Antigen-specific immune modulation with liver-targeting nanoparticles fosters immune protective regulatory T cells to delay Type 1 Diabetes

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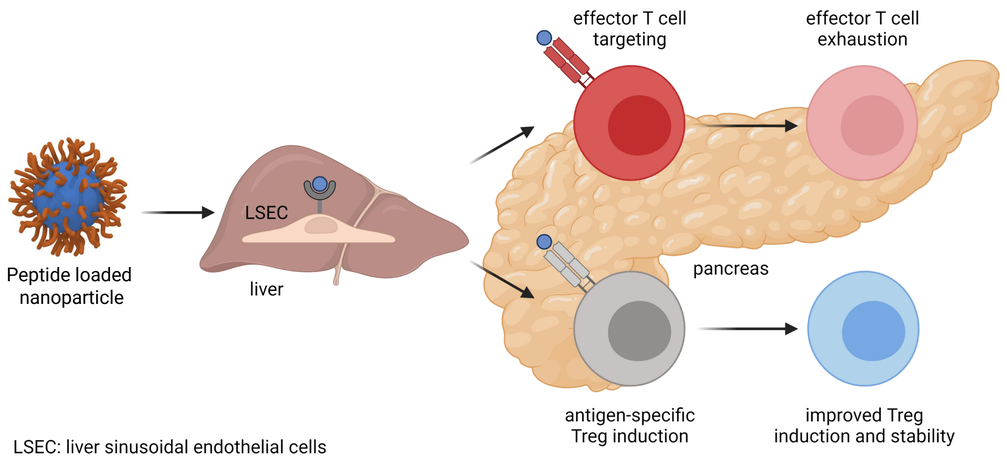
Introduction

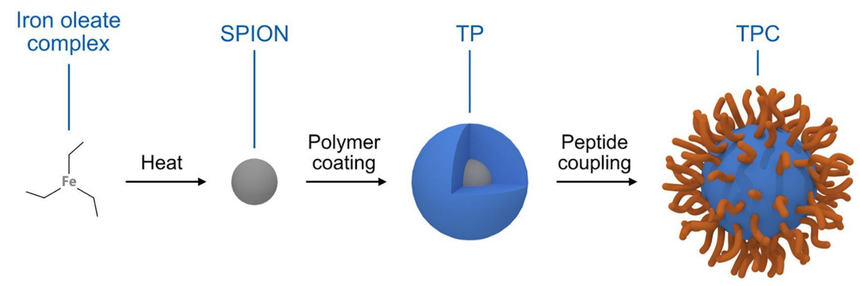
Type 1 Diabetes (T1D) is characterized by the loss of immune tolerance to beta-cells in the pancreas, resulting in their immune-mediated destruction. Restoring antigen-specific immune tolerance, thereby circumventing critical side effects of non-specific immunosuppression is a long-awaited goal for the prevention of T1D. We tested peptide-conjugated nanoparticles developed by Topas Therapeutics that leverage the tolerogenic capacity of liver sinusoidal endothelial cells (LSECs) to restore antigen-specific immune tolerance in T1D.



LSEC: liver sinusoidal endothelial cells

Design of T1D-targeting Topas Particle Mixtures (TPM-T1D)

Schematic of Topas Particle Conjugate (TPC) production



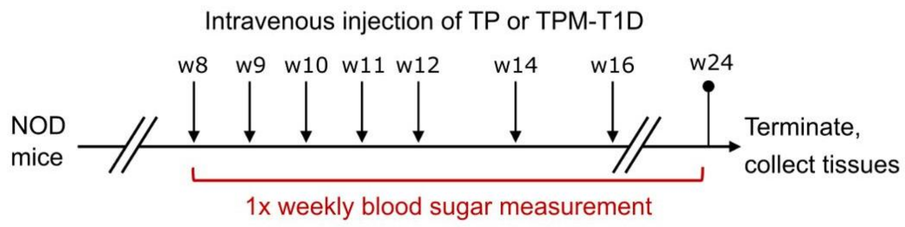
Diabetogenic peptides used in TPM-T1D

Peptide	Rationale	Sequence	TPC ID
Insulin beta chain (InsB) 9-23	Dominant pathogenic CD4 T cell epitope in both NOD and humans	SHLVEALYLVCGERG	TPC0013
Proinsulin p24-33	Early autoantigen in NOD mice	FFYTPMSRRE	TPC0115
IGRP206-214	Relevant CD8 autoantigen in NOD mice	VYLKTNVFL	TPC0041
2.5HIP (fused ChgA peptide)	Agonistic for mouse and human islet-infiltrating T cells; neoantigen	DLQTLALWSRMDQLAK	TPC0038
6.9HIP (fused IAPP2)		DLQTLALNAARDPNR	TPC0039

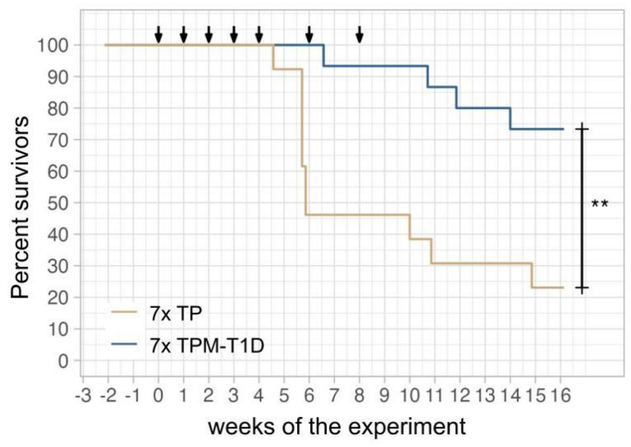
ChgA, chromogranin A; HIP, hybrid insulin peptide; fusion of insulin to other disease-relevant peptides. IAPP2, islet amyloid polypeptide 2; IGRP, islet-specific glucose-6-phosphatase catalytic subunit-related protein.

TPM-T1D treatment reduces onset of hyperglycemia in NOD mice

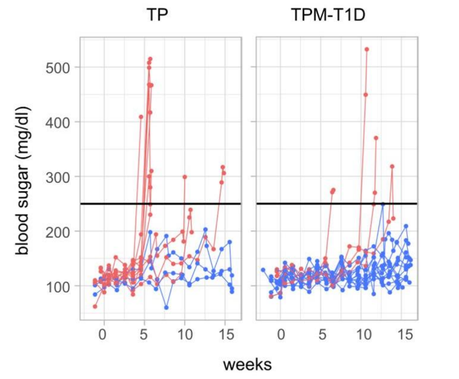
Experimental setup



Frequency of diabetes-free mice (“survivors”)

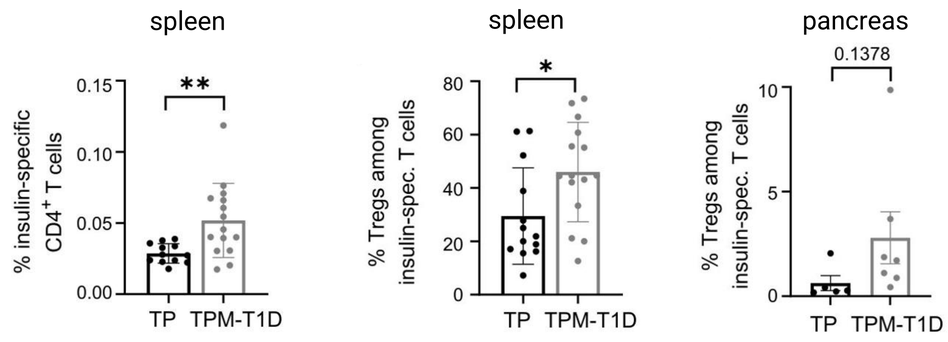


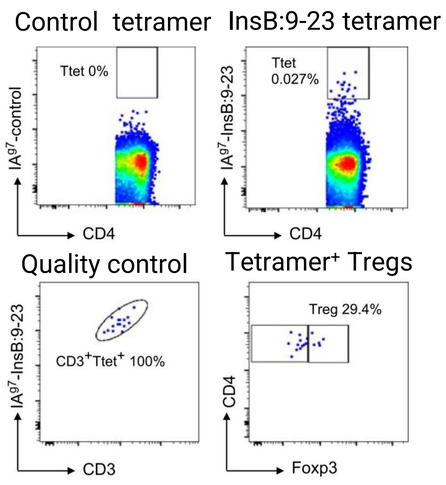
Blood sugar levels



TPM-T1D treatment fosters antigen-specific Tregs

Frequencies of insulin-specific CD4⁺ T cells and Tregs in spleen and pancreas





Conclusion

These findings suggest that a combination of selected pancreatic peptides, delivered to LSECs, can induce antigen-specific Treg responses in T1D and hold up disease progression. In conclusion, this approach represents an innovative option for immune modulation to reinstate antigen-specific tolerance in autoimmune diseases, while avoiding the complications of broad immunosuppression.

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