Approcci personalizzati nel diabete tipo 1:

Terapia immunologica

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CENTRO REGIONALE PER LA MEDICINA DI PRECISIONE

Il sottoscritto Prof. Francesco Dotta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Eli Lilly

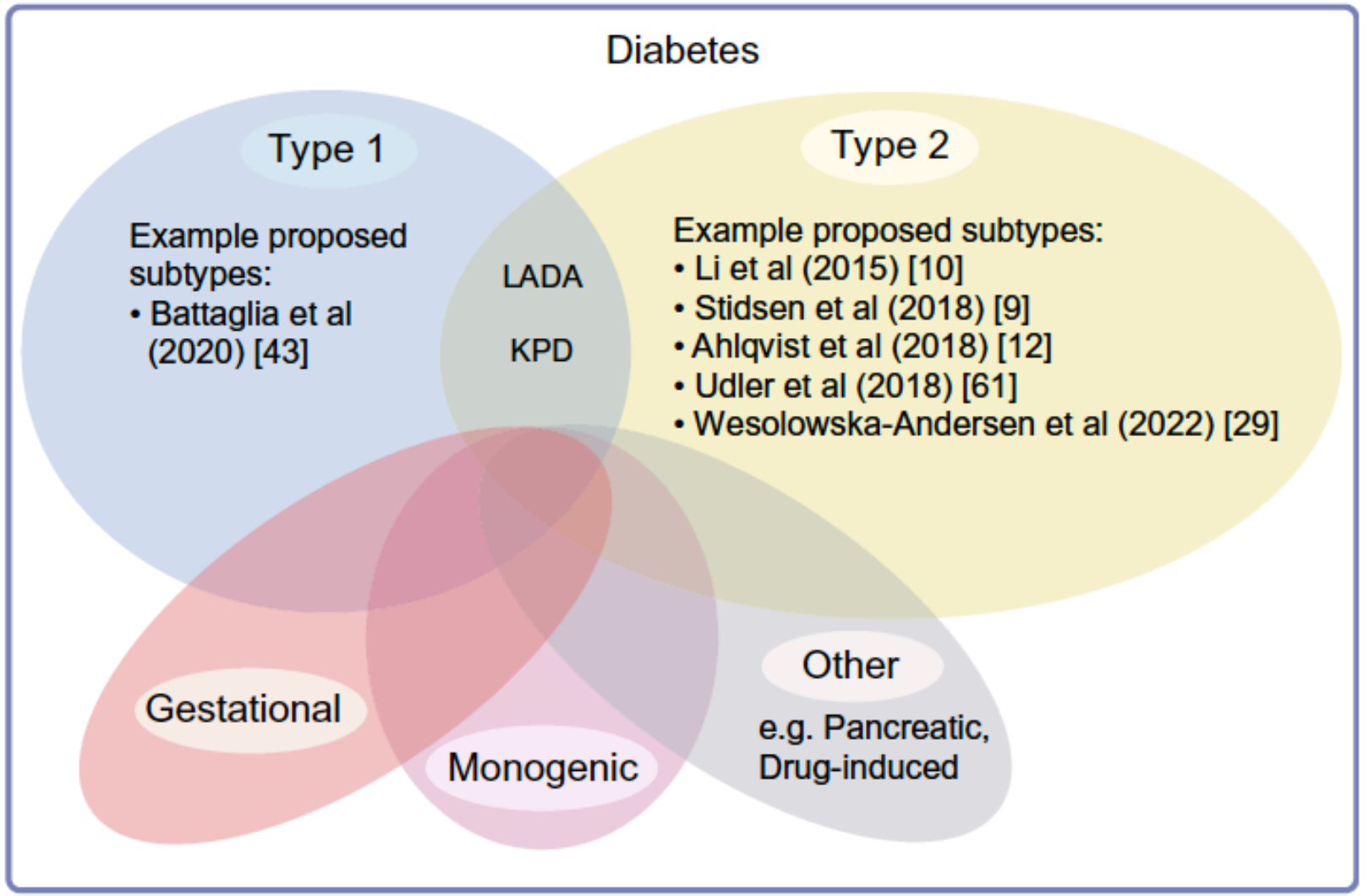
- Sanofi

- Johnson & Johnson

-Novo Nordisk

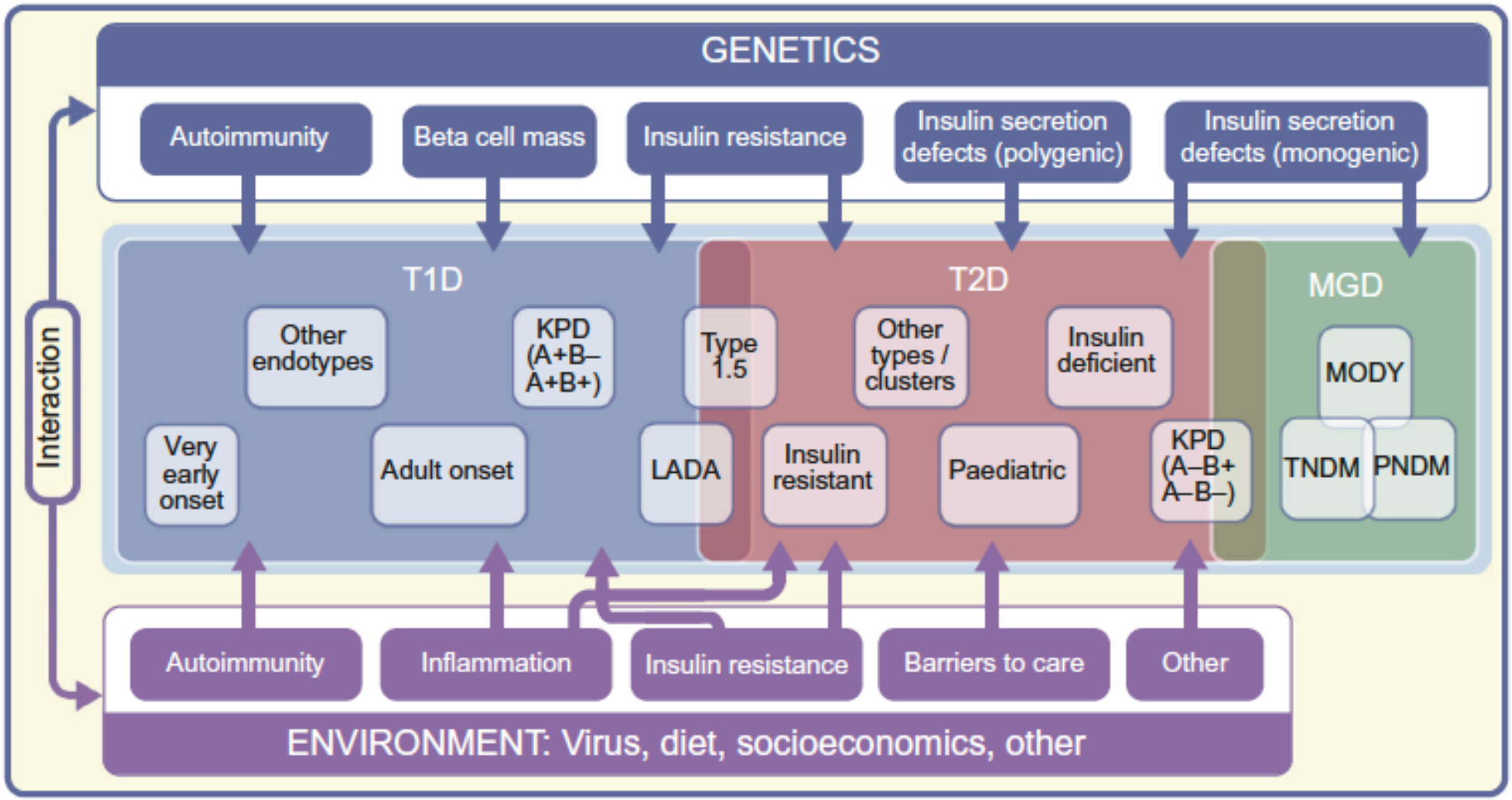
- GSK

Diabetes subtypes

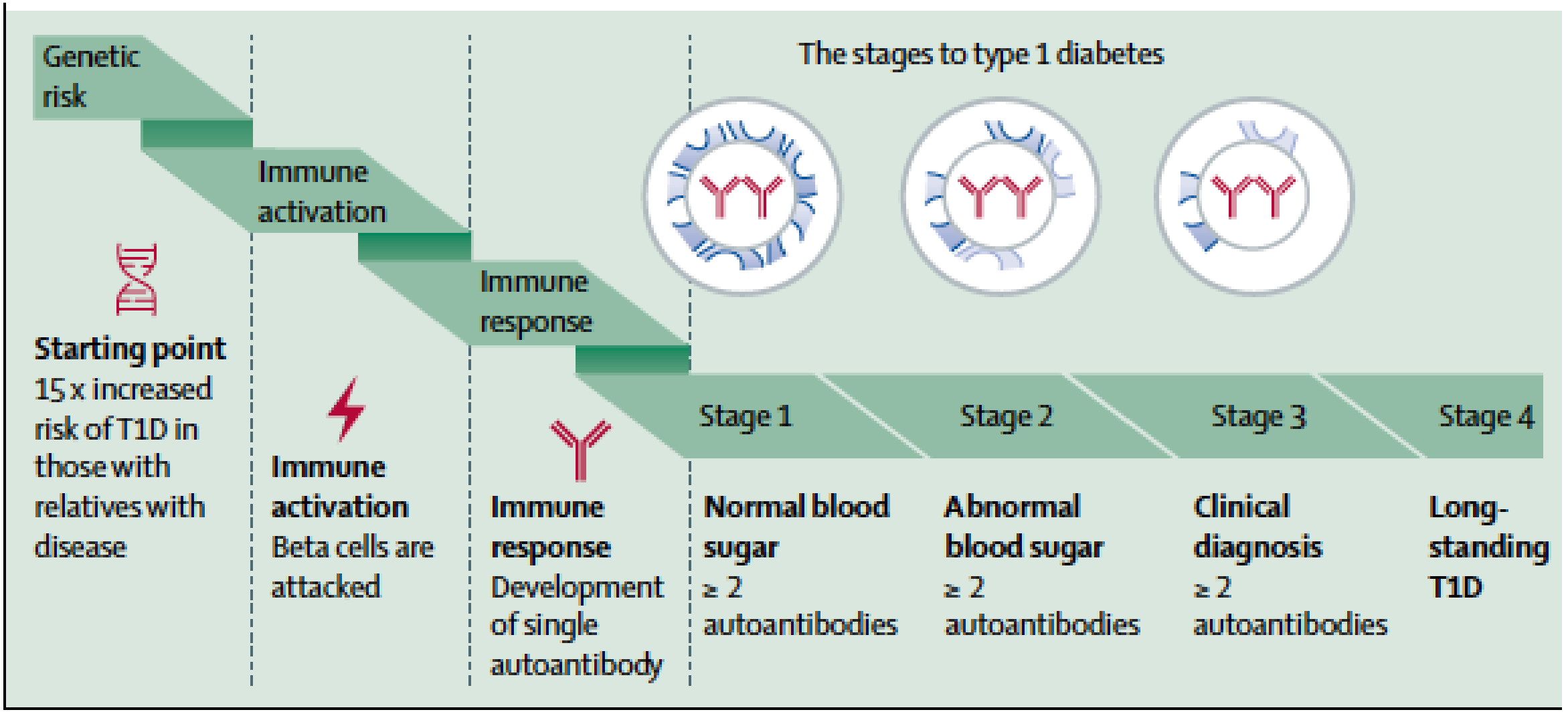


Diabetologia (2022) 65:1758–1769

The clinical consequences of heterogeneity within and between different diabetes types

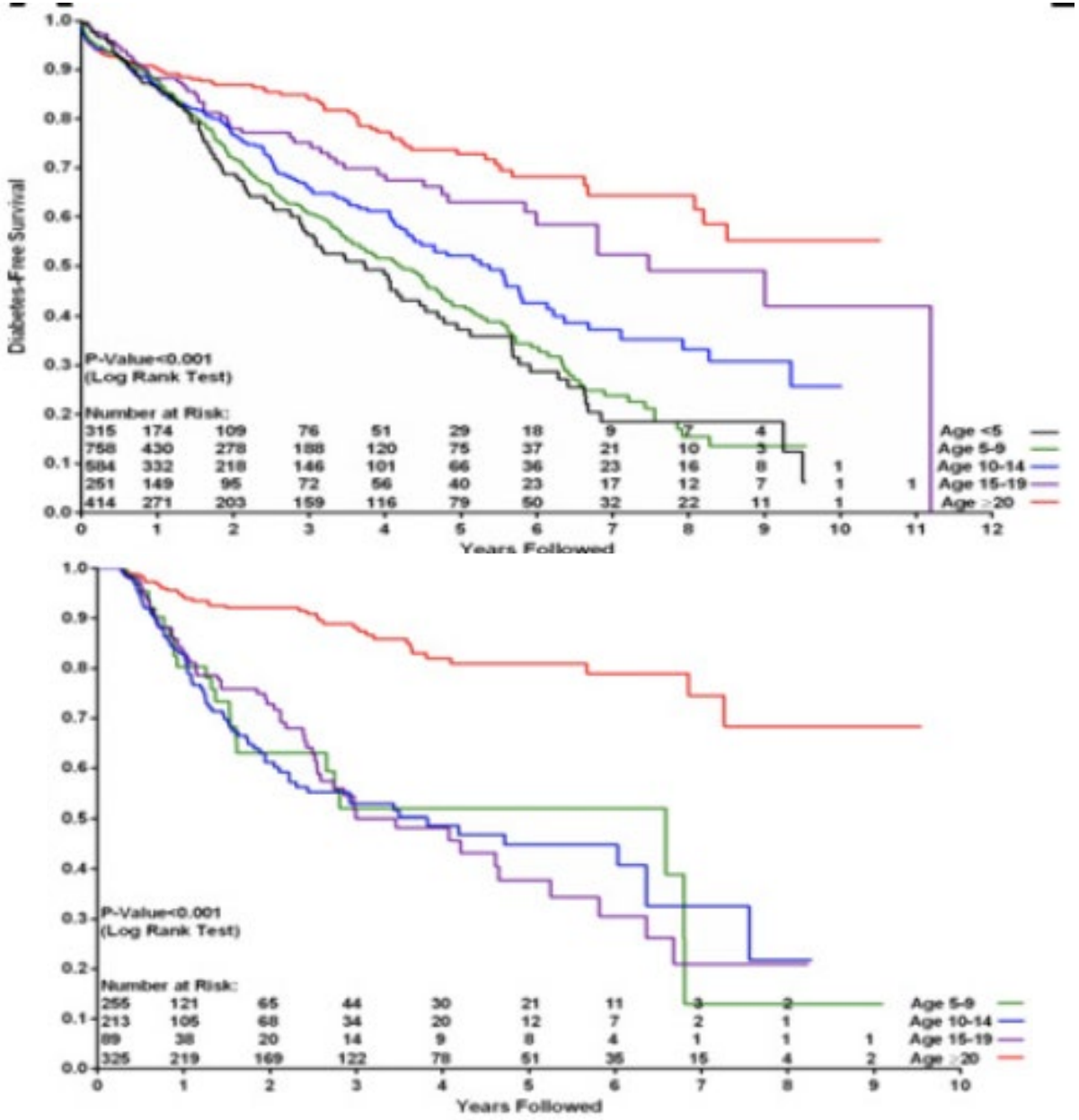


Diabetologia (2020) 63:2040–2048



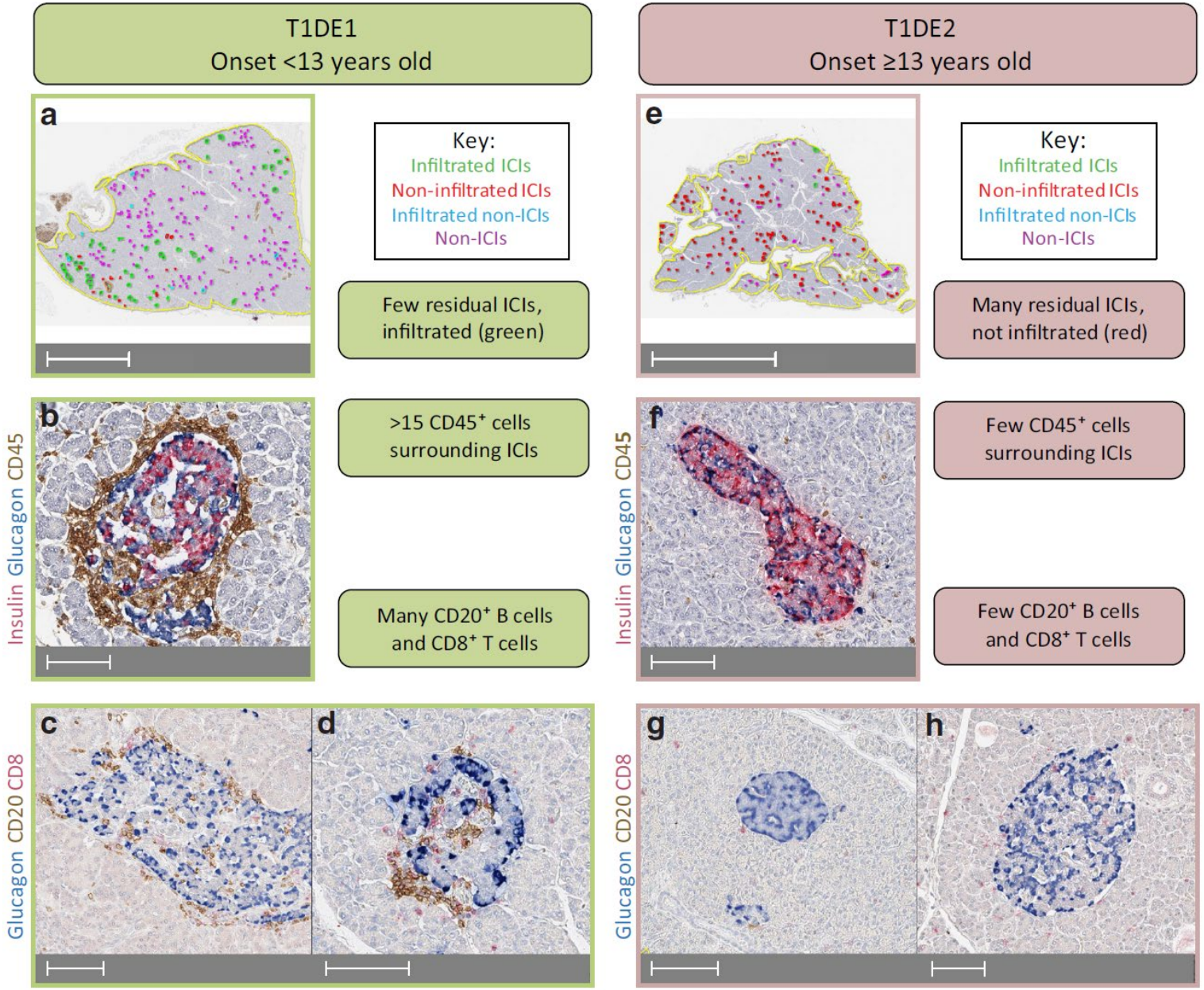
Di Meglio L et. Al. Lancet 2018

Effects of age on progression to type 1 diabetes



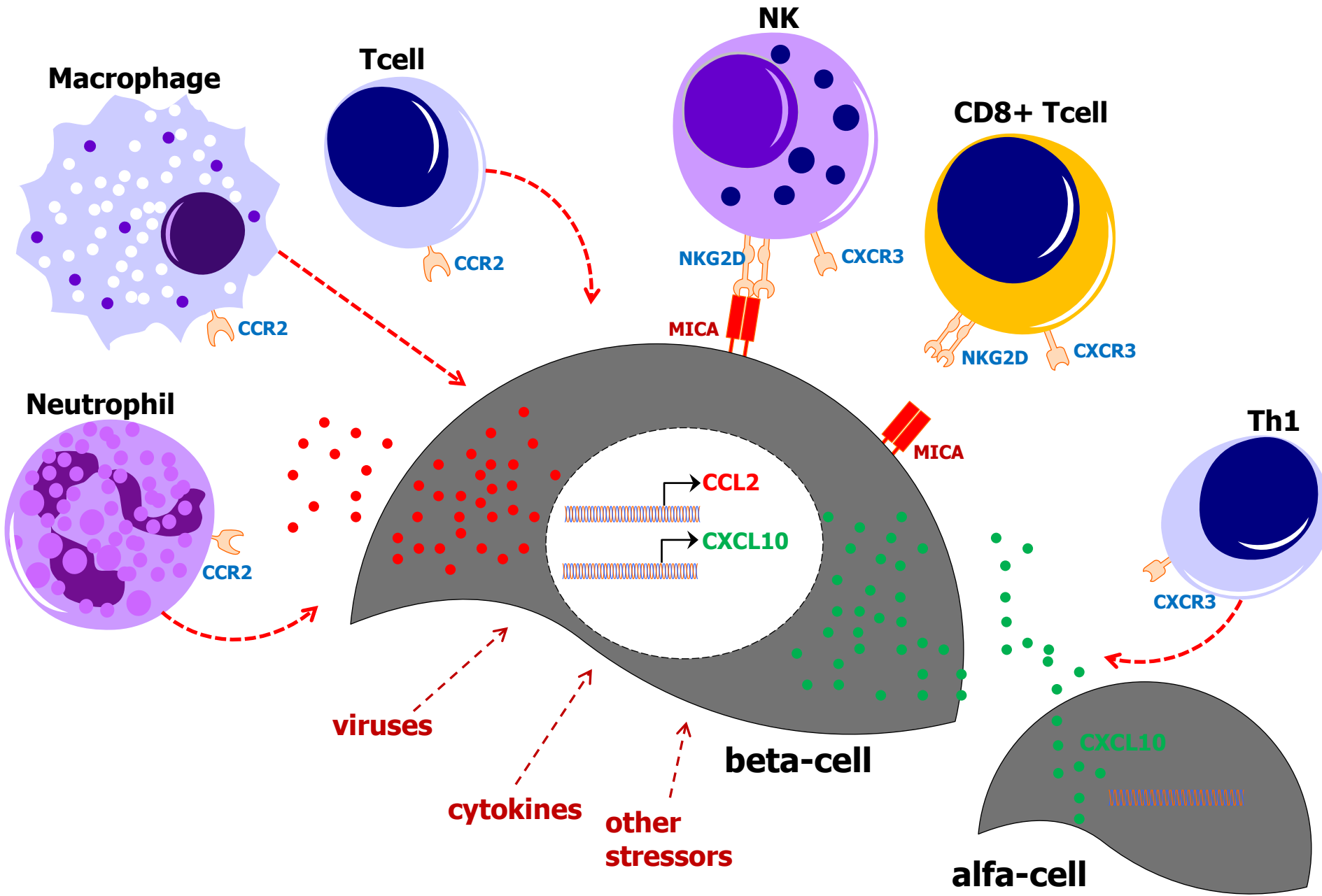
Diabetes Care 2018;41:653–661 | https://doi.org/10.2337/dc17-0806

Age-related T1D Endotypes



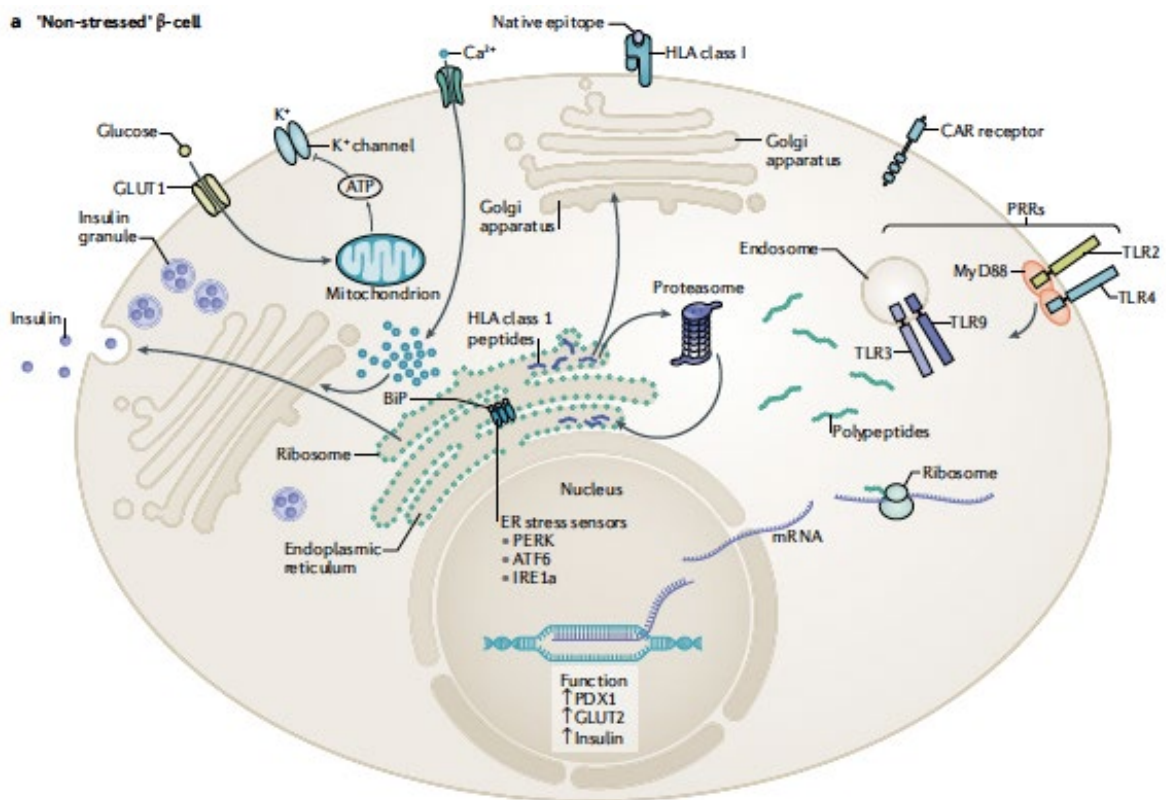
Diabetologia (2021) 64:15–25

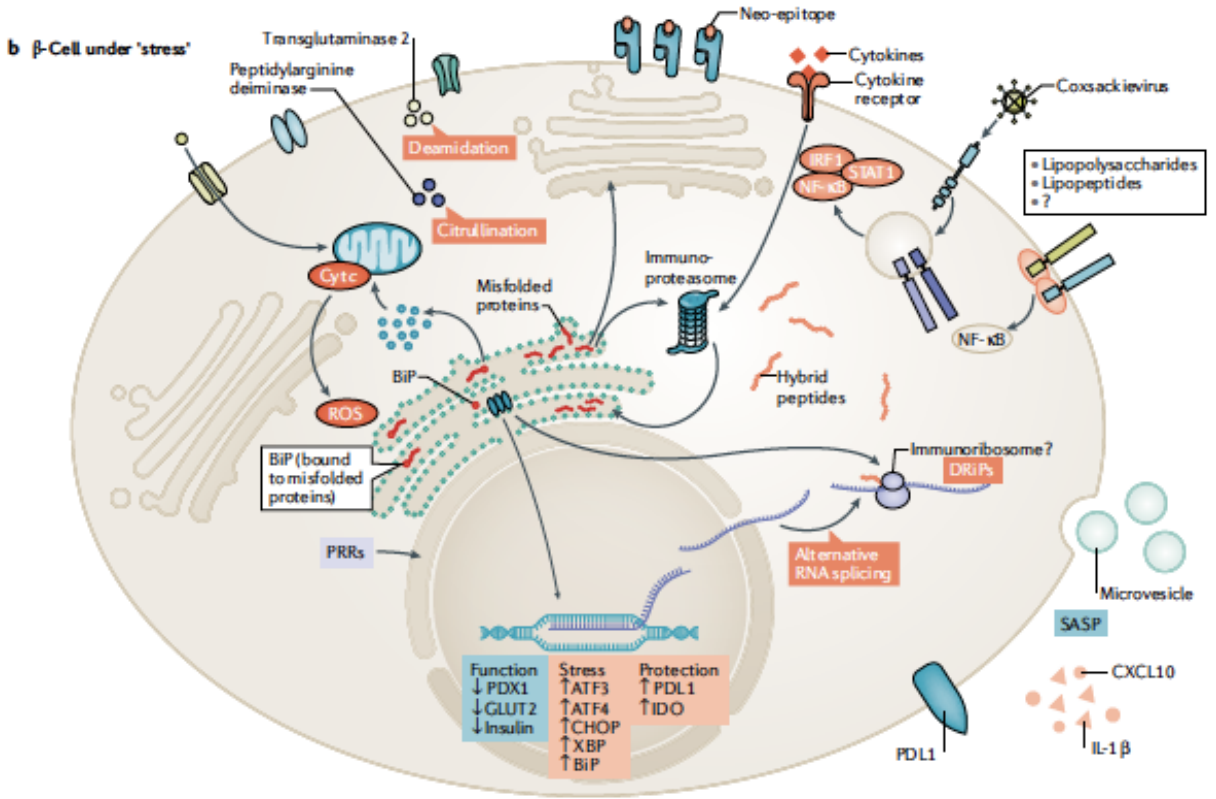
Type 1 diabetes: Complex dialogue between islet and immune system



Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?)

Bart O. Roep[1,2]✉, Sofia Thomaidou[3], René van Tienhoven[1] and Arnaud Zaldumbide[3]



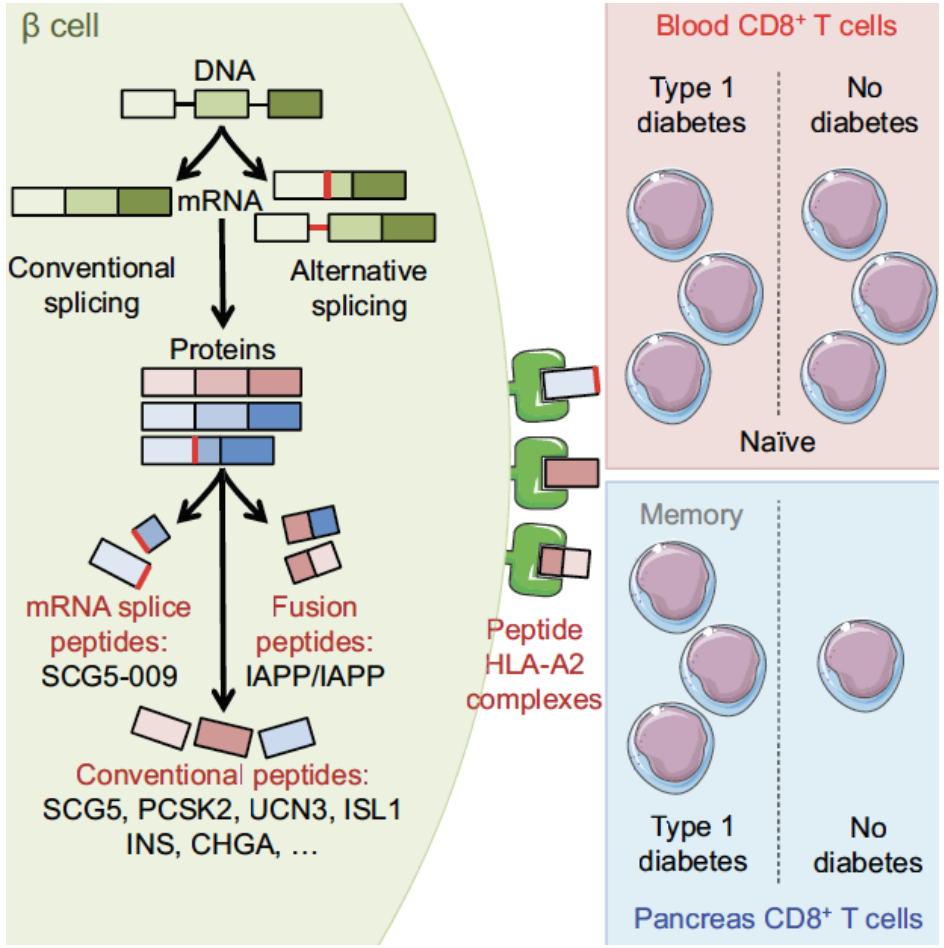


NATURE REVIEWS | ENDOCRINOLOGY

https://doi.org/10.1038/s41574-020-00443-4

Conventional and Neo-Antigenic Peptides Presented by β Cells Are Targeted by Circulating Naïve CD8+ T Cells in Type 1 Diabetic and Healthy Donors

Sergio Gonzalez-Duque,[1,2,3,4] Marie Eliane Azoury,[1,2,3] Maikel L. Colli,[5] Georgia Afonso,[1,2,3] Jean-Valery Turatsinze,[5] Laura Nigi,[6] Ana Ines Lalanne,[1,2,3] Guido Sebastiani,[6] Alexia Carré,[1,2,3] Sheena Pinto,[7] Slobodan Culina,[1,2,3] Noémie Corcos,[1,2,3] Marco Bugliani,[8] Piero Marchetti,[8] Mathieu Armanet,[9] Marc Diedisheim,[1,2,3,10] Bruno Kyewski,[7] Lars M. Steinmetz,[11,12] Søren Buus,[13] Sylvaine You,[1,2,3] Daniele Dubois-Laforgue,[1,2,3,10] Etienne Larger,[1,2,3,10] Jean-Paul Beressi,[14] Graziella Bruno,[15] Francesco Dotta,[6] Raphael Scharfmann,[1,2,3] Decio L. Eizirik,[5,16] Yann Verdier,[4,16] Joelle Vinh,[4,16] and Roberto Mallone[1,2,3,10,17,*]



- Peptide HLA class I presentation by β cells is increased by inflammatory cytokines
- Peptide sources feature several insulin granule proteins, e.g., SCG5, PCSK2, UCN3
- SCG5-009 mRNA splice products and IAPP fusion peptides are also presented
- In type 1 diabetes, peptide-reactive CD8+ T cells are enriched in the pancreas

Cell Metab. 2018

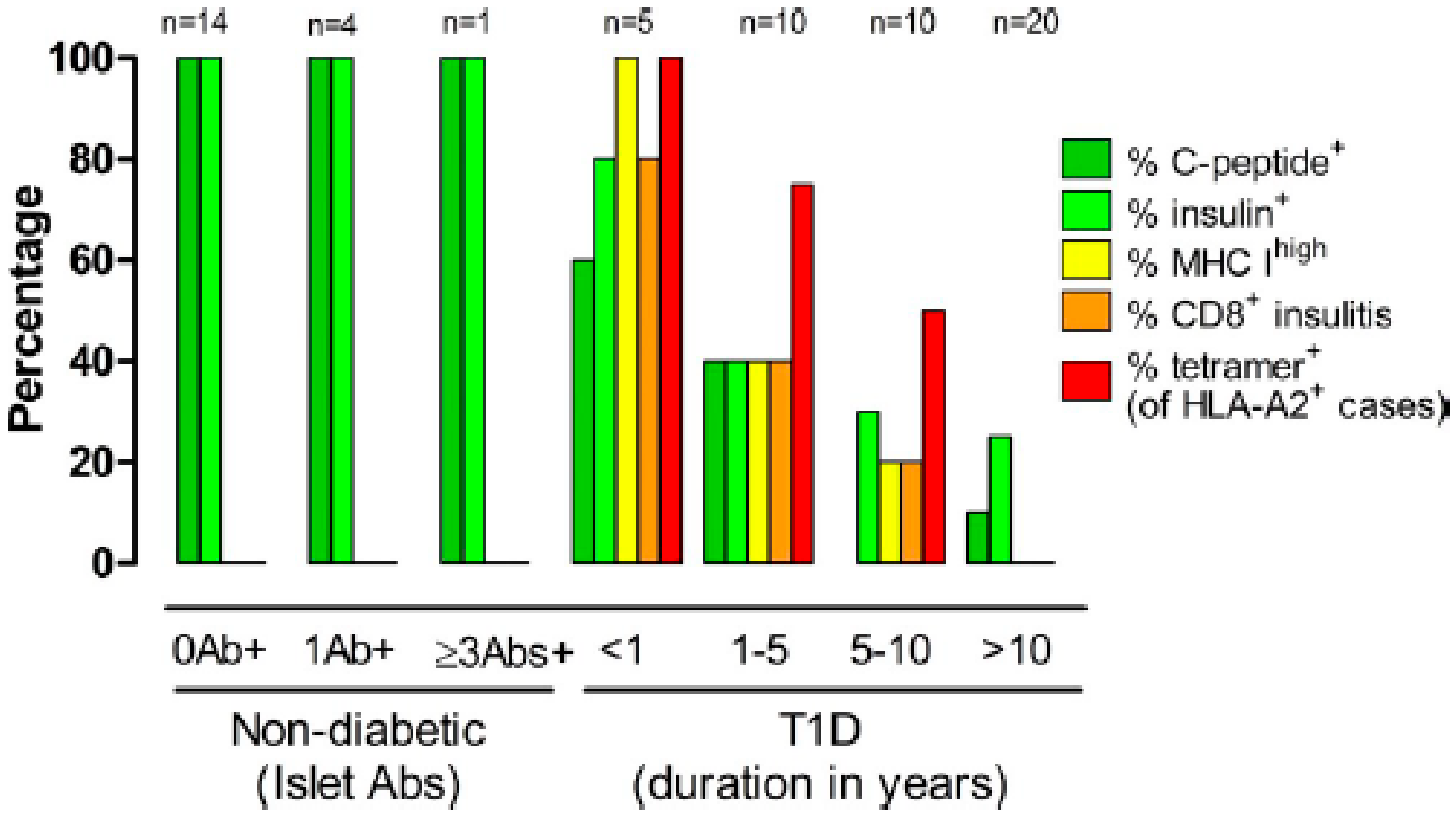
Neoantigens in T1D

Table 1. List of the main autoantigens targeted by the adaptive immune response in human T1D

Autoantigen	Expression	Subcellular location	Function	Autoantibodies	Autoreactive T cells
Amylin, IAPP, ppIAPP	β-cells	Secretory granules	Glucose homeostasis	Yes	$CD4^+$, $CD8^+$
Carboxypeptidase H/E	Neuroendocrine cells	Secretory granules	Proinsulin to insulin processing	Yes	Not reported
ChgA	Neuroendocrine cells	Secretory granules	Precursor of several biologically active peptides	Not reported	$CD4^+$, $CD8^+$
GAD65	Neuroendocrine cells	Synaptic-like microvesicles	GABA synthesis	Yes	$CD4^+$, $CD8^+$
GAD67	Islet cells (not β-cells), neurons	Synaptic-like microvesicles	GABA synthesis	Yes	$CD4^+$
GRP78	Not restricted	Endoplasmic reticulum	Protein folding	Yes	$CD4^+$
HSP60	Ubiquitous	Mitochondria	Protein folding	Yes	$CD4^+$
IA-2	Neuroendocrine cells	Secretory granules	Regulation of hormone secretion	Yes	$CD4^+$, $CD8^+$
IA-2β	Neuroendocrine cells	Secretory granules	Regulation of hormone secretion	Yes	$CD4^+$
ICA69	β-cells	Secretory granules	Unascertained	Yes	$CD4^+$
IGRP	β-cells	Endoplasmic reticulum	Glucose metabolism	Not reported	$CD4^+$, $CD8^+$
Insulin gene enhancer protein isl-1	Not restricted	Nucleus	DNA-binding transcriptional activator	Not reported	$CD8^+$
P4Hb	Not restricted	Endoplasmic reticulum	Formation and rearrangement of disulfide bonds	Yes	Not reported
PDX1	β-cells	Nucleus	Role in pancreas development and β-cell differentiation and function	Yes	Not reported
Peripherin	Neuroendocrine cells	Filaments	Unascertained	Yes	Not reported
Pre-proinsulin, Proinsulin, Insulin, oxPTM-insulin	β-cells	Secretory granules	Glucose homeostasis	Yes	$CD4^+$, $CD8^+$
Tetraspanin-7, Glima 38	Neuroendocrine cells	Plasma membrane	Signal transduction	Yes	Not reported
Urocortin-3	β-cells, α-cells	Secretory granules	May regulate insulin secretion	Not reported	$CD8^+$
ZnT8	β-cells	Secretory granules	Zinc uptake in β-cell secretory granules	Yes	$CD4^+$, $CD8^+$

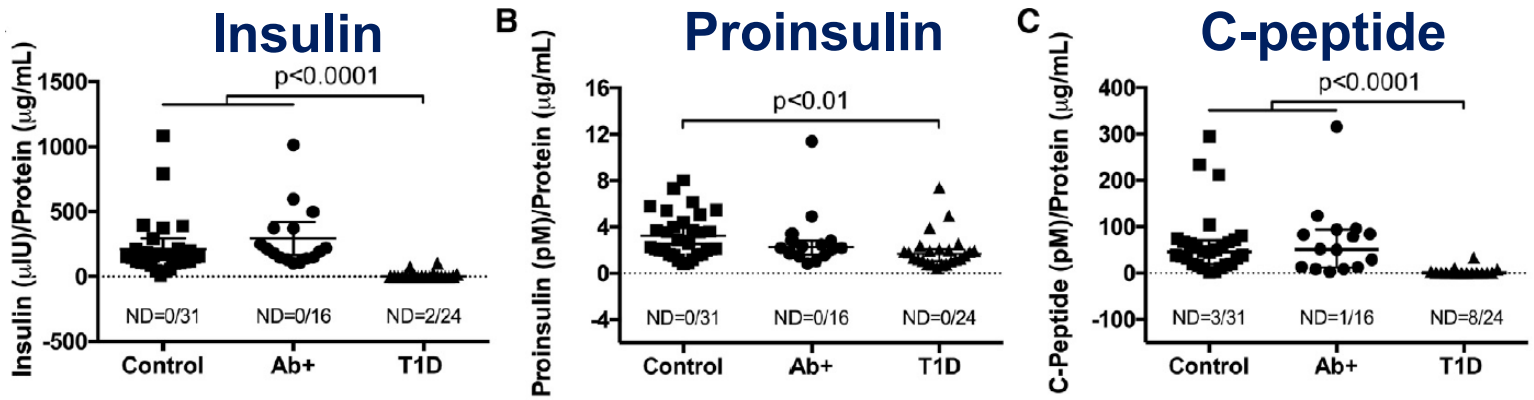
ChgA, chromogranin A; GABA, γ-amino butyric acid; GAD, glutamic acid decarboxylase; GRP78, glucose-regulated protein 78; HSP60, heat shock protein 60; IA-2, insulinoma-associated antigen 2; IAPP, islet amyloid polypeptide; ICA69, islet-cell antigen 69; IGRP, islet-specific glucose-6-phosphatase catalytic subunit-related protein; oxPTM-insulin, oxidative post-translational modifications-insulin; P4Hb, prolyl 4-hydroxylase subunit β, protein disulfide-isomerase; PDX1, pancreatic duodenal homeobox protein 1; ppIAPP, IAPP precursor protein; ZnT8, zinc transporter 8.
Adapted from Purcell *et al.*[23] and Roep and Peakman.[90]

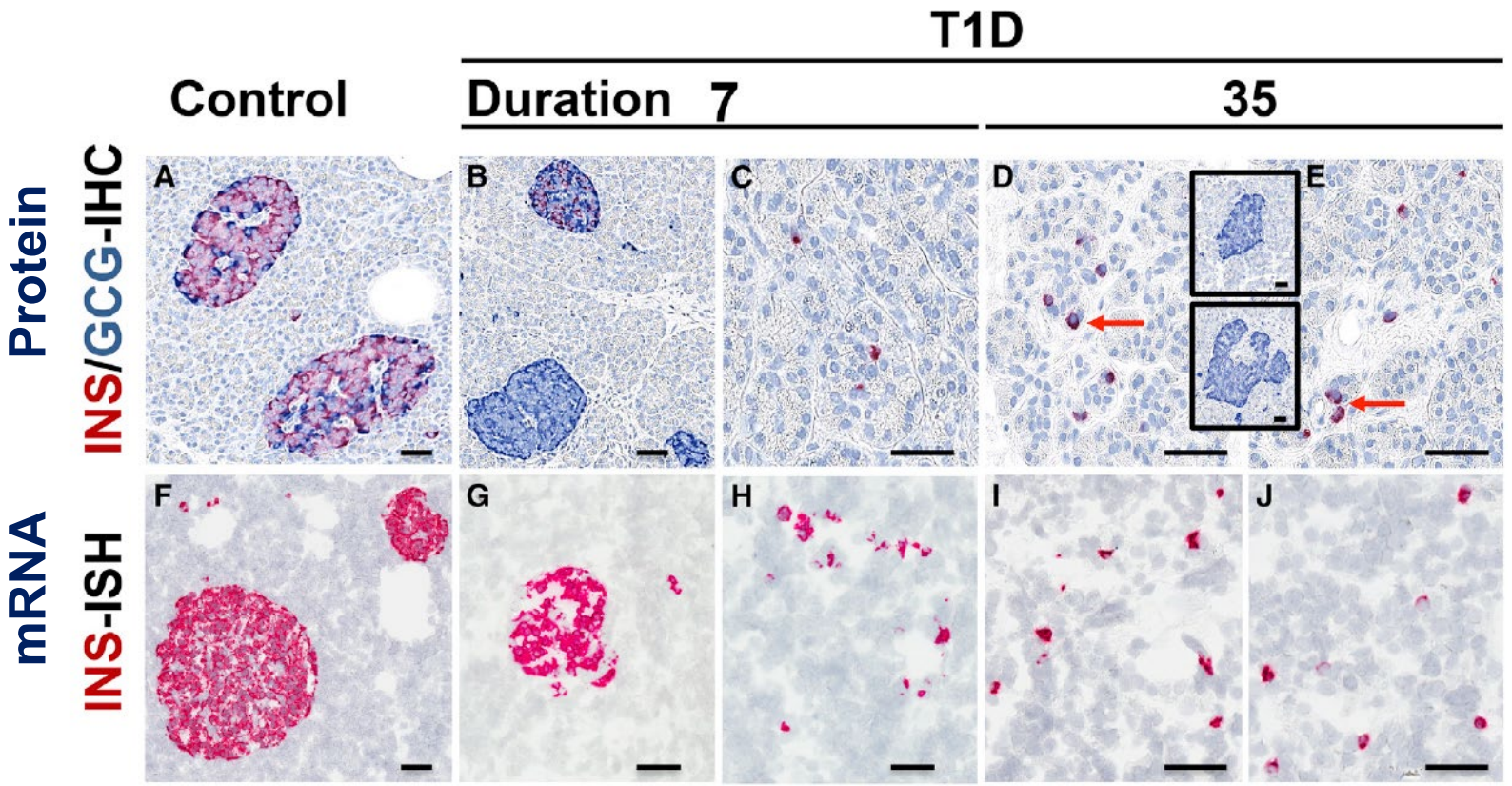
Residual beta cells and insulitis at different disease stages



J.Exp. Med. 2012

Dedifferentiated beta-cells in T1D?





- ❑ Persistent proinsulin but low/absent insulin protein
- ❑ Long-lasting INS messenger RNA
- ❑ Absence of actively transcribed INS mRNA → low/no insulin promoter activity

Wasserfall C et al. 2017, Cell Metabolism

Diabetologia (2014) 57:187–191
DOI 10.1007/s00125-013-3067-x

ARTICLE

The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells

Richard A. Oram · Angus G. Jones · Rachel E. J. Besser · Bridget A. Knight · Beverley M. Shields · Richard J. Brown · Andrew T. Hattersley · Timothy J. McDonald

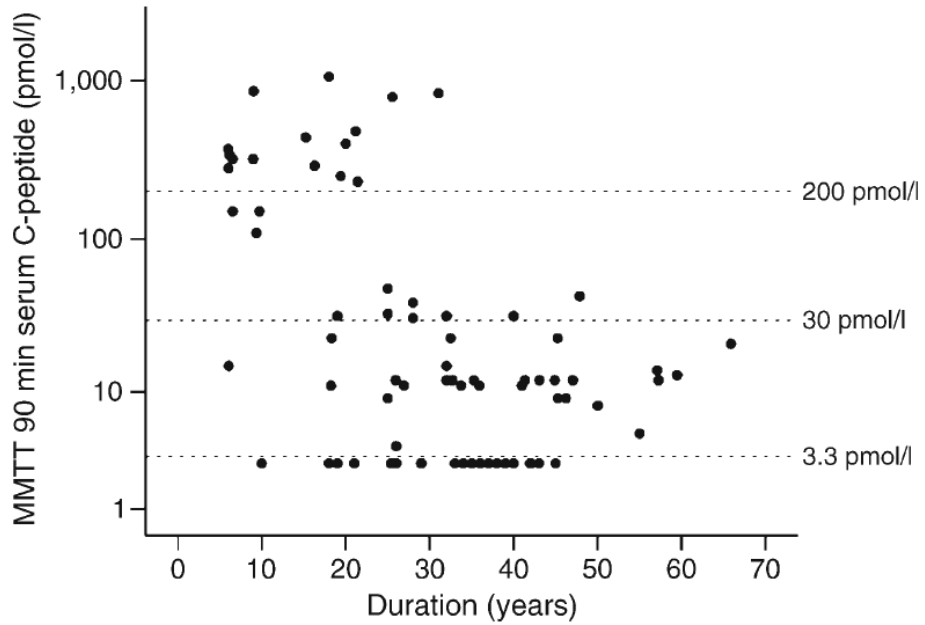


Fig. 1 Scatterplot of serum C-peptide at 90 min after a mixed meal ($\log_{10}$ scale) against duration of diabetes. Dotted reference lines indicate 200, 30 and 3.3 pmol/l. MMTT, mixed-meal tolerance test

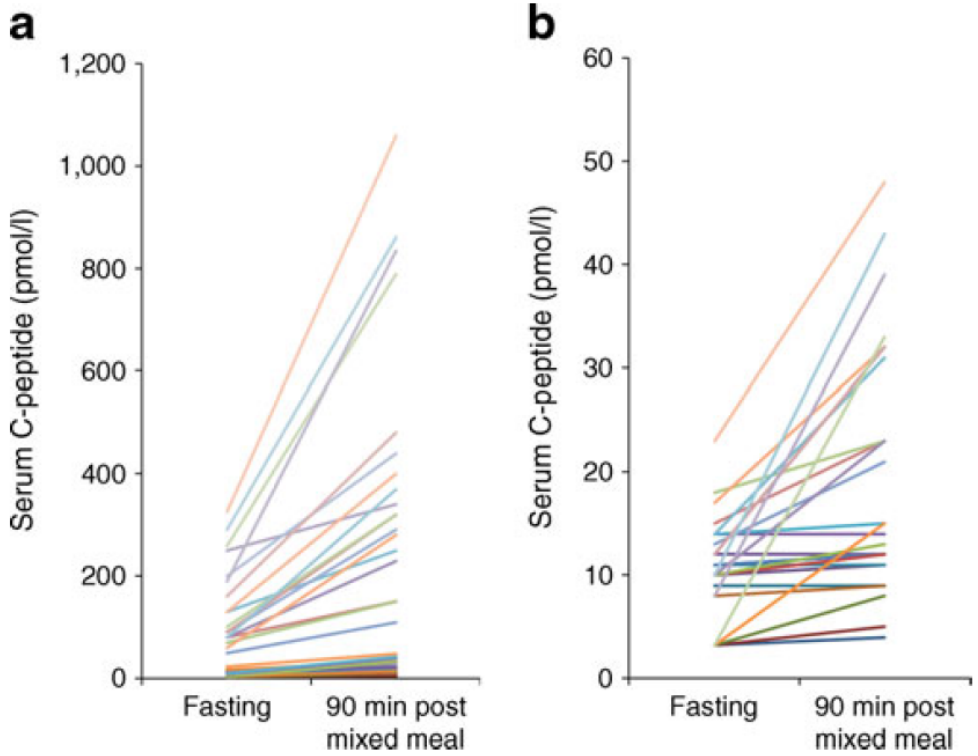
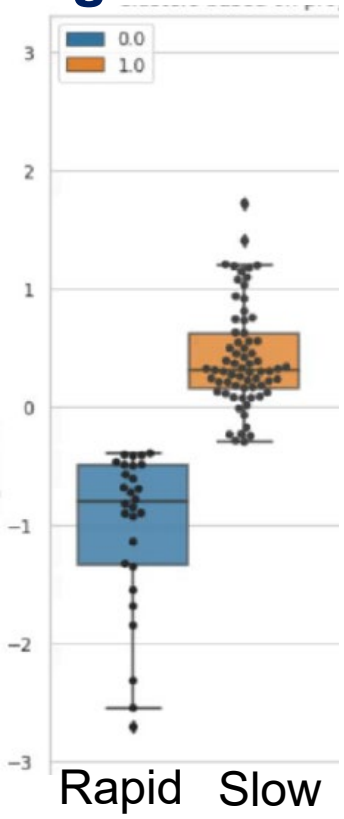


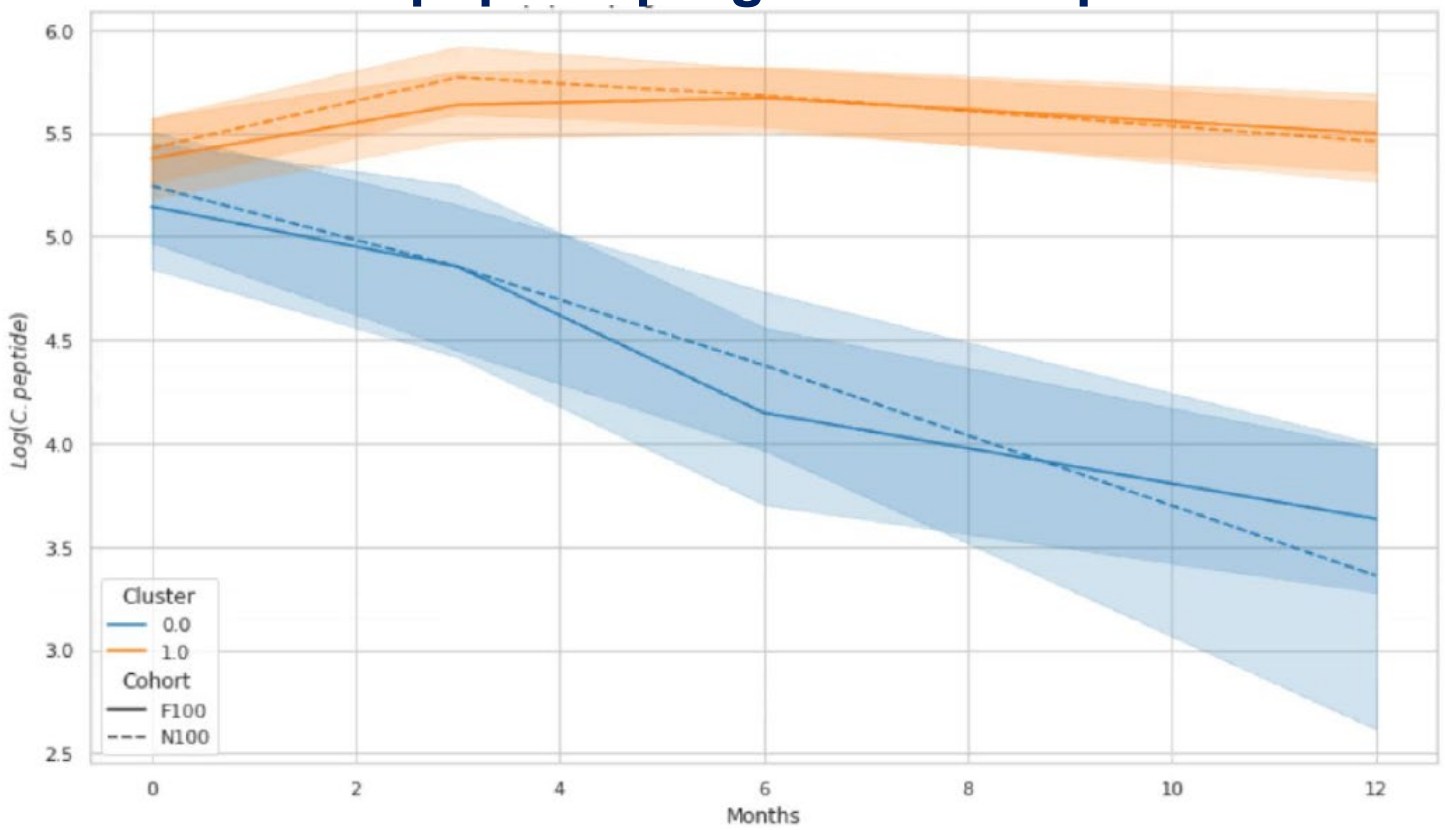
Fig. 2 The effect of a meal stimulus on serum C-peptide levels in participants with detectable insulin ($n=54$). (**a**) Paired fasting and mixed meal results for all patients with detectable C-peptide. Each line represents an individual patient. (**b**) Results for all patients with fasting C-peptide below 30 pmol/l ($n=36$). Of 54 patients, 34 (80%) had a serum C-peptide value that rose after the mixed meal. None had a fall in the C-peptide value after the meal

Identification of Rapid Progressors and Slow progressor among T1D individuals of INNODIA 100s cohort

Progression Clusters



C-peptide progression slopes



UCPH Team; Jose Juan Almagro Armenteros- Caroline Brorrson- Piotr Chmura- Soren Brunak

INNODIA Biomarkers Research study to identify novel T1D endotypes

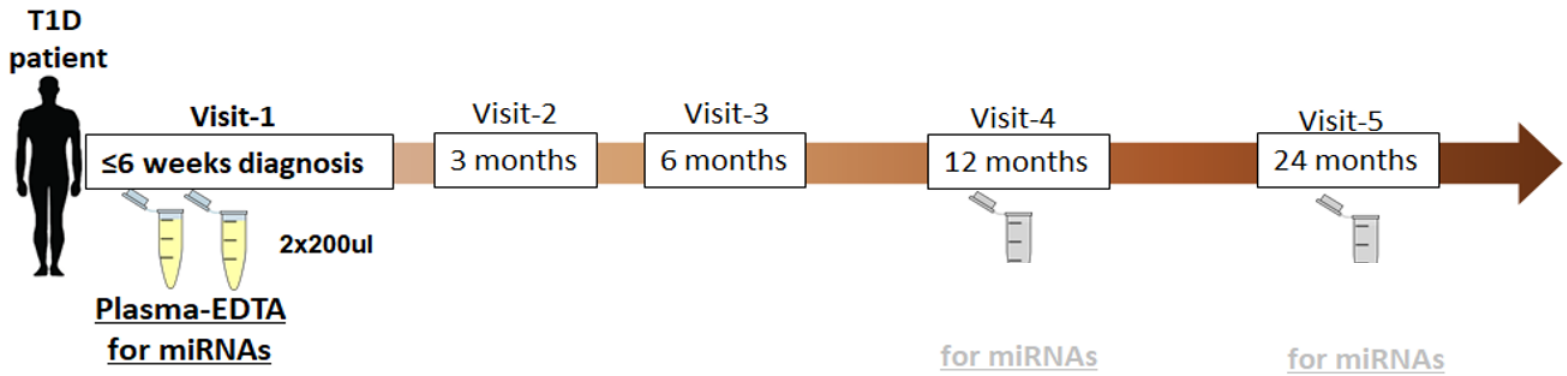
MMTT		✓	✓	✓	✓
C-pep	✓	✓	✓	✓	✓
Serum	✓	✓	✓	✓	✓
Cells	✓	✓	✓	✓	✓
AA	✓			✓	✓
Omics*	✓			✓	✓
Stool /urine	✓	✓	✓	✓	✓

* Including micro-RNA and whole blood RNA

- Genotyping
- Immunomics
- Lipidomics
- Trancriptomics
- Proteomics
- Microbiome
- miRNA/Small RNAs

Experimental Design for the analysis of miRNAs/small RNAs

INNODIA 100s cohort
+
Additional INNODIA T1D subjects
=
115 T1D individuals



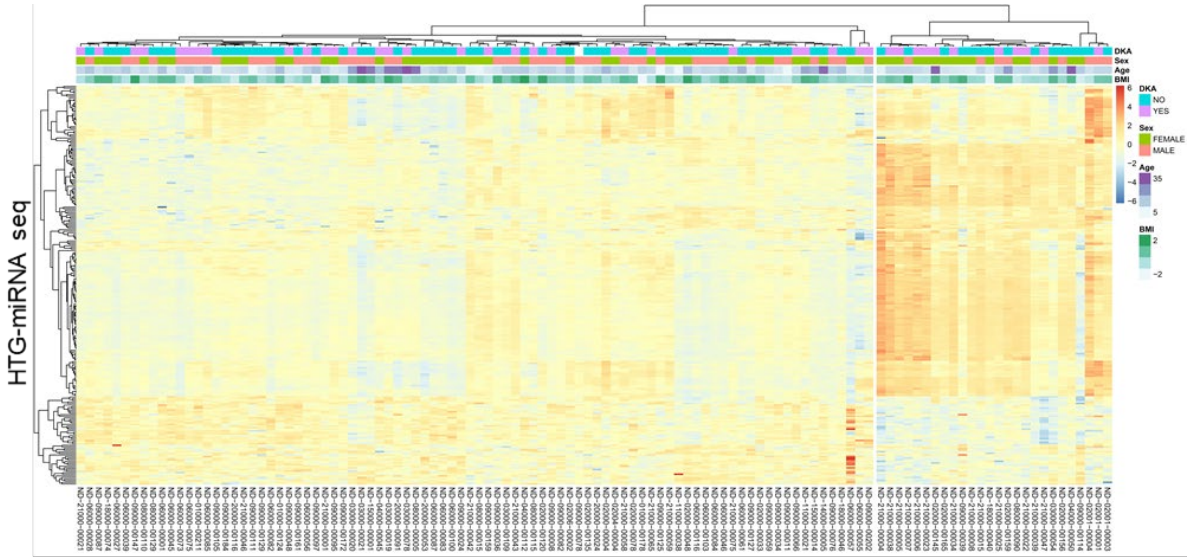
→ HTG miRNA Edge Seq

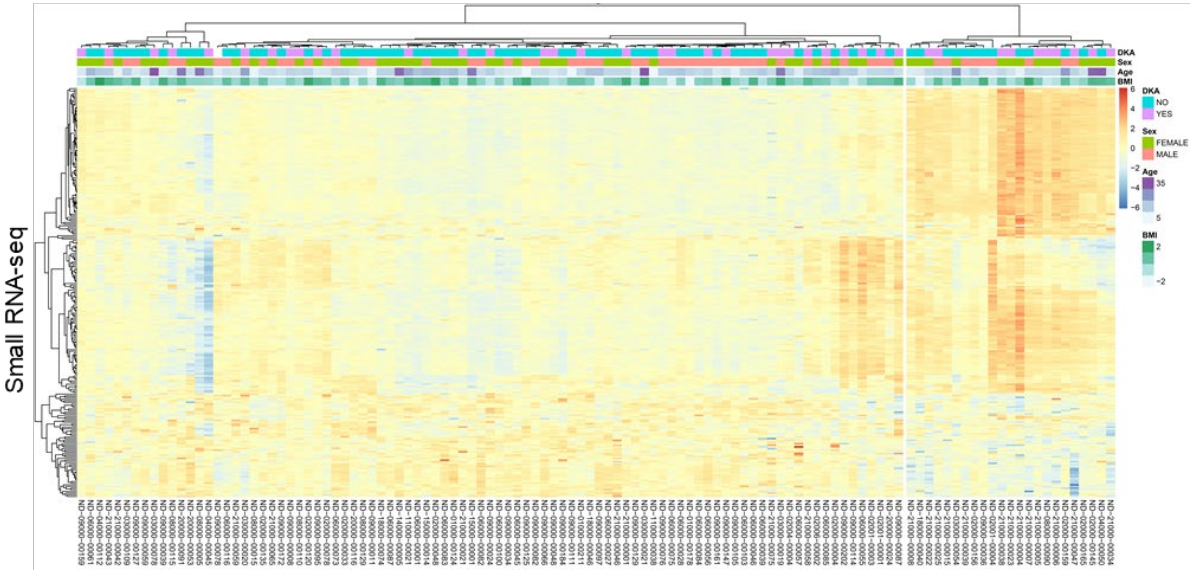
→ Small RNA-Seq

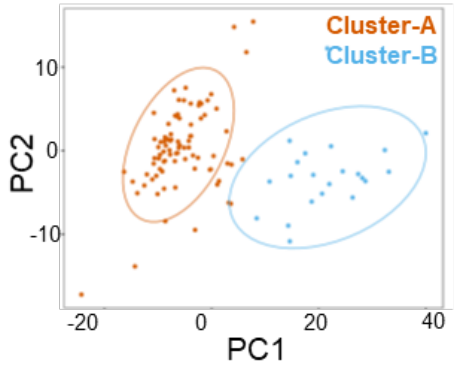
MicroRNAs/Small RNAs signature → RNA from 170 µl Plasma (Aliquot B) qRT-PCR Single Assay validation

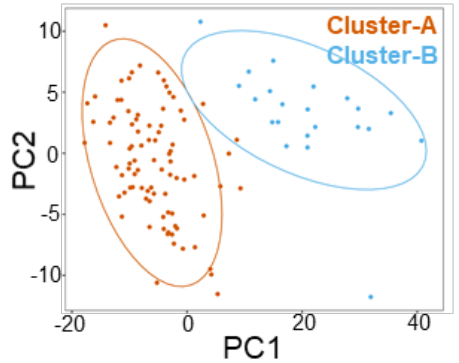
High-Throughput Small RNAs Platforms concordance effort → Biomarkers signature identification → Signature validation in multiple labs/multiple approaches

Two-seq platforms profiling reveals two distinct T1D subjects groups

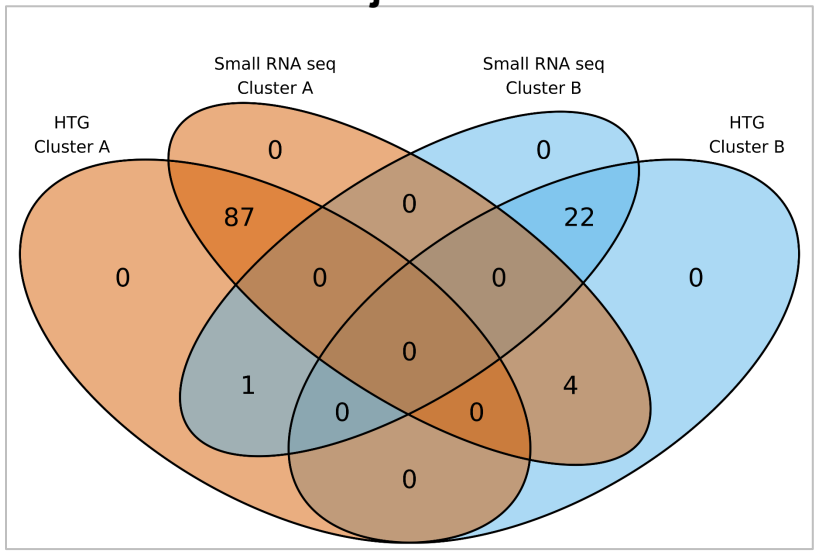








T1D subjects/Cluster

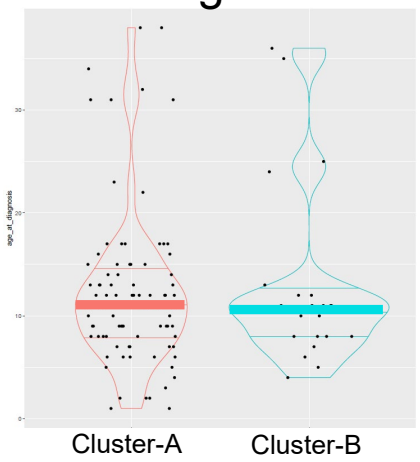


109/115 were consistently included in Cluster-A or Cluster-B in both platforms

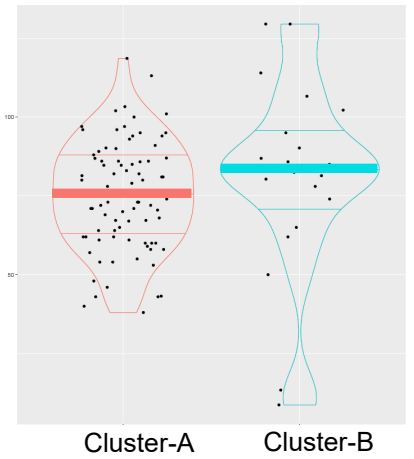
T1D patient clusters do not differ for main clinical parameters at baseline

Gender

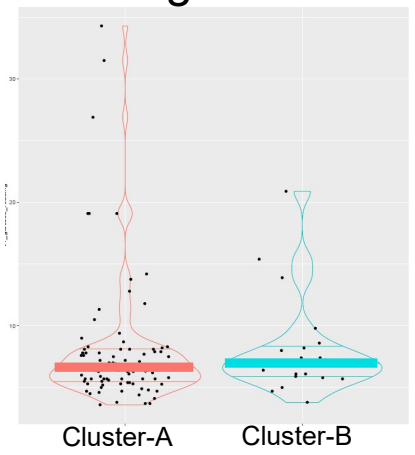
Age



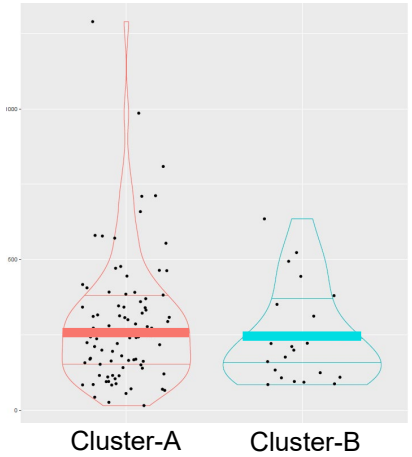
HbA1c



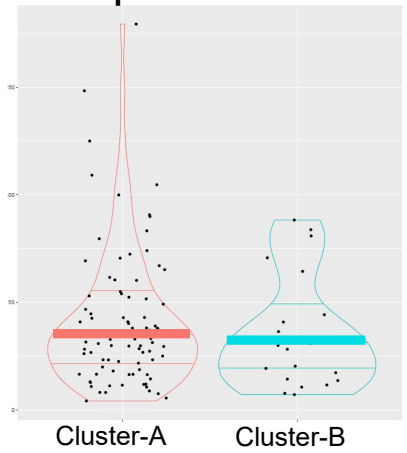
Fasting Glucose



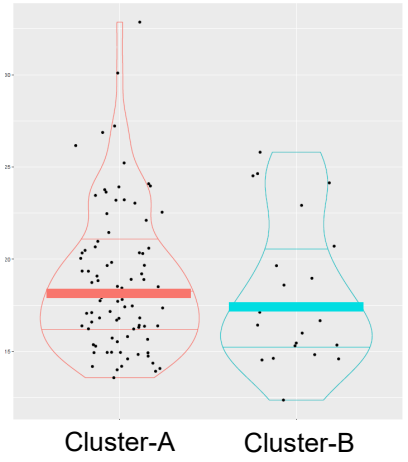
Fasting C-Peptide



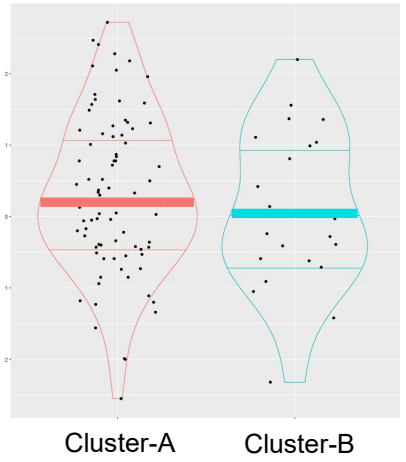
Fasting C-Peptide/Glucose



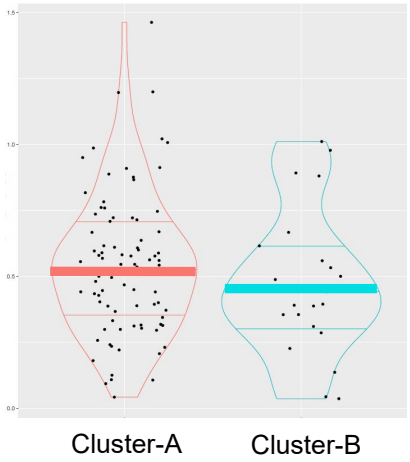
BMI



BMI- SDS



Insulin dose/kg

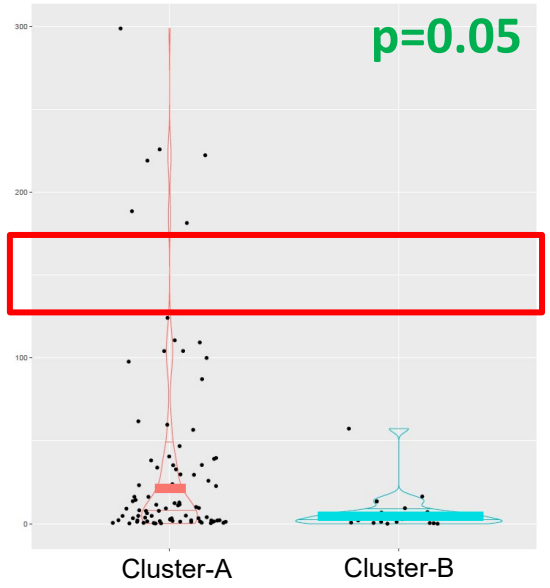


Logit Model (R); p-values using Wald z-statistic (p<0,05)

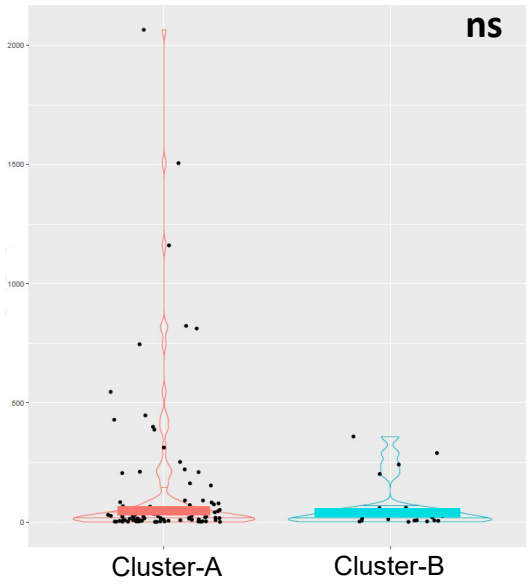
Unpublished results

Cluster-A T1D subjects showed significantly higher IAA titers at baseline

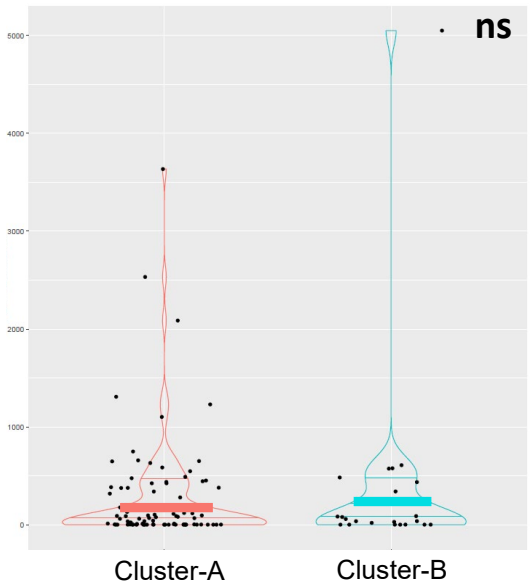
IAA titers (V1)



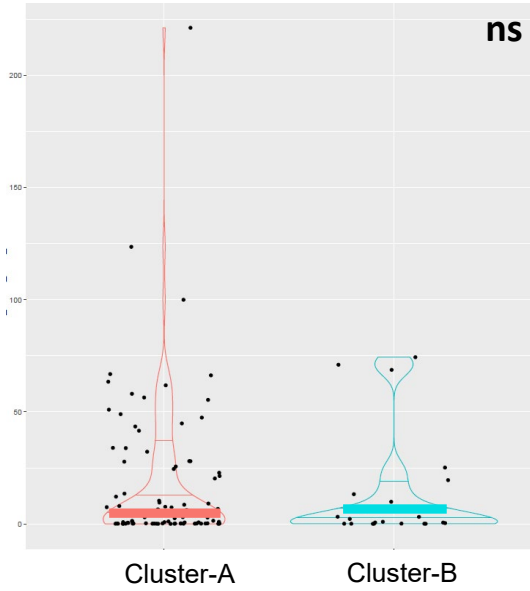
GADA titers (V1)



IA-2A titers (V1)



ZNT8A titers (V1)

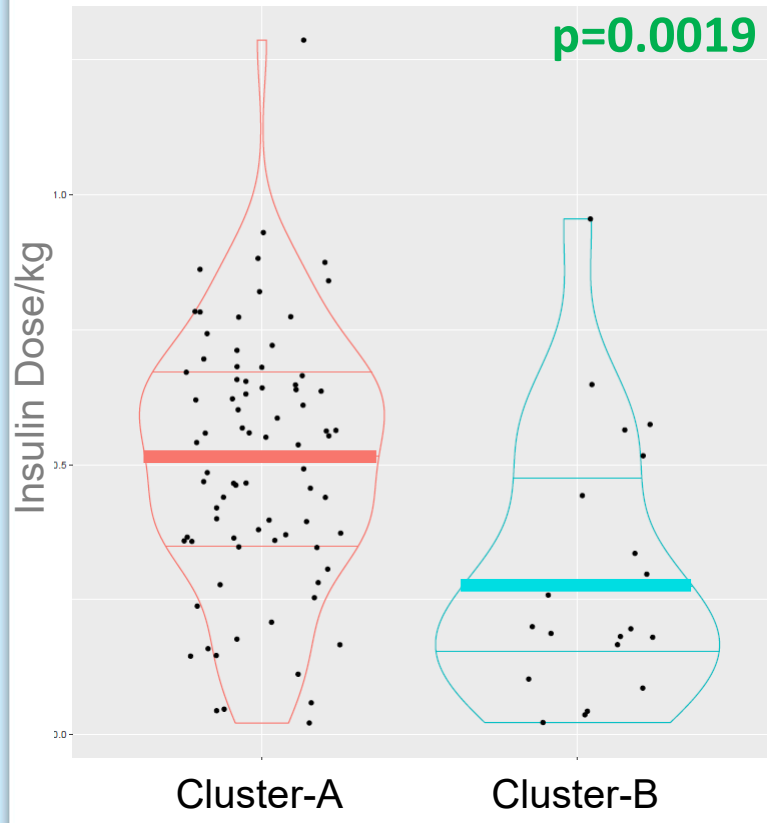


Logit Model (R); p-values using Wald z-statistic (p<0,05)

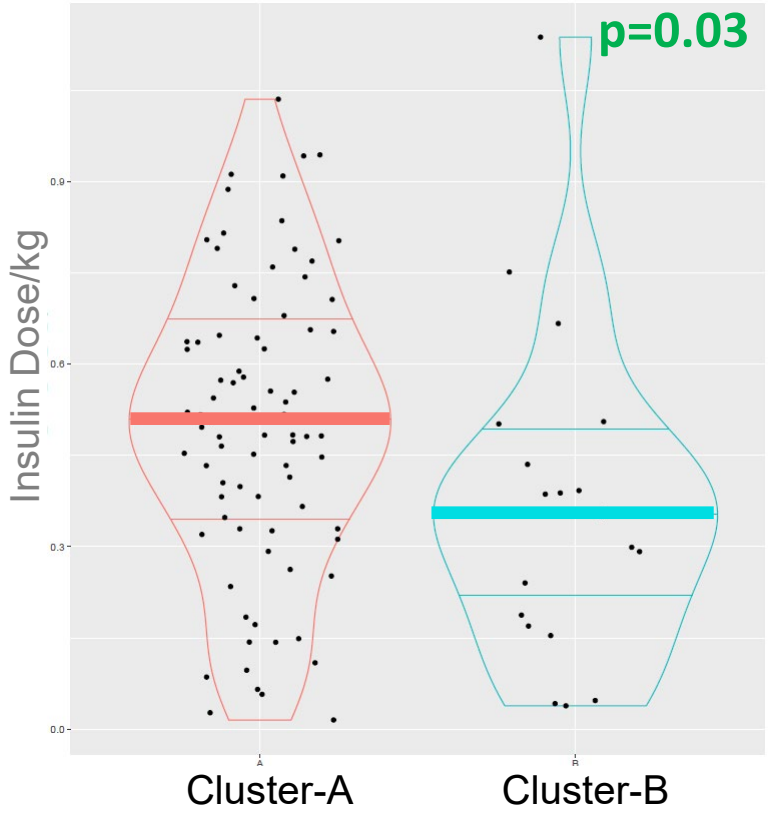
Unpublished results

Cluster-A T1D subjects show a higher insulin requirement at 3- and 6-months

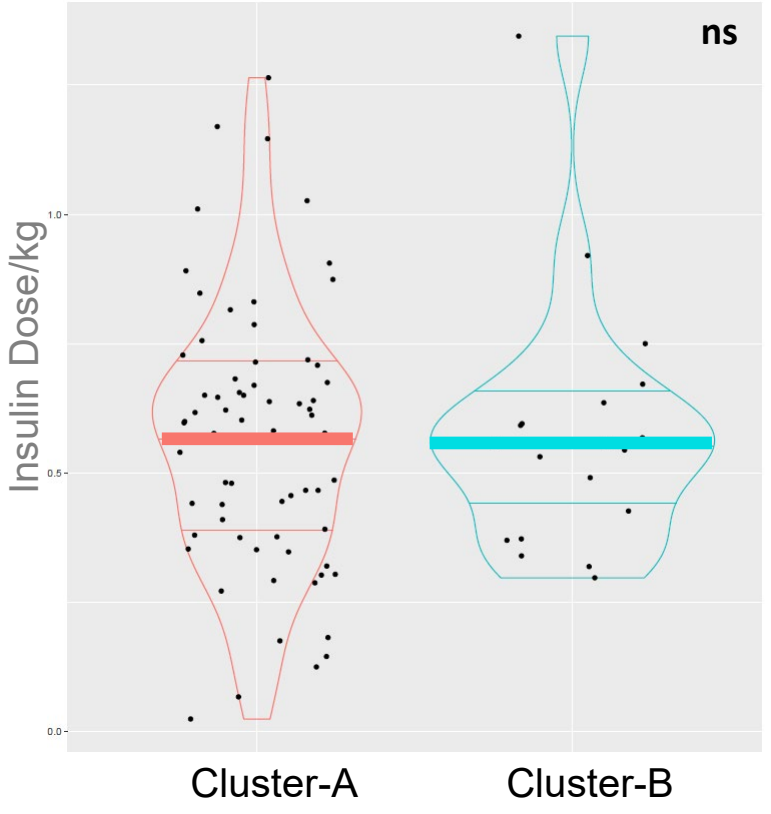
Insulin Requirement
3-months (V2), insulin dose/kg



Insulin Requirement
6-months (V3), insulin dose/kg



Insulin Requirement
12-months (V4), insulin dose/kg

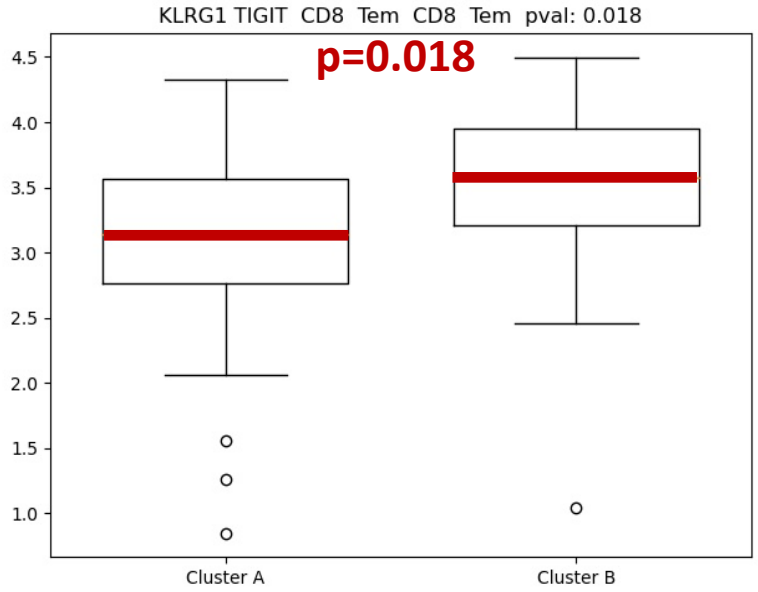


Logit Model (R); p-values using Wald z-statistic (p<0,05)
Median values and quartiles are shown.

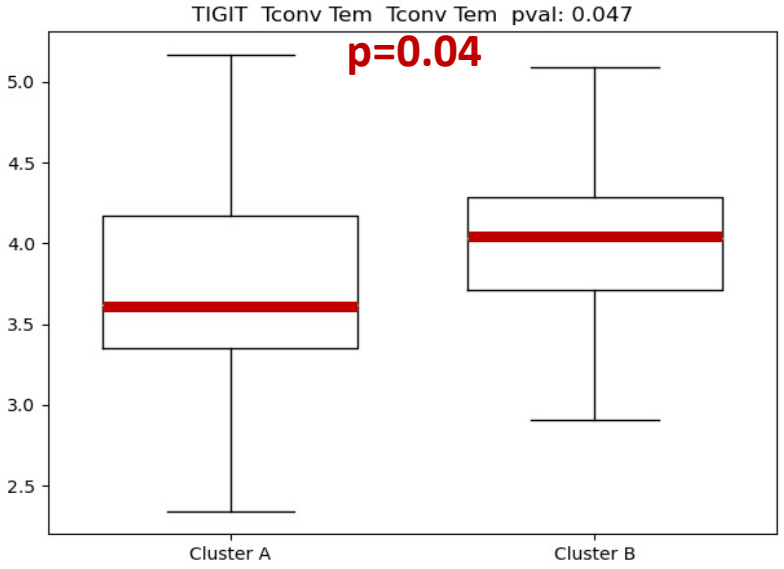
Unpublished results

Cluster-B T1D subjects showed higher frequencies of CD8 and CD4 exhausted Memory T-cells

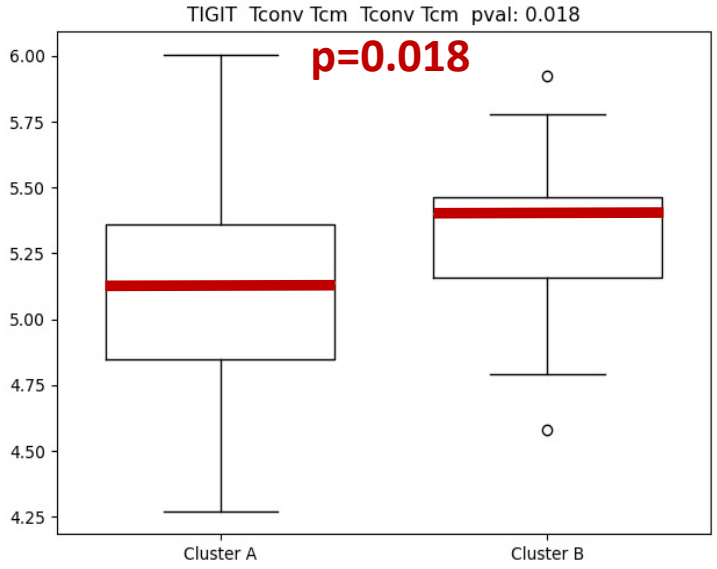
CD8 Tem KLRG1⁺ TIGIT⁺



CD4 Tem TIGIT⁺



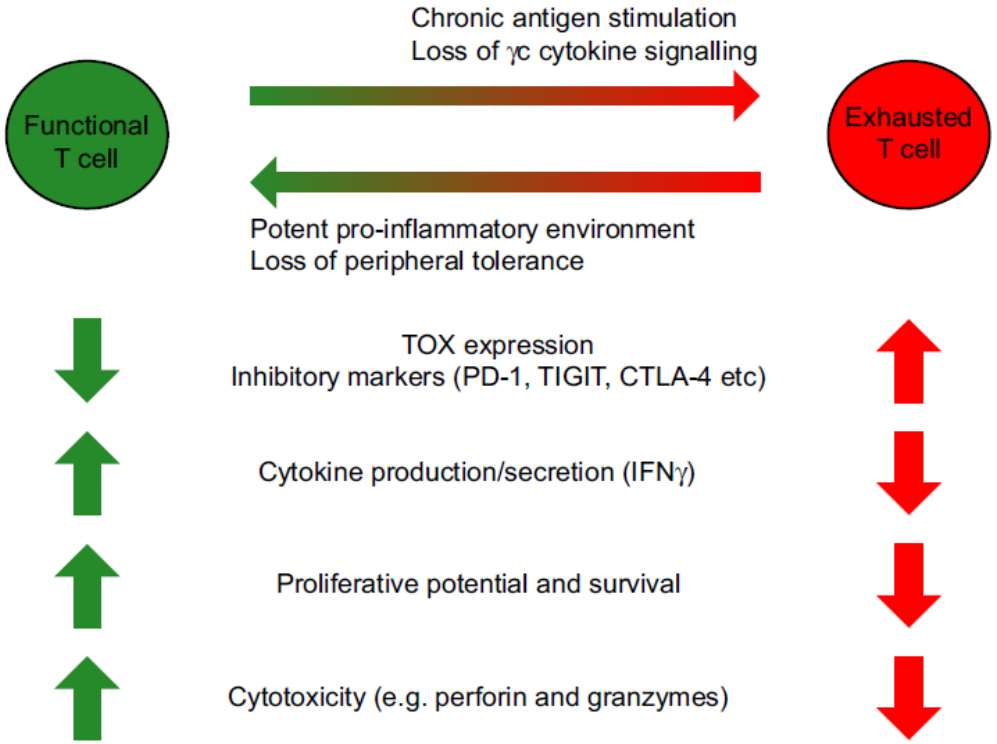
CD4 Tcm TIGIT⁺



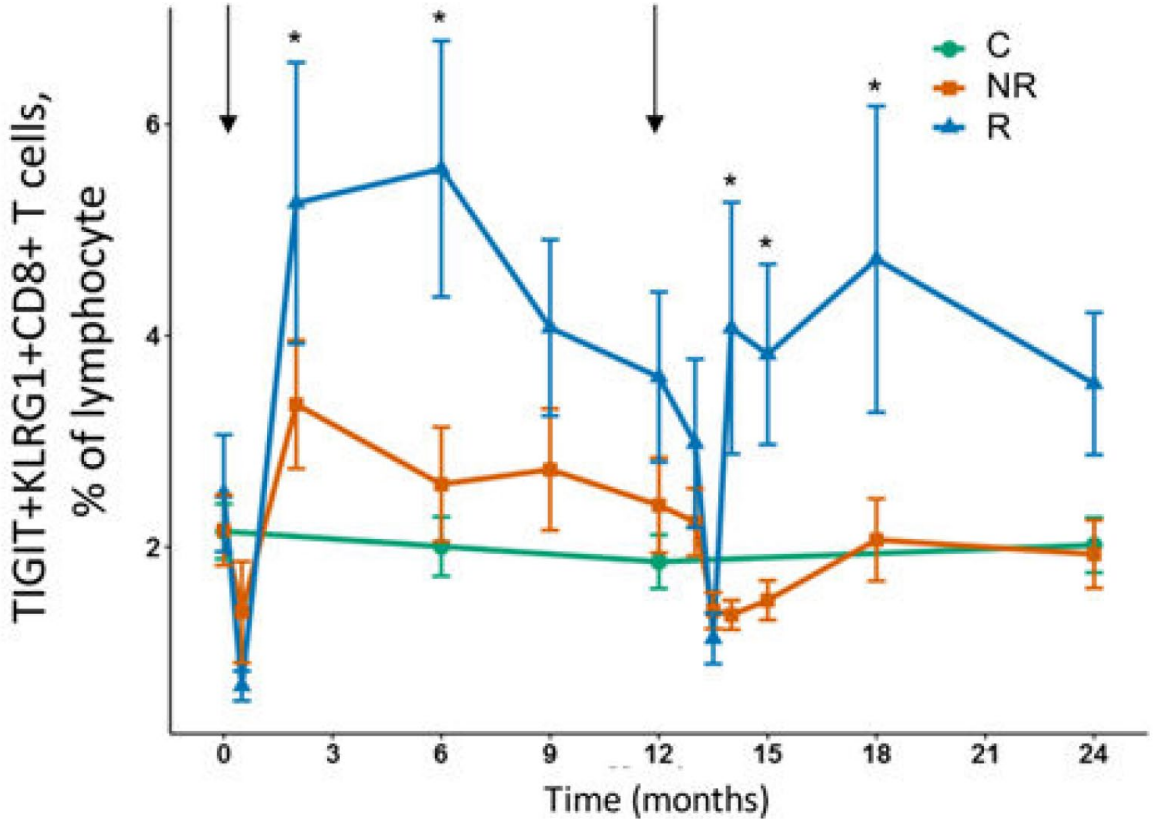
Unpublished results

T-cell exhaustion in T1D

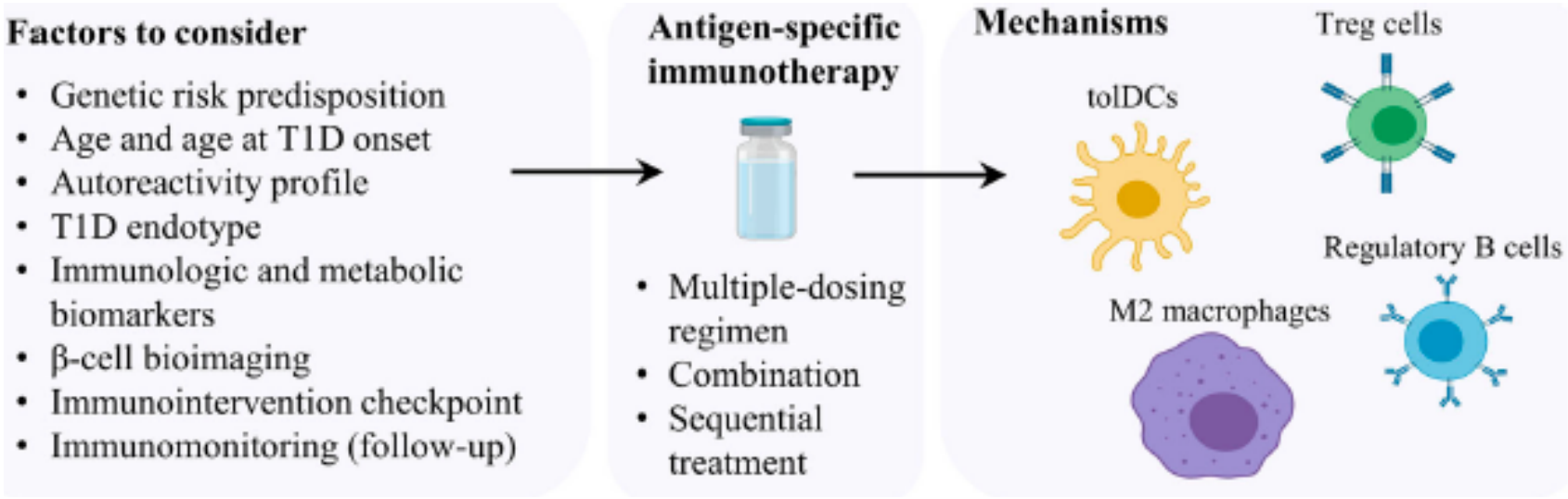
T-cell exhaustion is associated with reduced cytokines production

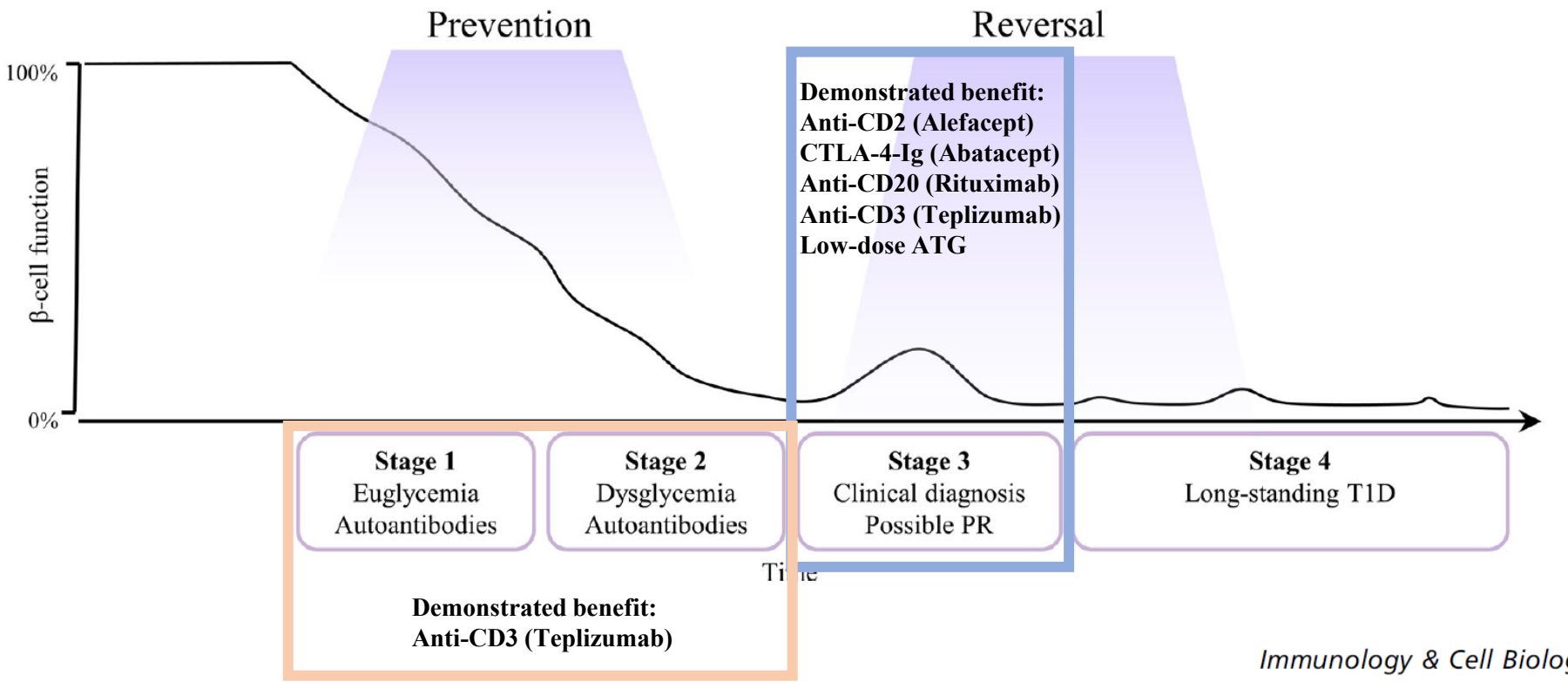


T1D subjects, **RESPONDERS** to aCD3 immunotherapy, showed higher levels of partially exhausted CD8 Tem KLRG1+ TIGIT+



Long SA, et al .2016- *Sci. Immunol.*





Immunology & Cell Biology 2021; 1–14

Immune and metabolic markers in the peripheral blood

Immune biomarker	Selected examples
Autoantibodies [appear years before clinical diagnosis (*12*)]	ICA, IAA, ICA512(IA-2), anti-ZnT8, anti-GAD65
Antigen-specific $CD8^+$ T cells	Class I MHC tetramers, T cell libraries, ELISAs: Reactivity to proinsulin, insulin, GAD65, ZnT8, altered peptides
Antigen specific $CD4^+$ T cells	ELISAs, T cell proliferation, T cell activation (by CD154). Antigens: GAD65, proinsulin, insulin
Metabolic biomarkers	
β cell function	C-peptide response to oral glucose, mixed meal, arginine
β cell stress	Levels of proinsulin relative to insulin or C-peptide
β cell death	Unmethylated *INS* DNA, miRNAs, exosomes

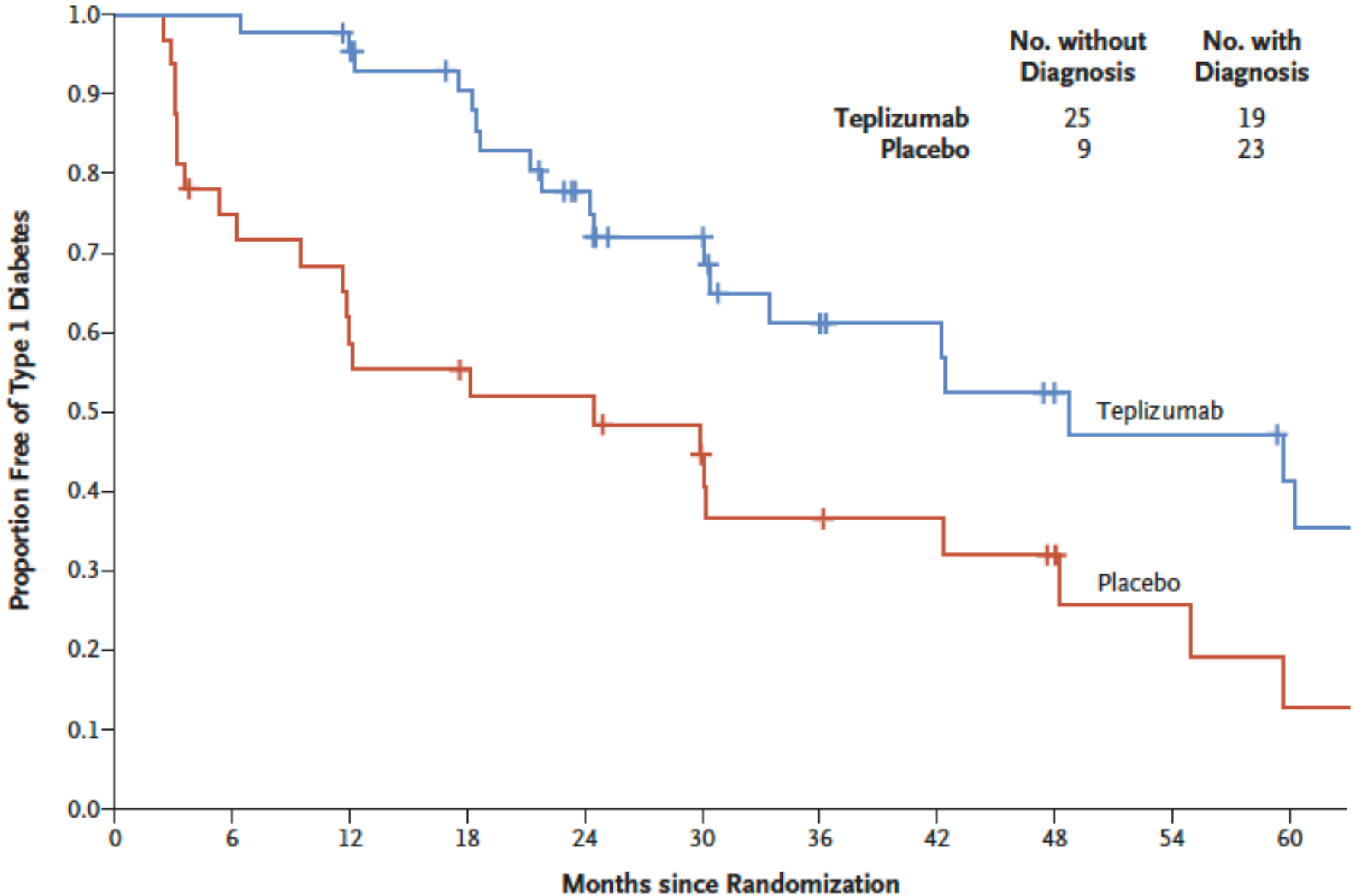
An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

Characteristic	Teplizumab (N=44)	Placebo (N=32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)

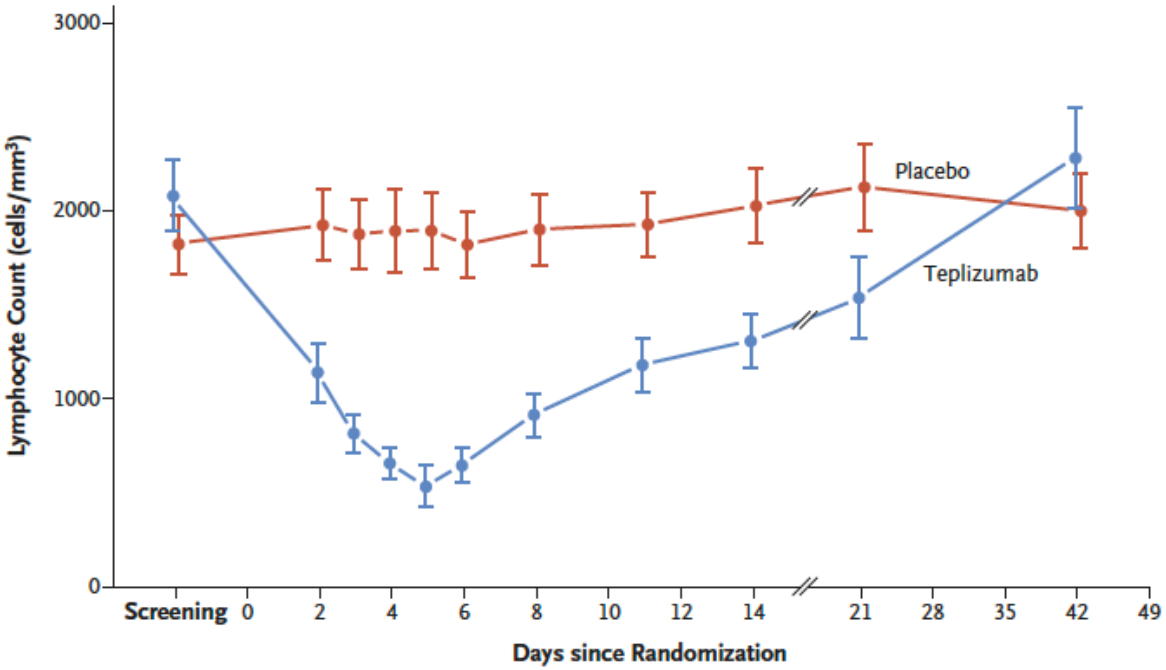
Table 2. Adverse Events during Active Follow-up.*

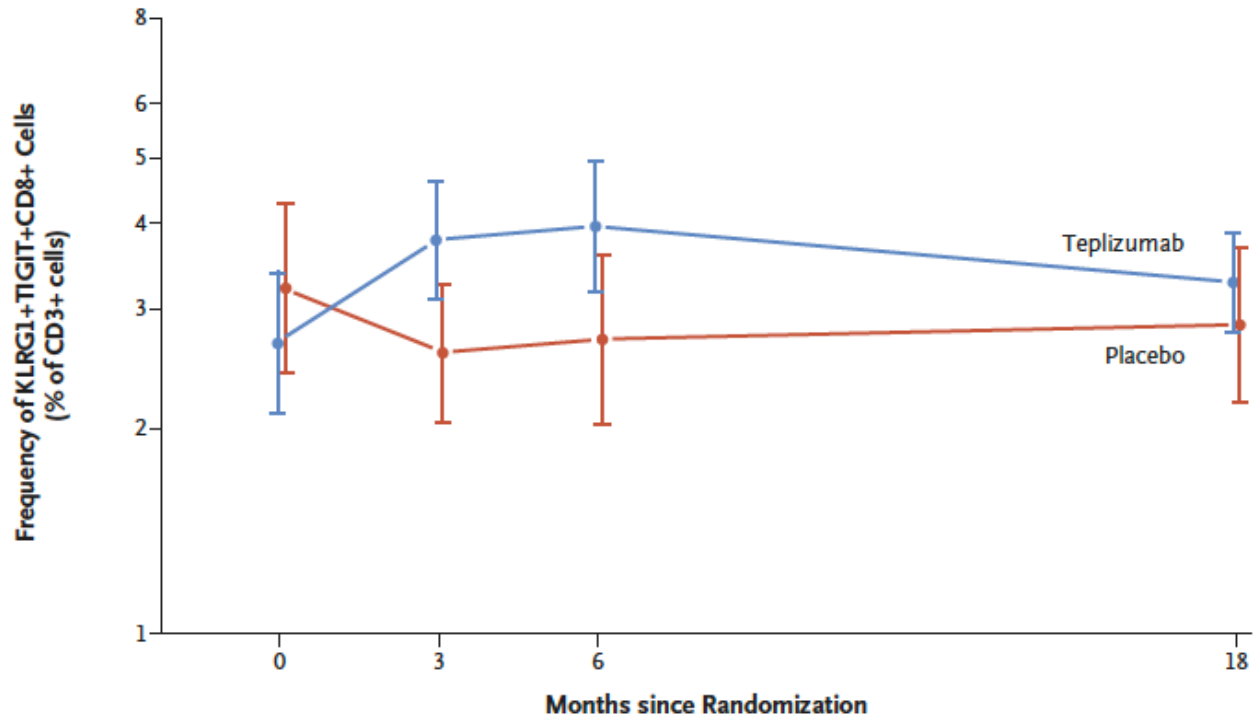
Adverse Event Category	Teplizumab		Placebo	
	Events (N=112)	Participants (N=44)	Events (N=23)	Participants (N=32)
	no.	*no. (%)*	*no.*	*no. (%)*
Blood or bone marrow†	45	33 (75)	2	2 (6)
Dermatologic or skin†	17	16 (36)	1	1 (3)
Pain	11	5 (11)	5	3 (9)
Infection	8	5 (11)	5	3 (9)
Gastrointestinal	5	4 (9)	3	3 (9)
Metabolic or laboratory	7	4 (9)	2	2 (6)
Pulmonary or upper respiratory	6	4 (9)	0	0
Constitutional symptoms	3	2 (5)	0	0
Allergy or immunologic	2	2 (5)	0	0
Cardiac, general	1	1 (2)	1	1 (3)
Endocrine	0	0	2	2 (6)
Vascular	1	1 (2)	1	1 (3)
Neurologic	1	1 (2)	0	0
Ocular or visual	1	1 (2)	0	0
Musculoskeletal or soft tissue	2	1 (2)	0	0
Hepatobiliary or pancreatic	0	0	1	1 (3)
Syndrome	1	1 (2)	0	0
Hemorrhage or bleeding	1	1 (2)	0	0

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

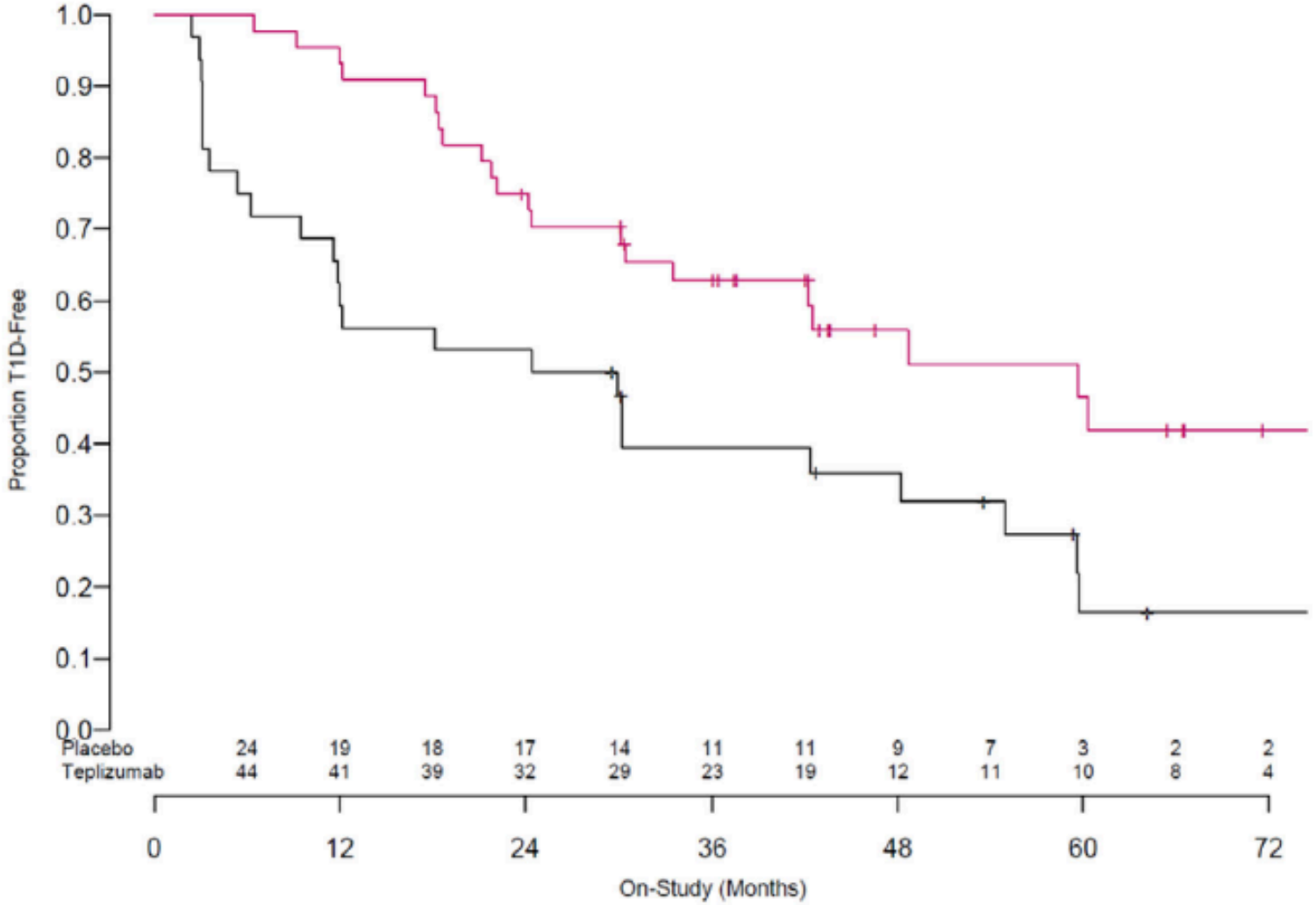


An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes



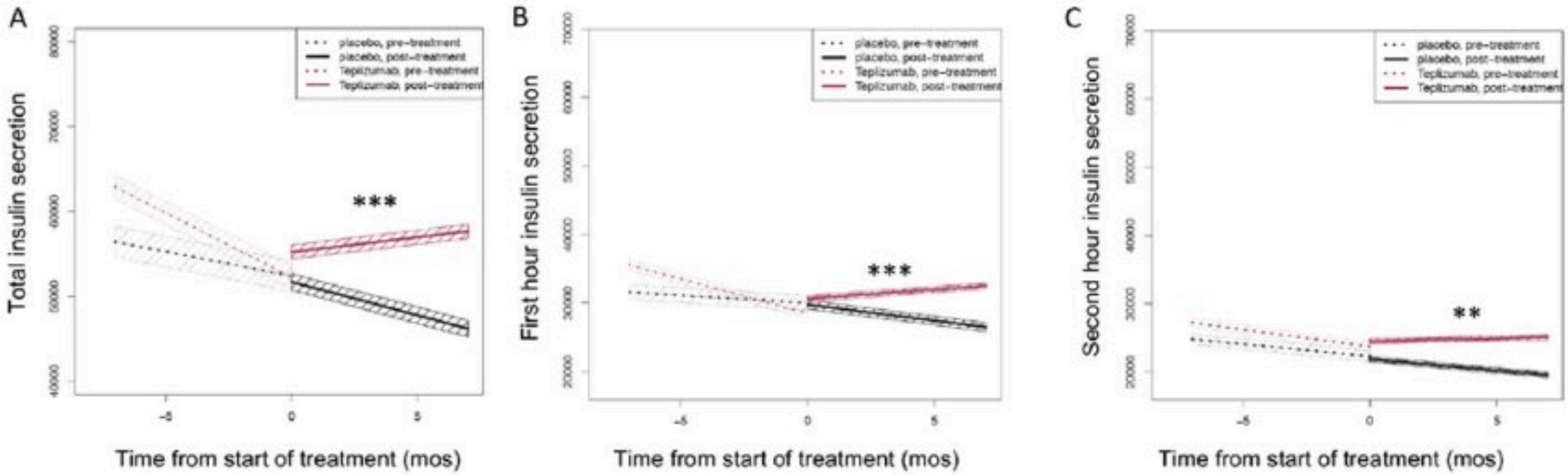


Teplizumab improves and stabilizes beta cell function in antibody positive high-risk individuals



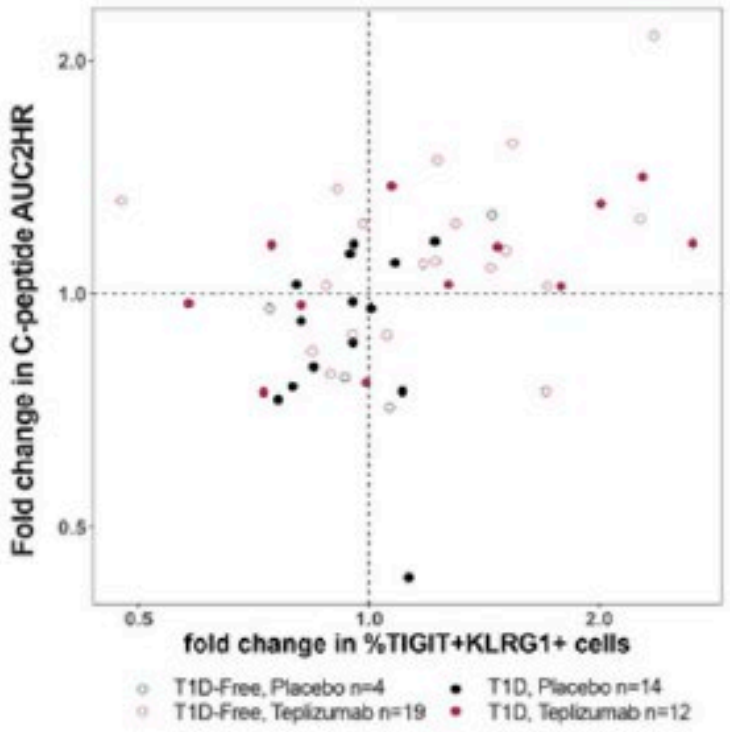
Sci Transl Med. 2021 March 03; 13(583):

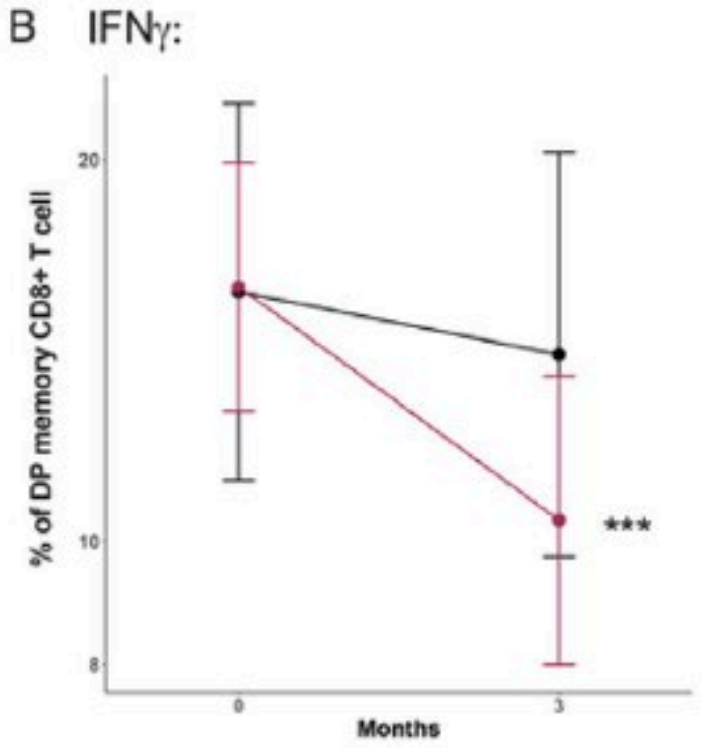
Teplizumab improves and stabilizes beta cell function in antibody positive high-risk individuals

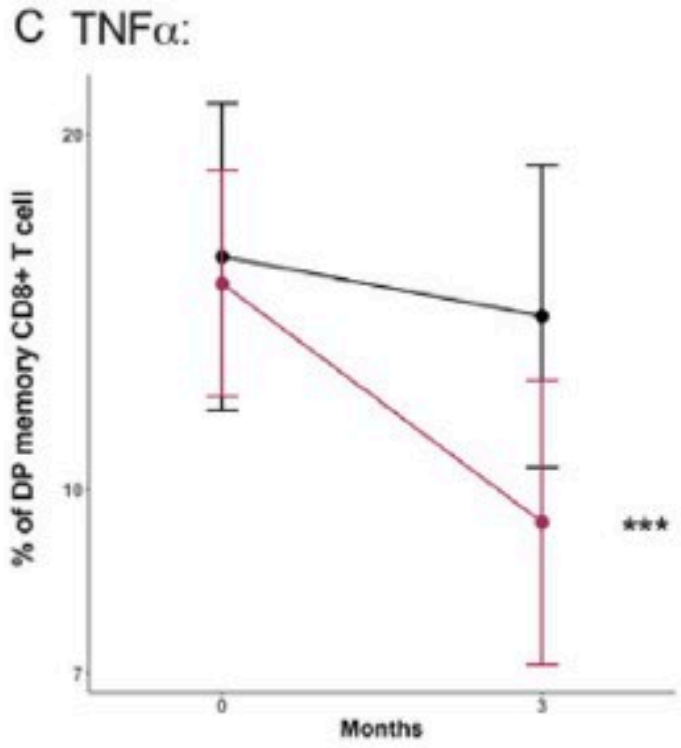


Sci Transl Med. 2021 March 03; 13(583):

Teplizumab improves and stabilizes beta cell function in antibody positive high-risk individuals







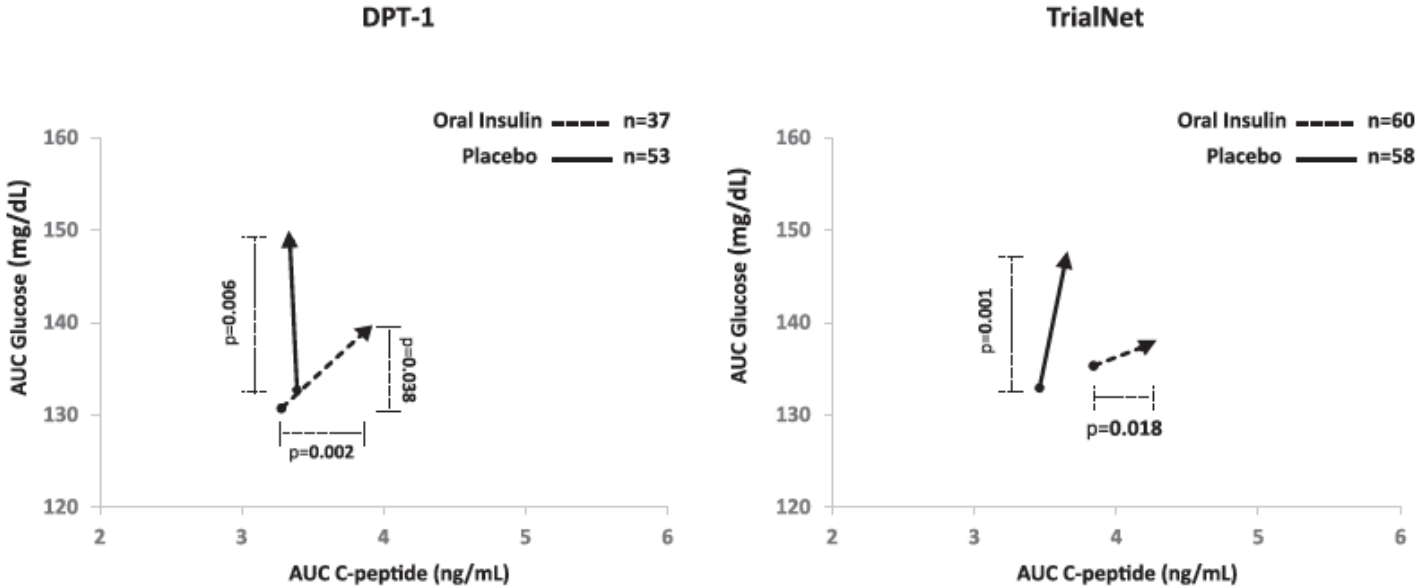
Functional changes in T cells are associated with improvements in metabolic function

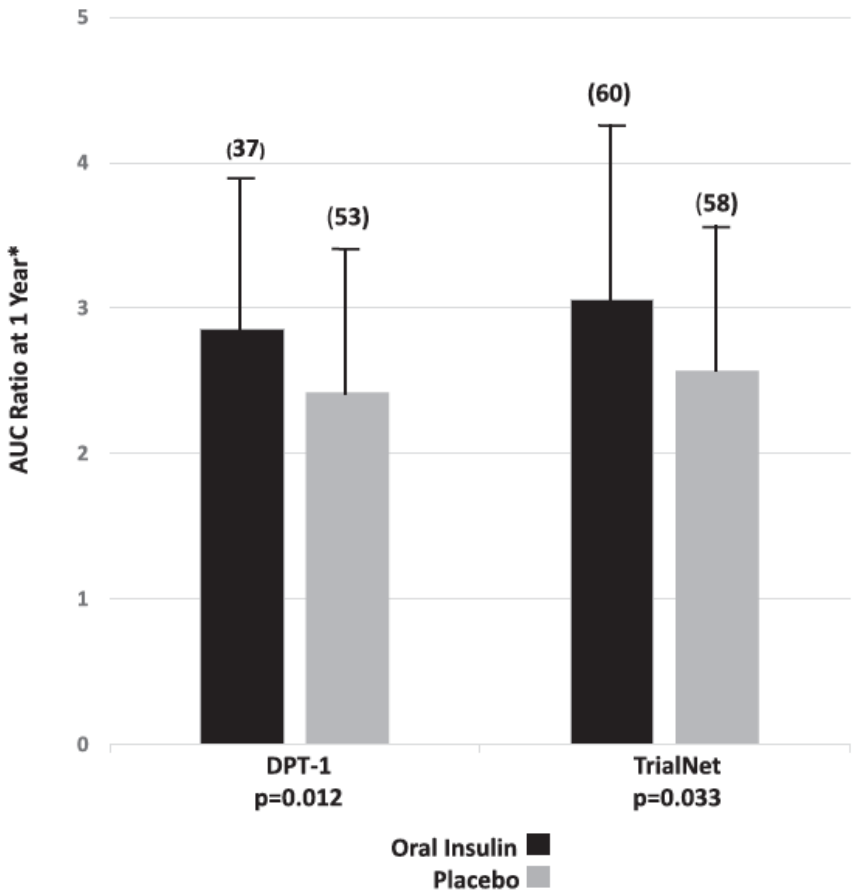
Sci Transl Med. 2021 March 03; 13(583):

Slowed Metabolic Decline After 1 Year of Oral Insulin Treatment Among Individuals at High Risk for Type 1 Diabetes in the Diabetes Prevention Trial–Type 1 (DPT-1) and TrialNet Oral Insulin Prevention Trials

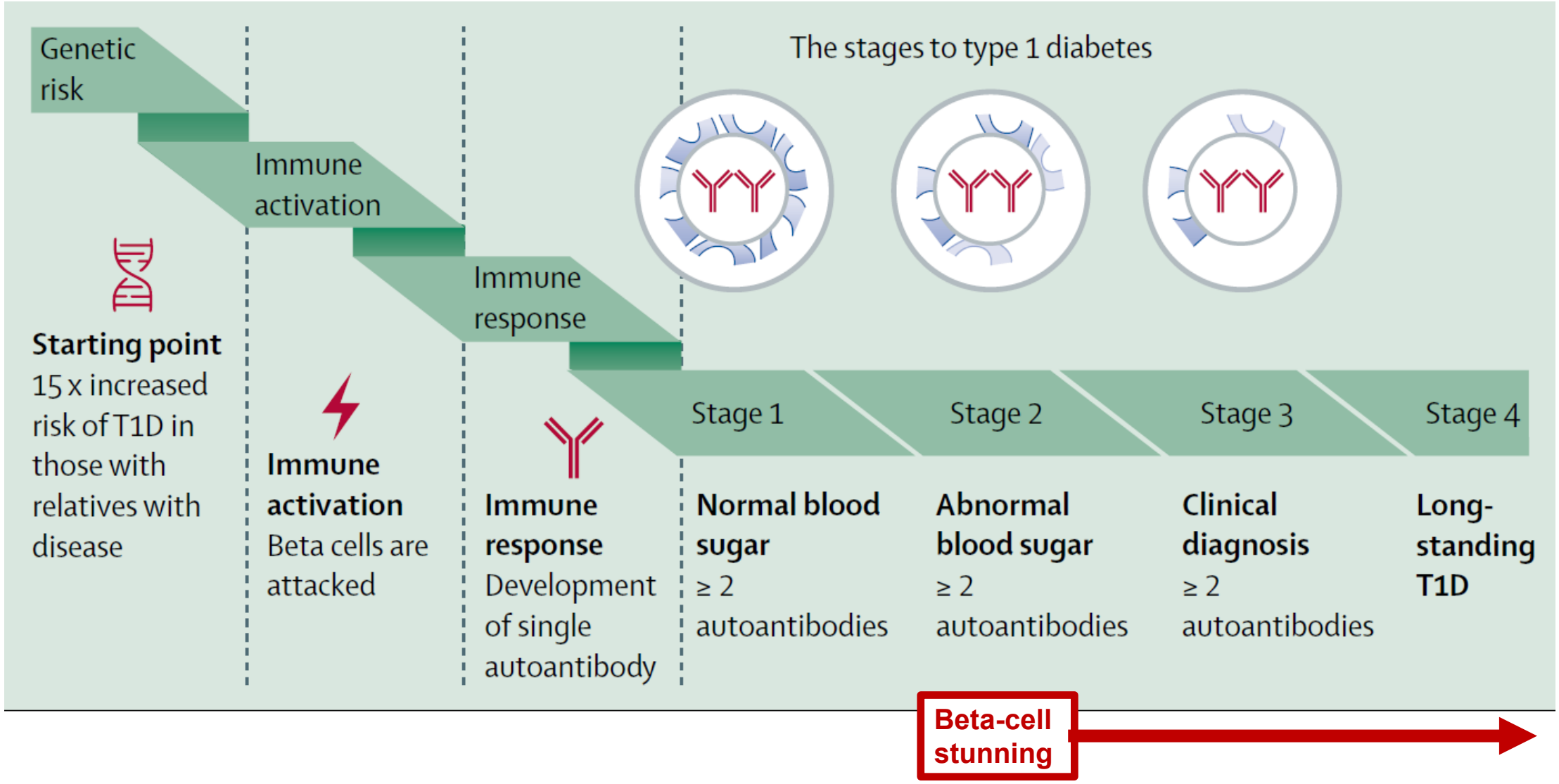
Jay M. Sosenko,[1] Jay S. Skyler,[1] Kevan C. Herold,[2] Desmond A. Schatz,[3] Michael J. Haller,[3] Alberto Pugliese,[1] Mario Cleves,[4] Susan Geyer,[4] Lisa E. Rafkin,[1] Della Matheson,[1] and Jerry P. Palmer,[5] for the Type 1 Diabetes TrialNet Study Group*

Diabetes 2020;69:1827–1832 | https://doi.org/10.2337/db20-0166



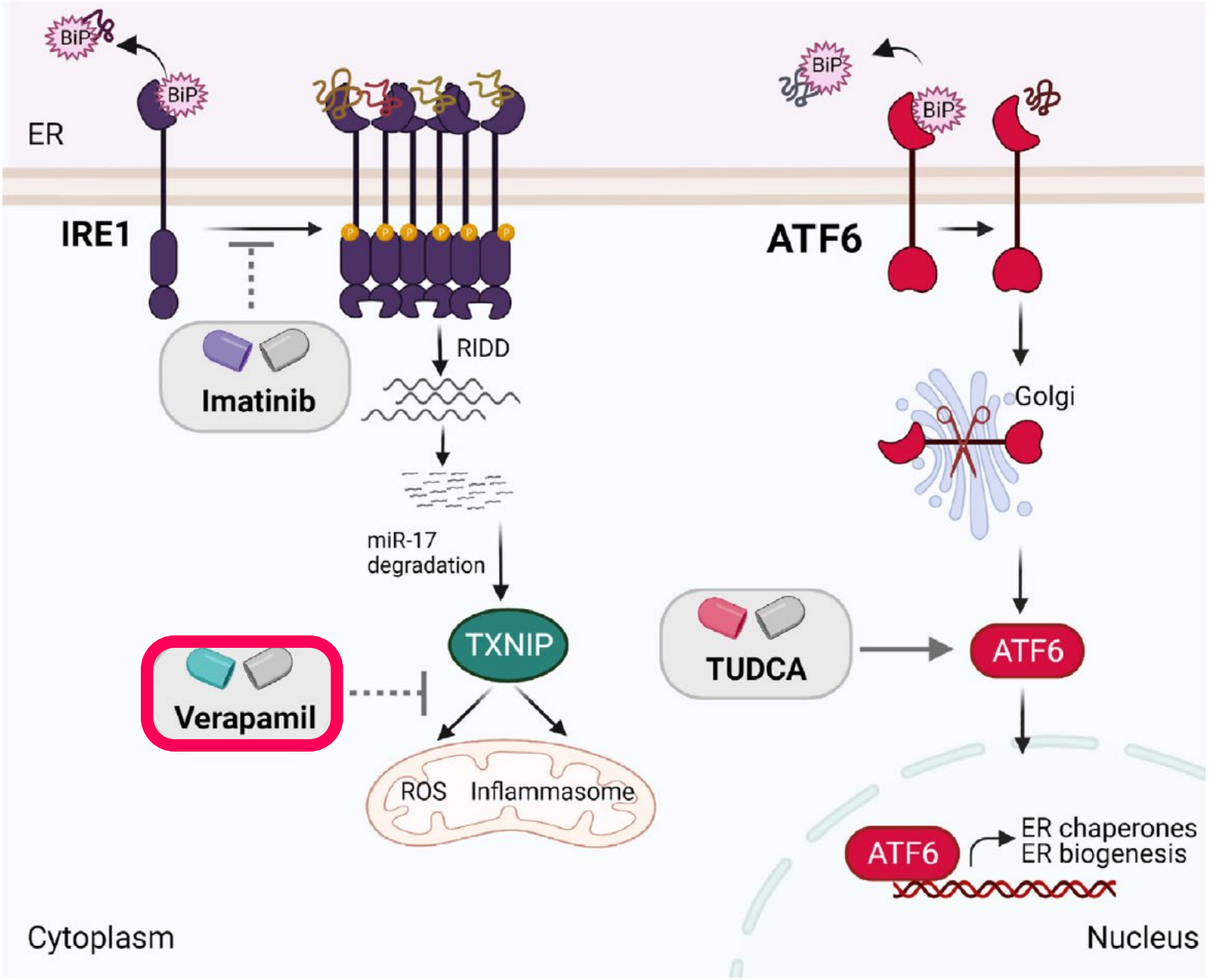


The path to progressive beta-cell stunning and death in T1D



Di Meglio L et. Al. Lancet 2018

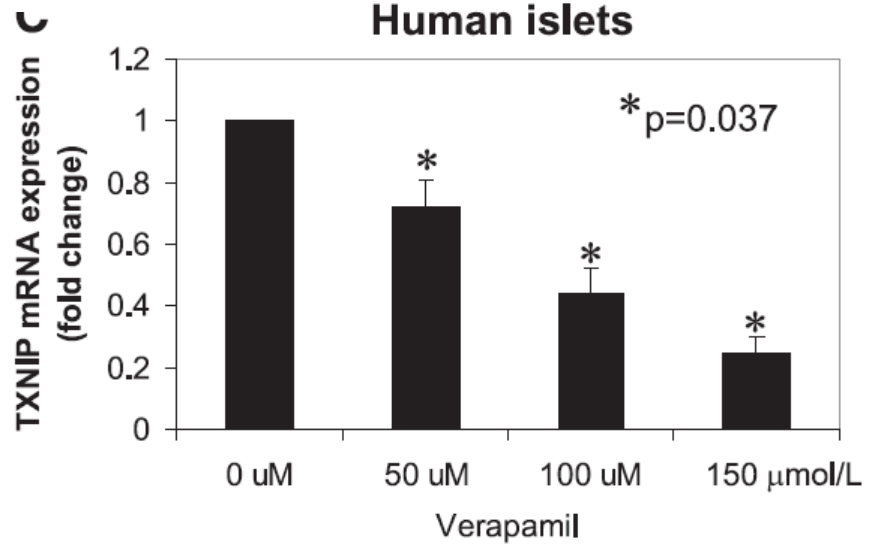
Intervention on stunned beta-cells

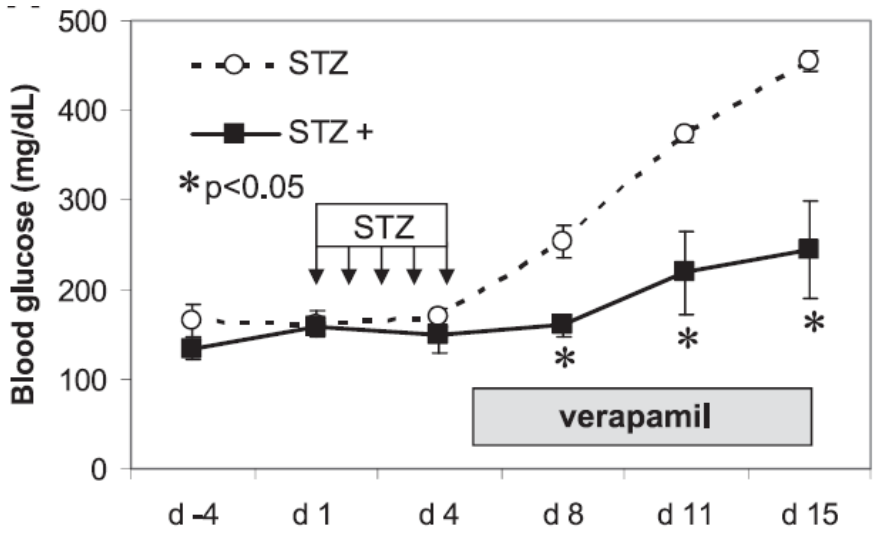


ORIGINAL ARTICLE

Preventing β-Cell Loss and Diabetes With Calcium Channel Blockers

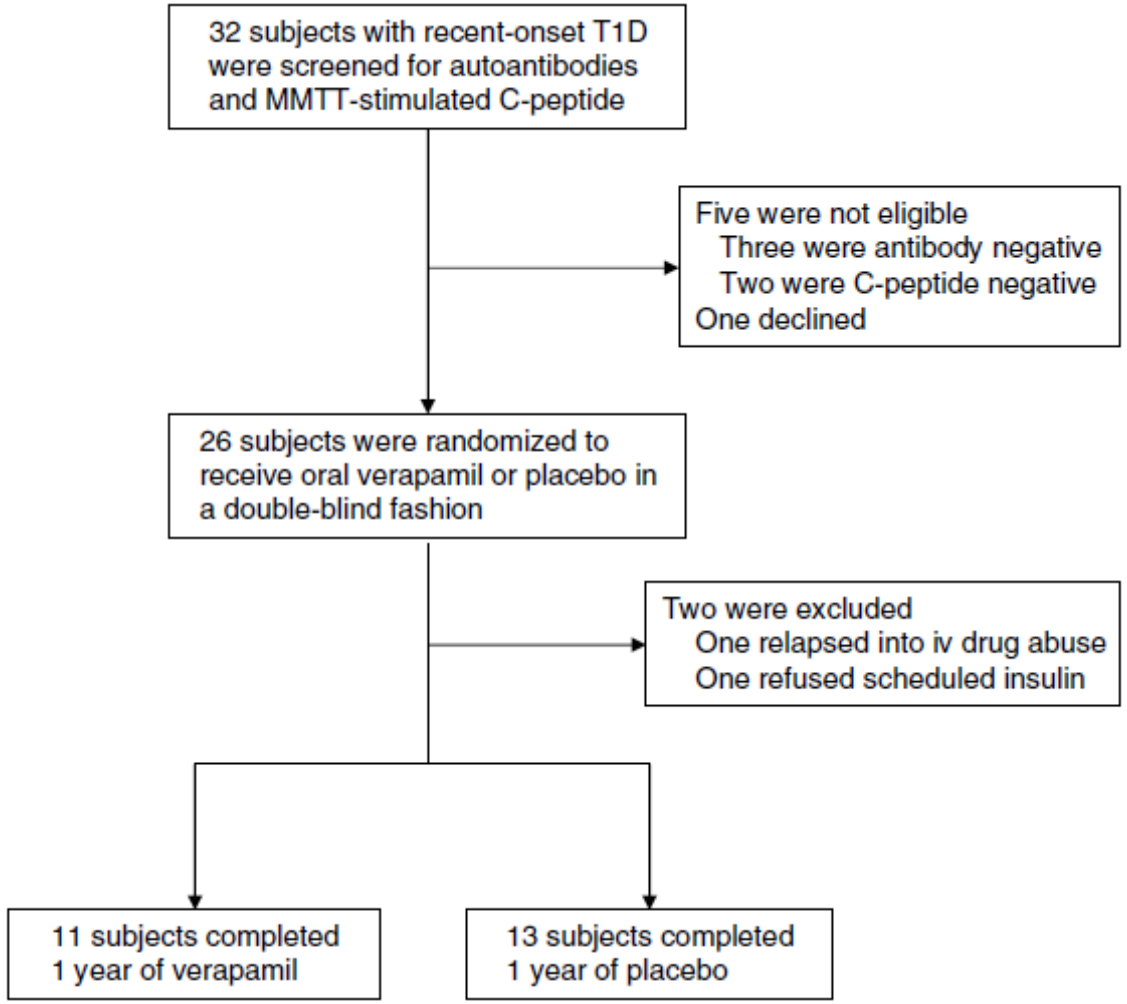
Guanlan Xu, Junqin Chen, Gu Jing, and Anath Shalev

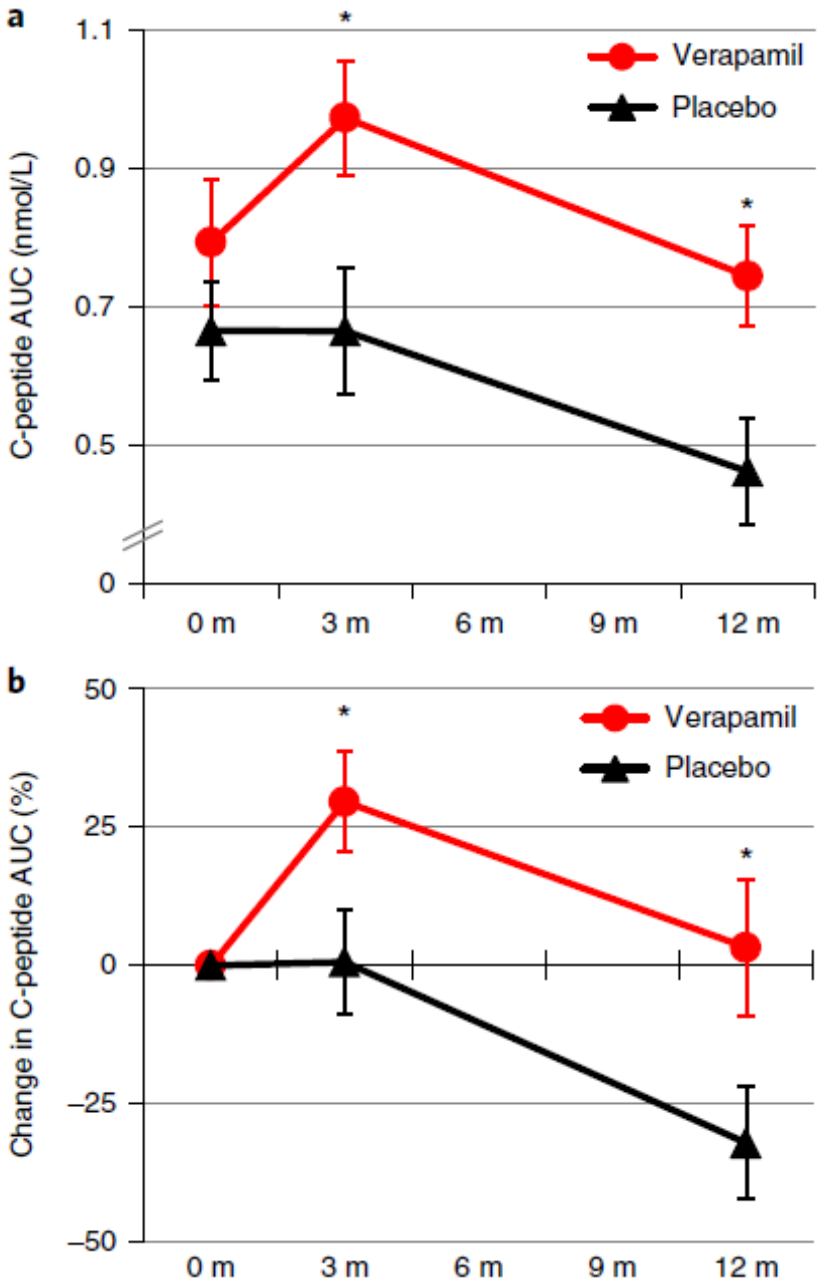




Xu G. et al. 2012, Diabetes

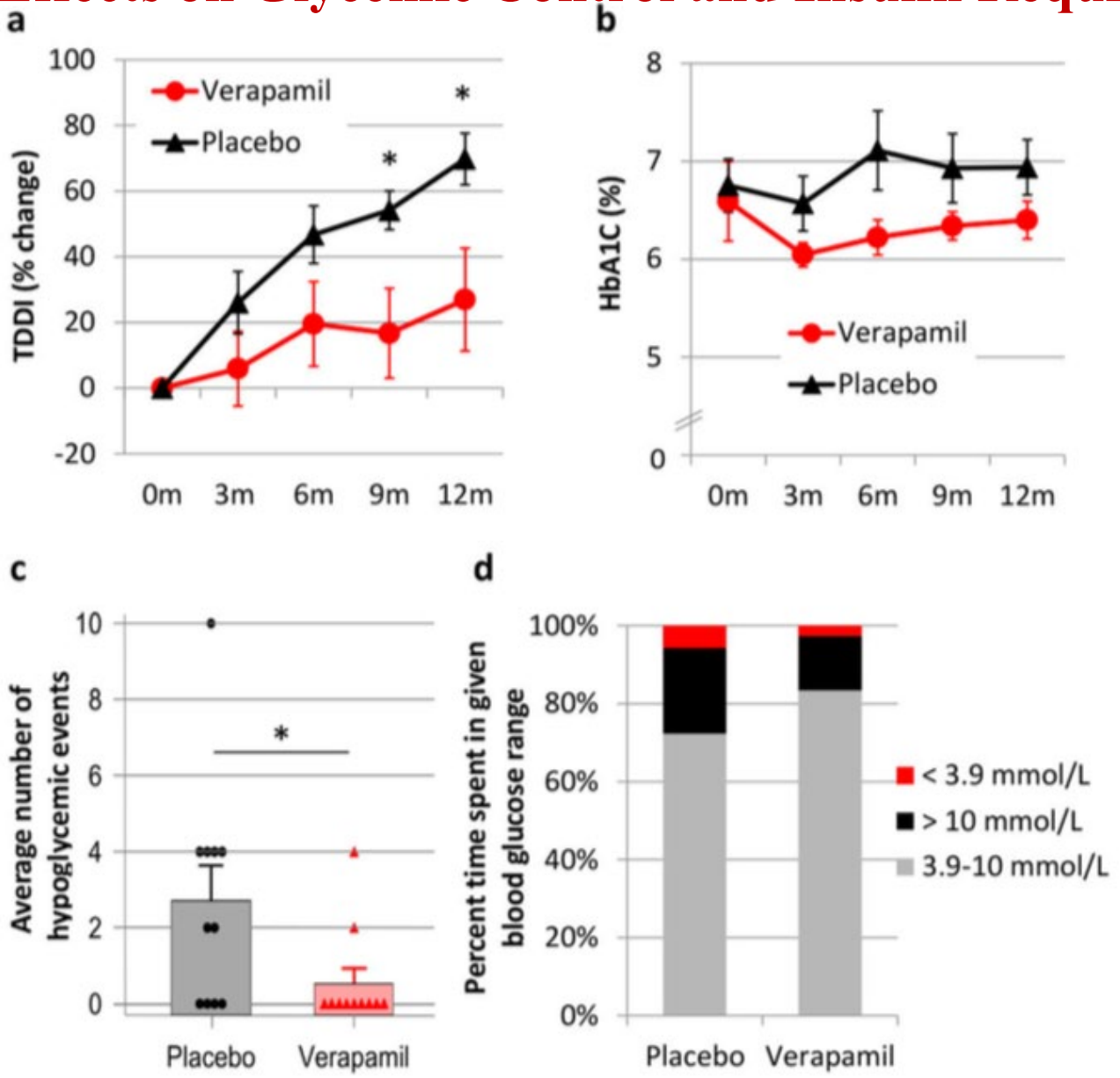
Verapamil inhibits TXNIP activation and ameliorates beta-cell function in T1D



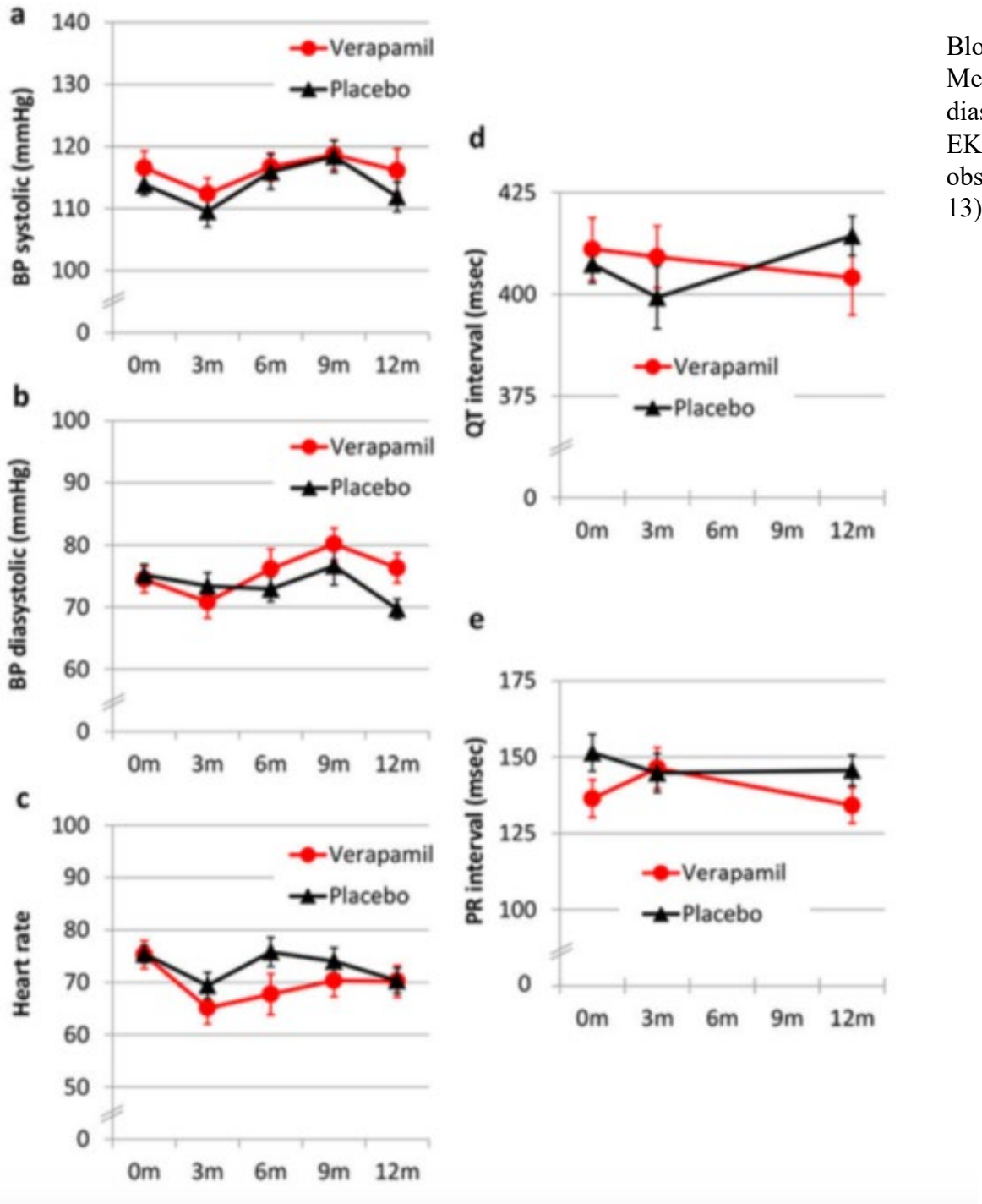


Ovalle F. et al. 2018 Nat.Med;

Verapamil Effects on Glycemic Control and Insulin Requirements.



(a) Mean percent change in total daily dose of insulin (TDDI) during the trial in the verapamil. **(b)** Mean values for %HbA1c as measured at 0, 3, 6, 9, and 12 months. **(c)** Average number of hypoglycemic episodes of blood glucose ≤ 2.2 mmol/L per month. (d) Percent time spent at the target blood glucose range of 3.9–10 mmol/L (grey), above 10 mmol/L (black) or below 3.9 mmol/L (red) as assessed by CGM.

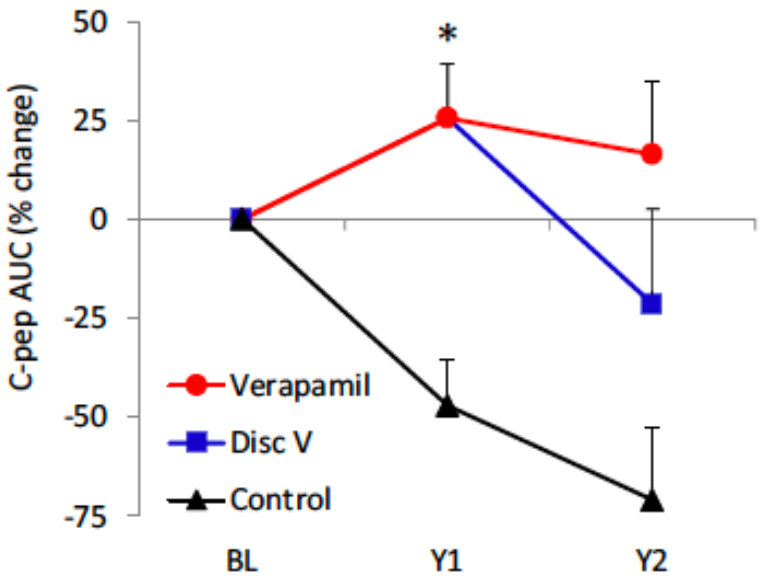


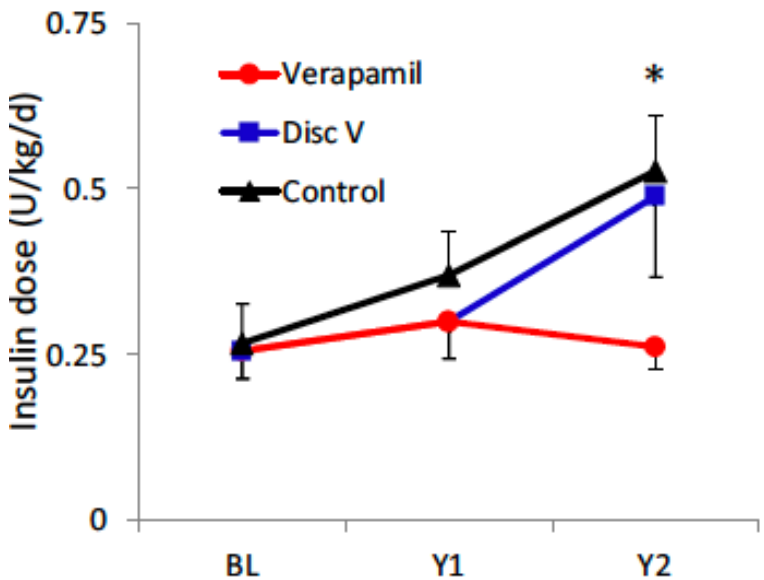
Blood Pressure and Heart Rate throughout the Trial. Mean values for systolic (**a**) and diastolic (**b**) blood pressure (BP), heart rate **(c)** and EKG-measured QT (**d**) and PR **(e)** intervals observed in the verapamil (n = 11) and placebo (n = 13) groups during the 12 month trial.

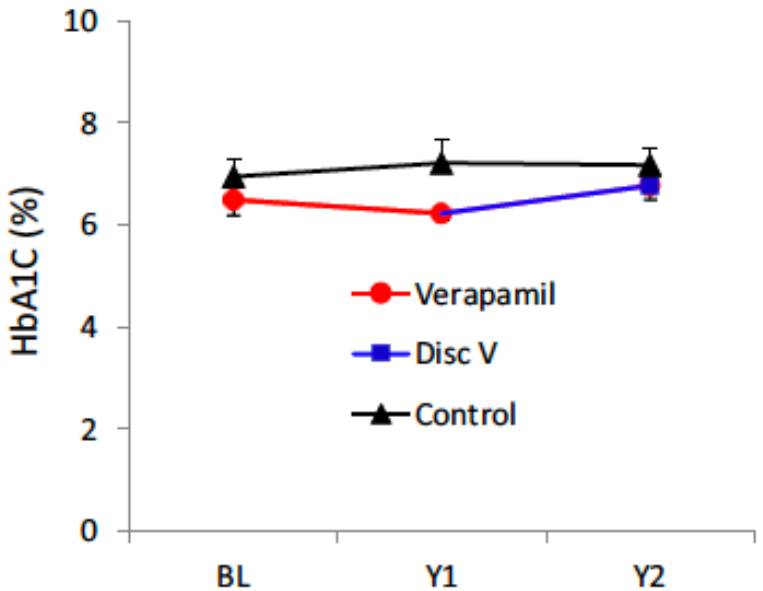
NATURE COMMUNICATIONS | (2022)13:1159 | https://doi.org/10.1038/s41467-022-28826-3 |

Exploratory study reveals far reaching systemic and cellular effects of verapamil treatment in subjects with type 1 diabetes

Guanlan Xu[1,2], Tiffany D. Grimes[1,2], Truman B. Grayson[1,2], Junqin Chen[1,2], Lance A. Thielen[1,2], Hubert M. Tse[1,3], Peng Li[1,4], Matt Kanke[5], Tai-Tu Lin[6], Athena A. Schepmoes[6], Adam C. Swensen[6], Vladislav A. Petyuk[6], Fernando Ovalle[1,2], Praveen Sethupathy[5], Wei-Jun Qian[6] & Anath Shalev[1,2]✉





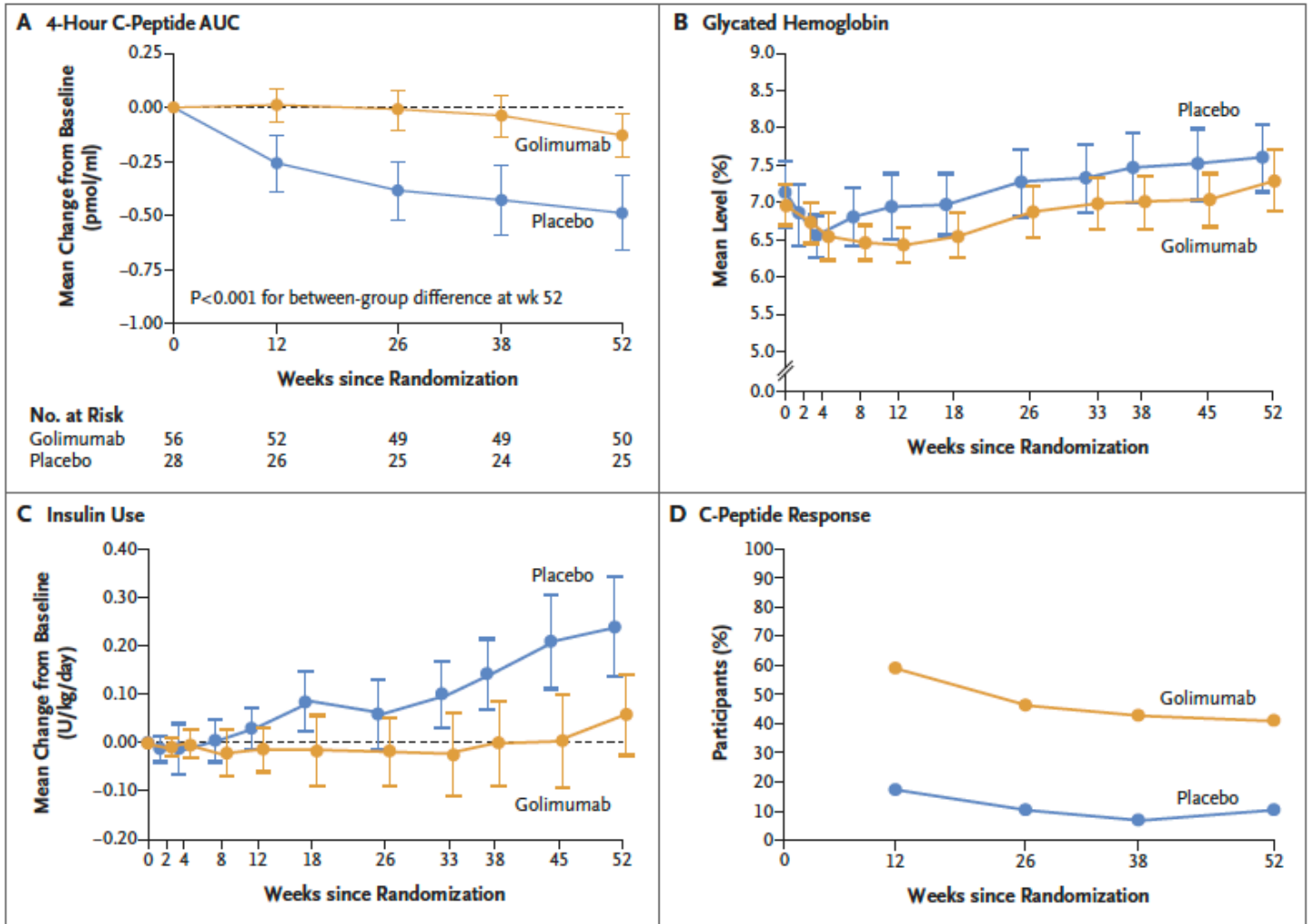


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 19, 2020 VOL. 383 NO. 21

Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes

T. Quattrin, M.J. Haller, A.K. Steck, E.I. Felner, Y. Li, Y. Xia, J.H. Leu, R. Zoka, J.A. Hedrick, M.R. Rigby, and F. Vercruysse, for the T1GER Study Investigators*



Golimumab in Youth with New-Onset Type 1 Diabetes

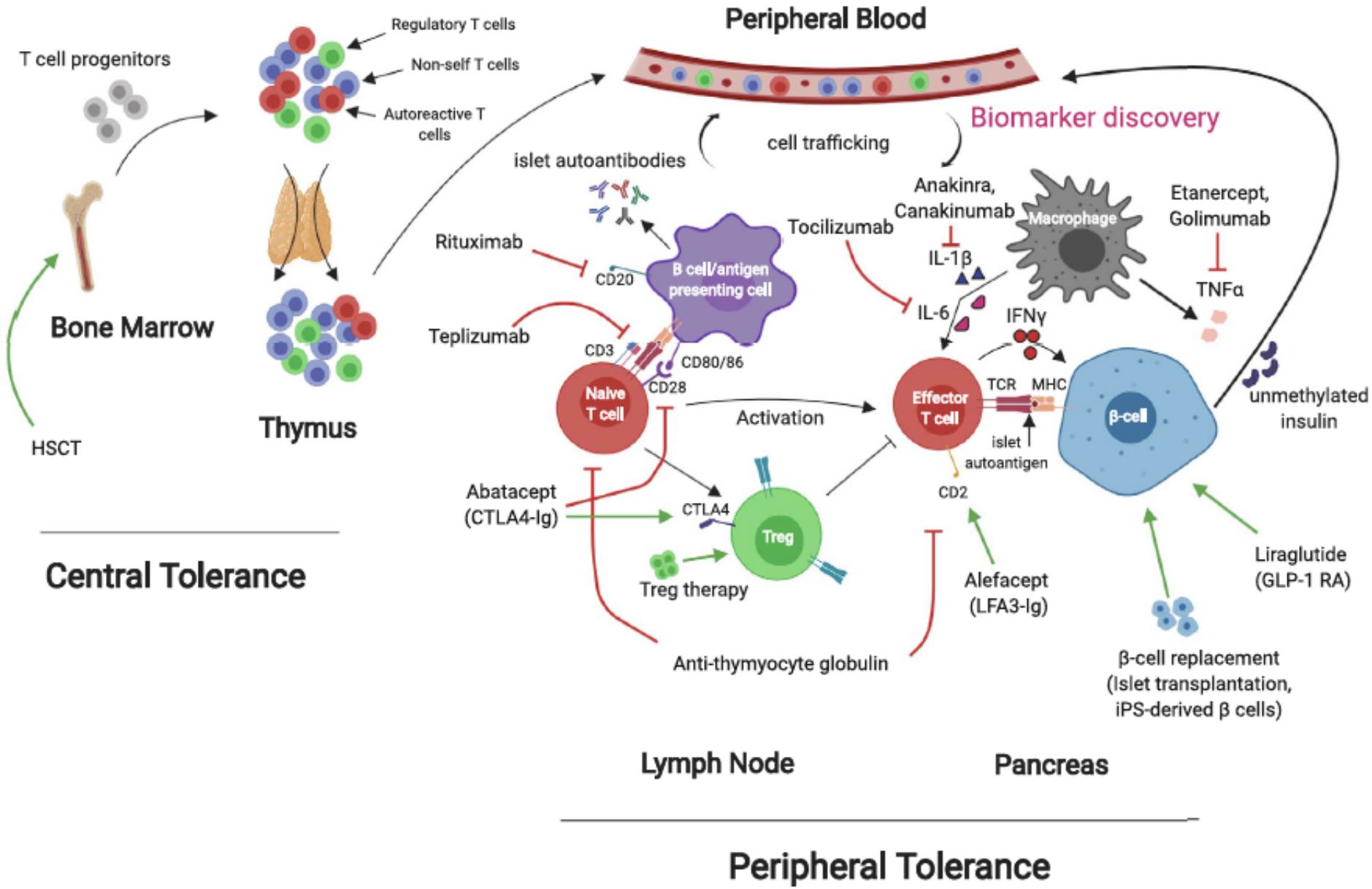
PHASE 2, MULTICENTER, DOUBLE-BLIND, RANDOMIZED TRIAL

84 Patients (6–21 years of age) with newly diagnosed type 1 diabetes

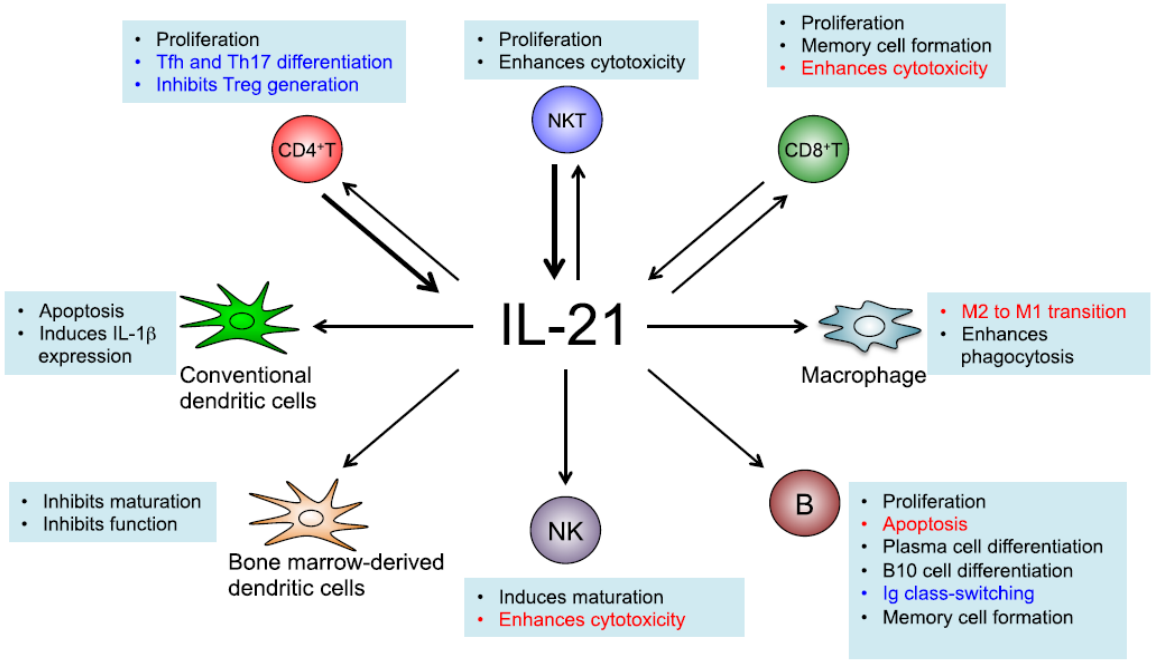
	Golimumab		Placebo
	N=56		N=28
Mean (±SD) 4-hour C-peptide AUC at 52 wk (mixed-meal tolerance test)	0.64±0.42 pmol/ml	(P<0.001)	0.43±0.39 pmol/ml
Change in glycated hemoglobin at 52 wk	0.47%	(P=0.80)	0.56%
Increase in daily insulin use at 52 wk	0.07 U/kg	(P=0.001)	0.24 U/kg
Mean no. of hypoglycemic events	38.2	(P=0.80)	42.9

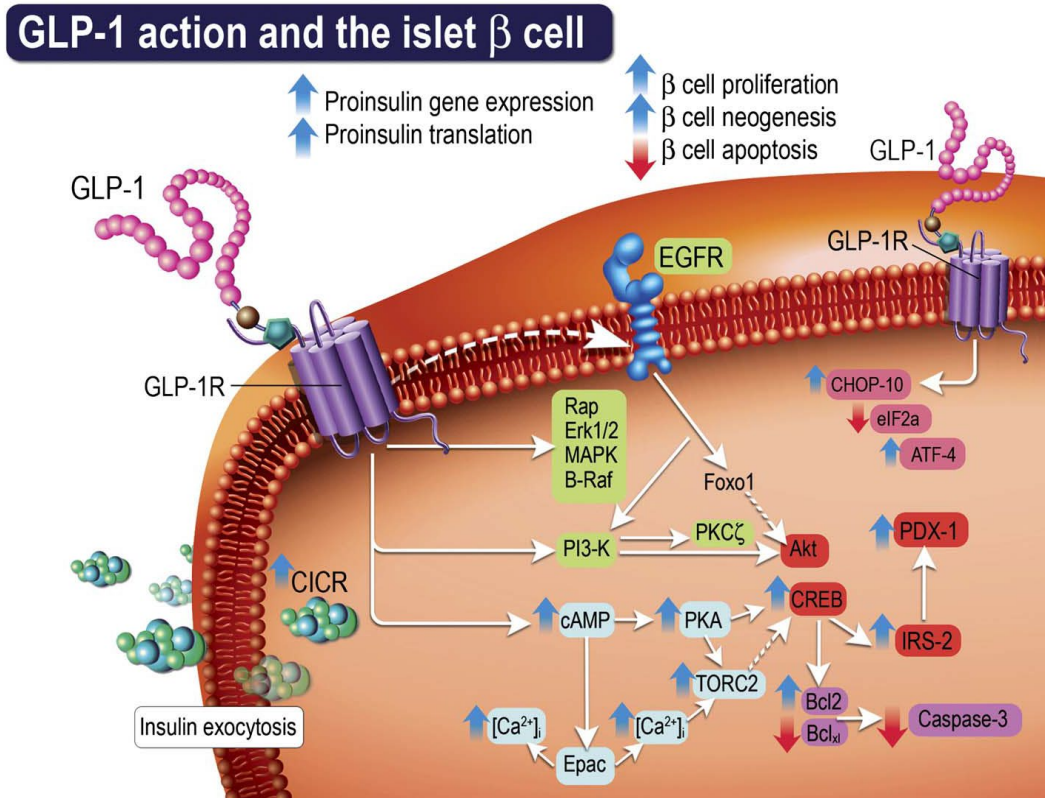
Golimumab resulted in better production of endogenous insulin and less use of exogenous insulin

Combination therapeutic strategies



Combined intervention: anti-Interleukin-21+ Liraglutide





Inflammation reduction

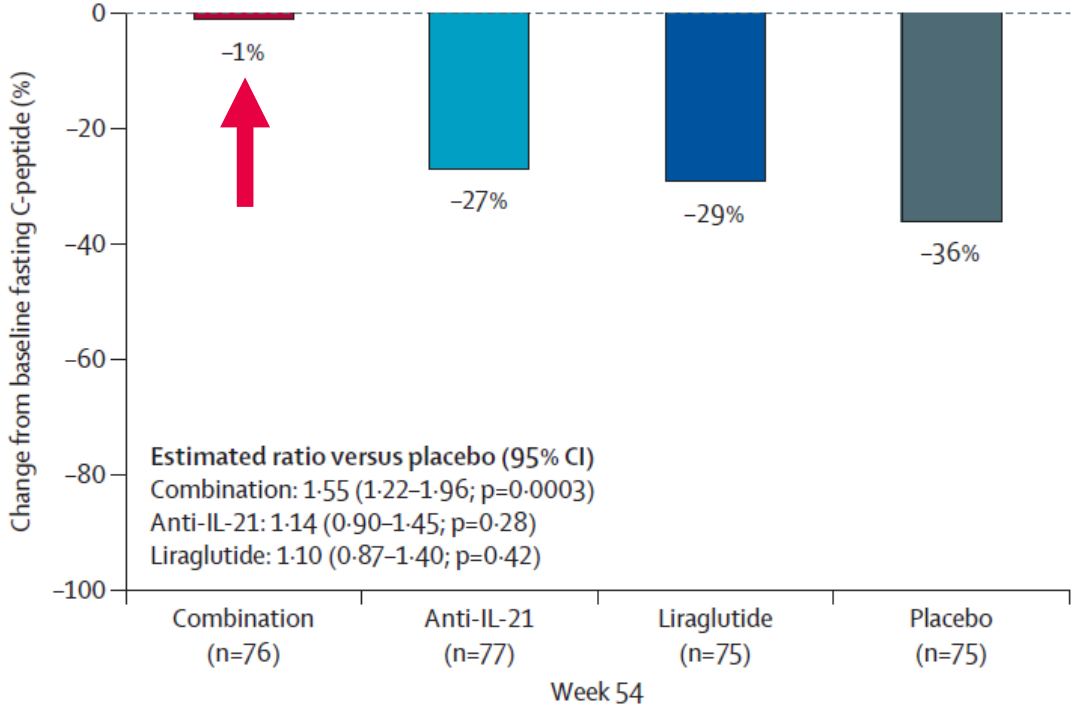
Improvement of the beta-cell function

Combined intervention: anti-IL21+ Liraglutide

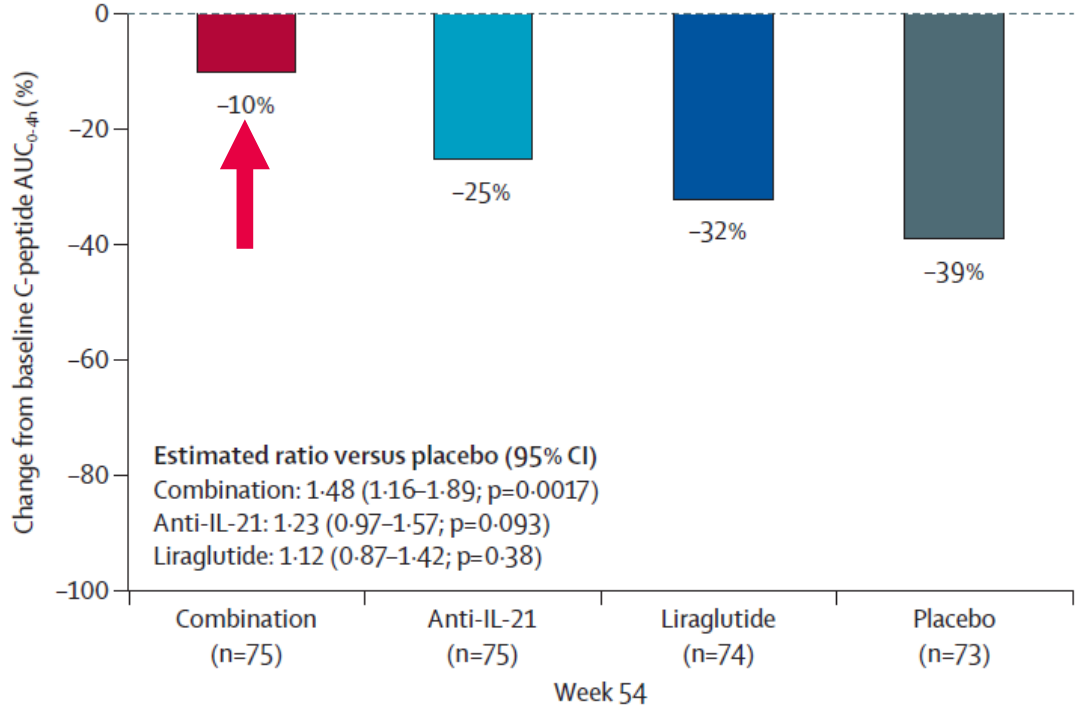
Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial

*Matthias von Herrath, Stephen C Bain, Bruce Bode, Jesper Ole Clausen, Ken Coppieters, Leylya Gaysina, Janusz Gumprecht, Troels Krarup Hansen, Chantal Mathieu, Cristobal Morales, Ofri Mosenzon, Stine Segel, George Tsoukas, Thomas R Pieber, on behalf of the Anti-IL-21–liraglutide Study Group investigators and contributors**

Change Fasting C-peptide



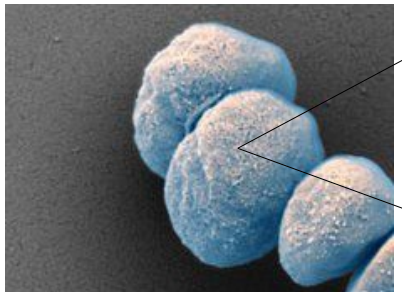
Change C-peptide AUC

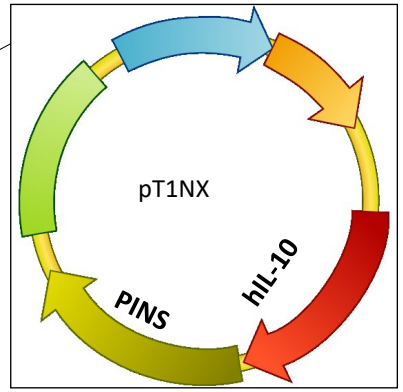


Von Herrath M. et al Lancet, Diab Endocr. 2021

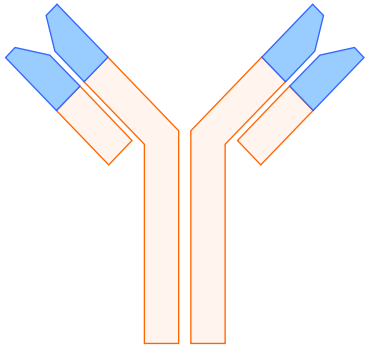
Combination of Ag-specific and non-specific intervention in T1D

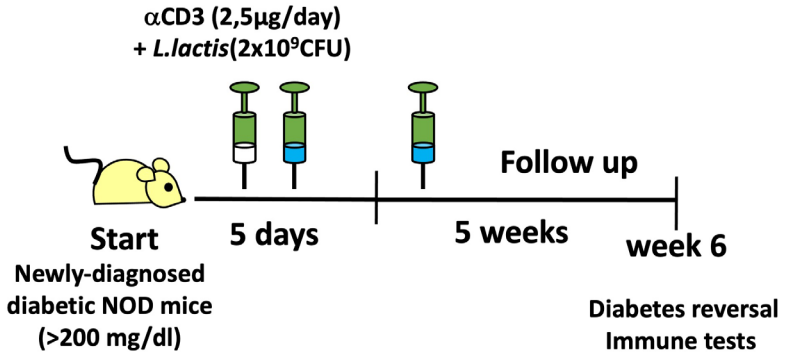
Lactococcus lactis

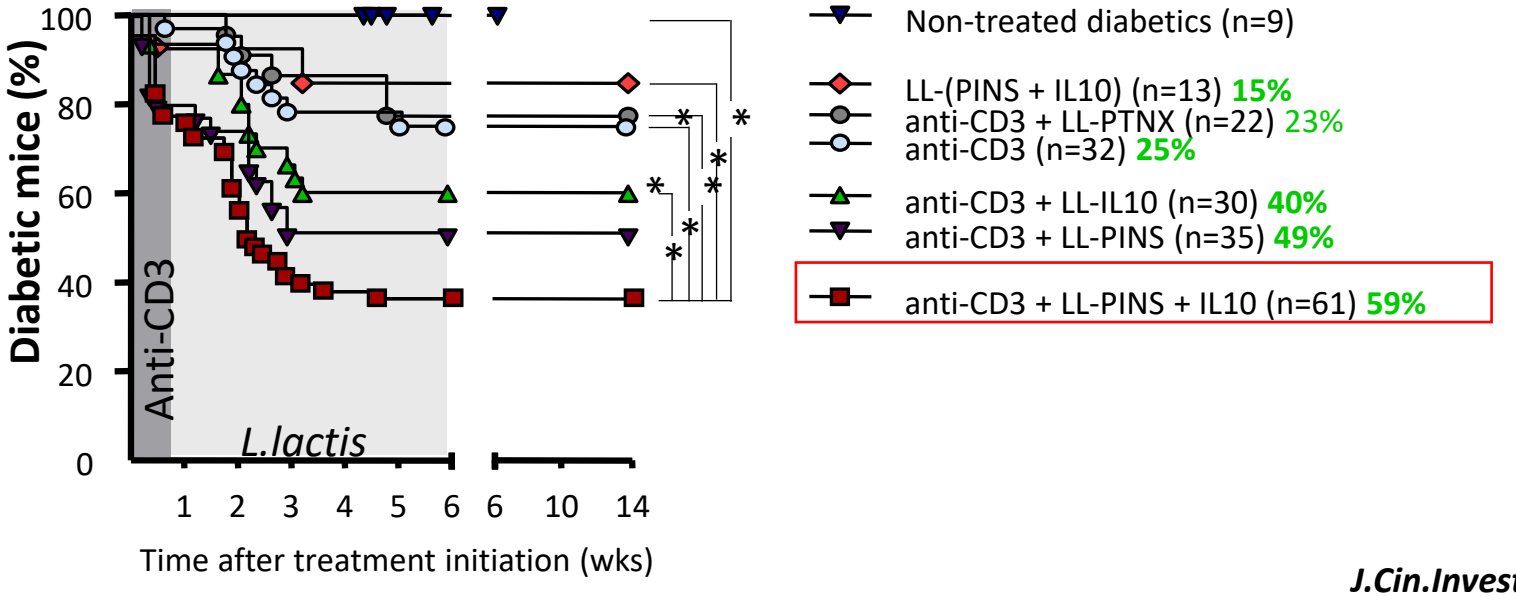




anti-CD3 antibodies







J.Cin.Invest 2012,; Diabetes 2015 & 2017;
Front. Immunol. 2020

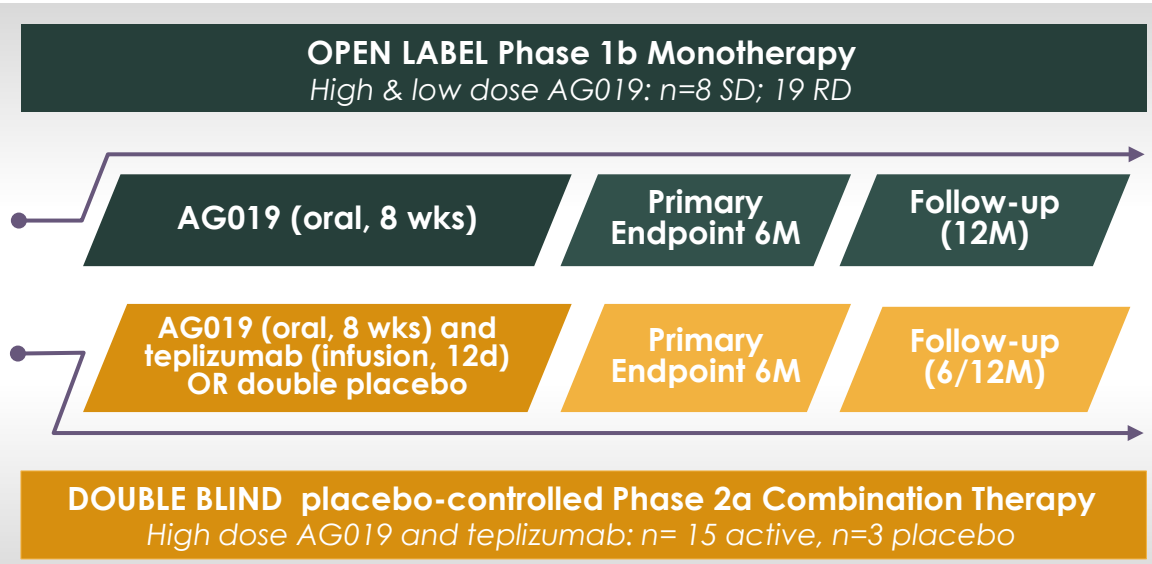
AG019 Phase 1b/2a in Recent-Onset T1D – Clinical Study Design

"A Study to Assess the Safety and Tolerability of Different Doses of ***AG019 Administered Alone or in Combination With Teplizumab*** *in Participants With* ***Recently Diagnosed Type 1 Diabetes Mellitus (T1D)"***

- **Treatment of new-onset T1D** within 5 months from diagnosis (**Stage 3**)
- Oral antigen-specific immunotherapy intended to restore immune tolerance -> preserve functional β-cell mass
- AG019 Monotherapy and AG019 + Teplizumab Combination therapy

Population:
- 12-42 years of age
- Stimulated C-peptide >0.2 nmol/L
- Treatment start within 150 days of diagnosis (*)

ClinicalTrials.gov-NCT03751007



Primary endpoint:
Safety & tolerability at 6 months follow-up

Secondary endpoints – PK/PD
- Systemic and local exposure of *L. lactis* and hPINS/hIL-10
- C-peptide preservation
- Mechanistic assessments & biomarkers for immunological changes (**)

(*) Recent-onset in this study is defined as within 150 days of diagnosis. Other studies (e.g. teplizumab studies PROTECT and Protégé) use other definitions, e.g. 42 days..
(**) In a subset of patients, preproinsulin (PPI) and islet specific CD4+ and CD8+ T-cell responses were measured using a peptide activation assay and Class I MHC tetramers, respectively.

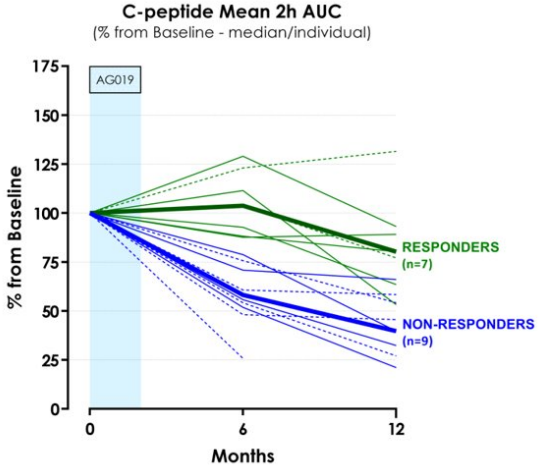
AG019 Phase 1b/2a in Recent-Onset T1D - Favorable stabilization of C-peptide & Antigen-Specific Immunological Effects

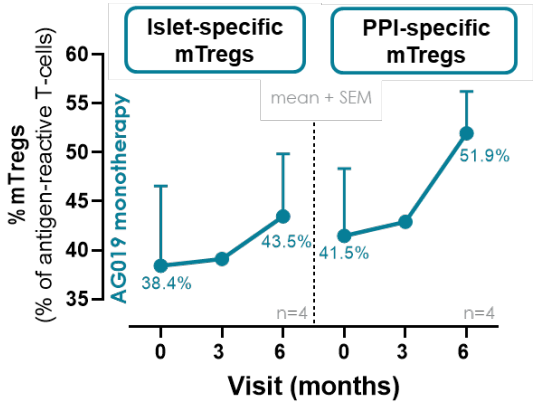
OVERALL CONCLUSIONS

- **Excellent safety profile** for AG019 either as monotherapy or in association with teplizumab, no serious adverse events were reported - **Primary endpoint met** for both Phase 1b & Phase 2a.
- **Stabilization/increase of C-peptide levels** (marker for disease progression) was shown during the first 6 months in 56% (5/9) of adult patients for AG019 monotherapy. C-peptide stabilization/increase was shown in 79% (11/14) of all patients after 6 months for AG019/teplizumab combination therapy which remained stable up to 12 months in 77% (10/13) of all patients.
- **Stabilization of HbA1c and IDAA1c levels** (indicators of long-term glycemic control in T1D) was shown for AG019 monotherapy and AG019/teplizumab combination therapy.
- **Increase in islet- and PPI-reactive memory Tregs and Tr1 cells** and **decline in frequency of proinflammatory conventional T-cells & disease-specific CD8 T cells** was shown for both therapies.

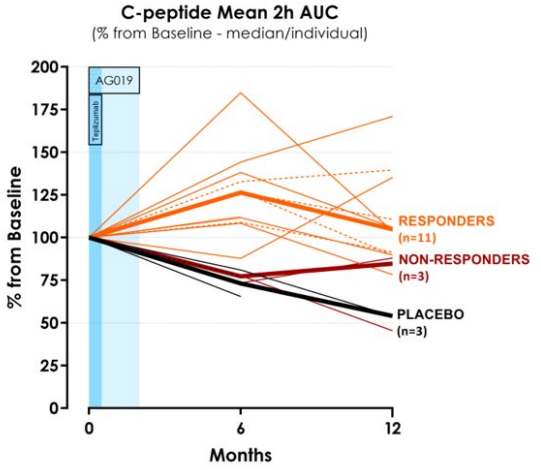
'Responders' were designated if the coefficient of variance on C-peptide AUC was ≤ 9.7%, or if change from baseline was non-negative (Greenbaum et al. 2012) - Per Protocol population

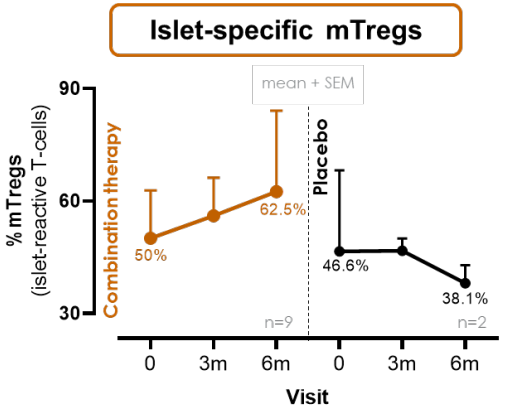
AG019 MONOTHERAPY

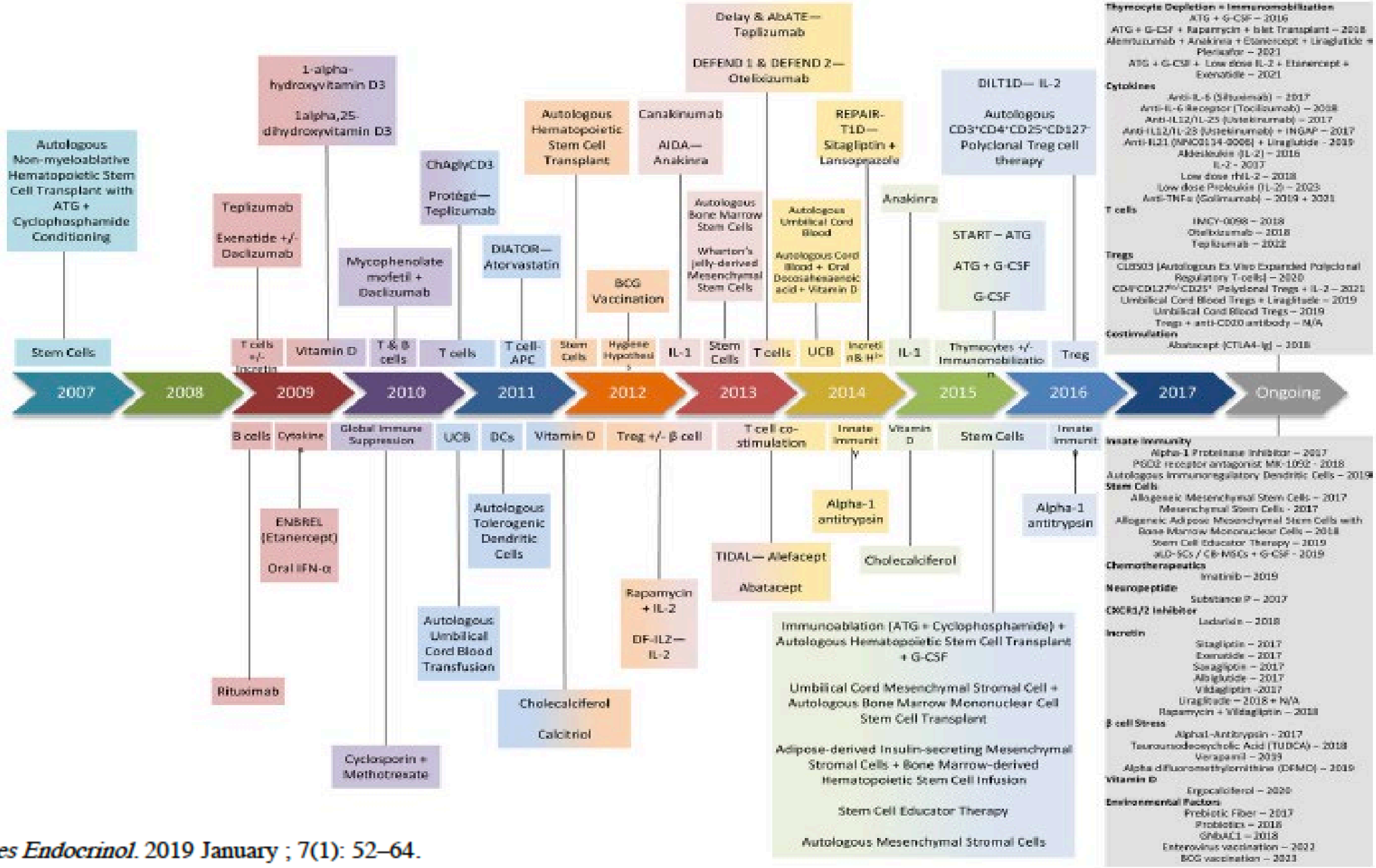




AG019/TEPLIZUMAB COMBINATION THERAPY

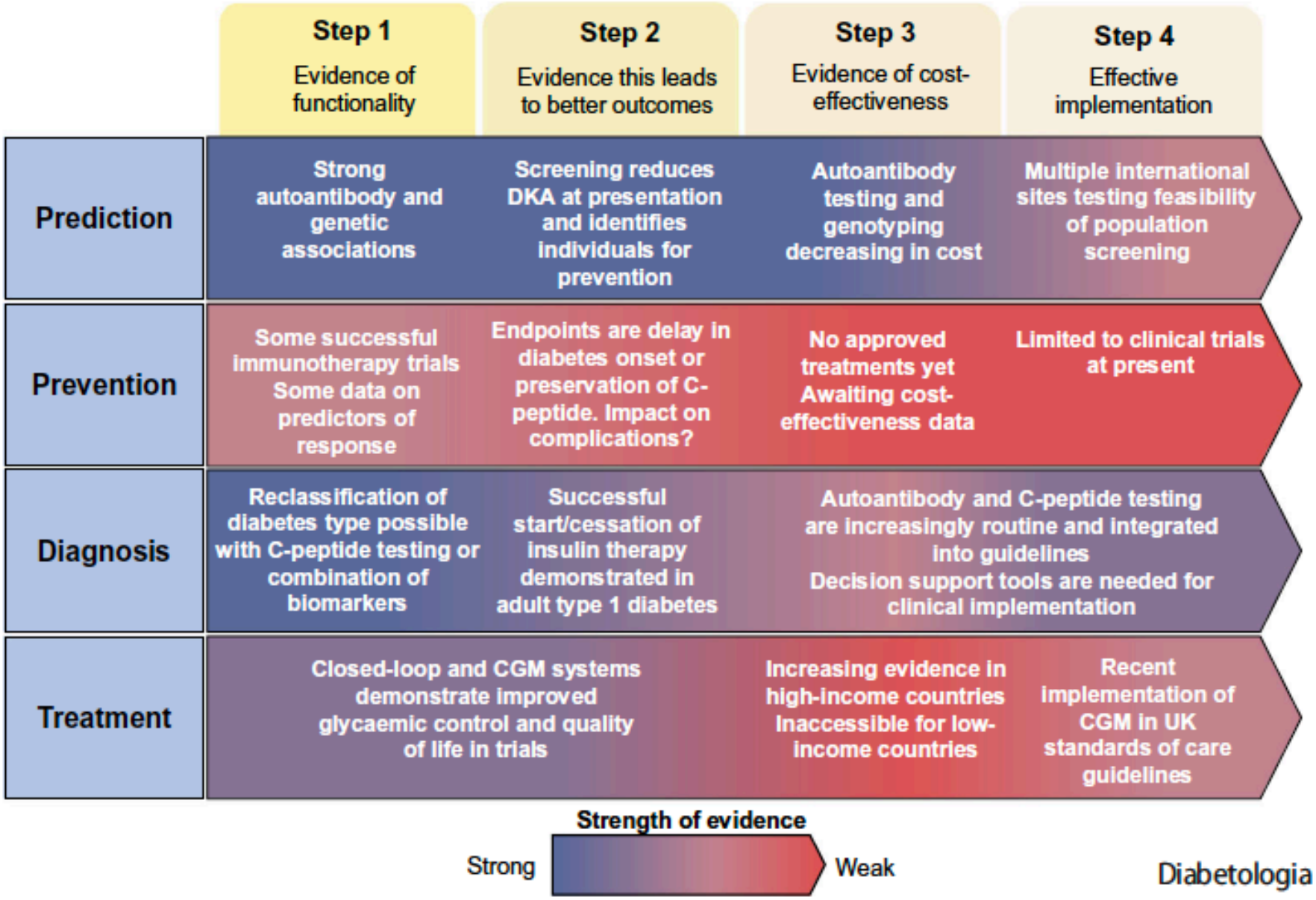






Lancet Diabetes Endocrinol. 2019 January ; 7(1): 52–64.

Roadmap for precision medicine in type 1 diabetes



Diabetologia (2022) 65:1854–1866

Failures to meet trial endpoints and advance therapies into clinical settings can be ascribed to a series of:

- Flawed guiding hypotheses
- **Possible subcategories of T1D etiologies,**
- Potential impact of environmental, temporal, and demographic/geographic factors, patterns of loss of **β**-cell mass/function,
- Our ability to quantify functional and dysfunctional **β**-cell mass in living patients;
- Ability of residual **β**-cells to compensate for declining **β**-cell mass/function prior to clinical onset of the disease,
- The need for earlier intervention to prevent progression from multi-autoantibody positivity (Stage 1 disease) to dysglycemia (Stage 2).

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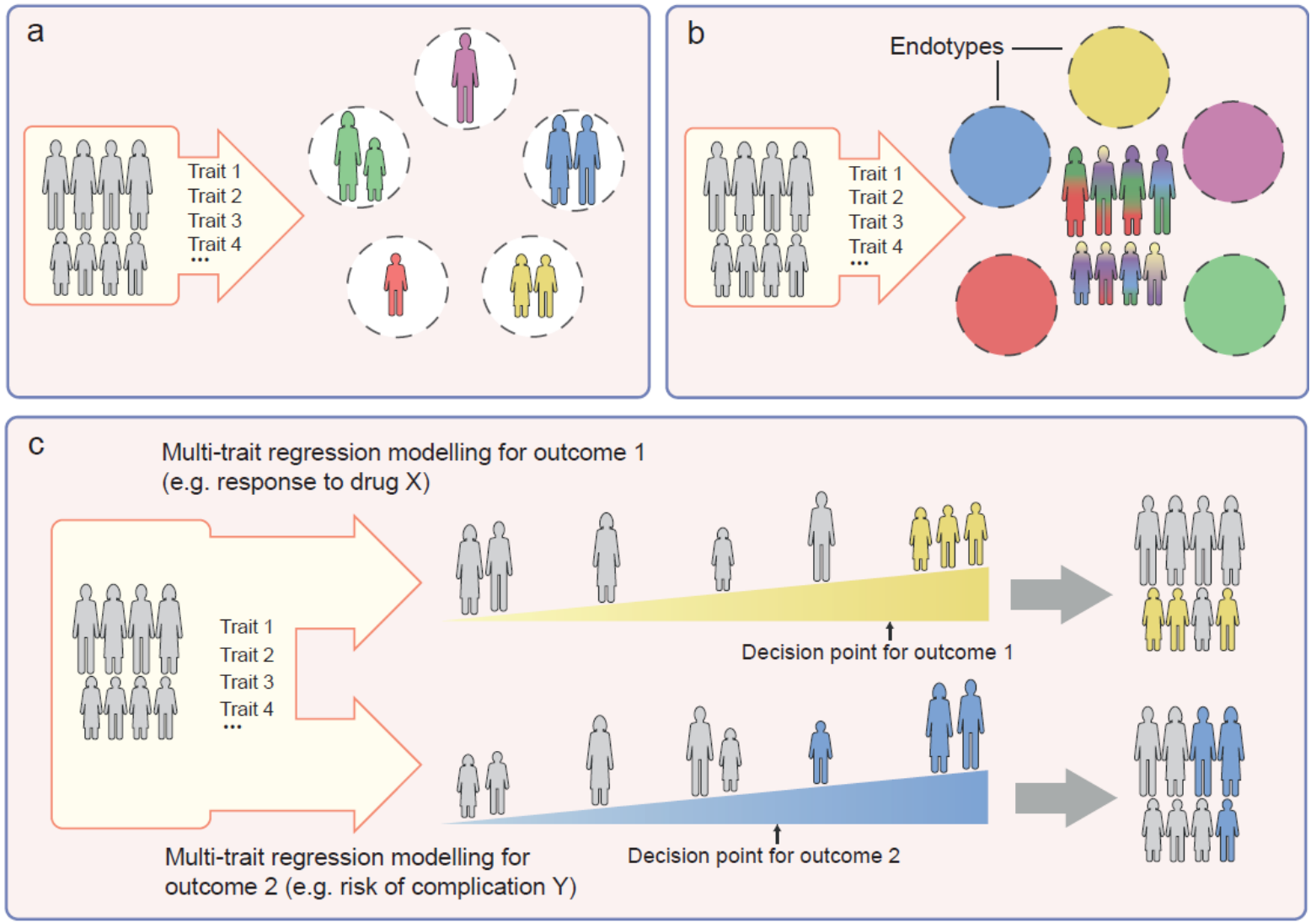
Strategies for identifying diabetes subtypes



Diabetologia (2022) 65:1758–1769