Supplementary Table 1: Nasal B:9-23 peptide protocols implemented in the *type 1 diabetes* Physiolab platform

	Initial treatment			Follow-up treatment				
Protocol	Age (wks)	Dose (µg)	Schedule	Age (wks)	Dose (µg)	Schedule	Laboratory Result	Protected virtual mice[A]
Daniel [1]	4	40	3 consecutive days	9	40	3 consecutive days, every 4 wks until 32 wks	Protective	12 out of 12
Kobayashi [2]	4	20	5 consecutive days	5	20	once a wk for 5 wks	Not protective	0 out of 12
von Herrath [3]	10	40, 100	3x/wk for 2 wks	12	40	once a wk for 5 wks	Not protective	0 out of 12

[A]: Virtual mice considered protected when blood glucose did not cross 16.67mmol/L throughout the course of simulation

Supplementary Table 2: Pharmacokinetic (PK) effects of nasal B:9-23 therapy explored in silico

Peripheral LT[A] (including NALT)	
PK effect	**Impact on *type 1 diabetes* pathogenesis**
Th1 deletion	protective
Th2 deletion	pathogenic
aTreg deletion	pathogenic
nTreg deletion	pathogenic
Th1 induction	pathogenic
Th2 induction	protective
aTreg induction	protective
nTreg induction	protective
Central LT	
PK effect	**Impact on *type 1 diabetes* pathogenesis**
Conventional $CD4^+$ thymic deletion	protective

The therapeutic effect of nasal B:9-23 immunization was explored in silico under three major scenarios in the peripheral LTs: 1) Th1 deletion or induction, 2) Th2 deletion or induction and 3) Treg deletion or induction. All scenarios were considered pathogenic or protective according to previously published results. In the thymus, $CD4^+$ T cell deletion of conventional and perhaps pathogenic T cells is considered to be beneficial for the course of *type 1 diabetes*.

Supplementary Table 3: Variations in the underlying pathophysiology of virtual NOD mice

Virtual mouse	T cell differentiation bias	Inflammation contribution to beta cell exhaustion	Dynamic NK cell representation	Innate Treg suppression of adaptive Treg	High Treg proliferation rate	Age of dabetes onset
VM1	Th1	yes	no	no	no	19 wks
VM2	Balanced	yes	no	no	no	19 wks
VM3	High Th1	yes	no	no	no	19 wks
VM4	Th2	yes	no	no	no	24 wks
VM5	Th1	yes	yes	no	no	19 wks
VM6	Balanced	yes	yes	no	no	19 wks
VM7	Th1	yes	no	yes	no	19 wks
VM8	Th1	yes	no	no	yes	19 wks
VM9	Th1	no	no	no	no	19 wks
VM10	Balanced	no	no	no	no	19 wks
VM11	Th1	no	yes	no	no	19 wks
VM12	Balanced	no	yes	no	no	19 wks

Twelve virtual NOD mice (VM) were generated according to some well but also poorly described biological phenomena to occur and have an impact on *type 1 diabetes* pathogenesis. Each one VM represents different possible scenarios of all these parameters being operative or not, since currently it is not well understood how they can precisely affect *type 1 diabetes* onset. Nevertheless, all VM that represent the in silico platform used for the purposes of the present study develop diabetes.

Supplementary Table 4: The number of predictions tested in wet lab

Predicted by the T1D Physiolab platform	Results obtained in the wet-lab	Results shown in
Low-frequency nasal B:9-23 peptide immunization protects virtual NOD mice from T1D development, while high-frequency immunization does not	Low -requency immunization was more beneficial in protecting real NOD mice from T1D development, while high-frequency immunization only delayed but did not overall protect from the disease	Fig. 3
Low-frequency immunization induces aTreg in the blood and NALT but not in the PDLN 2-3 weeks after immunization following the low and not the high-frequency immuni-zation protocol	Low-frequency immunization induced Treg (cannot distinguish aTreg from iTreg) in the spleen and blood but not in the PDLN at the window that was predicted and only with the low-frequency immunization protocol	Fig. 3
Low-frequency immunization decreases insulitis but increases aTreg numbers in the pancreatic islets	Upon low but not high- frequency immunization reduced insulitis was seen, while Treg ($Foxp3^+$) frequency was elevated in both low and high-frequency immunized mice in pancreatic islets with high degree of insulitis. Low-frequency immunization showed highest Treg frequency.	Fig. 4
Low-frequency immunization increases intraislet IL-10 and IL-4 produced by the infiltrating lymphocytes	Low-frequency immunization induced IL-10 production by intraislet lymphocytes but no significantly elevated levels of IL-4 were seen (ELISPOT assay)	Fig. 5
Low-frequency immunization- induced tolerance is sensitive to IL-10 but not to IL-4 neutralization	Upon IL-10 neutralization the tolerogenic effect mediated by low-frequency immunization was lost (IL-4 neutralization was not conducted)	Fig. 7
The platform is not developed to make predictions regarding immunological events taking place in the spleen	In the spleen IFNγ was induced after lo-frequency immunization, while IFNγ/IL-4 in the blood and IL-10 in the PDLN were seen	Fig. 6
Efficacy of low-frequency nasal therapy was predicted to decrease if treatment is started at a later age	Treatments that began at 9 instead of 4 wks of age showed a lesser protective effect, consistent with the simulation results	Suppl Fig. 1~~2~~

Supplementary FIG. 1: Multiphasic age dependent efficacy for nasal B:9-23 peptide therapy. Graphic representation of Daniel protocol (*A*). Nasal B:9-23 peptide treatment was simulated in VM according to this protocol but starting at various ages and efficacy was assessed. Note that age at treatment has been normalized to the average age of onset observed in the laboratory for NOD mice (15 wks compared to 19 wks in the VM cohort) (*B*). *C*: NOD mice were treated with the Daniel protocol starting at 4 or 9wks of age and blood glucose was monitored over time. More than 12 mice were analyzed per group in two independent experiments. *, $p<0.05$ between PBS and Daniel immunization protocol initiated at 4 wks of age.