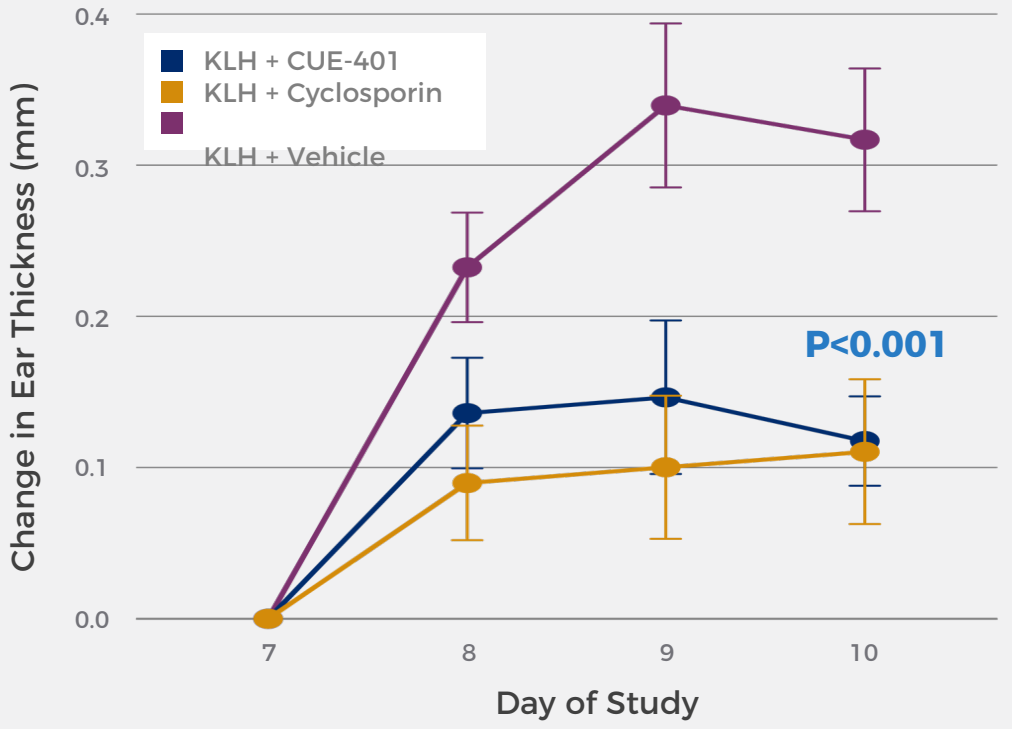
Significant inhibition and delay of disease onset



n= 15 per treatment group

Delayed Type Hypersensitivity – T Cell Mediated

Significant inhibition of cutaneous inflammation



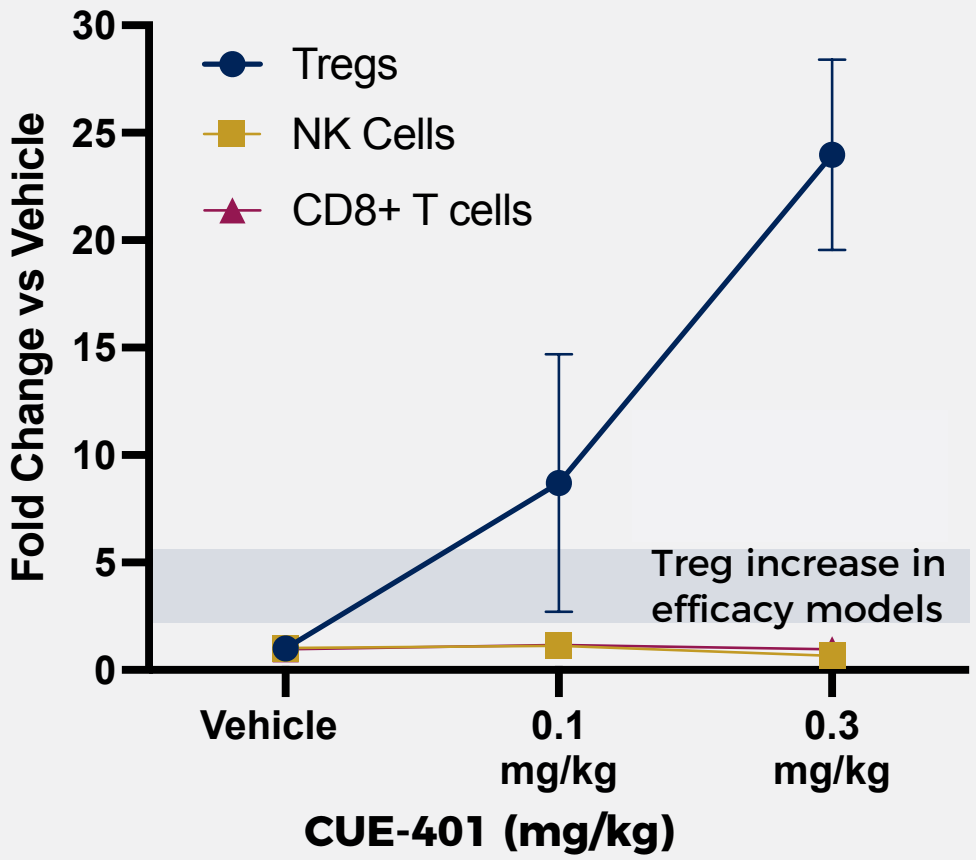
n= 10 per treatment group

■ CUE-401 Single Dose on Day 2

■ Cyclosporin dosed daily

■ CUE-401 dosed once on Day 1

CUE-401: Significant Activity in Non-Human Primates (NHP)
Supports Potential Strong Translatability to Humans



Dose levels leading to ~2-5-fold increase in Treg frequency across multiple murine disease models

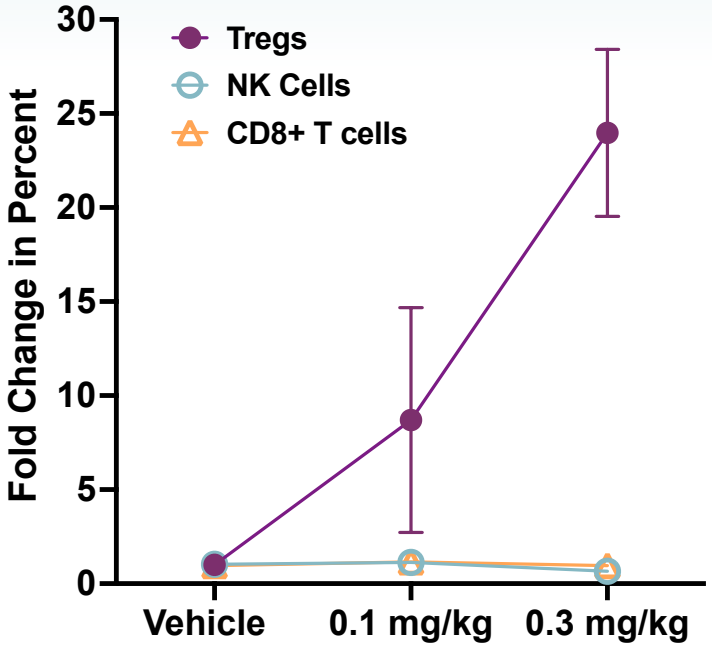
In NHP, ~25-fold increase in Treg frequency was observed at low CUE-401 dose levels

- Supports strong potential for CUE-401 to promote meaningful increase in Tregs in humans at well tolerated dose levels

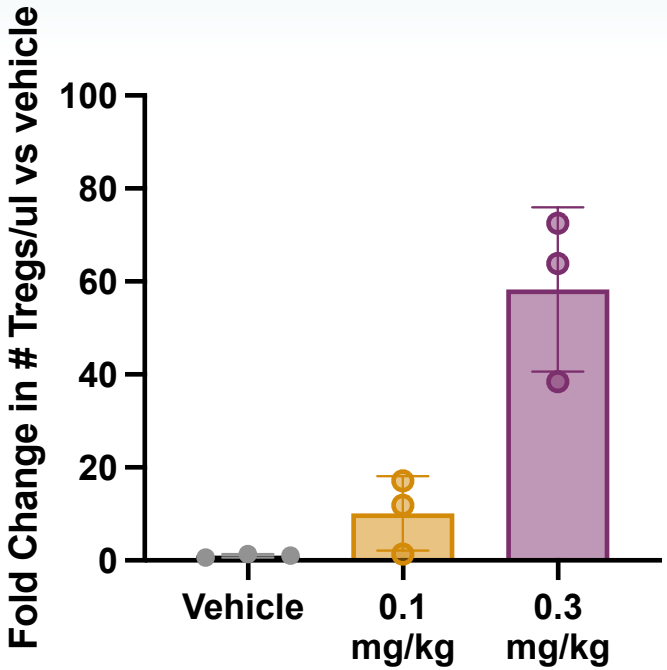
CUE-401 did not significantly expand other immune cells (NK, CD8, Teff) at these dose levels

NHP Data Indicates Significant Fold Increase in Tregs After Single Dose of CUE-401

CUE-401 - Fold change in % of Tregs



CUE-401 - Fold change in number of Tregs/ul



Nektar-358 NHP data suggests 15-fold increase in NHP setting – Dixit et al 2021, ACR 2017

(Slide 26 *Third-party slide; not a head-to-head comparison)

Highly Differentiated Approach to Immune Balance

	CUE-401	Treg Expanders (E.g. IL-2 muteins)	Treg Cell Therapies	Tolerizing Vaccines	Cytokine Blockers
TGFβ–mediated suppression of inflammatory cell types	YES	NO	NO	NO	NO
Expansion of nTregs	YES	YES	YES	NO	NO
Generation of iTregs	YES	NO	YES / NO	NO	NO
Disease antigen agnostic	YES	YES	NO	NO	YES
Potential for disease antigen-specific Tregs	YES	NO	YES	YES	NO
Manufacturing & supply chain	**Standard**	**Standard**	Complex	Complex	**Standard**
Company Examples	CUE BIOPHARMA	Nektar	Quell Sonoma	EVOQ	Numerous Lg Pharma

Differentiated Efficacy and Safety

Unique Biology Compared with Isolated Regulatory T cell Approaches

Efficacy Profile

Increased quantity of Tregs
Proliferation of existing Tregs while inducing new self-antigen Tregs from effector cell pool

Antigen specificity of generated Tregs
Transformed autoreactive T cells (Teff) should maintain their antigen specificity (i.e. T cell receptors) resulting in more targeted and efficient suppression

Overall reduction in autoreactive Teff cells
Both transform autoreactive cells to Tregs and suppress autoreactive Teff proliferation

Effect in multiple immune cell types reduces overall inflammatory environment
Stabilizes immune homeostasis by reducing overall inflammatory environment

Safety Profile

Attenuation of both TGF-β and IL-2 prevents or limits off target signaling
Results in limited binding to tissues not expressing both IL-2 and TGF-β receptors

Short-term exposure to CUE-401 and minimal effect in T memory cells reduces risk of broad immunosuppression
Expect that several doses will provide a prolonged tolerizing outcome for autoreactivity, while exposure to infection will not be affected

Targeted effector T cell and nTreg binding localize pharmacology to sites of autoimmune activity
Both autoreactive effector and nTregs are concentrated at sites of active inflammation

Intermittent dosing expectation (every 6 months or longer) resulting in long periods of remission based on the tolerizing capacity of CUE–401

CUE-401: IND Enabling Studies are Ongoing

IND Submission Planned Q2 2026

CUE-401

CMC	• Highly manufacturable and stable • Processes and assays established to support release of material for GLP toxicology and clinical studies
IND-Enabling Toxicology	• Existing datasets informed GLP study design that will define clinical starting dose and safety monitoring plan
Preclinical Pharmacology	• Disease-modifying activity in multiple models informs breadth of clinical opportunity and PD markers for the clinic
Regulatory and Clinical	• Successful FDA Pre-IND interaction allows derisking of the early development strategy • CRO identification ongoing to support FIH study

CUE-401: Rapid & Efficient Path to Clinical Proof of Concept

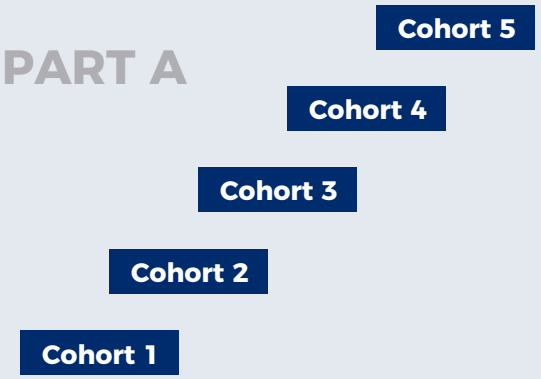
Healthy Volunteer / Atopic Dermatitis First-in-Human Phase 1

PART A

Single Ascending Dose in Healthy Volunteers

Phase 1a Study Design:

- Blinded, randomized, placebo controlled
- n=40 subjects over 5 dose levels
- ~6 months total duration



Primary endpoint:

- Safety and tolerability

Secondary endpoints (PoM):

- PK/PD
- T cell phenotyping
- Treg/Teff ratios
- T/B/NK

PART B

Multiple Dose in Atopic Dermatitis Patients

Phase 1b Study Design:

- Blinded, randomized, placebo controlled
- n=20 subjects over 2 dose levels
- 12 weeks follow-up per patient to look for prolonged efficacy as surrogate for long-term benefit

Primary endpoint:

- Safety and tolerability

Secondary endpoints (PoC):

- EASI scores
- PK/PD
- T cell phenotyping
- Treg/Teff ratios
- T/B/NK

CUE-401: Leading Disease Indication Options for Phase 2 / 3

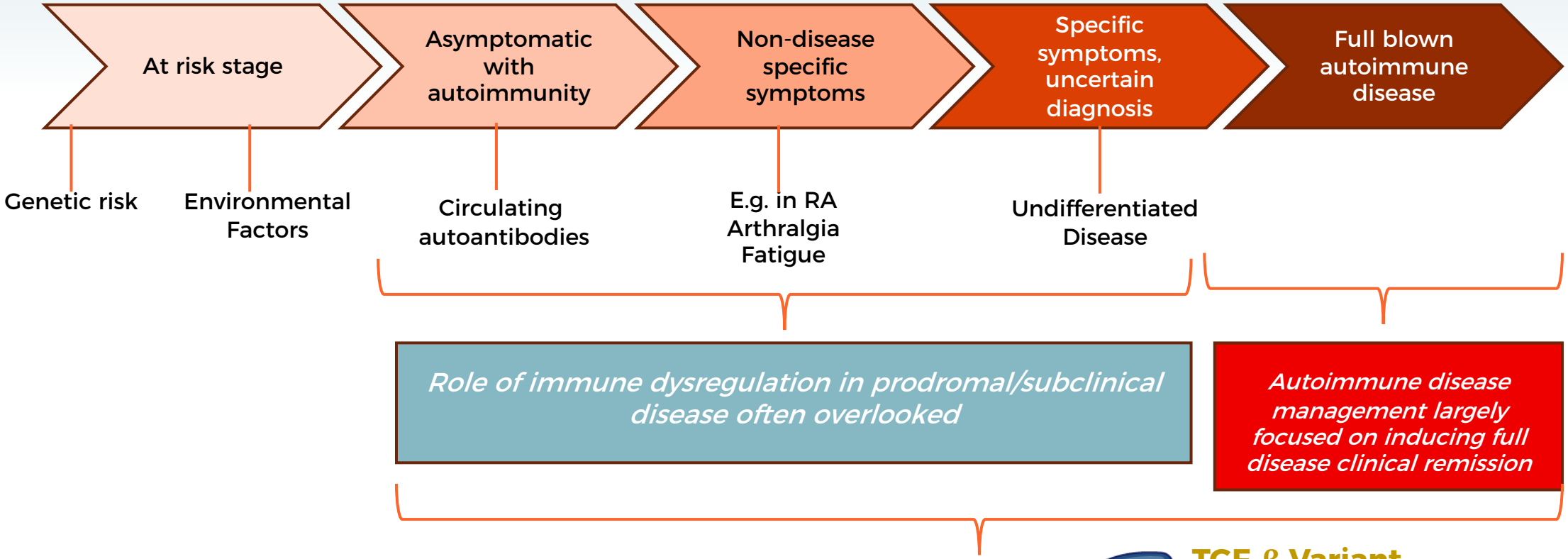
Phase 1b PoC May Provide Support for Multiple Opportunities

	Rheumatoid Arthritis	Inflammatory Bowel Disease	Graft vs Host Disease	Systemic Lupus Erythematosus	Primary Biliary Cirrhosis
Biologic Rationale	Decreased Treg function, abnormal Treg:Teff ratio	Decreased Treg function, abnormal Treg:Teff ratio	Local Treg dysfunction, decreased Tregs in cGVHD	Decreased Treg function, abnormal Treg:Teff ratio	Decreased Treg function, abnormal Treg:Teff ratio
Treg Validation	Low dose IL-2 Treg expansion, improved Treg:Teff, with preliminary clinical benefit	Treg transfer in Crohn's and UC	Low dose IL-2 Treg expansion & with partial responses	Low dose IL-2 Treg expansion with SLEDAI reductions	Preclinical data
Execution	Competition high but large population makes recruitment reasonable. Good endpoints.	High unmet need, good endpoints and recruitment reasonable	Some competition but increasing number of patients being treated, high unmet need	Competition and endpoints make execution challenging, but large market	Very high unmet need but small population. Recruitment reasonable.
Market Potential	~$44B (2032)[3]	~$44B (2032)[3]	~$6B (2034)[1]	~$6B (2034)[2]	~$1B (2034)[4]

1.Biospace August2, 2024. 2. Global News Wire Jan 16,2025(Source Research and Markets). 3. Fortune Business Insights May,5, 2025. 4. BioSpace August 5,2024 (Source IMARC Group)

CUE-401: Redefining the Management of Autoimmune Disease

With the Potential to Address Disease Control, Maintenance and Restoration*

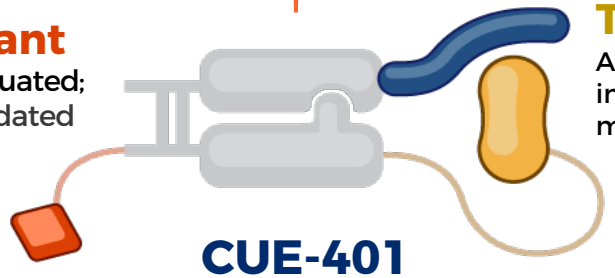


The ideal autoimmune therapeutic can aid in:

1. Controlling Inflammation
2. Resetting the Immune system
3. Homeostasis & Tissue Repair

IL-2 Variant
Affinity attenuated; clinically validated

TGF-β Variant
Affinity attenuated; improved safety and manufacturability



CUE-401

* Lu. R et al. Journal of Immunity, June 2016, 1-12
Scherer, H.U. Nature Reviews Rheumatology. Vol 18 July 2022

Additional Relevant Publications

https://www.cuebiopharma.com/cue-401-publications/

Critical Role of TGF-β and IL-2 Receptor Signaling in Foxp3 Induction by an Inhibitor of DNA Methylation

Freudenberg K, Lindner N, Dohnke S, Garbe AI, Schallenberg S, Kretschmer K. Critical Role of TGF-β and IL-2 Receptor Signaling in Foxp3 Induction by an Inhibitor of DNA Methylation, Front. Immunol. 2018 Feb 2;9:125.

Epigenetic conversion of conventional T cells into regulatory T cells by CD28 signal deprivation

Mikami N, Kawakami R, Chen KY, Sugimoto A, Ohkura N, & Sakaguchi S. Epigenetic conversion of conventional T cells into regulatory T cells by CD28 signal deprivation, Proc. Natl. Acad. Sci. 2020. 117 (22) 12258-12268.

Conversion of Peripheral CD4+CD25− Naive T Cells to CD4+CD25+Regulatory T Cells by TGF-β Induction of Transcription Factor Foxp3

Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, McGrady G, Wahl SM. Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J Exp Med. 2003 Dec 15;198(12):1875-86.

Antigen-specific transforming growth factor β–induced Treg cells, but not natural Treg cells, ameliorate autoimmune arthritis in mice by shifting the Th17/Treg cell balance from Th17 predominance to Treg cell predominance

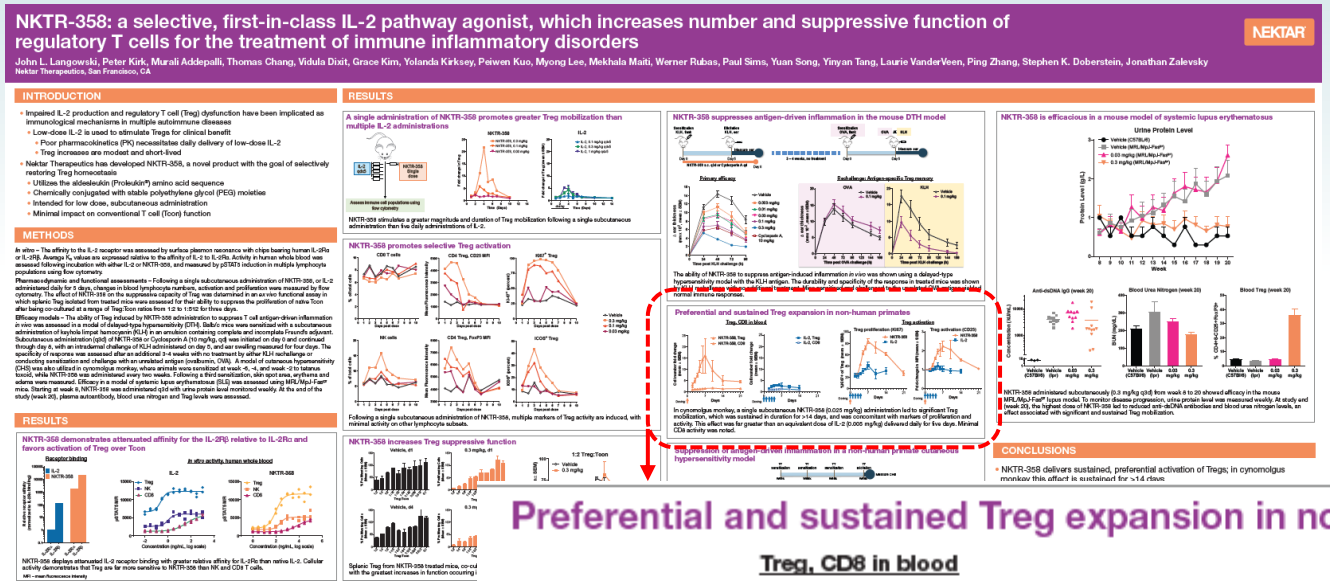
Kong N, Lan Q, Chen M, Wang J, Shi W, Horwitz DA, Quesniaux V, Ryffel B, Liu Z, Brand D, Zou H, Zheng SG. Antigen-specific transforming growth factor β-induced Treg cells, but not natural Treg cells, ameliorate autoimmune arthritis in mice by shifting the Th17/Treg cell balance from Th17 predominance to Treg cell predominance. Arthritis Rheum. 2012 Aug;64(8):2548-58.

Induced, but not natural, regulatory T cells retain phenotype and function following exposure to inflamed synovial fibroblasts

Yang S, Zhang X, Chen J, Dang J, Liang R, Zeng D, Zhang H, Xue Y, Liu Y, Wu W, Zhao J, Wang J, Pan Y, Xu H, Sun B, Huang F, Lu Y, Hsueh W, Olsen N, Zheng SG. Induced, but not natural, regulatory T cells retain phenotype and function following exposure to inflamed synovial fibroblasts. Sci Adv. 2020 Oct 28;6(44):eabb0606.

Thank You

Nektar 385 ACR 2017


NKTR-358: a selective, first-in-class IL-2 pathway agonist, which increases number and suppressive function of regulatory T cells for the treatment of immune inflammatory disorders

John L. Langowski, Peter Kirk, Murali Addepalli, Thomas Chang, Vidula Dixit, Grace Kim, Yolanda Kirksey, Peiwen Kuo, Myong Lee, Mekhala Maiti, Werner Rubas, Paul Sims, Yuan Song, Yinyan Tang, Laurie VanderVeen, Ping Zhang, Stephen K. Doberstein, Jonathan Zalevsky

Nektar Therapeutics, San Francisco, CA

NEKTAR

INTRODUCTION

- Impaired IL-2 production and regulatory T cell (Treg) dysfunction have been implicated as immunological mechanisms in multiple autoimmune diseases
  - Low-dose IL-2 is used to stimulate Tregs for clinical benefit
    - Poor pharmacokinetics (PK) necessitates daily delivery of low-dose IL-2
    - Treg increases are modest and short-lived
- Nektar Therapeutics has developed NKTR-358, a novel product with the goal of selectively restoring Treg homeostasis
  - Utilizes the aldesleukin (Proleukin®) amino acid sequence
  - Chemically conjugated with stable polyethylene glycol (PEG) moieties
  - Intended for low dose, subcutaneous administration
  - Minimal impact on conventional T cell (Tcon) function

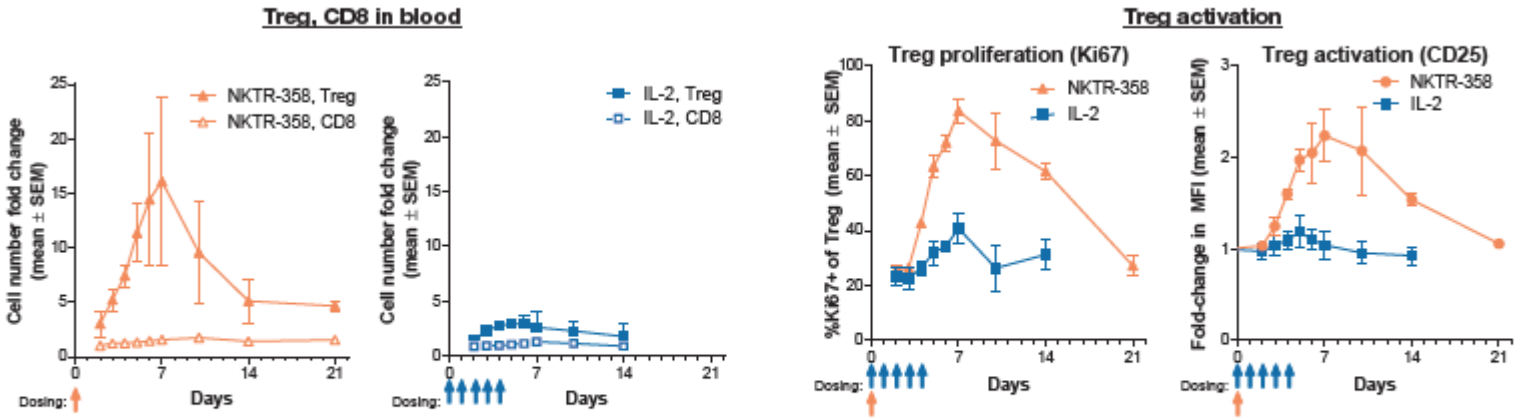
METHODS

RESULTS

CONCLUSIONS

- NKTR-358 delivers sustained, preferential activation of Tregs; in cynomolgus monkey this effect is sustained for >14 days

Preferential and sustained Treg expansion in non-human primates



In cynomolgus monkey, a single subcutaneous NKTR-358 (0.025 mg/kg) administration led to significant Treg mobilization, which was sustained in duration for >14 days, and was concomitant with markers of proliferation and activity. This effect was far greater than an equivalent dose of IL-2 (0.005 mg/kg) delivered daily for five days. Minimal CD8 activity was noted.