SIGNIFICANCE

Using a therapeutic inhibitory peptide (TP_{CD154}), specific for CD40, we are able to prevent Type 1 Diabetes (T1D) onset in the NOD mouse model and control a pathogenic effector subset of CD4 T cells phenotypically described as CD4CD40+.

Blocking CD40 and CD154 interactions has previously been shown to prevent disease onset. However, using monoclonal antibodies as a therapy can lead to numerous complications including thrombotic events and hindering immune responses to new and/or latent infections.

Blockade CD40 – CD154 prevents diabetes and controls the CD4CD40+ expansion

Structure and Activity Relationship (SAR)

Additional amino acids outside of the KGYY region are critical to the function of TP_{CD154}. As the size changes and amino acids are eliminated the efficacy changes as well.

TP_{CD154} is modeled from a 15-mer sequence found in CD154

CONCLUSIONS

• Diabetes is prevented by blocking CD40 and CD154 interactions in NOD mice
• The CD4+CD40+ population is contained - not depleted
• The TP_{CD154} is as effective at preventing disease as the CD154 antibody and shows a high affinity for CD40 on T cells
• SAR experiments show the size of the peptide and sequence of amino acids are critical in its function

ACKNOWLEDGEMENTS

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The Blockade of CD40 With a Small Therapeutic Peptide Prevents Type 1 Diabetes

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The 15-mer peptide ablates islet infiltrates

60% of the islets in 10-mer treated NOD mice show level 4 insulitis (100% infiltration) whereas 3% of the islets in 15-mer treated NOD show level 4 insulitis.

TP_{CD154} shows a high affinity for CD4CD40+ cells

NOD splenic cells were stained with fluoresceinated TP_{CD154} and CD40 antibody.

Percent Hyperglycemic

Percent Hyperglycemic

Gly-2
Gly-9
Gly-11
Gly-12
Gly-15

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