Update on Clinical Trials in T1D

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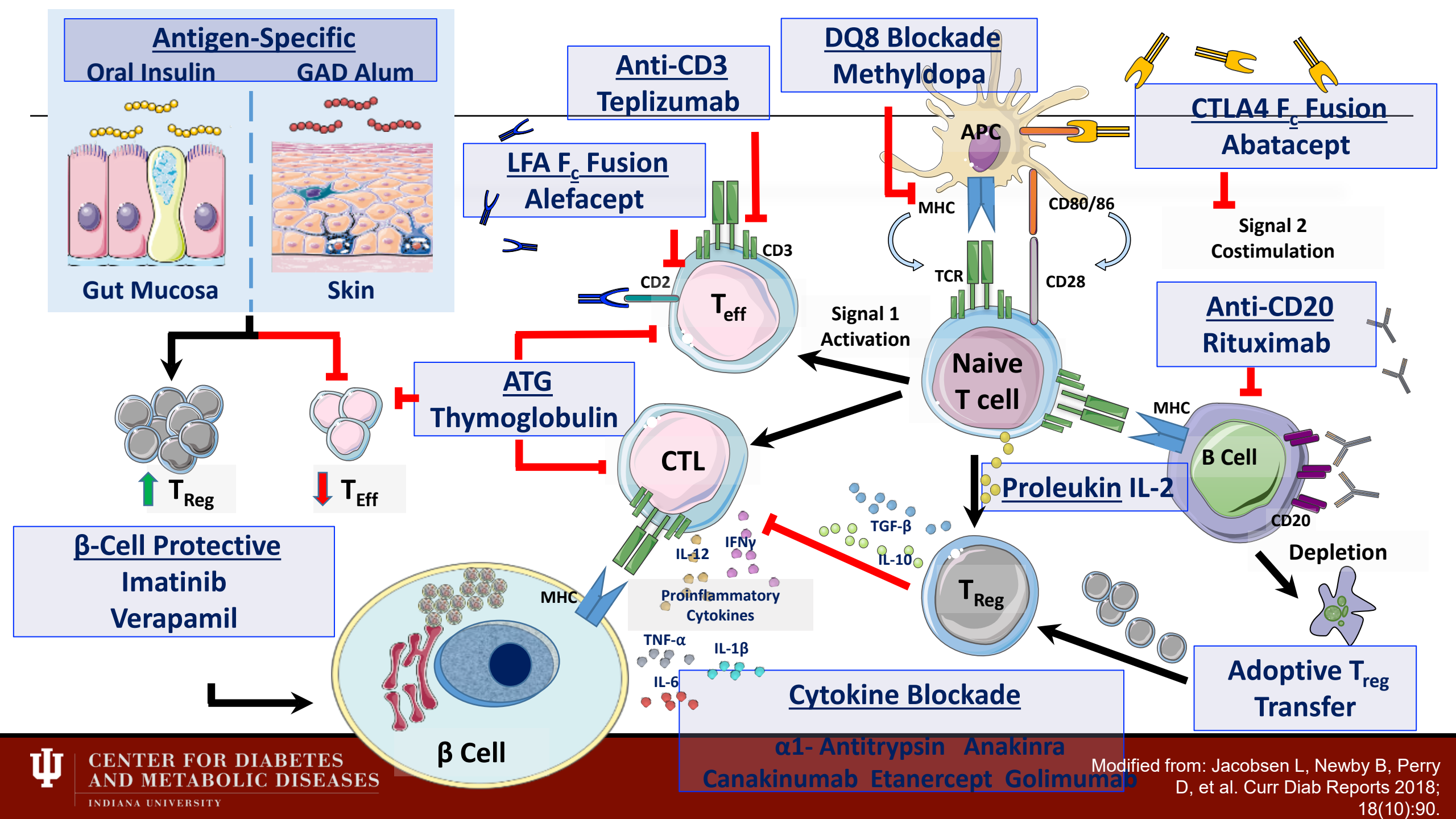
Disclosures

- Consultant and speaker for Sanofi, scientific advisory boards for Diamyd and Wink Therapeutics, speaker for Med Learning



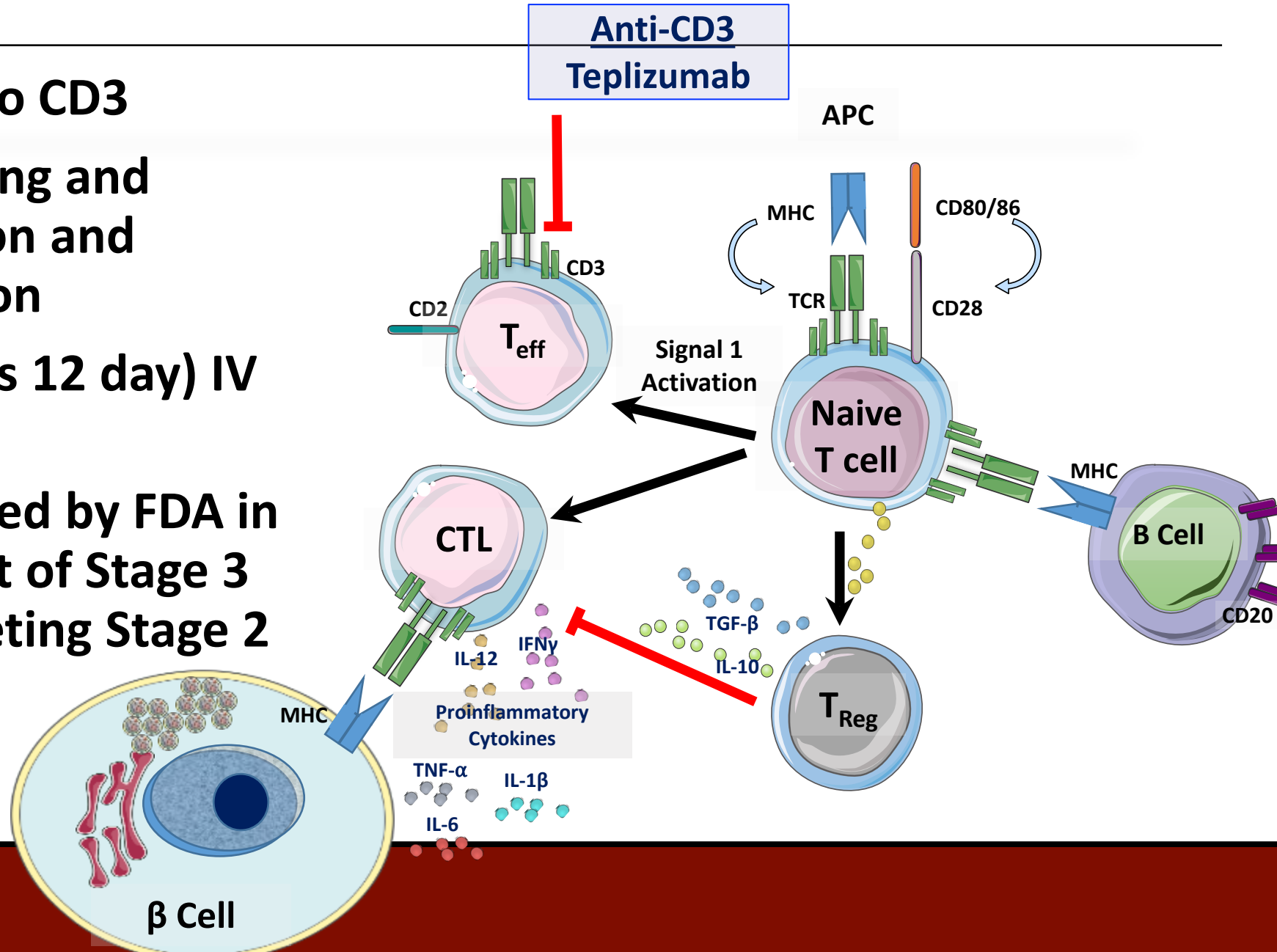
Modified from: Jacobsen L, Newby B, Perry D, et al. Curr Diab Reports 2018; 18(10):90.

Today's talk

- Focus on a subset of drugs that have shown efficacy in a large trial and I think have potential in prevention
- Disclaimer: This talk is only 20 minutes
- Only one of these other drugs is currently approved for clinical care in T1D disease modification by regulatory authorities
- I am not going to talk about some very promising mechanisms early on in the pipeline
- Trial data can feel repetitive and overwhelming- I've got you with hot takes!

Teplizumab

- Monoclonal antibody to CD3
- Partial agonistic signaling and subsequent deactivation and promotion of exhaustion
- Given as 14 (some trials 12 day) IV infusion
- 14 day infusion approved by FDA in 2022 to delay the onset of Stage 3 disease in persons meeting Stage 2 criteria



Teplizumab for Delay of T1D in Relatives At-Risk

- RCT testing single course of teplizumab IV infusion vs. placebo
- 76 participants (44 on teplizumab and 32 placebo)
  - >= 8 years of age, relatives with stage 2 disease
- Primary Endpoint: time to diabetes development
- Petite T1D (announced at ISPAD) in 23 children under 8 showed comparable safety (~51 wk fu)
  - 3 didn't complete infusion (anemia, elevated LFTs, rash then PICC line DVT)
  - 1 participant diagnosed with a low grade glioneuronal tumor 12 months after treatment and asthma exacerbation 16 months after treatment

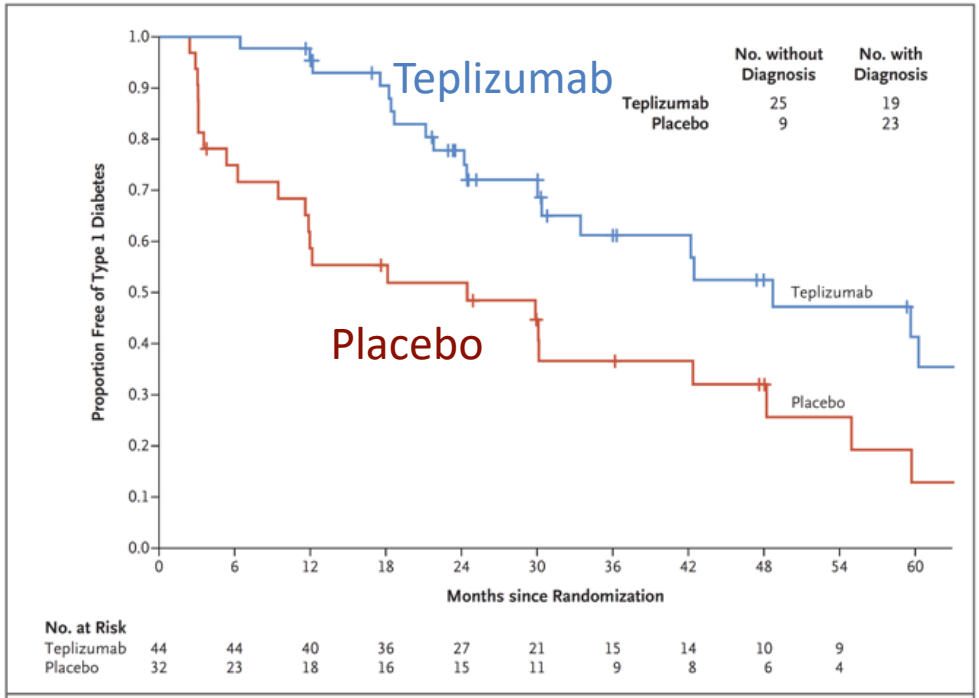


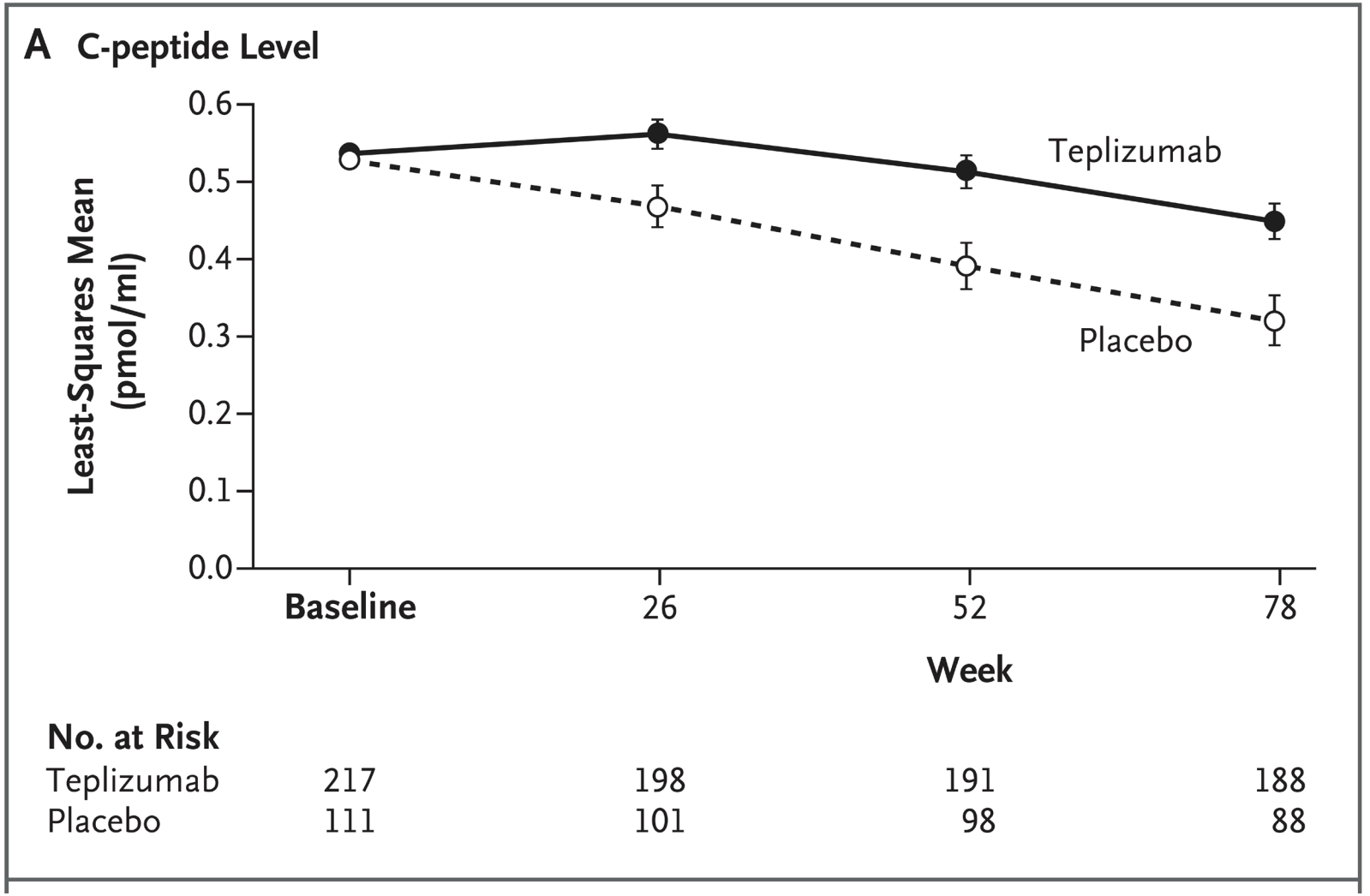
Figure 1. Effects of Teplizumab on Development of Type 1 Diabetes.

Shown are Kaplan–Meier estimates of the proportions of participants in whom clinical diabetes was not diagnosed. The overall hazard ratio was 0.41 (95% confidence interval [CI], 0.22 to 0.78; two-sided P=0.006 by adjusted Cox proportional-hazards model). The median time to diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group. The numbers of participants with or without a diagnosis of clinical type 1 diabetes (upper right) represent data at the conclusion of the trial. Tick marks indicate censored data.

Herold et al. N Engl J Med. 2019 Aug 15;381(7):603-613. Gitelman et al. *Diabetologia*. 2025. Sims et al. Sci Transl Med. 2021 Mar 3;13(583):eabc8980.

PROTECT Study

- New onset T1D
- Children and adolescents
- 2 12-day courses, 26 weeks apart
- No increased issues with clinical infections (during COVID pandemic)



Ramos et al. *N Engl J Med.* 2023 Dec 7;389(23):2151-2161.

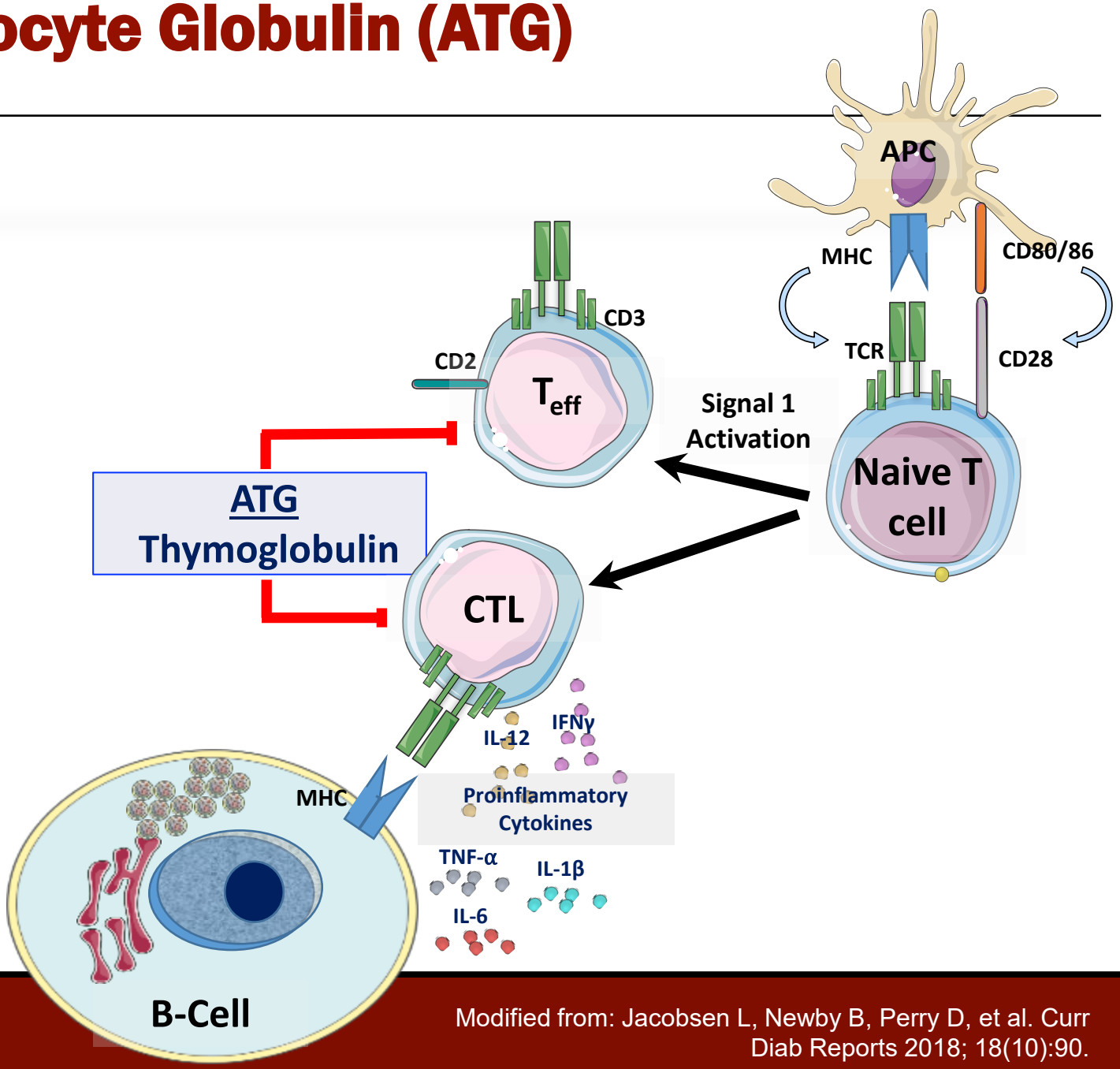
Next steps for teplizumab in T1D?

- Expansion of regulatory approval (being reviewed under FDA accelerated approval program)?
- Optimal timing of dosing?
- Does a repeat dose help?
- Combination therapy?

- Regulatory approval of this drug is a huge achievement in our field
- This is the first step with durable diabetes delay likely requiring a combination regimen with an induction + maintenance approach
- Teplizumab is just the beginning!

Antithymocyte Globulin (ATG)

- Two intravenous infusions of antibody against human thymocytes
- Depletes pathogenic T cells, followed by increased regulatory T cell frequency and hematopoietic mobilization
- Side effects can include serum sickness that can require treatment with steroids



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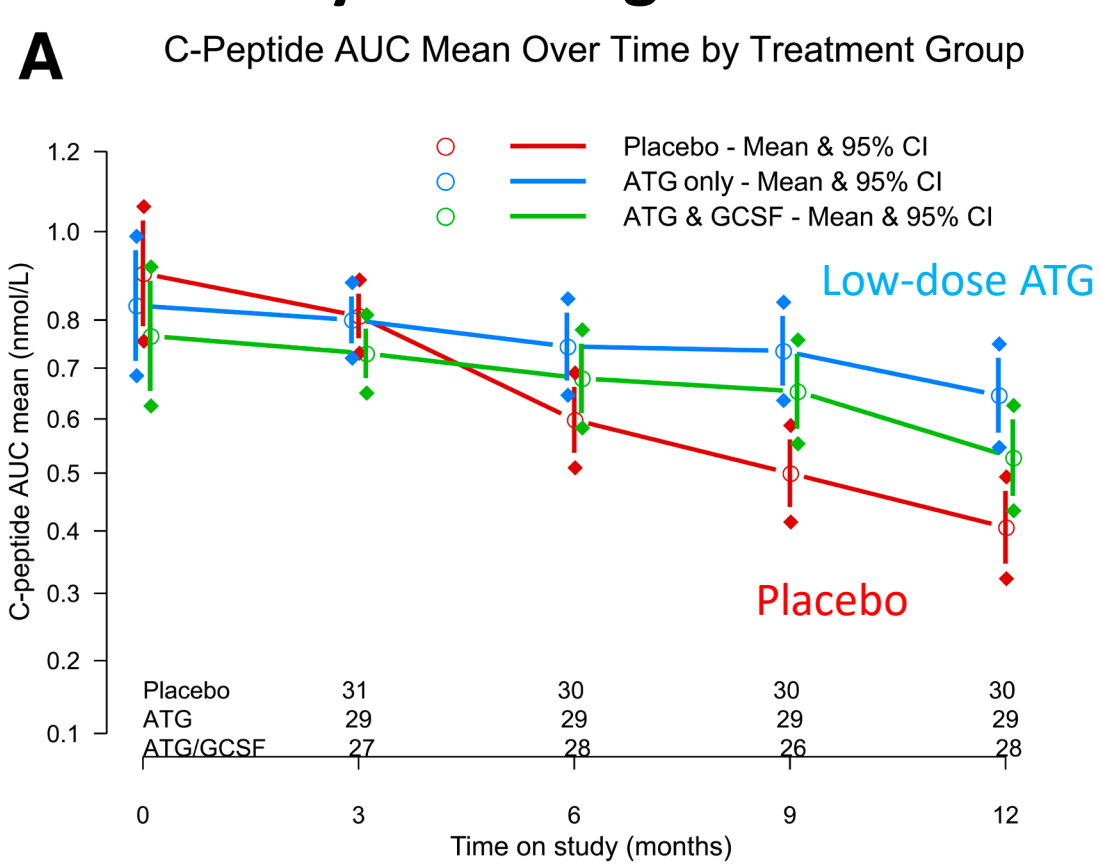
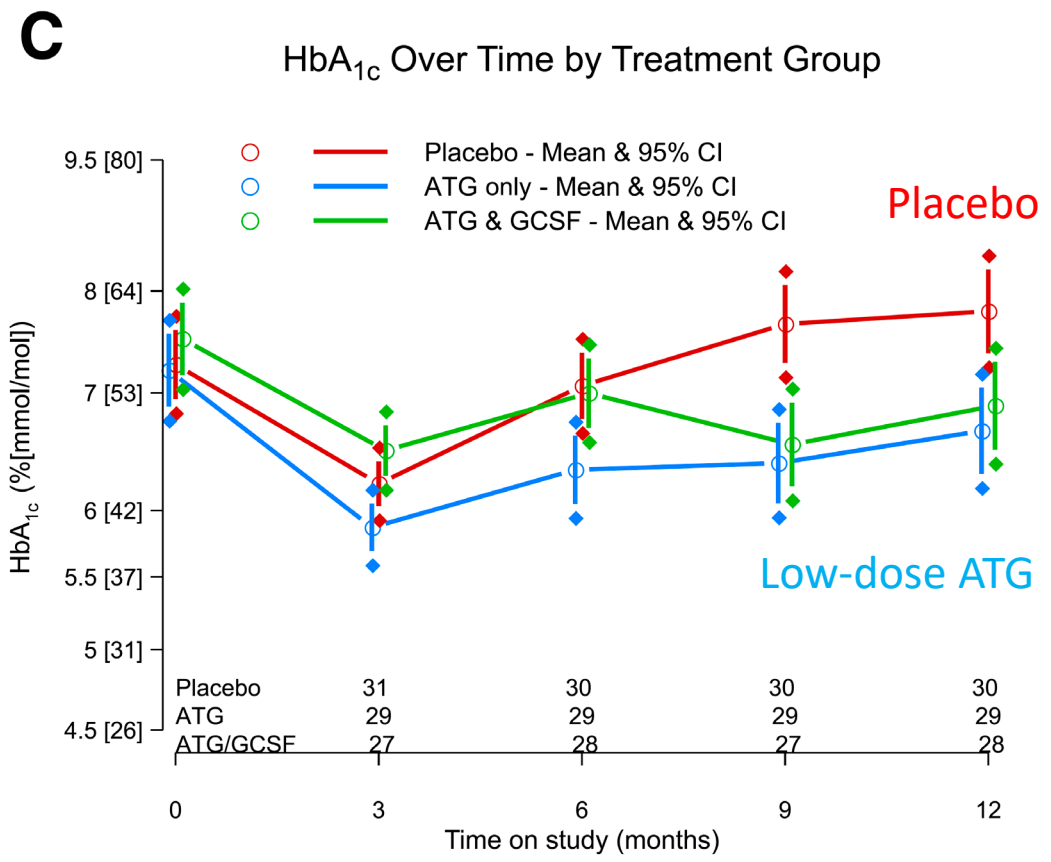
Low-Dose ATG study

- New-onset T1D
- 12–45 years of age



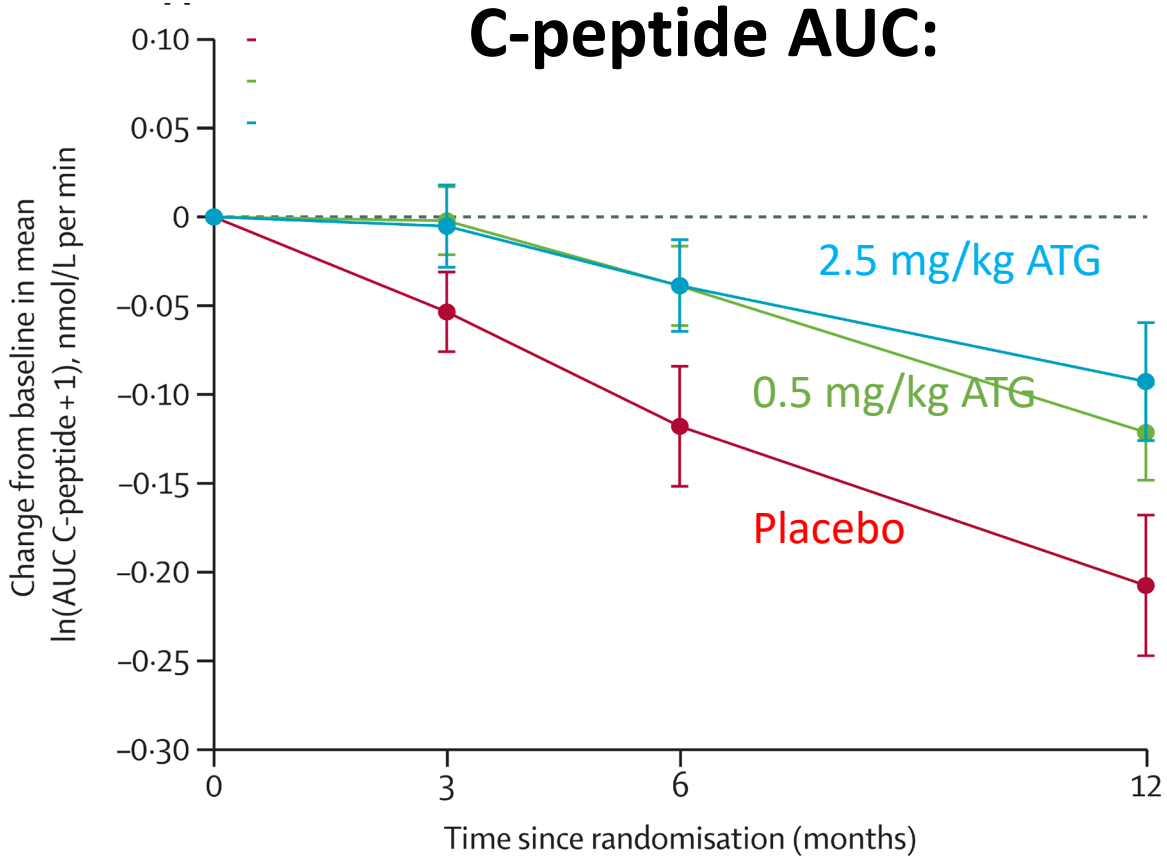


Haller MJ, Long SA, Blanchfield JL, et al. Diabetes 2019;68:1267–1276

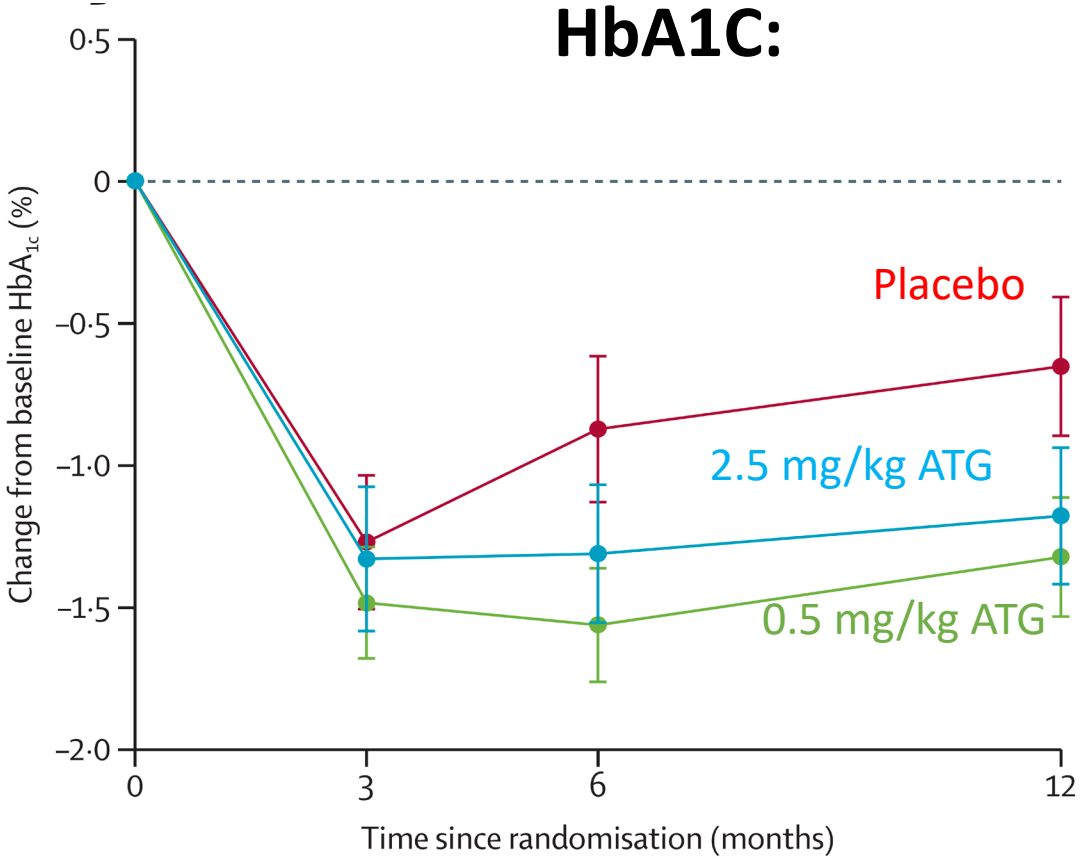
MELD-ATG

- New onset T1D, 5--25 years of age, testing different doses of drug
- Lower dose really reduced serum sickness

C-peptide AUC:



HbA1C:



Mathieu et. al. Lancet 2025 Sep 27;406(10510):1375-1388.

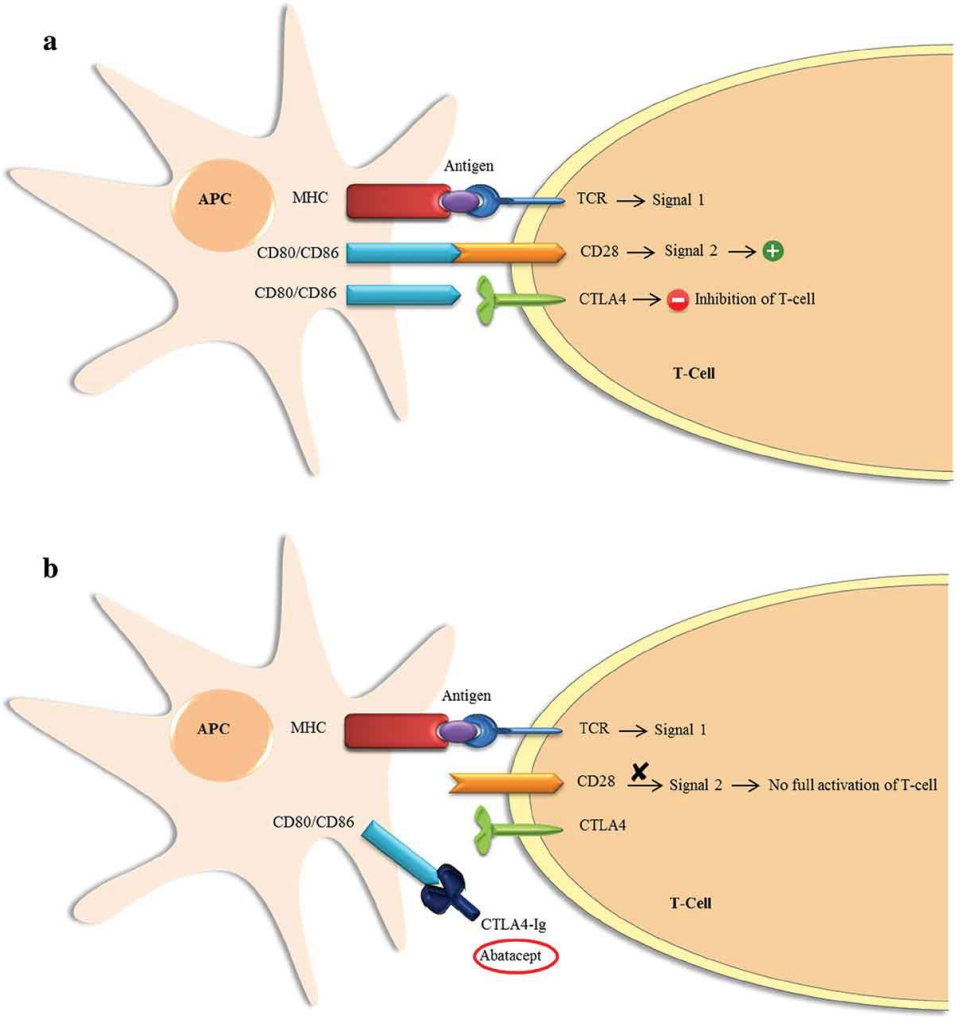
Next Steps for Low-Dose ATG

- Prevention trial in TrialNet in individuals with higher risk Stage 2 T1D 12-35 → PAUSED and now redesigned to not include a placebo arm
- Human ATG is coming from SAB Bio

- ATG could be another induction agent similar to teplizumab but easier to give
- Human ATG could be a game changer as it will address serum sickness

Abatacept: Cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4-Ig)

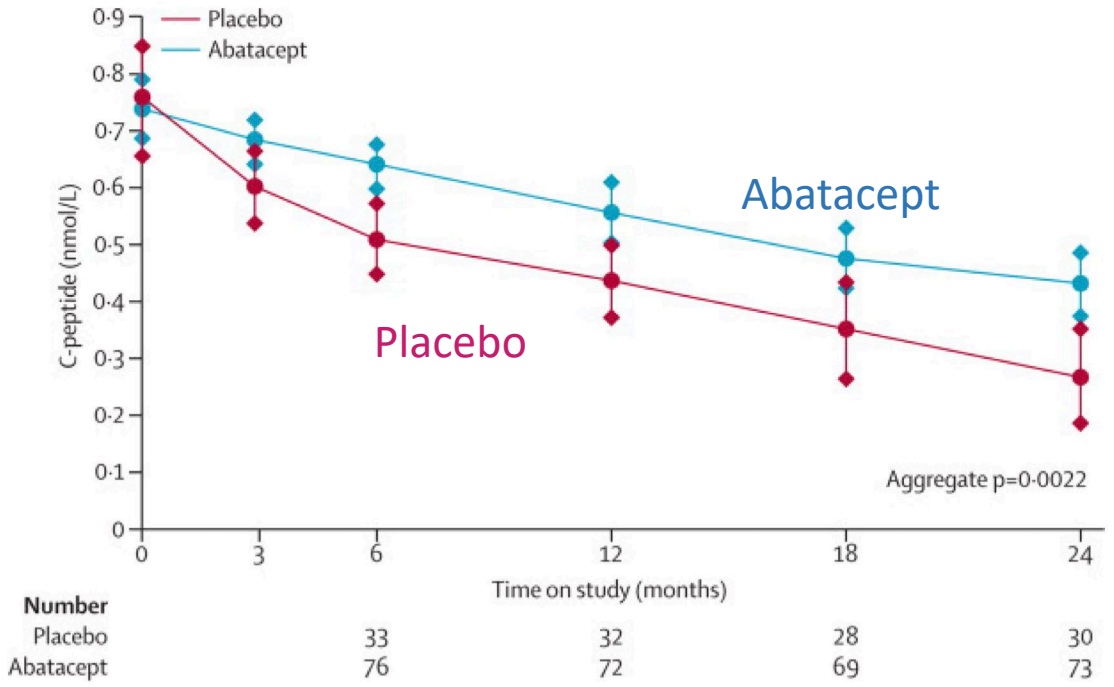
- Blocks the second costimulatory signal required for full T cell activation.
- Promising side effect profile
- Prior trials required monthly IV infusion; more recently subcutaneous dosing available



Rachid O, et al. Expert Opin Investig Drugs 2020; 29(3):221-236

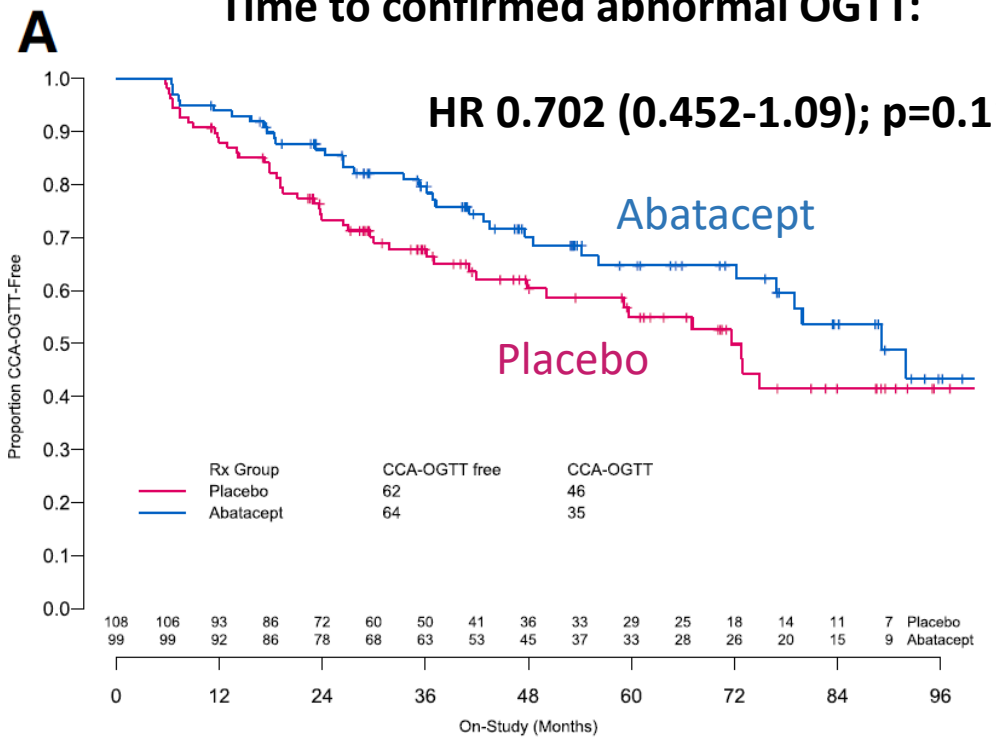
Abatacept in new onset diabetes

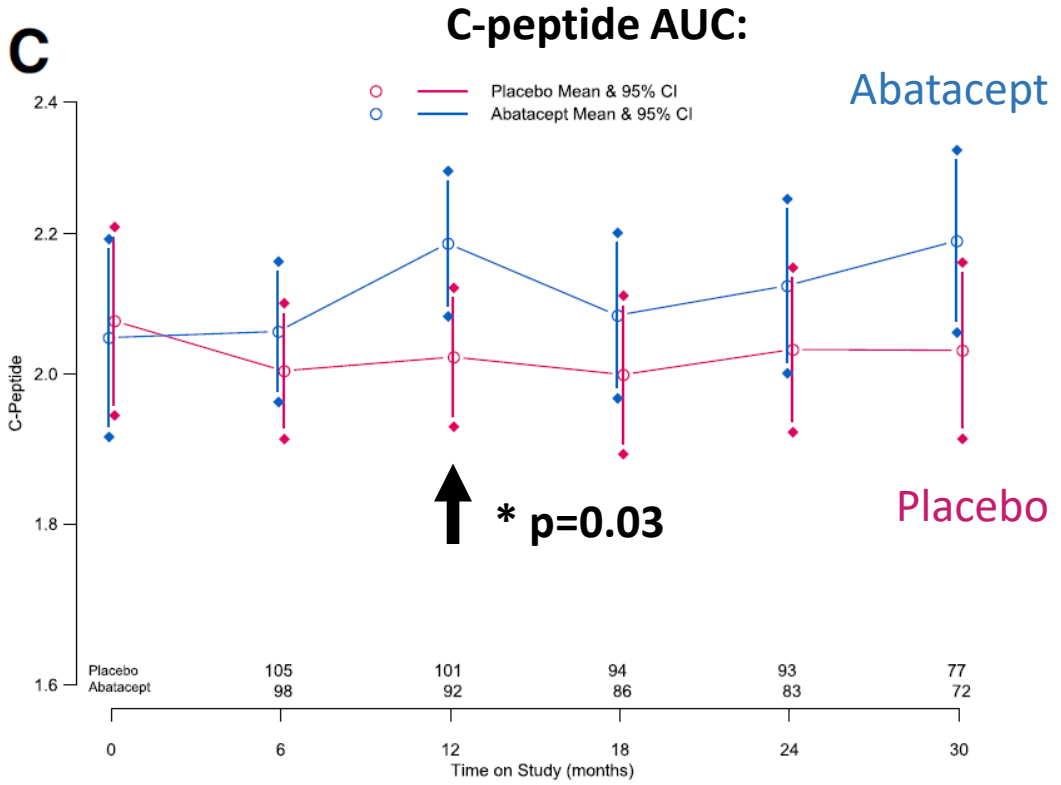
- In new onset T1D (age 6-36 years) was able to delay the reduction in beta cell function in association with reductions in inducible T-cell costimulatory T-follicular helper cells



Abatacept in Stage 1 Type 1 Diabetes

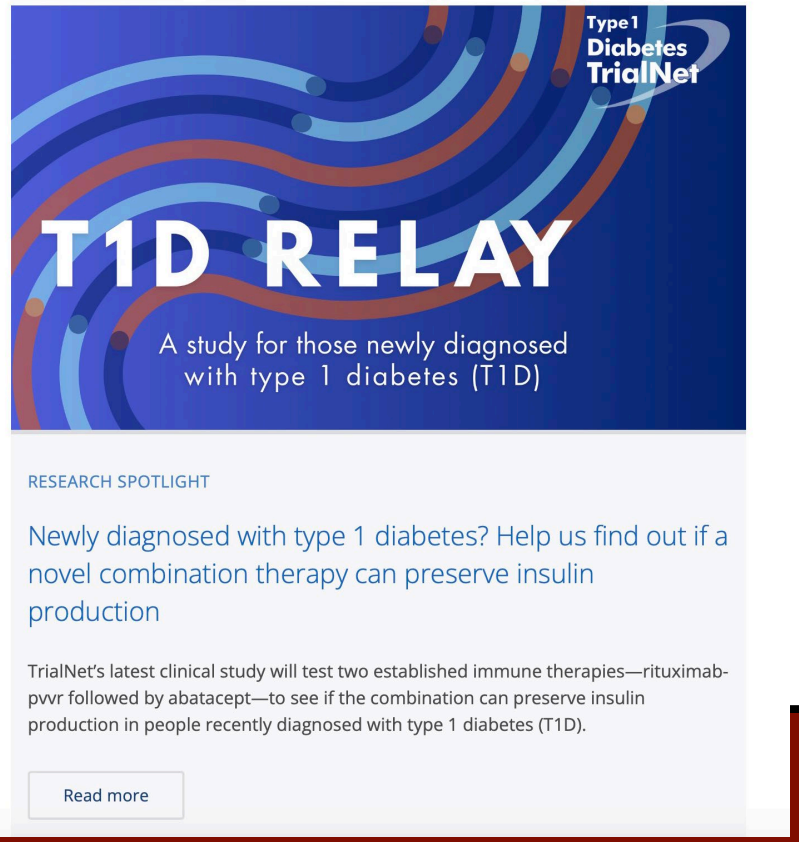
- **Monthly infusions x 12 months in autoantibody positive, normoglycemic children and adults age 6-45**





Russell WE, et al. Diabetes Care 2023; 46:1005–13

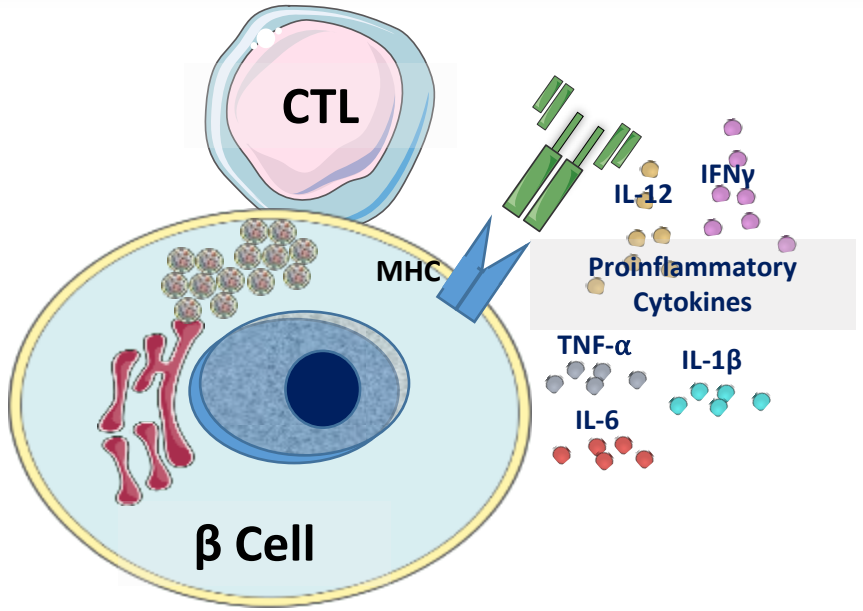
What's next for abatacept



- Despite negative primary outcome, drug had an impact to increase C-peptide at 12 months
- May be option for combination therapy
- Part of RELAY study (new onset T1D 8-45 years)
  - Rituximab vs. Rituximab + abatacept
- Other agents targeting costimulation have a lot of buzz- I think this is not the last we have heard about this pathway

TNF alpha inhibition

- Inhibits proinflammatory cytokine produced by immune cells
- Golimumab: Subcutaneous injections given every 2 weeks

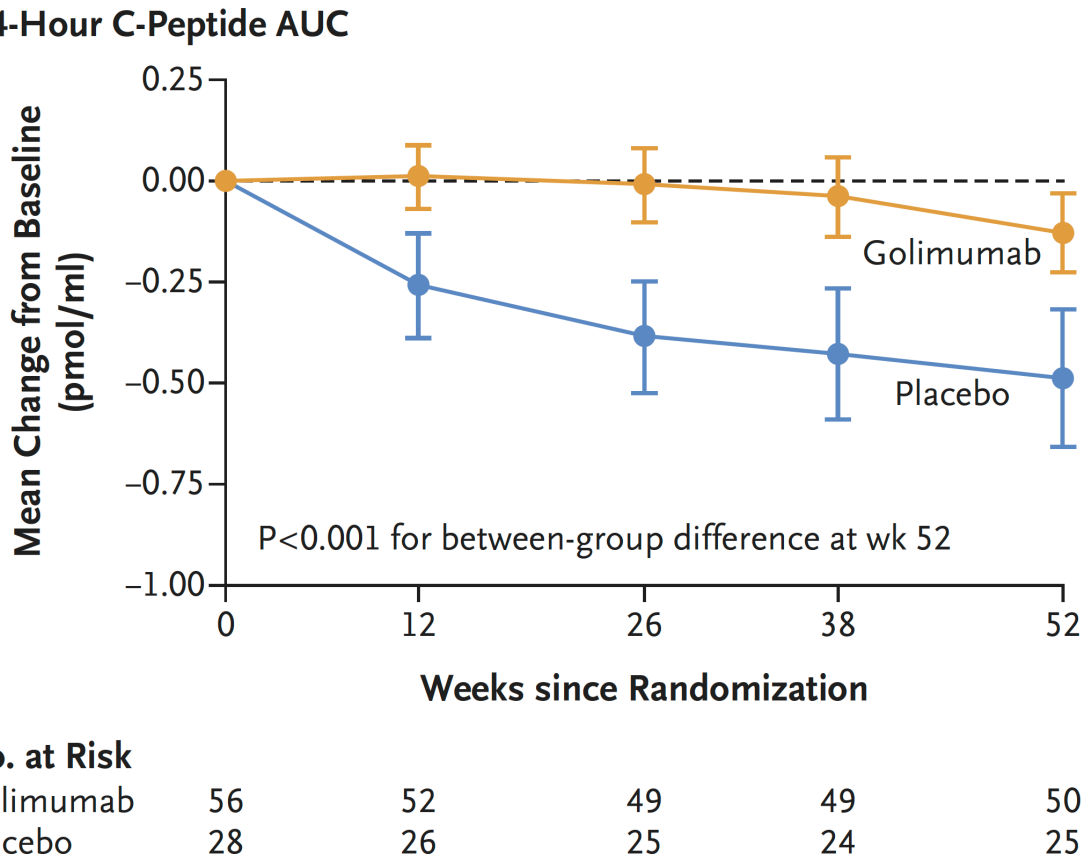


Cytokine Blockade

α1- Antitrypsin Anakinra
Canakinumab Etanercept Golimumab

T1GER study: Golimumab

- Children and young adults with new onset stage 3 T1D
- 6-21 years of age
- Well tolerated- 2 withdrawals in study (1 due to injection site pain and 1 due to intermittent lymphopenia/neutropenia)



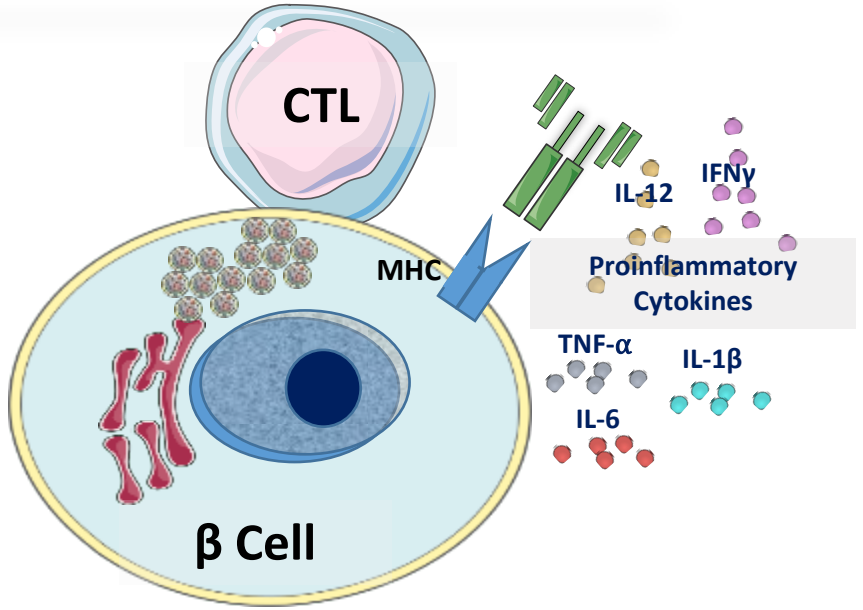
What's next for TNF-alpha

- TrialNet had stage 2 study planned with Golimumab but company that made drug (Jannsen) exited T1D market
- TrialNet working on development of TNF-alpha based Stage 1 study
- WAVE-T1D- combination trial in new onset- ATG +TNFa or verapamil

- This is a very promising pathway with drugs that have great side effect profiles and can be taken as long-term maintenance therapies in little kids
- Let's move this one to prevention!

JAK Inhibitors

- Target JAK Stat pathway (downstream of interferon signaling)
- Relevant to immune cell cytokine activation but also beta cell cytokine response
- Take by mouth
- Already being used for rheum conditions, atopic dermatitis, alopecia areata
- Black box warning for blood clots, severe infections

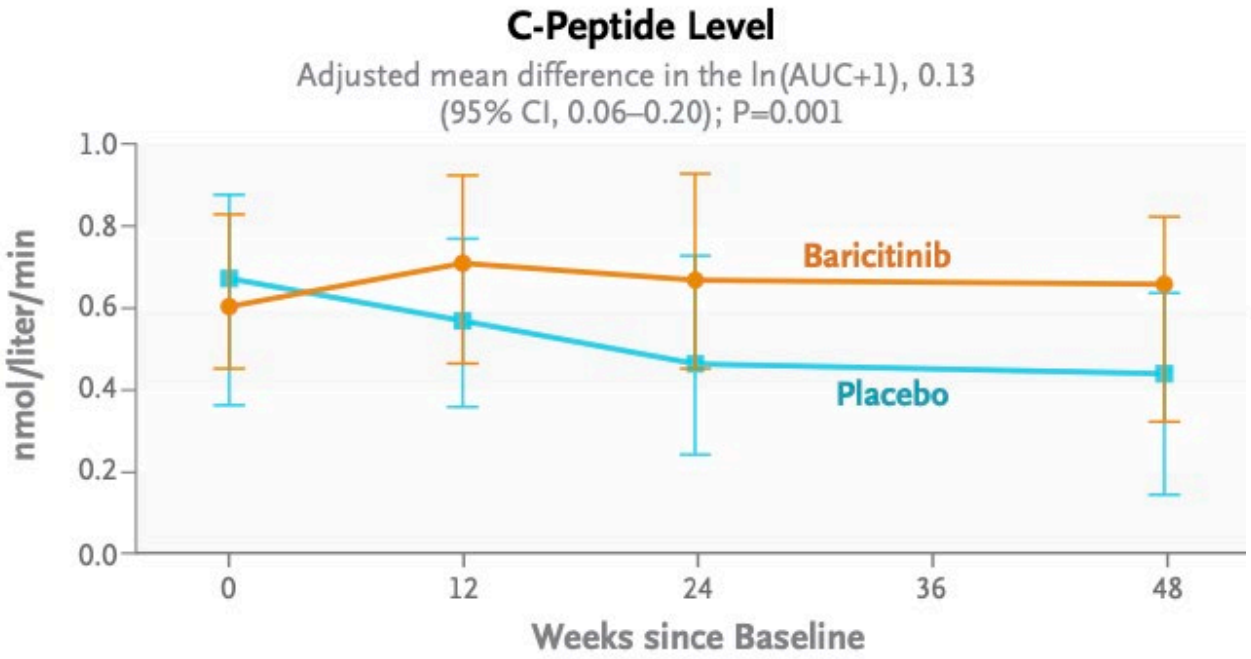


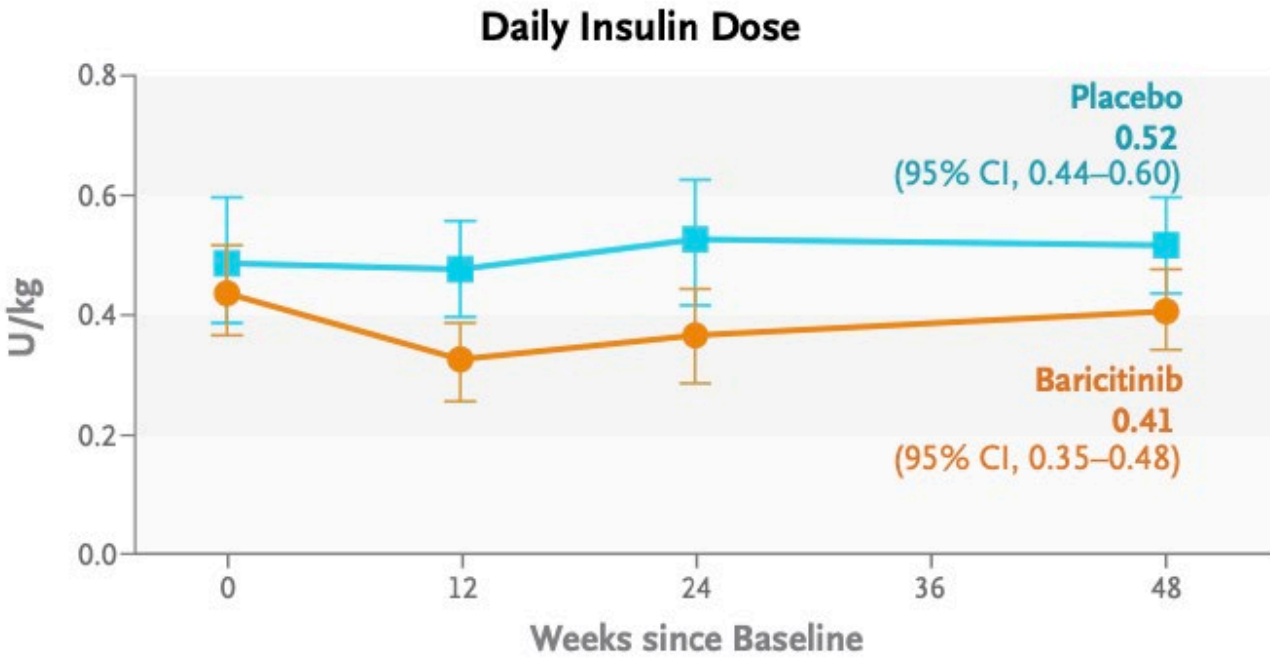
Cytokine Blockade

α1- Antitrypsin Anakinra
Canakinumab Etanercept Golimumab

BANDIT Trial: Baricitinib in new onset T1D

- Oral administration with drug for 48 weeks stabilized C-peptide in 91 individuals 10-30 years old within 100 days of T1D diagnosis





Waibel et al. NEJM 2023

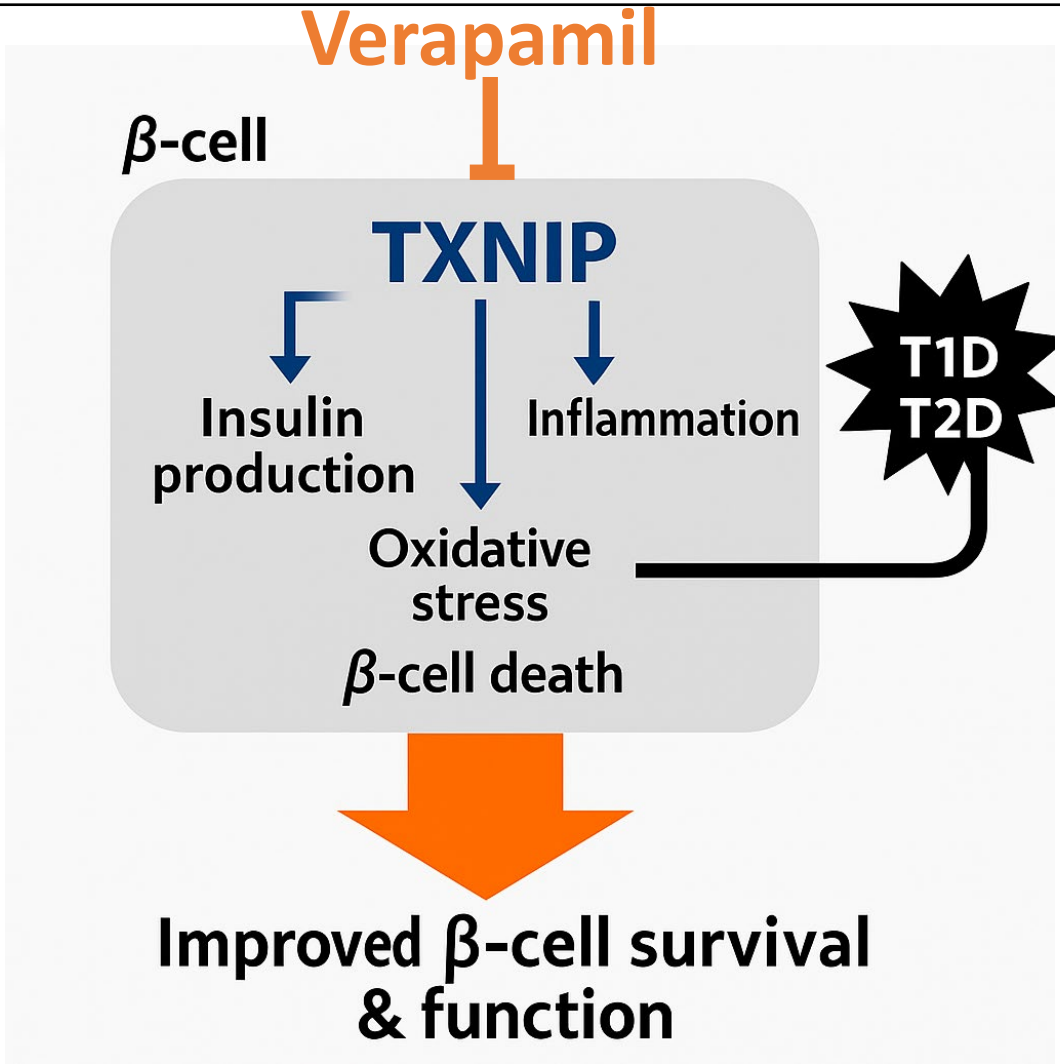
Next Step for JAK Inhibitors

- Next steps: TrialNet JAKPOT new-onset study testing two other JAK inhibitors in new onset disease
- Lilly just announced plans for Stage 2/3 trial with Baracitinib (BARICADE)

- Promising pathway for maintenance therapy as can be taken by mouth
- May have additional benefit since is targeting immune system and beta cells
- Tyk-2 inhibitors more selective so better side effect profile and approved for psoriasis

Verapamil

- Calcium channel blocker that inhibits a protein that causes beta cell oxidative stress
- Oral medication

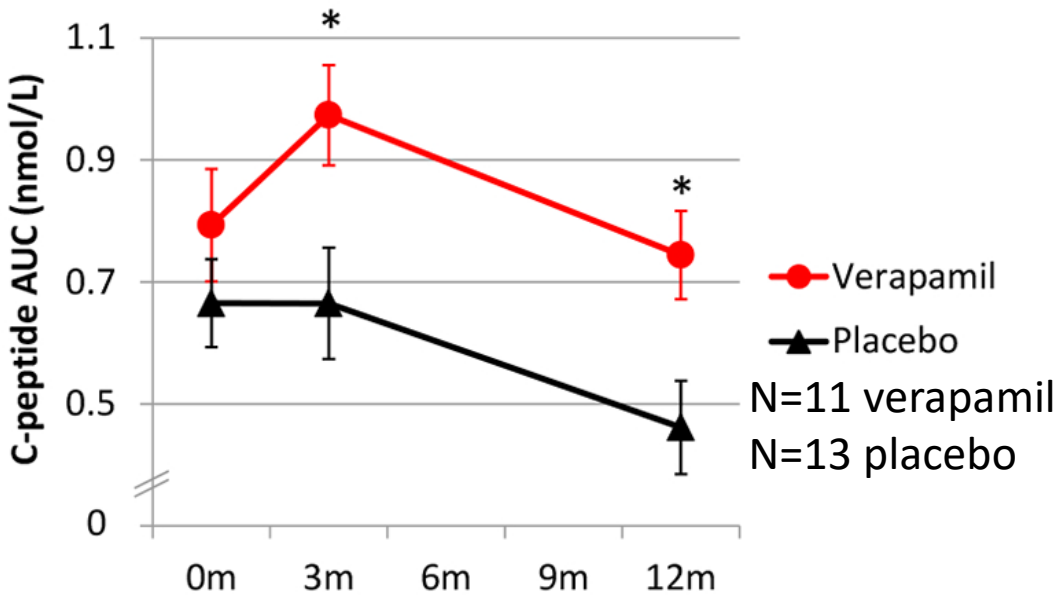


Modified from Jing et al. Front Endocrinol (Lausanne). 2024 Oct 4;15:1476

Verapamil in New-onset T1D

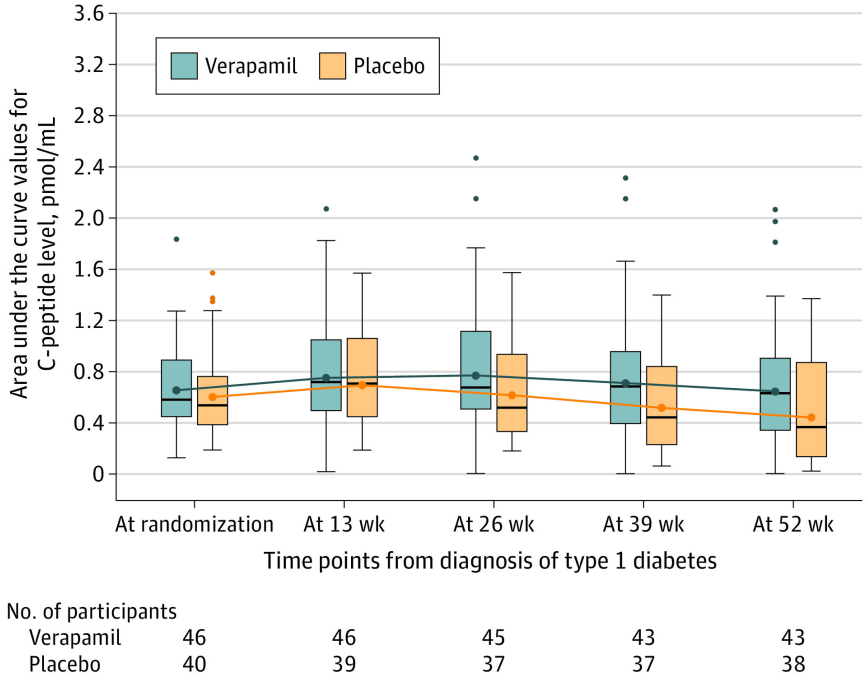
- 1 year oral administration compared to placebo

Adult Study:



Pediatric Study:

Breakthrough T1D™ Formerly JDRF



No. of participants					
Verapamil	46	46	45	43	43
Placebo	40	39	37	37	38

Innodia Vera-T1D Study in adults- Technically negative ? underpowered

Ovalle F, Grimes T, Xu G, et al. Nat Med 2018;24:1108–1112
Forlenza GP, McVean J, Beck RW, et al. JAMA. 24 Feb 2023 [Epub ahead of print]. e232064

Next Steps for Verapamil

- Mechanisms still being elucidated; may also have an immune effect
- Stay tuned for CLVR mechanistic data
- More specific TXNIP drug under development

- Smaller effect size
- This safe, inexpensive medication could be used in combination with more aggressive immunotherapies
- ?Early-stage disease

Conclusions

- It is time for a paradigm shift in the way we are treating type 1 diabetes!
- Exciting things are happening in disease modification!
- Next steps in therapy
  - getting some other drugs approved
  - more combinations/creative approaches to trials
  - Stage 1?
- An approved therapy in stage 3 is really going to impact the trial landscape
- More screening and more study participation is really the next step to help the most at-risk individuals.
- Please make sure your patients know about studies and know they they need to get enrolled fairly quickly to be eligible
- Thanks for your attention!

Thank You!

- Study participants and donors
- IU Center for Diabetes and Metabolic Diseases
- Wells Center for Pediatric Research
- NIDDK R01DK121929; NIDDK R01DK133881; JDRF 4-SRA-2022-1205-M-B, Helmsleyn Charitable Trust
- Type 1 Diabetes TrialNet

Breakthrough T1D™ Formerly JDRF

T1D Exchange

Type 1 Diabetes TrialNet

NIH National Institute of Diabetes and Digestive and Kidney Diseases

nPOD Network for Pancreatic Organ Donors with Diabetes