Autoimmune & Inflammation
401: Potential first-in-class bifunctional cytokine

CUE-401: A Potential First-in-Class Bifunctional Cytokine

Novel bispecific fusion protein	Broad in Vivo Efficacy Across Immune-mediated Disease Models	Near term value inflection with clear path to clinic
• **Combines** affinity-attenuated **IL-2 and TGF-β cytokines** delivering two key Treg-supporting signals in a single molecule • Engineered to attenuate TGF-β activity and **preferentially enable signaling on IL-2 receptor expressing cells**, to enhance specificity and reduce potential for off-target effects • Designed to **promote FOXP3^{+} Treg induction** and **expansion**	• Robust **in vivo proof-of-mechanism** and functional efficacy in various animal models of disease including autoimmune gastritis, EAE model of multiple sclerosis and GVHD • **Suppresses pro-inflammatory cytokine signaling** while promoting immune tolerance	• Manufacturing production established • IND-enabling studies completed • **IND submission** and **P1 study start by year end 2026** • Broad landscape of potential **opportunities to address high unmet need** in autoimmune disease

Abbreviations: EAE = Experimental autoimmune encephalomyelitis; GVHD = graft-versus-host disease

2025 Nobel Prize Recognized Importance in Understanding of FOXP3$^+$ Tregs as Central Regulators of Immune Tolerance[1,2]

Nature publication provides external validation of dual IL-2 and TGF-β agonism as a differentiated approach for durable immune tolerance with reduced off-target effects[3]

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

Scientific background

Scientific background to the Nobel Prize in Physiology or Medicine 2025: Immune tolerance. The identification of regulatory T cells and FOXP3 (pdf)

PRESS RELEASE
6 October 2025

The Nobel Prize in Physiology or Medicine 2025

The Nobel Assembly at Karolinska Institutet has decided to award the Nobel Prize in Physiology or Medicine 2025 to:

Mary E. Brunkow
Institute for Systems Biology, Seattle, USA

Fred Ramsdell
Sonoma Biotherapeutics, San Francisco, USA

Shimon Sakaguchi
Osaka University, Osaka, Japan

"for their discoveries concerning peripheral immune tolerance"

They discovered how the immune system is kept in check

nature

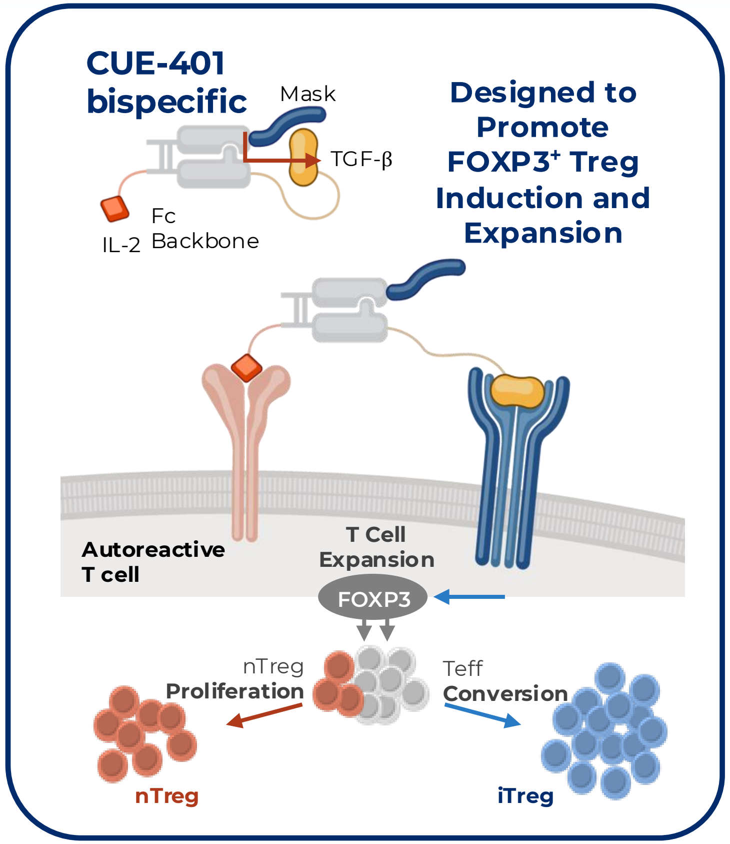
Explore content ⌄ About the journal ⌄ Publish with us ⌄

nature > articles > article

Article | Open access | Published: 11 March 2026

Facile induction of immune tolerance by an interleukin-2–TGFβ surrogate agonist

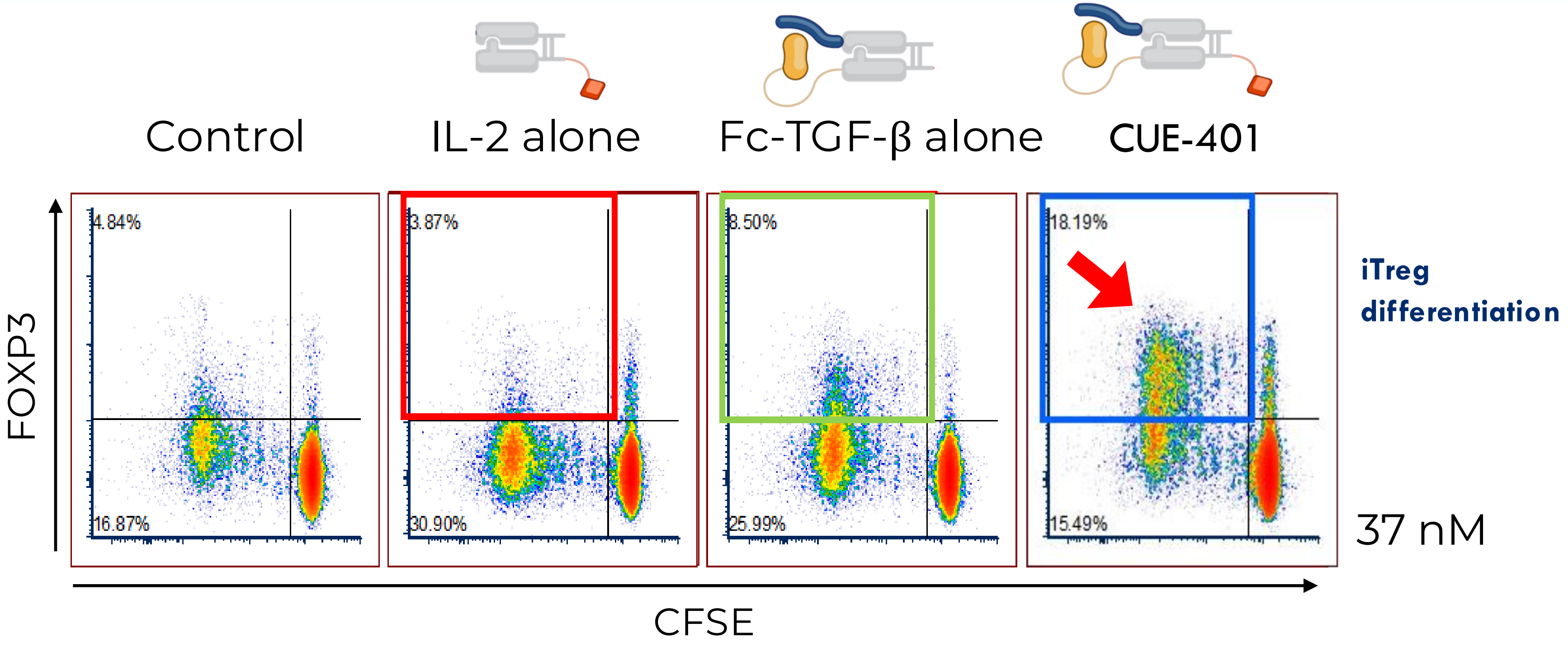
CUE-401: Bi-functional Agonist Combining Affinity-attenuated IL-2 and TGF-β Cytokines



1. N. Mikami, R. Kawakami, K.Y. Chen, A. Sugimoto, N. Ohkura, & S. Sakaguchi, Epigenetic conversion of conventional T cells into regulatory T cells by CD28 signal deprivation, Proc. Natl. Acad. Sci. U.S.A. 117 (22) 12258-12268, https://doi.org/10.1073/pnas.1922600117 (2020); 2. Press release. NobelPrize.org. Nobel Prize Outreach 2026. Wed. 6 May 2026. https://www.nobelprize.org/prizes/medicine/2025/press-release/ 3. Sun et al. 2026 Nature Reviews

Dual IL-2 and TGF-β Signaling Drives Immune Reprogramming Toward Tolerance

In vitro studies demonstrate FOXP3 induction and proliferation with CUE-401 dual agonism



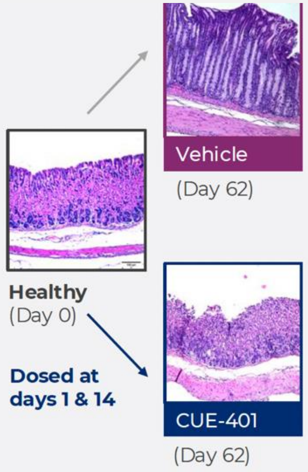
Source: Sponsored Research Collaboration with Dr. Richard DiPaolo, St. Louis University;
Abbreviations: CFSE = Carboxyfluorescein succinimidyl ester; iTreg = induced T regulatory cell; moDC =monocyte-derived dendritic cells

IL-2 and TGF-β Agonism Demonstrates Activity Across Inflammatory Diseases, Supporting a Platform for Immune Tolerance

Broad in vivo efficacy across immune-mediated disease models

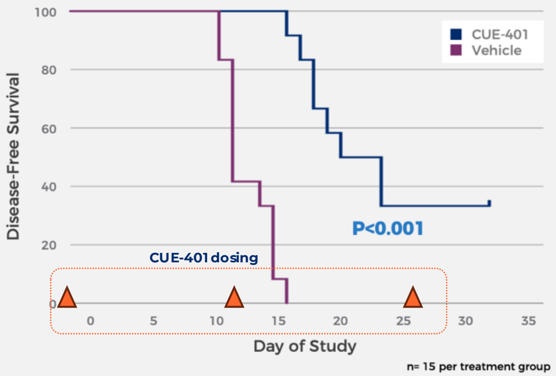
Suppresses pro-inflammatory cytokine signaling

Prevention of Autoimmune Gastritis

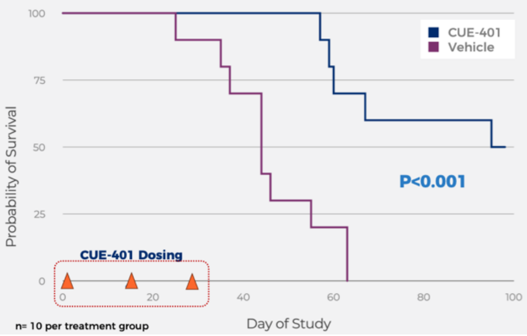


Attenuation of Disease Development and Delay of Onset in EAE

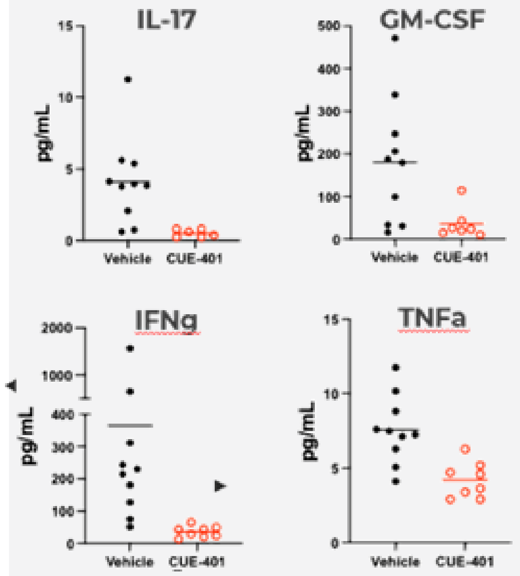
Across 35 days



GVHD: Delayed Development and Increased Overall Survival[1]

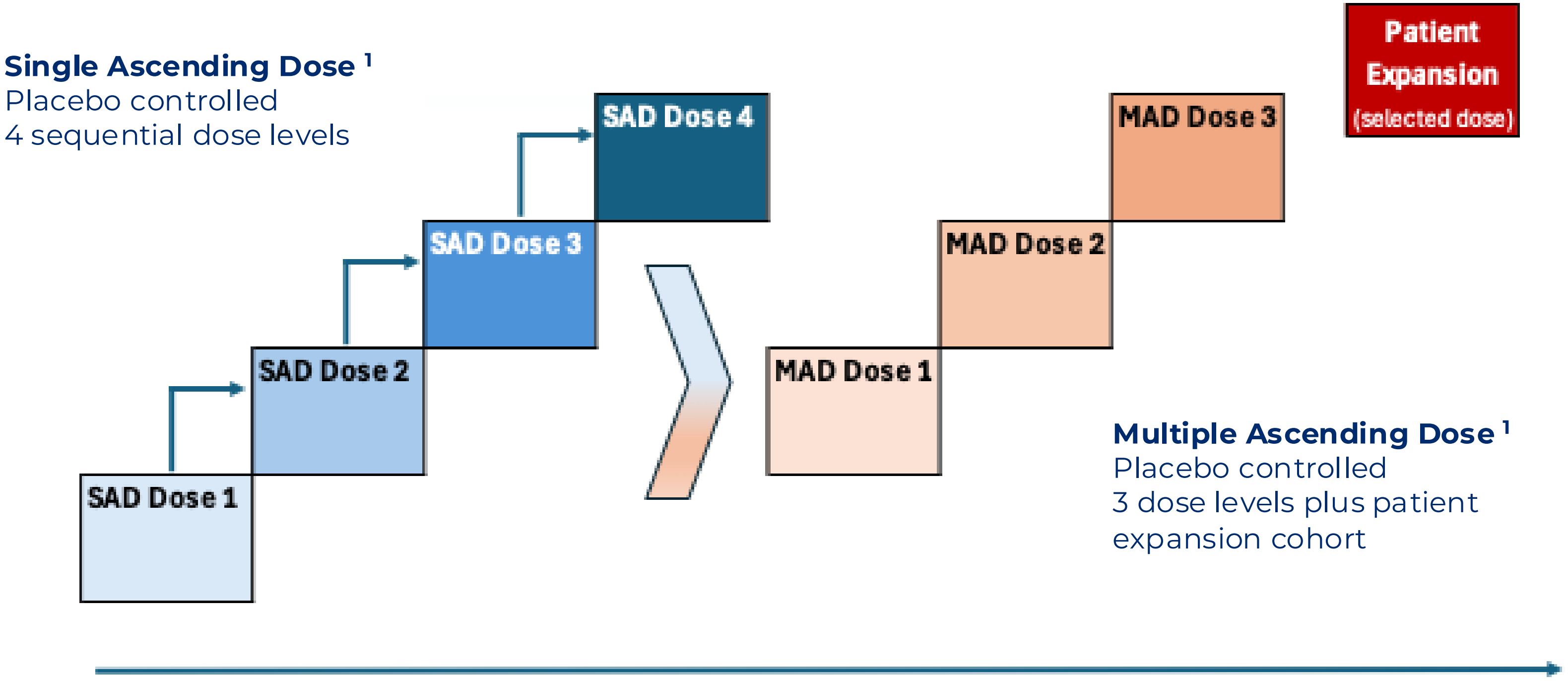


Suppresses pro-inflammatory cytokine signaling



Source: Peterson et al 2018 J of Autoimmunity; Girgis N et al., 2025,CUE-401: A Novel TGF-beta/IL-2 Fusion Protein for the Induction Expansion of FOXP3+ Regulatory T Cells. Cytokines conference, Seattle, Washington USA
Note: [1] Wild-type IL-2 accelerates disease in xenogeneic GVHD model

Phase 1 Single and Multiple Ascending Dose Study In Healthy Volunteers with Patient Cohort Expansion



[1] Optional cohorts may be added to refine dose levels given the potential for a narrow therapeutic window.

- **Safety and tolerability**
- **Immunogenicity**
- **Biomarker driven PK/PD characterization**
- **Exploratory efficacy in patients**

CUE is Advancing a Portfolio of Potentially Transformative Therapies Aimed at Enabling Functional Cures Across Immunological Disorders

Enhanced clinical-stage pipeline

- CUE-221: a **novel anti-IgE program** with a unique dual-mechanism of action in Phase 2 for allergic disease augmenting the portfolio that includes CUE-401
- CUE-401: Designed to be a first-in-class **bifunctional IL-2 and TGF-β** molecule which highlights the Nobel Prize winning science of regulatory T cells for autoimmune disease, advancing into Phase 1 development

Multiple near-term milestones

- **IND submissions in food allergy** (CUE-221) and **autoimmune disease** (CUE-401)
- **CUE-221 Phase 2 data** expected in **2H 2026** (Ascendant CSU study)
  - Advancement of **CUE-221 to global Phase 2b trial in food allergy**
- **CUE-401 Phase 1** first-in-human study expected to be **initiated by YE 2026**

Well-positioned for significant value inflections

- Company **funded** with a cash runway projected to **cover milestones**
- Creates a **complementary** team with expertise across the portfolio to support the company's strategic acceleration of growth