Proinsulin peptide C19-A3 immunotherapy in new-onset type 1 diabetes is well-tolerated and associated with reduced total daily insulin usage

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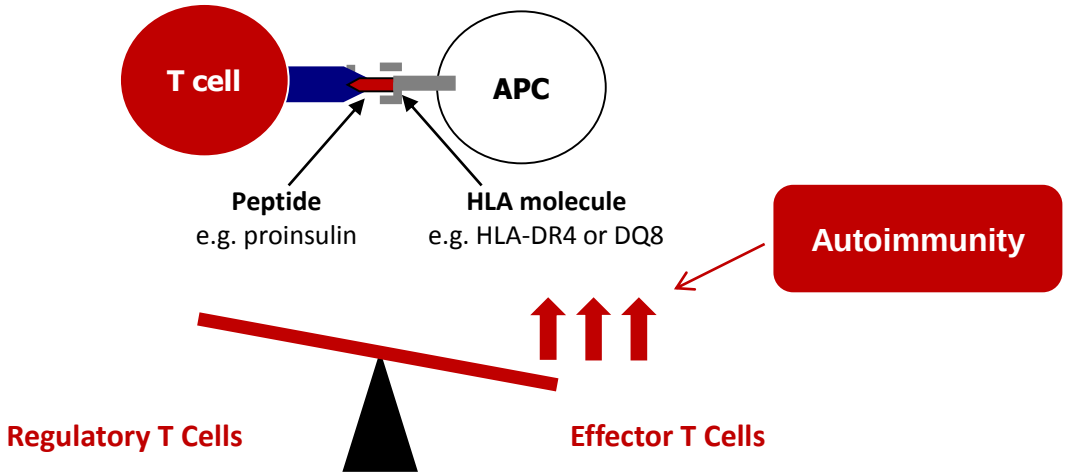
Type 1 Diabetes

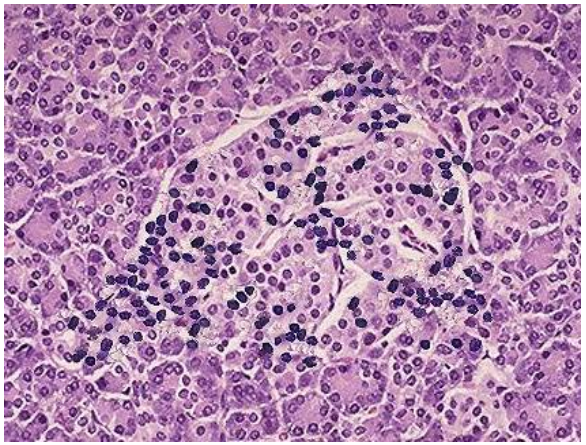
- T1D is an autoimmune disease
- **5-10%** of cases of diabetes
- Auto-reactive T-cells are involved in destruction of β-cells
- Particular HLA molecules are associated with susceptibility to T1D (HLA-DR4 and HLA-DQ8)

Pathogenesis of Type 1 Diabetes

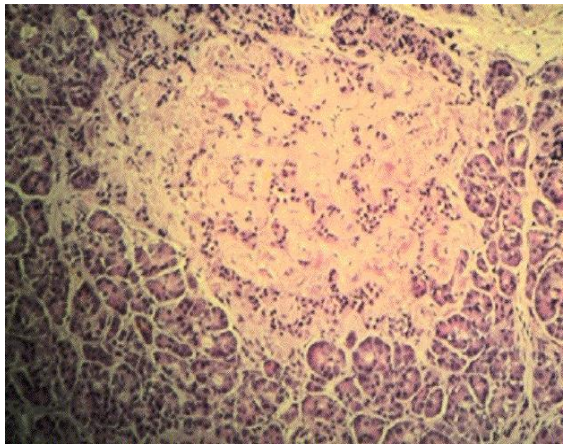
- T cells recognise peptides of self proteins such as Proinsulin presented by HLA molecules and become activated



Pathogenesis of Type 1 Diabetes

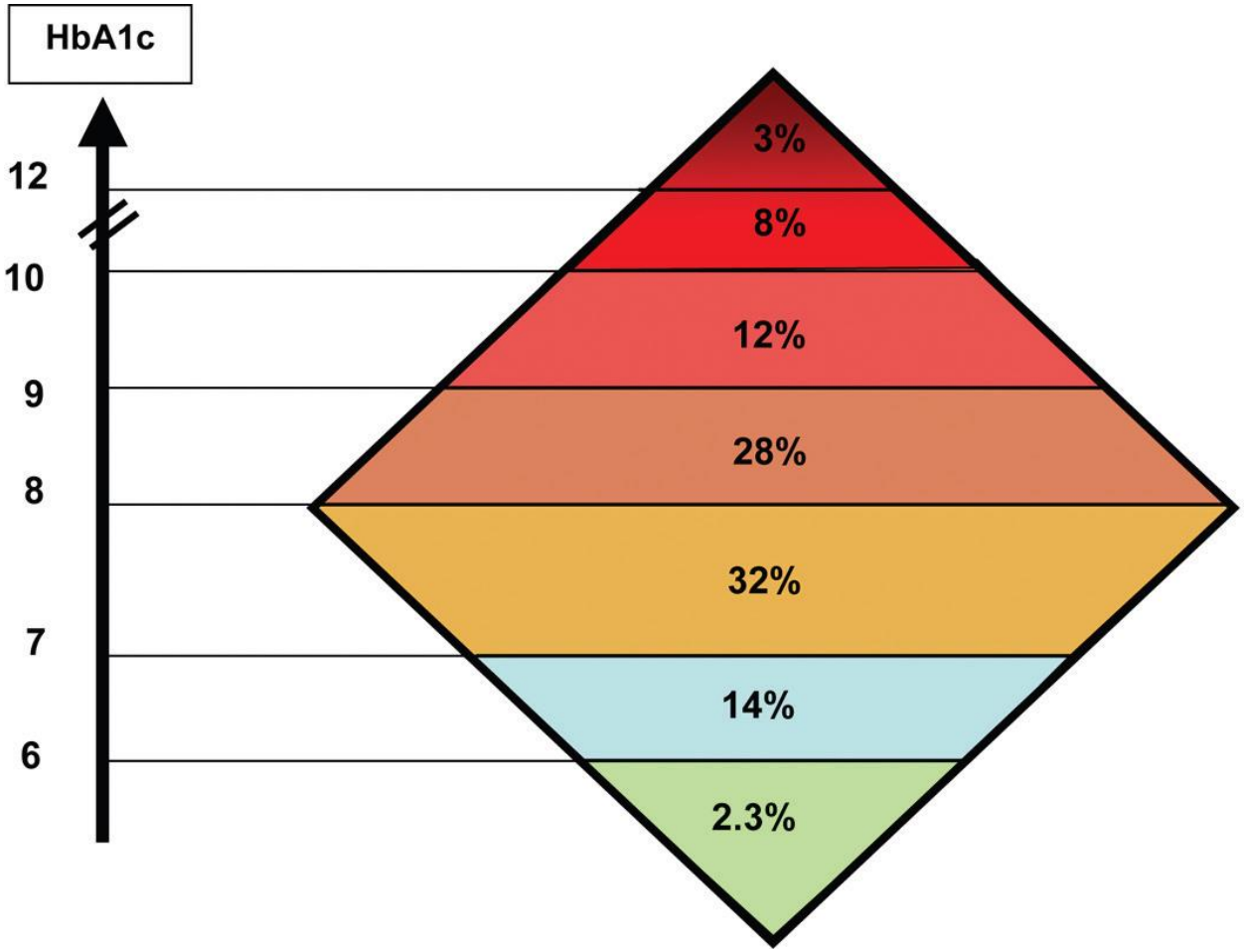


T-cell Infiltration



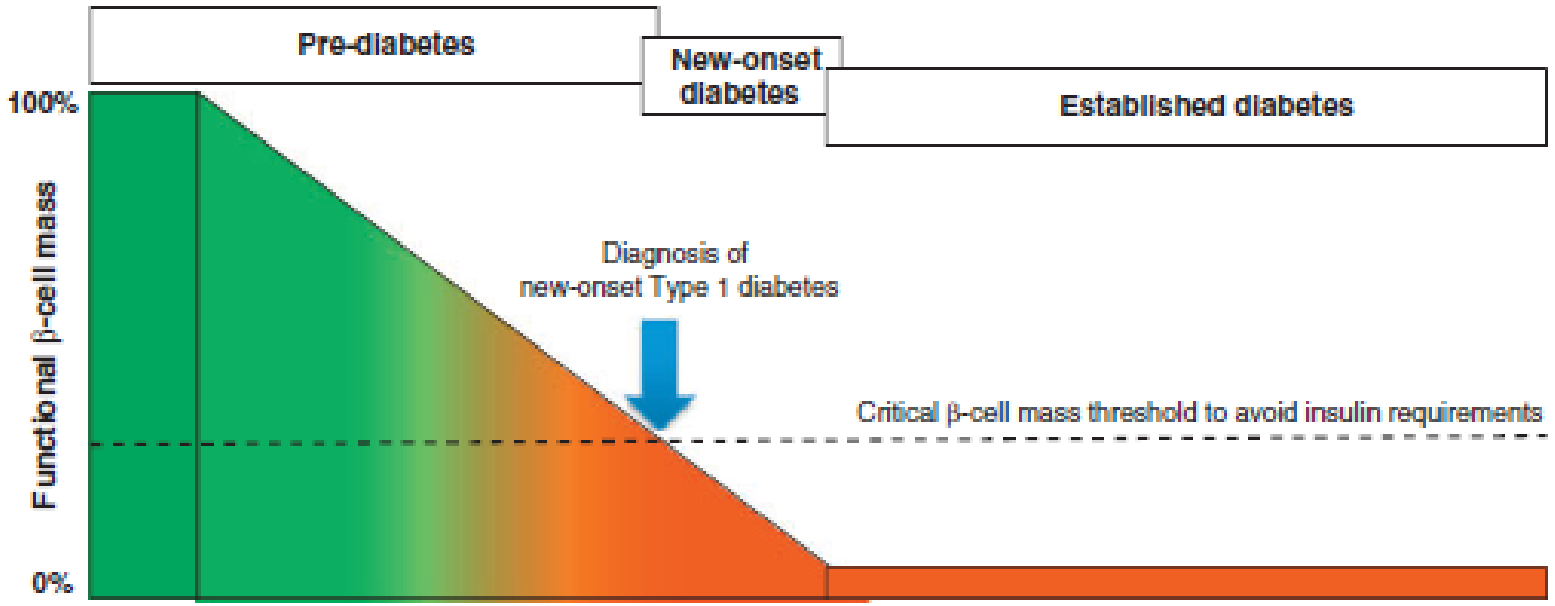
Islet Destruction

The Challenge in Managing T1DM



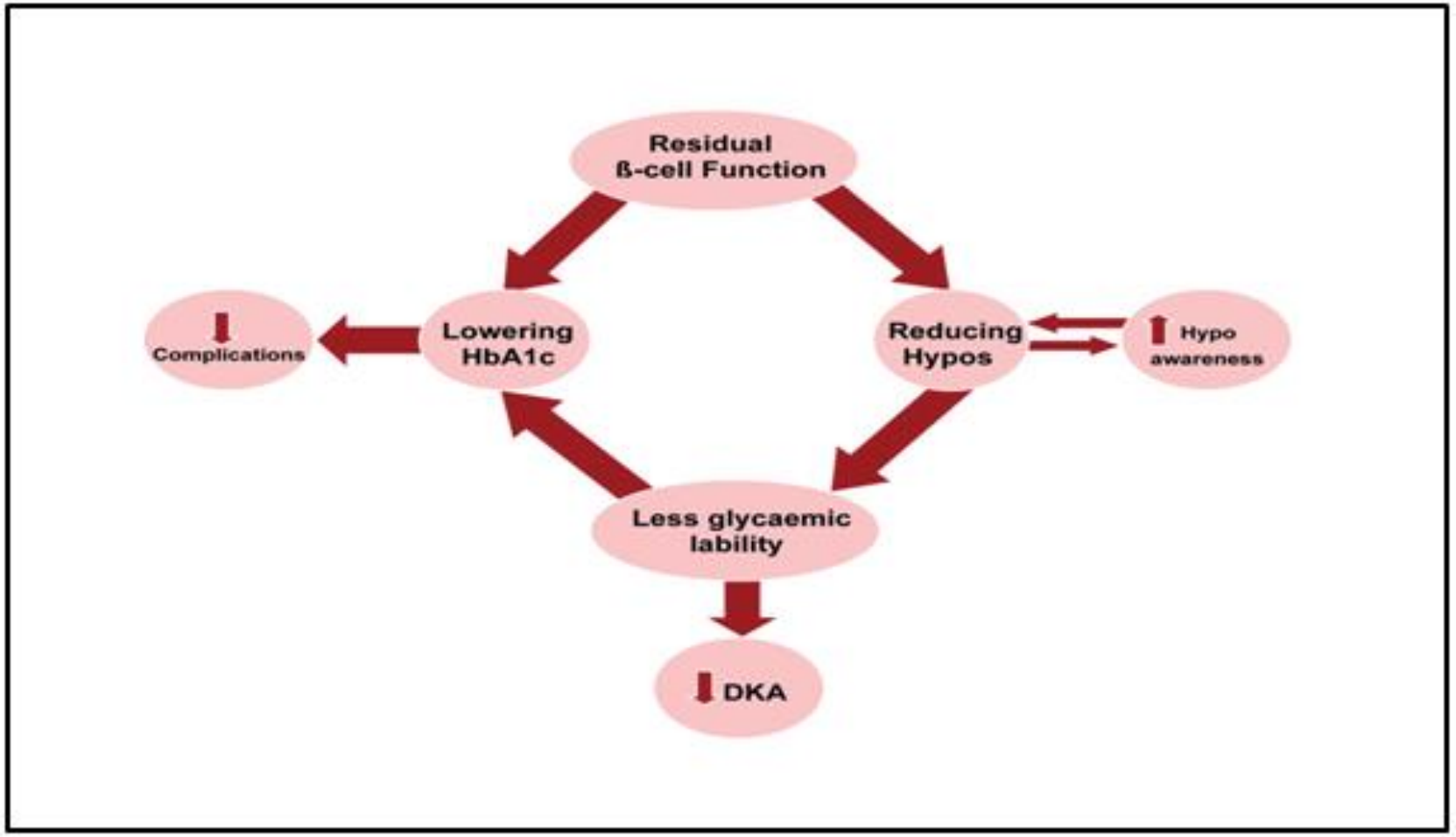
Alhadj Ali *et al,* 2009, *BJDVD*. 248-253.

Natural History of T1DM



George *et al*, 2012, *Diabetic Medicine*. 179-188.

Benefits of beta cell Preservation



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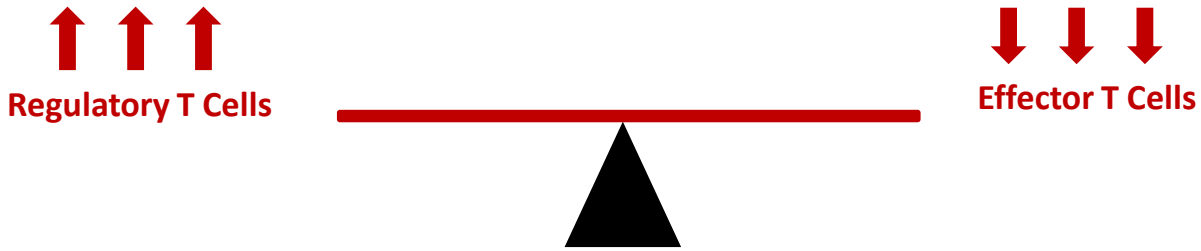
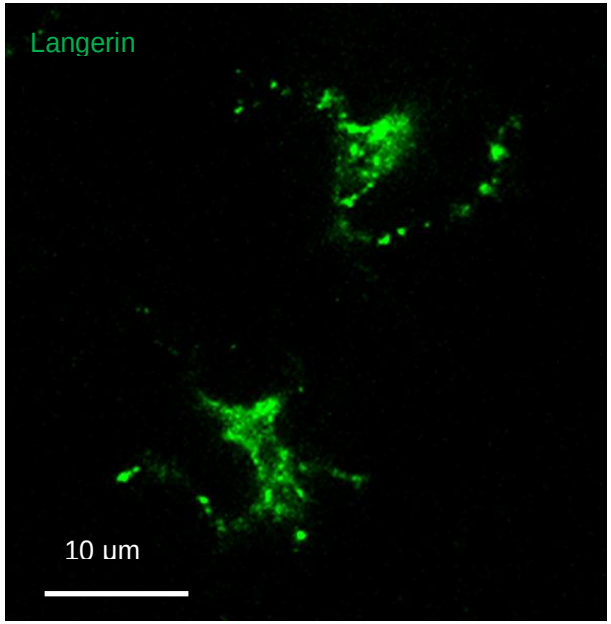
Antigen Specific Therapy

- Administration of short peptides corresponding to T cell target sequences was shown to be an effective method of restoring tolerance and reversing disease in animal models of T1D



Immunomodulation

- To halt the ongoing autoimmune process, preventing β-cells from further destruction and allowing them for a potential regeneration



Alhadj Ali *et al,* 2015*, Immunology*. 411-422.

Phase 1b Study :
Proinsulin (PI) Peptide Immunotherapy in New-Onset Type 1 Diabetes

MonoPept1de

Kings College London	Newcastle	Cardiff	Bristol	Chester

DVDC DIABETES VACCINE DEVELOPMENT CENTRE

JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

Questions?

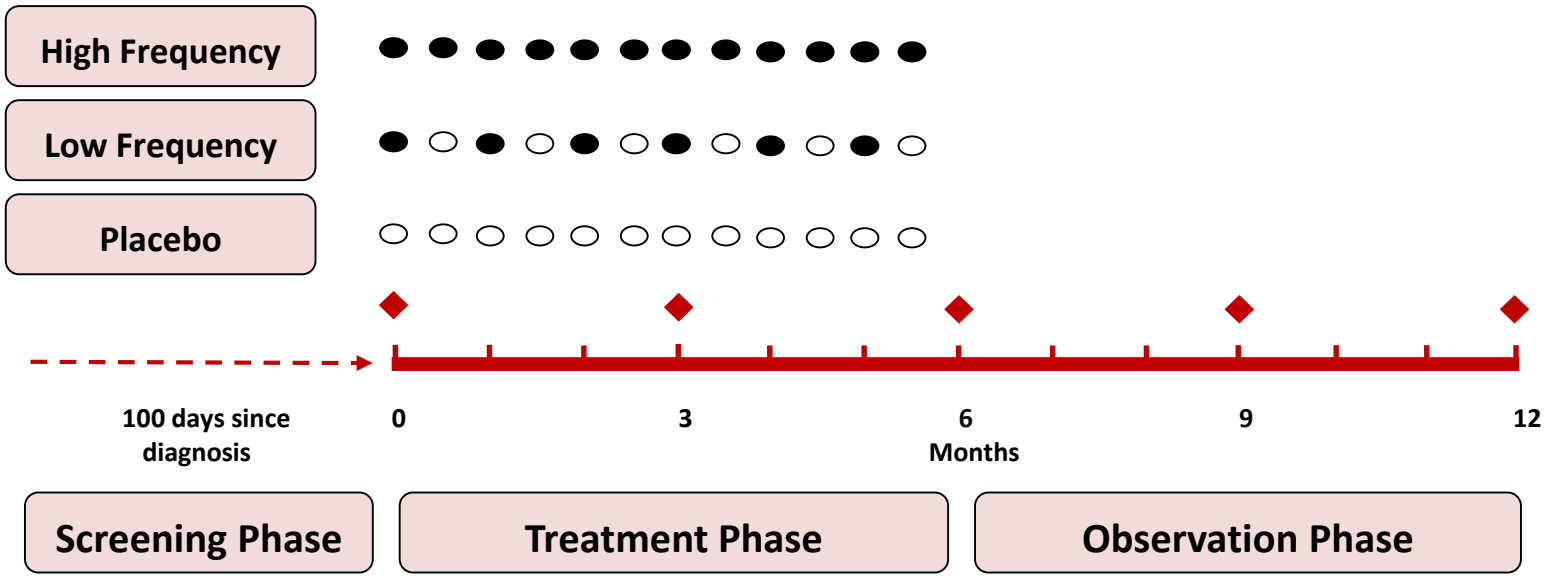
1. Does repeated dose peptide immunotherapy cause hypersensitivity?

2. Does peptide immunotherapy exacerbate disease?

3. Does peptide immunotherapy preserve c-peptide?

MonoPept1de

Inclusion Criteria:
- Age 18-45
- HLA-DRB1*0401 genotype
- 1 out of 3 autoantibodies positive (GAD, IA2 or ZnT8)
- Stimulated C-peptide on MMTT >200pmol/l



Intradermal placebo injection

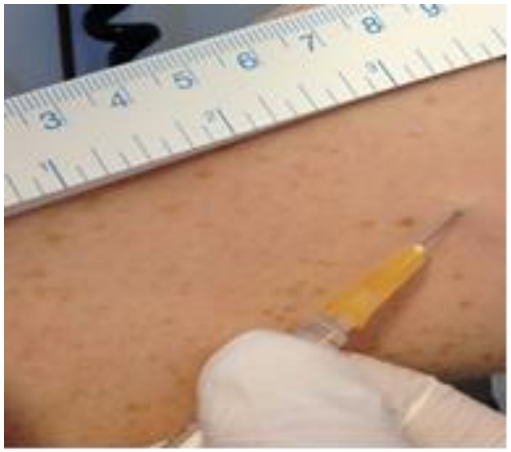
Intradermal 10 µg C19-A3 peptide injection

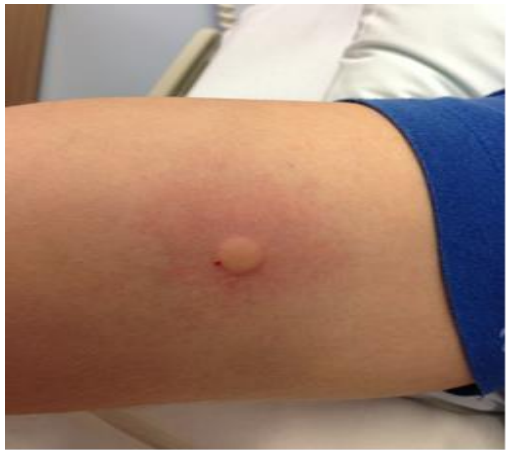
Mixed Meal Tolerance Test (MMTT)

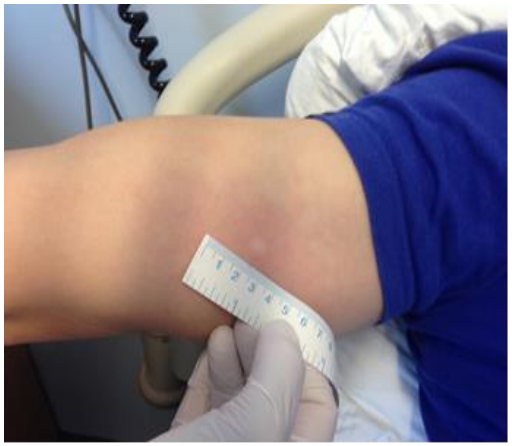
MonoPept1de Baseline Characteristics

Characteristic	Placebo (N=8)	Low Frequency (N=10)	High Frequency (N=9)
Mean Age - yr	28.9 ± 8.18	26.6 ± 5.48	30 ± 5.66
Gender – no (%)			
Female	25%	40%	33.3%
Male	75%	60%	66.7%
Body Mass Index (Kg/m²)	23.05 ± 2.63	24.21 ± 5.52	25.56 ± 5.44
Number of diabetes related antibodies (%)			
1	12.5%	50%	11.1%
2	25%	30%	11.1%
3	62.5%	20%	77.8%
Mean time from diagnosis to first dose (days)	95 ± 22.8	82.5 ± 16.04	91 ± 15.5
Mean Glycated haemoglobin (mmol/mol)	62.5 ± 13.7	58.4 ± 14.9	51.7 ± 6.83
Average total daily insulin dose (IU/Kg/day)	0.42 ± 0.20	0.38 ± 0.18	0.30 ± 0.07
Stimulated C-peptide AUC - nmol/L/min	0.58 + 0.25	0.81 + 0.76	0.99 + 0.73

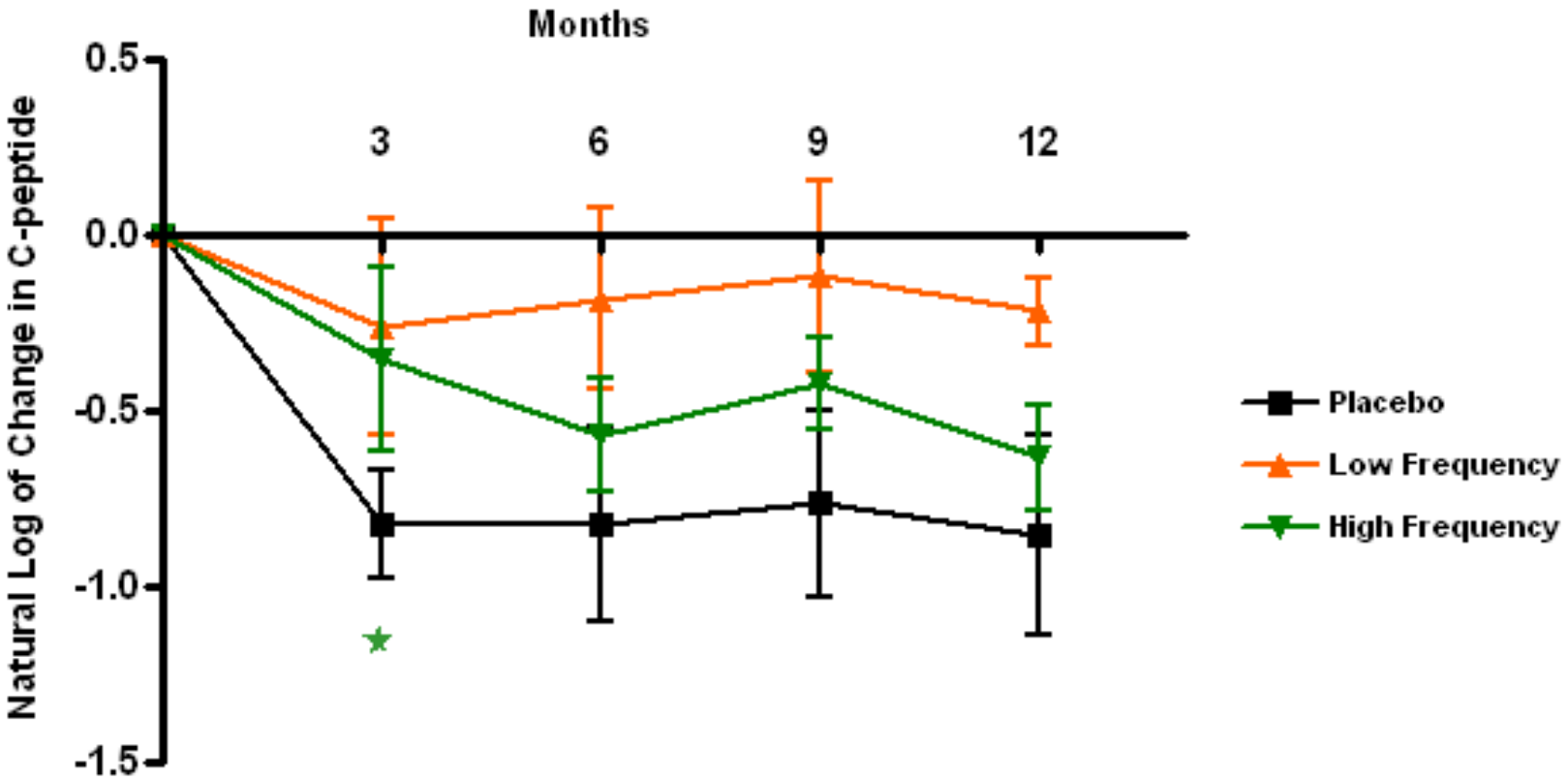
Skin Reactions at Injection Site





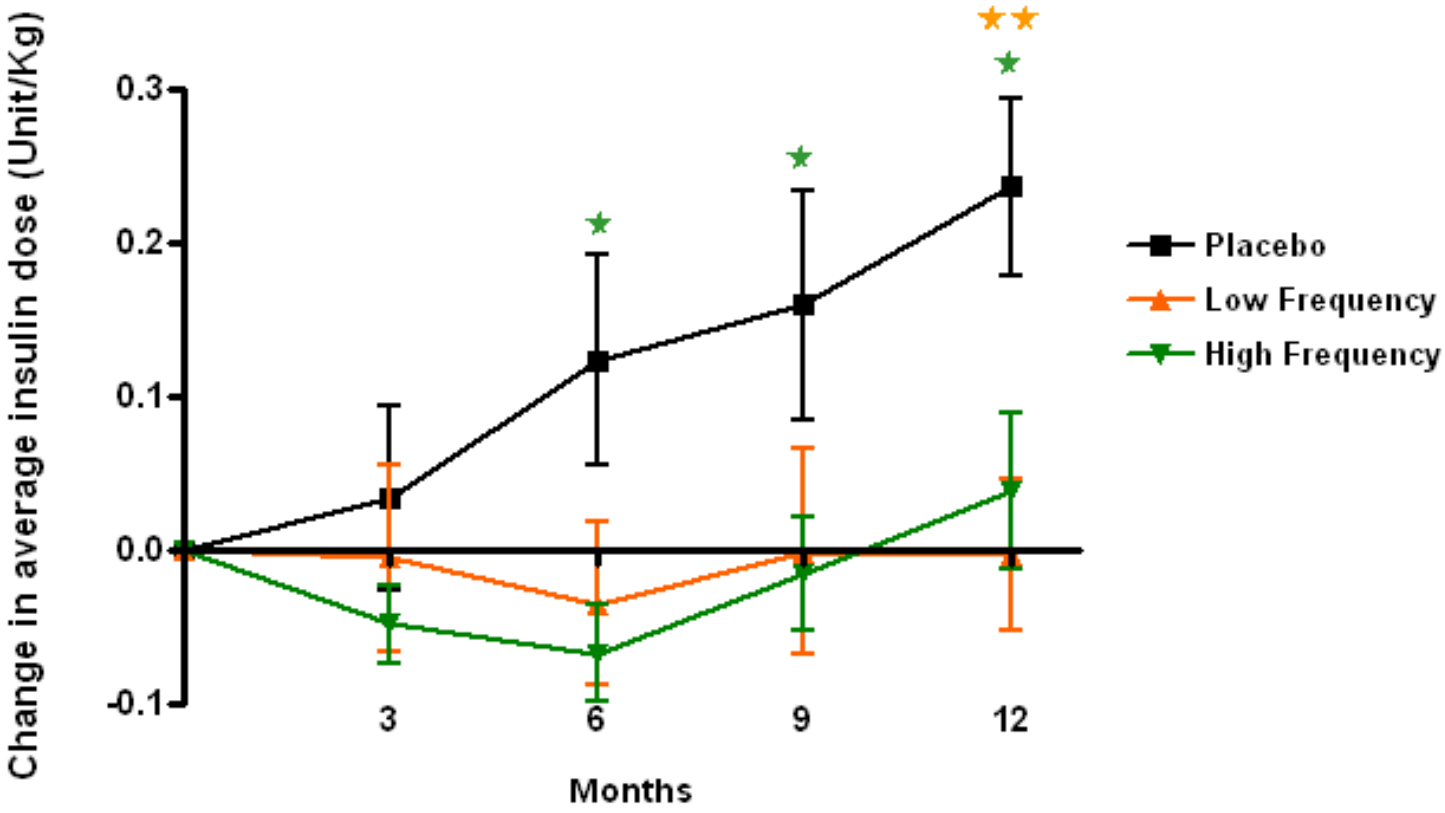


C-Peptide



Alhadj Ali *et al*, *Science Trans Med*. 9,eaaf 7779 (2017)

Insulin Use



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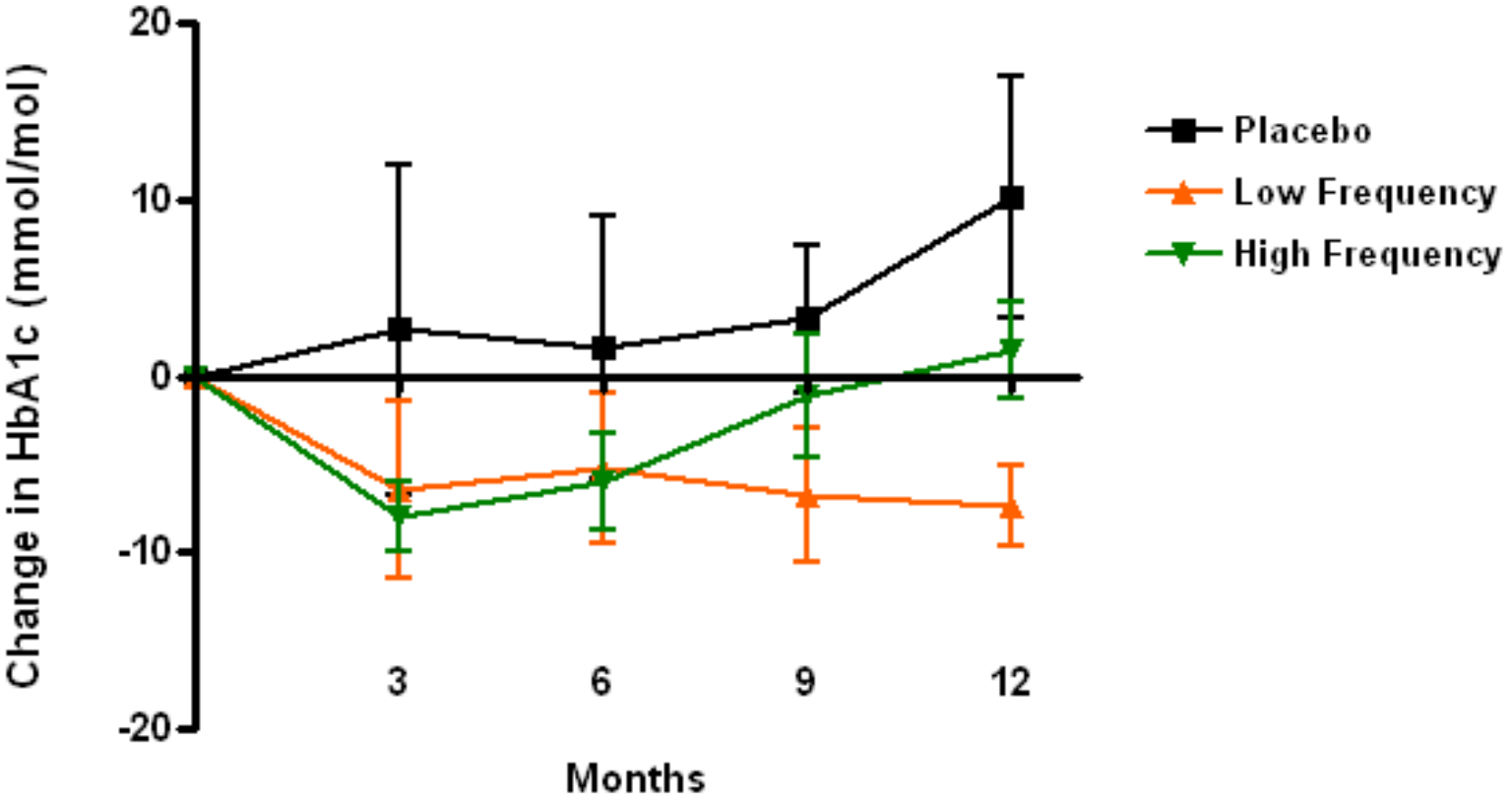
HbA1c



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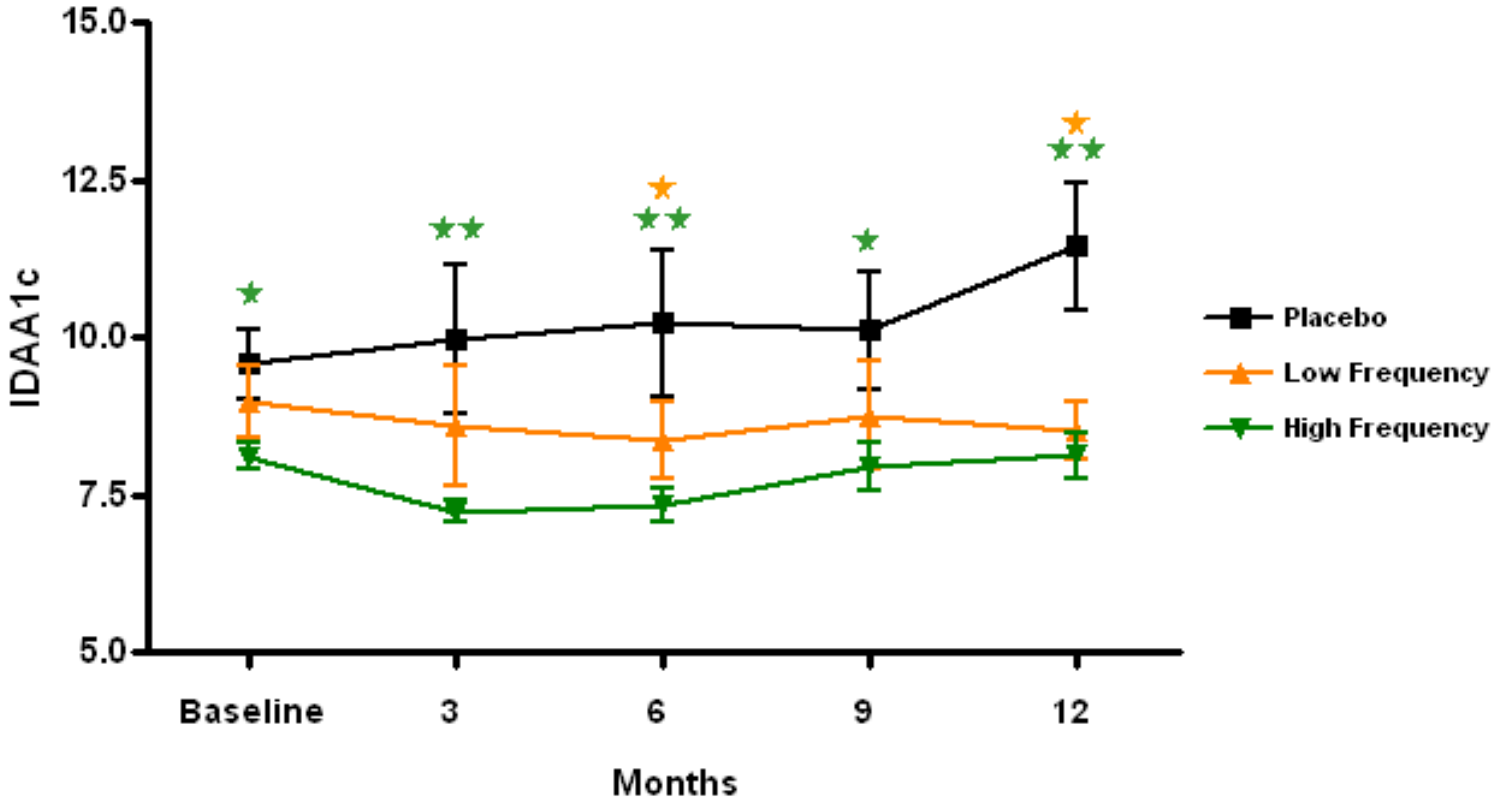
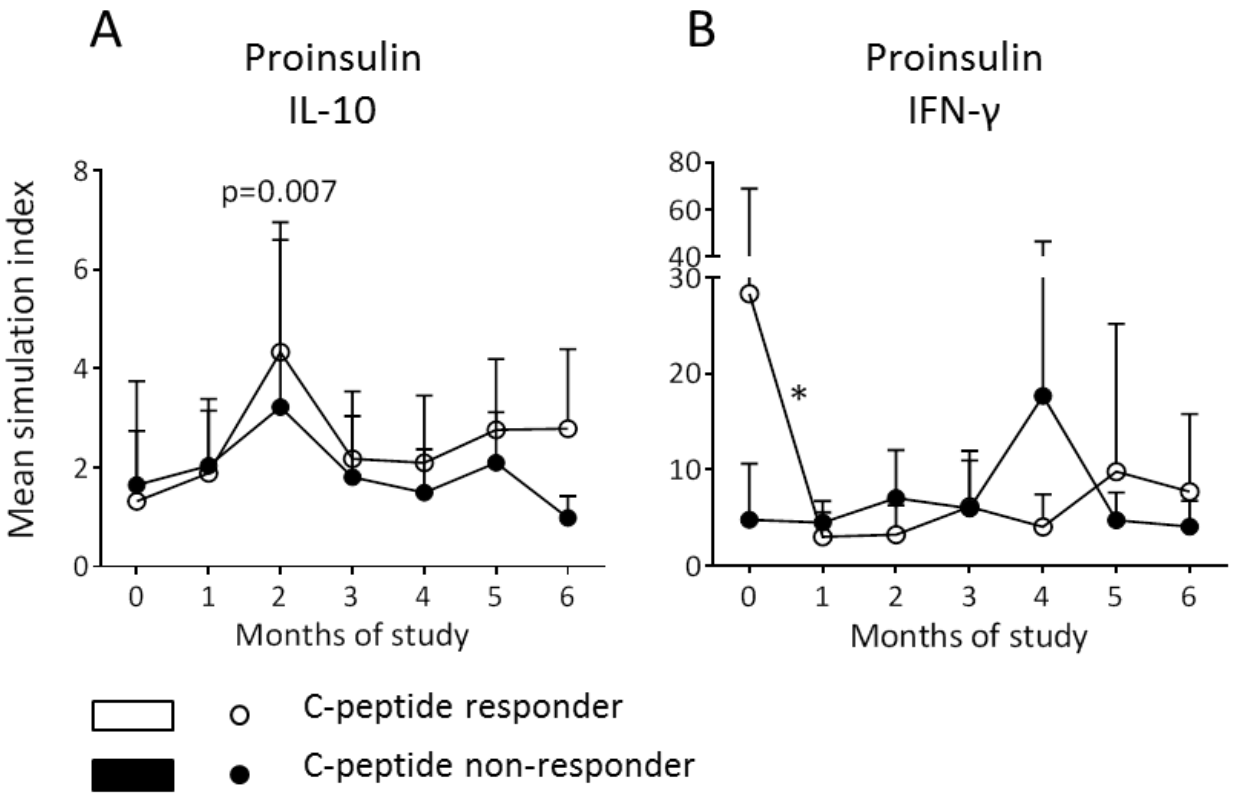
Insulin Dose Adjusted HbA1c (IDAA1C)



IDAA1C * **= HbA1c (%) + [4 × insulin dose (unit/kg/day)]**

Alhadj Ali *et al*, *Science Trans Med*. 9,eaaf 7779 (2017)

T cell responses to Proinsulin Peptide C19-A3



Response to treatment is defined as an increase (a positive change from baseline) or maintenance (change of <50% of the interassay coefficient of variation of the C-peptide assay) in C-peptide response to a mixed meal tolerance test

Conclusion

- PI C19-A3 peptide immunotherapy in the dosing regimen used was safe and well tolerated
- Treatment with PI C19-A3 associated with reduced or stable daily insulin use
- The stable insulin use in either of the treated groups was not associated with poorer glycaemic control
- This phase 1b trial paves the route for future phase 2 trials in new-onset T1D to examine effectiveness of PI C19-A3

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Competing Interests

- UCB has licensed the rights to C19-A3 from King's College London
- UCB did not sponsor or fund the Phase 1b study for C19-A3 presented in this abstract

Thank You