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AMD-SID Lombardia 2022

Beta cells protection

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Piazza Duca d'Aosta, 3 - Milano

Beta cells protection

1. Introduction
2. Beta cells death in type 1 diabetes
3. Beta cells protection in type 1 diabetes
4. The death receptor TMEM219 and its signaling
   - In vitro studies
   - In vivo studies
5. Future perspectives
6. Conclusions

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The unmet clinical need in T1D and beta cells protection

- In patients with T1D β cells mass and function are diminished, leading to insufficient insulin secretion and hyperglycemia
- Several stress factors (glucolipotoxicity, oxidative stress and immune attack/infiltration) play a role in beta cell dysfunction/injury.
- In the recent years numerous antidiabetic drugs are available and the quality/intensity of diabetes care have improved.
- There are still no therapies in clinical use that target the fundamental pathological processes that cause β-cell failure and destruction.
- How beta cell loss can be prevented is unknown.

Donath, M. et al. Nat Rev Immunol 2019
Chen C et al, Molecular Metabolism, 2017
Nguyen KH et al. Endocrinology 2011
Kim MS et al. J Pediatr Endocrinol Metab 2014
Peet A et al. Eur J Endocrinol 2015

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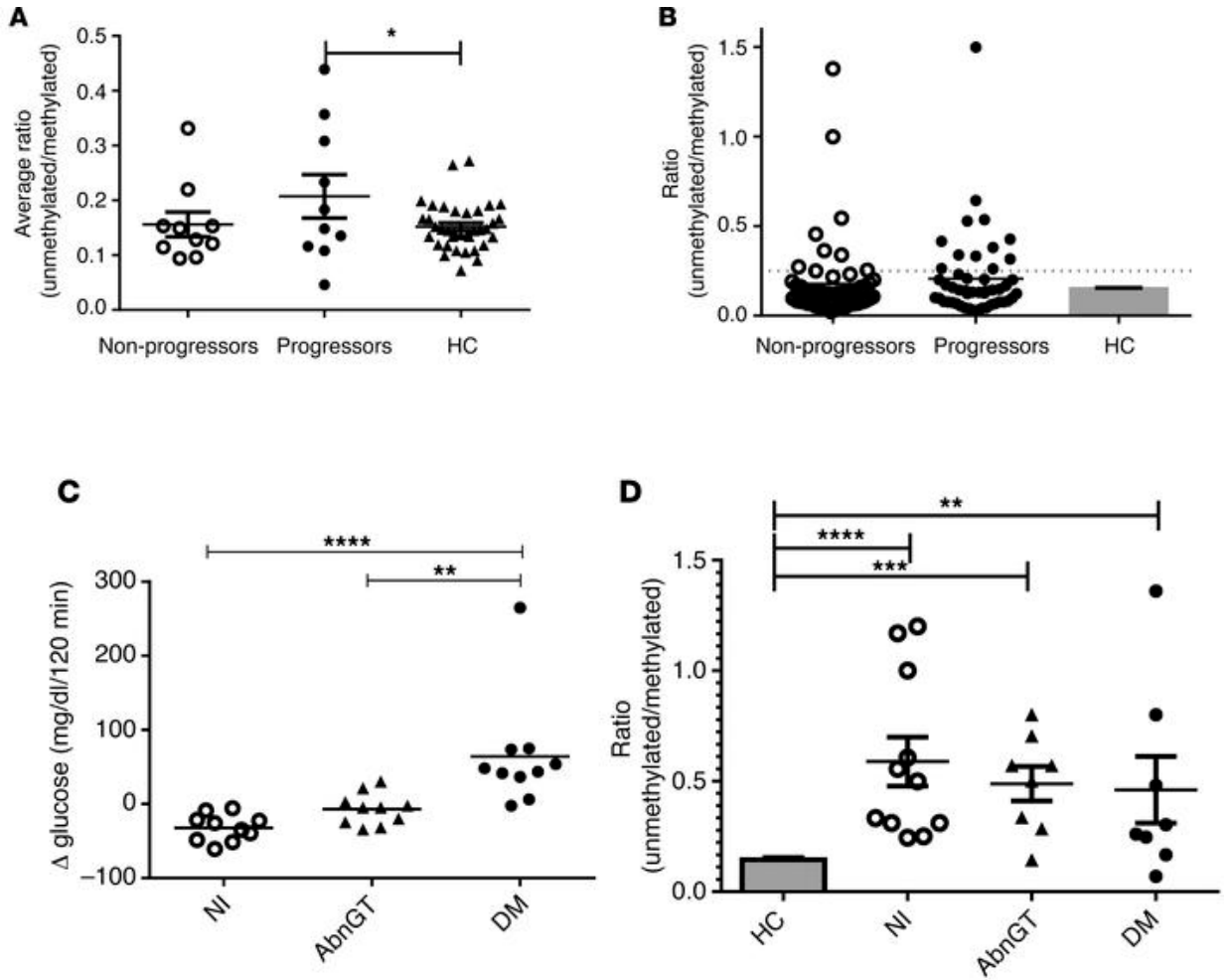
Beta cell death in T1D

- During progression of diabetes beta cells most likely die from a combination of necrosis and apoptosis.
- The cause of long-term beta cell loss remains unclear.
- It is possible that ongoing beta cell destruction in T1D is intrinsic.
- The β cell killing that characterizes T1D is thought to begin years before patients present clinically with metabolic decompensation.
- It is possible that beta cells are more vulnerable to immune attack, more immunogenic in T1D.
- A pool of residual beta cells («sleeping»?) exists in long-term T1D.

Wilcox NS et al. Herold KC J Autoimmun 2016
Oram RA et al. Diabetologia 2019

Beta cell death is associated with progression to T1D and glucose intolerance in patients at risk for T1D

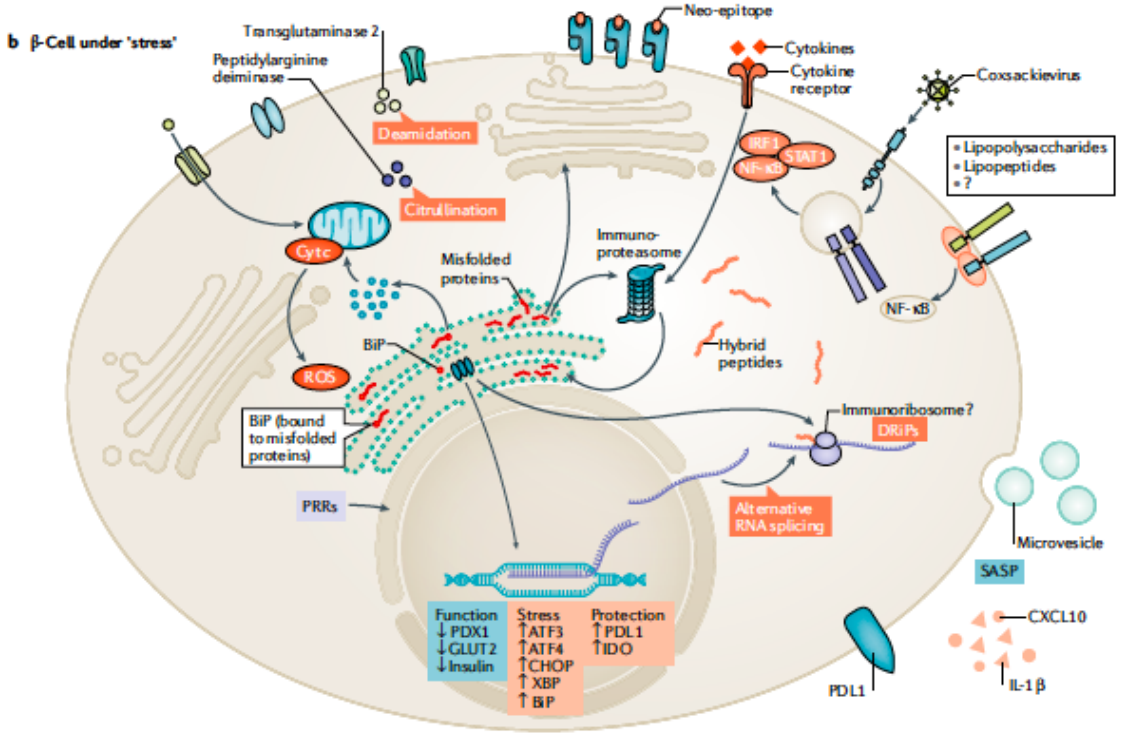


Herold KC et al. J Clin Invest 2015

A new emerging model: a role for vulnerable beta cells in T1D

Box 3 | Evidence supporting a role for β-cells in T1DM pathogenesis

- Smaller size of pancreas and islet mass in patients with type 1 diabetes mellitus (T1DM) and individuals at risk[73]
- Genetic risk associated with *INS* gene polymorphism associated with β-cell function[14,15,93–95,97]
- Genetic risk associated with polymorphisms in genes with protein products involved in β-cell protection, health and vitality[69]
- β-Cell stress[31,103,106]
- Abnormal β-cell function preceding diagnosis of T1DM (in spite of sufficient β-cell mass)[101,102]
- HLA class I upregulation on endocrine cells in inflamed islets[7,69]
- HLA class I upregulation preceding islet inflammation[7,69]
- Paucity of insulitis in individuals with islet autoantibodies[70]
- Development of post-translational modifications (such as deamidation, citrullination and transpeptidation)[26,133,134,138,177]
- Stress-induced ribosomal errors; post-transcriptional modification[31]
- Alternative splicing of islet autoantigens[99,131,136,178]



Beta cells are stressed in T1D and more vulnerable to immune attack
Beta cells appeat to be more immunogenic in T1D

Roep, B et al. Nat Rev Endocrinol 2021

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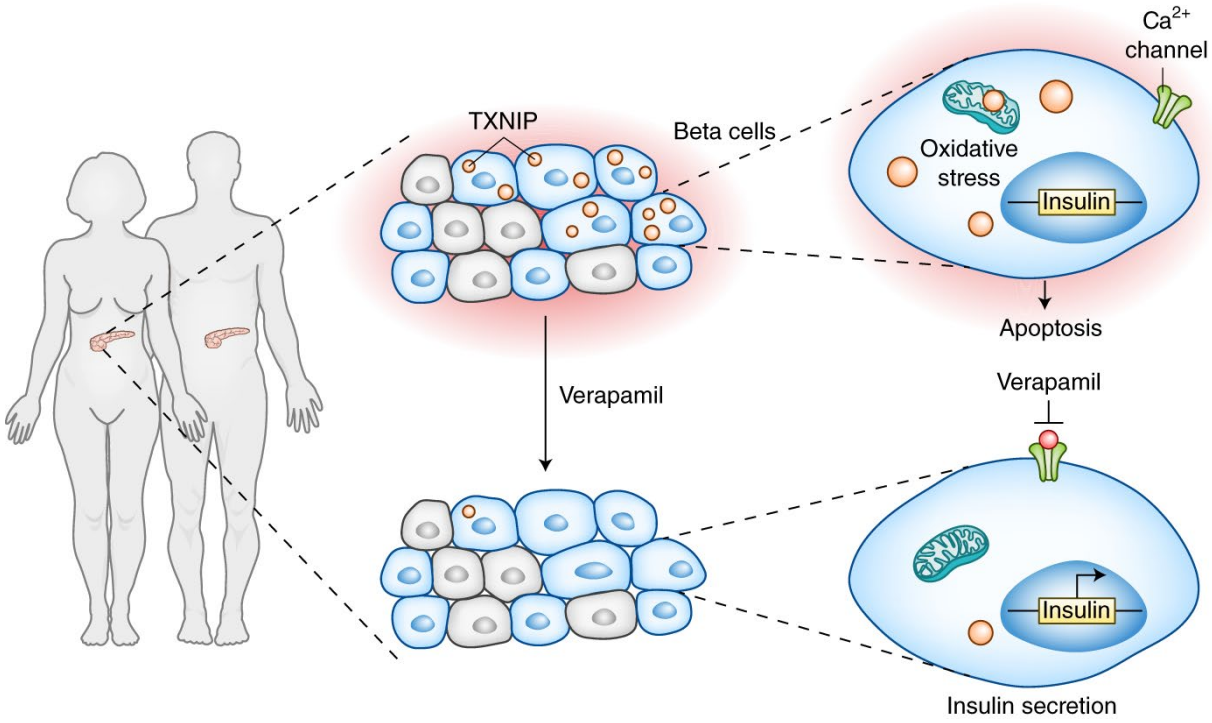
Targeting TXNIP signal with Verapamil in T1D



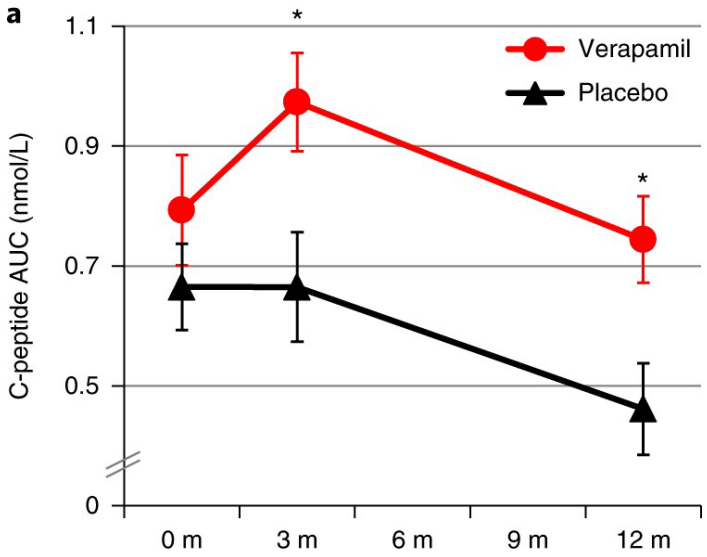
- Thioredoxin-interacting protein (TXNIP) is a cell redox regulator overexpressed in beta cells in T1D
- TXNIP overexpression induces beta cell apoptosis
- TXNIP deficiency promotes endogenous beta cell survival and prevents diabetes in vivo
- Verapamil downregulates TXNIP expression, promotes beta cells survival in vitro and reverses diabetes onset in vivo (B6, ob/ob models)

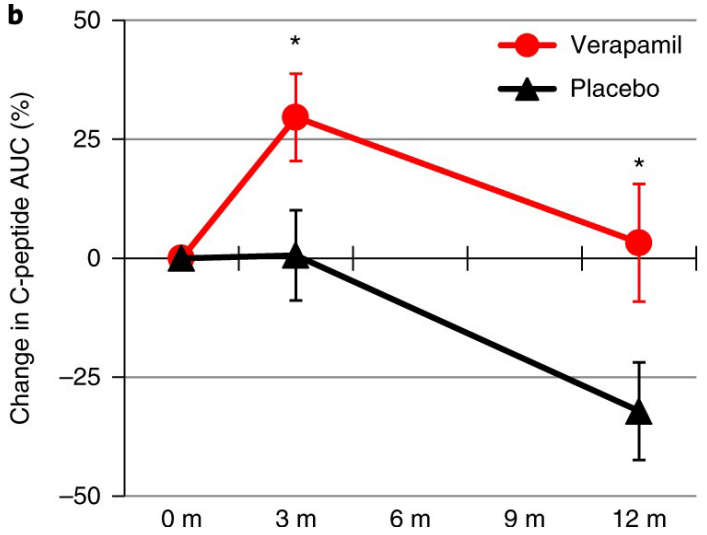
Ovalle F, et al. Nat Med 2018
Lam T, Nat Med 2018
Xu G et al., Diabetes 2012
Chen J et al. FASEB J 2008
Zhou, et al. Nat Immunol 2010

Verapamil preserved beta cells function in new-onset T1D

A phase 2 clinical trial with verapamil added to standard insulin therapy in patients with recent-onset T1D (n=10 per group) for 12 months demonstrated :

- An improved mixed-meal-stimulated C-peptide AUC at 3 and 12 months
- A reduction in exogenous insulin requirement
- A reduction in hypoglycemic events





Ovalle F, et al. Nat Med 2018

Blocking the tyrosin kinase signal with Imatinib in T1D

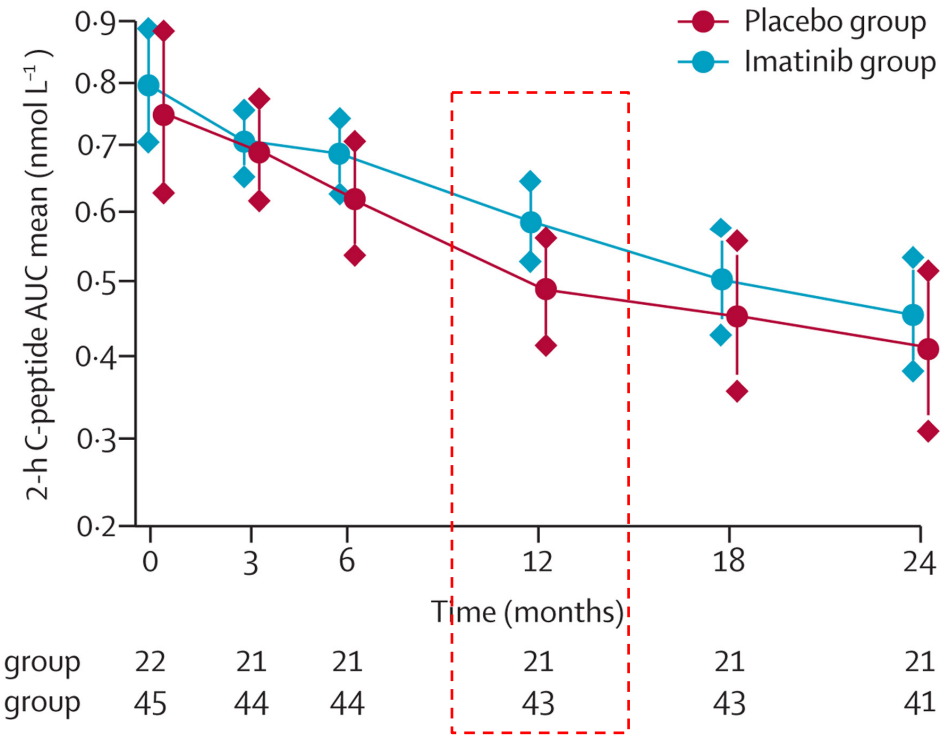
- Tyrosine kinases are enzymes responsible for the activation of signal transduction cascades.
- Inhibitors of Tyrosine kinases have anticancer effects.
- Imatinib, a tyrosine kinase inhibitor, has been successfully employed in chronic leukemia.
- In beta cells imatinib showed 3 major effects:
  - counteracts high endoplasmic reticulum stress
  - reduces apoptosis.
  - increases glucose-stimulated insulin secretion and insulin sensitivity
- Imatinib prevented and induced remission of diabetes in vivo in the NOD mouse model

Hagerkvist R et al. FASEB J 2007
Louvet C et al. PNAS 2008
Gitelman SE et al. Lanced Diabetes Endocrinol 2021

Imatinib improves beta-cell glucose sensitivity in new-onset T1D

A phase 2 clinical trial with imatinib added to standard insulin therapy in patients with recent-onset T1D (22 vs. 45) for 12 months demonstrated:

- An improved mixed-meal-stimulated C-peptide AUC at 3 and 12 months but not at 24 months
- No significant differences in HbA1C, hypogycemic events, exogenous insulin requirement
- Improvement of beta cell senistivity
- High percentage of adverse events



Gitelman SE et al. Lanced Diabetes Endocrinol 2021
Skyler AJ Lanced Diabetes Endocrinol 2021

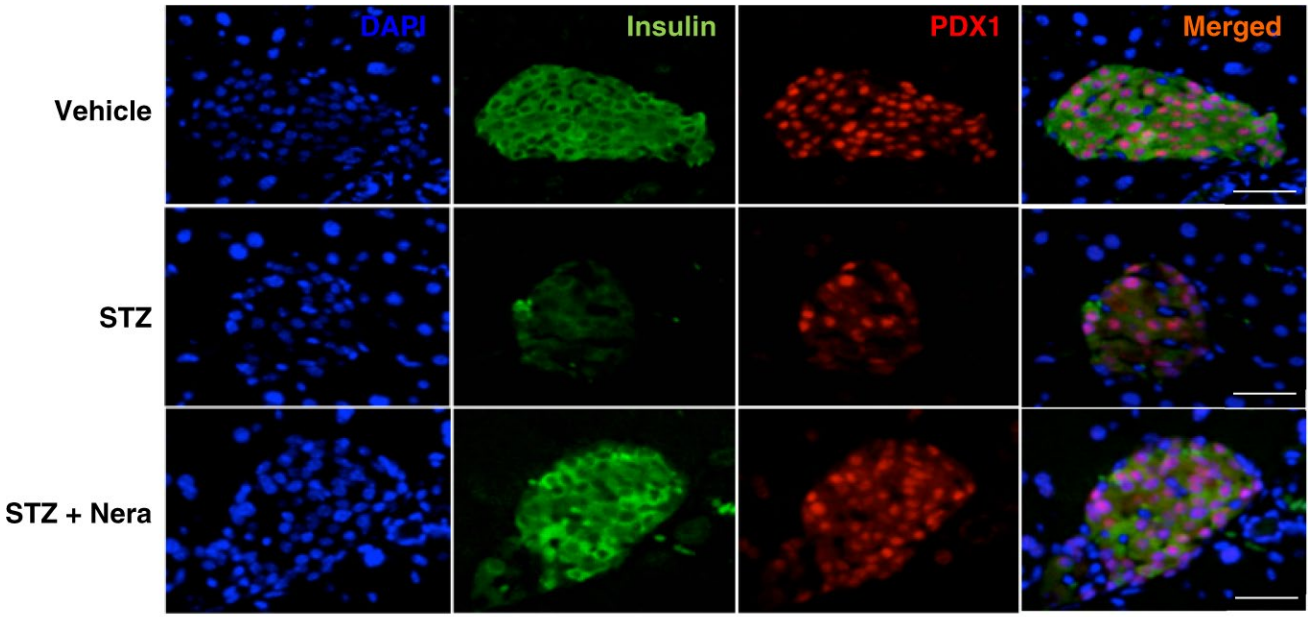
Beta cells protection: other strategies

- Pramlintide (analog of amylin co-secreted with insulin) improves glucose metabolism
- GLP1R agonists protects beta cells from damage, reduce glucagon secretion and preserve insulin sensitivity
- Glucagon receptor antagonists counteract glucagon increased release and normalize blood glucose
- Studies on beta cell protective effects are ongoing for other antidiabetic drugs (SGLT inhibitors, DPP4 inhibitors…)

Wang et al. PNAS 2015
Drucker DJ Cell Metabol 2018

Blocking beta cell death with Neratinib

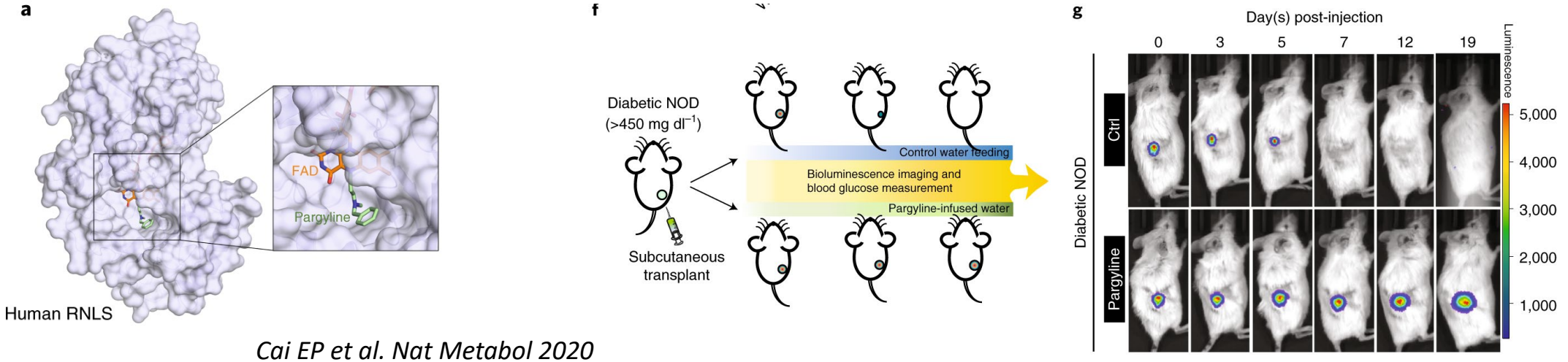
- MST1 is a transcription factor that mediates beta cell death in vitro.
- MST1 deficiency restores functional β-cells and normoglycemia in vitro and vivo.
- Neratinib, an FDA-approved drug targeting HER2/EGFR dual kinases, is a potent MST1 inhibitor.
- Neratinib attenuates hyperglycemia and improves β-cell function, survival and β-cell mass in diabetic in vivo models.



Ardestani A et al Nat Med 2014
Ardestani A et al. Diabetologia 2016
Ardestani A et al Nat Commun 2019

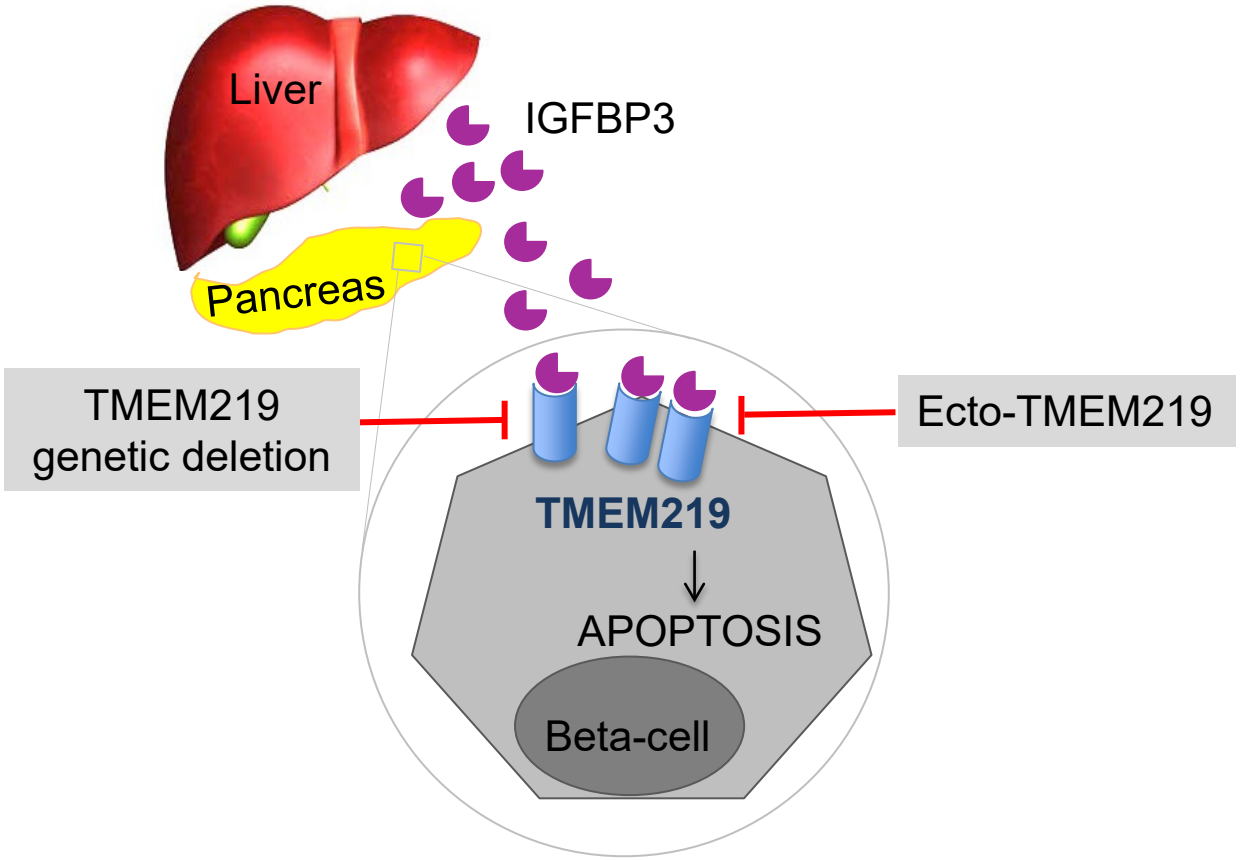
Protecting vulnerable beta cells with the RNLS inhibitor Pargyline

- CRISPR screen for protective mutations identified the T1D-GWAS based candidate RNLS
- RNLS overexpression sensitizes beta cells to ER stress and autoimmunity in vitro and in vivo
- RNLS genetic deletion made beta cells resistant to autoimmune killing in vitro and in vivo
- The FDA-approved drug Pargyline binds RNLS and protects beta cells against autoimmunity
- RNLS deletion/inhibition protects human stem/beta cells against ER stress and immune recognition



Cai EP et al. Nat Metabol 2020
Crunkhorn S Nat Rev Dreug Disc 2020

A new target in beta cells protection: the IGFBP3/TMEM219 axis



D'Addio F et al. Cell Stem Cell 2015
Nguyen KH et al. Endocrinology 2011
Kim MS et al. J Pediatr Endocrinol Metab 2014
Peet A et al. Eur J Endocrinol 2015

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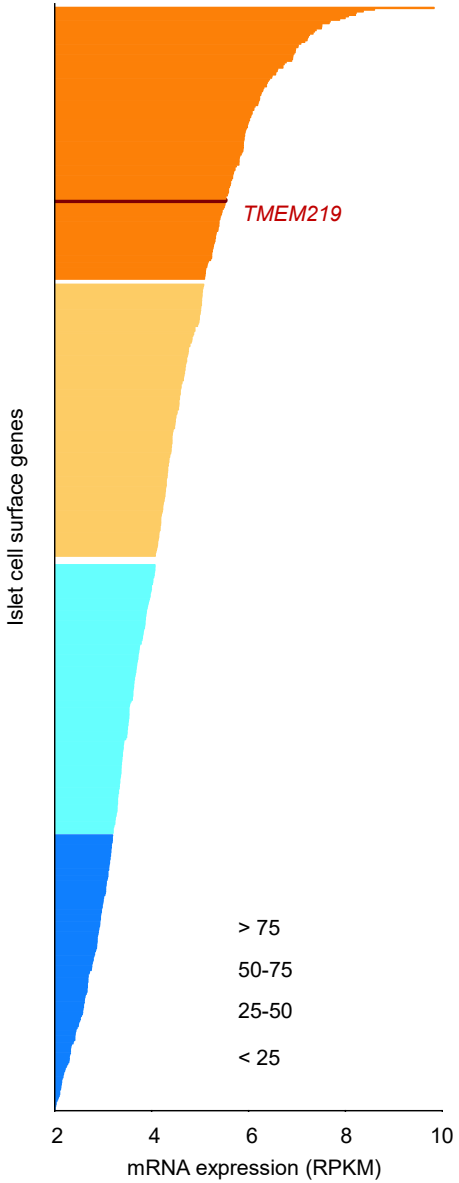
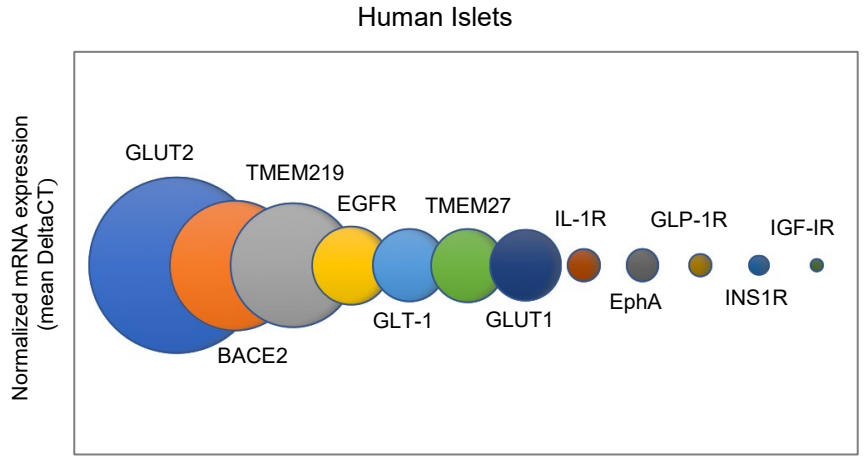
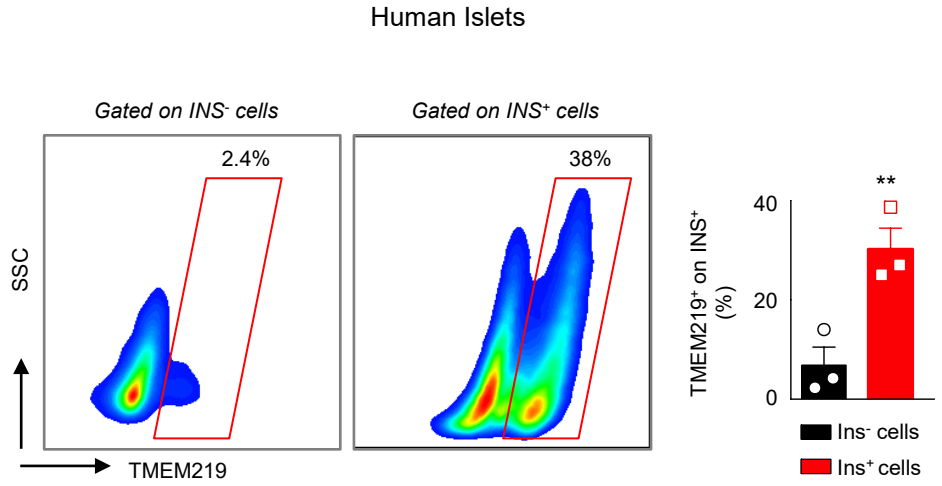
The death receptor TMEM219 is expressed on islet beta cells

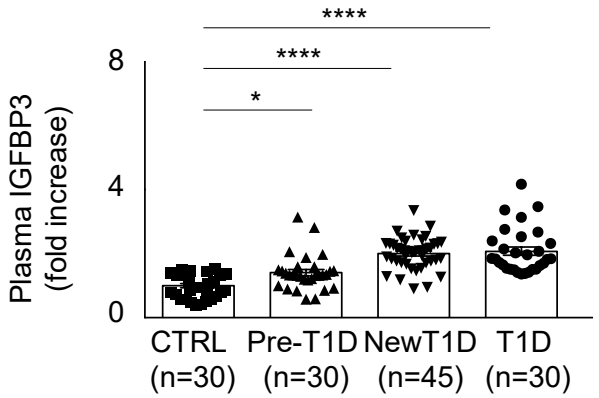


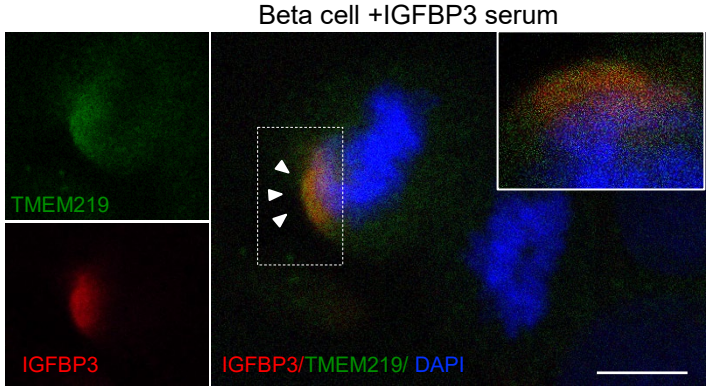


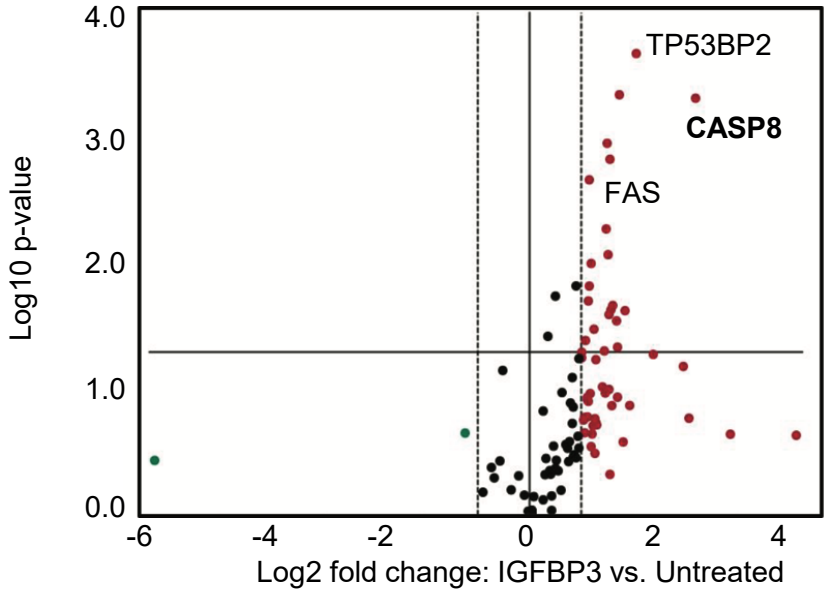


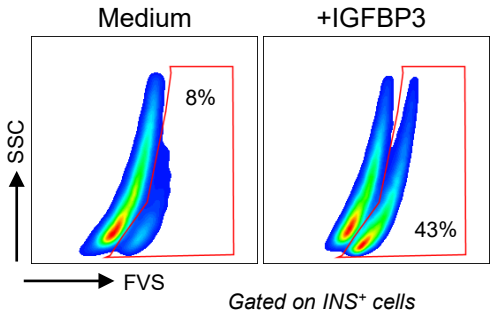
D'Addio F/Fiorina P et al. Nat Commun 2022

The IGFBP3/TMEM219 axis is dysregulated in T1D and mediates beta cell death



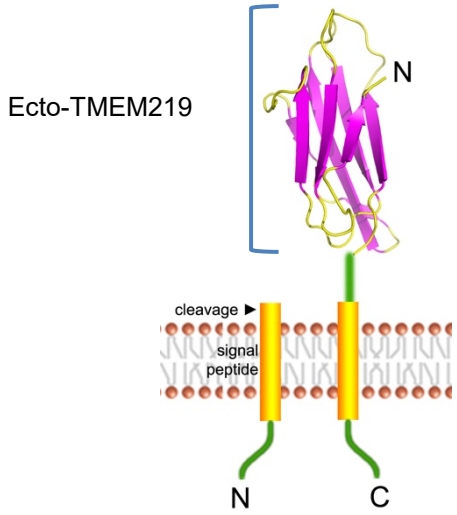


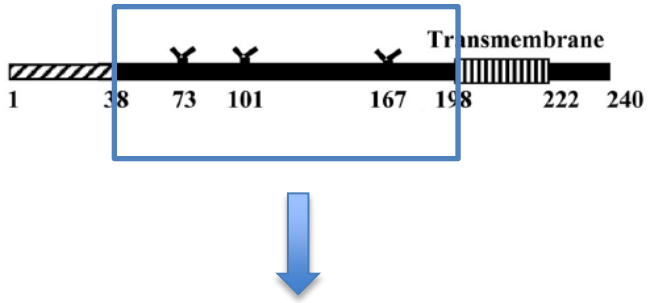




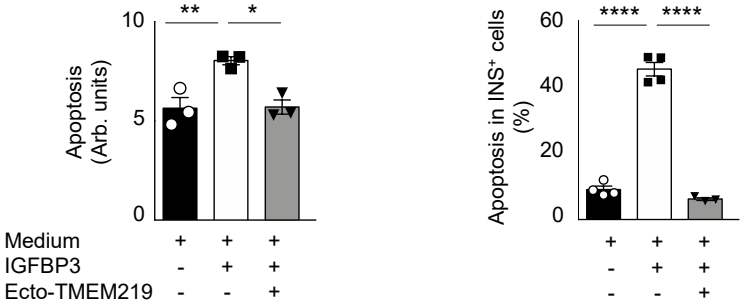
D'Addio F/Fiorina P et al. Nat Commun 2022

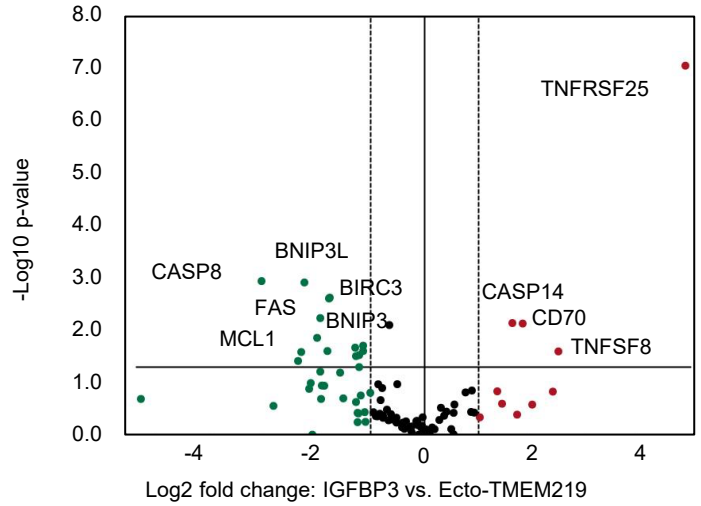
Targeting the TMEM219 deleterious signaling with the newly generated recombinant protein ecto-TMEM219 protects beta cells





Human islets apoptosis





D'Addio F/Fiorina P et al. Nat Commun 2022

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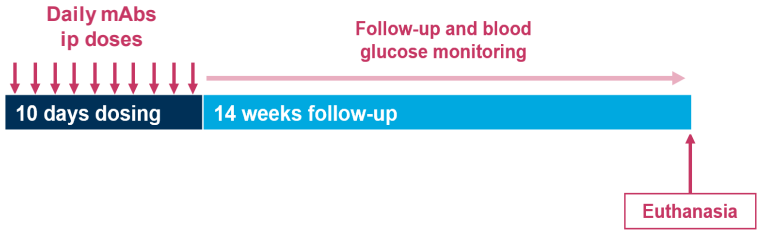
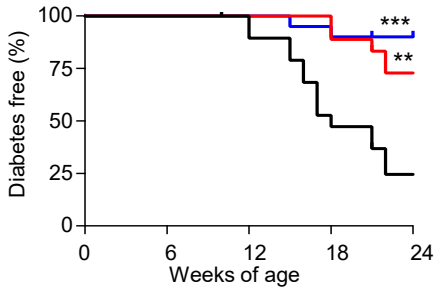
TMEM219 pharmacological targeting: the NOD mouse model

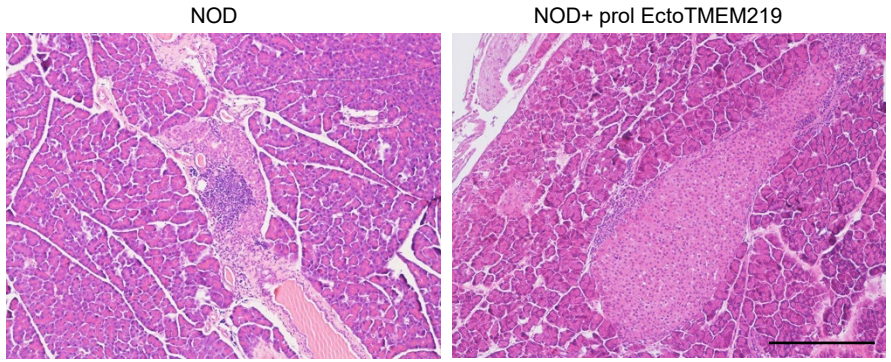
The prevention model



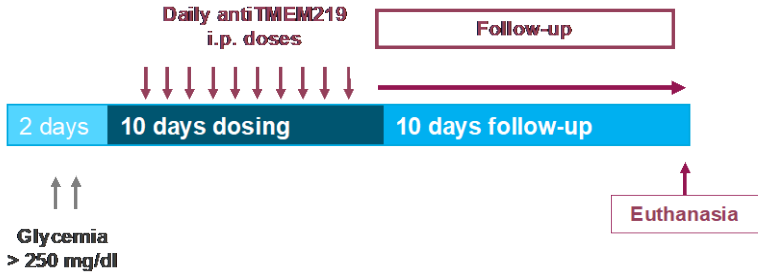
Female NOD
10 weeks of age

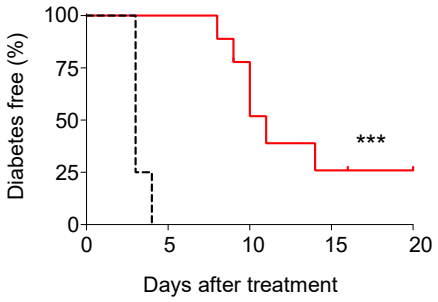


NOD (n=20)
NOD+EctoTMEM219 (n=20)
NOD+prol Ecto-TMEM219 (n=20)

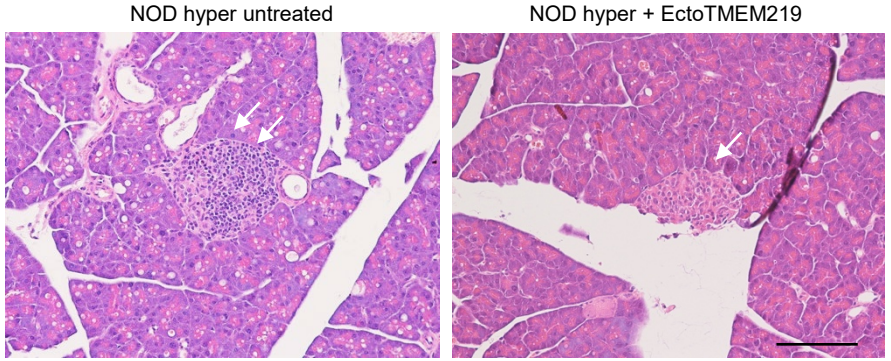


The reversal model





NOD (n=8)
NOD+EctoTMEM219 (n=8)

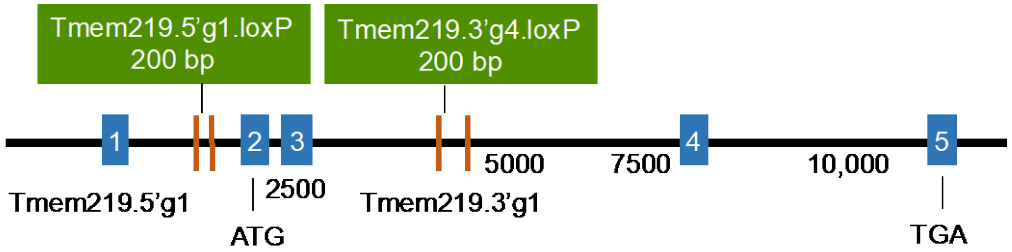


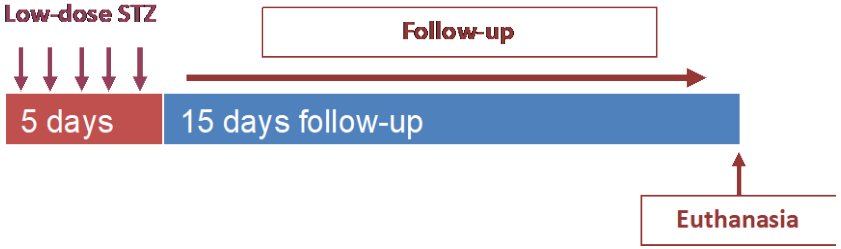
D'Addio F/Fiorina P et al. Nat Commun 2022

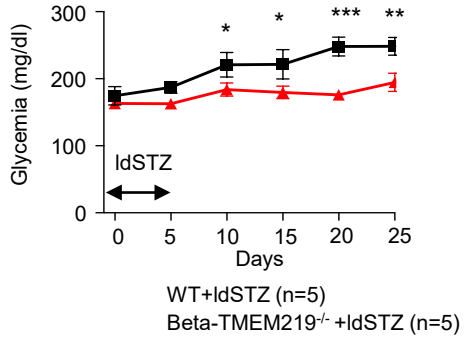
TMEM219 conditional deletion on beta cells

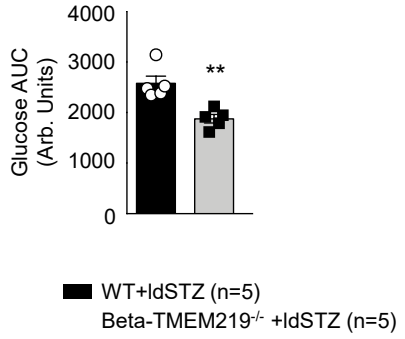
Beta-TMEM219$^{-/-}$

Beta cells do not express TMEM219



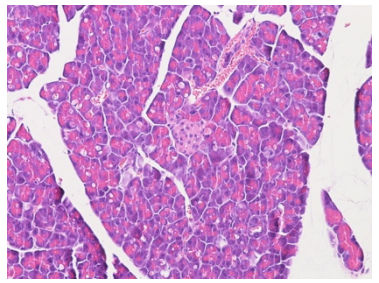




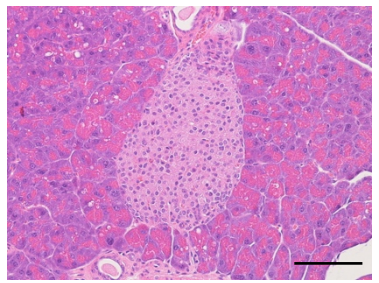


*p<0.05
**p<0.01
***p<0.001

WT+ldSTZ



Beta-TMEM219$^{-/-}$ +ldSTZ



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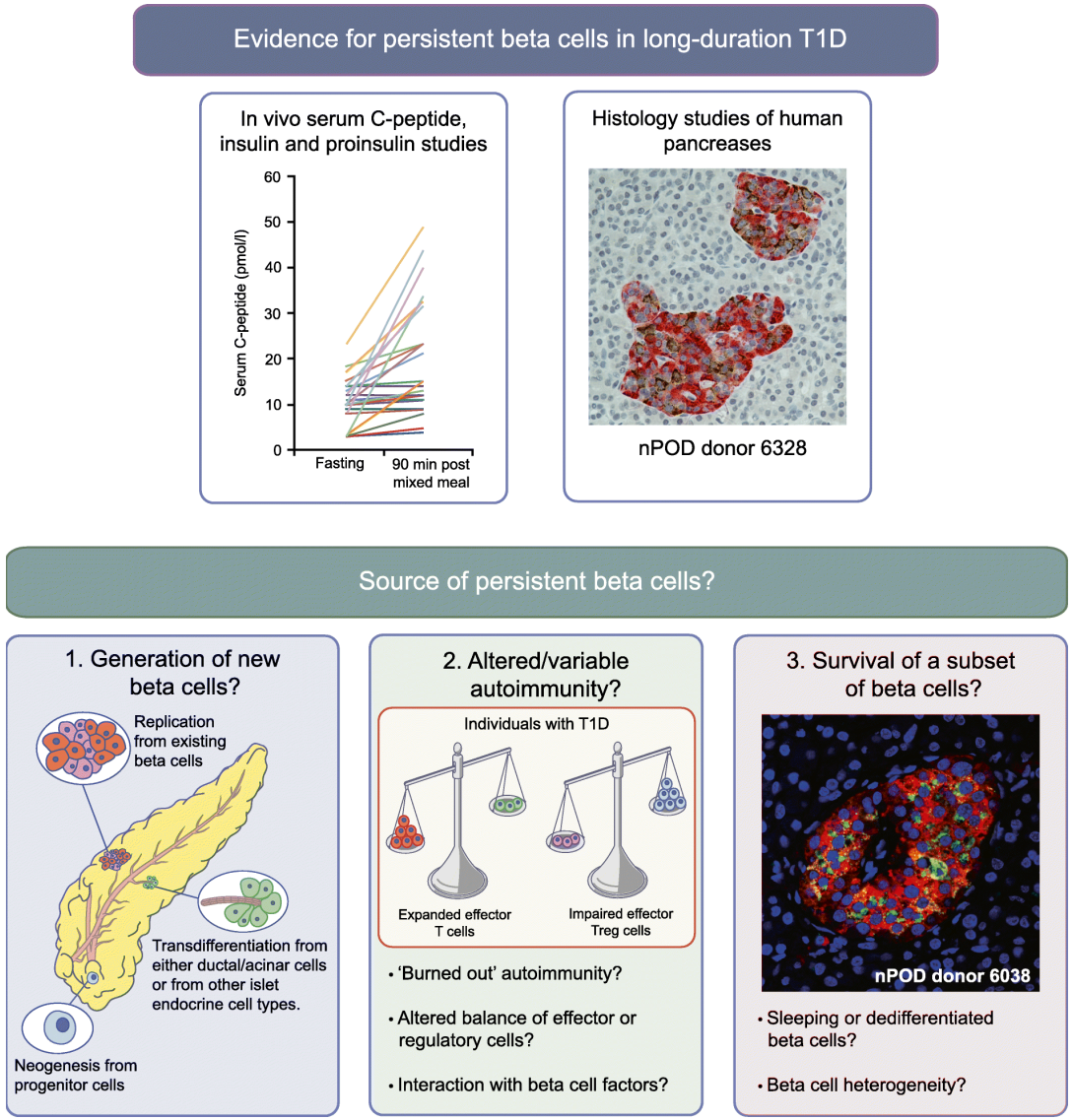
Beta cells in T1D: sleeping or dead?



- Certain subpopulations of beta cells are more resistant to immune destruction.
- A reduction in the intensity of autoimmunity may occur over time.
- New beta cells have the capacity to regrow.
- New beta cells may differentiate from the islet niche.

Can we awake/rejuvenate sleeping beta cells?

Oram RA et al. Diabetologia 2019

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Conclusions

- Beta cell death occurs in T1D and leads to loss of beta cell mass and function
- Beta cells are stressed and more immunogenic in T1D
- Targeting beta cell stressors, vulnerability to immune system and abnormal proapoptotic signaling may prevent beta cell apoptosis and dysfunction
- Strategies directed at prolonging the survival of the beta cell may be successful in delaying or even preventing the onset of T1D.
- A pool of residual beta cells resistant to autoimmunity persists in long-term T1D and may represent a future therapeutic target

Acknowledgements

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Prof. Gian Vincenzo Zuccotti

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www.casadiabete.it

FONDAZIONE ROMEO ED ENRICA INVERNIZZI

UNIVERSITÀ DEGLI STUDI DI MILANO

EFSD European Foundation for the Study of Diabetes

SID Società Italiana di Diabetologia Regione Lombardia

Sistema Socio Sanitario Regione Lombardia ASST Fatebenefratelli Sacco