

Evaluation of CD8 Treg Prevalence and MTX-101-Mediated Activation of Peripheral Blood Mononuclear Cells From Newly-Diagnosed Pediatric and Adult T1D Patients

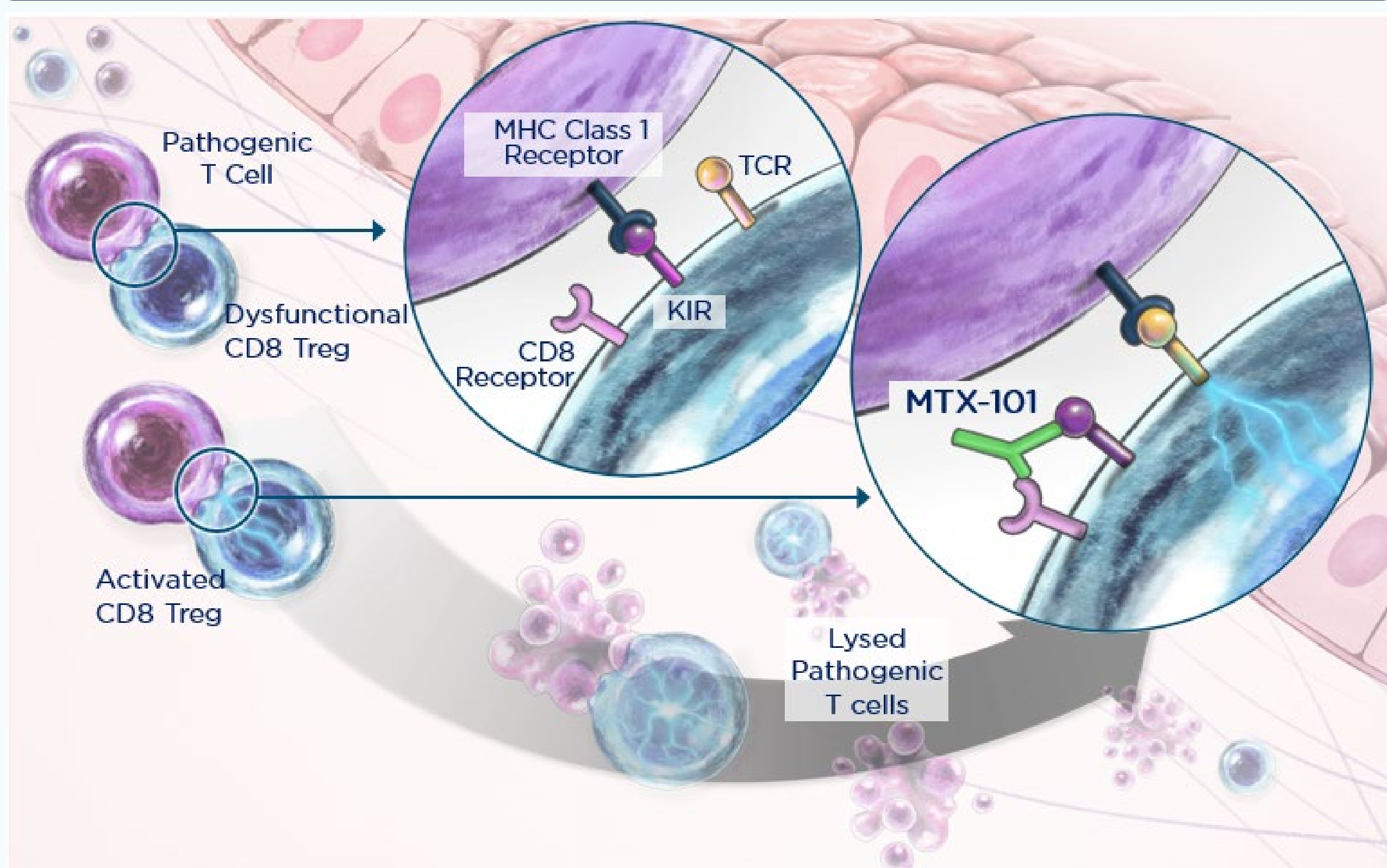
Daniel T. Patton, Allison R. O'Rourke, Meghan E. Maurer, Joylynn B. Gallegos, Kaelen S. Encarnacion, Eyayu K. Belay, Hali Broncucia, Jason W. Chien, Peter A. Gottlieb, Courtney A. Crane

Background and Methods

Regulatory CD8 T cells (CD8 Treg) are responsible for the selective killing of pathogenic T cells to maintain peripheral immune tolerance. CD8 Treg are not broadly immunosuppressive, as their selective depletion does not impact anti-viral or anti-microbial responses in animal models. CD8 Treg appear dysfunctional in patients with autoimmune diseases, including T1D, in part due to expression of inhibitory KIR receptors which serve as autoimmune checkpoints.

This study sought to characterize the phenotype and functional state of CD8 Treg isolated from adult and pediatric patients with newly diagnosed Stage 3 T1D, and to evaluate if observed dysfunctions could be reversed following treatment with a bispecific CD8 Treg modulator, MTX-101. Using flow cytometry and single-cell analysis, we evaluated the prevalence and phenotype of CD8 Treg isolated from the peripheral blood of newly-diagnosed Stage 3 T1D patients <40 years of age (n=40 aged 12–18; n=20 aged 18–40).

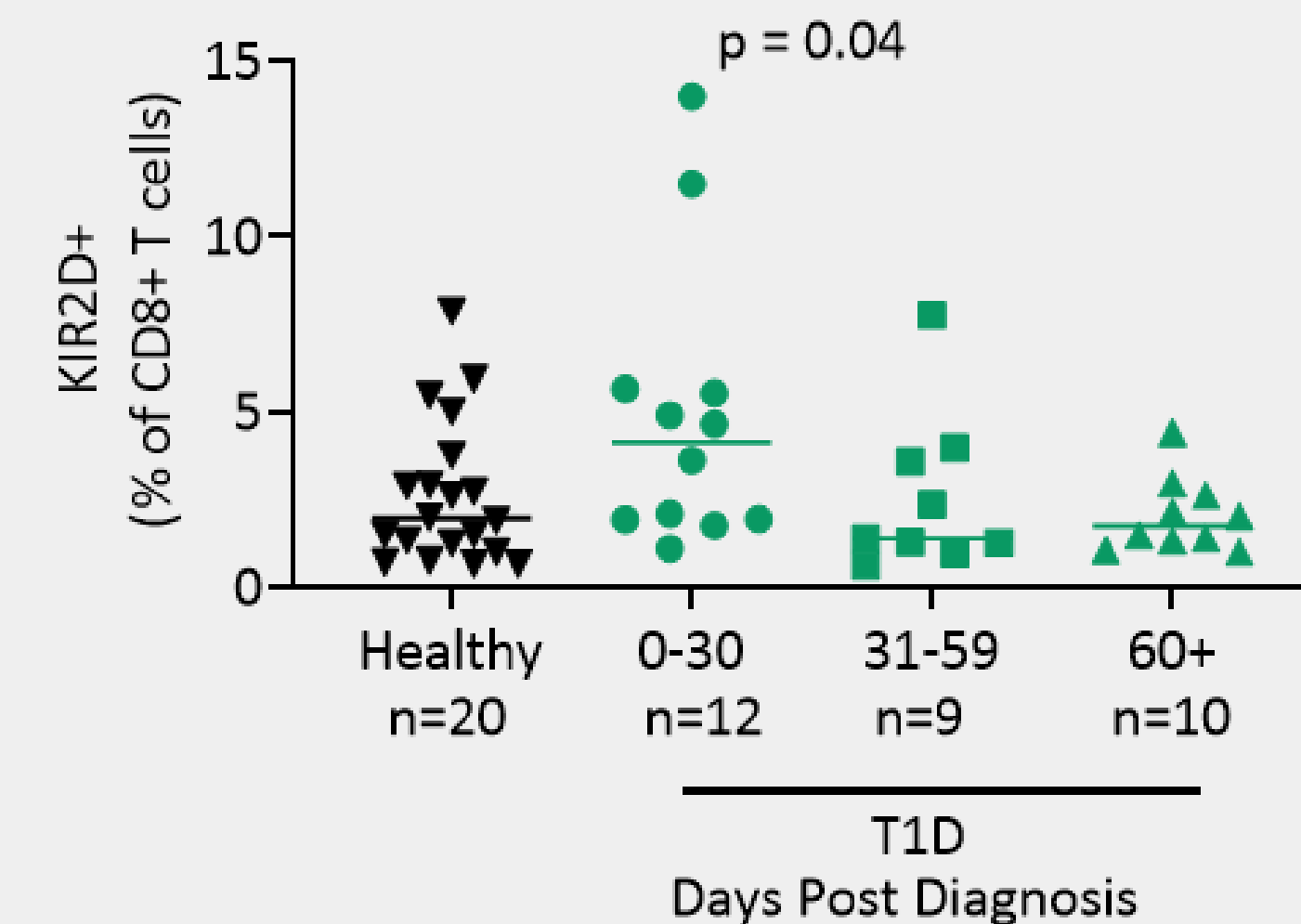
Therapeutic Hypothesis



Model of the postulated mechanism of action for MTX-101. MTX-101, a bispecific antibody targeting inhibitory KIR and CD8, supports TCR restricted CD8 Treg activation and cytolytic capacity, restoring immune tolerance and preventing downstream inflammation and tissue destruction.

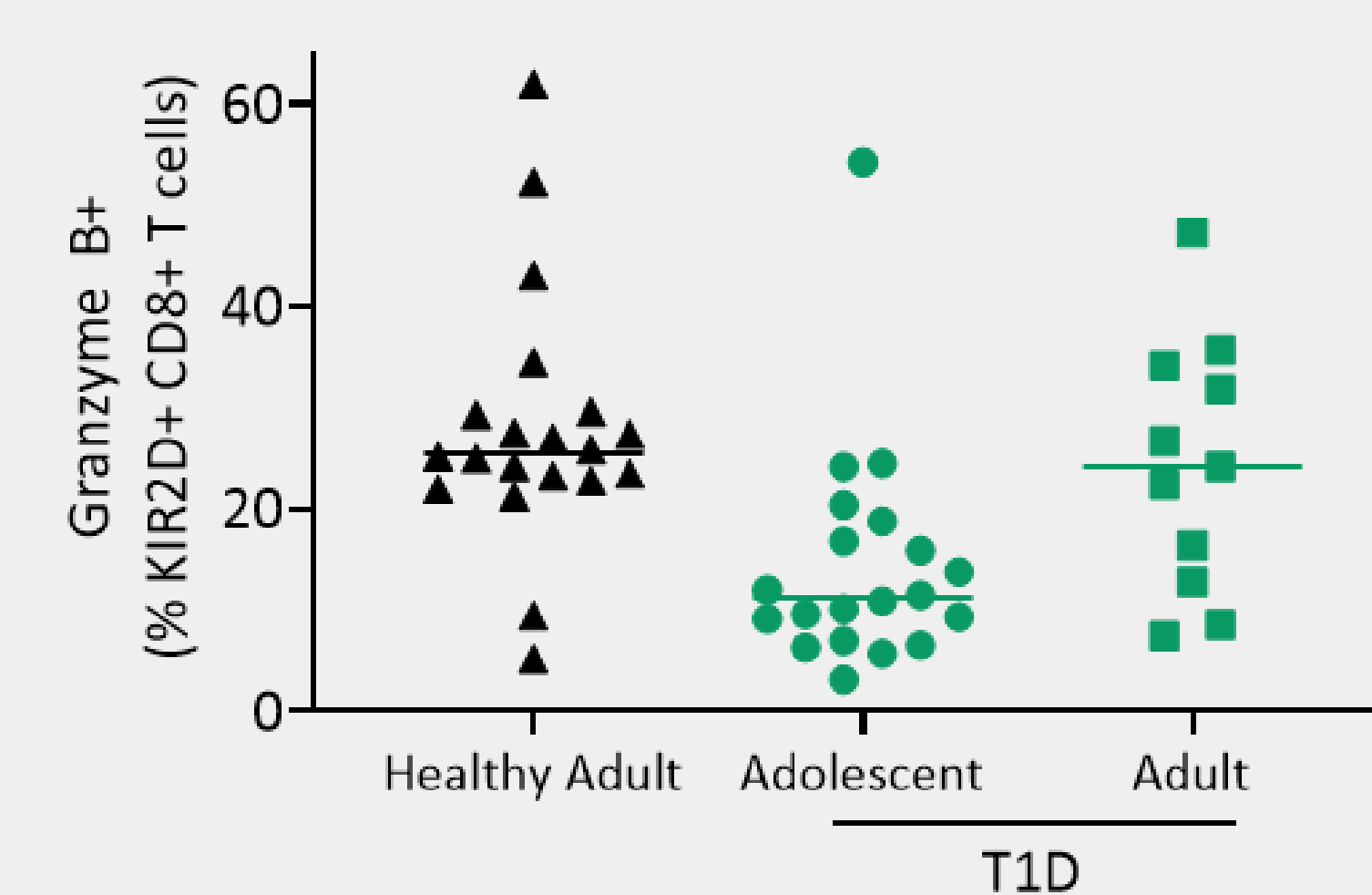
CD8 Treg Are Increased in Newly Diagnosed T1D Patients

CD8 Treg are decrease over time after diagnosis



• PBMC evaluated for CD8 Treg (KIR2D+ CD8) prevalence (of total CD8 T cells) from patients with newly diagnosed Stage 3 T1D

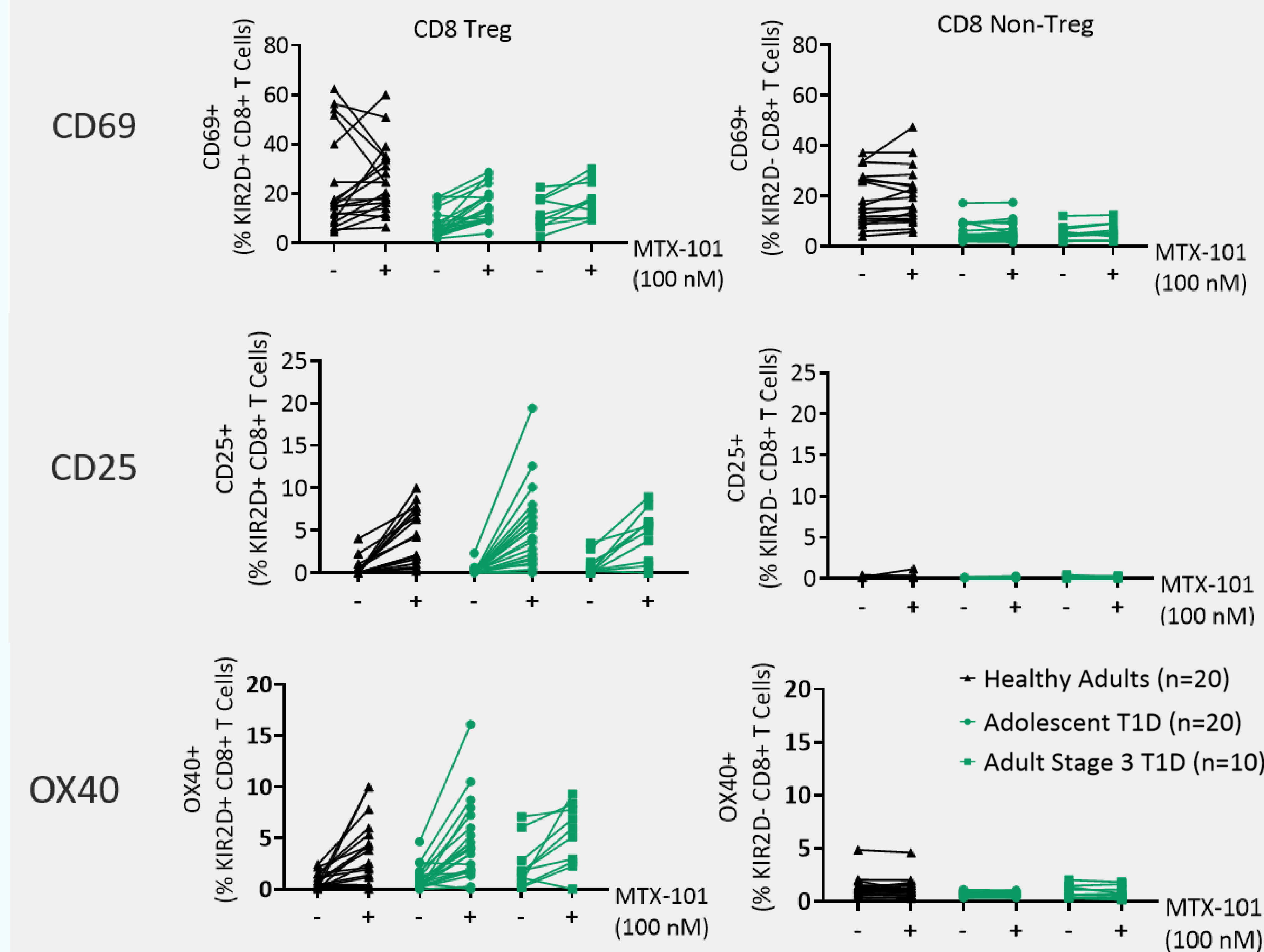
Granzyme B content is reduced in adolescent CD8 Treg



• PBMC from T1D patients evaluated for intracellular cytolytic effector Granzyme B using flow cytometry

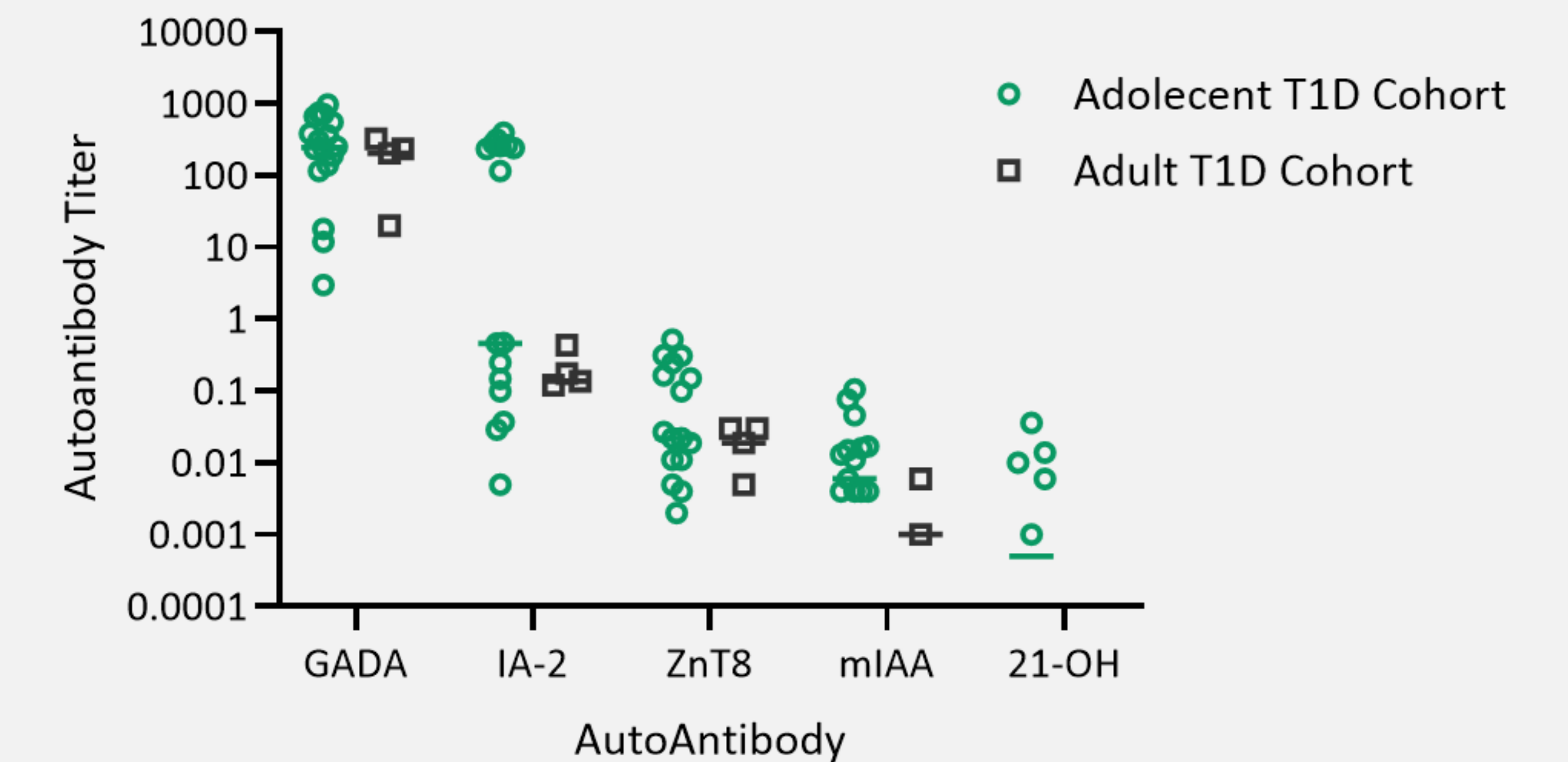
MTX-101 Selectively Activates CD8 Treg in Adult and Adolescent T1D Patient PBMC

CD8 Treg rapidly increase activation markers in response to MTX-101



Equivalent Autoantibody Production

Autoantibodies detected in patients within 6 months of diagnosis



Results

- CD8 Treg are increased in T1D patients closer to diagnosis, no alterations in other immune cell frequencies observed (e.g. KIR2D+ NK cells)
- Adolescent T1D patients CD8 Treg appear dysfunctional, and have reduced Granzyme B
- MTX-101 can selectively activate CD8 Treg in patient PBMC without activating effector CD8 T cells

Conclusions

- MTX-101 is a selective immune modulating therapeutic that may restore tolerance in adolescent Stage 3 T1D patients
- Early clinical data in adults show that MTX-101 can restore CD8 Treg function to reduce autoreactive T cells and protect pancreatic islet function