

Progress Toward Prevention and Reversal of Type 1 Diabetes

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Disclosures

DSMB for Investigator-initiated trial:

Targeting Type 1 Diabetes Using POLyamines (TADPOL)—
Difluoromethylornithine (DFMO)

Insulet Omnipod 5 Advisory Board

Learning Objectives

- >> Identify the many types of T1D prevention and reversal therapies.
- >> Recognize the hurdles to T1D prevention and reversal.
- >> What may be right for me and my family?

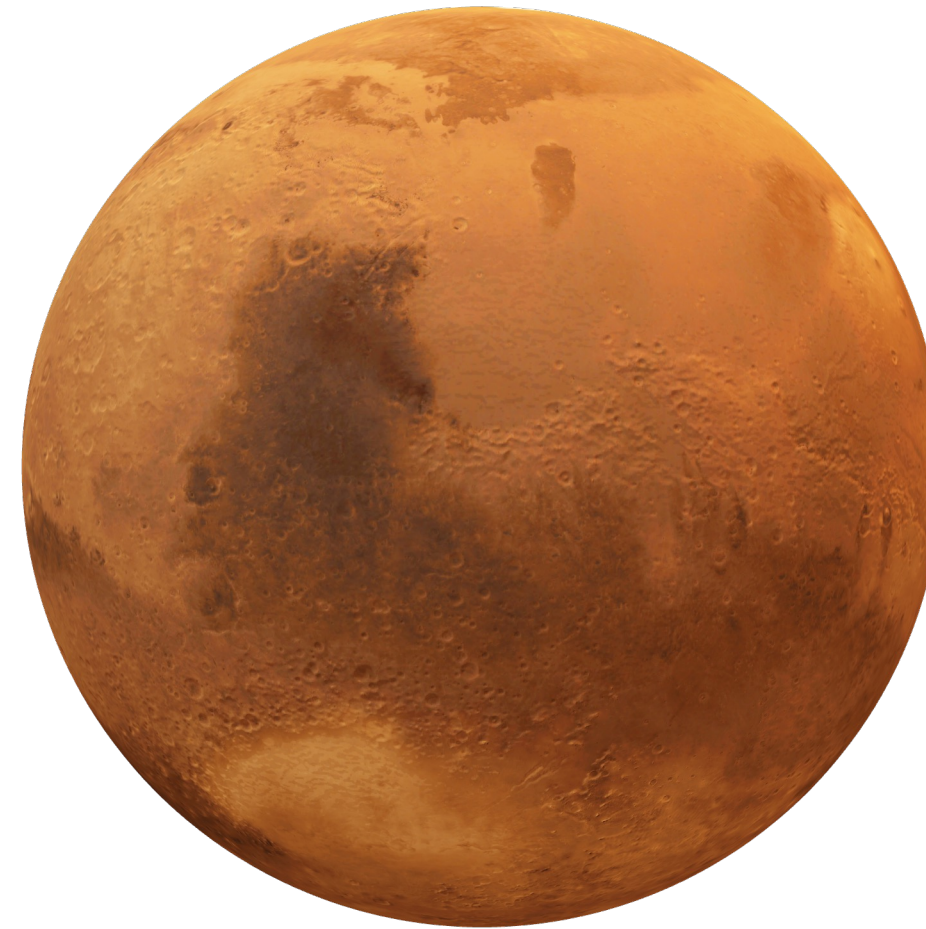




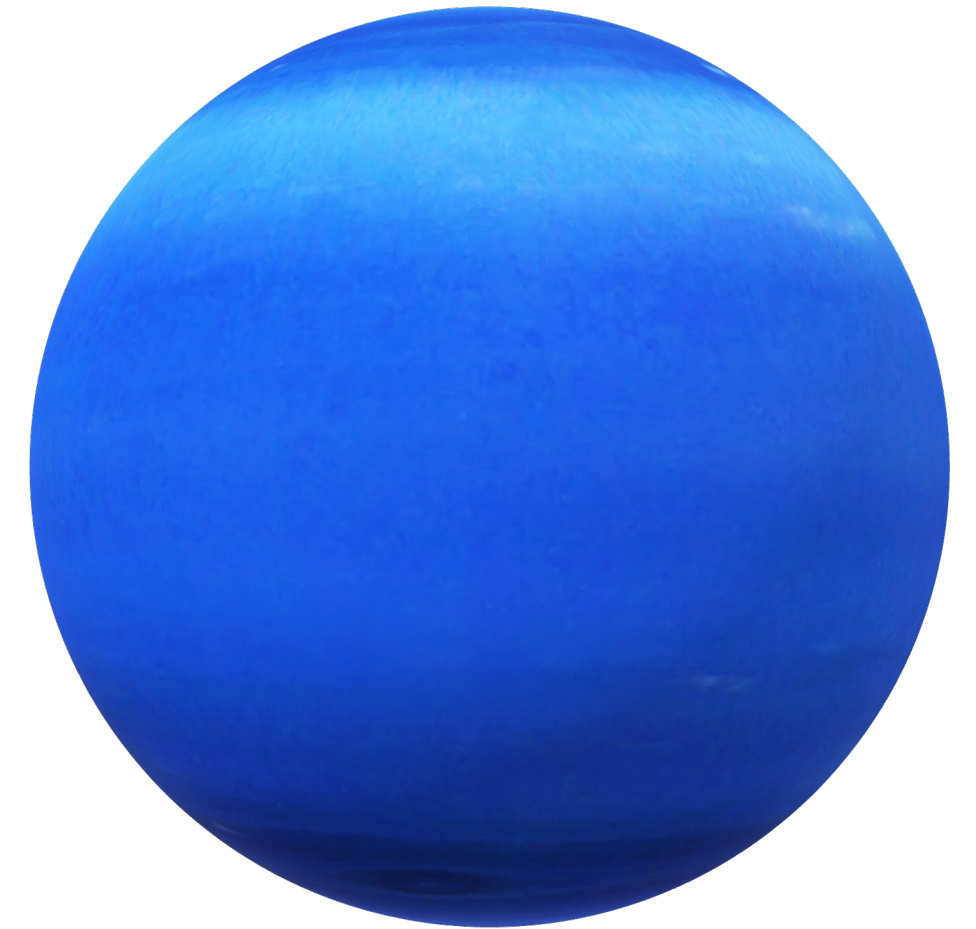
Is There Anything I Can Do?!



Technology

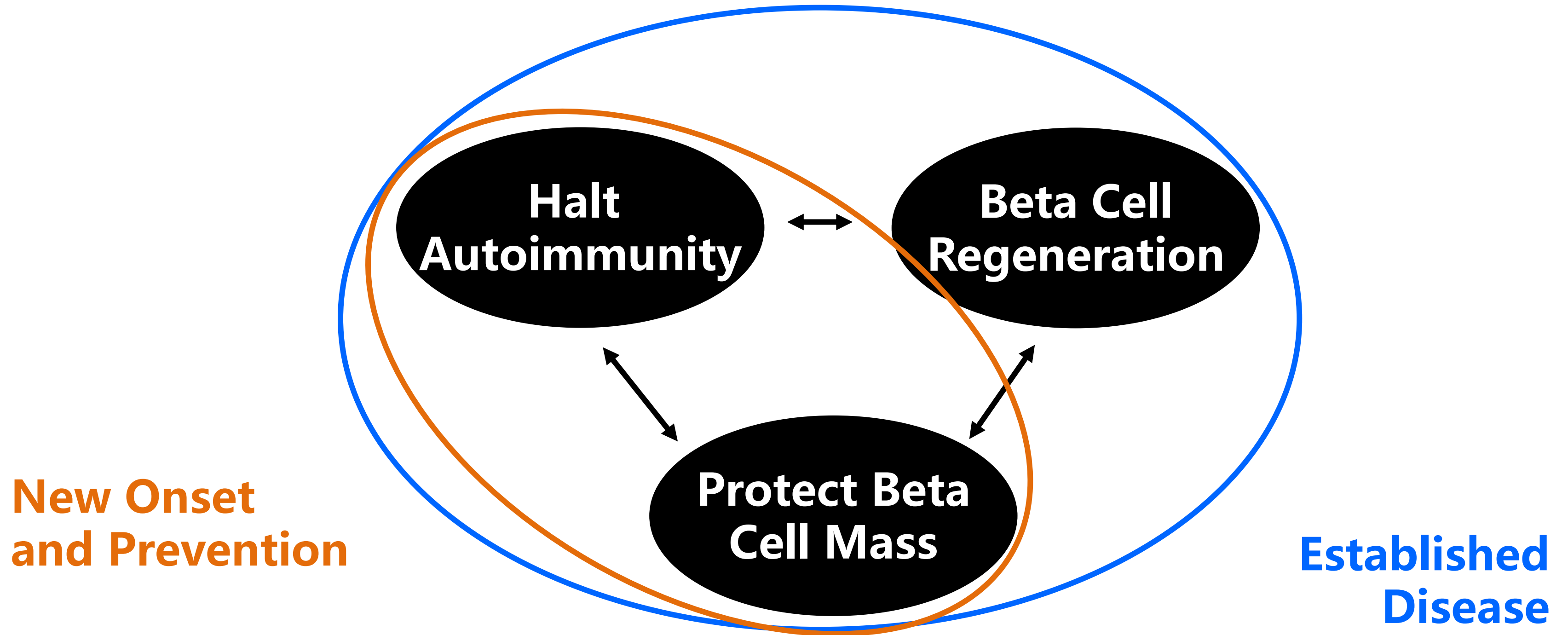


**Immune & Beta Cell
Protective Therapies**



**Beta Cell
Replacement**

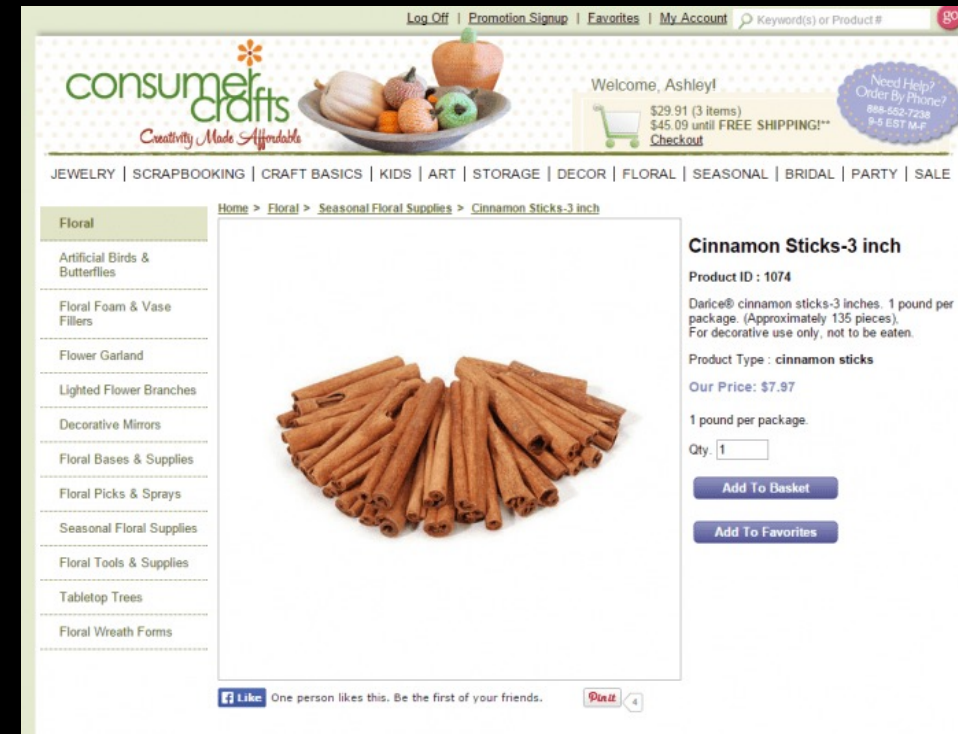
Keys to T1D Prevention and Reversal



"T1D Prevention & Reversal"



What Society Thinks It Means



What the Internet Thinks It Means



What Insurance Thinks It Means



What Loved Ones Think It Means



What PWD Think It Means



What Endos Think It Means

The Problem

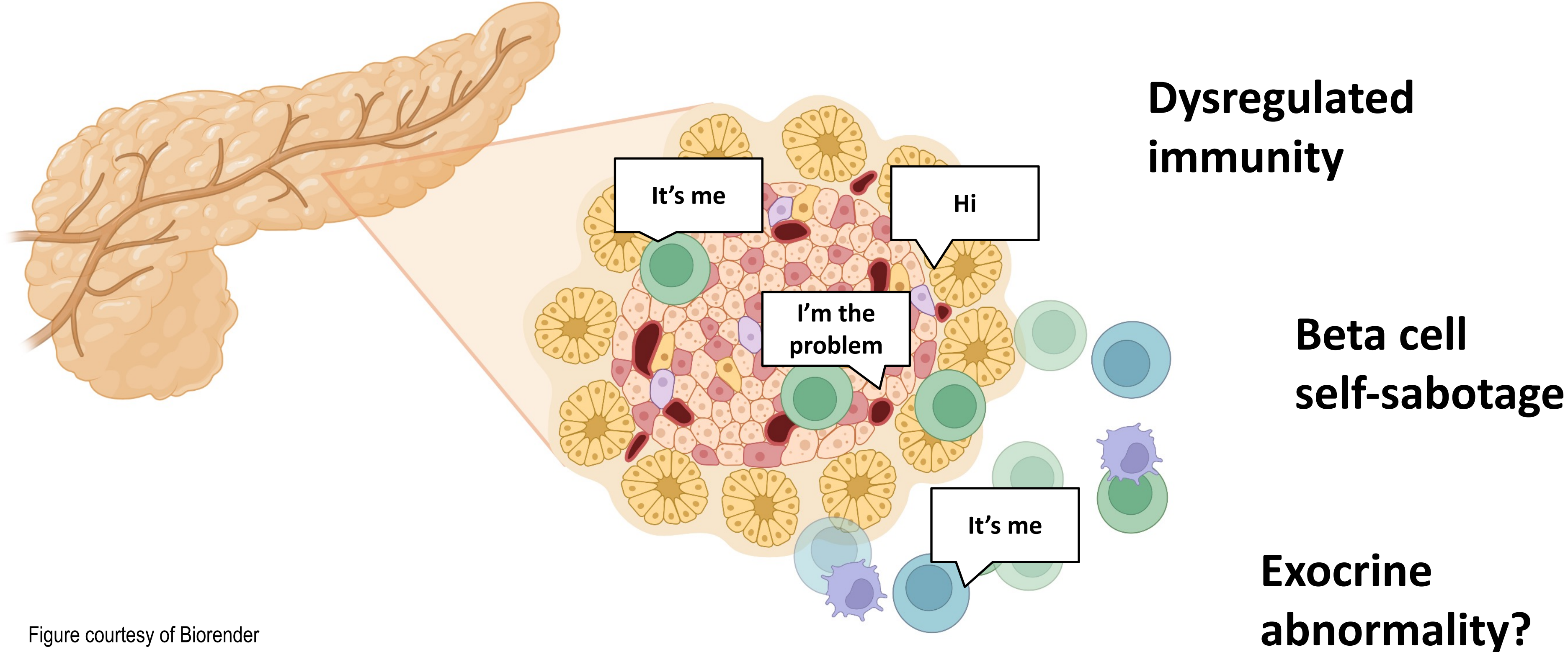


Figure courtesy of Biorender
Lyrics courtesy of T. Swift 2022

The Endocrine Pancreas in T1D

Immune Invasion & Beta Cell Dysfunction

INS/GCG/CD3

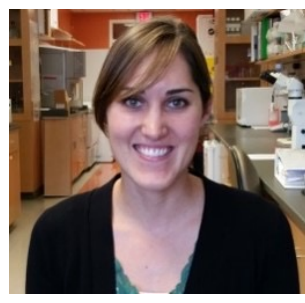
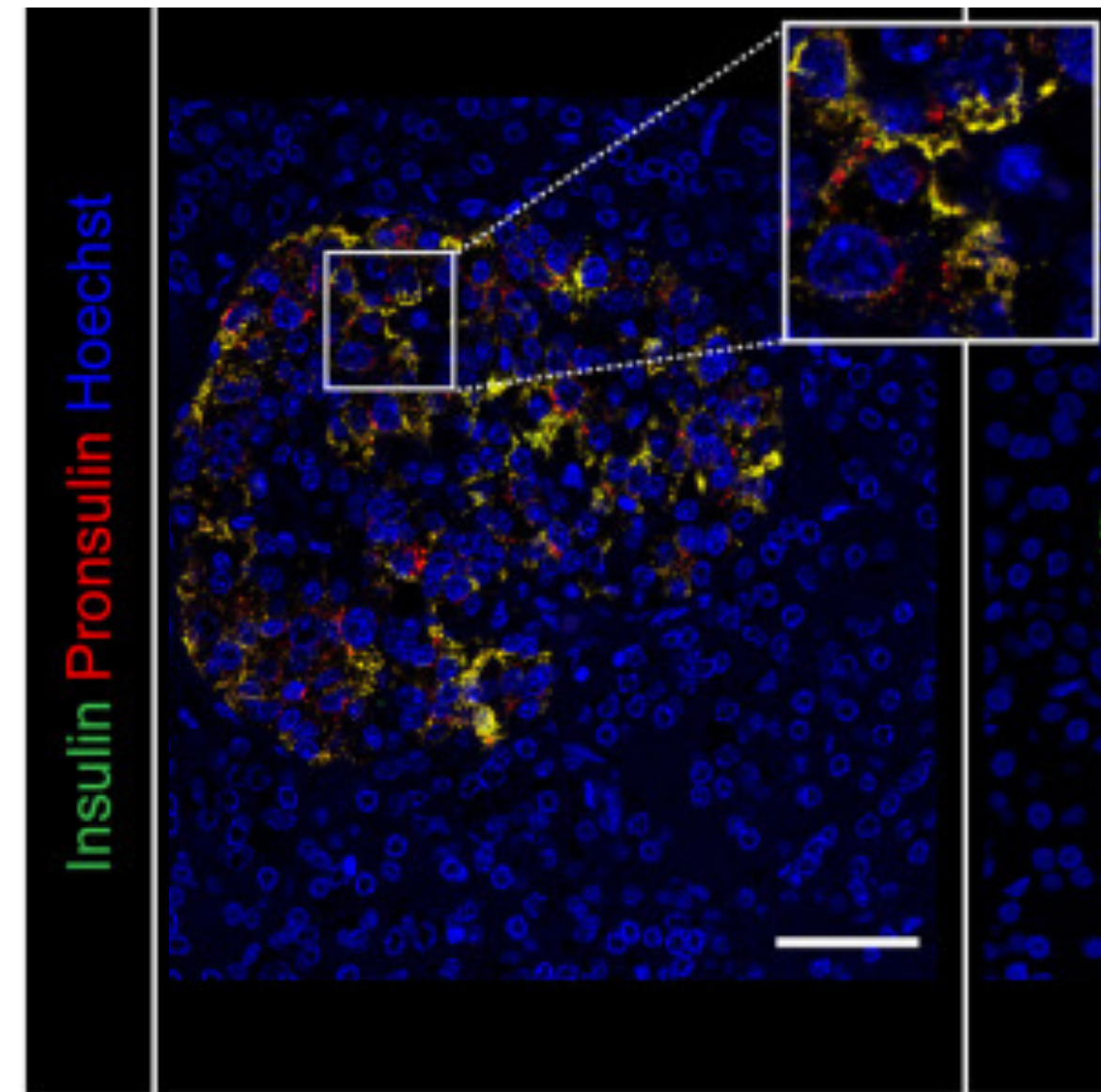
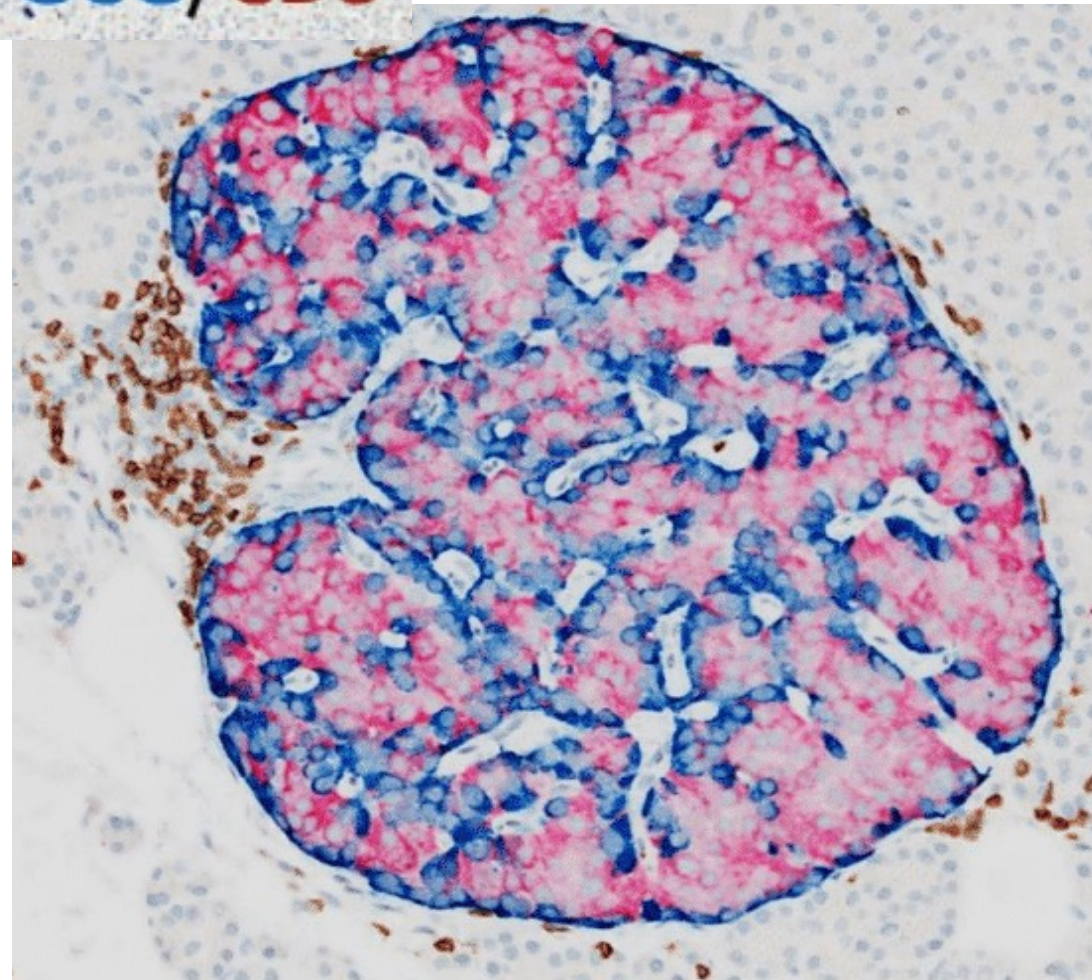


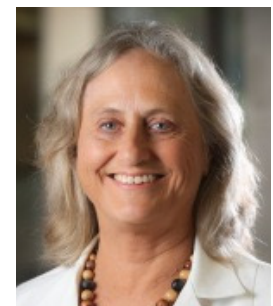
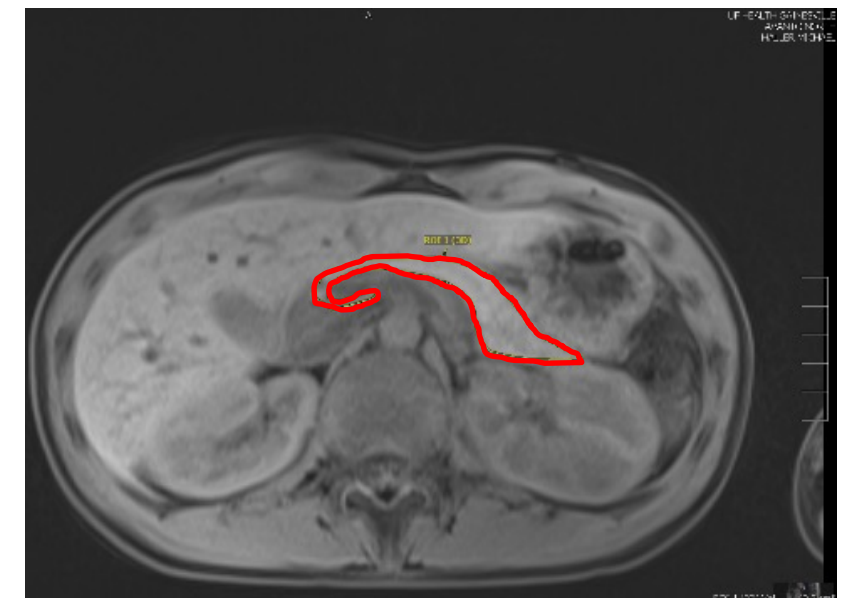
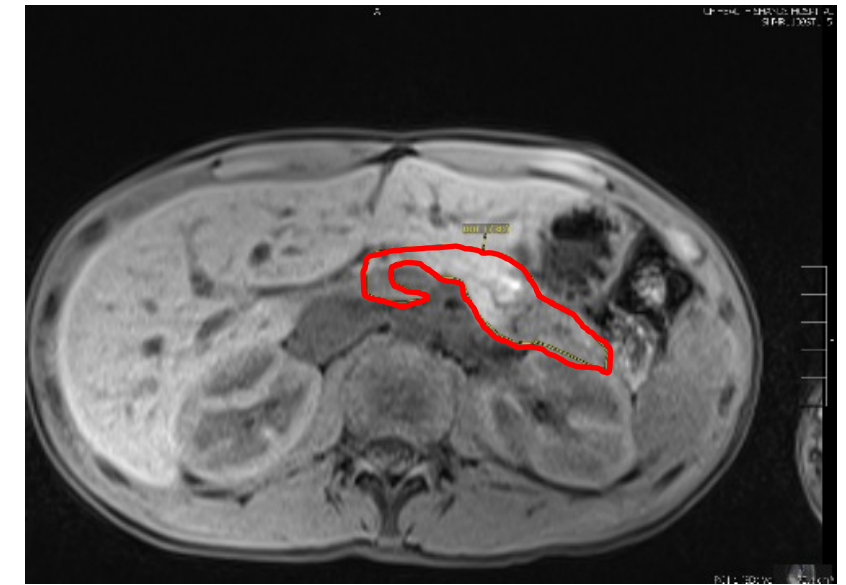
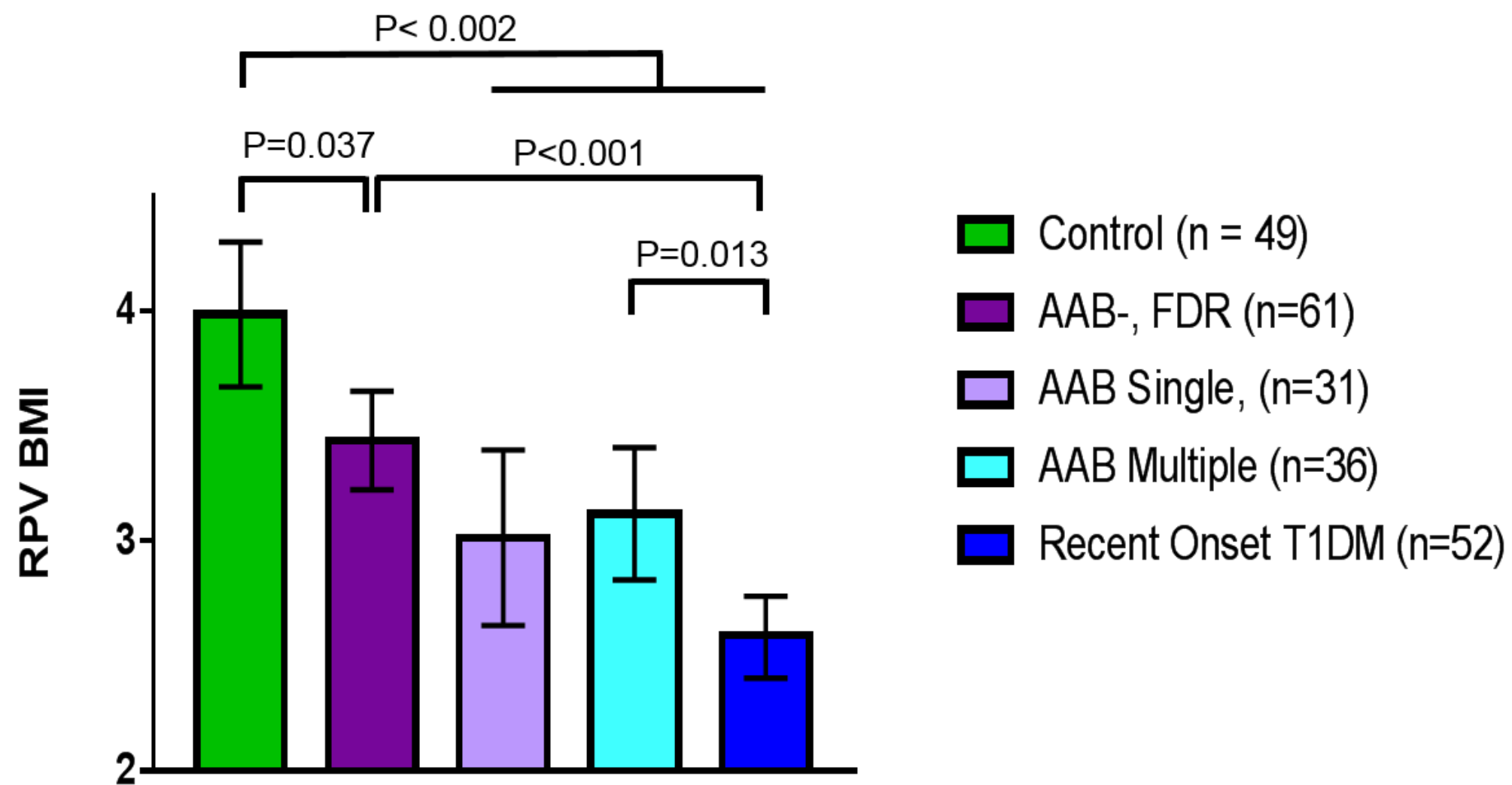
Image courtesy of Irina Kusmartseva PhD
& Maria Beery MS at UF

Rodriguez-Calvo et al Diabetes 2021

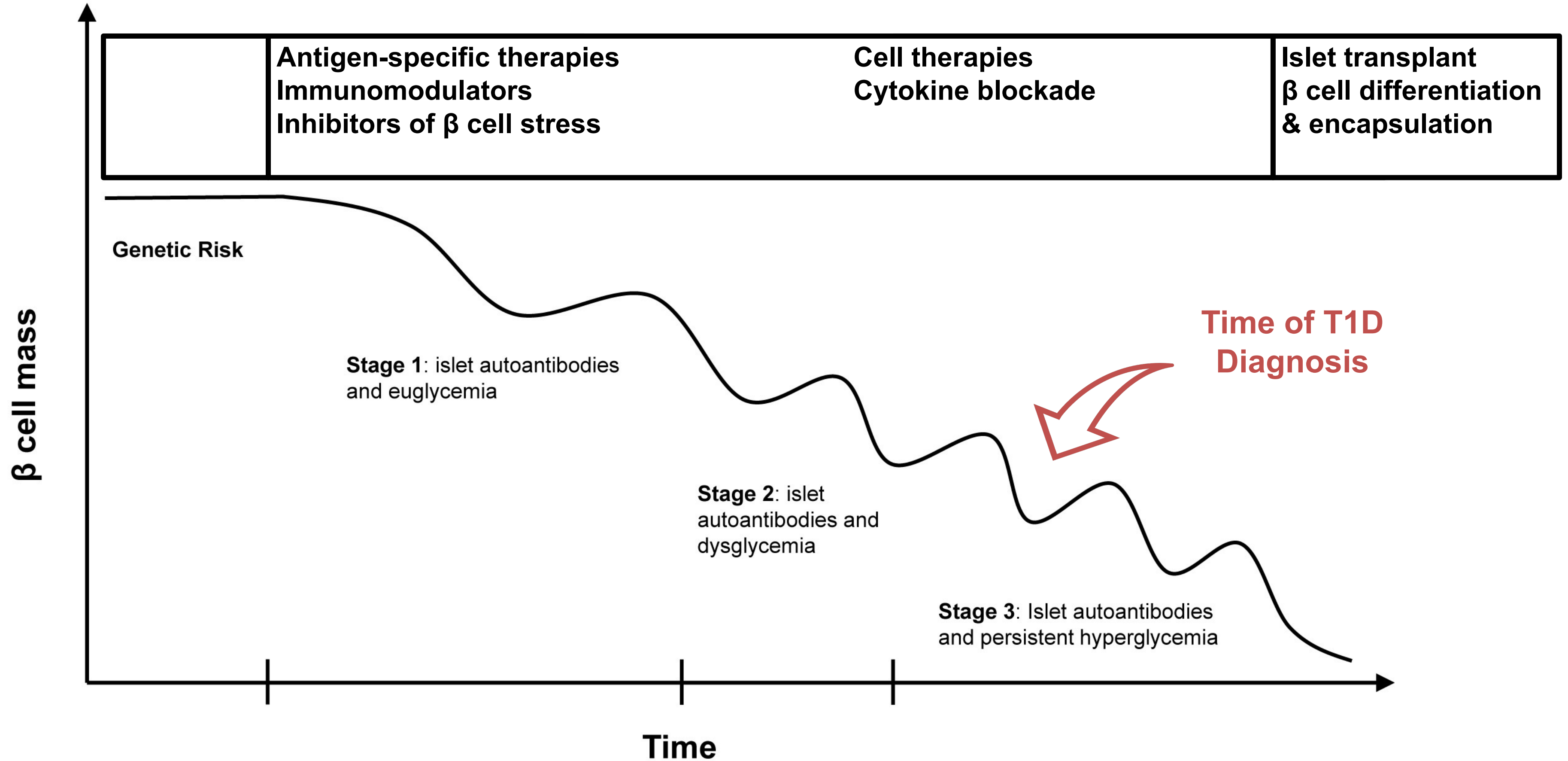
The Exocrine Pancreas in T1D

Loss of Pancreas Mass

Pancreas is smaller - even in relatives!



Stages of T1D & Intervention Categories





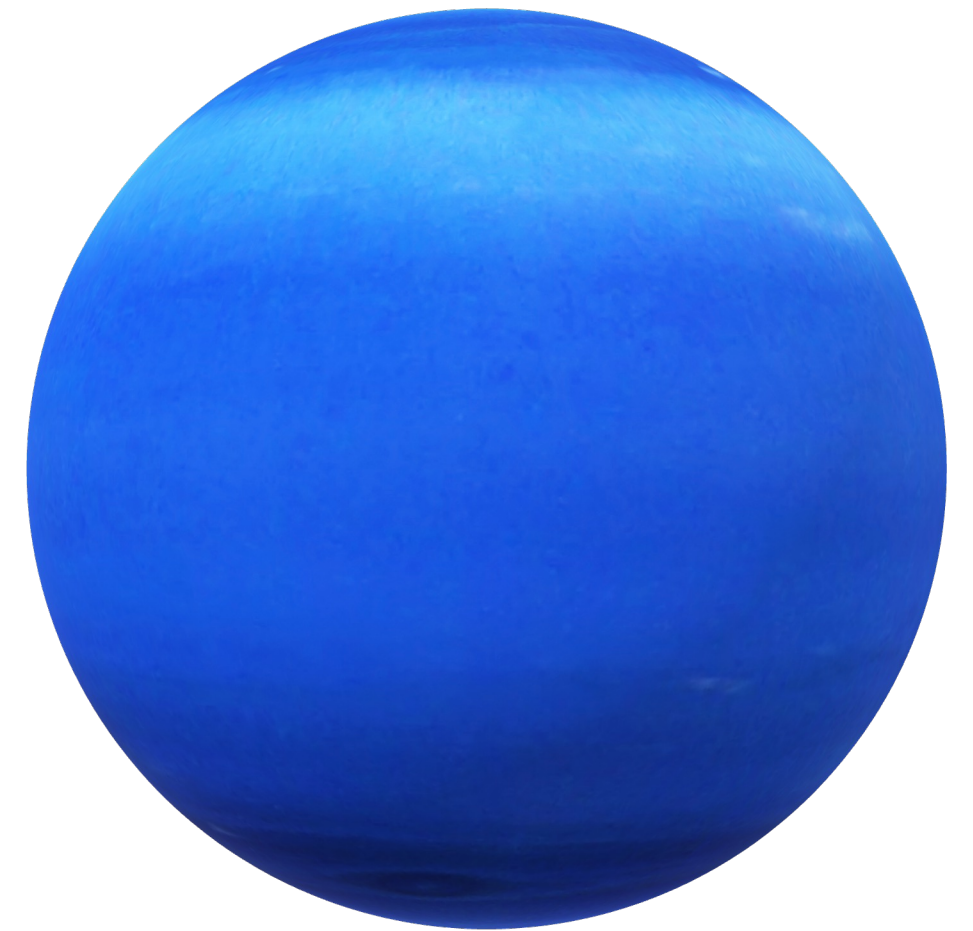
Is There Anything I Can Do?!



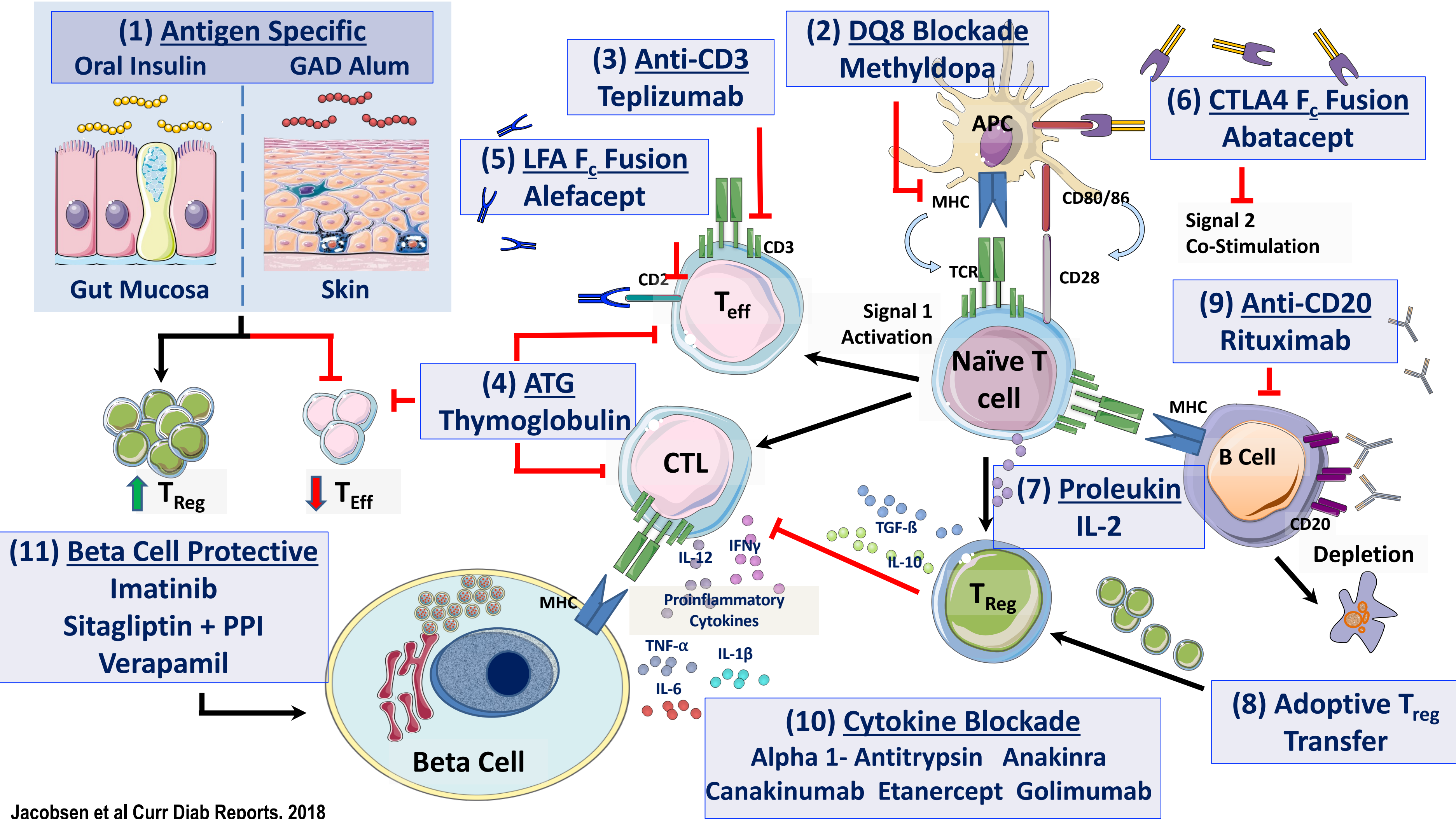
Technology

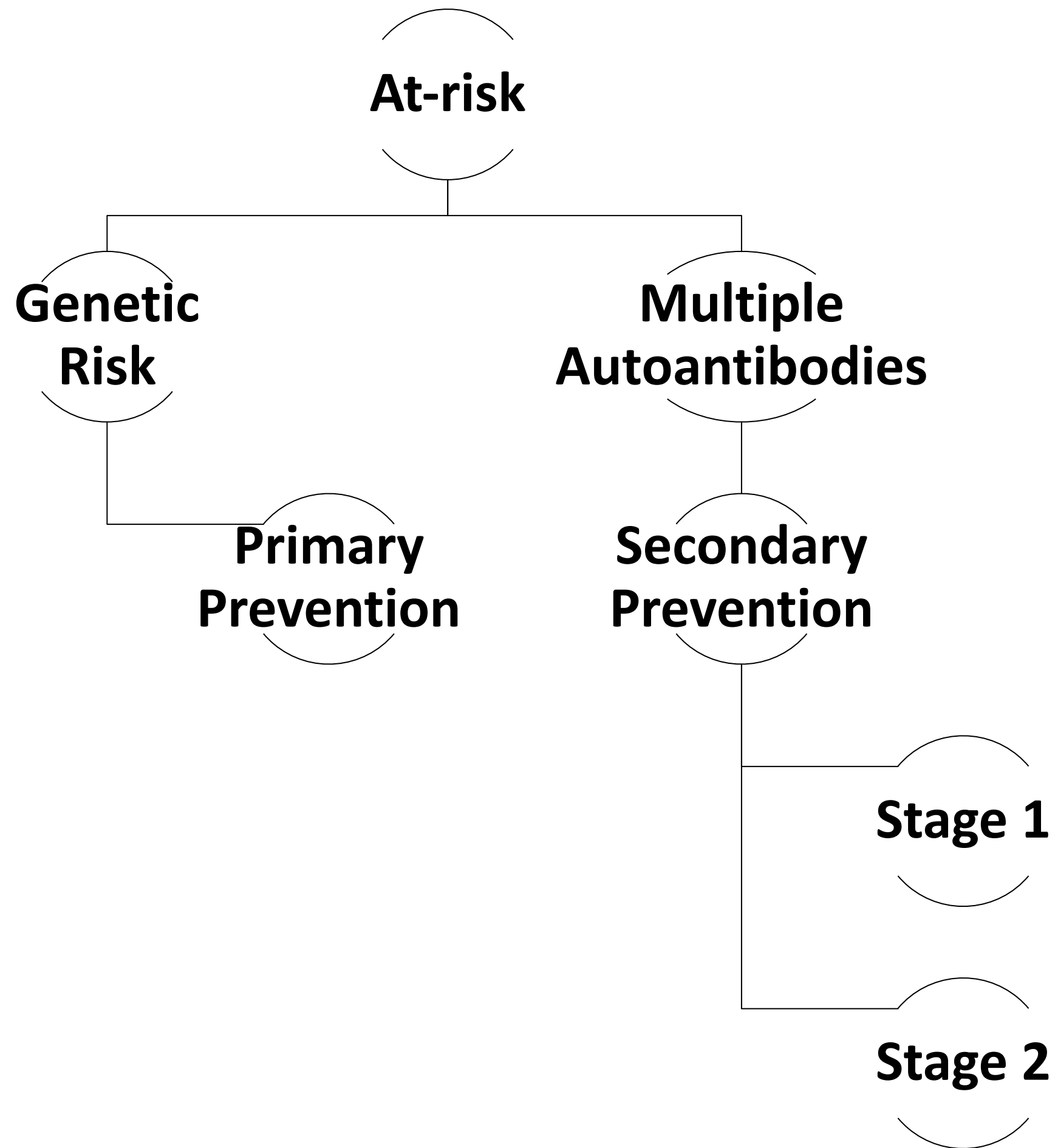


**Immune & Beta Cell
Protective Therapies**

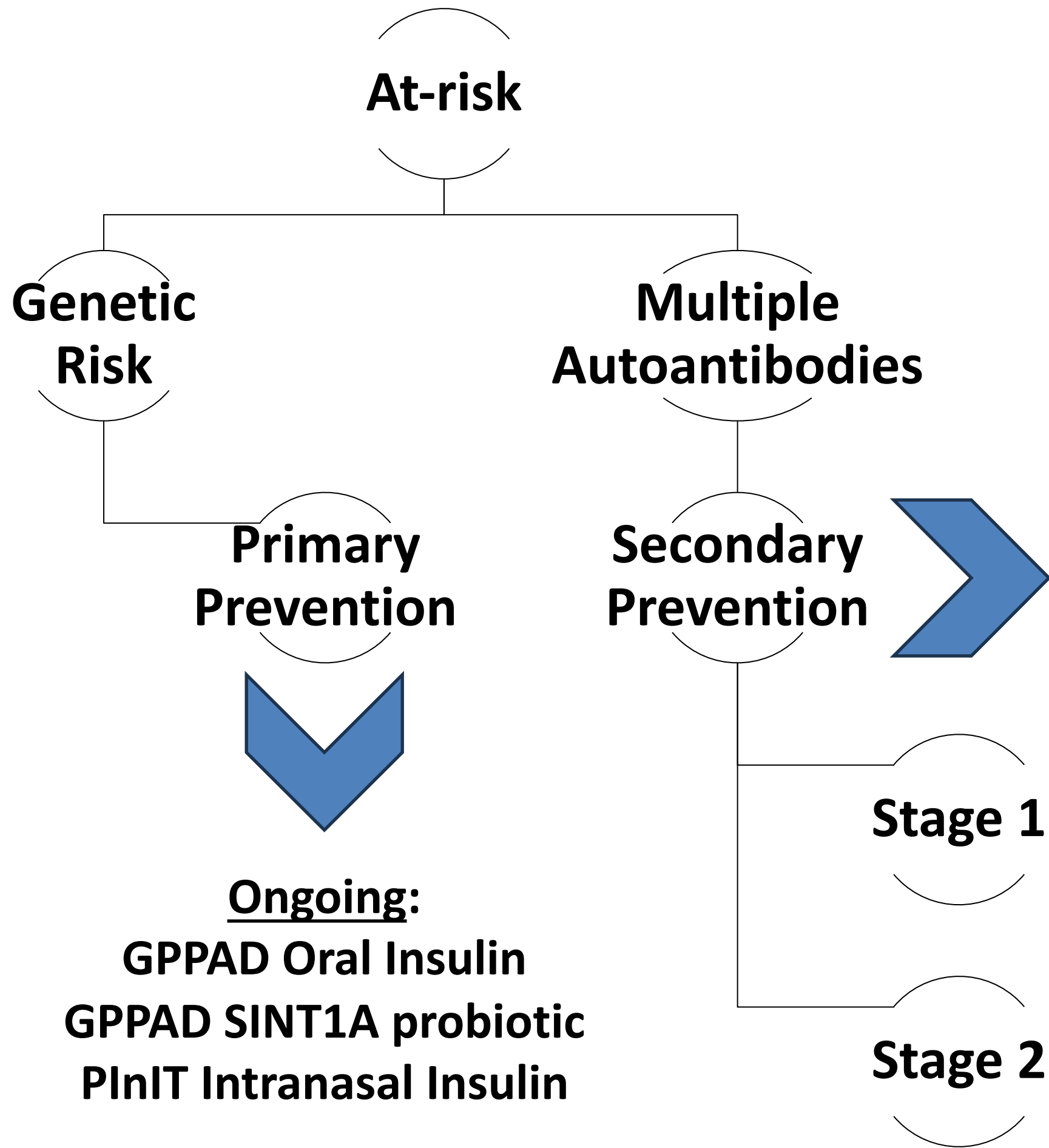


**Beta Cell
Replacement**



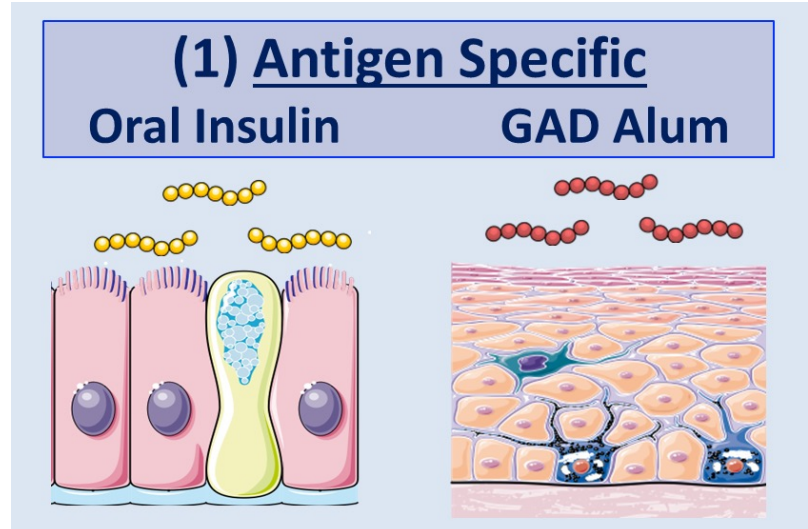


**Prevention
Therapies in
At-Risk**

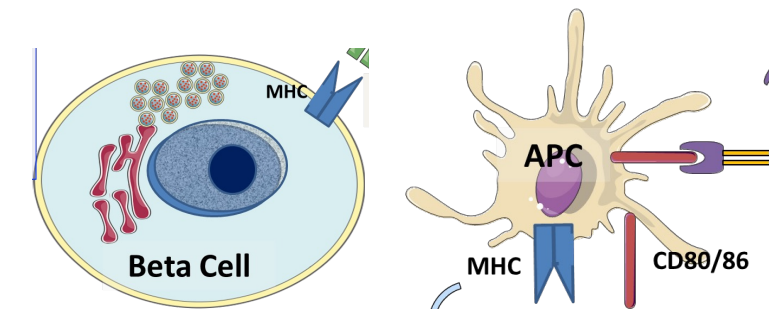


Ongoing:
 GPPAD Oral Insulin
 GPPAD SINT1A probiotic
 PlnIT Intranasal Insulin

Negative:
 IV/SQ, Nasal,
 Oral* Insulin
 GAD-Alum



Hydroxychloroquine
 Abatacept



Positive:
 TrialNet Teplizumab



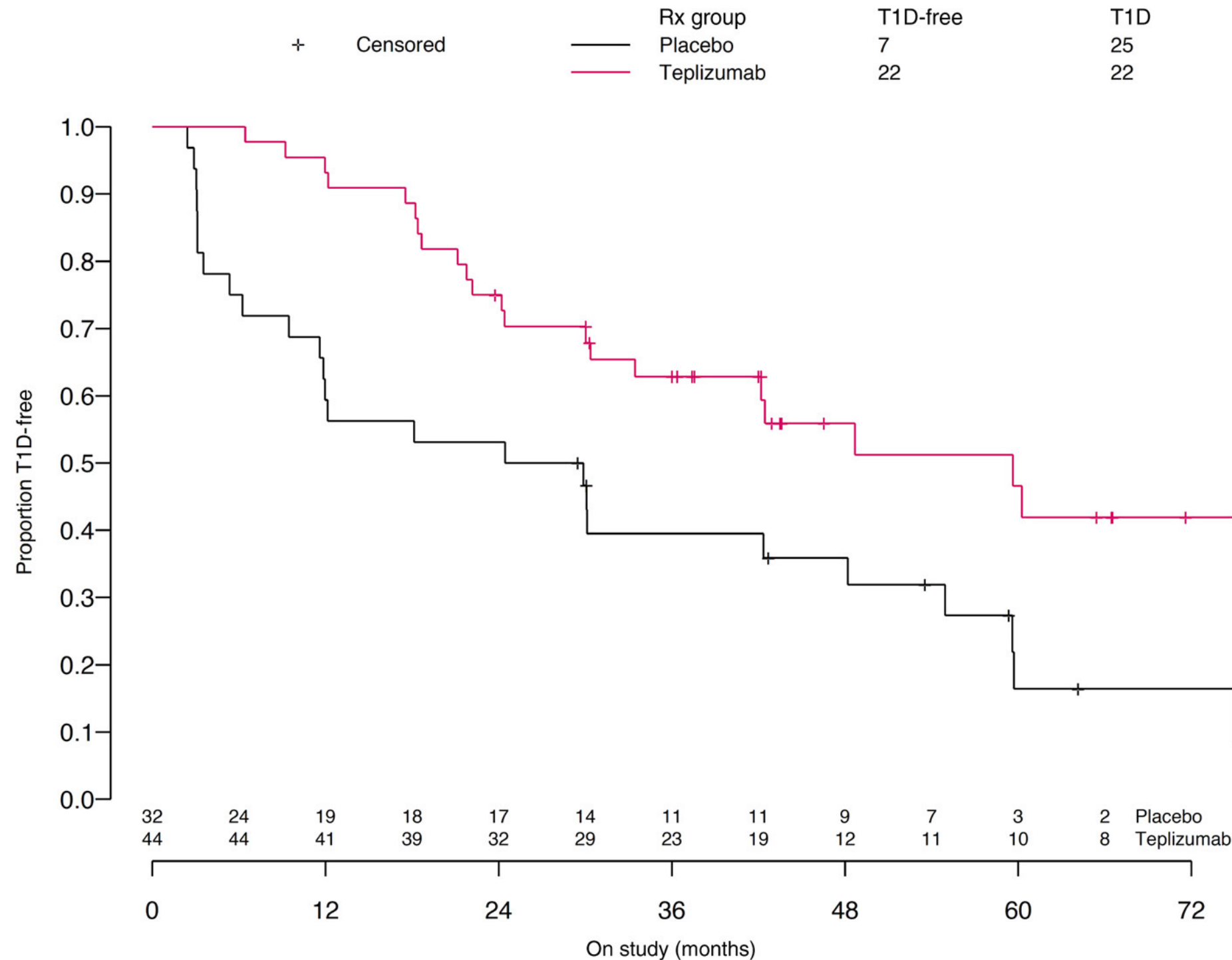
Ongoing:
 TrialNet Low-dose
 Anti-thymocyte
 globulin (ATG)



Fr1da Oral Insulin



Delay ~~Prevent~~ Beta Cell Loss



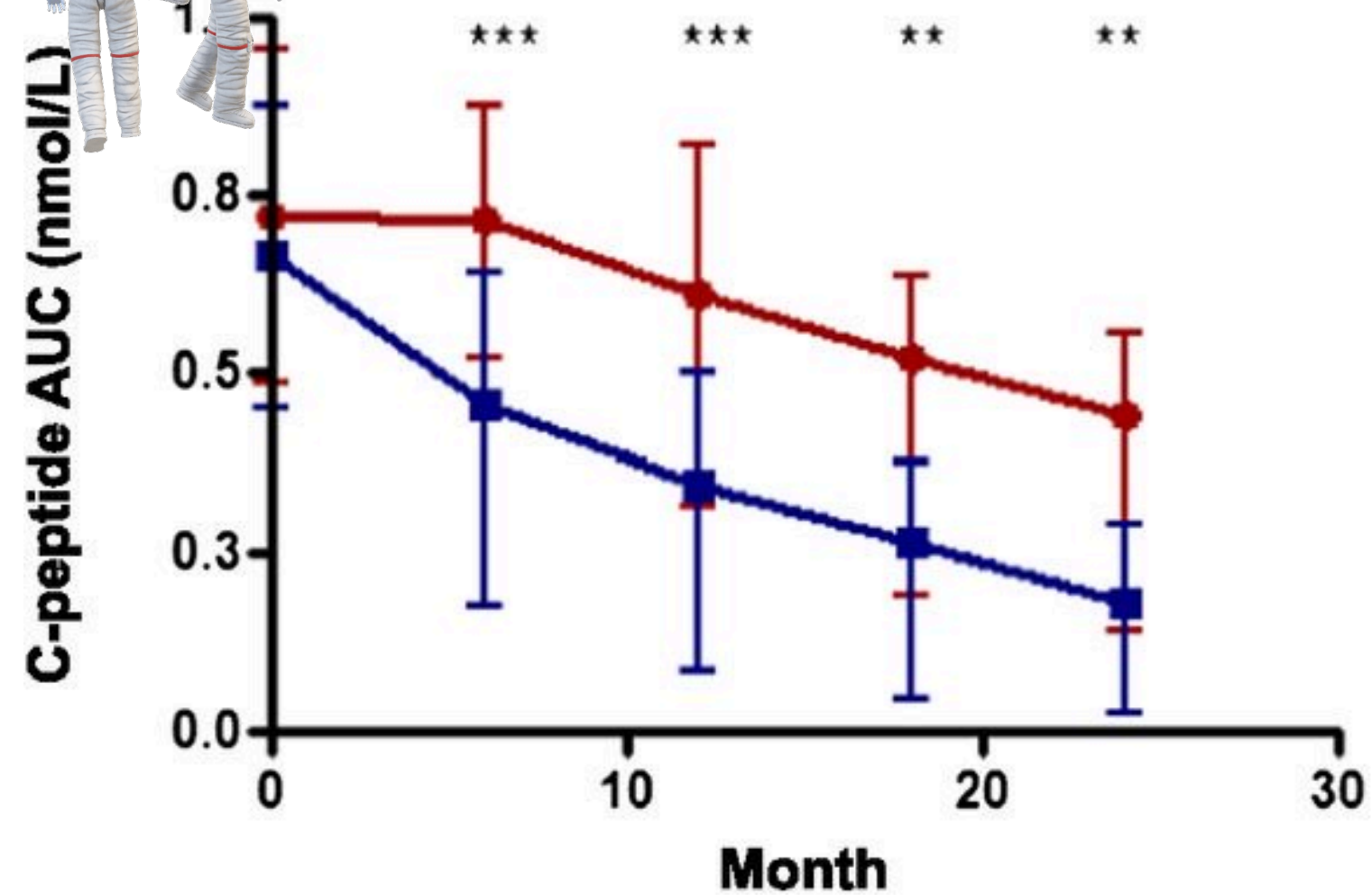
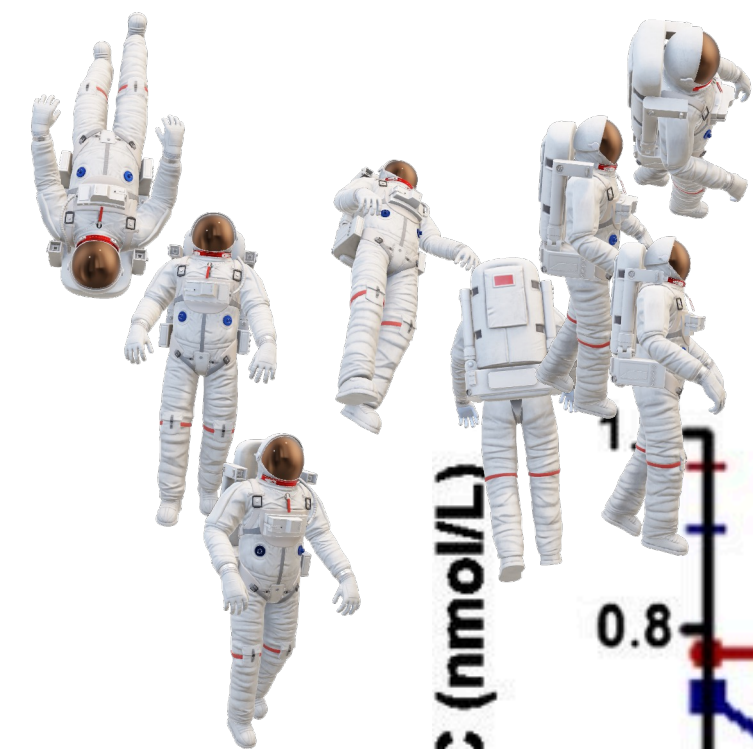
Criteria:

- At least 2 autoantibodies
- Mildly abnormal glucose
- Ages 8 and up

14-day IV infusion

Did everyone respond?



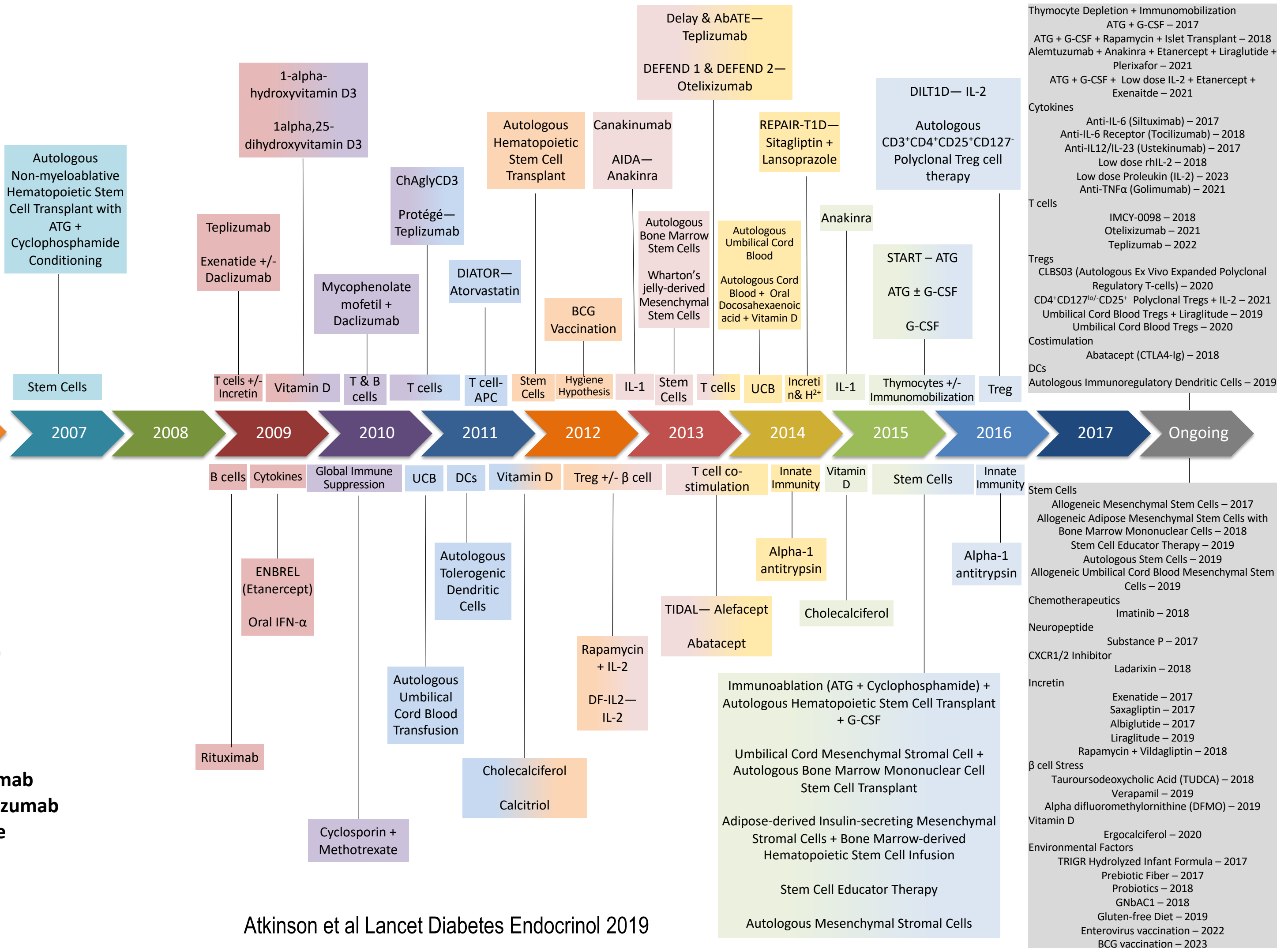


Disease- Modifying New Onset T1D Therapies

Cyclosporine
(broad immune suppression and kidney toxicity)

1986

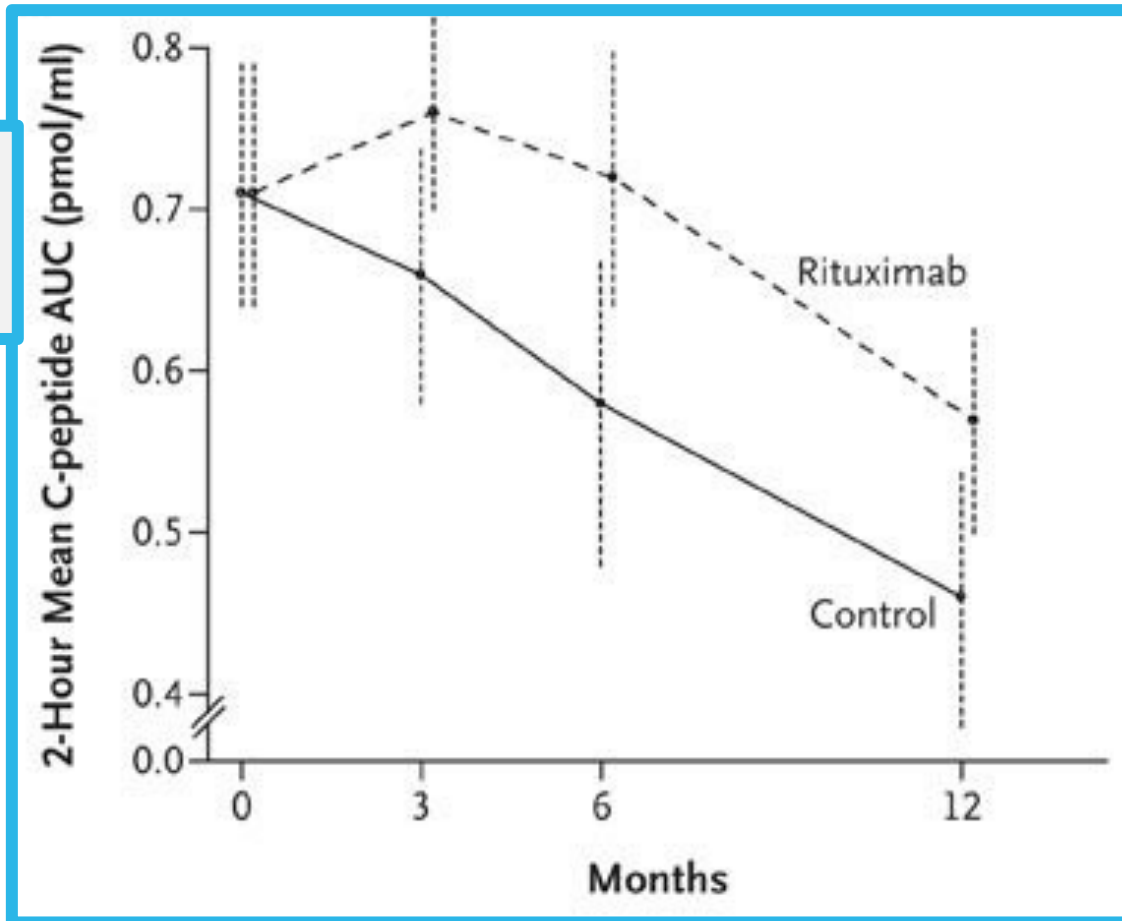
- Negative:**
 Cyclosporine
 Azathioprine
 BCG Vaccine
 Otelixizumab (anti-CD3)
 ITN High-dose ATG
 Alpha-1-Antitrypsin
 Insulin, GAD
 Vitamin D
 Canakin-, Tocliz-, Ustekin-umab
 Mycophenolate mofetil + daclizumab
 Sitagliptin + lansoprazole
 IL2 + Rapamycin



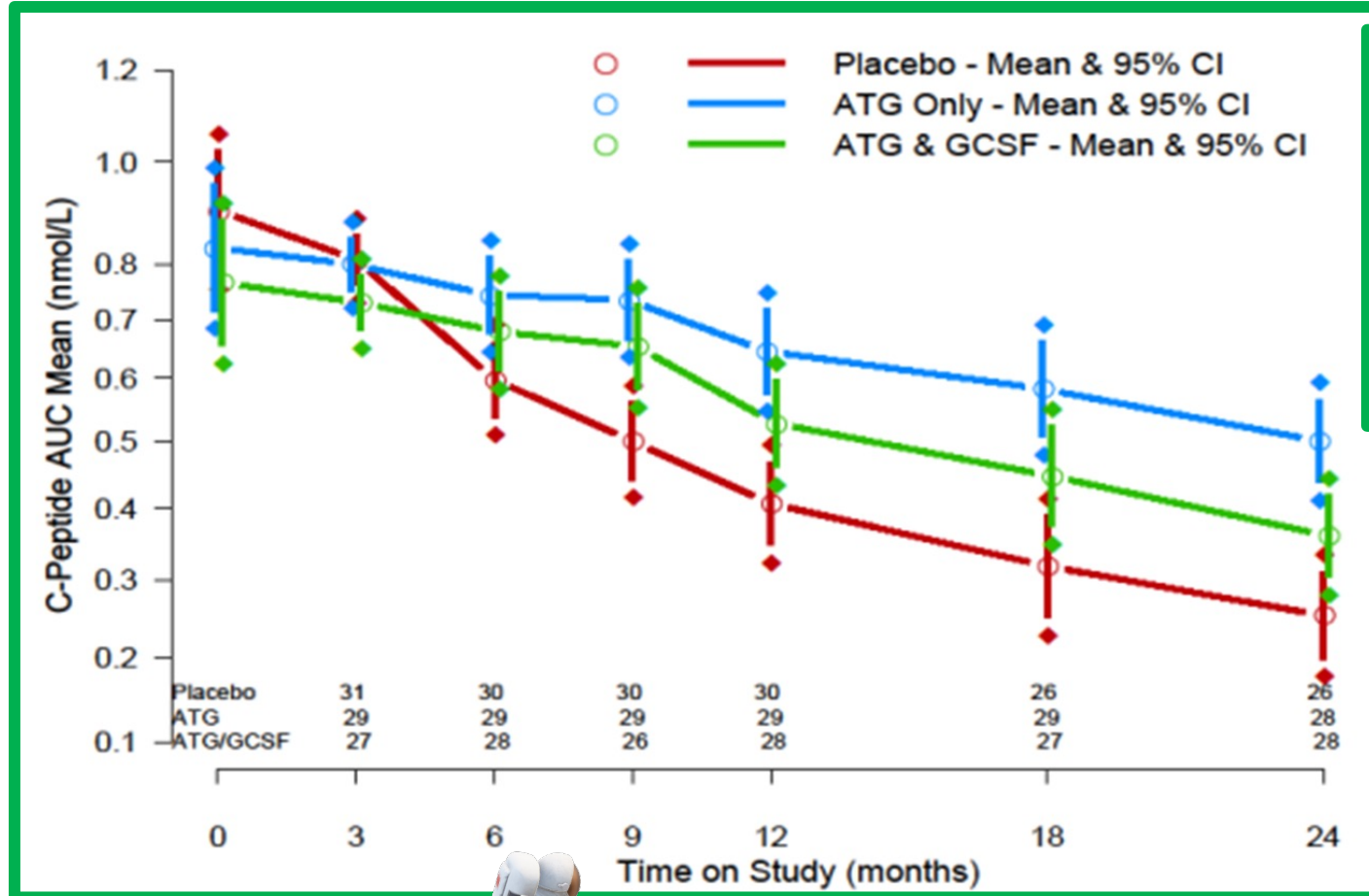
New Onset T1D Trials

Using B cell and T cell-directed Therapies

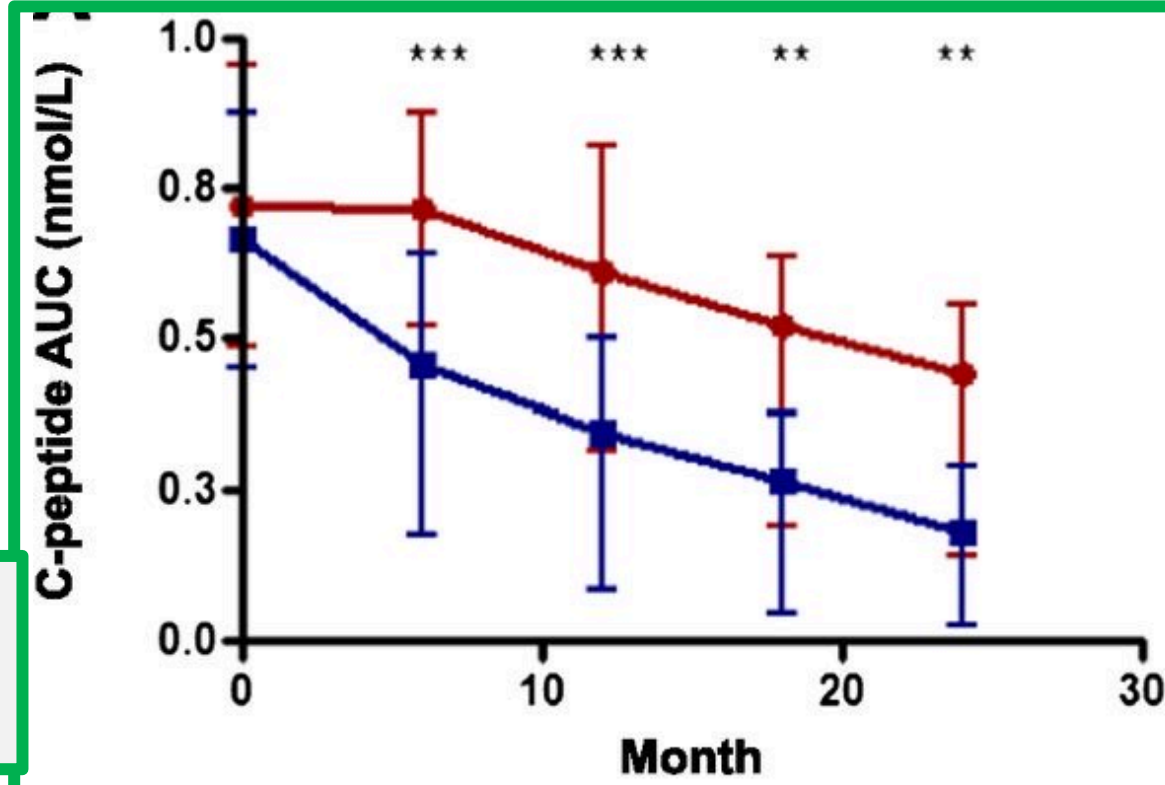
Rituximab
anti-CD20



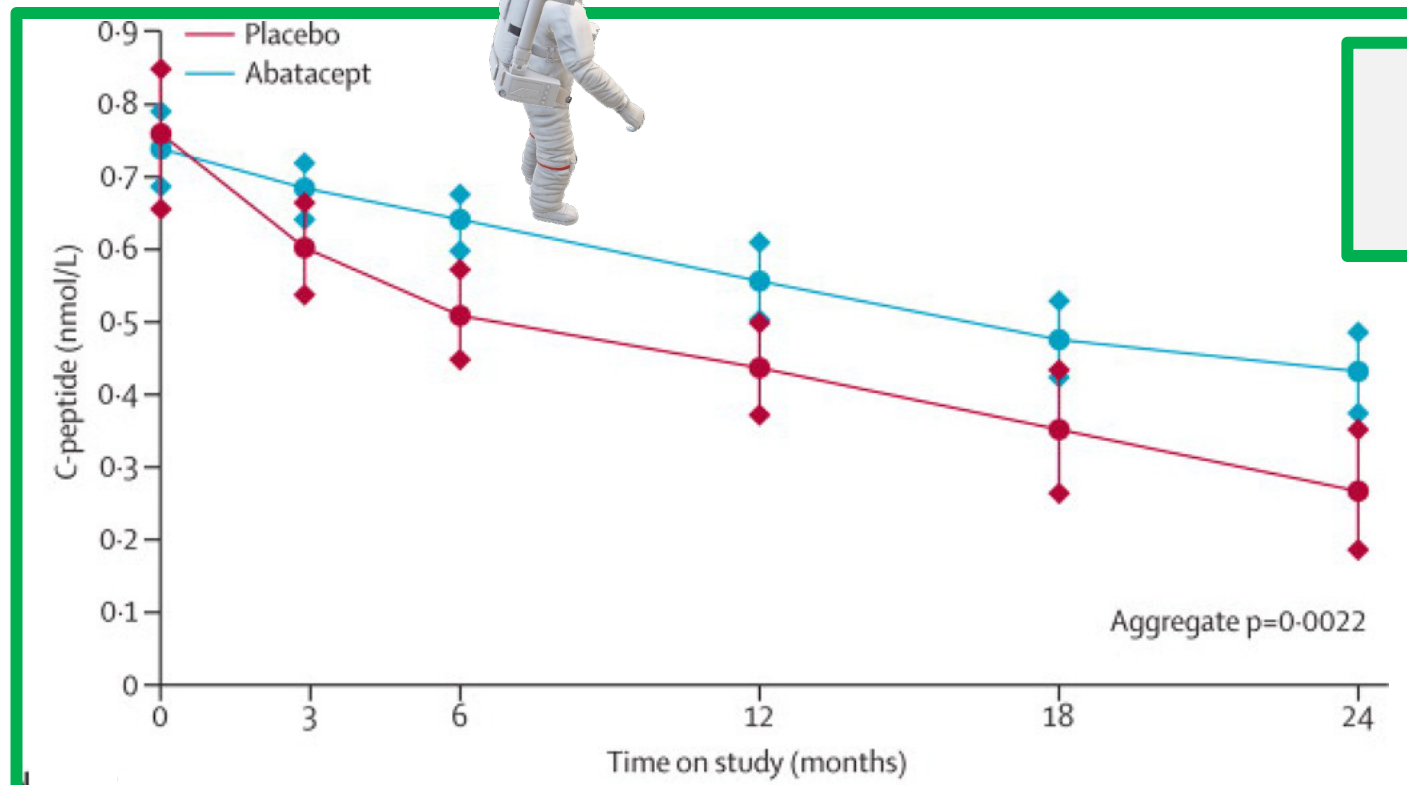
Anti-thymocyte
globulin (ATG)
polyclonal T cell
antibodies



Teplizumab
anti-CD3



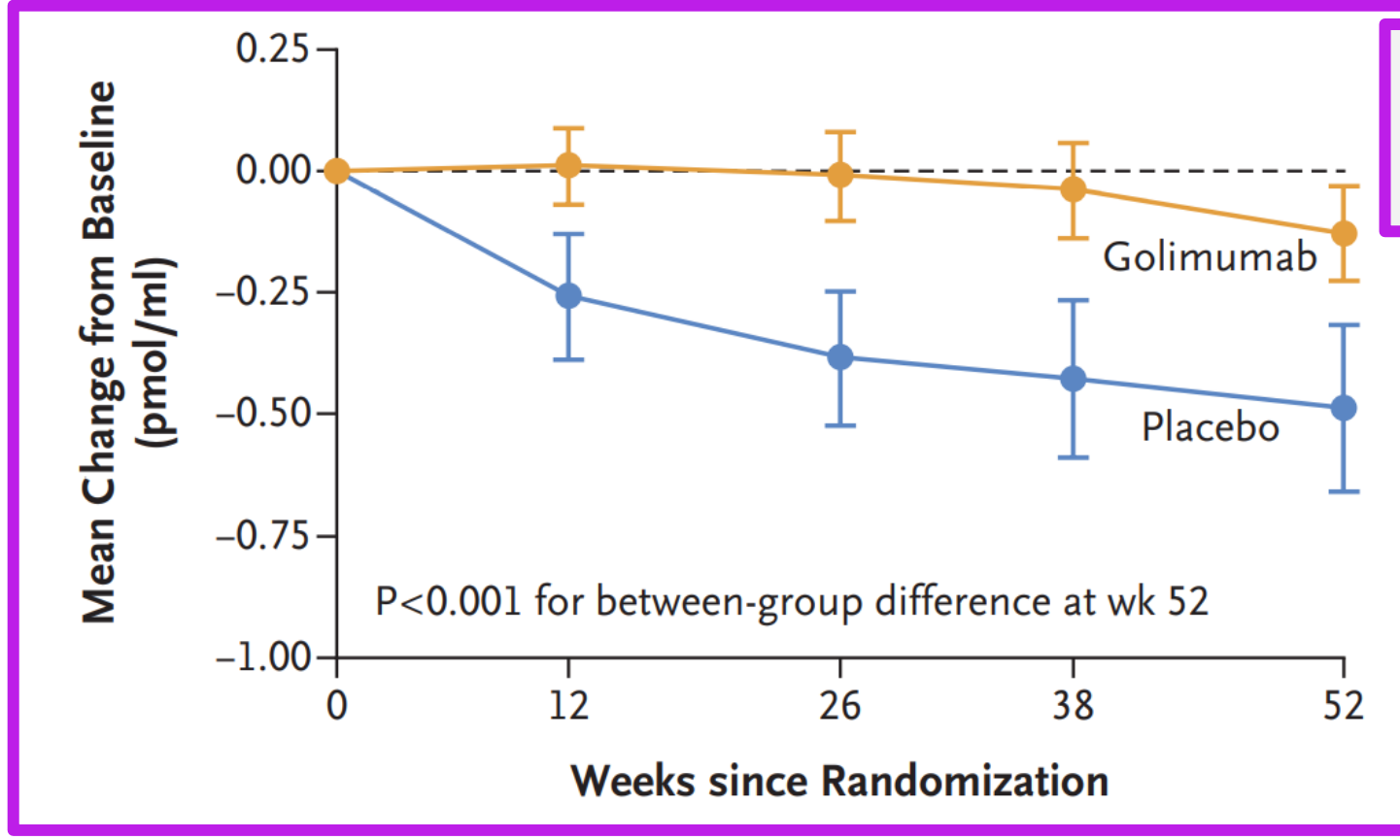
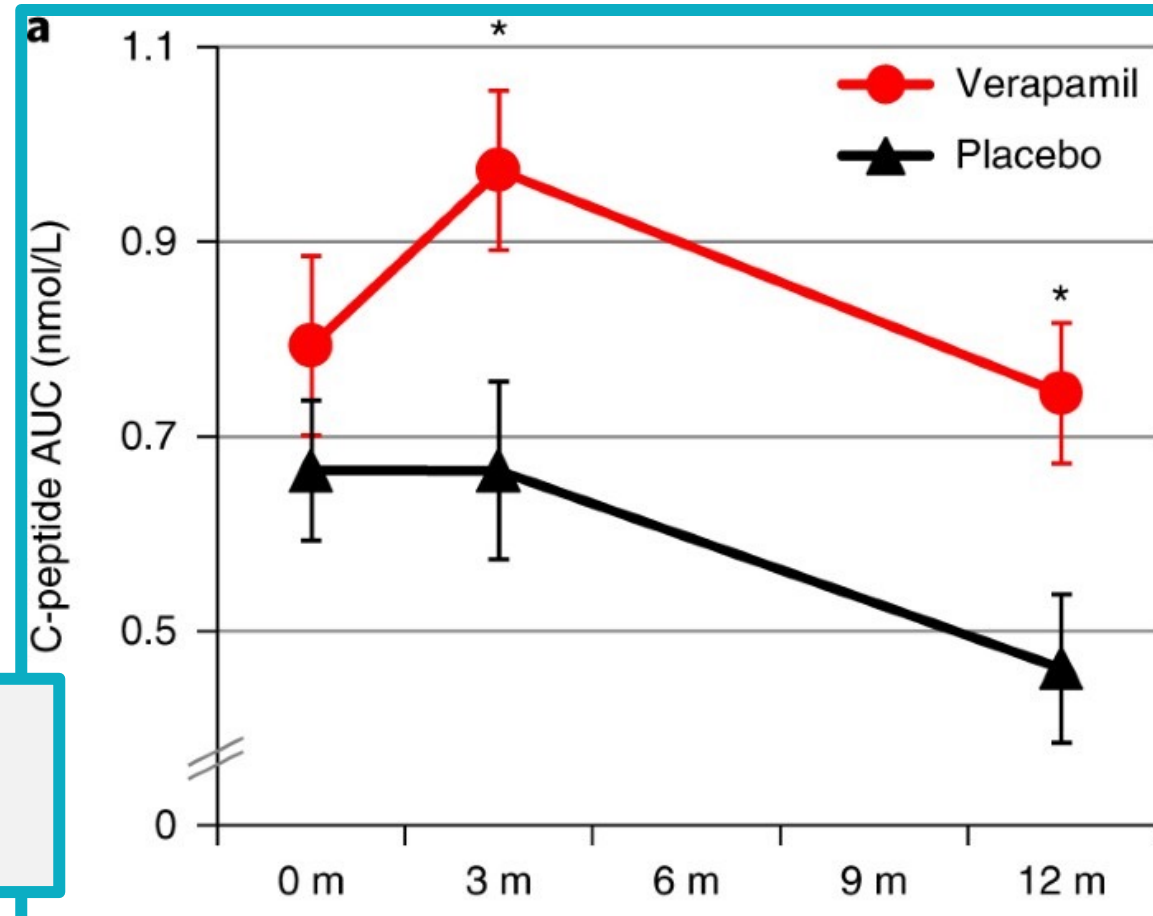
Abatacept
CTLA4-Ig



New Onset T1D Trials

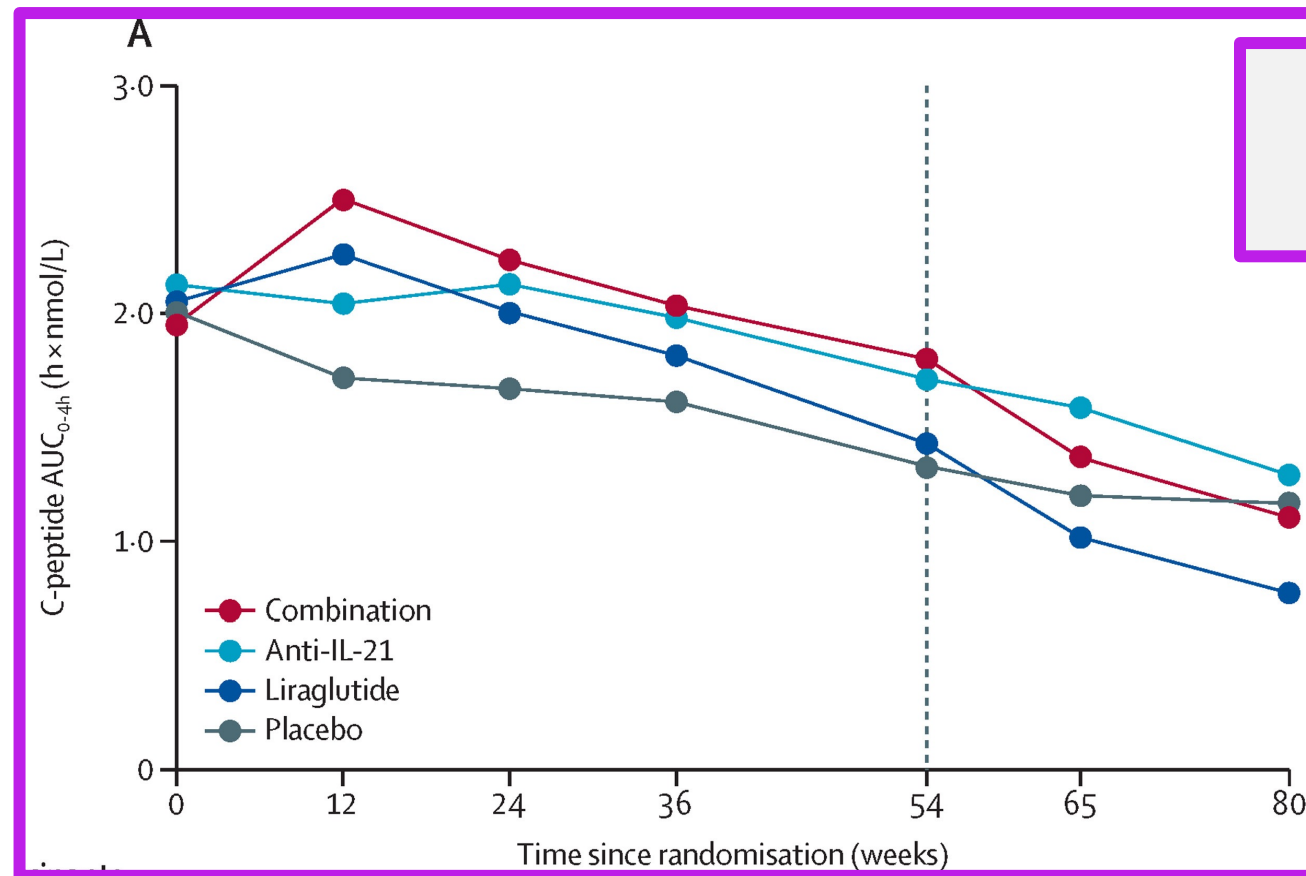
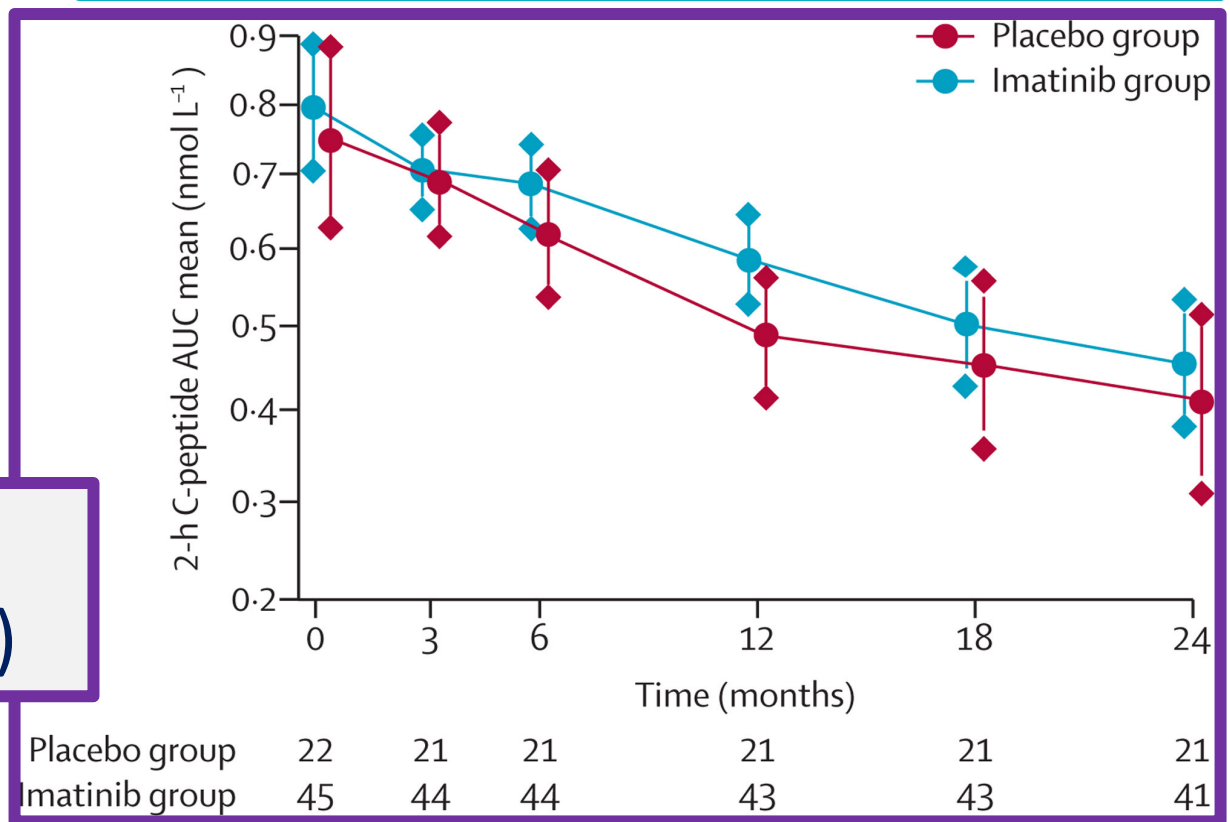
Using Calcium Channel, Tyrosine Kinase, Cytokine-directed Therapies

Verapamil
CCB



Golimumab
anti-TNF α

Imatinib
TKI (Gleevec)

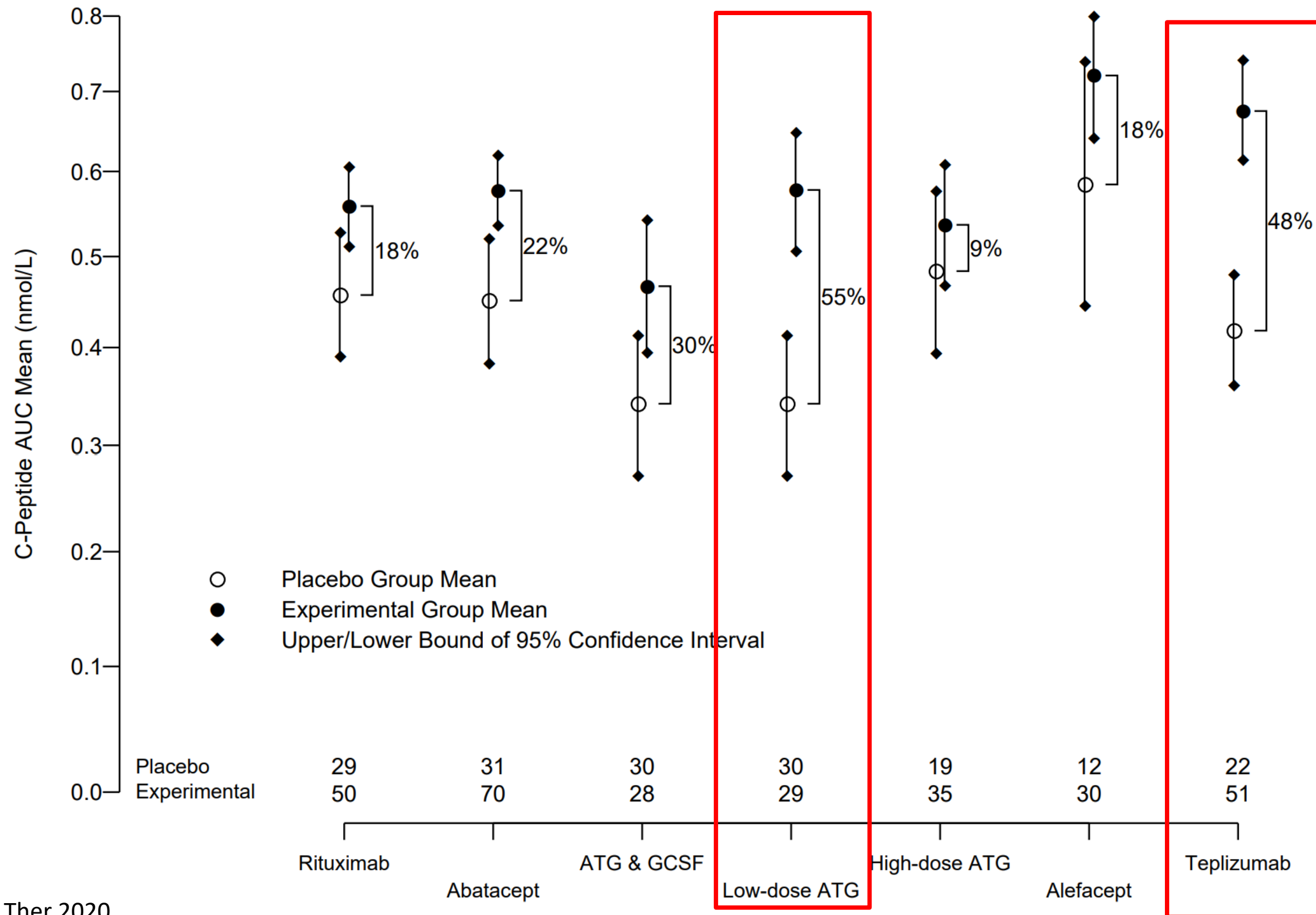


Anti-IL21 +
Liraglutide

Placebo group	22	21	21	21	21	21
Imatinib group	45	44	44	43	43	41

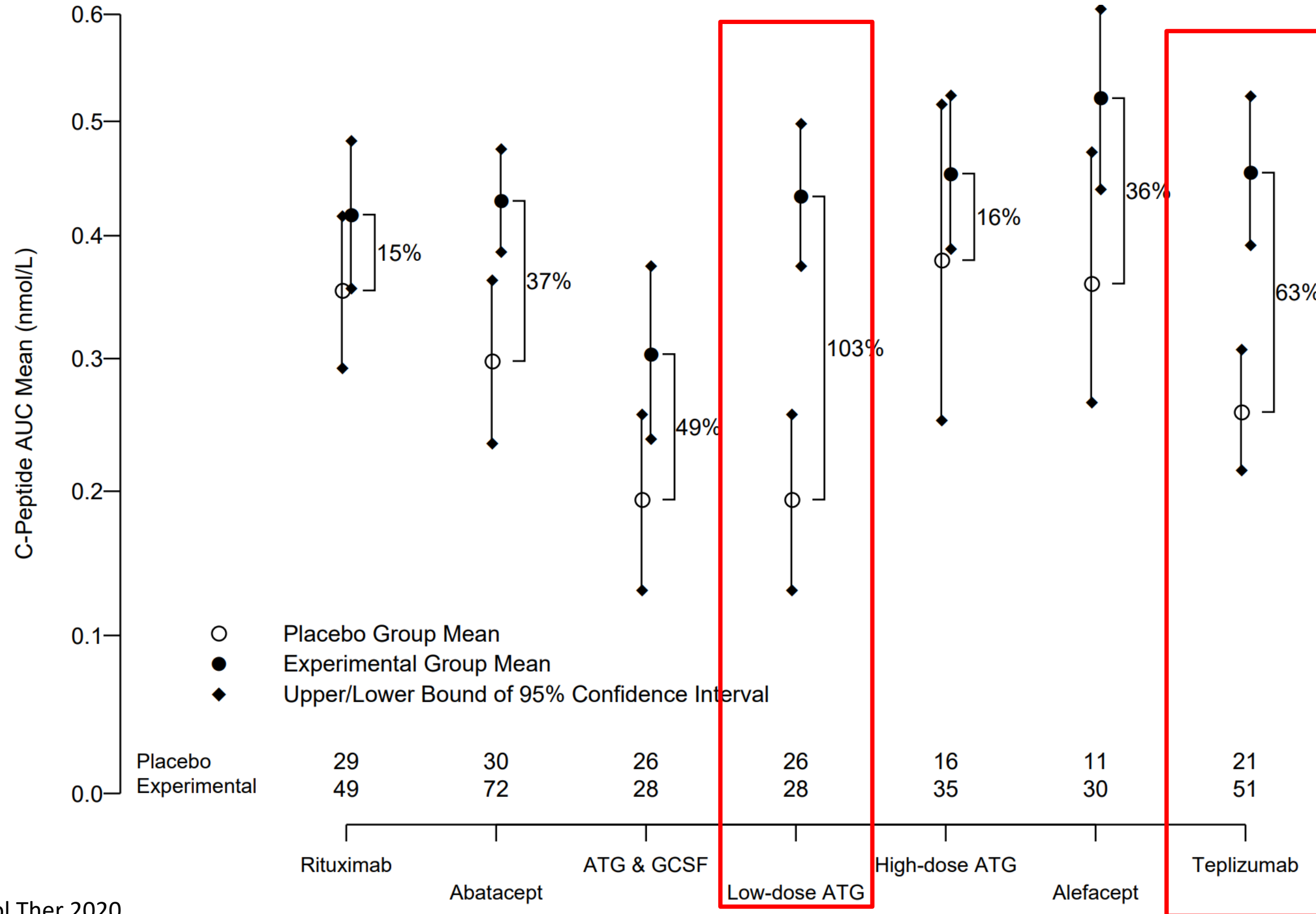
Treatment Group Means at 1 Year by Study

(adjusted for baseline C-peptide & age)



Treatment Group Means at 2 Years by Study

(adjusted for baseline C-peptide & age)



Hurdles to Beta Cell Preservation

The population:

Identifying those at-risk – screening and monitoring
(relatives vs general population)

The science:

Biomarkers needed & Combinations therapies

The approval:

FDA & Pharma

Is it worth it?

How long to treat?





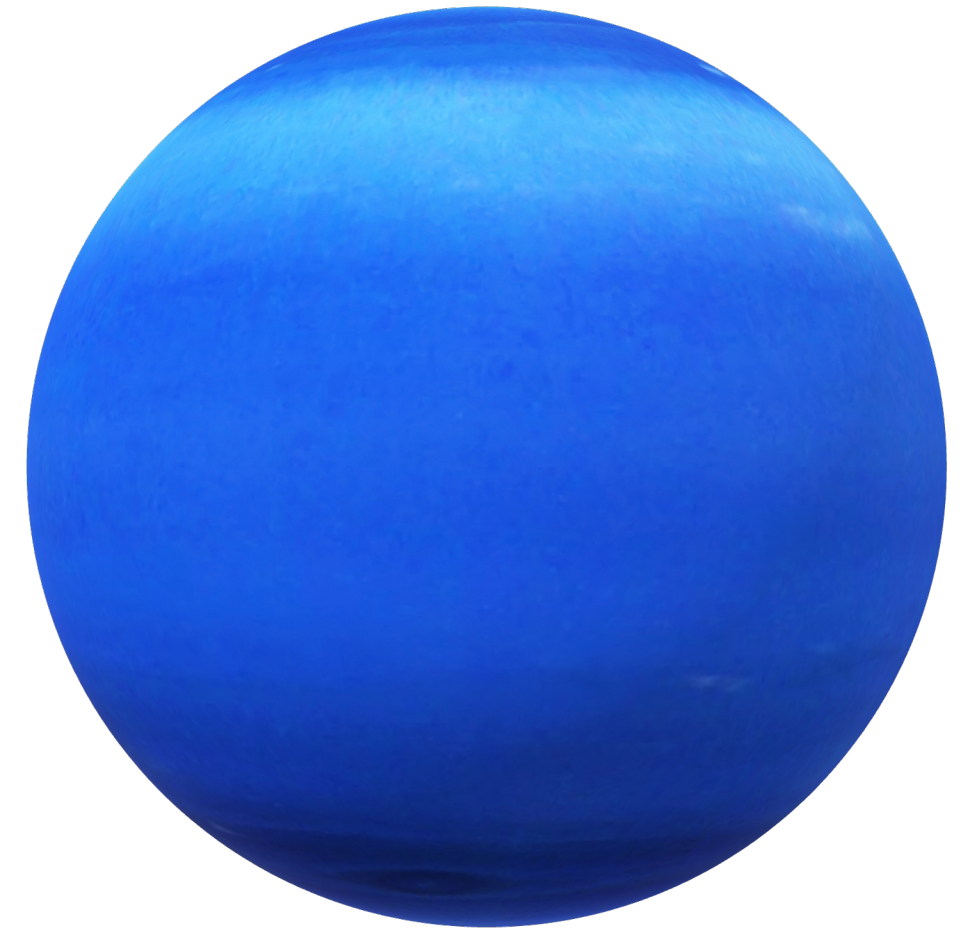
Is There Anything I Can Do?!



Technology

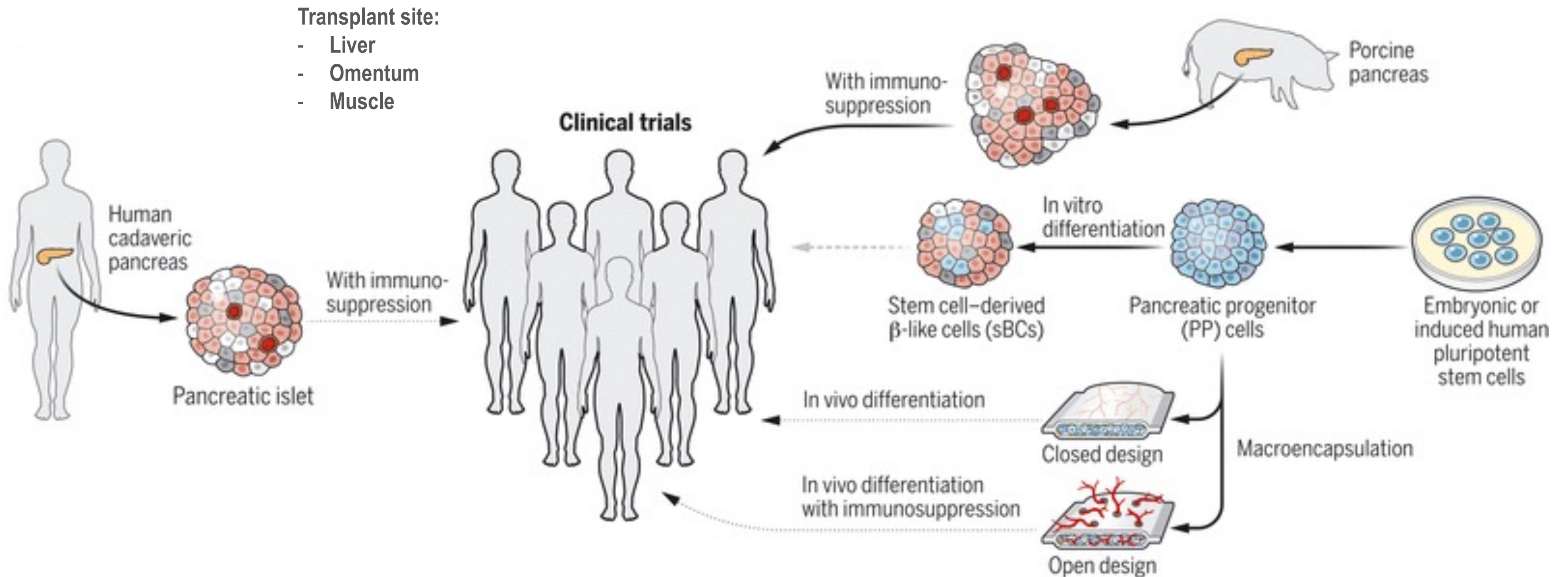


**Immune & Beta Cell
Protective Therapies**



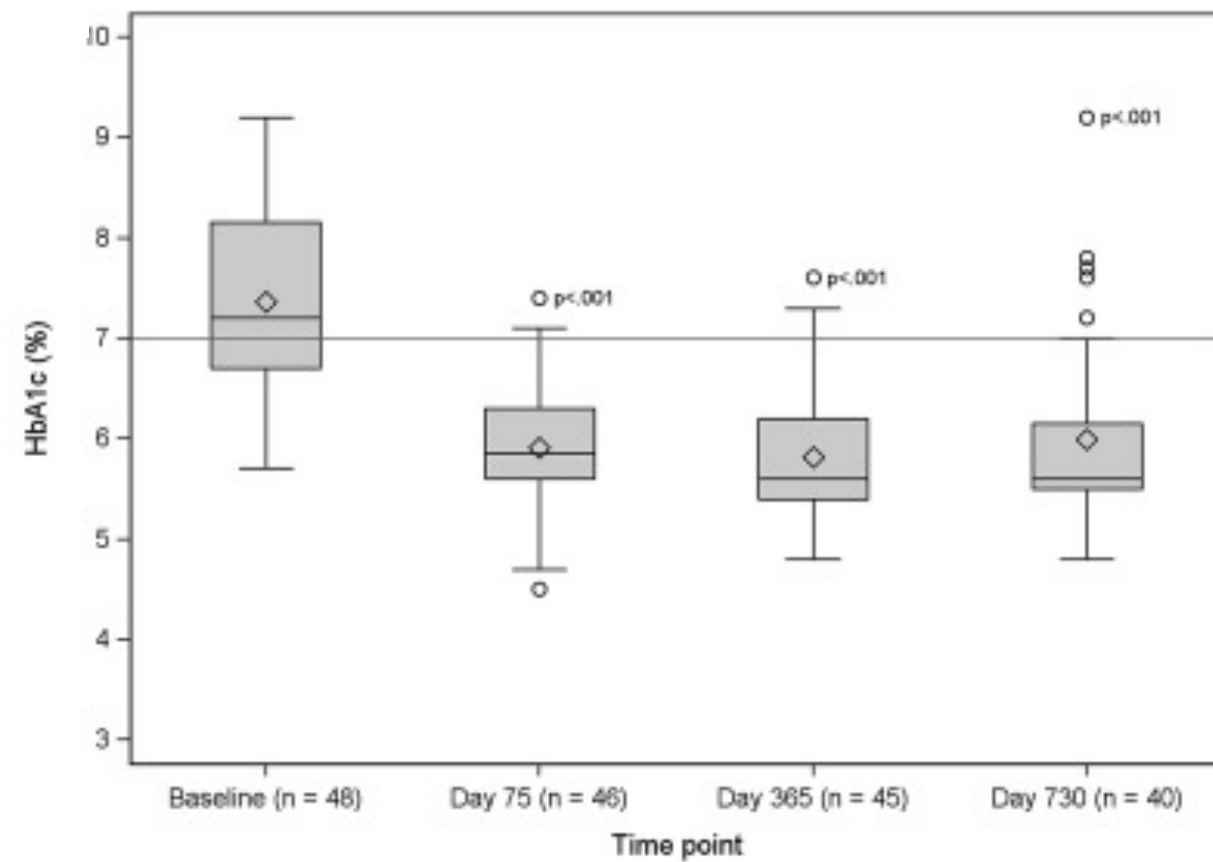
**Beta Cell
Replacement**

Beta Cell Replacement Therapies

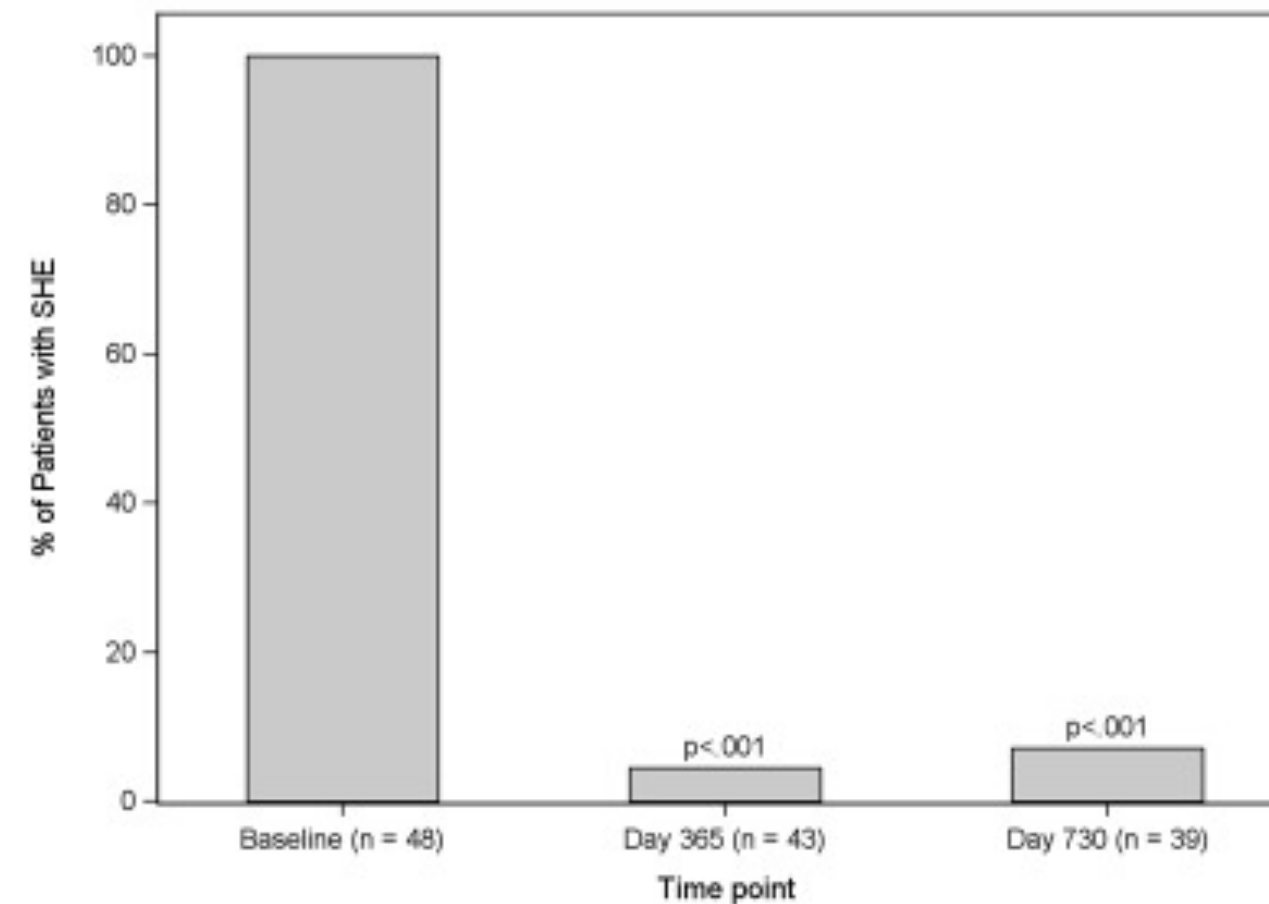


Purified Human Pancreatic Islet Transplant

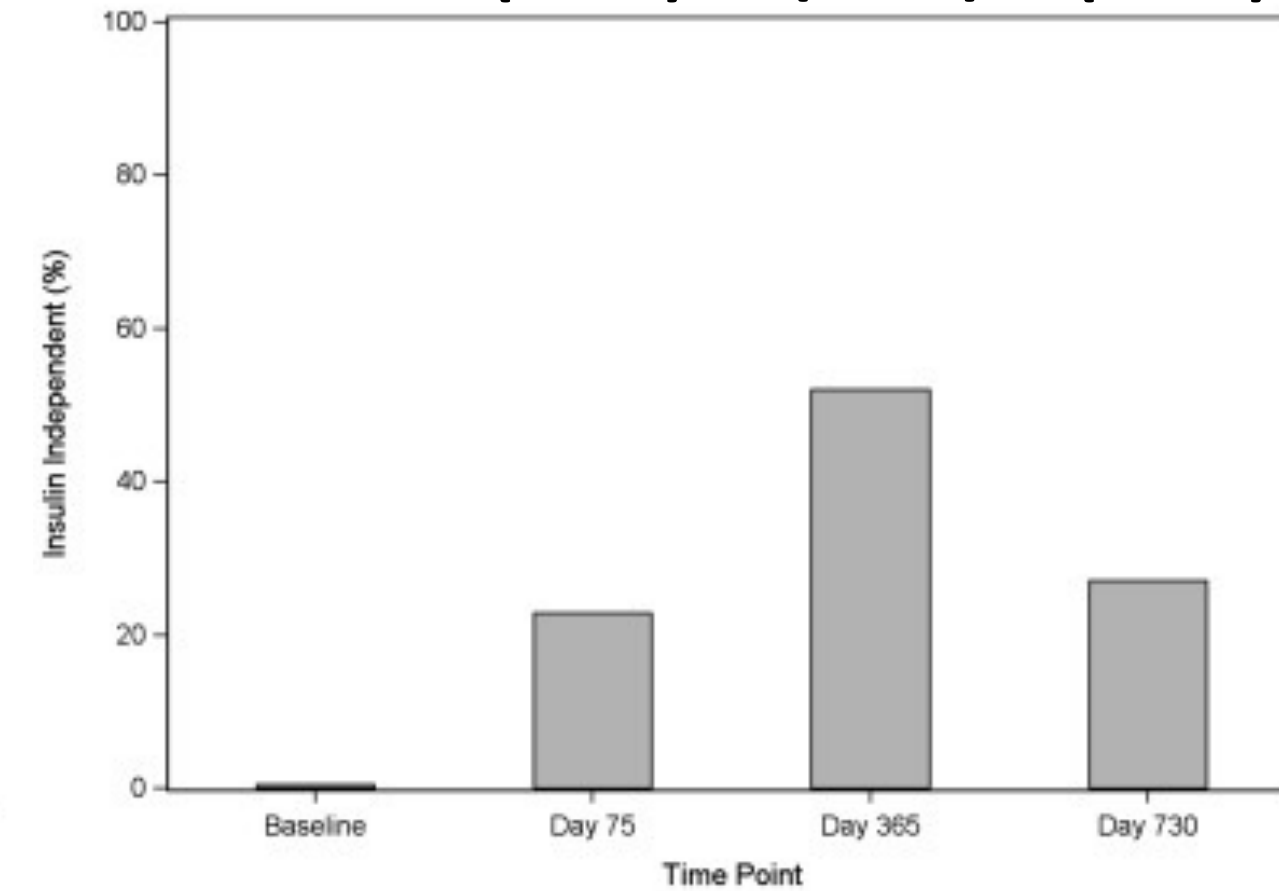
**Baseline median
HbA1c 7.2% (5.7–9.2%)**



**Severe hypoglycemic
events resolved in all but 2**



11/48 (23%) 25/48 (52%) 20/48 (42%)



FDA Approval of Lantrida

Purified Human Pancreatic Islet Transplant Product

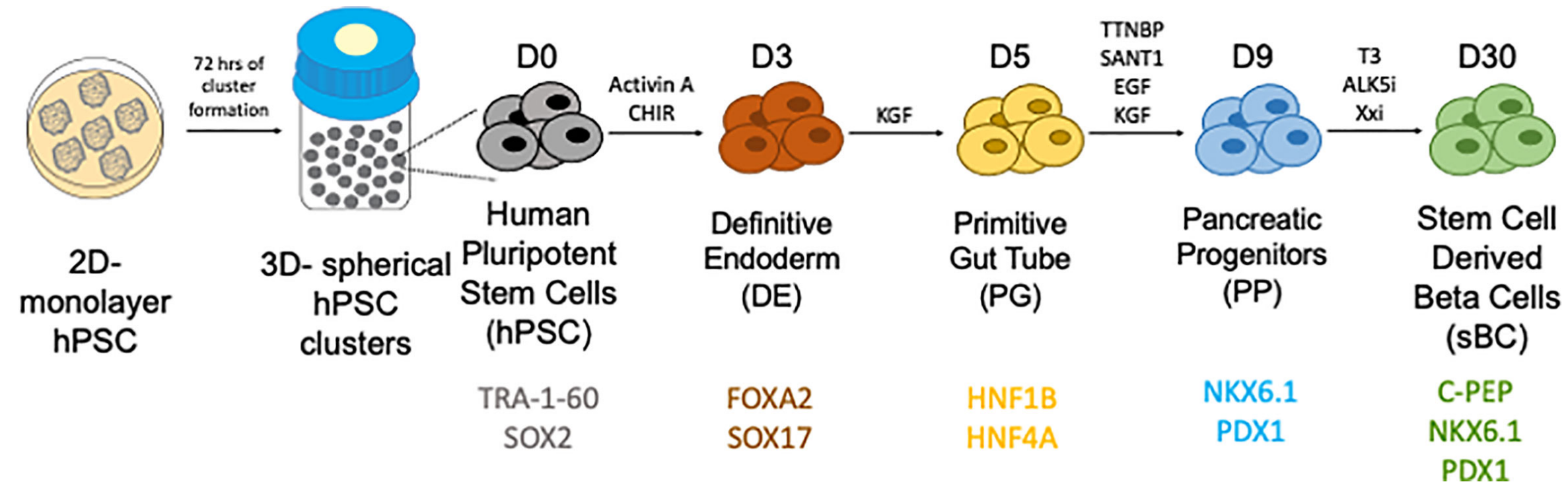
- Two studies, which totaled 30 participants, showed varying levels of success for Lantidra (donislecel)
- 5 never insulin independent
- 4 (13.3%) insulin independent <1 year
- 11 (36.7%) for 1-5 years
- 10 (33.3%) for >5 years

Table 23. Total Treatment-Emergent Adverse Events by UIH-001 and UIH-002

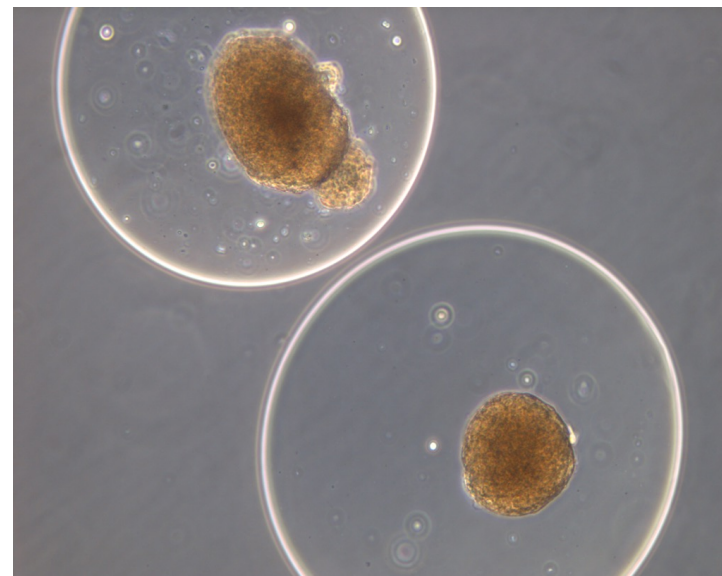
Adverse Event Severity	N	UIH-001	UIH-002
Death	1	0	1
Life-Threatening	11	4	7
Severe	124	46	78
Moderate	420	161	259
Mild	1344	513	831
Missing Severity Category	142	92	50

Source: Generated by Clinical reviewer

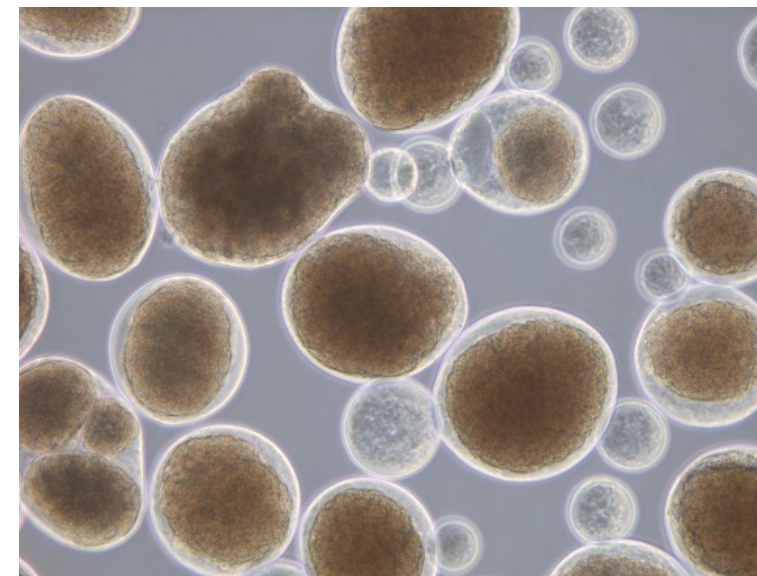
Making Beta Cells from Stem Cells



Traditional Microcapsules

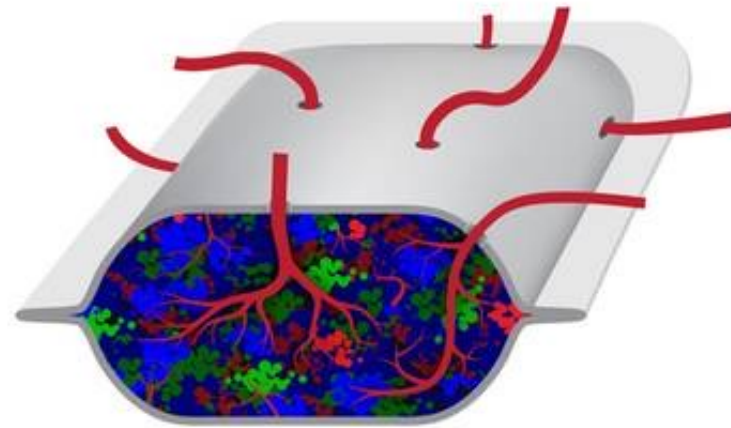


Conformal Capsules

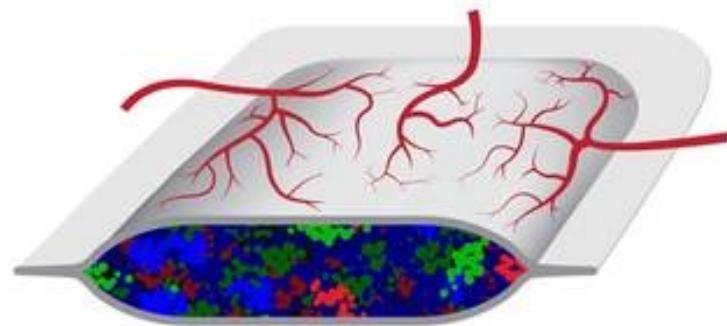


Encapsulating (“Hiding”) Beta Cells From the Immune System

PEC-Direct™



PEC-Encap™



VX-880 (stem cell-derived beta cells + immunosuppression)

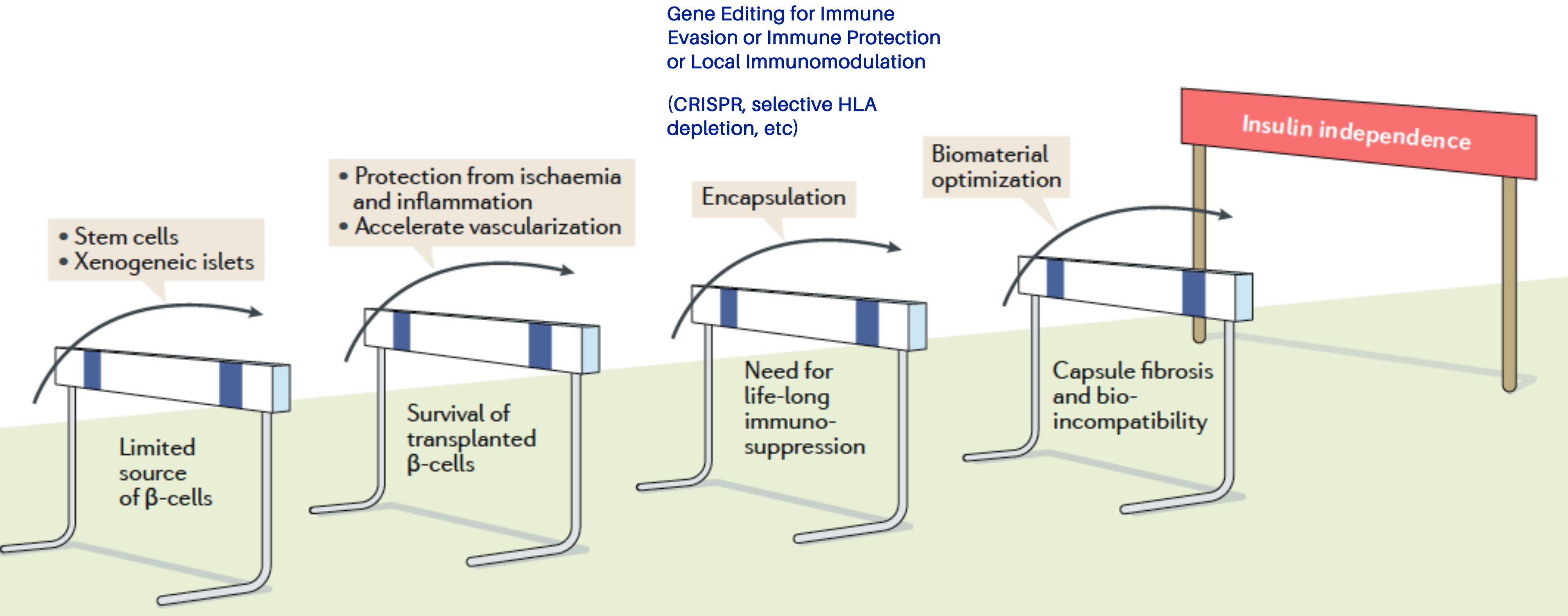
- Prelim results first 6 recipients (17 planned)
- All went from no C-peptide to making C-peptide
- All had reduced HbA1c, insulin use, and severe hypos
- 1 is off insulin still at 21 months of follow up
- 1 is off insulin still at 12 months
- 2 not off insulin and withdrew
- Other 2 not followed long yet

<https://clinicaltrials.gov/study/NCT04786262>

VX-264 (VX-880 + “a proprietary immunoprotective device that allows us to eliminate the need for immunosuppression”) - surgically implanted

ViaCyte → Vertex

Hurdles in Beta Cell Replacement





Is There Anything I Can Do?!



Available now:
Any age
Any T1D duration
Your preference



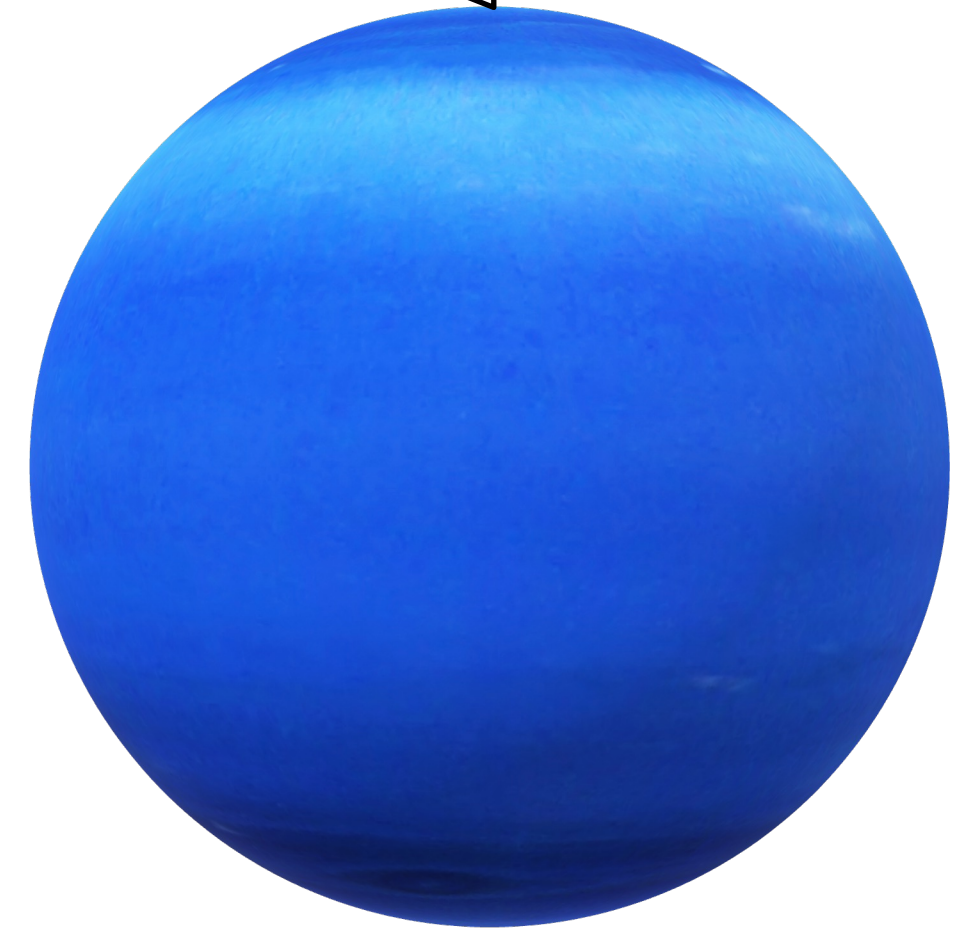
Technology

1 FDA/Rest Research:
Ages vary
Short T1D duration
(before majority of
beta cell loss occurs)



**Immune & Beta Cell
Protective Therapies**

1 FDA/Rest Research:
Hypoglycemia unawareness,
severe hypoglycemic events
Adults with longer T1D
duration



**Beta Cell
Replacement**

In Summary




- >> T1D prevention & reversal comes in many forms.
 - > Tzield (stage 2) and Lantrida (IAH/SHE) FDA approved
 - > Generalizability? Not for all. Need choices!
- >> The hurdles to T1D prevention and reversal are enormous but achievable – is the timeline knowable?
 - > Probably not.
- >> Is there a therapy right for me and my family?
 - > Stay tuned (active area of research)

Acknowledgements

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