

PEDIATRIC TRACK

THE FUTURE OF NON-INSULIN THERAPEUTICS FOR PEDIATRICS



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EPIC DIABETES CONFERENCE

MAY 21, 2022 | WEBINAR

EMPOWERING P ATIENTS
FOR
INDIVIDUALIZED CARE



I HAVE THE FOLLOWING CONFLICTS:

ADVISORY BOARD FOR PROVENTION BIO



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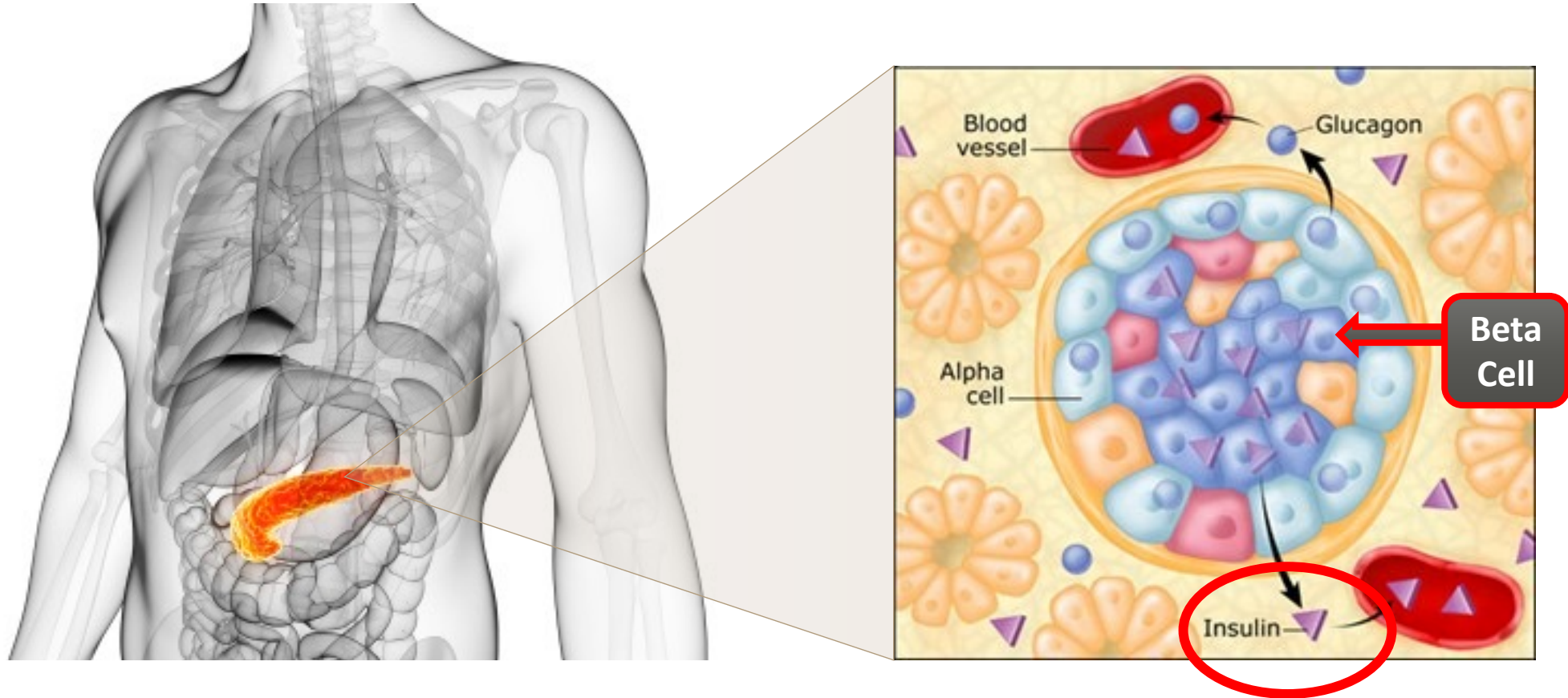
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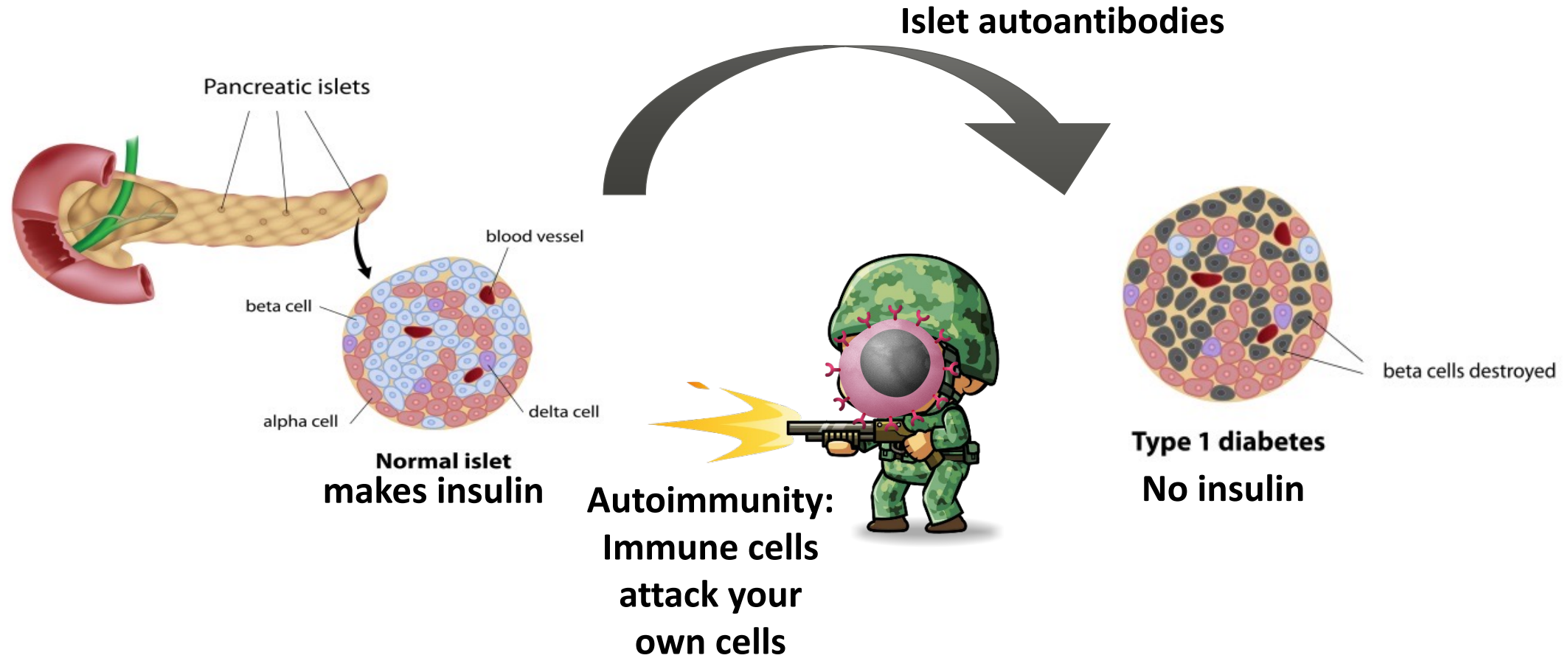


Pathway to Type 1 Diabetes

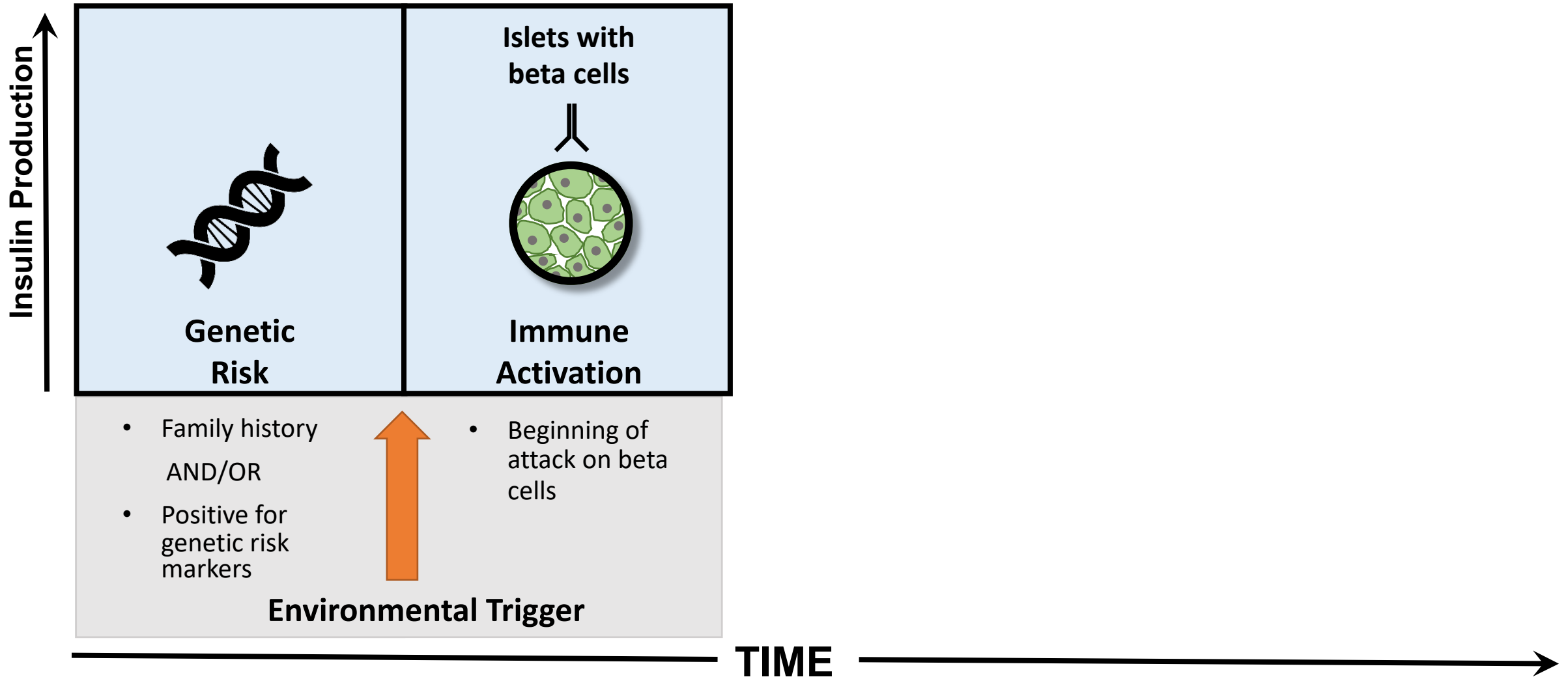
Introducing the Islet



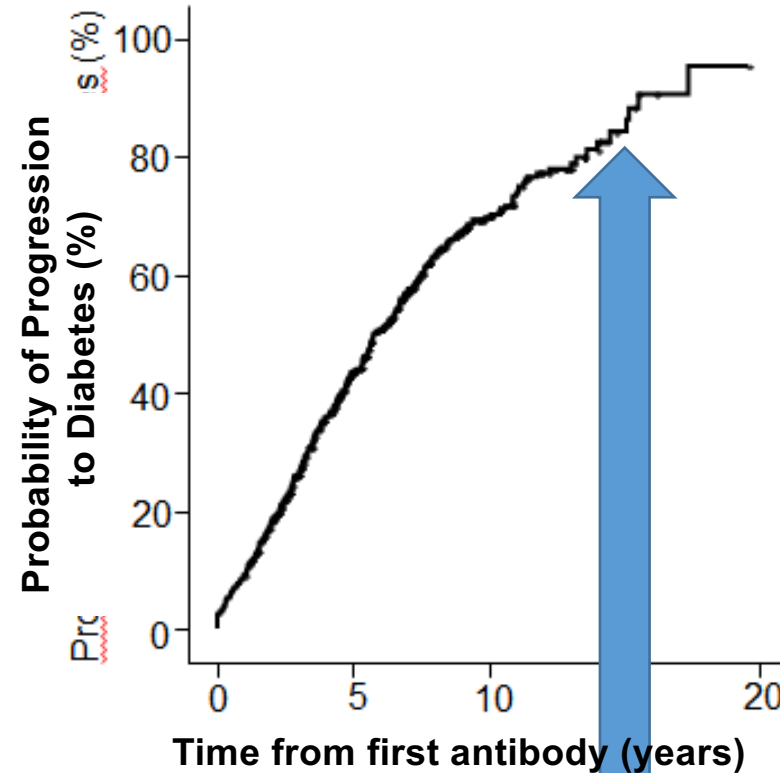
TYPE 1 DIABETES: islet autoimmunity



PATHWAY TO TYPE 1 DIABETES



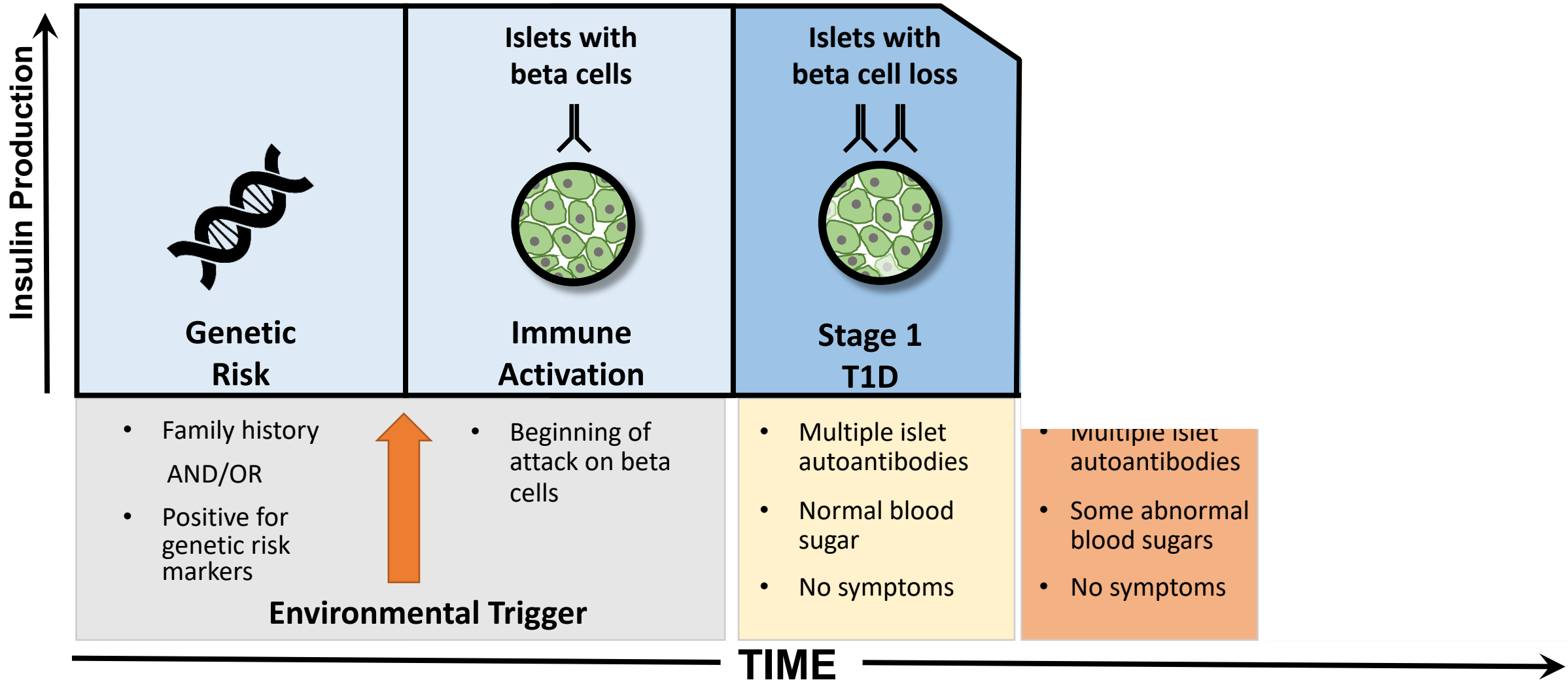
What happens to Children with Multiple Islet Autoantibodies?



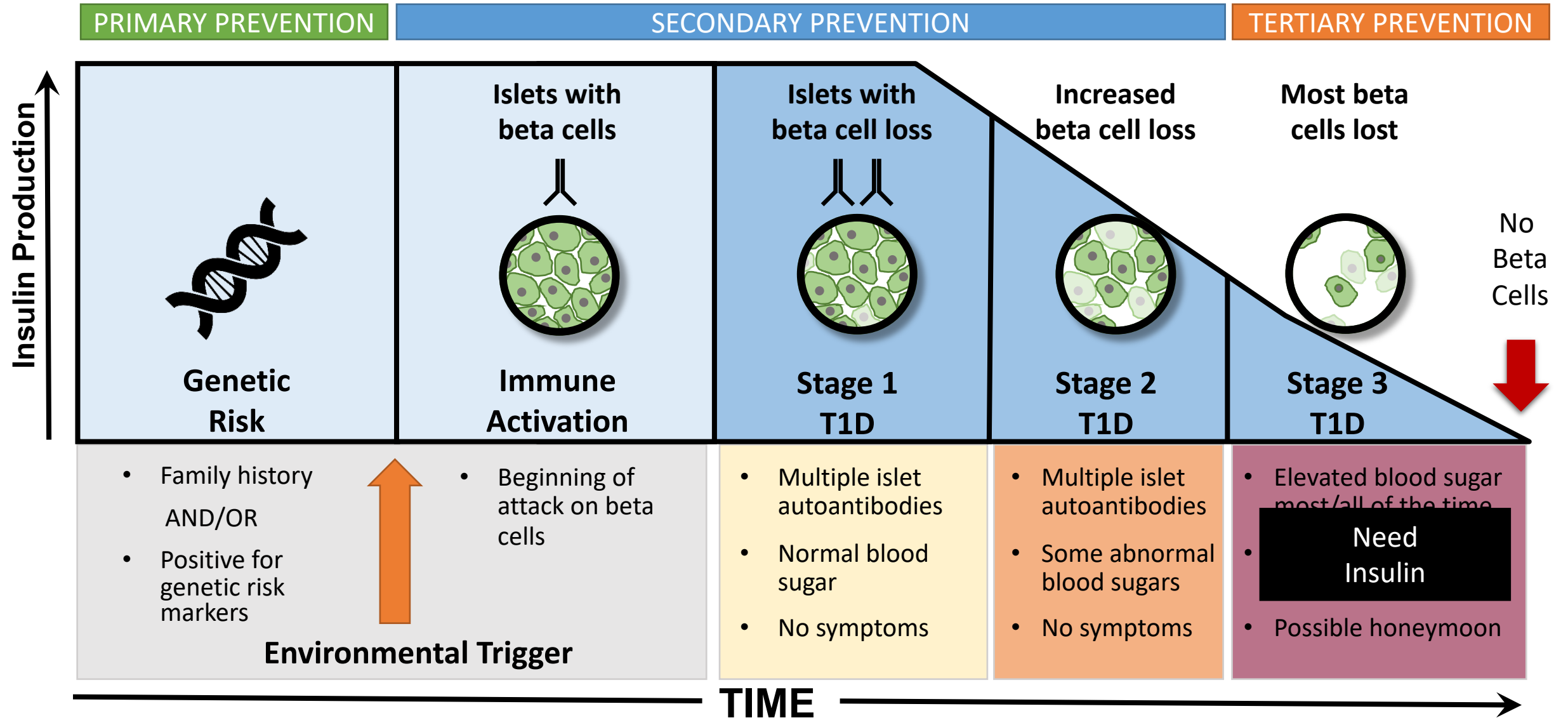
~50% in 5 years
~70% in 10 years
~100% lifetime risk

Over the course of 15 years:
>80% progress
from multiple autoantibodies
to T1D

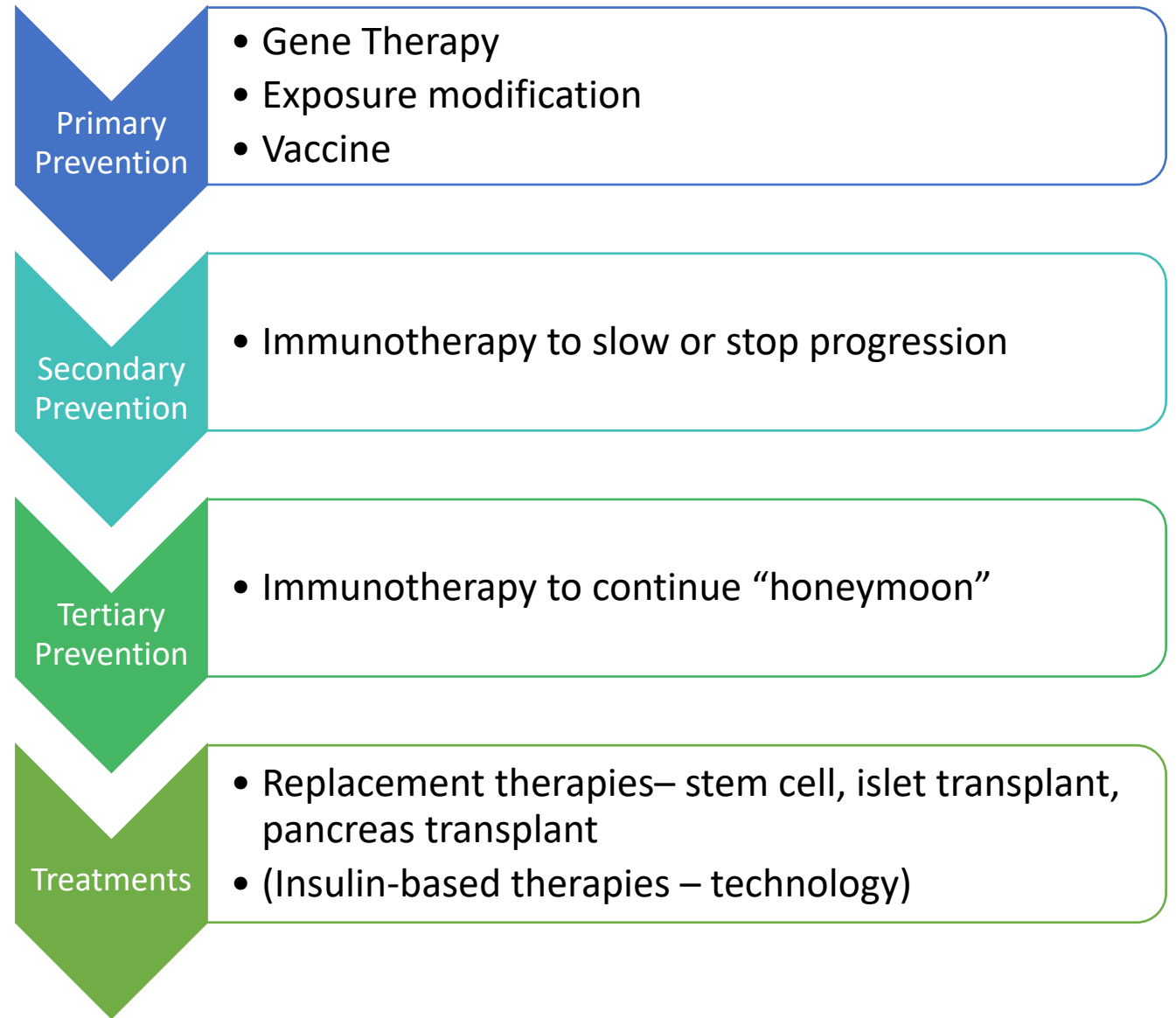
PATHWAY TO TYPE 1 DIABETES



PREVENTING TYPE 1 DIABETES



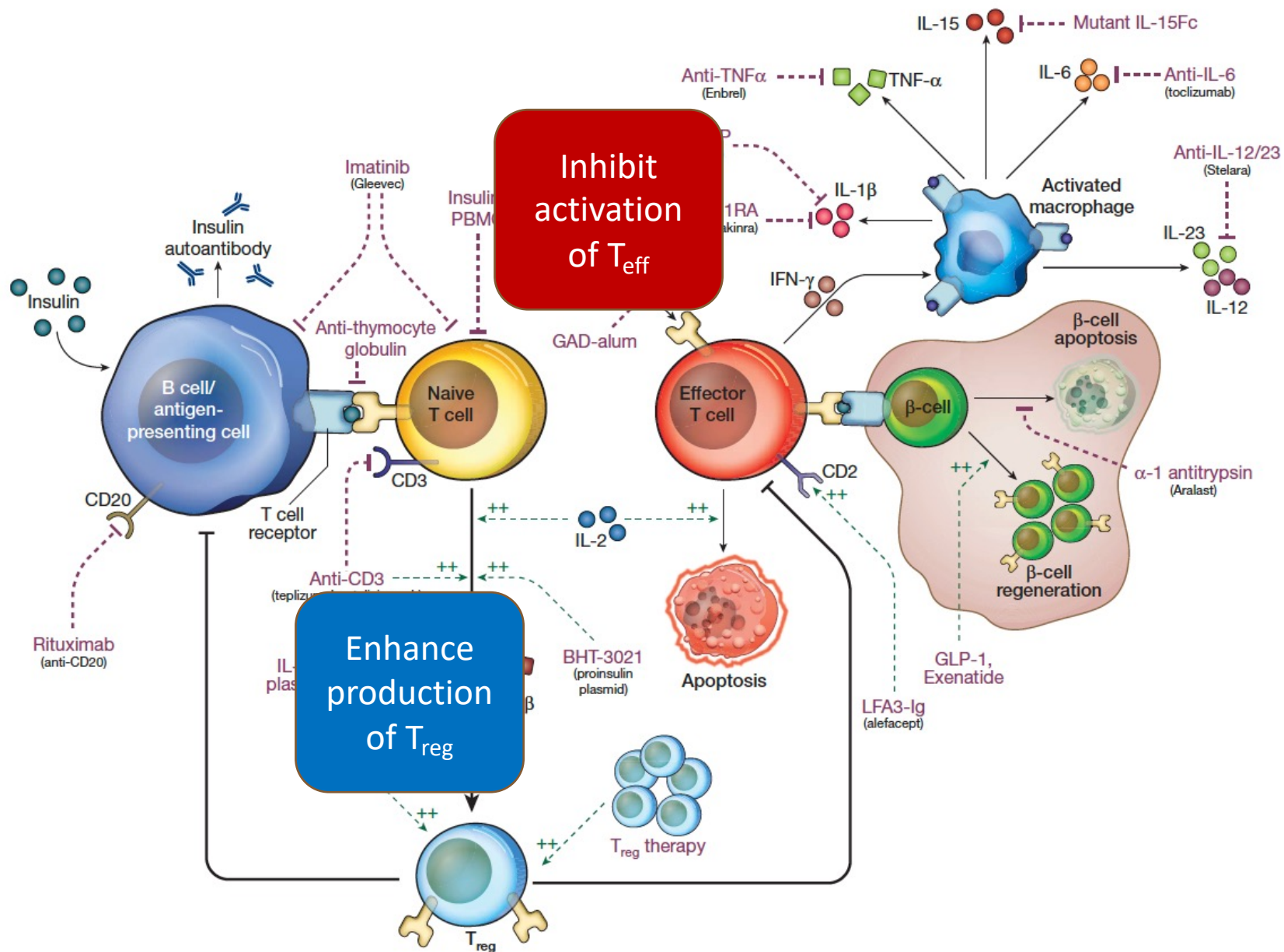
Non-insulin treatments for T1D



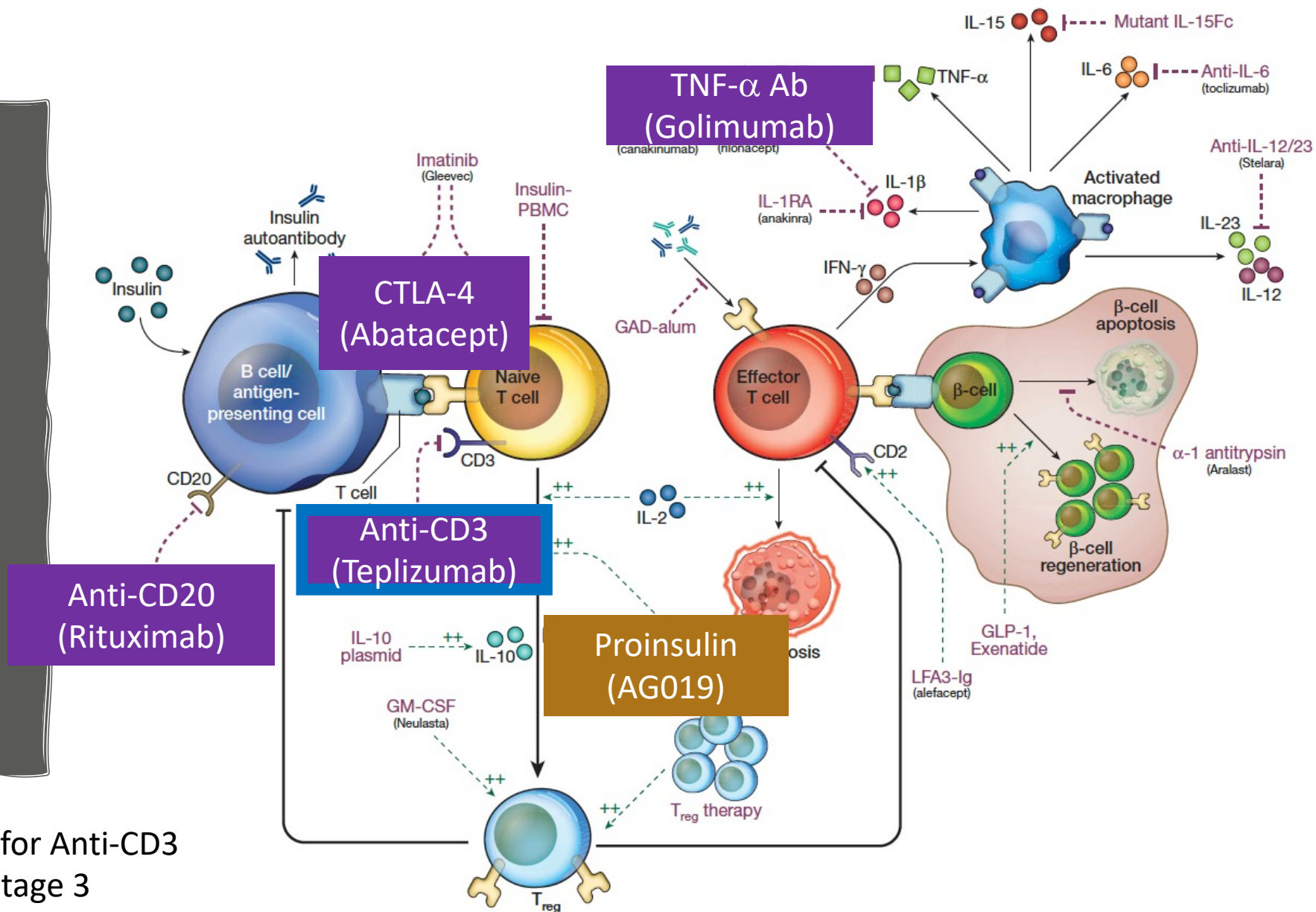


Prevention Approaches

Targets of Attack



What Has Worked?

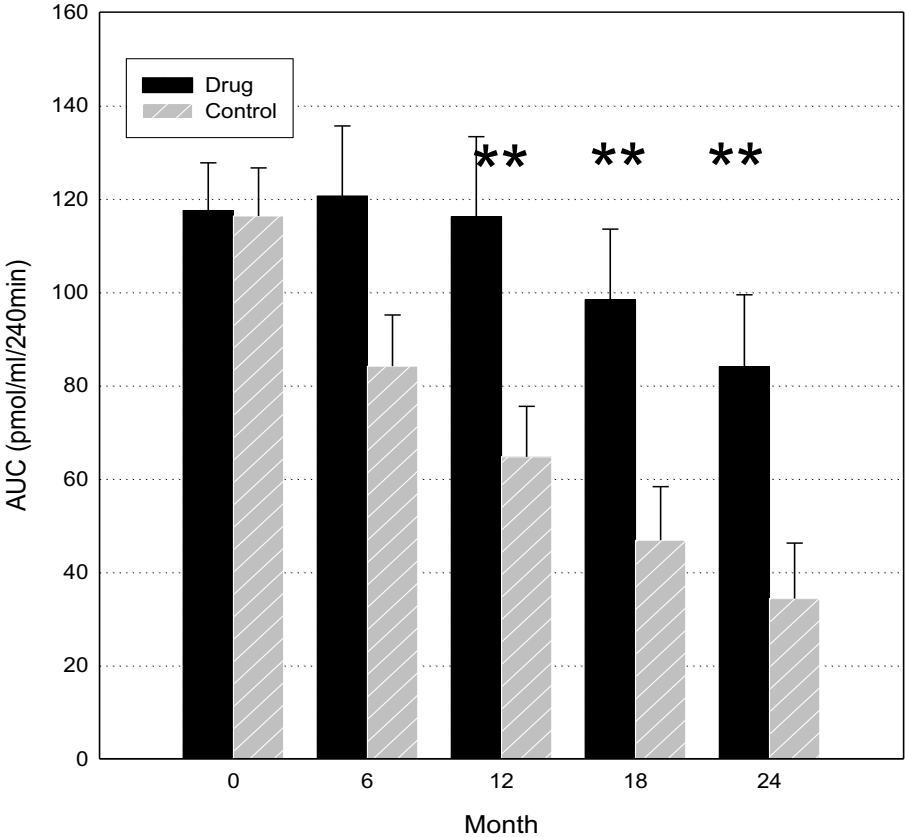


Results all in Stage 3 except for Anti-CD3 which is Stage 2 and Stage 3



A single course of anti-CD3 (Teplizumab) in new onset T1D improves insulin secretion for 2 years

Phase 1/2



(** p<0.02)

Herold K. et al., *Diabetes* 2005; 54:1763-9.



Teplizumab Delays T1D Diagnosis

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

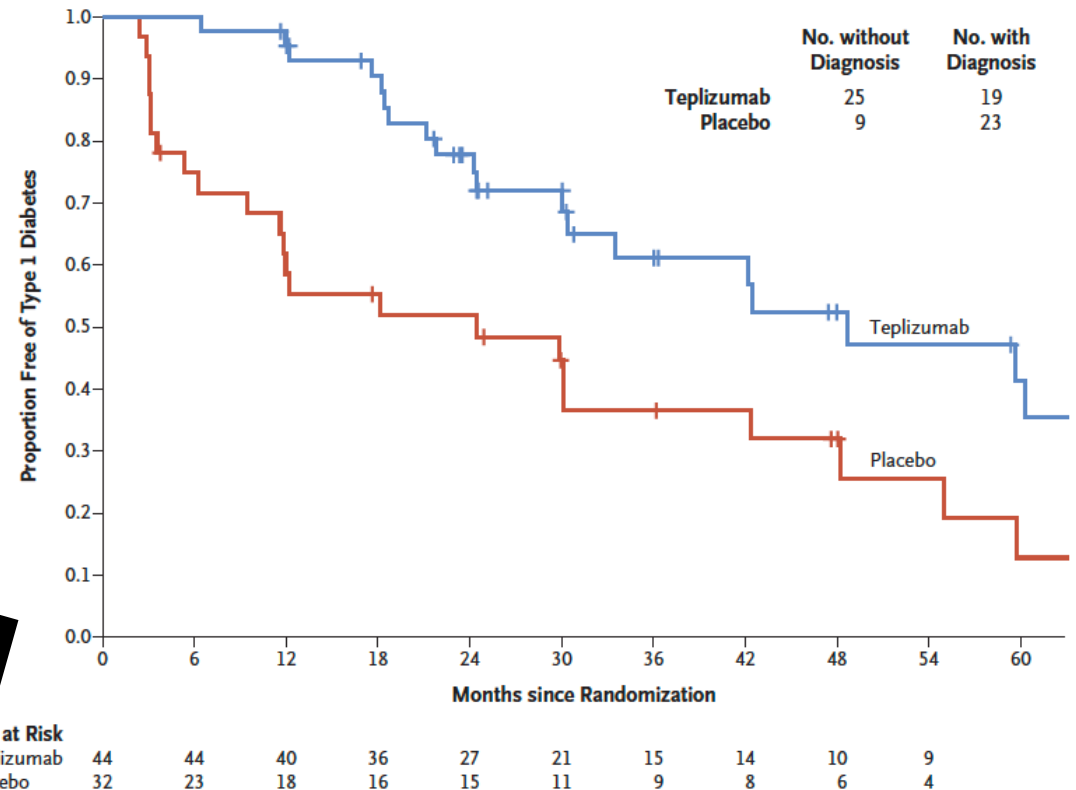
AUGUST 15, 2019

VOL. 381 NO. 7

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

Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group*

2 year delay of clinical T1D(stage 3) onset in those at high risk for developing disease (relatives, 2+ T1D AA+ and dysglycemia) with 1 course of teplizumab



Teplizumab preserves insulin production in T1D

	Study 1	AbATE	DELAY	Protégé	TrialNet At Risk
Date(s) Published	2002, 2005 NEJM	2013 Diabetes	2013	2011, 2013 Lancet	2019 NEJM
Participant Age (years)	8-30	8-30	8-30	8-35	8-45
n=	40	77	58	513	76
T1D stage studied	3	3	3	3	2
Timing of treatment	≤ 6 weeks from diagnosis	≤ 8 weeks from diagnosis	4-12 months from diagnosis	≤ 12 weeks from diagnosis	Antibody + with dysglycemia
Outcome	+	+	+	-	+
C-peptide AUC (insulin production)	↑145% (p=0.02)	↑92 (p=0.002)	↑27% (p=0.03)	↑24% (p=0.027)	~2 year delay in T1D onset



Teplizumab Clinical History and Experience

- Drug experience
 - >20 years
 - >6 T1D trials
 - ~829 individuals 8-35 years old (any dose)
 - ~475 children <18 years old (any dose)
 - ~176 children <18 years old (same dose treatment dose as PROTECT study)
- Populations
 - Children and adults (~8 – 40 years old)
 - T1D: pre-symptomatic, newly diagnosed & months following diagnosis
 - Psoriasis, renal and islet cell transplants
- Demonstrated “durable” metabolic and clinical effects
 - Improved c-peptide (insulin) production
 - Lower exogenous insulin use
 - Improved HbA1c



Future of T1D Trials

Challenges

- Number of possible participants
- Identification of early-stage T1D
- Subtypes of T1D?
- Risk/Benefit profile
 - Consideration for age and stage

Strategies

- Goal: universal screening
- Better understanding of pathways to T1D
- Combination Therapies
- Younger Children
- Multi-Arm Trials



Conclusions

- There are promising therapies in the pipeline
- Our first therapeutic to slow disease is on the horizon
- Combination therapies will likely be part of the “tool box”
- We need to identify early-stage T1D
 - Building momentum to screening





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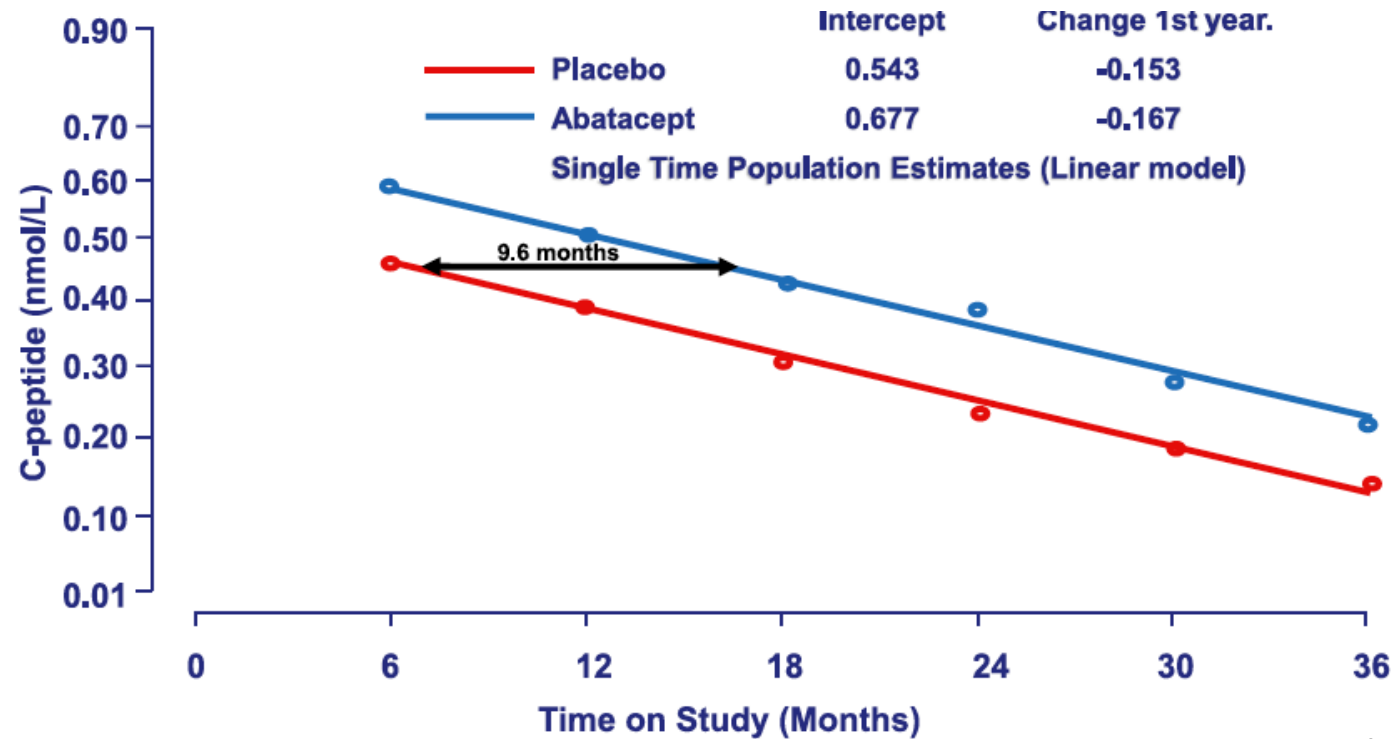


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Extra Slides



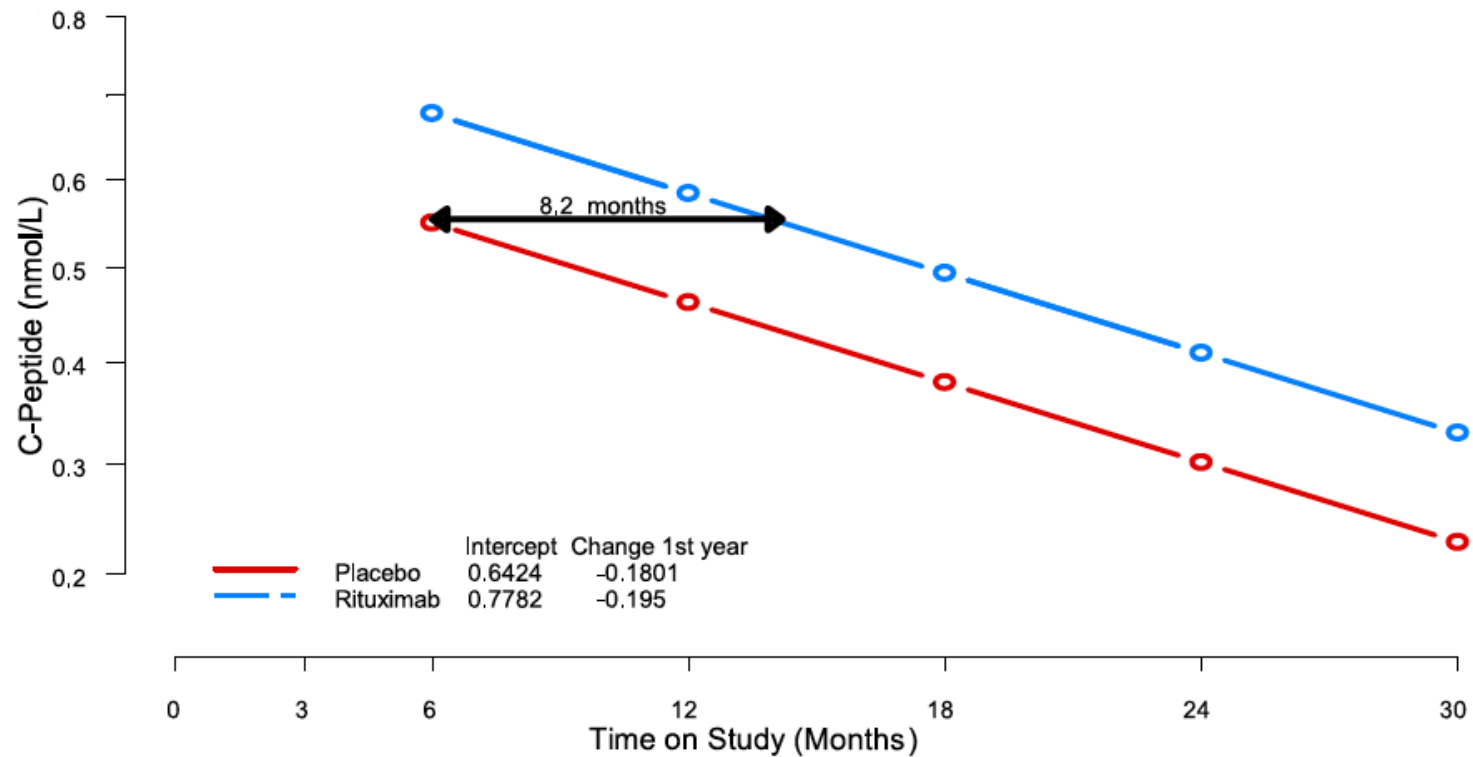
Abatacept Delays Fall in C-peptide 3 Years After Initial Treatment



Orban et al., Diabetes Care, 2014



Rituximab Delays Fall in C-Peptide 2 years after Initial Treatment

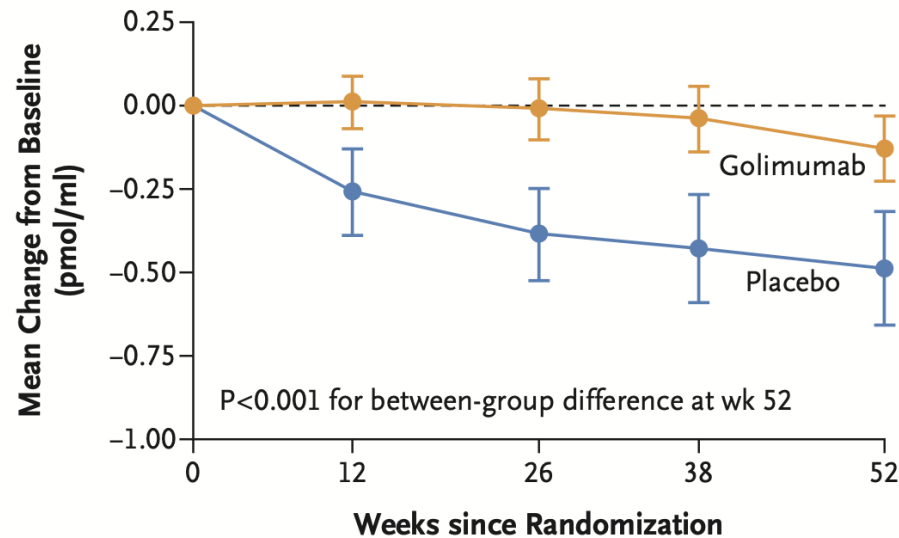


Pescovitz et al., Diabetes Care, 2014



Golimumab Improves Endogenous Insulin Production and Reduces Exogenous Insulin Use in 6-21 year olds with New Onset T1D

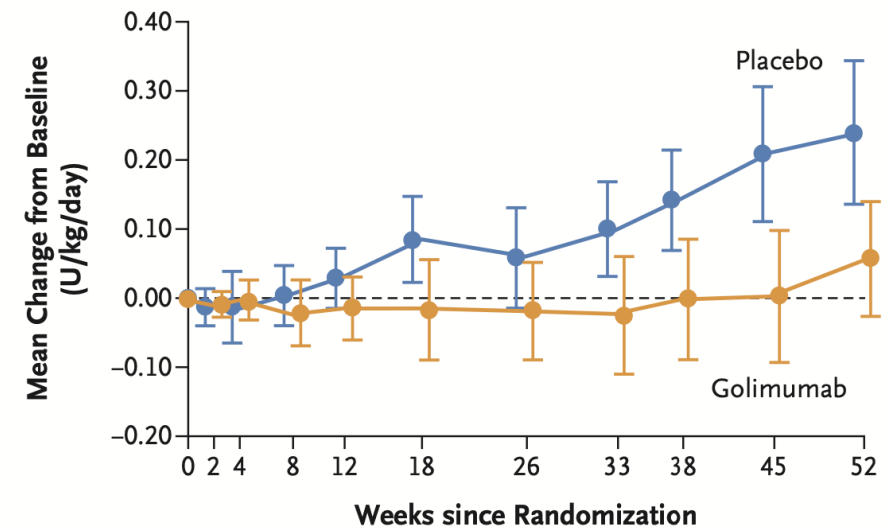
4-hour C-Peptide AUC



No. at Risk

Golimumab	56	52	49	49	50
Placebo	28	26	25	24	25

Insulin Use



Quattrin T et al., NEJM, 2020

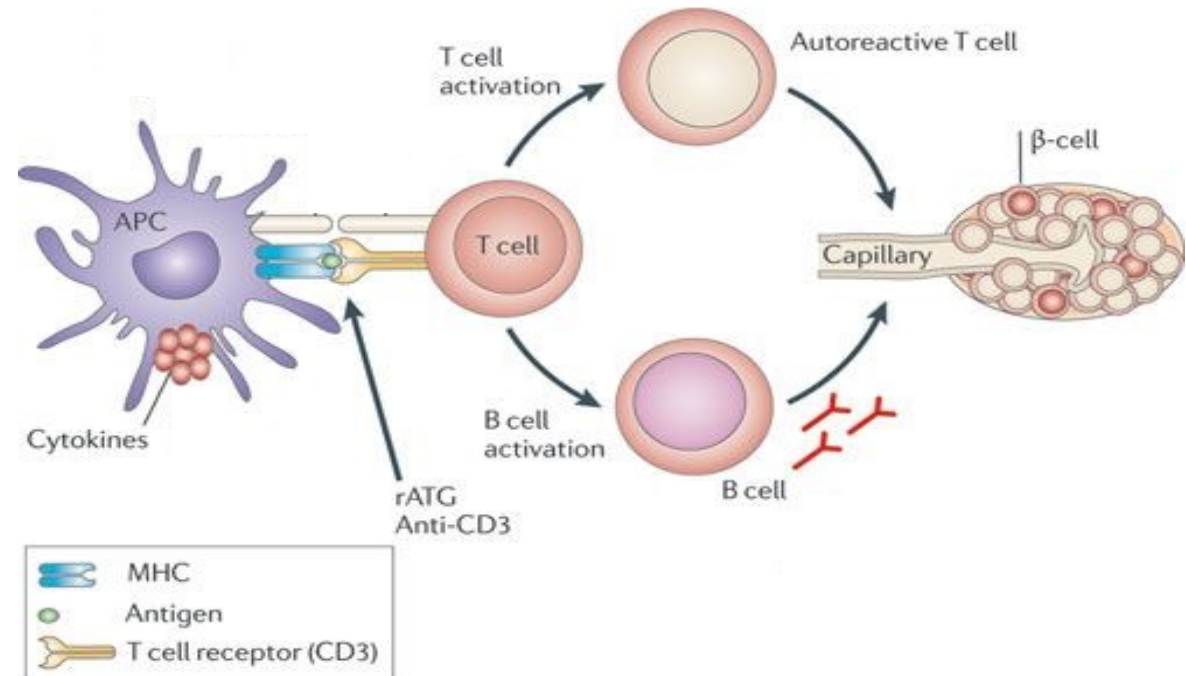


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Slide courtesy of Kimber Simmons, MD MS

Teplizumab Mechanism of Action

- Impairs effector T-cells
- Enhances regulatory T-cells
- May be tolerance enhancing



Lynch and Herold, 2011



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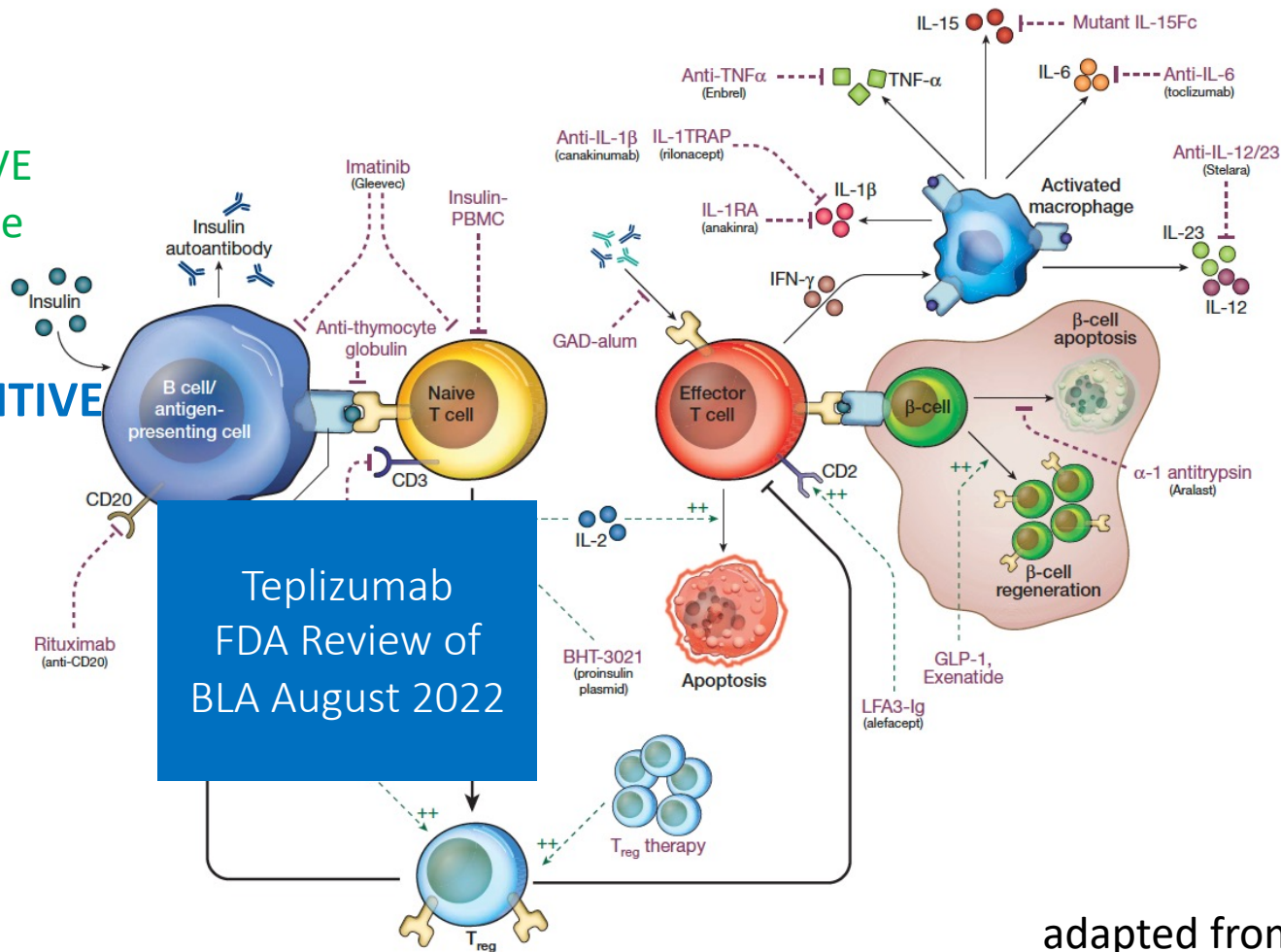
Slide courtesy of Kimber Simmons, MD MS

There is a Lack of Clinical Trials Available in Stage 2 although Several are in Development

STAGE 1
AUTOANTIBODY POSITIVE
 normal glucose tolerance

STAGE 2
AUTOANTIBODY POSITIVE
 Dysglycemia

STAGE 3
 NEW-ONSET T1D



adapted from Bluestone et al., 2010

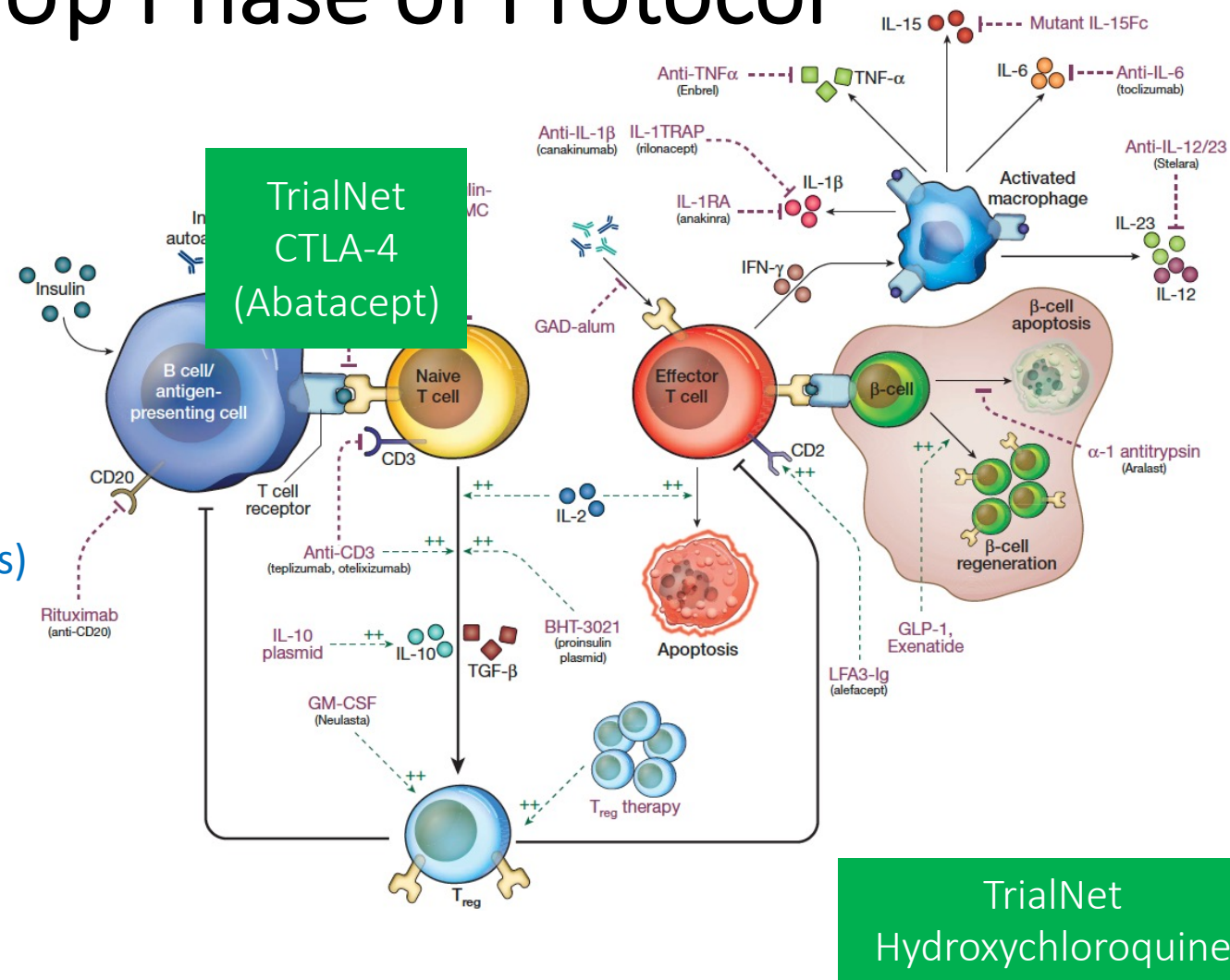


Trials in Stage 1 are Nearing Enrollment or in Follow-Up Phase of Protocol

STAGE 1
AUTOANTIBODY POSITIVE
normal glucose levels

STAGE 2
AUTOANTIBODY POSITIVE
Dysglycemia (abnormal glucose levels)

STAGE 3
High Glucose/NEW-ONSET T1D

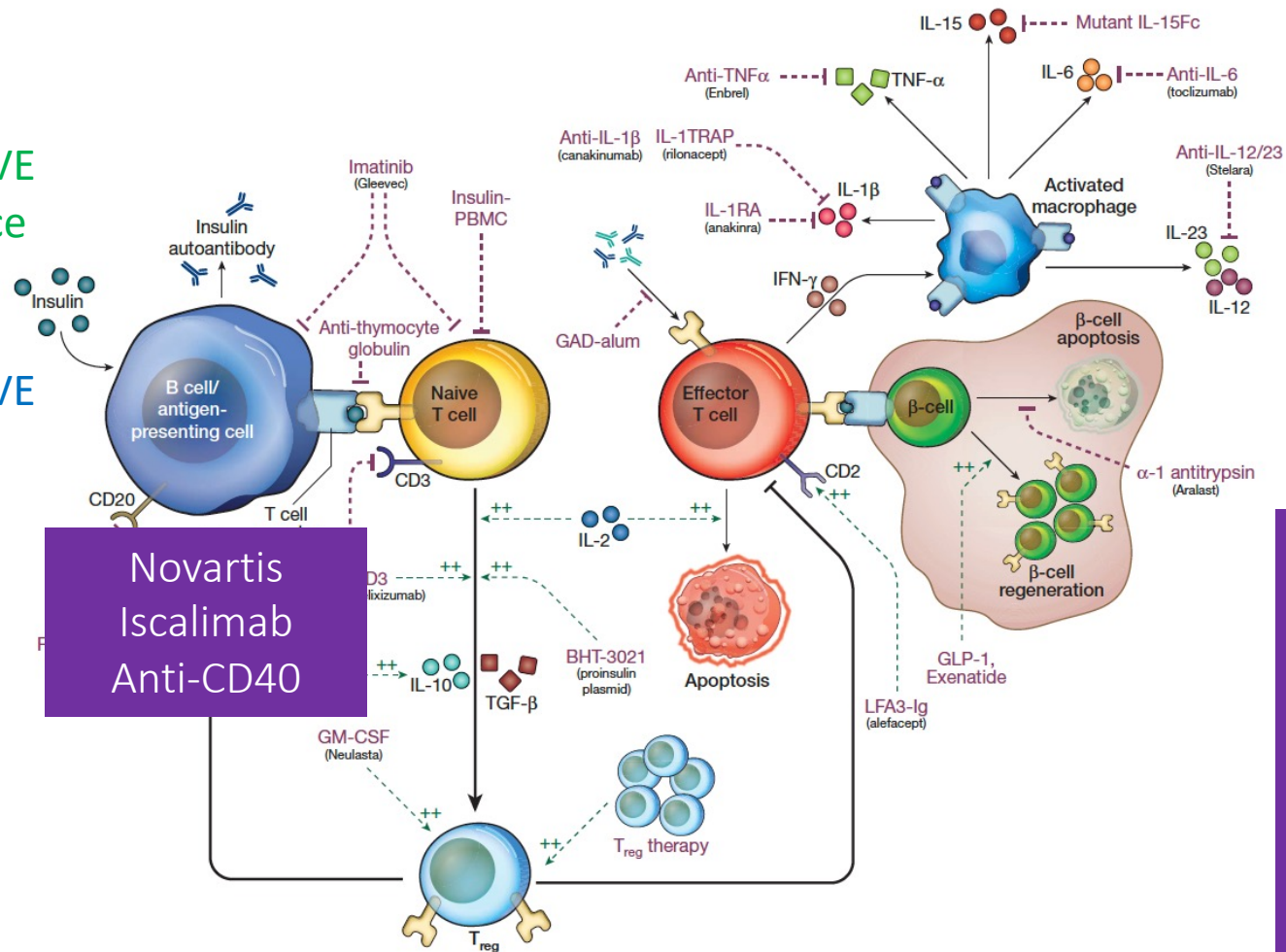


Trials in Stage 3 (New-Onset) T1D

STAGE 1
AUTOANTIBODY POSITIVE
 normal glucose tolerance

STAGE 2
AUTOANTIBODY POSITIVE
 Dysglycemia

STAGE 3
NEW-ONSET T1D



Novartis
 Iscalimab
 Anti-CD40

TrialNet
 Plasmid Immunotherapy:
 (pre- proinsulin (PPI),
 transforming growth
 factor β 1 (TGF- β 1),
 interleukin-10 (IL-10),
 and interleukin-2 (IL-2)

adapted from Bluestone et al., 2010



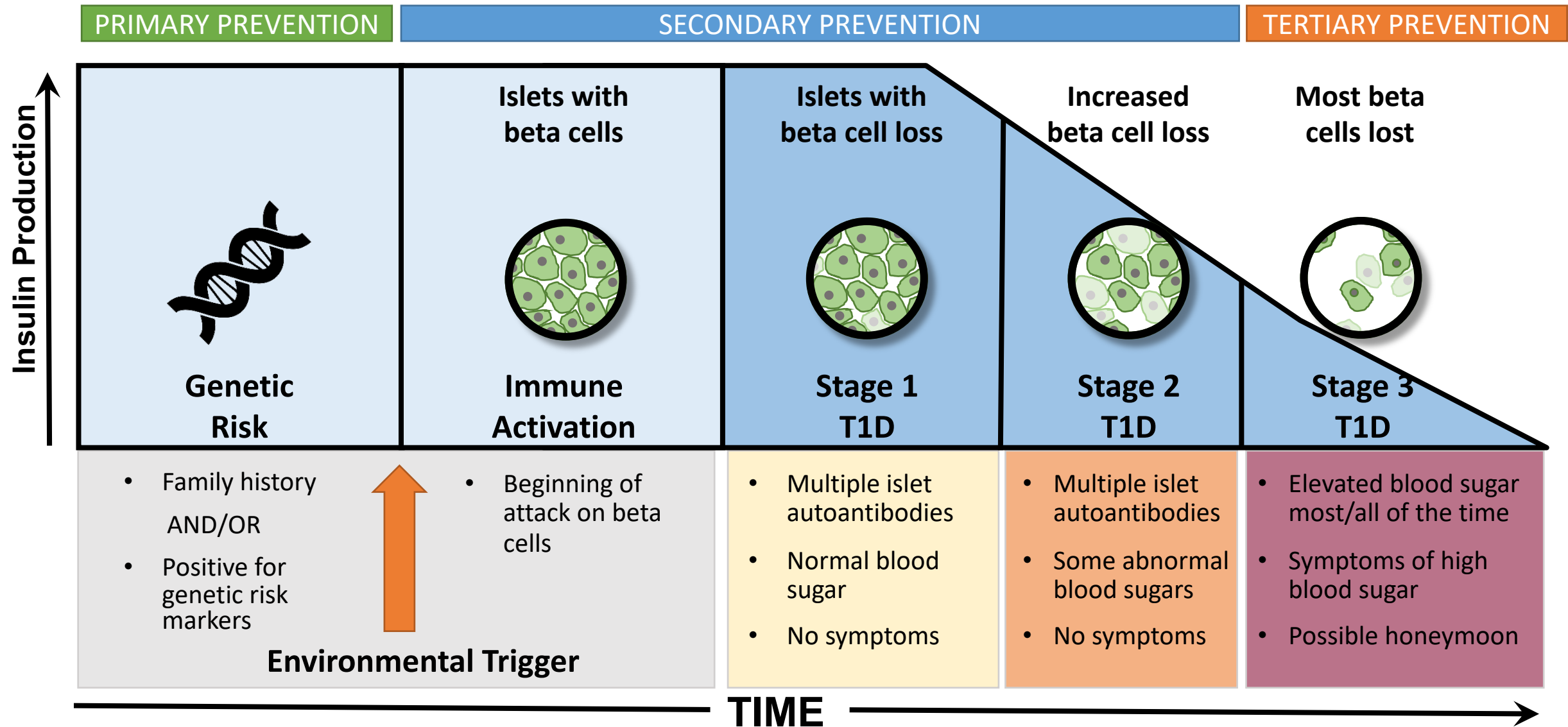
Islet Transplant

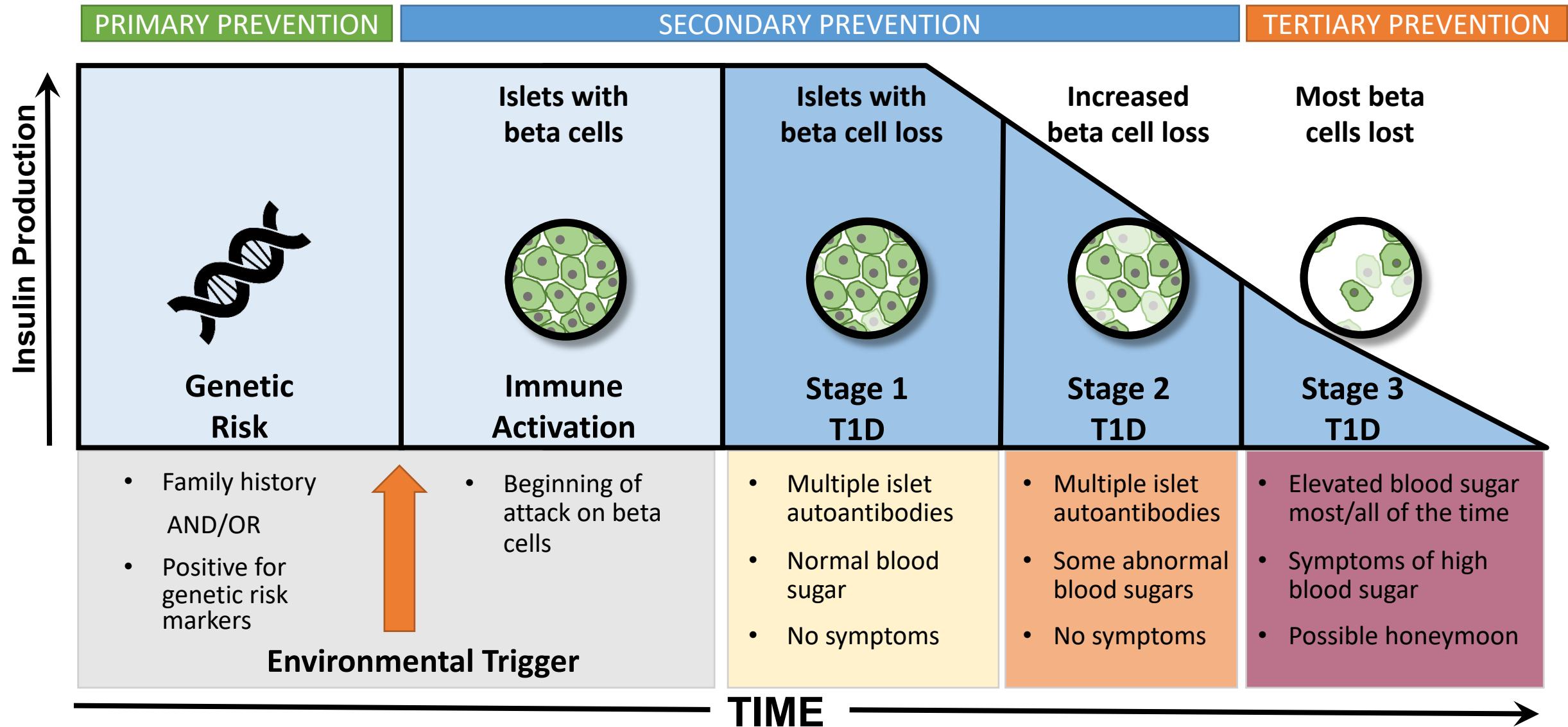




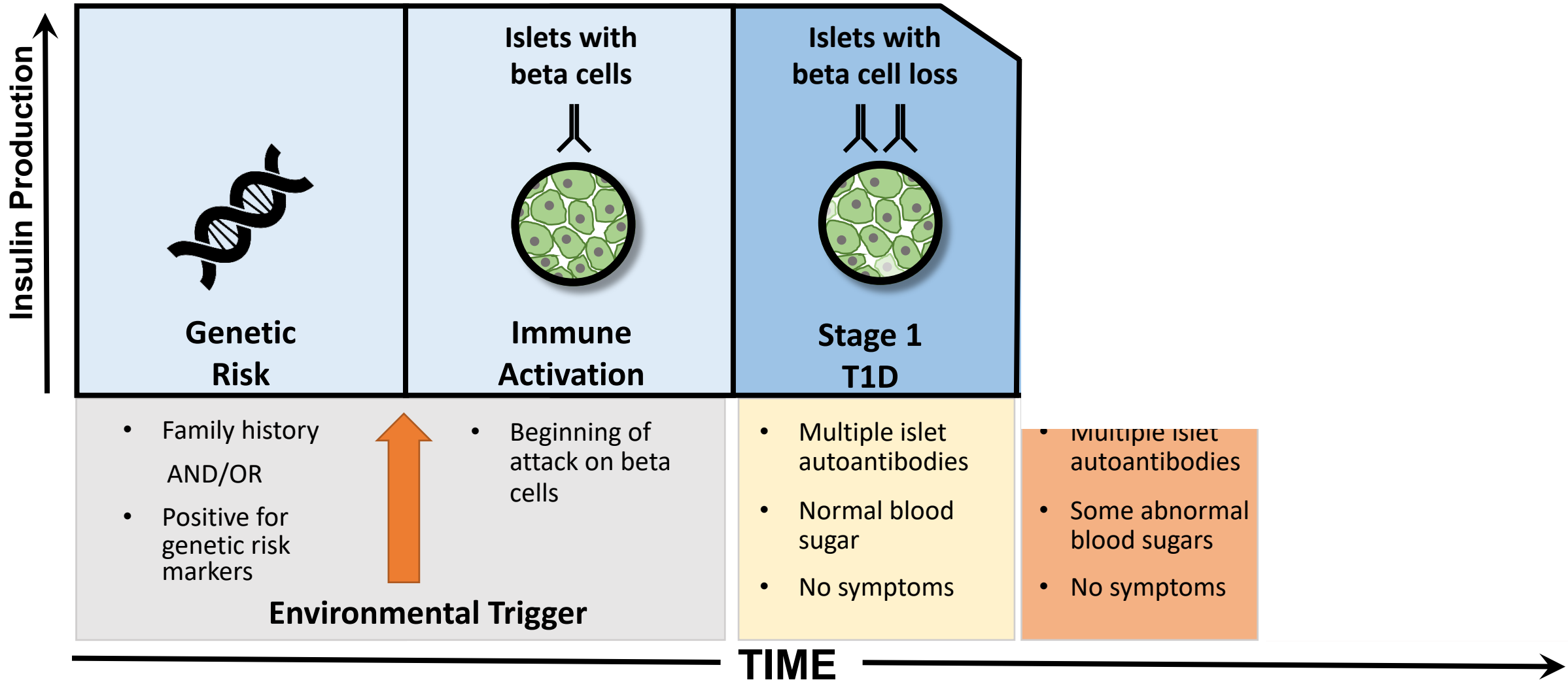
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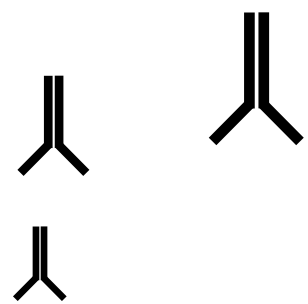
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PATHWAY TO TYPE 1 DIABETES





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