Prevenzione farmacologica nel T1D

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Dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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Outline

1. Introduction
2. Teplizumab
3. Other immunotherapies
4. New approaches
5. Conclusions

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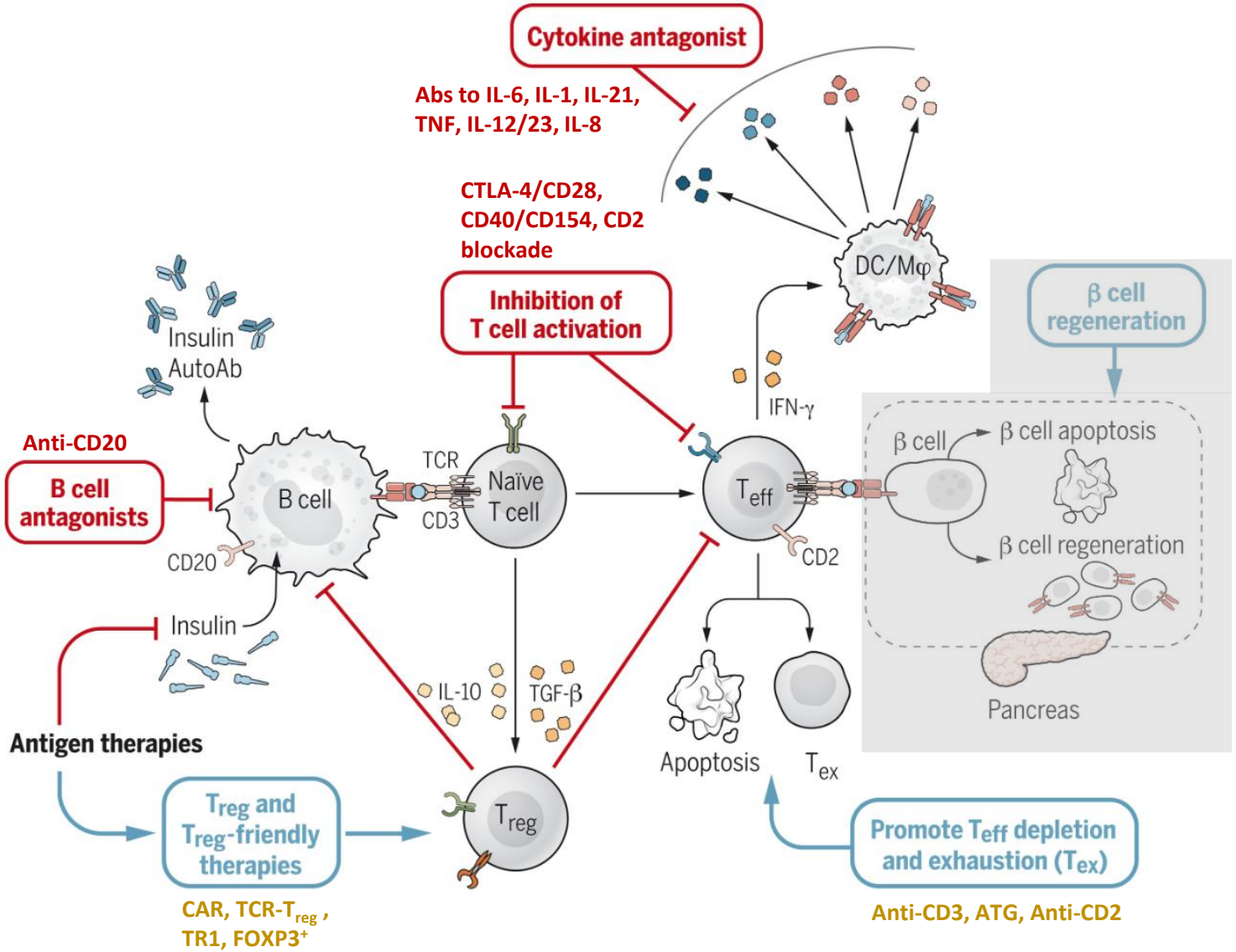
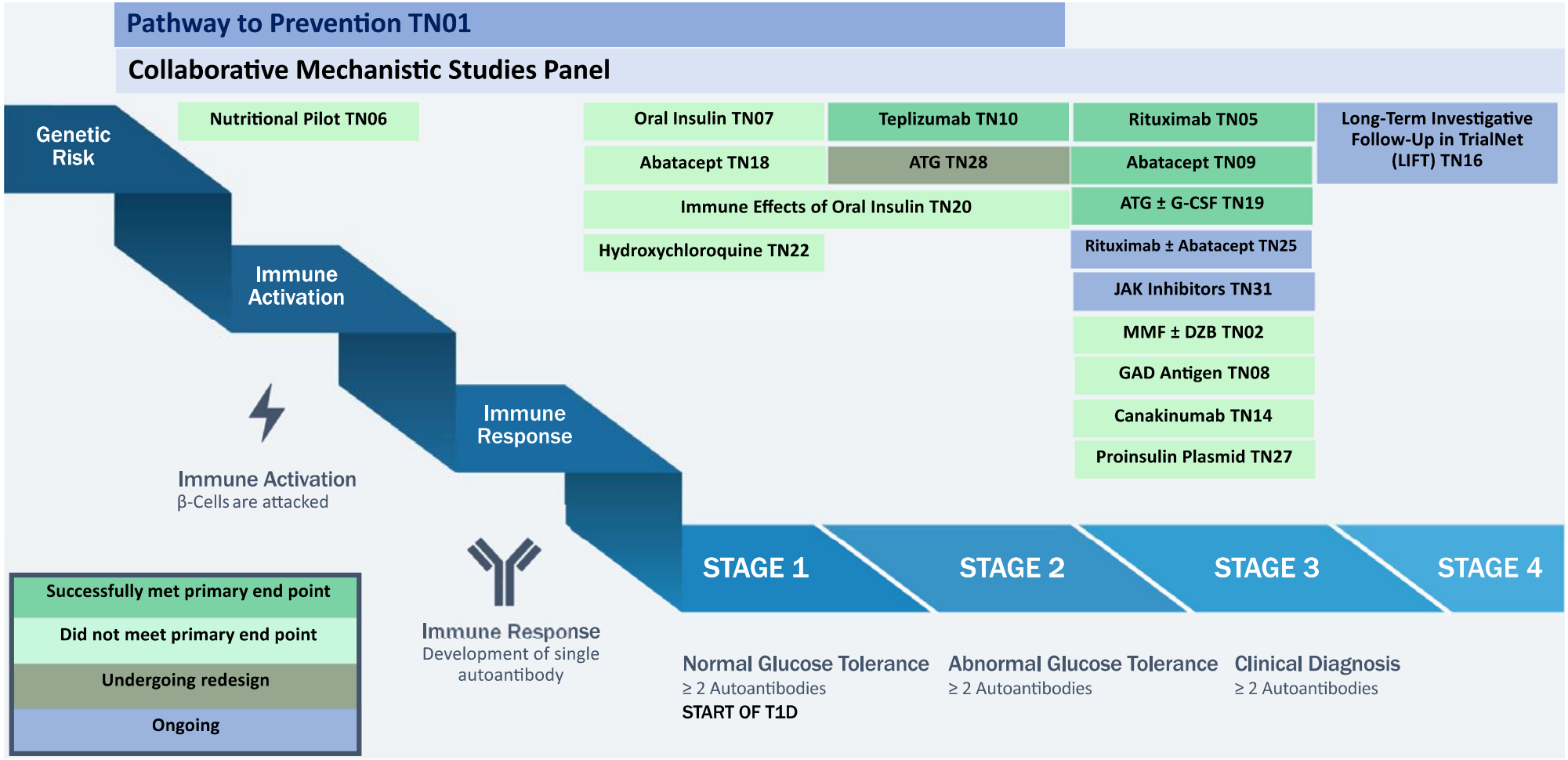
Immunotherapy for T1D is gaining momentum



Bluestone JA et al., Science 2021

Clinical studies conducted and ongoing within TrialNet in T1D



Jacobsen L et al. Diabetes Care 2025

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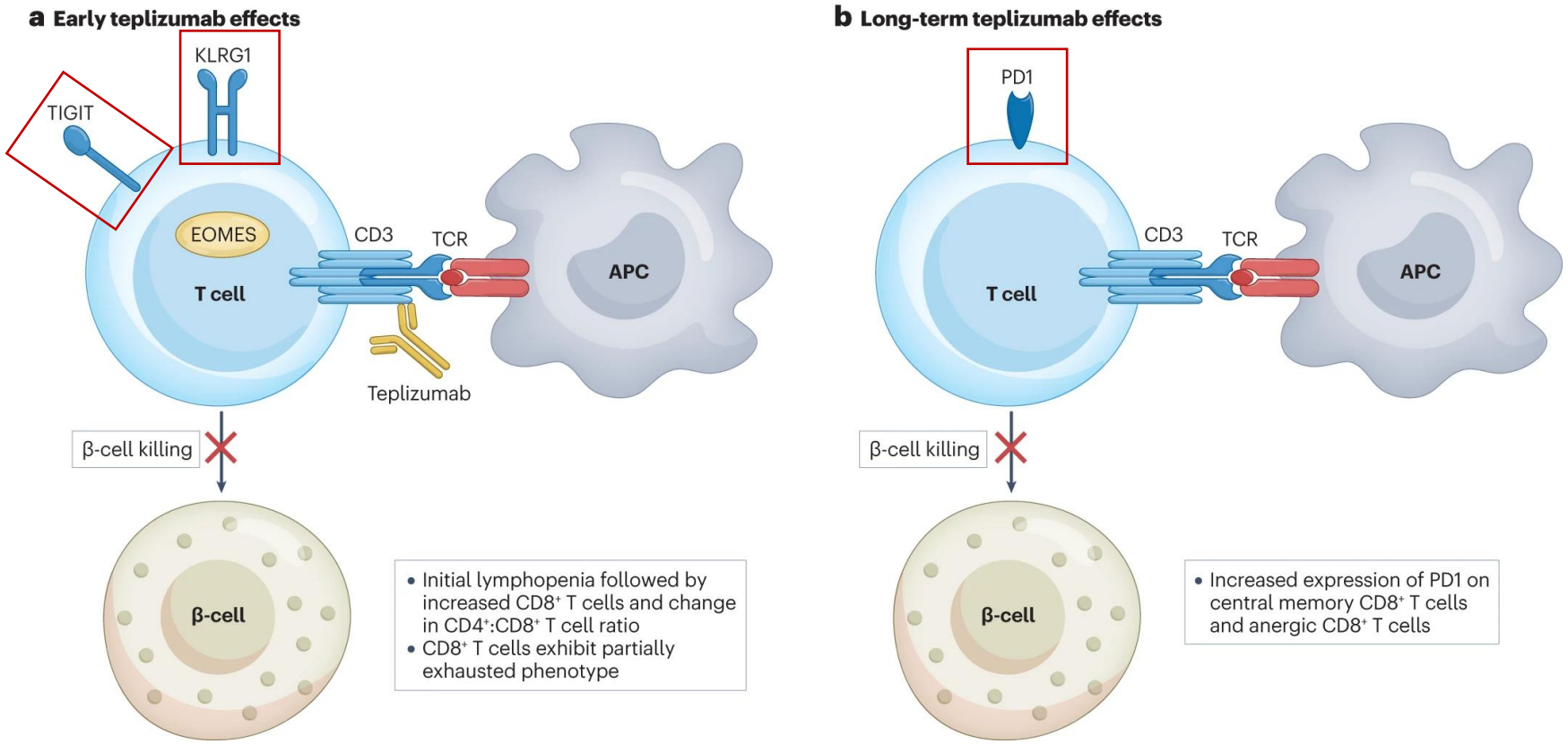
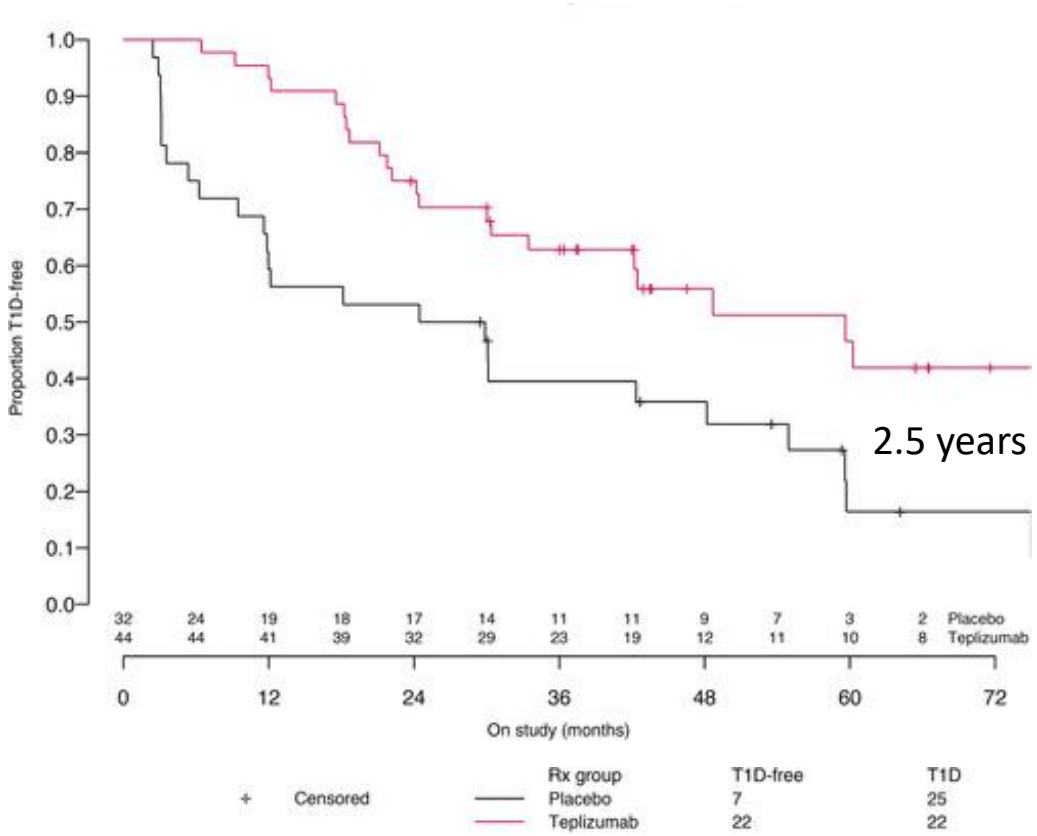
Teplizumab (anti-CD3 mAb)

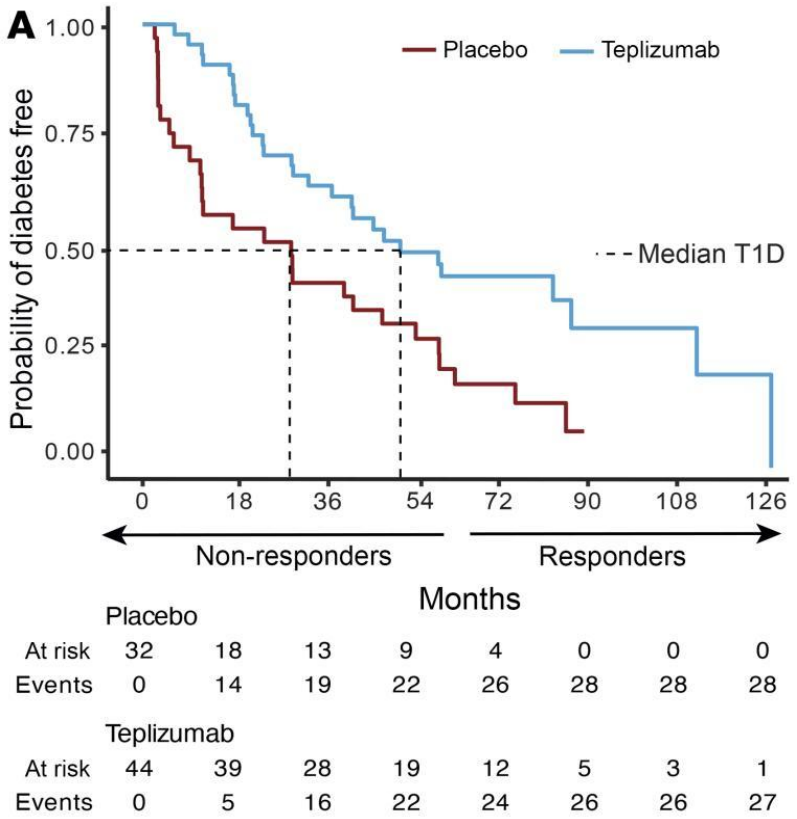


Herold K et al. Nat Rev Immunol 2024

Stage 2: Teplizumab delays T1D onset



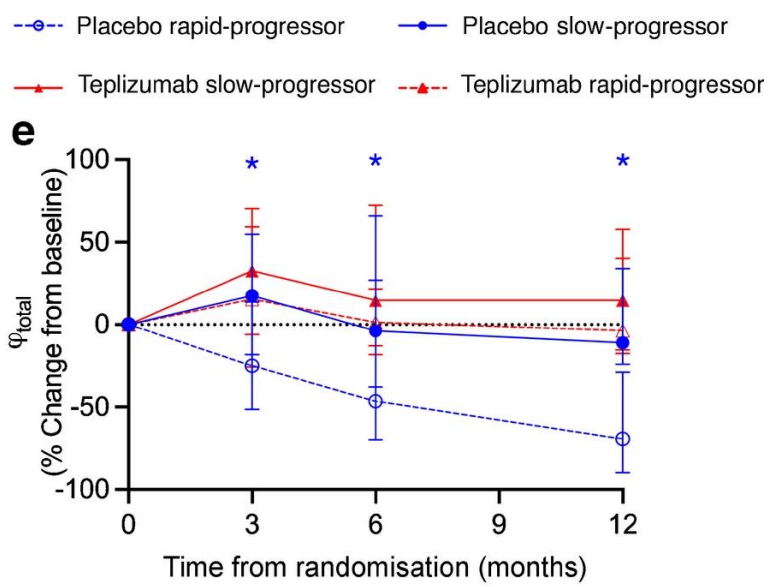
Responders: undiagnosed/diagnosed Stage 3 after 60 months

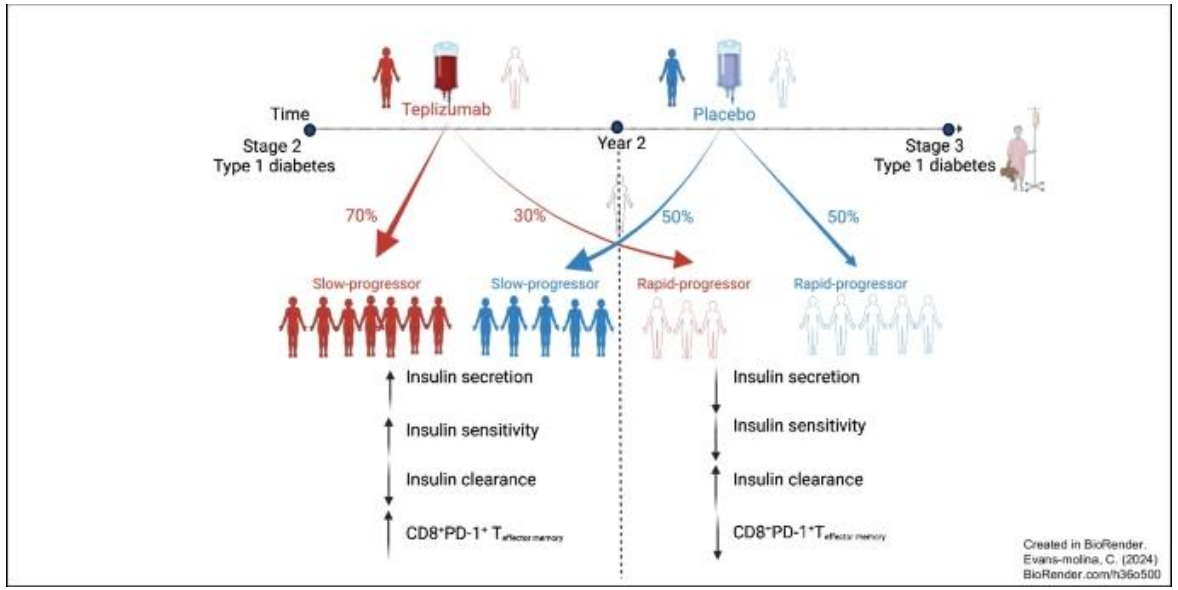


Sims EK et al. Sci Transl Med, 2021
Herold KC et al. NEJM, 2019
Delgado A et al. JCI 2024

Stage 2: Teplizumab slow progressors display higher insulin secretion

Insulin secretion



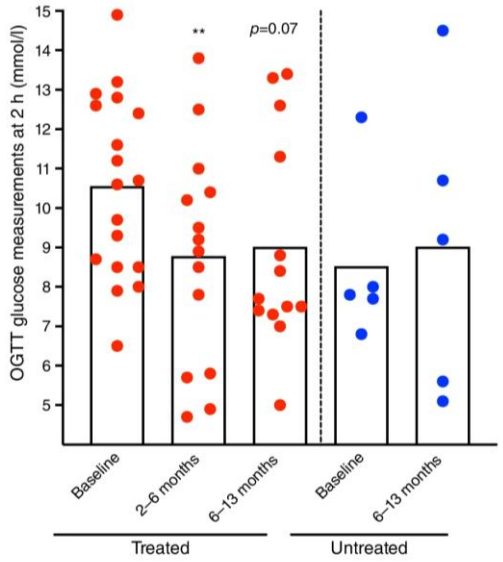


Slow progressors: diagnosed Stage 3 after 24 months

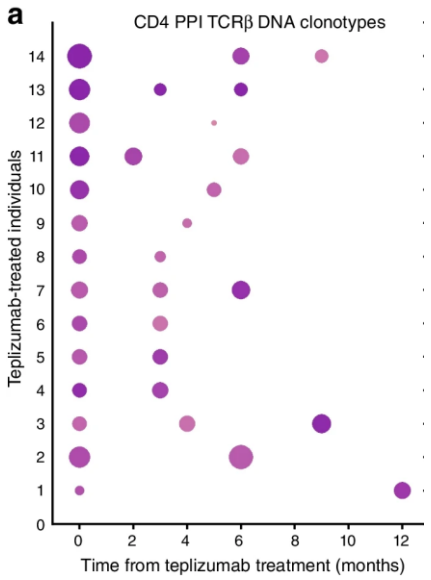
Galderisi A/Petrelli A et al. Diabetologia 2025

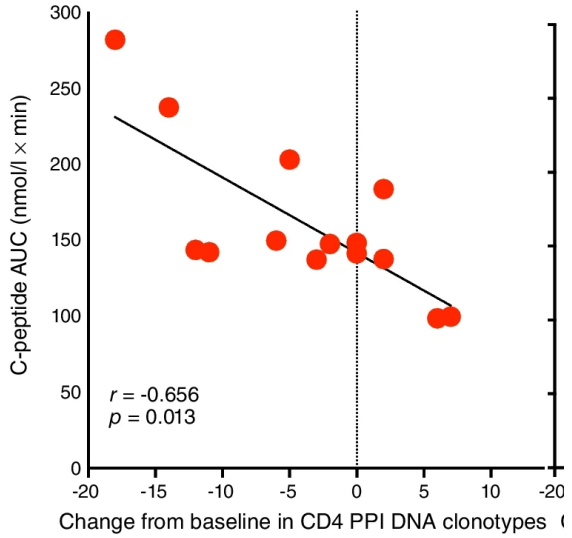
Stage 2: Teplizumab a real-world evaluation in n=30 pts

Early glycaemic improvements



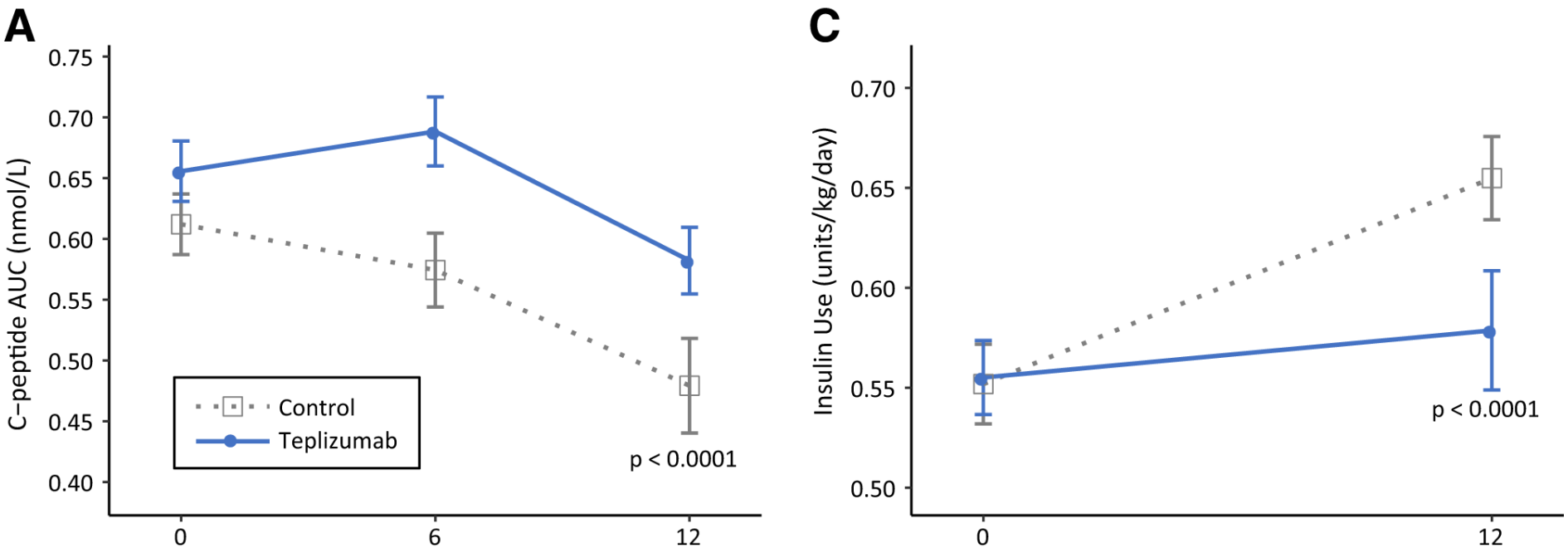
Reduced CD4 preproinsulin-specific TCR





Karakus KE et al. Diabetologia 2026

Stage 3: Preserves β-Cell Function across multiple trials



Herold KC et al. Diabetes Care 2023

βETA PRESERVE Study

A Randomized, Double-blind, 2-arm, Phase 3 Study to Investigate Efficacy and Safety of Teplizumab Compared With Placebo in Participants 1 to 25 Years of Age With Newly Diagnosed Stage 3 Type 1 Diabetes (T1D)

To join this study, participants must:

- Be 1 to 25 years of age
- Have been recently diagnosed (**within a month**) with T1D.
- Be **positive** for at least **one T1D autoantibody**

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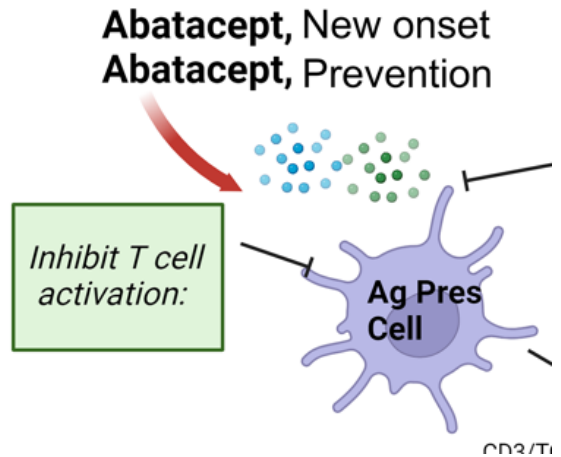
Recent advances in T1D immunotherapy guide future directions

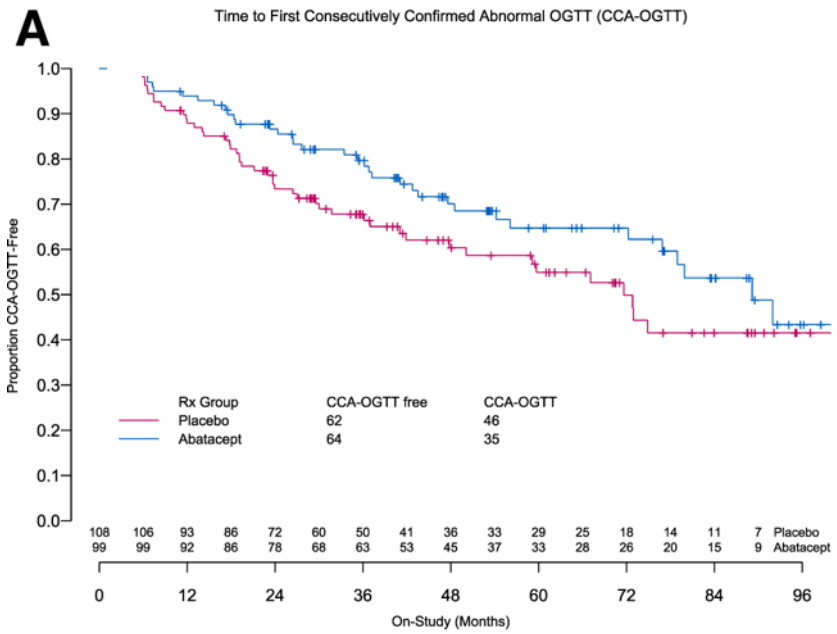
	Intervention	Trial name and targeted population (age)	Outcome
Immune modulation	Teplizumab (anti-CD3 Ab)	TN-10 study: stage 2 disease (8–45 years)	Delay in time to T1D (24,25)
		Protégé study: new-onset T1D (8–35 years)	Negative primary outcome (1 year of insulin use and HbA_{1c}) (64), but 14-day full-dose regimen preserved 2-year C-peptide AUC (65)
		PROTECT: new-onset T1D (8–17 years)	Increased week-78 C-peptide vs. placebo (26)
	Low-dose ATG	New-onset T1D (12–45 years)	Higher 12-month C-peptide AUC vs. placebo (27)
	Golimumab (anti–TNF-α Ab)	T1GER: new-onset T1D (6–21 years)	Higher 52-week C-peptide AUC vs. placebo (10)
	Abatacept (CTLA4-Ig)	TN-18 study: stage 1 disease (6–45 years)	No significant difference in progression to glucose intolerance; increased 12-month C-peptide AUC vs. placebo (20)
		TN-09 study: new-onset T1D (6–45 years)	Higher 2-year C-peptide AUC vs. placebo (66)
	Alefacept (fusion protein binding CD2)	T1DAL: new-onset T1D (12–35 years)	No significant difference at 12-month primary end point but higher 24-month C-peptide area AUC vs. placebo (67,68)
	Rituximab (anti-CD20 Abs)	TN-05: new-onset T1D (8–40 years)	Higher 12-month C-peptide AUC vs. placebo (69)
β-Cell protection	Verapamil (calcium channel blocker)	New-onset T1D (18–44 years)	Higher 12-month C-peptide AUC vs. placebo (13)
		CLVer: new-onset T1D (7–17 years)	Preserved 52-week C-peptide AUC (14)
	Imatinib (tyrosine kinase inhibitor)	New-onset T1D (12–45 years)	Higher 12-month C-peptide AUC vs. placebo (70)
	Baricitinib (JAK1/2 inhibitor)	BANDIT: new-onset T1D (10–30 years)	Higher 12-month C-peptide AUC vs. placebo (12)
Combination	Anti–IL-21 and liraglutide (GLP-1 receptor agonist)	New-onset T1D (18–45 years)	Combination treatment, but not IL-21 alone, preserved 54-week C-peptide AUC vs. placebo (9)

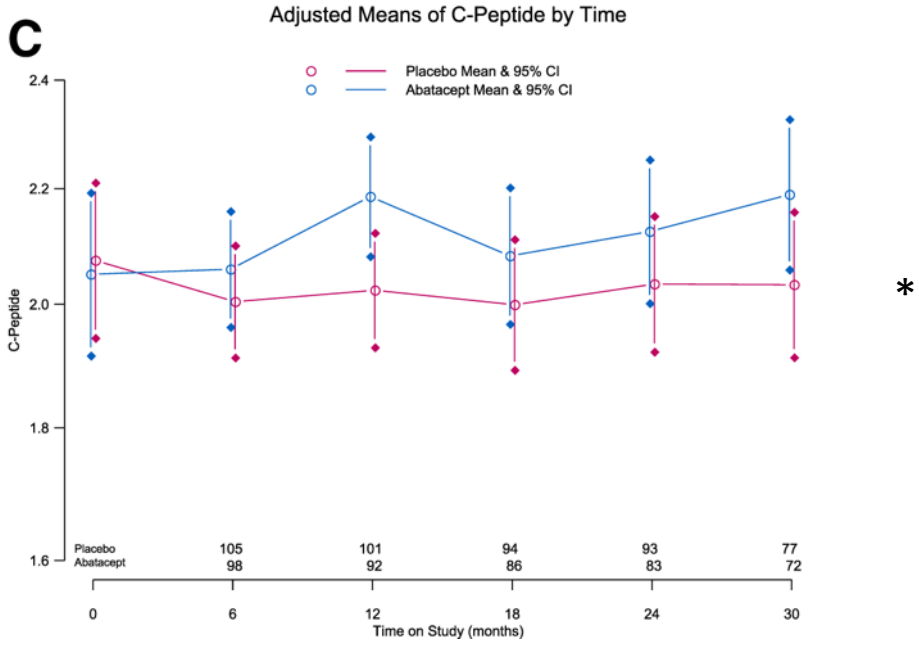
Mallone R et al. Diabetes 2025

Stage 1: Abatacept (CTLA4Ig)



Abatacept did not delay the progression of Stage 1 to Stage 2 but preserved insulin secretion.





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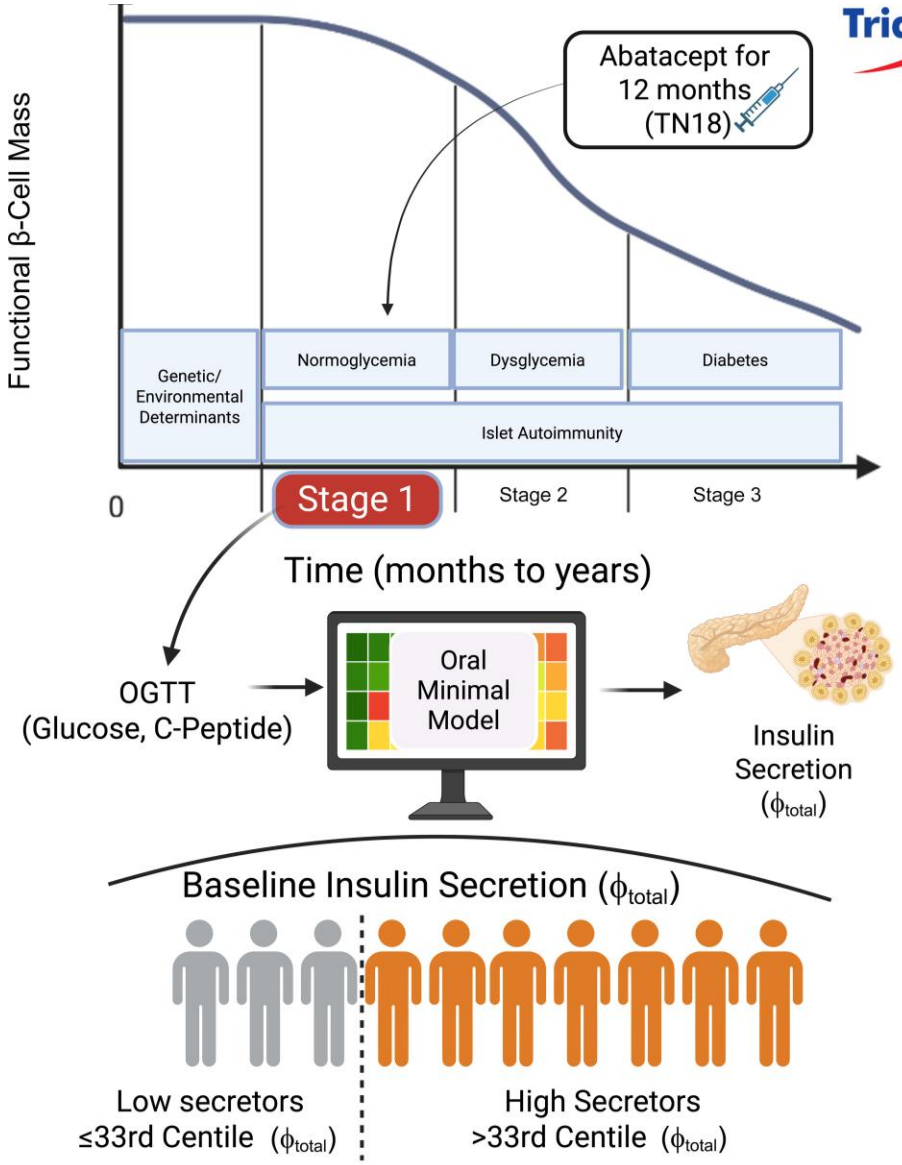
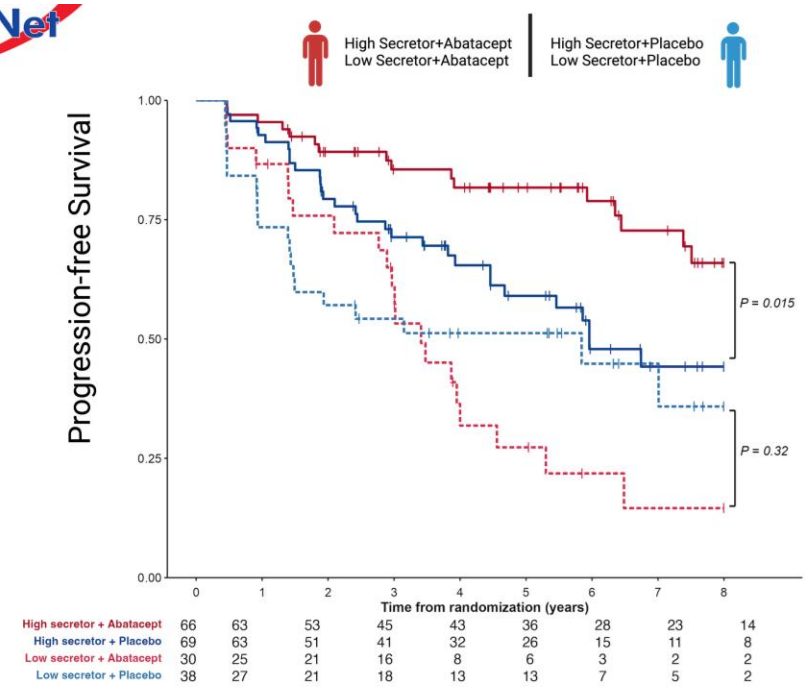
Abatacept n=101, placebo n=111

Russell WE et al. Diabetes Care 2023

Stage 1: Baseline insulin secretion determines response to Abatacept





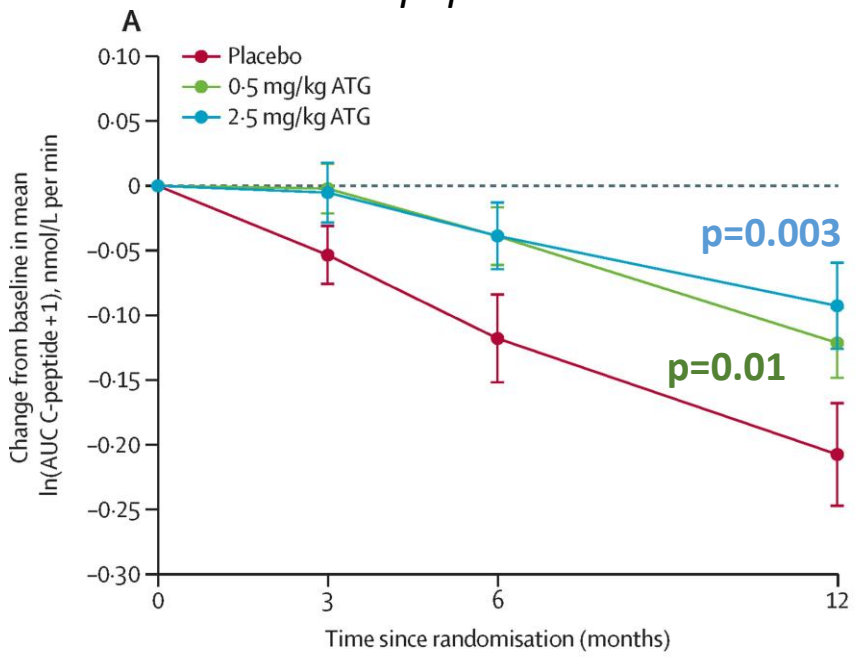
	vs High Secretors	vs Low Secretors
Δ Progression-Free Survival	**+15.8** months (*P* < *0.001*)	-7.7 months (*P* = ns)

Baseline insulin secretion modifies abatacept effect : treatment reduced progression risk in high but not in low secretors (HR = 2.92, *P* = 0.015)

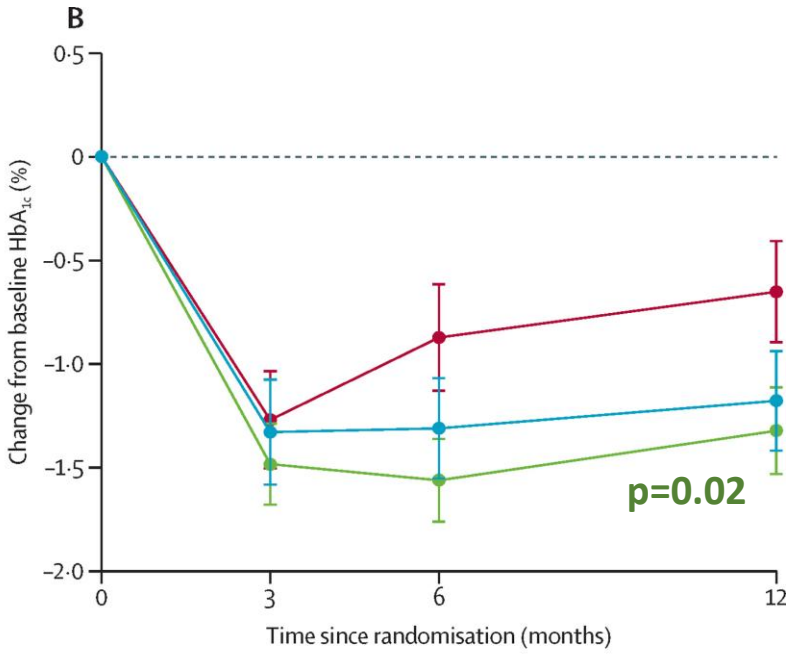
Galderisi A et al. Diabetes 2025

Stage 3: low dose ATG reduced loss of β-cell function in young adults

C-peptide decline



HbA1C reduction



Adverse events

Cytokine release syndrome
- 33% in the 2·5 mg/kg ATG
- 24% in the 0·5mg/kg ATG

Serum sickness occurred
- 82% in the 2·5 mg/kg ATG
- 32% in the 0·5 mg/kg ATG

N=1 AutoAb+
Age 6-25 years
Stage 3: 3-9 weeks
Random C-peptide: 0.2 nmol/l

Mathieu C et al. Lancet 2025

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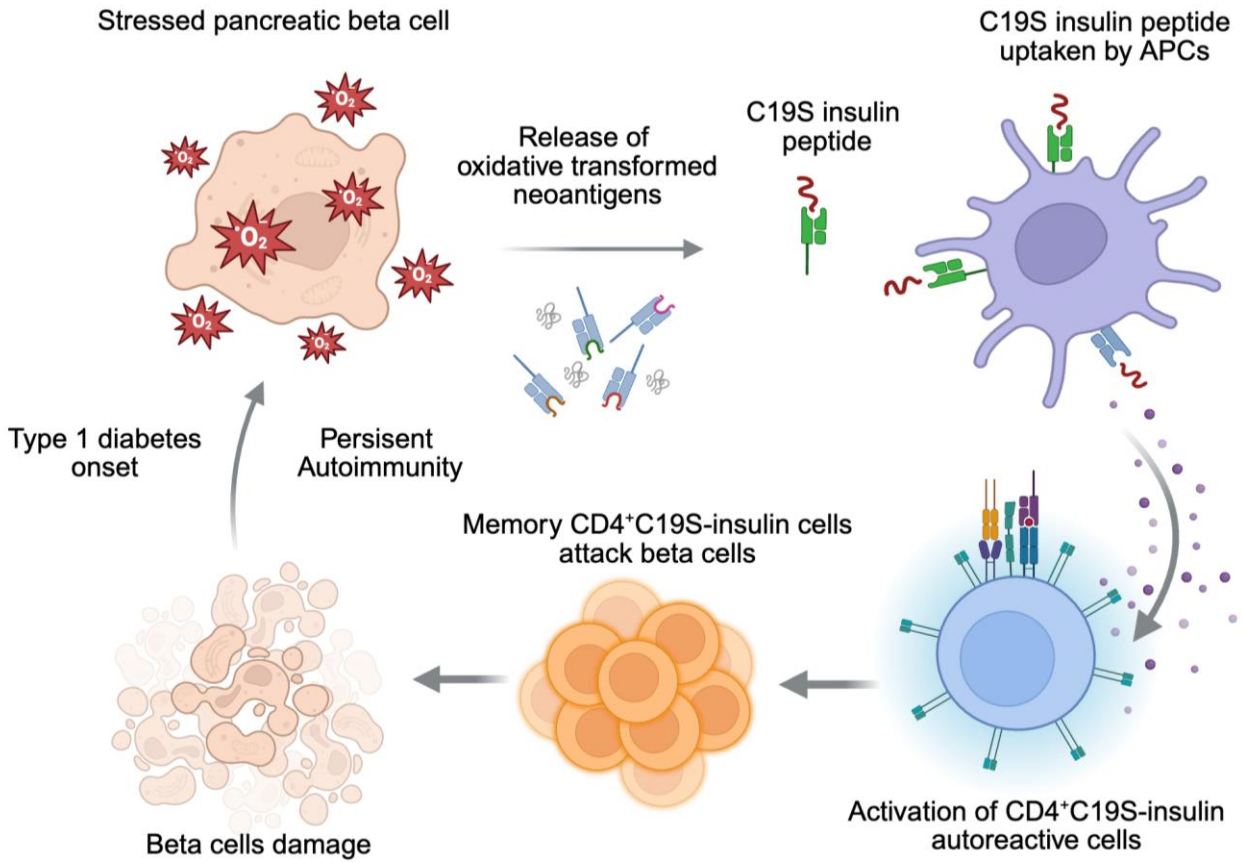
Targeting emerging autoreactive CD4 T cells against neoantigens

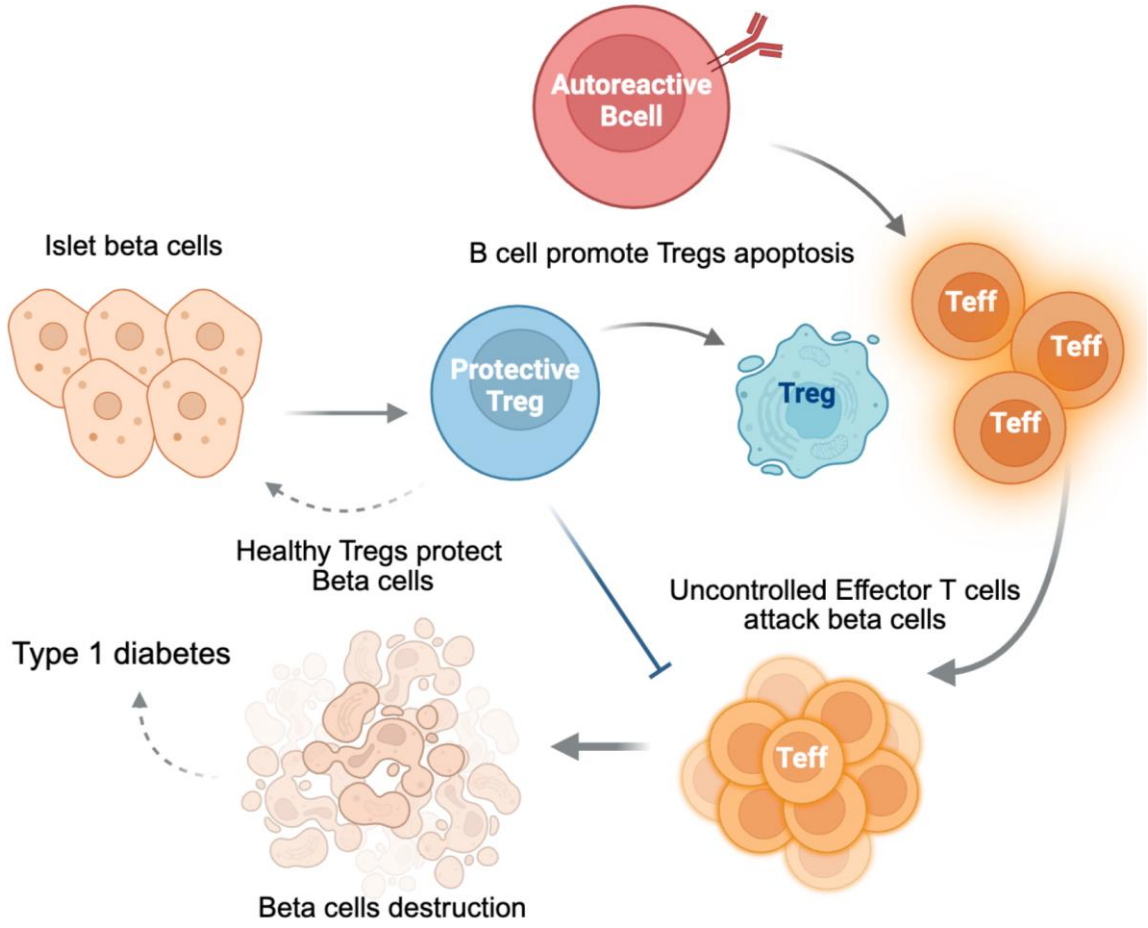
A distinct, microenvironment-driven route of neoantigen formation fuels sustained autoreactivity in T1D



Srivastava N et al. Nat Immunol 2026

Targeting Autoreactive B cells to restore Islet Tolerance in T1D

- Absence of B-cell promotes islet transplant tolerance and enhances islet-protective Treg.
- B cells negatively regulate Treg function.
- B cells regulate the progression of anti-islet immunity
- The B-cell–Treg interaction is a druggable target



Wilson CS et al. Diabetes 2026

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Conclusions

- T1D is an immune-mediated disease that can now be therapeutically modulated.
- Immunotherapies showed that T1D can be delayed and β-cell function preserved.
- Teplizumab represents a milestone: T1D onset can be delayed in at-risk individuals.
- Interventions appear more effective in early or pre-symptomatic stages of T1D.
- Future progress will likely depend on:
  - ✓ earlier identification of at-risk individuals
  - ✓ combination immunotherapies
  - ✓ combination with β-cell protective or regenerative strategies

Acknowledgements

Prof. Paolo Fiorina

The Team