Tolerization Therapy for Treating Type 1 Diabetes Mellitus

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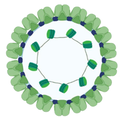
Background

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease characterized by chronic hyperglycemia that lacks a curative treatment. Restoration of the immune tolerance to the primary self-antigen (pSAg) of an autoimmune disease is the ideal approach to cure patients. However, to date, successful tolerization approaches for T1DM have not become available. Simian Virus 40 (SV40) gene delivery vectors possess safety, non-immunogenicity, and tolerogenic properties, making them highly effective in inducing tolerance to pSAgs of autoimmune diseases. Consequently, SV40 vectors provide a strong foundation for developing a curative tolerization therapy for T1DM[a].

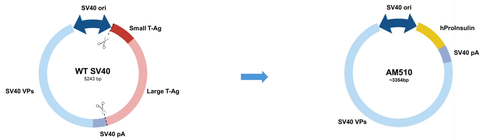
Nimvec™ Platform System

Nimvec™ = non immunogenic SV40-based viral vector[b]



Circular double-stranded DNA genome.
Does not integrate in the host's genome.
No pre-existing immune memory in humans.
Viral Proteins (VPs) are not expressed in target cells
Non-immunogenic, allowing re-administration

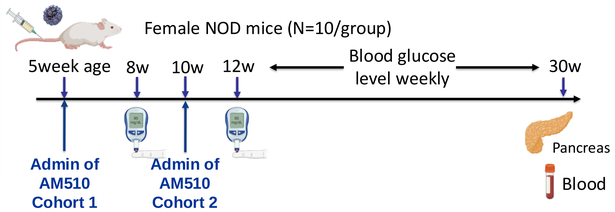
AM510 = Nimvec™ vector encoding the pSAg proinsulin



AM510 = Produced in SuperVero™ cell line[c]

Methodology

NOD mouse experimental design

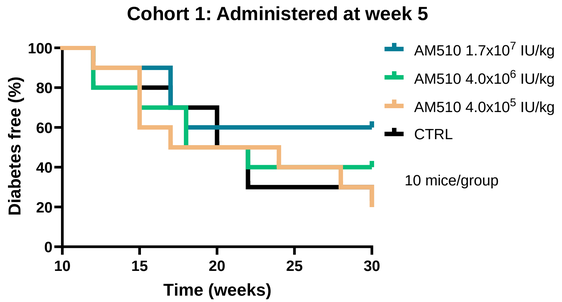


Determinations

1. Assessment of glycemia (weekly from week 12)
2. Immunohistochemistry (IHC) of the pancreas (end point)
3. Measurement of C-peptide and anti-SV40 antibodies in the blood (end point)

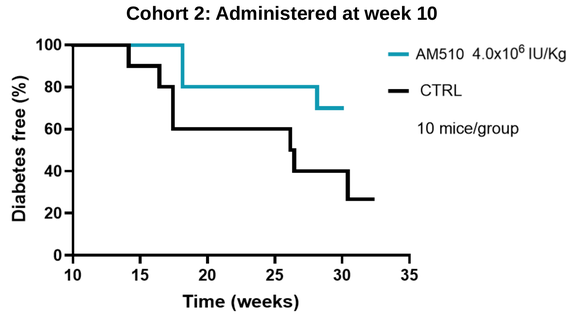
Results

Tolerization with AM510 protects NOD mice from T1DM in a dose dependent manner



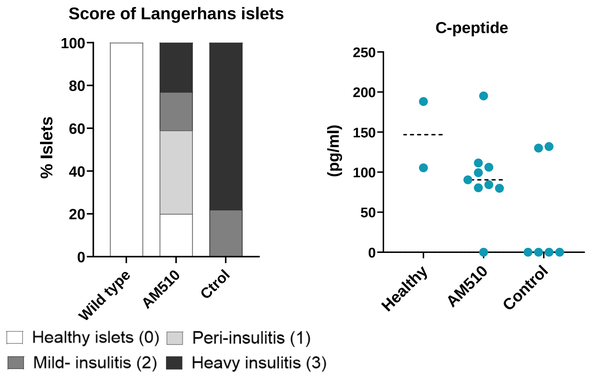
Results

NOD mice are also protected just before the disease onset



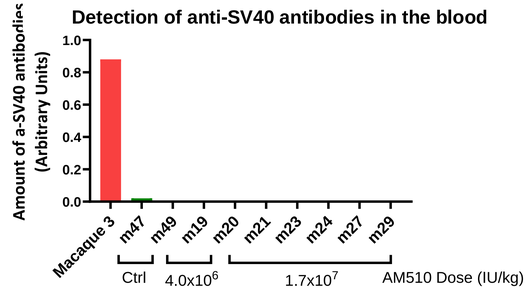
Results

AM510 protects pancreatic Langerhans islets from insulitis. β-cells continue to release C-peptide (and insulin)



Results

Nimvec is non-immunogenic as no humoral immune response was observed



Conclusions & Future Directions

I.V administration of Nimvec™ AM510 encoding human proinsulin:

- Prevents autoimmune destruction of pancreatic insulin-producing β-cells
- Protects NOD mice from developing T1DM
- Nimvec™ AM510 is well-tolerated and non-immunogenic

Amarna Therapeutics aims to conduct:

- IND-enabling dose range finding studies
- Toxicology and Biodistribution studies
- A clinical phase I/IIa safety & efficacy study

References

a) De Haan, P. et al. Viral Gene Delivery Vectors: the Next Generation Medicines for Immune-Related Diseases. Hum Vaccin Immunother 17: 14-21, 2021

b) Toscano MG & De Haan P. How Simian Virus 40 Hijacks the Intracellular Protein Trafficking Pathway to Its Own Benefit … and Ours. 9: 1160, 2018

c) Toscano MG et al. Generation of a Vero-Based Packaging Cell Line to Produce SV40 Gene Delivery Vectors for Use in Clinical Gene Therapy Studies. Mol Ther Methods Clin Dev. 2017

Abstract 872-P - Disclosure: Henk Streefkerk and Peter de Haan are consultants of Amarna Therapeutics. The other authors are employees of Amarna Therapeutics. Contact: *henk.streefkerk@amarnatherapeutics.com*