MOZART THERAPEUTICS

Orchestrating The Immune System

Phase 1B Study Evaluating MTX-101 in Type 1 Diabetes Adults Decreases Pathogenic Self-Reactive CD4 and CD8 T cells, Improves β-Cell Viability and Improves C-peptide Production

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BACKGROUND/AIMS:

- Regulatory CD8 T cells (CD8 Treg) selectively kill pathogenic T cells to maintain peripheral immune tolerance.
- CD8 Treg are dysfunctional in patients with autoimmunity, in part due to expression of inhibitory KIR receptors (KIR2DL1/2/3), which serve as autoimmune checkpoints.
- MTX-101 is a bispecific CD8 Treg-targeted biologic that disrupts KIR-mediated inhibition of CD8 Treg activation
- We conducted an interim analysis of the first 5 adult patients treated with MTX-101 to evaluate the pharmacokinetics (PK), and pharmacodynamics (PD) of MTX-101 in Stage 3 type 1 diabetes (T1D).
- MTX-101 treated patient serum, whole blood, and peripheral blood mononuclear cells (PBMC) were analyzed before and after dosing to determine if MTX-101 can selectively activate CD8 Treg to kill pathogenic T cells in patients
- Assessment of serum analytes, receptor occupancy, immune phenotyping, and functional ex vivo assays illustrate the effects of selective modulation of the CD8 Treg network for the first time in patients

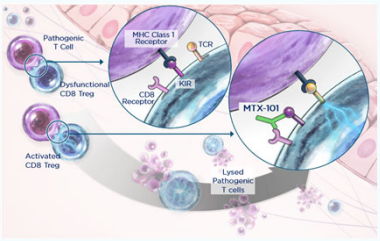
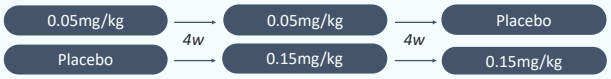


Figure 1. Model of the postulated mechanism of action for MTX-101. MTX-101, a bispecific antibody targeting inhibitory KIR and CD8, supports TCR restricted CD8 Treg activation and cytolytic capacity, restoring immune tolerance and preventing downstream inflammation.

Safety & Proof of Mechanism Phase 1b Study Design:



Study Objectives	PK	RO	Selectivity	Activation	Killing
Stage 3 T1D patients	✓	✓	✓	✓	✓

* For safety and clinical data, please attend Mozart's oral presentation entitled 'MTX-101: a Novel Bispecific CD8 Treg Modulator that Restores CD8 Treg Functions to Suppress Pathogenic T cells in Type 1 Diabetes' 11:30AM on April 23

Sustained MTX-101 Target Engagement in T1D Patients

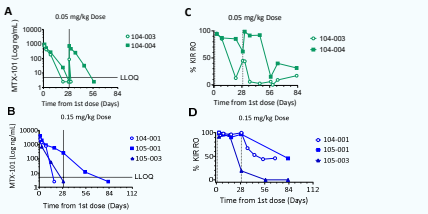


Figure 2. PK and KIR receptor occupancy (RO) are correlated and dose-proportional. (A-B) Concentration of MTX-101 in human serum was determined by a sandwich immunoassay to evaluate PK. (C-D) KIR receptor occupancy was measured using flow cytometry. KIR RO is calculated as the degree of MTX-101 blocking of anti-KIR antibody, relative to anti-KIR antibody binding at saturating levels in the absence of drug. Samples assessed through Day 83 or Day 111 are shown.

MTX-101 Transiently Increased Serum Cytokines in T1D Patients

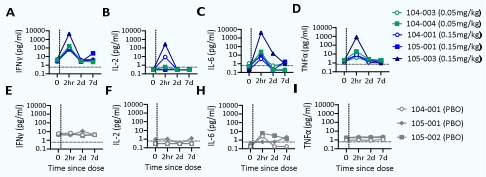


Figure 3. Serum cytokines transiently increased in T1D patients 2hr after exposure to MTX-101. Levels of IFNγ (A,E), IL-2 (B,F), IL-6 (C,H) and TNFα (D,I) were measured using an MSD V-Plex Inflammatory Panel 1 assay. (A-D) MTX-101. (E-I) Placebo. LLOQ is indicated by a horizontal dotted line. Dosing denoted by vertical dotted line.

Selective CD8 Treg Activation by MTX-101

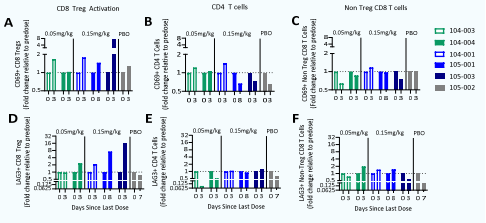


Figure 4. CD8 Treg activation markers CD69 and LAG3 are transiently elevated following MTX-101 dosing. T cell activation markers CD69 (A-C) and LAG3 (D-F) were detected in PBMCs by flow cytometry on CD8+ KIR2D+ CD8 Treg (A,D), CD4+ cells (B,E), or CD8+ KIR2D- Non Treg cells (C,F). All populations are first gated on Cells> singlets> Live> DUMP-> CD3+. Fold change was calculated from D1 pre-dose measurement.

MTX-101 Selectively Induces CD8 Treg Proliferation

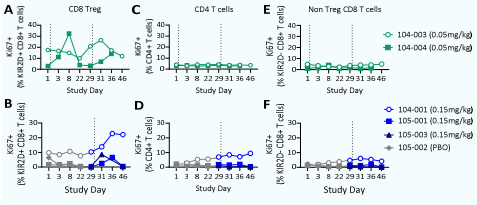


Figure 5. CD8 Treg proliferation marker Ki67 elevated following MTX-101. Ki67 was detected in PBMCs using flow cytometry on CD8+ KIR2D+ CD8 Treg (A,B), Total CD4+ cells (C,D), or CD8+ KIR2D- Non Treg CD8 cells (E,F). All populations gated on: Cells> singlets> Live> DUMP-> CD3+. (A, C, E) Patients dosed twice with 0.05mg/kg MTX-101 on days 1 and 29 and (B, D, F) Patients dosed once with 0.15mg/kg MTX-101.

MTX-101 Does Not Increase Exhaustion Markers

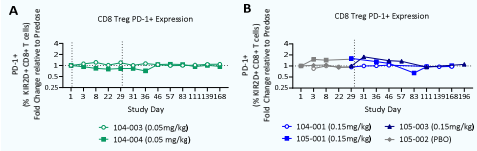


Figure 6. Exhaustion marker PD-1 not elevated post MTX-101. PD-1 was detected in PBMCs by flow cytometry on CD8+ KIR2D+ CD8 Treg cells. Gating: Cells> Singlets> Live> DUMP-> CD3+> CD8+>KIR2D+>PD-1+. Fold change calculated from the day 1 pre-dose timepoint. (A) Patients dosed twice with 0.05mg/kg MTX-101 on days 1 and 29 and (B) Patients dosed once with 0.15mg/kg MTX-101. Dosing denoted by vertical dotted line.

Reduction of Pathogenic CD8 and CD4 T Cells with MTX-101

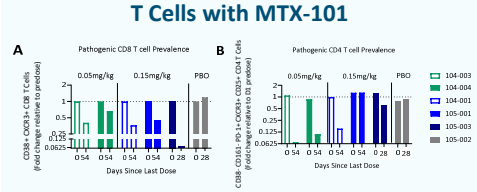


Figure 7. Reduced Pathogenic CD8 and CD4 T cells after MTX-101 dosing. Cluster analysis of flow cytometry data identified suspected CD8+ (A) or CD4+ (B) pathogenic T cell subsets in PBMCs. Clustering analysis was done using an unbiased tSNE, X-Shift, and MEM approach. Fold change was calculated from predose measurement (B). All populations were first gated on Cells>singlets>Live>DUMP-> CD3+ then CD8+ or CD4+ T cells.

Acknowledgements: The authors would like to acknowledge the Patients, clinicians and families who gave their time for this trial. We would also like to thank our collaborators at 360Biolabs, Novotech and Sonic Clinical Trials and everyone at the trial sites.

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Reduced Autoantigen Responses by Pathogenic CD4 T Cells in T1D

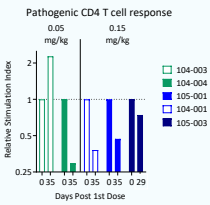


Figure 8. Reduced secretion of plasma IL-2 following autoantigen restimulation in patients who received MTX-101. Whole blood was cultured for 24hr with T1D peptides in a modified Novoleukin assay. Plasma IL-2 was measured by MSD S-Plex Multiplex. Stimulation Index was calculated by dividing the test by the negative control peptides. Data are represented relative to the pre-dose time point.

MTX-101 Decreases Beta Cell Damage in a Pancreatic Organoid Co-culture Model

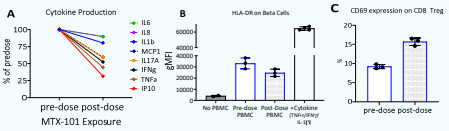
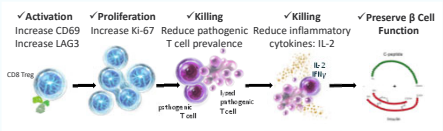


Figure 9. PBMC from MTX-101 treated T1D patients produce lower levels of cytokines, reduce beta cell damage, and have an activated CD8+ Treg phenotype in a pancreatic organoid co-culture. Organoids derived from primary human islets were co-cultured with patient PBMC for 3 days prior to analysis by flow cytometry and MSD. (A) All measured cytokines except IL-6 and MCP-1 showed a significant drop after MTX-101 exposure ($p<0.05$) (B) MTX-101 treated PBMC induce less β cell HLA-DR expression, an early marker of insulitis, (C) CD8 Treg increase CD69 expression in co-culture after MTX-101 treatment.

RESULTS AND CONCLUSIONS



- In Stage 3 T1D patients, MTX-101 has antibody-like PK and binds the target KIR2DL and CD8 receptors on CD8 Treg
- MTX-101 selectively activates and drives expansion of CD8 Treg without evidence of exhaustion or broad immune suppression
- MTX-101-treated patient PBMC have reduced pathogenic T cell prevalence and responses to autoantigen restimulation ex vivo, consistent with their elimination
- MTX-101 is a promising and novel targeted approach with the potential for durable disease modification in T1D patients