

Diabete tipo 1 e endocrinopatie autoimmuni: connessioni e implicazioni cliniche

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Sistema Socio Sanitario



Regione
Lombardia

ASST Fatebenefratelli Sacco



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MEDICAL SCHOOL

Outline

1. Introduction
2. Autoimmune Polyendocrine Syndromes
 - a. Definition
 - b. Epidemiology
 - c. Etiopathogenesis
 - d. Clinical features
3. Type 1 Diabetes
4. Immunotherapy
5. Conclusions

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The Nobel Prize in Physiology or Medicine 2025



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

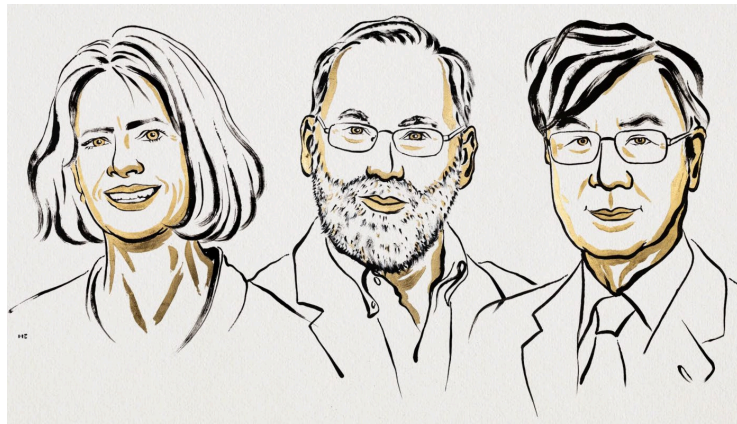
Sonoma Biotherapeutics,
San Francisco, USA

Shimon Sakaguchi

Osaka University,
Osaka, Japan

"for their discoveries concerning peripheral immune tolerance"

They discovered how the immune system is kept in check



Is there an interplay between immunology and endocrinology?

Craig L. Bennett · Mary E. Brunkow · Fred Ramsdell
Kathy C. O'Briant · Qili Zhu · Ramsay L. Fuleihan
Ann O. Shigeoka · Hans D. Ochs · Phillip F. Chance

A rare polyadenylation signal mutation of the *FOXP3* gene (AAUAAA→AAUGAA) leads to the IPEX syndrome

Immunogenetics (2001)

The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of *FOXP3*

[Craig L. Bennett](#), [Jacinda Christie](#), [Fred Ramsdell](#), [Mary E. Brunkow](#), [Polly J. Ferguson](#), [Luke Whitesell](#),
[Thaddeus E. Kelly](#), [Frank T. Saulsbury](#), [Phillip F. Chance](#) & [Hans D. Ochs](#) 

[Nature Genetics](#) **27**, 20–21 (2001)

Regulatory T-cell deficiency and autoimmune skin disease: Beyond the scurfy mouse and immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Takashi Hashimoto, MD,^a Hayato Takahashi, MD, PhD,^b and Shimon Sakaguchi, MD, PhD^c

J ALLERGY CLIN IMMUNOL DECEMBER 2018

Generating functionally stable and antigen-specific T_{reg} cells from effector T cells for cell therapy of inflammatory diseases

[NORIHISA MIKAMI](#) , [RYOJI KAWAKAMI](#) , [ATSUSHI SUGIMOTO](#), [MASAYA ARAI](#) , AND [SHIMON SAKAGUCHI](#) 

SCIENCE TRANSLATIONAL MEDICINE · 22 Oct 2025

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Autoimmune Polyendocrine Syndromes (APS)

Autoimmune Polyendocrine (polyglandular) Syndromes (APSs) are a group of rare disorders characterized by the coexistence of two or more autoimmune diseases affecting endocrine glands.

These syndromes arise from a breakdown in immune tolerance, leading the immune system to attack multiple hormone-producing organ

Characteristics of the Autoimmune Polyendocrine Syndromes

Table 1. Classification and Characteristics of Autoimmune Polyendocrine Syndromes.*					
Characteristic	APS-1		APS-2		IPEX
Main manifestations	Addison's disease, hypoparathyroidism, chronic mucocutaneous candidiasis		Addison's disease, auto-immune thyroid disease, type 1 diabetes		Autoimmune enteropathy, neonatal type 1 diabetes, eczema
Other, associated manifestations	Primary ovarian insufficiency, autoimmune thyroid disease, type 1 diabetes, gastritis, enteritis with malabsorption, hepatitis, pancreatitis, pneumonitis, nephritis, vitiligo, alopecia, nail dystrophy, enamel hypoplasia, keratitis, retinitis		Autoimmune gastritis, alopecia, vitiligo, celiac disease, primary ovarian insufficiency		Autoimmune thyroid disease, hemolytic anemia, thrombocytopenia
Typical age at onset	Childhood, adolescence		Adolescence to adulthood		Infancy
Prevalence	1:100,000		1:1000		1:1,000,000
Treatment	Hormone replacement, antifungal therapy, immunosuppressive therapy for hepatitis, malabsorption, nephritis, pneumonitis, keratitis		Hormone replacement		Hormone replacement, bone marrow transplantation
Complications, including death	Adrenal and hypocalcemic crises, cancer in mouth and esophagus		Adrenal crisis, complications of diabetes		Infections
Genes and mode of inheritance	AIRE, autosomal recessive and dominant		Polygenic: MHC and others		FOXP3, X-linked
Immune phenotype	Autoantibodies against interferon- ω and interferon- α (>95%), organ-specific intracellular proteins		Autoantibodies against 21-hydroxylase, GAD65, IA-2, thyrotropin receptor, TPO		Autoantibodies against GAD65, lymphocytosis, eosinophilia, overproduction of cytokines, hyper IgE
Association with diabetes	Yes (in 18%)		Yes (in 20%)		Yes (in majority)

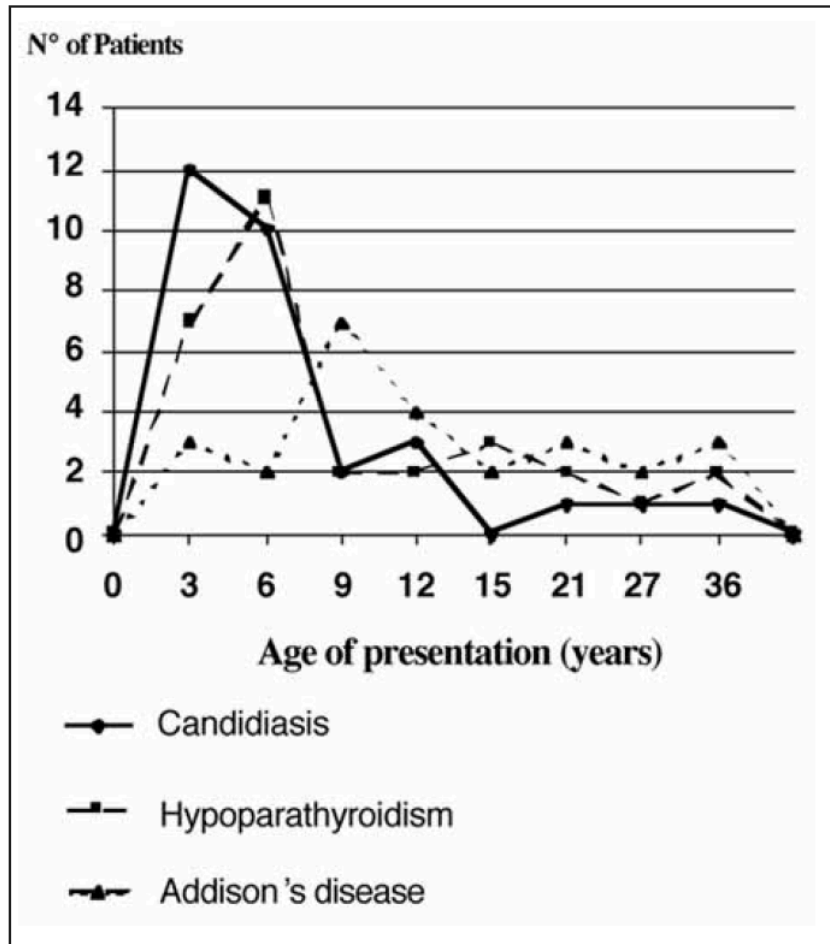
* AIRE denotes autoimmune regulator; APS-1 autoimmune polyendocrine syndrome (APS) type 1; APS-2 APS type 2; FOXP3 forkhead box P3; GAD65 glutamic acid decarboxylase 65; IA-2 islet antigen 2; IPEX X-linked immunodysregulation, polyendocrinopathy, and enteropathy; MHC major histocompatibility complex; and TPO thyroid peroxidase.

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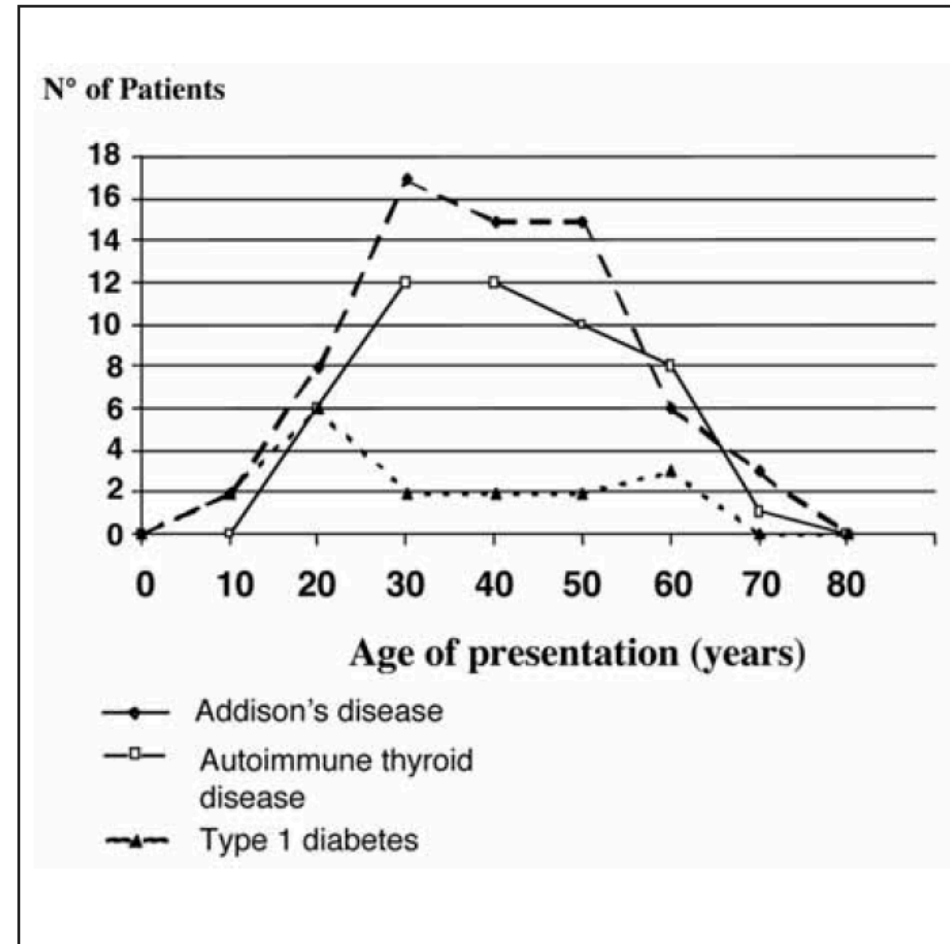
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Time course of APSs

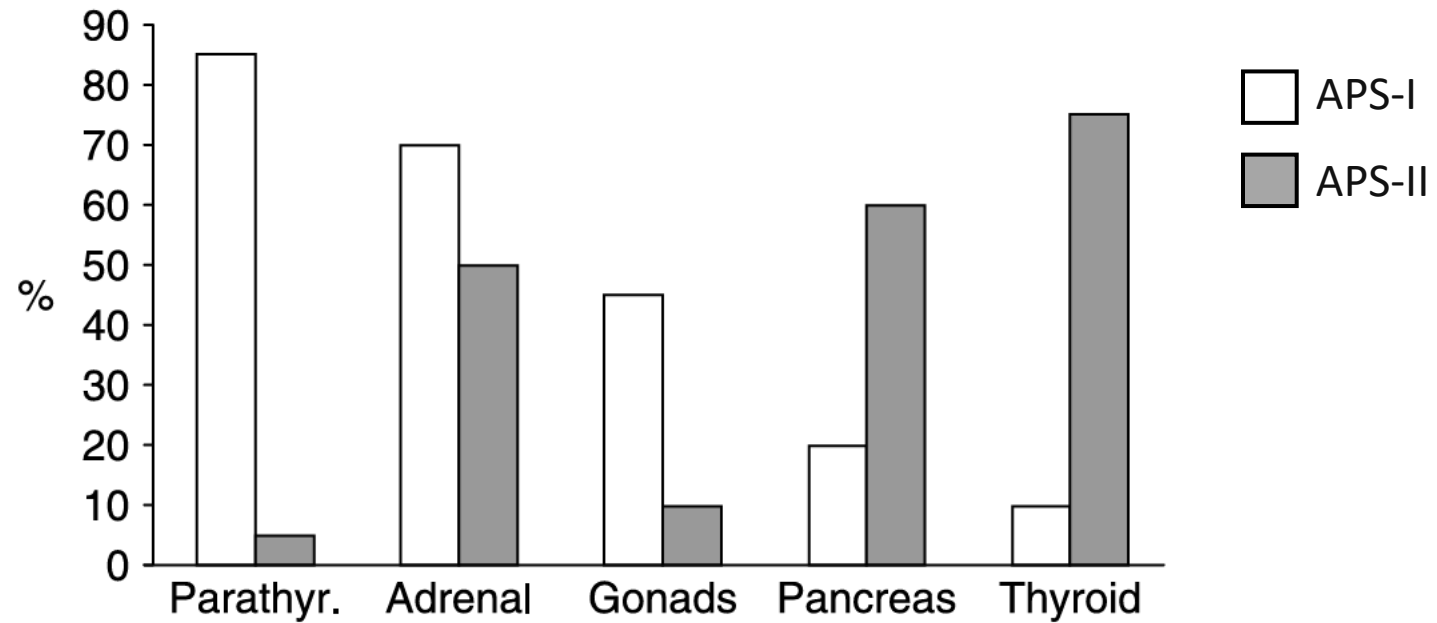
APS-I



APS-II

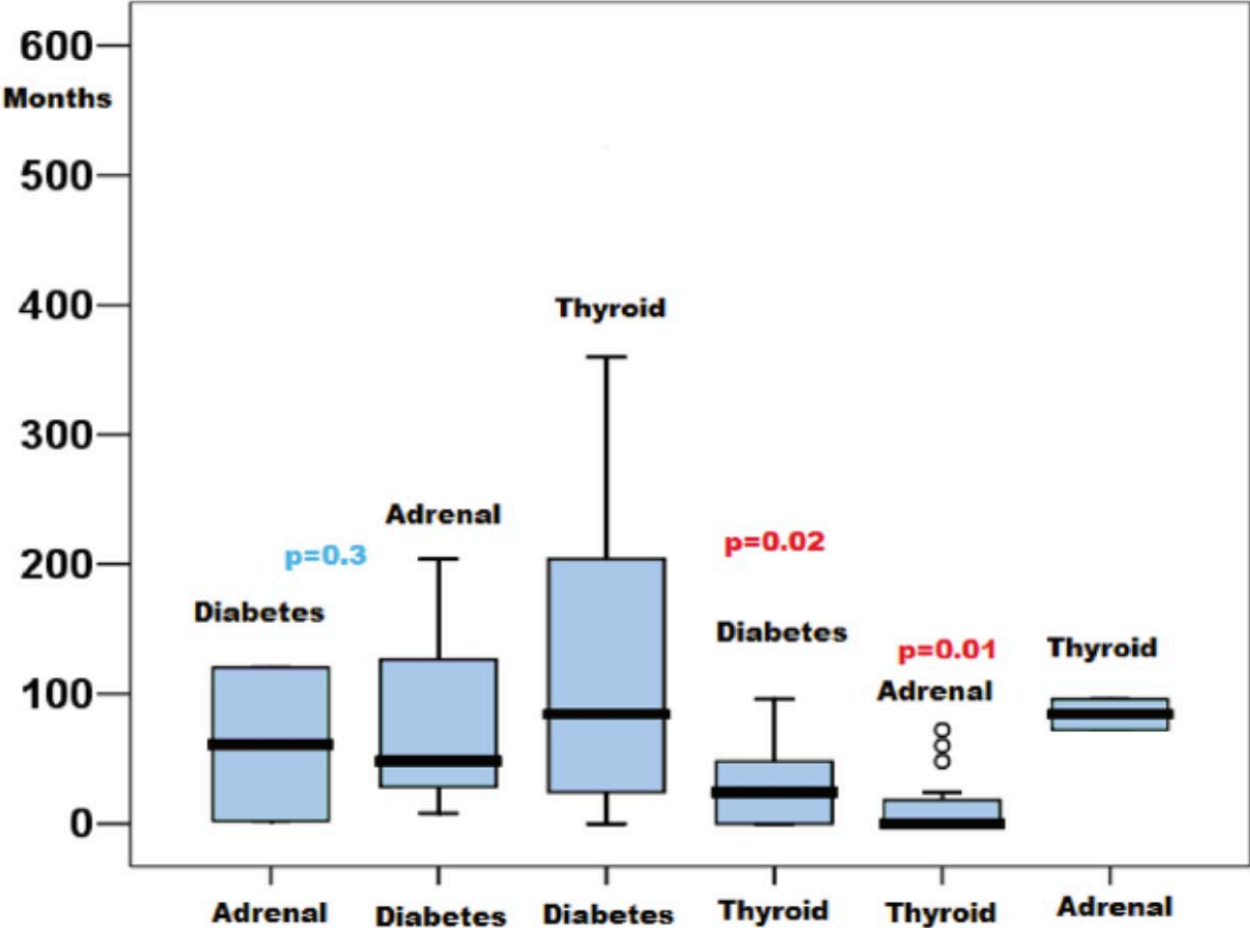


Prevalence of APS-I and APS-II



Prevalence of most frequent autoimmune endocrine component diseases APS-I vs APS-II

Variability in timing of appearance between the first and second AID



Outline

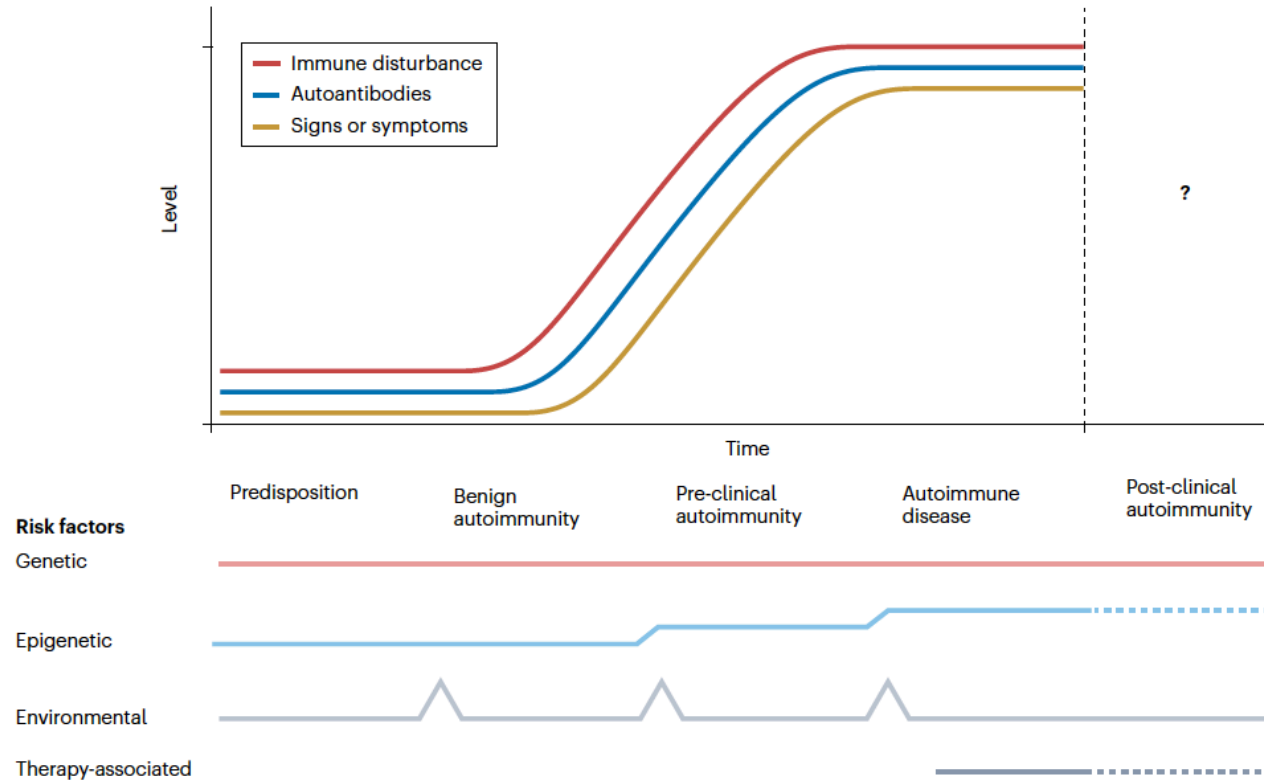
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Genetic Basis of APSs: Polymorphisms, Mutations, Inheritance

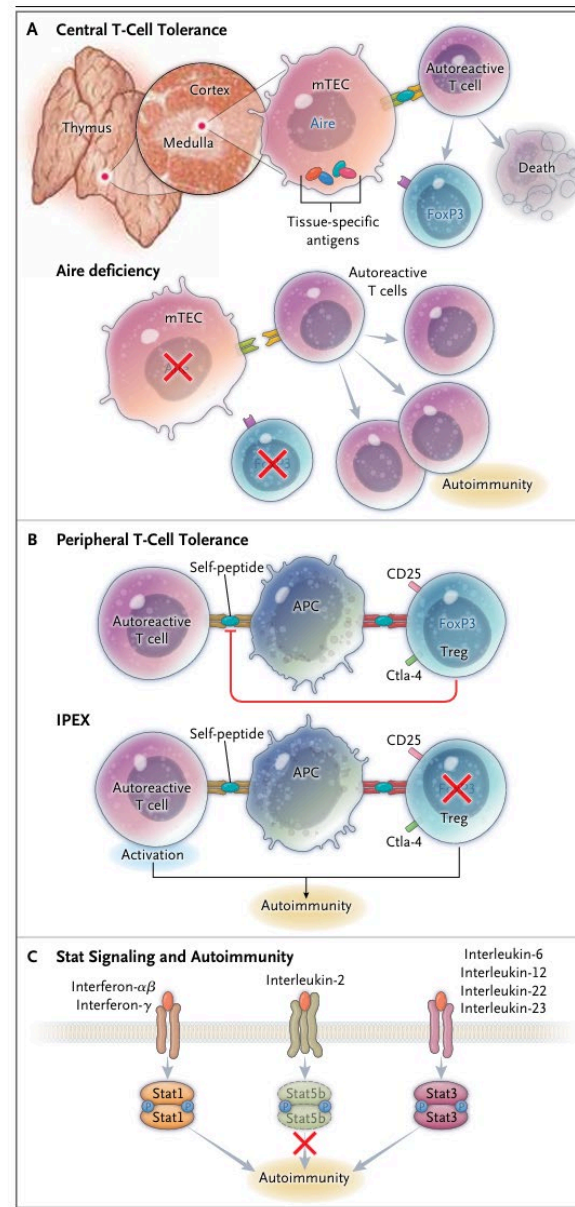
Gene	Proposed Mechanism of Action	Polymorphism/Mutation	Disease	Inheritance
<i>HLA</i>	Antigen presentation	DR3-DQ2/DR4-DQ8 DR3-DQ2 DR3-DQ2/DRB1*0404-DQ8 DR3-DQ2/DR4-DQ8 DR3 DR5	Type 1 diabetes Celiac disease Addison's disease Graves' disease Hypothyroidism	Multigenic
<i>MICA</i>	Priming of naïve T cells	5, 5.1 4, 5.1 5.1	Type 1 diabetes Celiac disease Addison's disease	Multigenic
<i>PTPN22</i>	T-cell receptor signaling pathway through interaction with regulatory kinases	Tryptophan substitution for arginine at position 620	Type 1 diabetes SLE RA Graves' disease Hypothyroidism Vitiligo	Multigenic
<i>CTLA4</i>	Receptor on activated CD4 ⁺ and CD8 ⁺ T cells; decreases T-cell activation	CT60 CT60; +49A/G CT60; +49A/G ++49A/G ++49A/G	Type 1 diabetes Graves' disease Hypothyroidism Celiac disease Addison's disease	Multigenic
<i>AIRE</i>	"Peripheral" antigen presentation in the thymus	Multiple reported mutations	APS-I	Autosomal recessive
<i>FOXP3</i>	Transcription factor important for maturation of CD4 ⁺ /CD25 ⁺ regulatory T cells	Multiple reported mutations	IPEX	X-linked

APS, autoimmune polyendocrine syndrome; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Timeline of pathogenicity in AIDs



Key pathways involved in the pathogenesis of APSs



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Clinical features for APS-I and APS-II

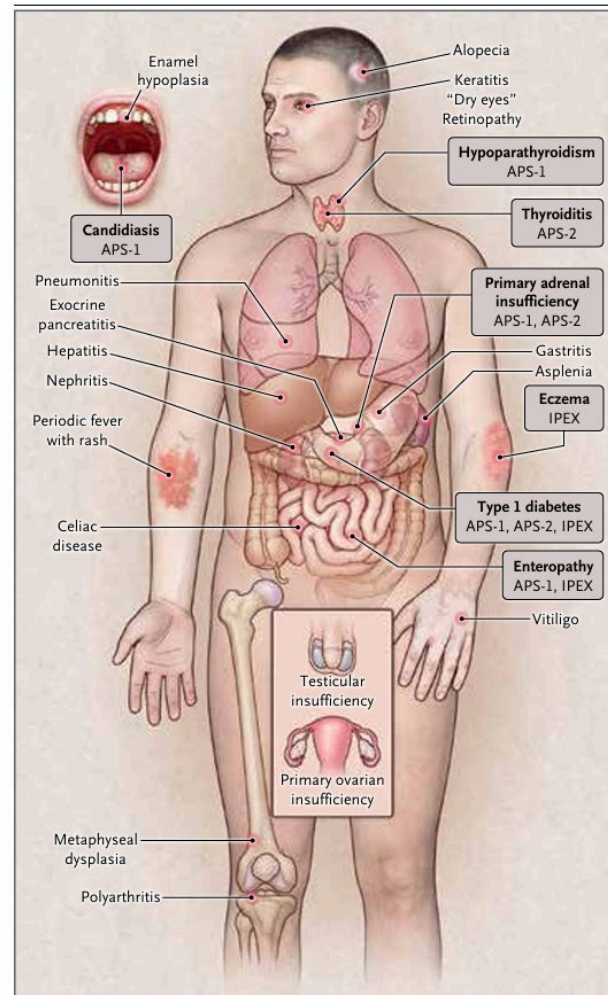


Figure 1. Organ-Specific Manifestations of Autoimmune Polyendocrine Syndromes.

Shown are the main manifestations of autoimmune polyendocrine syndrome type 1 (APS-1), APS-2, and X-linked immunodysregulation, polyendocrinopathy, and enteropathy (IPEX). Primary adrenal insufficiency is a characteristic of both APS-1 and APS-2; type 1 diabetes is a characteristic of APS-1, APS-2, and IPEX; and enteropathy is a characteristic of APS-1 and IPEX.

Recommended Follow-Up for APS-I and APS-II

Component Disease	Frequency at Age 40 Yr (%)	Recommended Evaluation
Autoimmune Polyendocrine Syndrome Type I		
Addison's disease	79	Sodium, potassium, ACTH, cortisol, plasma renin activity, 21-hydroxylase autoantibodies
Diarrhea	18	History
Ectodermal dysplasia	50-75	Physical examination
Hypoparathyroidism	86	Serum calcium, phosphate, PTH
Hepatitis	17	Liver function test
Hypothyroidism	18	TSH; thyroid peroxidase and/or thyroglobulin autoantibodies
Male hypogonadism	26	FSH/LH
Mucocutaneous candidiasis	100	Physical examination
Obstipation	21	History
Ovarian failure	72	FSH/LH
Pernicious anemia	31	CBC, vitamin B ₁₂ levels
Splenic atrophy	15	Blood smear for Howell-Jolly bodies; platelet count; ultrasound if positive
Type I diabetes	23	Glucose, hemoglobin A _{1c} , diabetes-associated autoantibodies (insulin, GAD65, IA-2)
Autoimmune Polyendocrine Syndrome Type II*		
Addison's disease	0.5	21-Hydroxylase autoantibodies ACTH stimulation testing if positive
Alopecia		Physical examination
Autoimmune hypothyroidism	15-30	TSH; thyroid peroxidase and/or thyroglobulin autoantibodies
Celiac disease	5-10	Transglutaminase autoantibodies; small-intestine biopsy if positive
Cerebellar ataxia	Rare [†]	Dictated by signs and symptoms of disease
Chronic inflammatory demyelinating polyneuropathy	Rare [†]	Dictated by signs and symptoms of disease
Hypophysitis	Rare [†]	Dictated by signs and symptoms of disease
Idiopathic heart block	Rare [†]	Dictated by signs and symptoms of disease
IgA deficiency	0.5	IgA level
Myasthenia gravis	Rare [†]	Dictated by signs and symptoms of disease
Myocarditis	Rare [†]	Dictated by signs and symptoms of disease
Pernicious anemia	0.5-5	Anti-parietal cell autoantibodies CBC, vitamin B ₁₂ levels if positive
Serositis	Rare [†]	Dictated by signs and symptoms of disease
Stiff-man syndrome	Rare [†]	Dictated by signs and symptoms of disease
Vitiligo	1-9	Physical examination

*In the population with type I diabetes.

[†]Rare reported disorders in subjects with APS-II.

ACTH, adrenocorticotrophic hormone; APS, autoimmune polyendocrine syndrome; CBC, complete blood count; FSH, follicle-stimulating hormone; GAD, glutamic acid decarboxylase; IA-2, insulinoma antigen 2; IgA, immunoglobulin A; LH, luteinizing hormone; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

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Increased risk of AIDs in T1D

Autoimmune disease	Prevalence in autoimmune T1D (%)	SIR ^a in autoimmune T1D	Organ-specific autoantibodies
Autoimmune thyroid disease^b - Graves' disease - Hashimoto's thyroiditis	15%–30%	1.83	TPO, TG
Celiac disease^c	4%–9%	2.73	EMA, TTG
Addison's disease	0.5%	2.41	21-OH ^d

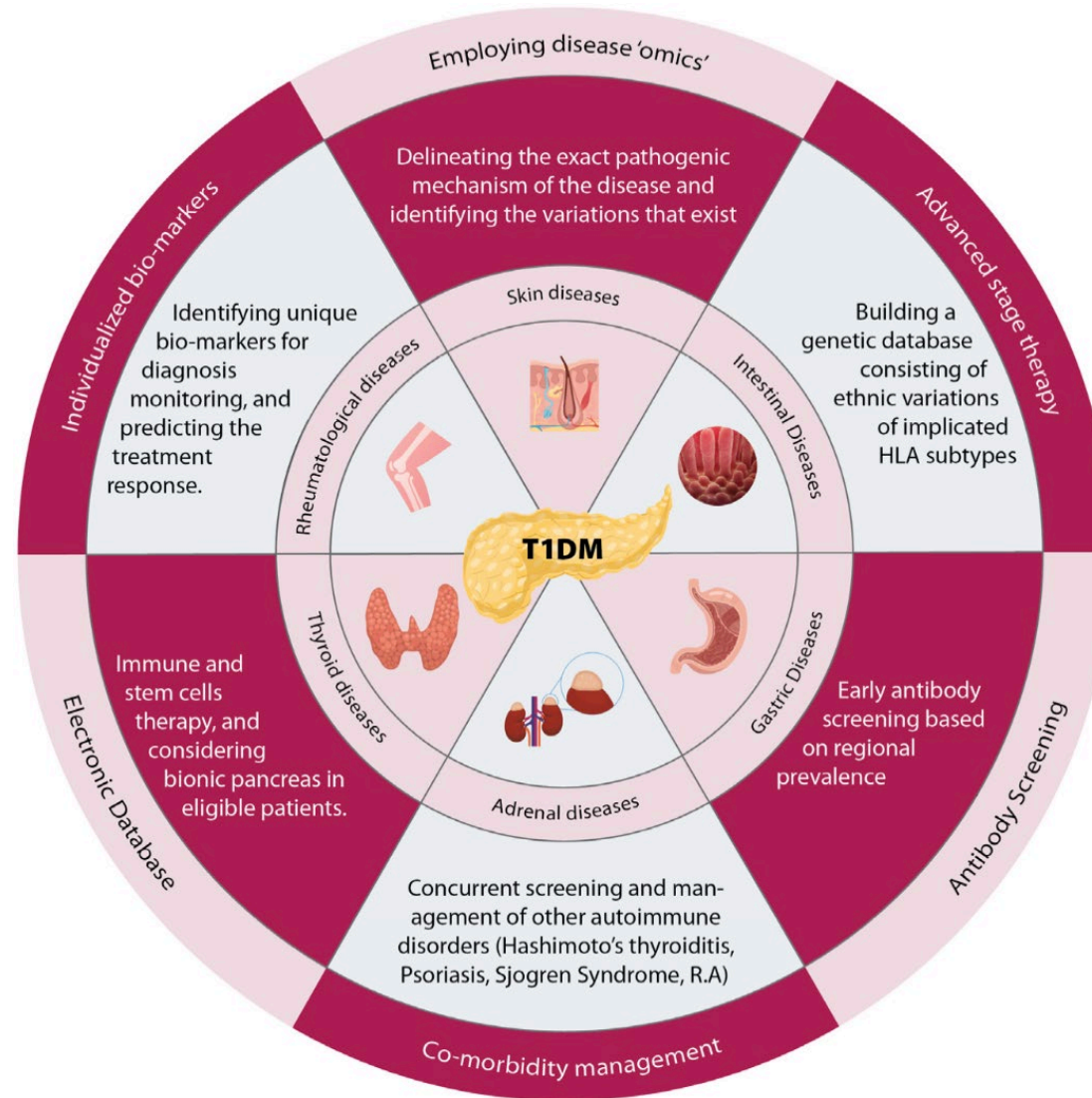
^aRatio between observed and expected disease frequency; ^bPresence of thyroid antibodies among new-onset autoimmune T1D patients is a frequent occurrence; ^cIndividuals with autoimmune T1D may require a repeat screening as the first screen is not positive for autoantibodies in a significant proportion; ^d15% of such individuals may develop it within a relatively short follow-up time. SIR>1: Greater than expected disease frequency

21-OH; 21-hydroxylase; AITD, autoimmune thyroid disease; EMA, endomysial; SIR, Standardized incidence ratio; TG, thyroglobulin; T1D, type 1 diabetes; TPO, thyroid peroxidase; TTG, transglutaminase

Increased risk of AIDs in offspring with T1D

Addison's disease (SIR: 2.41)	Celiac disease (SIR: 2.73)	Graves' disease/ hyperthyroidism (SIR: 1.86)	Hashimoto disease/ hypothyroidism (SIR: 2.35)
Pernicious anemia (SIR: 3.09)	Primary biliary cirrhosis (SIR: 3.63)	Rheumatoid arthritis (SIR: 2.12)	Sarcoidosis (SIR: 1.62)
Systemic lupus erythematosus (SIR: 2.04)	Ulcerative colitis (SIR: 1.23)	Asthma (SIR: 1.38)	Rheumatoid arthritis (SIR: 2.12)

Personalized Medicine as an approach to T1D and associated AIDs



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CD4⁺LVFOXP3

Autologous Lentiviral Vector LVFOXP3 CD4 T Cells for IPEX Syndrome

A first-in-human (FIH) Phase 1 clinical trial with a novel regulatory T (Treg) cell therapy product to treat IPEX syndrome is ongoing (NCT05241444). We administer autologous engineered CD4LVFOXP3 Treg-like cells, lentiviral vector (LV)-transduced CD4+ T cells expressing wild-type human FOXP3

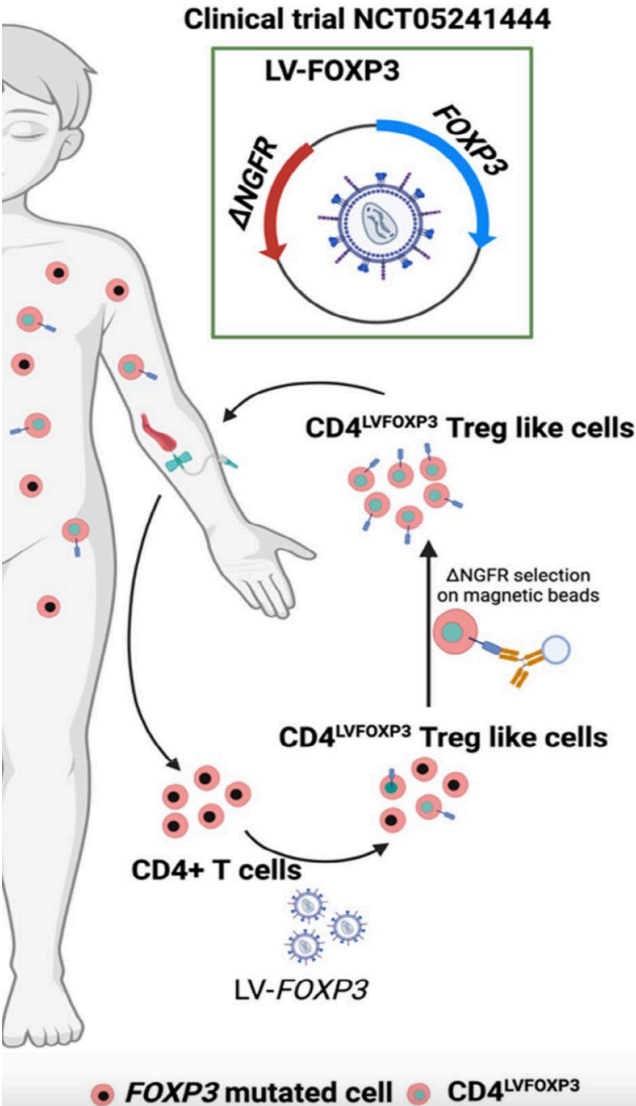
☐ NCT05241444 Recruiting

CD4⁺LVFOXP3 in Participants With IPEX

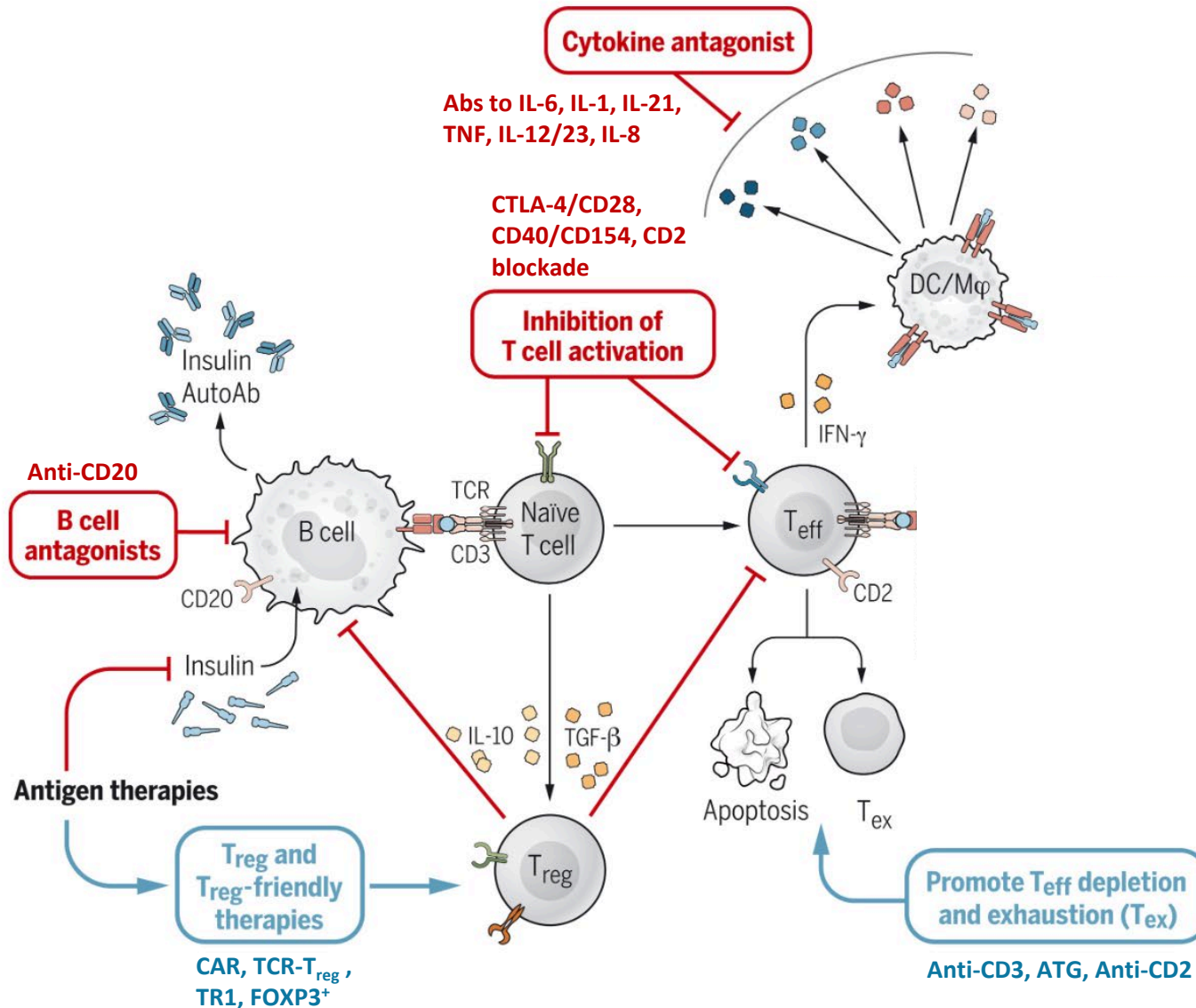
Conditions

IPEX

Study Start (Actual) ⓘ
2022-03-22
Primary Completion (Estimated) ⓘ
2027-02
Study Completion (Estimated) ⓘ
2037-02
Enrollment (Estimated) ⓘ
30
Study Type ⓘ
Interventional
Phase ⓘ
Phase 1



Immunotherapy for T1D is gaining momentum



Anti-Thymocyte Globulin (ATG)

ATG in newly diagnosed T1D

Stage 3

Study Finds Low-Dose Anti-Thymocyte Globulin (ATG) Preserves Insulin Production in People Newly Diagnosed With Type 1 Diabetes

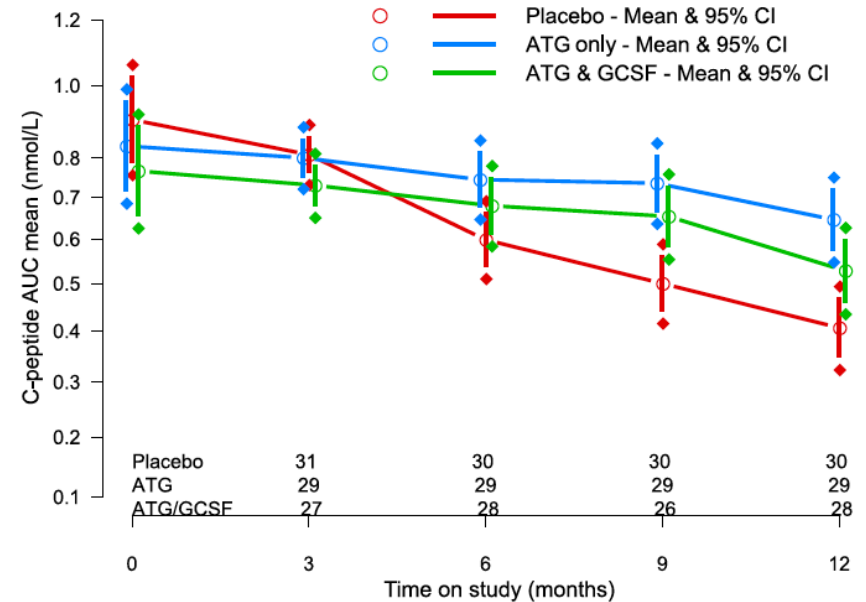


NEWS PROVIDED BY
Type 1 Diabetes TrialNet →
Jun 25, 2018, 10:00 ET



ORLANDO, Fla., June 25, 2018 /PRNewswire/ -- Findings from a new TrialNet research study show low-dose thymoglobulin (ATG) slows insulin loss in people newly diagnosed with type 1 diabetes. The findings were presented today at the 2018 American Diabetes Association's Scientific Sessions in Orlando, Florida.

C-Peptide AUC Mean Over Time by Treatment Group



Haller MJ et al., Diabetes Care 2018

Teplizumab
(Humanized Anti-CD3 mAb)

The PROTECT trial

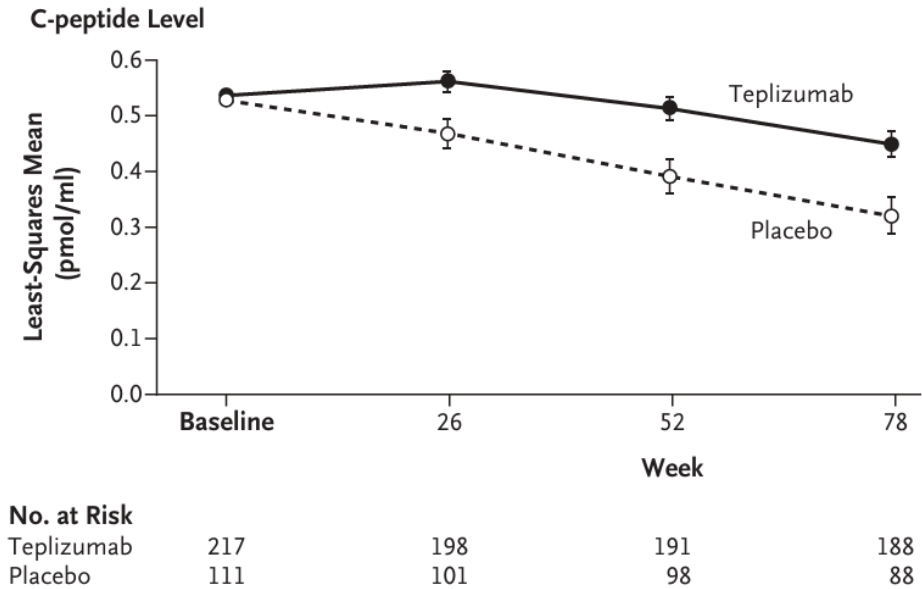


COMUNICATO STAMPA

Eseguita In Italia La Prima Infusione Di Teplizumab Che Ritarda L'insorgenza Del Diabete Di Tipo 1

Roma, 9 aprile 2025 - È stata eseguita la prima infusione in Italia di Teplizumab, un innovativo anticorpo monoclonale anti-CD3 che promette di rivoluzionare l'approccio preventivo al diabete di tipo 1.

La procedura, effettuata su una giovane di 23 anni, presso il Policlinico 'Paolo Giaccone' di Palermo, segna l'inizio di una nuova era nel trattamento precoce del diabete mellito di tipo 1. Il Teplizumab, approvato dalla Food and Drug Administration (FDA) statunitense nel novembre 2022, è infatti in grado di rallentare significativamente l'esordio clinico della malattia nei soggetti a rischio e cambiarne la storia naturale.



Newly diagnosed T1D (Stage 3)

n=217 treated vs. n=111 placebo

Phase 3, randomized, 9 mg/m² dose, two 12-day courses 20 weeks apart

Primary end point: AUC stimulated C-peptide levels at week 78

Ramos EL et al., NEJM 2023

Anti-CD3 nanoparticles

Treatment with anti-CD3-NPs reverse T1D in NOD mice

- Nanoparticles (NPs) encapsulating anti-CD3 mAb
- Targets high endothelial venules (HEVs) in the PLNs and pancreas
- Reduction of T effector cells and pro-inflammatory cytokines
- Strategy to deliver immune therapeutics to suppress T1D

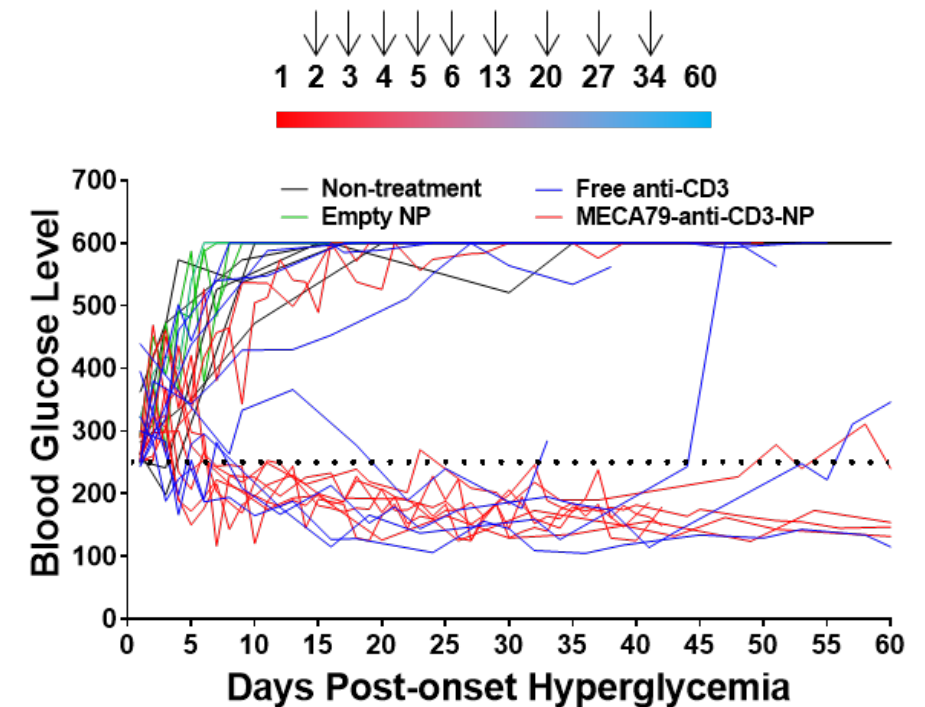
RESEARCH ARTICLE

ADVANCED
MATERIALS
www.advmat.de

Nanotargeted Delivery of Immune Therapeutics in Type 1 Diabetes

Sungwook Jung,* Moufida Ben Nasr, Baharak Bahmani, Vera Usuelli, Jing Zhao, Gianmarco Sabiu, Andy Joe Seelam, Said Movahedi Naini, Hari Baskar Balasubramanian, Youngrong Park, Xiaofei Li, Salma Ayman Khalefa, Vivek Kasinath, MacKenzie D. Williams, Ousama Rachid, Yousef Haik, George C. Tsokos, Clive H. Wasserfall, Mark A. Atkinson, Jonathan S. Bromberg, Wei Tao, Paolo Fiorina,* and Reza Abdi*

Adv. Mater. 2023, 35, 2300812



ImmunoStem
(PD-L1.Tg HSCs)

ImmunoStem reduces T cells autoimmune response

- Deficiency in PD-L1 expression in HSCs
- *ImmunoStem* are PD-L1.Tg HSCs with immunoregulatory properties
- *ImmunoStem* suppress autoreactive T cells
- *ImmunoStem* halt the progression of T1D in NOD mice
- Potential therapeutic avenue of *ImmunoStem*

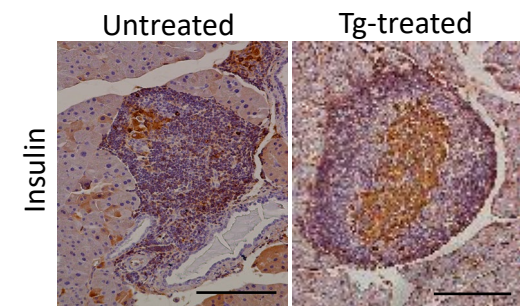
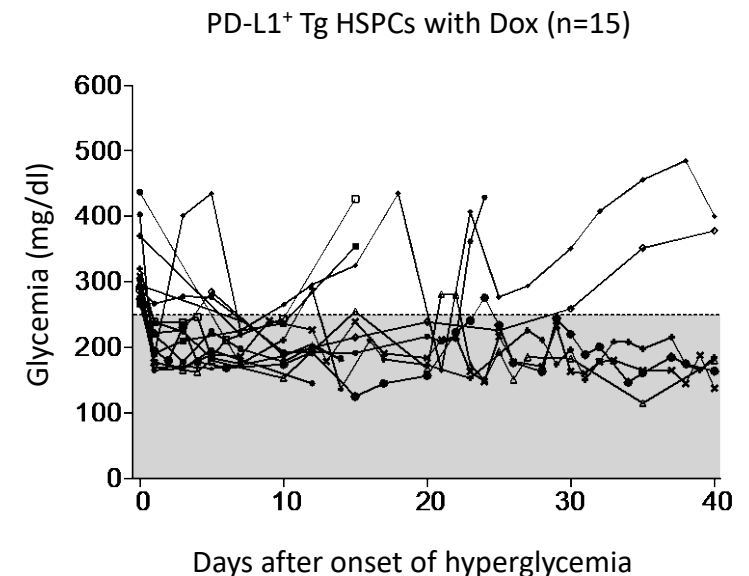
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

AUTOIMMUNITY

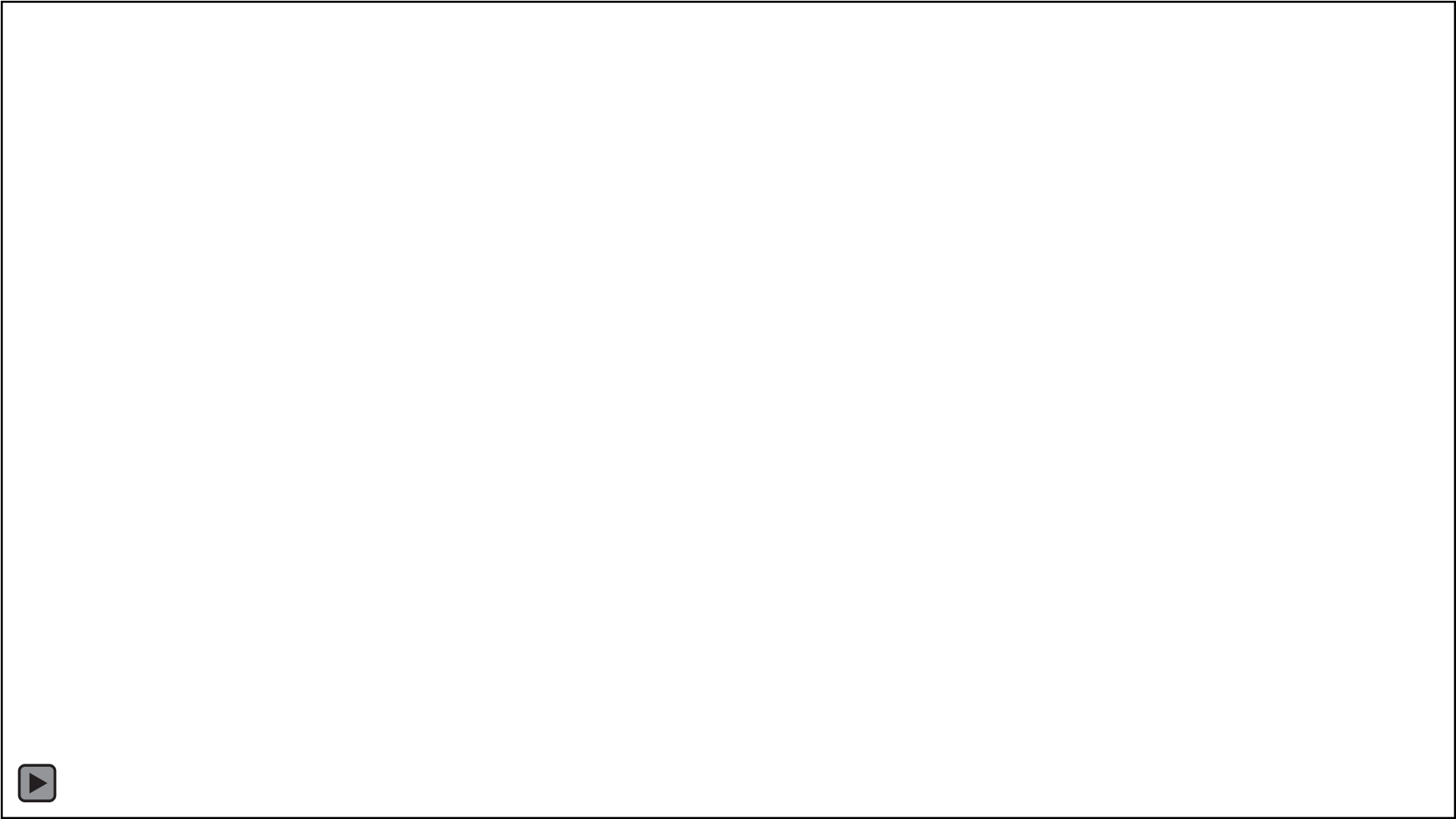
PD-L1 genetic overexpression or pharmacological restoration in hematopoietic stem and progenitor cells reverses autoimmune diabetes

Moufida Ben Nasr,^{1,2} Sara Tezza,¹ Francesca D'Addio,^{1,2} Chiara Mameli,³ Vera Uselli,^{1,2} Anna Maestroni,² Domenico Corradi,⁴ Silvana Belletti,⁴ Luca Albarello,⁵ Gabriella Becchi,⁴ Gian Paolo Fadini,⁶ Christian Schuetz,⁷ James Markmann,⁷ Clive Wasserfall,⁸ Leonard Zon,⁹ Gian Vincenzo Zuccotti,^{2,3} Paolo Fiorina^{1,2,10*}

15 November 2017



Summary



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Conclusions

- Autoimmune Polyendocrine Syndromes: where immunology and endocrinology meet
- Need for more immunological therapeutic approaches in Autoimmune Polyendocrine Syndromes
- Do we know all antigens?

Acknowledgements

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