Early-Stage Diabetes Diagnosis and Treatment

Louis Philipson, MD, PhD

THE UNIVERSITY OF CHICAGO

T1D Exchange

Kovler Diabetes Center:
Focus on T1D Clinical studies /

Early-Stage Diabetes Diagnosis and Treatment

Trials Updates

November 11, 2024

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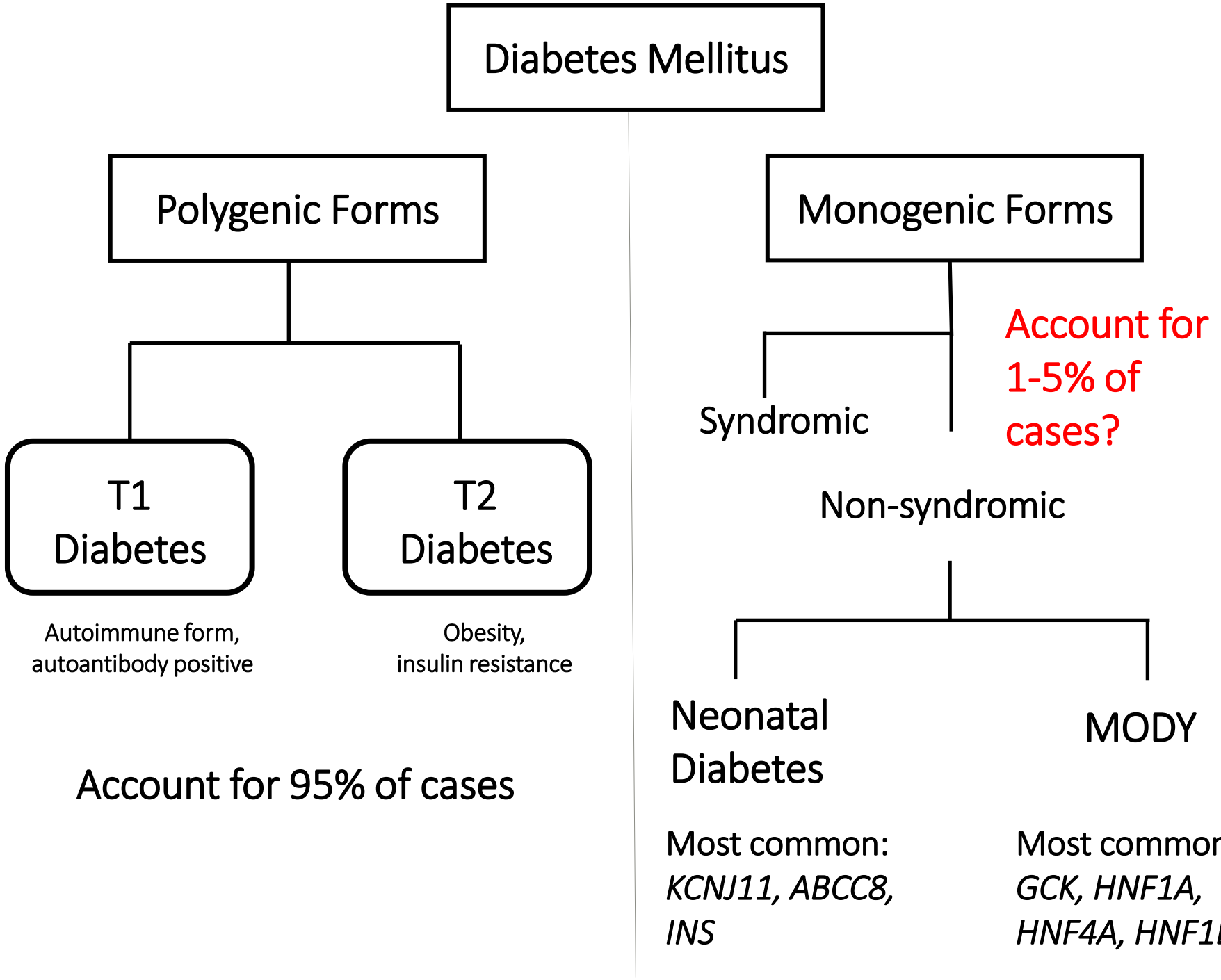
Research and Care

University of Chicago
Medicine


Diabetes Mellitus
Polygenic Forms
Monogenic Forms
T1 Diabetes
T2 Diabetes
Autoimmune form, autoantibody positive
Obesity, insulin resistance
Account for 95% of cases
Syndromic
Account for 1-5% of cases?
Non-syndromic
Neonatal Diabetes
MODY
Most common: KCNJ11, ABCC8, INS
Most common: GCK, HNF1A, HNF4A, HNF1B

Diabetes TrialNet

https://www.trialnet.org/

Pathway to Prevention screening is the first step for all TrialNet prevention studies.

[ATG Prevention Study (STOP-T1D)]
[JAK Inhibitors Newly Diagnosed Study (JAKPOT T1D)]
[Rituximab-pvvr / Abatacept Newly Diagnosed Study (T1D RELAY)]
[Tolerance Using Plasmid (TOPPLE) Study: Phase 1]

https://www.trialnet.org/our-research/newly-diagnosed-t1d

Risk Screening for Relatives

If you have a relative with T1D, you may be eligible for risk screening that can detect the early stages of T1D years before symptoms appear.
More

Risk Screening - Other

If you or your child has tested positive for type 1 diabetes related autoantibodies, we're here for you.
More

Monitoring

Depending on your risk screening results, you may be eligible for monitoring. We'll monitor you for disease progression and let you know if you become eligible for a study.
More

Prevention Studies

If your screening results show you are in the early stages of T1D, you may be eligible to join a prevention study testing ways to slow or stop disease progression.
More

Newly Diagnosed

For people newly diagnosed with T1D, we offer clinical studies testing ways to slow disease progression by preserving insulin production.
More

Long-Term Follow-up

If you are diagnosed with T1D while participating in one of our prevention studies, we're still here for you. You can continue to receive personal monitoring while helping us learn more.
More

T1D FACTS

Understanding the stages of type 1 diabetes

T1D starts with a genetic predisposition—gene(s) that put you at higher risk. If you have a family member with T1D, your risk is 1 in 20. Risk for the general population is 1 in 300. T1D progresses in three distinct stages. TrialNet risk screening can identify T1D in its earliest stages - sometimes years before symptoms appear.
Learn more

TrialNet TN-01

- Risk Screening
- Risk Screening - Other
- Prevention Studies
- Newly Diagnosed T1D
- Long-Term Investigative Follow-Up in TrialNet (LIFT)

Study Details

Currently Enrolling

Pathway to Prevention screening is the first step for all TrialNet prevention studies. Screening is offered at no cost to eligible individuals to evaluate their personal risk of developing the disease. This unique screening can identify the early stages of type 1 diabetes (T1D) years before any symptoms appear. It also helps researchers learn more about how T1D develops and plan new studies exploring ways to prevent it.

- Relatives of people with T1D are 15 times more likely to develop the disease than the general population.
- Increased risk of developing T1D is linked to the presence of five diabetes-related autoantibodies, regardless if you have a relative or not.
- The JDRF, ADA and Endocrine Society now classify having two or more of these autoantibodies as early stage T1D.

Screening in TrialNet

Who Can Participate

You qualify for free risk screening if you:

- Are between the ages of 2.5 and 45 years and have a parent, brother/sister, or child with T1D
- Are between the ages of 2.5 and 20 years and have an aunt/uncle, cousin, grandparent, niece/nephew, or half-brother/sister with T1D
- Have not been diagnosed with diabetes

OR

- Are between the ages of 2.5 and 45 years and have tested positive for at least one T1D related autoantibody outside of TrialNet (click here for more information)
- Have not been diagnosed with diabetes

Please Note:
TrialNet currently does not offer re-screening to those who tested negative for autoantibodies in the past.

Screening Options

Screening is free, quick, convenient and super important. Only a small blood sample is needed. TrialNet screening is available by appointment at one of our many locations. We also offer two options for test kits that can be mailed directly to you:

- **In-home Test Kit:** This free kit provides everything you need to collect a finger-stick blood sample from the safety of your home. You can ship it back free using FedEx contactless at home pick up.

- **Lab Test Kit:** You can take this free screening kit to any Quest Diagnostics or LabCorp lab for a blood draw.

T1Detect: Learn About Type 1 Diabetes Risk Screening

Messaging to families with T1D

Scientists and doctors used to believe that type 1 diabetes happened suddenly and without warning, but thanks to advances in screening and a better understanding of the human immune system, we now know that type 1 diabetes is not sudden and usually starts long before insulin is required.

https://www.jdrf.org/t1d-resources/t1detect/

- **TrialNet:** A free, research-based screening and clinical trial program for family members of people with type 1 diabetes. This network of experts has sites throughout the United States and screening can be done **through an at-home kit** or **in-person**. individuals between the ages of 2.5 and 45 years with a first-degree relative (parent, child, sibling) with T1D, ages 2.5 to 20 with a second-degree relative (cousin, grandparent) with T1D, OR ages of 2.5 to 45 years and have tested positive for at least one T1D related autoantibody outside of TrialNet.

- **ASK (Autoimmunity Screening for Kids):** screening for T1D and celiac disease
- for all children ages 1-17 years in the United States.
- No family connection to T1D is required

- **PLEDGE (Population Level Estimate of Type 1 Diabetes Risk Genes in Children):** screening of children younger than age 6 who are patients at Sanford Health in South Dakota.

- **Blood tests ordered by a doctor**
- The Fr1da study, the world's largest population-based screening for type 1 diabetes in children, was launched at Helmholtz Munich in 2015. The Fr1da offers islet autoantibody screening to children aged 2 to 10 years, living in Bavaria, Germany

T1D Disease Progression

The Path to Type 1 Diabetes

T1D Disease Progression

Type 1 Diabetes TrialNet

Genetic Risk

Immune Activation

Immune Response

The Stages to Type 1 Diabetes

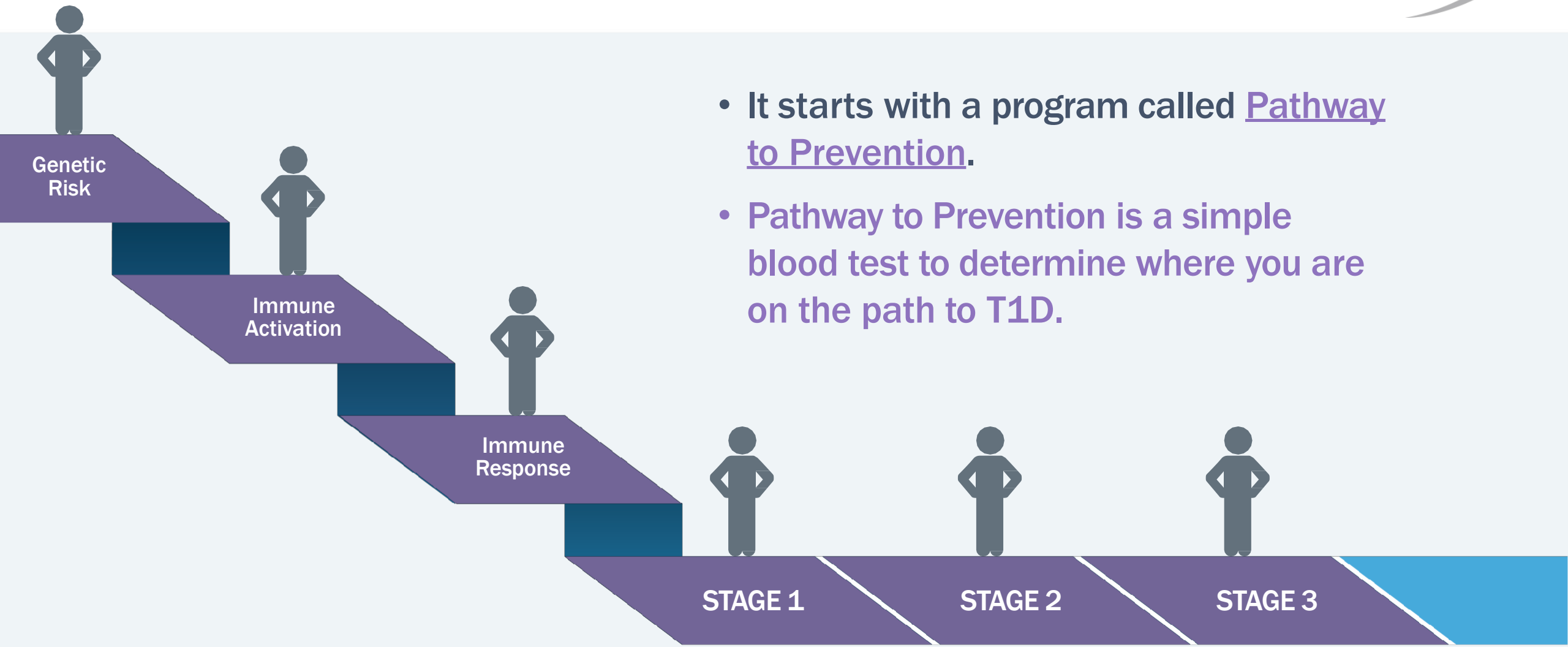
Starting Point
If you have a relative:
15x greater risk of developing T1D

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

STAGE 1	STAGE 2	STAGE 3	STAGE 4
Normal Blood Sugar ≥ 2 autoantibodies START OF T1D	Abnormal Blood Sugar ≥ 2 autoantibodies	Clinical Diagnosis ≥ 2 autoantibodies	Long-standing T1D

TrialNet Disease Intervention



- It starts with a program called Pathway to Prevention.
- Pathway to Prevention is a simple blood test to determine where you are on the path to T1D.

T1D Disease Progression

The Path to Type 1 Diabetes

T1D Disease Progression

Type 1 Diabetes TrialNet

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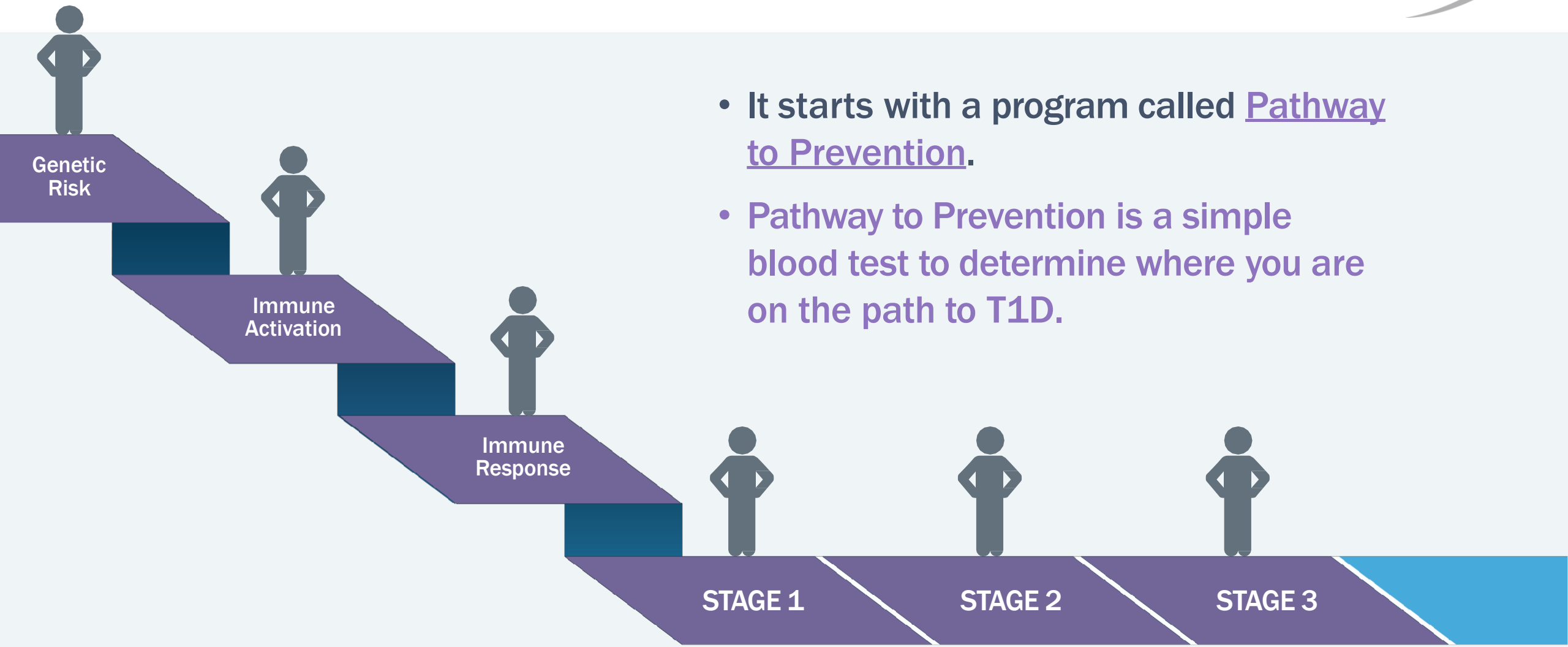

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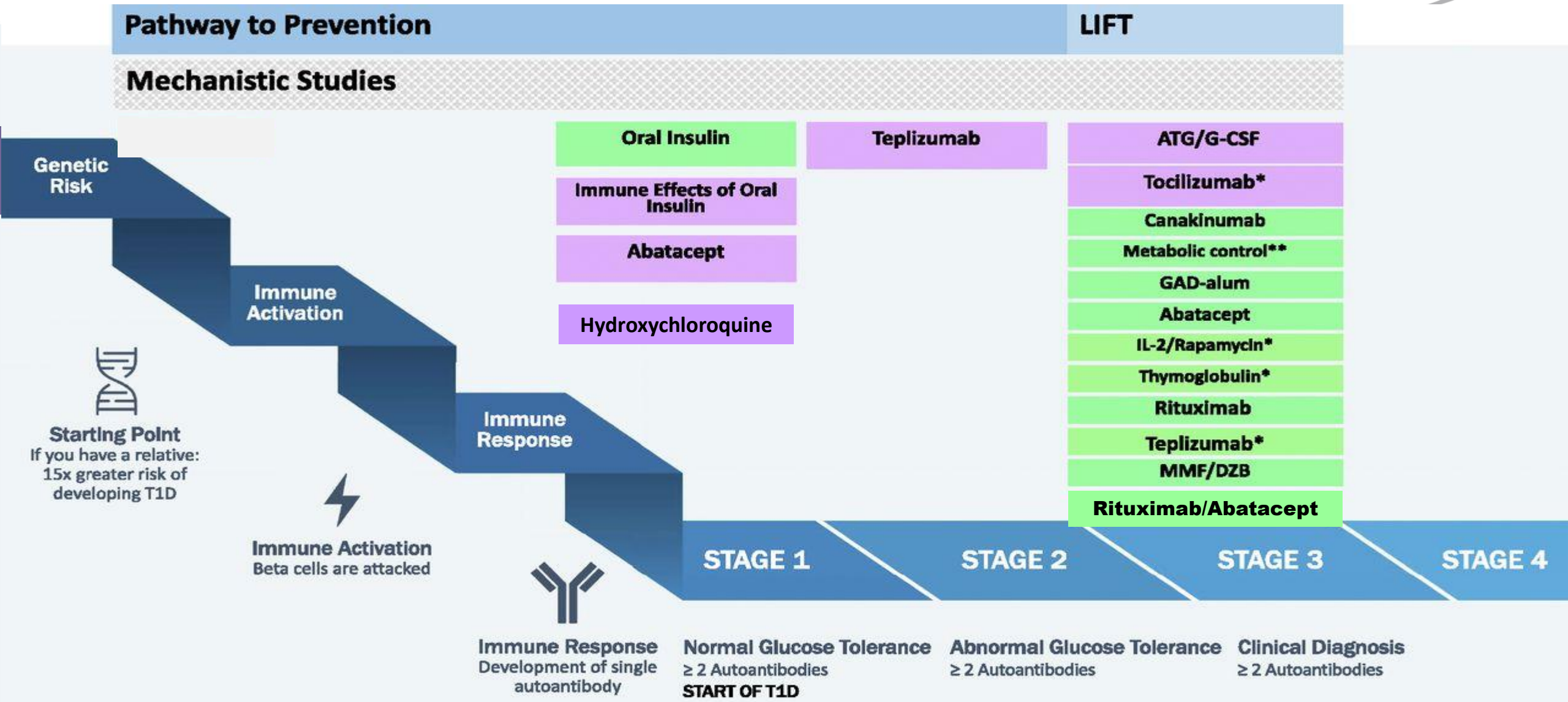
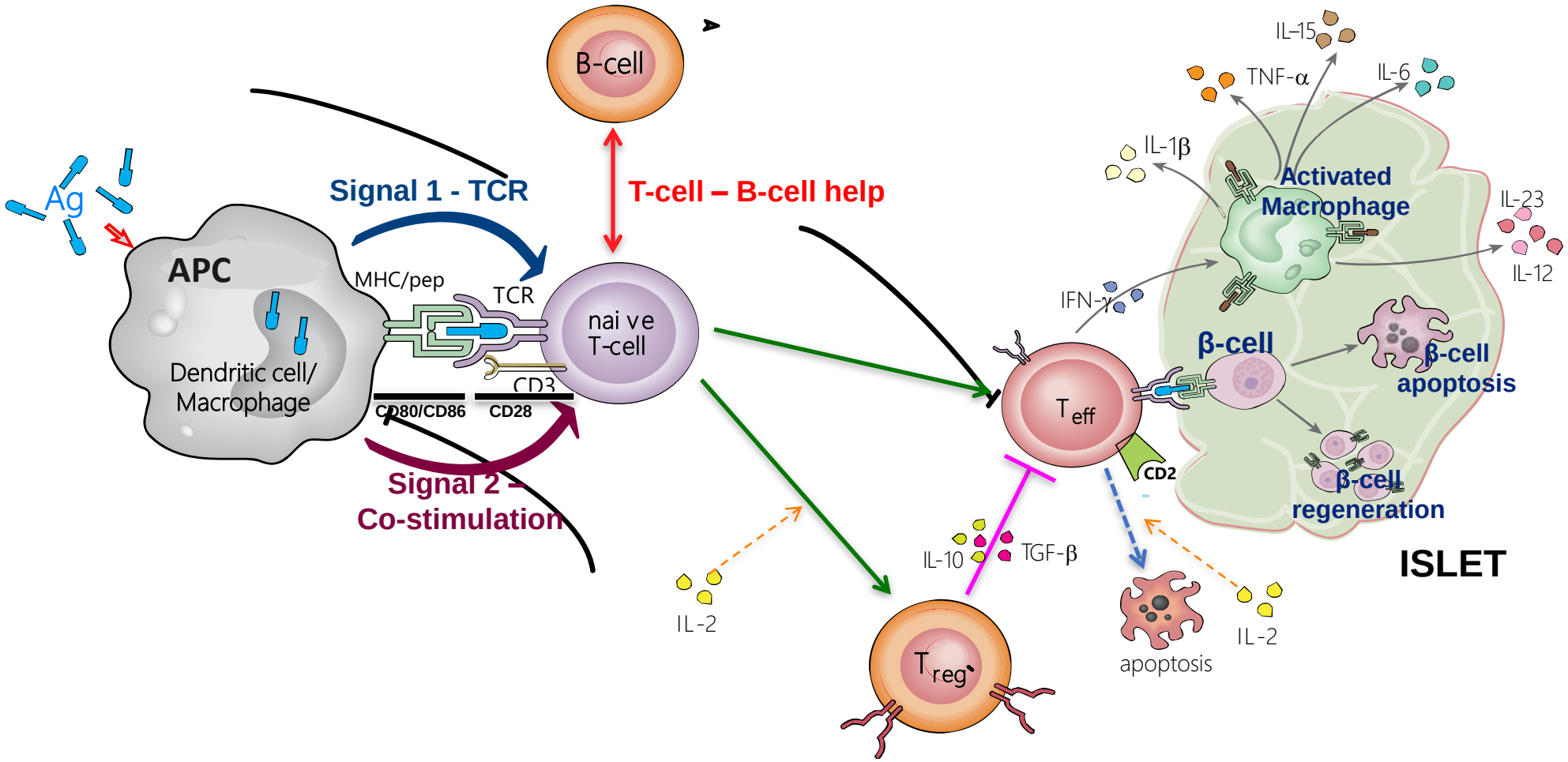
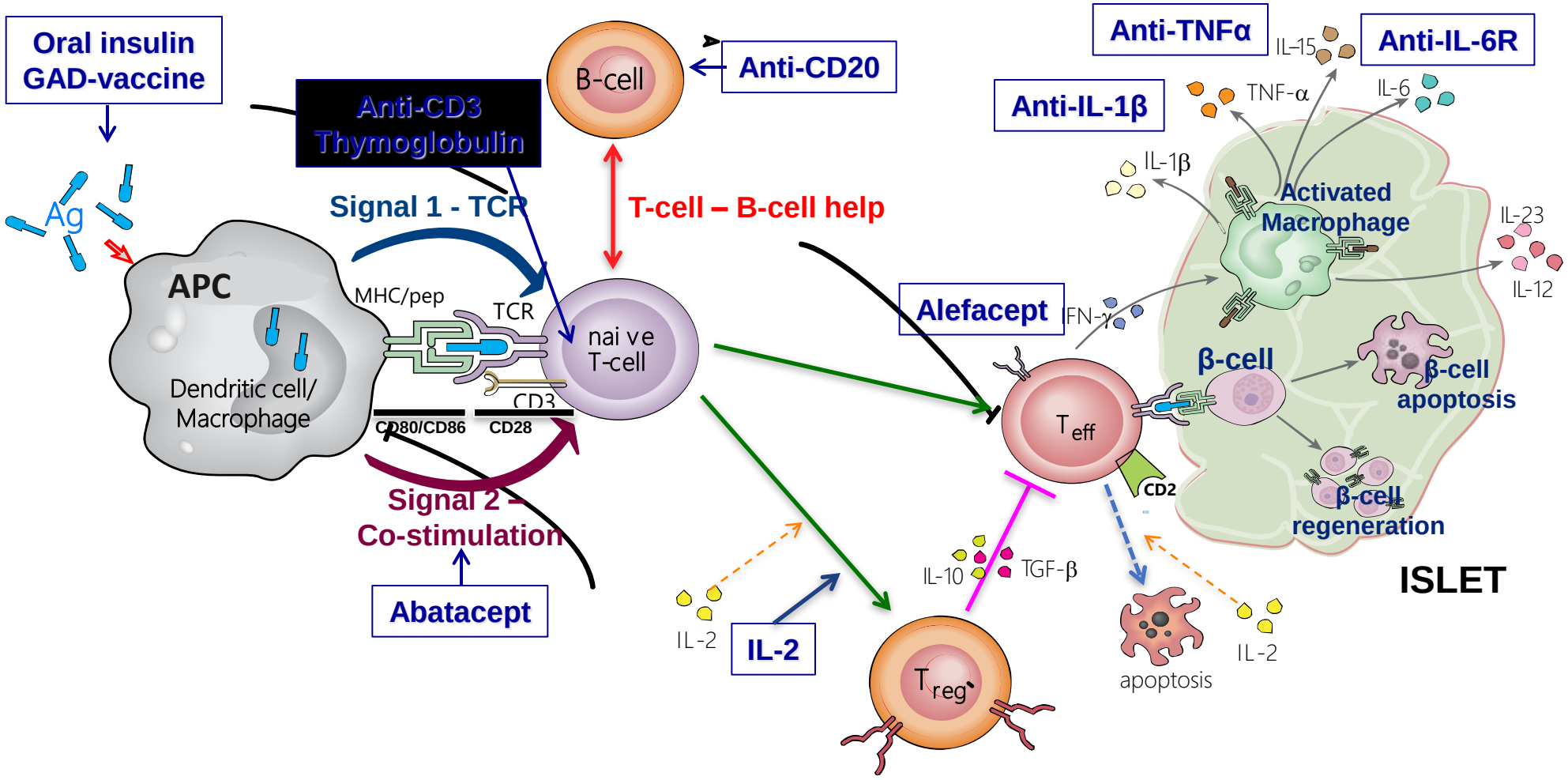


Immunopathogenesis of T1D - 2014



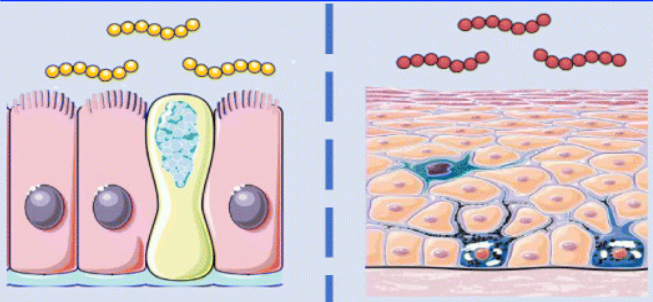
Interventions Target Different Mechanisms-2014



TrialNet Disease Intervention

Type 1 Diabetes TrialNet

(1). Antigen Specific
Oral Insulin GAD Alum



(2). DQ8 Blockade
Methyldopa

(3). Anti-CD3
Teplizumab

(4). ATG
Thymoglobulin

(5). LFA F_c Fusion
Alefacept

(6). CTLA4 F_c Fusion
Abatacept

(7). Proleukin
IL-2

(8). Adoptive T_{reg}
Transfer

(9). Anti-CD20
Rituximab

(10). Cytokine Blockade
Alpha 1 - Antitrypsin
Anakinra
Canakinumab
Etanercept

(11). Beta Cell Protective
Gleevec
Sitagliptin + PPI
Verapamil

Studies in Recent-Onset T1D – (2014 – Dr Skyler)

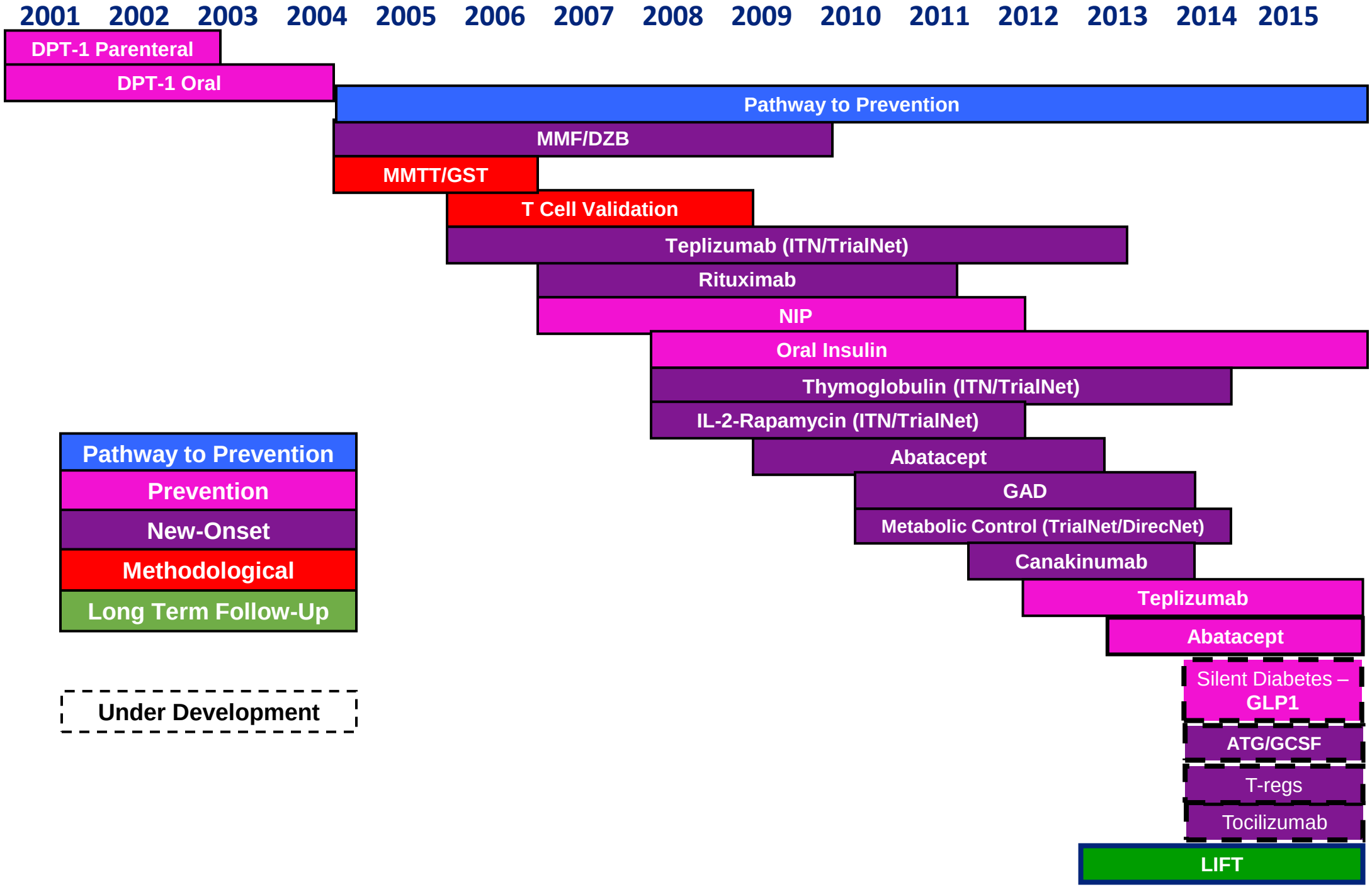
- Mycophenolate Mofetil +/- Anti-CD25
- Anti-CD20 (Rituximab)
- Abatacept [CTLA4-Ig] (Orencia)
- GAD-Alum Vaccine
- Canakinumab Anti-IL1β (Ilaris)
- Meticulous Metabolic Control *(with DirecNet)*
- *IL-2 + Rapamycin Pilot (ITN-led trial)*
- *Teplizumab Anti-CD3 (ITN-led trial)*
- *Thymoglobulin (ITN-led trial)*
- *Alefacept (ITN-led trial)*

Type 1 Diabetes TrialNet

Studies in Recent-Onset T1D – Dr Skyler-2014

Mycophenylate±Anti-CD25	No effect
Rituximab Anti-CD20	Transient effect
Abatacept CTLA4-Ig	Transient effect
GAD	No effect
Canakinumab Anti-IL1-β	No effect
Metabolic Control Study	No effect
IL2+Rapamycin (ITN-led)	Transient adverse effect
Teplizumab Anti-CD3 (ITN-led)	Transient effect
Thymoglobulin (ITN-led)	Possible effect in age 22-35
Alefacept (ITN-led)	No effect on primary end point

Type 1 Diabetes TrialNet


2001
2002
2003
2004
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2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
DPT-1 Parenteral
DPT-1 Oral
Pathway to Prevention
MMF/DZB
MMTT/GST
T Cell Validation
Teplizumab (ITN/TrialNet)
Rituximab
NIP
Oral Insulin
Thymoglobulin (ITN/TrialNet)
IL-2-Rapamycin (ITN/TrialNet)
Abatacept
GAD
Metabolic Control (TrialNet/DirecNet)
Canakinumab
Teplizumab
Abatacept
Silent Diabetes – GLP1
ATG/GCSF
T-regs
Tocilizumab
LIFT
Pathway to Prevention
Prevention
New-Onset
Methodological
Long Term Follow-Up
Under Development

For US residents only

Medication Guide | Prescribing Information | Important Safety Information | Healthcare Professionals

Tzield® (teplizumab-mzwv) Injection | 2mg/2mL

ABOUT TYPE 1 DIABETES | ABOUT TZIELD | PATIENT SUPPORT | SIGN UP TO LEARN MORE

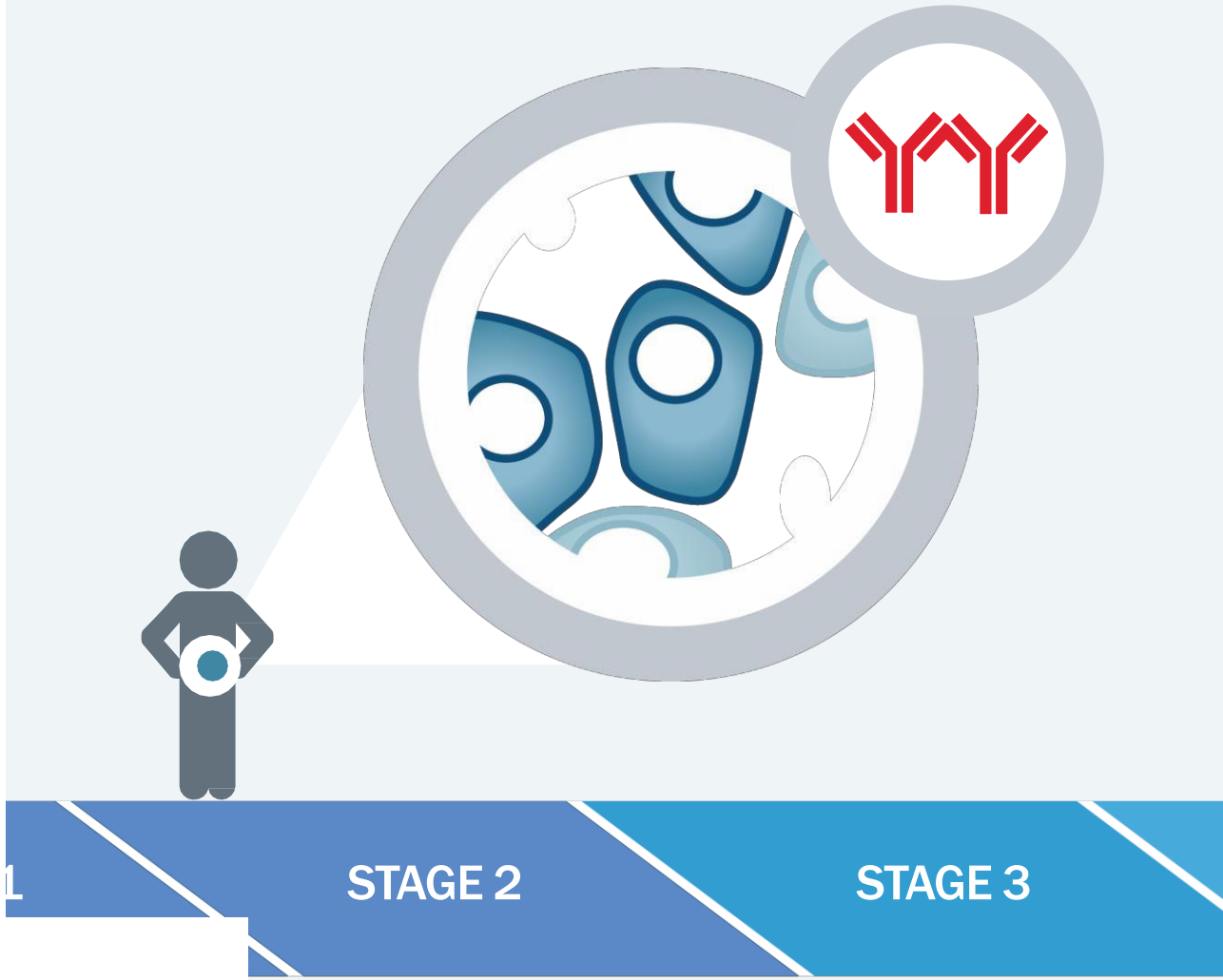
TrialNet Disease Intervention

Type 1 Diabetes TrialNet

TN10
Teplizumab (Anti-CD3)

Stage 2 Prevention Study

- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
- No symptoms



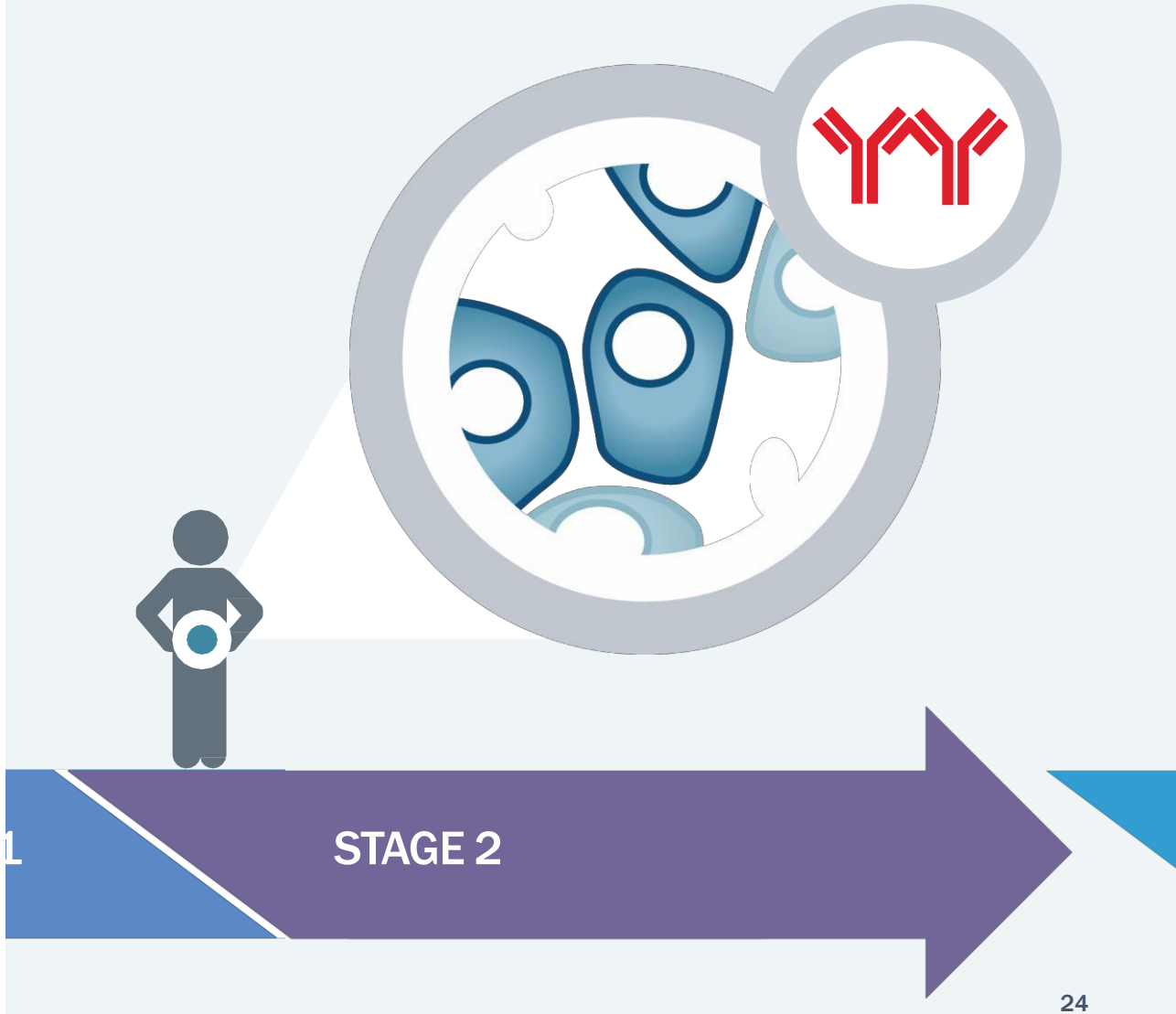
TZIELD is for people 8 years and older with **Stage 2 T1D**.

TrialNet Disease Intervention

TN10
Teplizumab (Anti-CD3)

Study Goal

- Delay conversion to stage 3 (clinical diagnosis)
- Maintain current level of beta cell production



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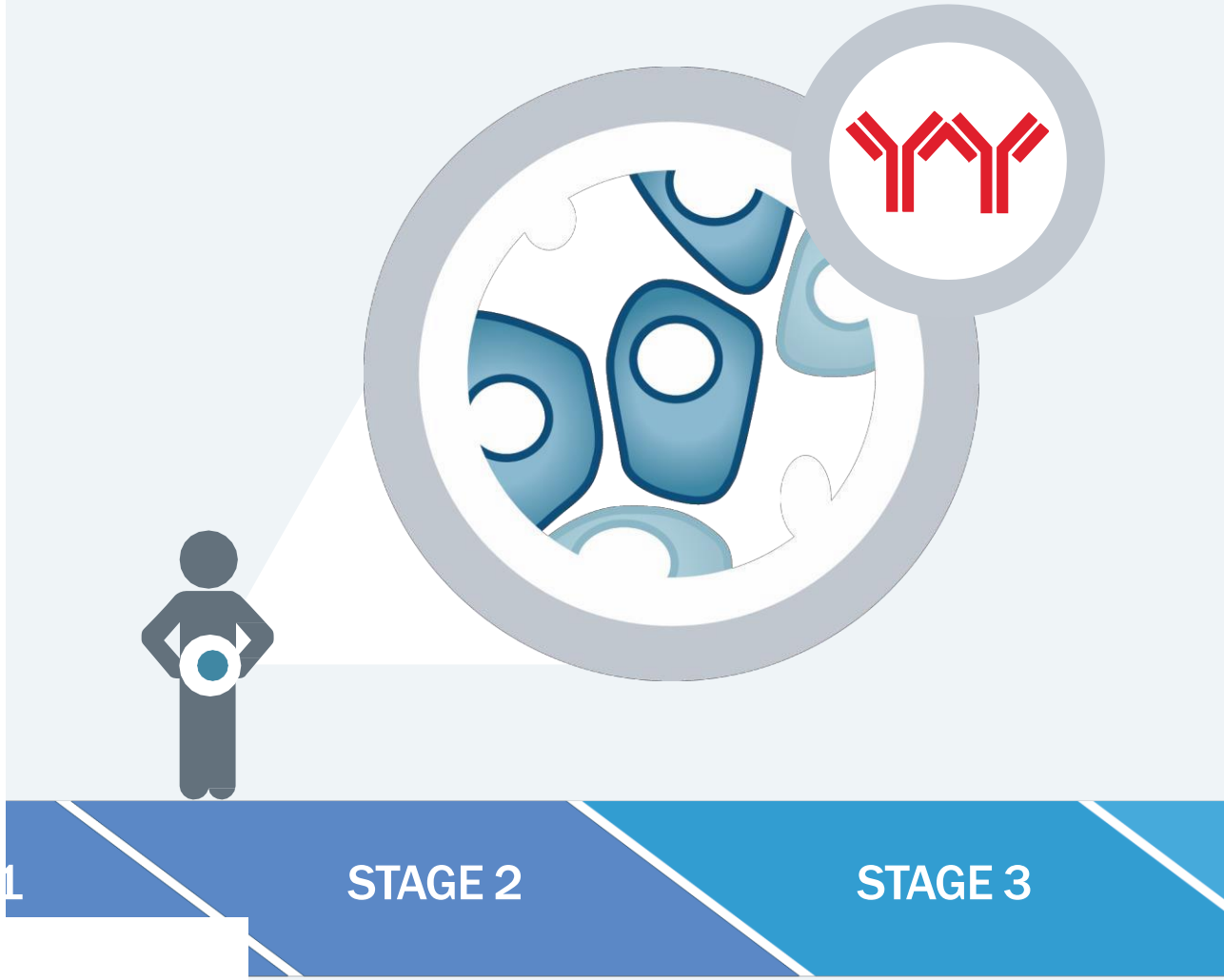

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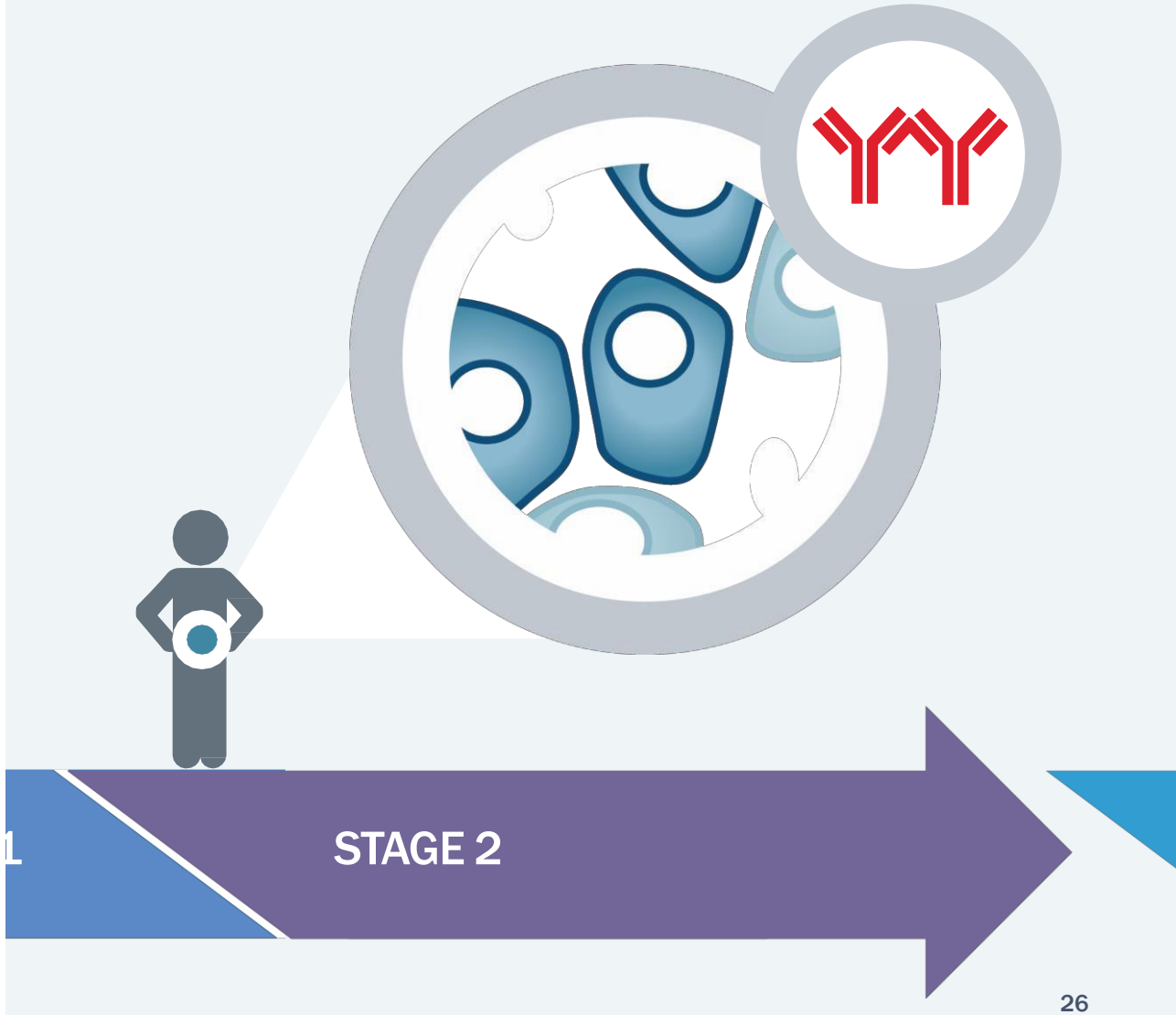
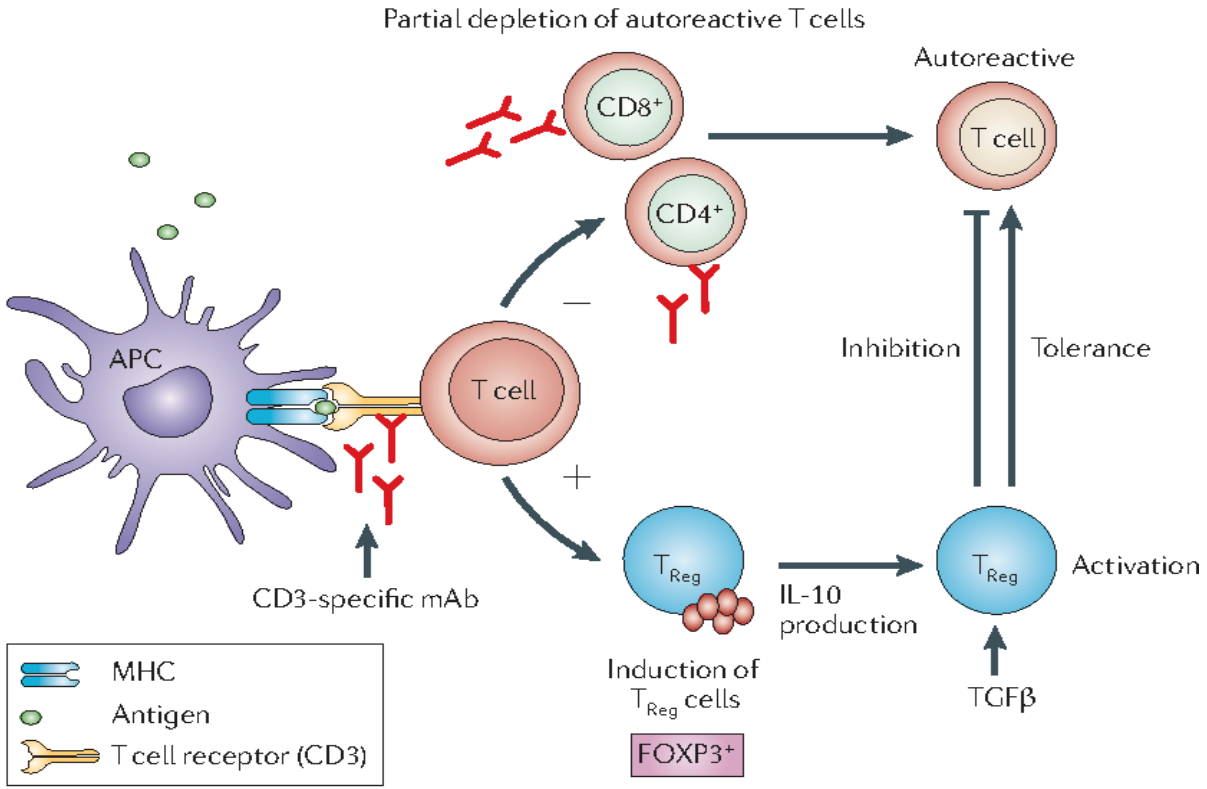


TrialNet Disease Intervention

TN10
Teplizumab (Anti-CD3)

MOA



STAGE 3

TrialNet Disease Intervention Stage 2

CURRENT

1. TN10 was for those identified in Stage 2
2. Teplizumab
    - TrialNet data from 2019: Teplizumab produces an average delay of onset 2 years to diagnosis
    - Stage 3- New Study: Enrolled by 6 weeks of diagnosis

Stage 2 FDA approval Provention Bio
➔ Sanofi ***Tzeild***

TrialNet Disease Intervention Stage 2

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Stage 2 FDA approval Provention Bio
➔ Sanofi ***Tzeild***

TN10 results lead to Tzeild approval in the US

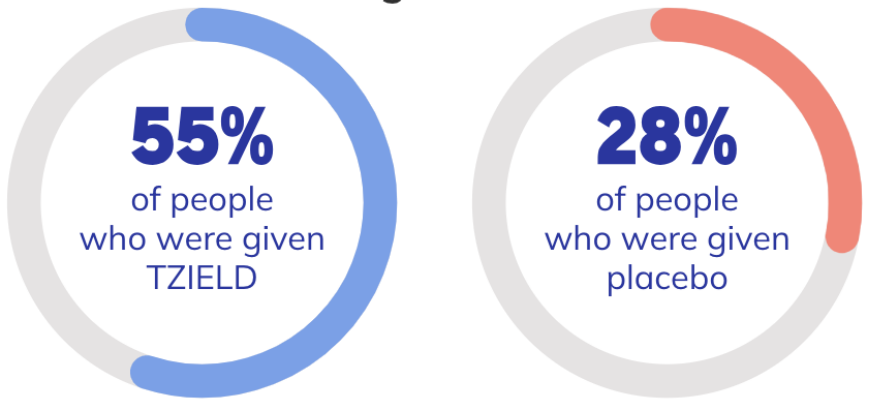
A CLINICAL TRIAL FOR TZIELD SHOWED:

With TZIELD, people had 2 more years before the onset of Stage 3 T1D, compared with **placebo**.

The median* time to diagnosis was 50 months for those who were given TZIELD, compared with 25 months for those who were given placebo.

More people who were given TZIELD had not been diagnosed with Stage 3 T1D by the end of the study, compared with people who were given **placebo**.

People who had not been diagnosed with Stage 3 T1D:



TZIELD IS AN INTRAVENOUS (IV) INFUSION

This means it's given through a needle into a vein in your arm. The infusions are:

ONCE A DAY EVERY DAY
for 14 days in a row

AT LEAST
30 minutes long

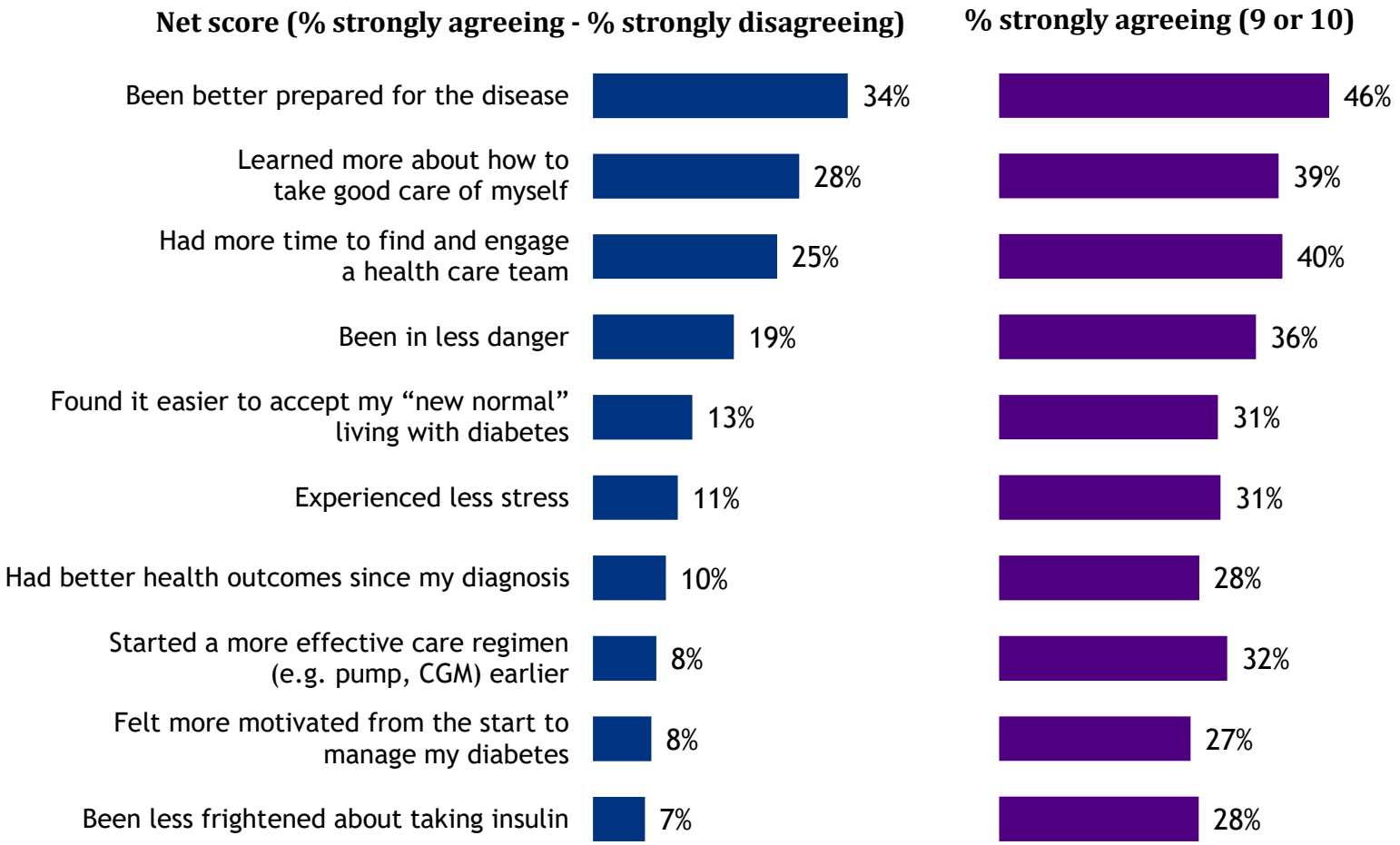
You will also need some extra time before and after each infusion.
This is so a nurse can prepare the infusion and monitor you or your child for a short period afterwards.

If you miss a scheduled infusion, your doctor will continue your treatment on the next scheduled day. You will not receive 2 infusions on the same day.

Impact of a two-year delay on PWD

All respondents

With a two-year delay before needing to start on insulin, I would have:



Q1: How do you think such a two-year delay before you had to start taking insulin would have affected your life with diabetes?
For each of these questions, tell us how much you agree or disagree with these statements (10 is "agree strongly" and 1 is "disagree strongly).

Base: All respondents (n=1,078).

TZIELD may cause serious side effects, including:

- **Cytokine Release Syndrome (CRS).** Signs and symptoms of CRS problems may include:
  - fever
  - feeling tired (fatigue)
  - muscle and joint pain
  - nausea
  - headache
  - increased liver enzymes in your blood

  These signs and symptoms may start during the first 5 days of TZIELD treatment. Tell your healthcare provider right away if you develop any signs and symptoms of CRS during treatment with TZIELD.
- **Decrease in white blood cells.** TZIELD may cause a decrease in a type of white blood cell called lymphocytes. A decrease in white blood cells is a serious, but common side effect that can affect your body's ability to fight infections.

Your healthcare provider will do blood tests to check your liver and your complete blood counts before you start treatment and during treatment with TZIELD. During and after your treatment with TZIELD, your healthcare provider will check for serious side effects, as well as other side effects, and treat you as needed. Your healthcare provider may temporarily or completely stop your treatment with TZIELD, if you develop liver problems, have a serious infection, or if your blood counts stay too low.

What are the possible side effects of TZIELD?

The most common side effects of TZIELD include:

- rash
- leukopenia (decrease in white blood cell counts)
- headache

- Cytokine Release and Cytokine Release Syndrome
  - Clinical Manifestations of Cytokine Release
  - Clinical Manifestations of Cytokine Release Syndrome
  - Liver Enzyme and Bilirubin Elevations
  - Rash
  - Symptom Management
- Infections
  - Serious Infections
  - EBV and CMV
- Hematologic Abnormalities
  - Lymphopenia
  - Neutropenia
  - Anemia
  - Thrombocytopenia
- Hypersensitivity Reactions

Cytokine Release Syndrome (CRS) is a clinical diagnosis made when the number and severity of symptoms is sufficient to be considered a constellation of significant symptoms[1]

- In clinical trials of teplizumab-mzwv, the designation of "syndrome" was at the discretion of the investigators based on CTCAE criteria*
- CRS manifestations in teplizumab-treated patients included fever, nausea, fatigue, headache, myalgia, arthralgia, increased ALT, increased AST, and increased total bilirubin. These manifestations typically occurred during the first 5 days of teplizumab treatment[2]

Kovler study pipeline at a glance

Status	Pre-Start Up (pending site selection)	Site Selection- waiting on documents	Pending IRB/Contracts approval	IRB Approved awaiting CRC approval	Supplies pending & Pharmacy /SIV to be scheduled	Enrolling	Follow-up	Complete	Ended by sponsor prior to site activation
Study	Medpace Abata	Enable Gasherbrum	TN28 Tzield registry		MLS OLE TN31 Bayer Seminal-AF	Radiant Monogenic Diabetes TN01 Designate- ***on Hold*** Tadpol (DFMO) Mineralys (HTN) EqT1D MAPT1D Diasome	Focus Dompe	Imcyse Protect MODY Amgen MDMC	AztraZeneca ImmpepB Novartis Ozempic T1D
Timeline	10+ months out	8+ Months out	<3 months out	<3-4 months out	<1 month out	Green Light	Enrollment closed	No active pts	Stopped

Type 1 Studies

	TrialNet TN01 (TN28 / TN 31)	Dompe "Gladiator"	ITN funded by NIAID "DESIGNATE" On HOLD	DFMO "Tadpol"
Phase & duration	**Observational**	**Phase 3 n=327** **2:1** **24 months**	**Phase 1b** **n= 120-160** **1:1:1:1** **52 weeks**	Phase I 12 months
DRUG	N/A	• CXCL8 (IL-8) inhibitor • **Ladarixin PO** • BID 14 days on/ 14 days off	Open-label **12 Weekly SQ injections**	**3 months of oral** difluoromethylornithine
C-peptide	N/A	<0.205nmol/L	> 0.15 pmol/mL	>0.2 pmol/mL (equivalent to >0.6ng/ml)
AGE	2+	14-45	8-45	6-40
DX	Pre Type 1	W/in 180 days of insulin use	Rando w/in 18 months of dx	Diagnosis of T1D within 100 days at the time of randomization
STATUS	Actively Enrolling	Follow-up	On Hold	Actively enrolling

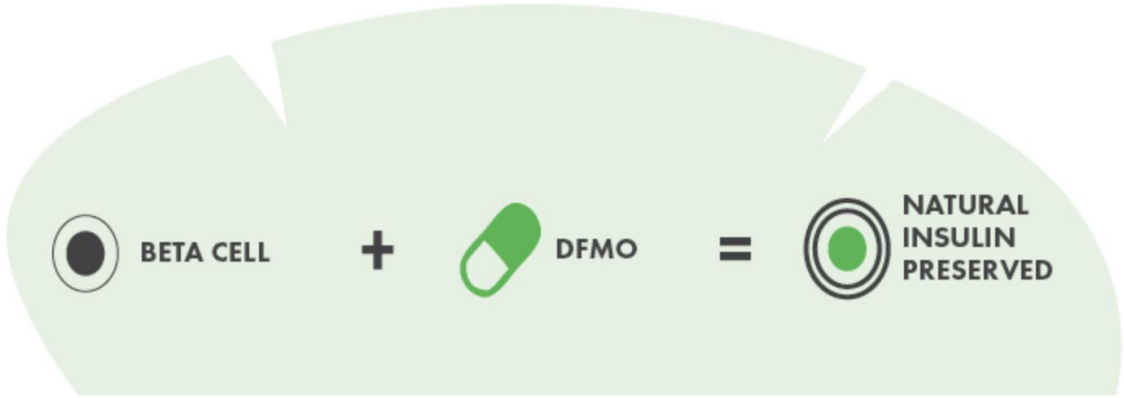
Green= Open to enrollment
Yellow- awaiting pharmacy
Blue= pending

DFMO

https://medicine.iu.edu/research-centers/pediatrics/research/diabetes/clini

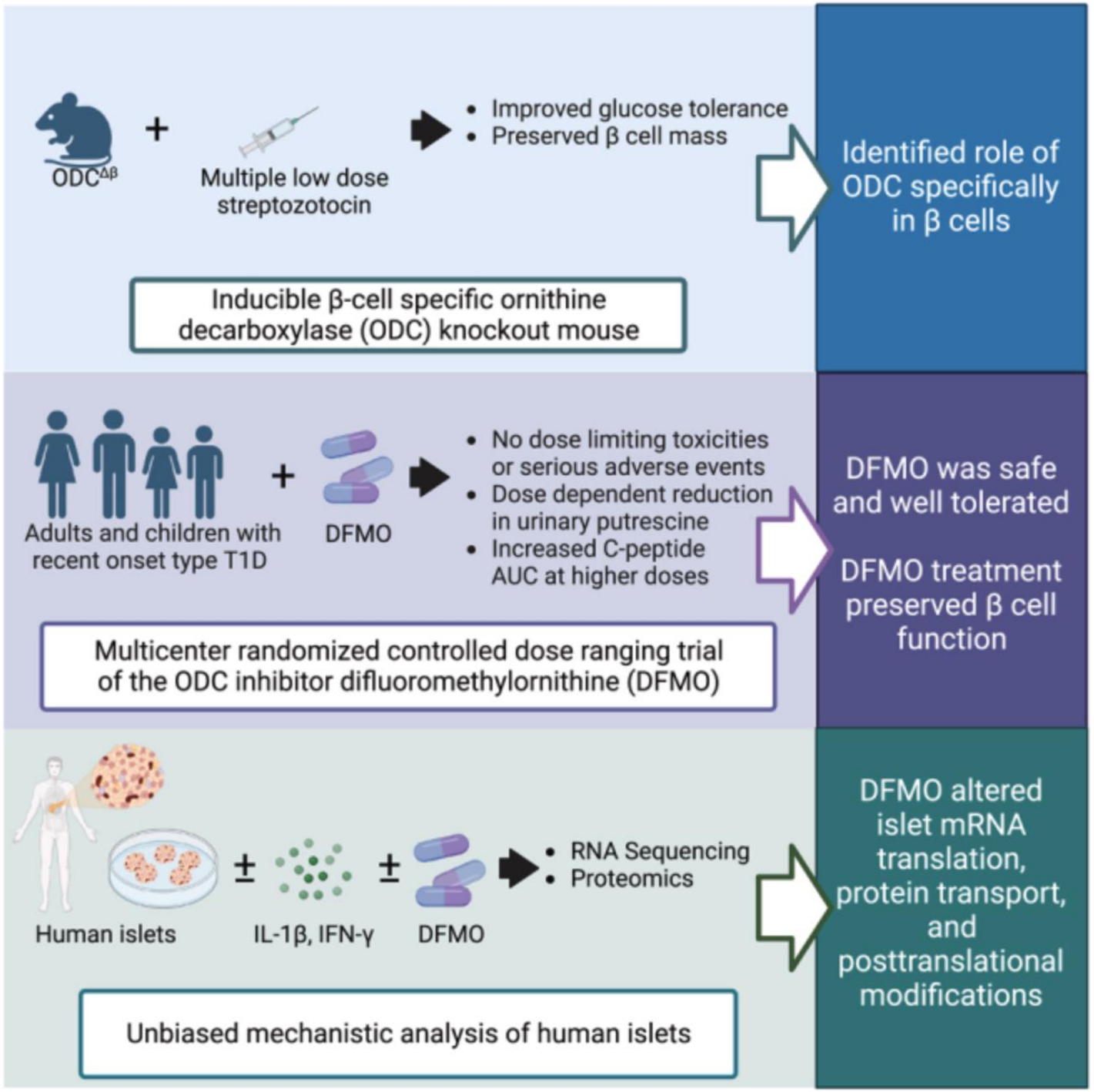
TA1DPOL
TArgeting type 1 Diabetes via POLyamines

- Difluoromethylornithine
- Participants 4-40 years of age with a clinical diagnosis of T1D within 100 days at the time of randomization



The purpose of this study is to determine if an investigational drug known as DFMO has an effect on reducing the amount of stress that is experienced by the body's beta cells (the cells that make insulin) and preserves residual c-peptide (the body's own insulin production). An investigational drug means it is not approved by the Food and Drug Administration (FDA).

TADPOL



TADPOL

TArgeting type 1 Diabetes via POLyamines

DFMO "TADPOL"- Dr. S. Greeley/Cathleen Mulcahy RN APN IRB23-0368

JDRF Grant with Indiana University, 4 year study, 6 months of oral pill
Participants 4-40 years of age with a clinical diagnosis of T1D within 100 days at the time of randomization
(12 pts at this site) Screening </=45 days from tx start, Treatment </= 100 days from Dx

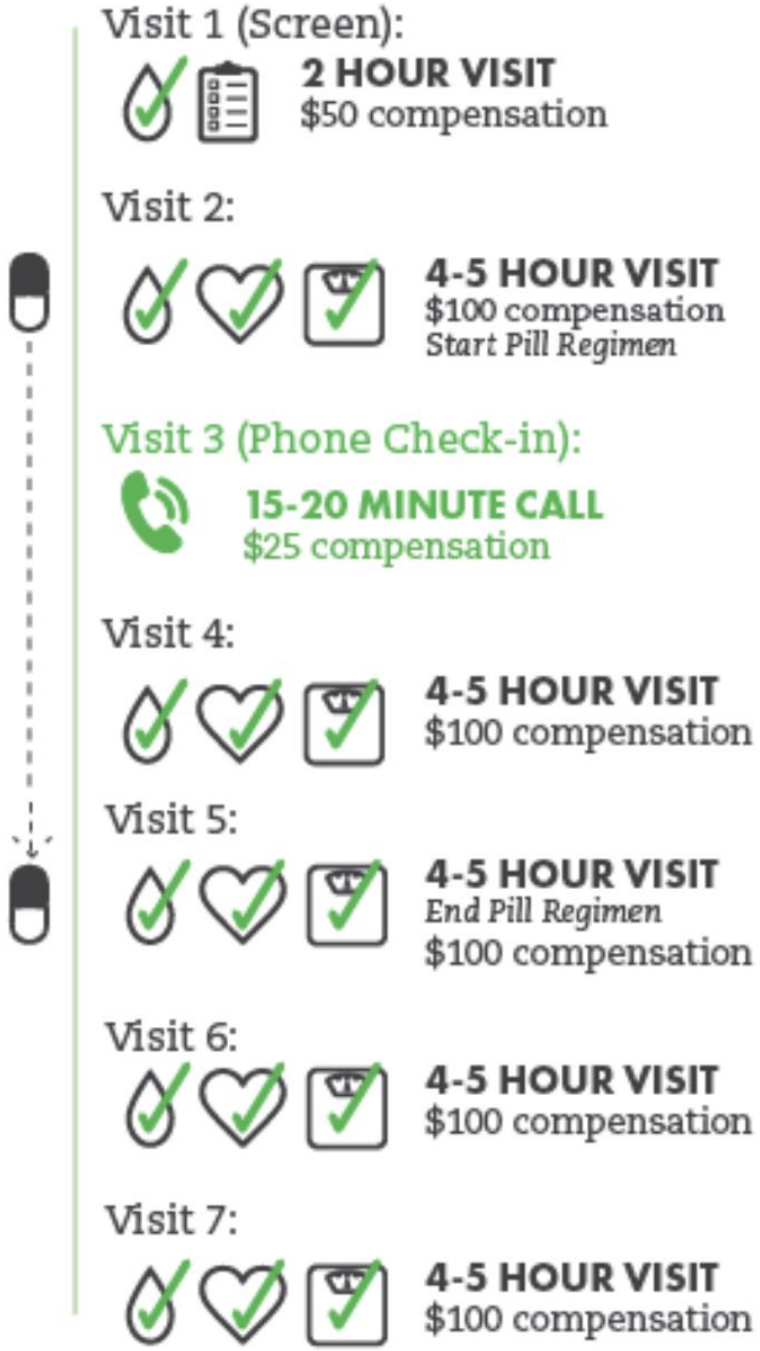
DFMO: difluoromethylornithine, developed in 1978 and later used to treat West African sleeping sickness, now approved for use in neuroblastoma

Sims EK, Kulkarni A, Hull A, Woerner SE, Cabrera S, Mastrandrea LD, Hammoud B, Sarkar S, Nakayasu ES, Mastracci TL, Perkins SM, Ouyang F, Webb-Robertson BJ, Enriquez JR, Tersey SA, Evans-Molina C, Long SA, Blanchfield L, Gerner EW, Mirmira RG, DiMeglio LA. Inhibition of polyamine biosynthesis preserves β cell function in type 1 diabetes. Cell Rep Med. 2023 Nov 21;4(11):101261.

an ornithine decarboxylase (ODC) inhibitor, delays the onset of type 1 diabetes (T1D) by reducing β cell stress, BUT: mice with β cell ODC deletion are protected against toxin-induced diabetes, suggesting a cell-autonomous role of ODC during β cell stress. DFMO dose-dependently reduces urinary putrescine levels and, at higher doses, preserves C-peptide area under the curve without apparent immunomodulation. Transcriptomics and proteomics of DFMO-treated human islets exposed to cytokine stress reveal alterations in mRNA translation, nascent protein transport, and protein secretion.

TADPOL

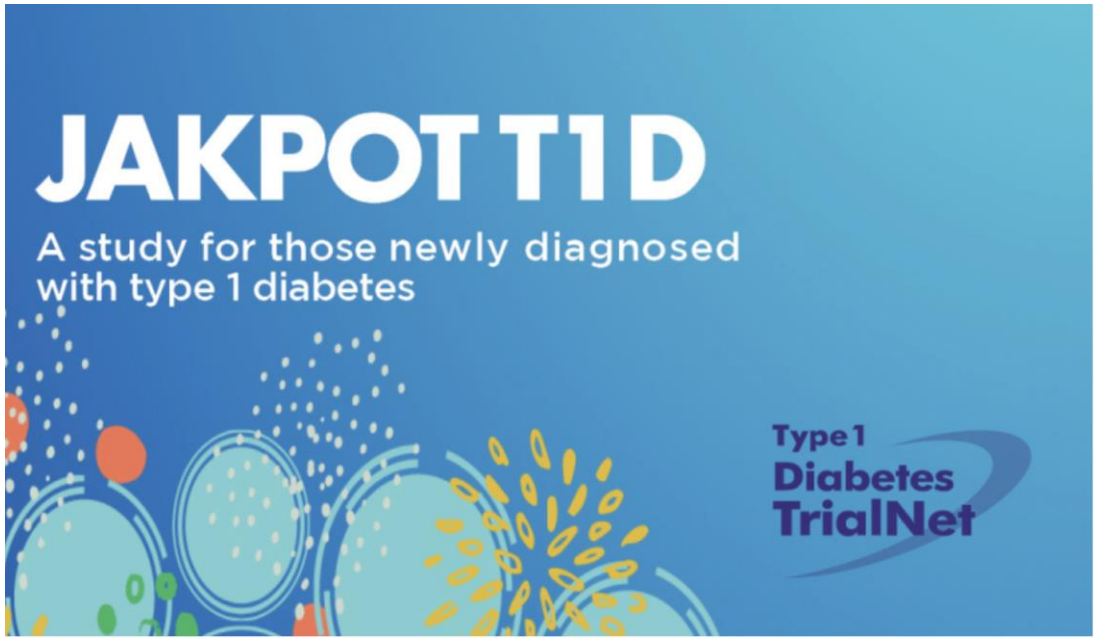
- A continuous glucose monitor (CGM)
- 12 months of expert diabetes management by our team
- Financial compensation



TADPOL
TArgeting type 1 Diabetes via POLyamines

JAKPOT T1D TN31

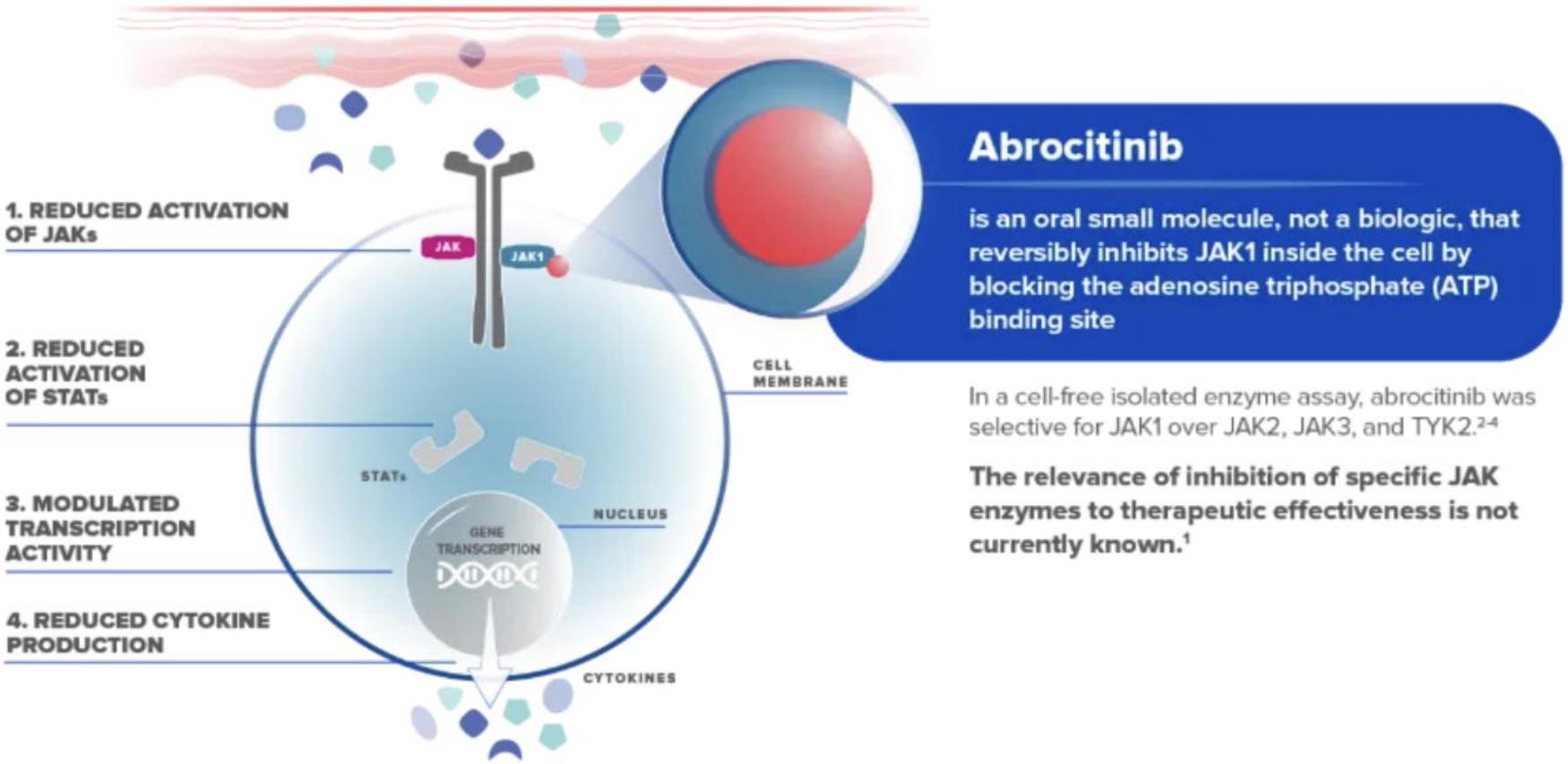
- JAK Inhibitors Newly Diagnosed Study (JAKPOT T1D)
- abrocitinib and ritlecitinib



JAK inhibitors: abrocitinib and ritlecitinib

- Abrocitinib and ritlecitinib are in a new class of autoimmune treatments called Janus kinase (JAK) inhibitors.
- Abrocitinib is approved by the U.S. Food and Drug Administration (FDA) to treat eczema. https://cibinqo.pfizerpro.com/
- Ritlecitinib is FDA approved for use in severe alopecia areata and is being studied as a treatment for several autoimmune diseases, including alopecia, ulcerative colitis, Crohn's disease, vitiligo, and rheumatoid arthritis.
- https://litfulo.pfizerpro.com/
- Iznardo et al. Efficacy and Safety of JAK1 Inhibitor Abrocitinib in Atopic Dermatitis. Pharmaceutics. 2023 Jan 23;15(2):385

Abrocitinib (CIBINQO) is an oral, small molecule JAK1 inhibitor



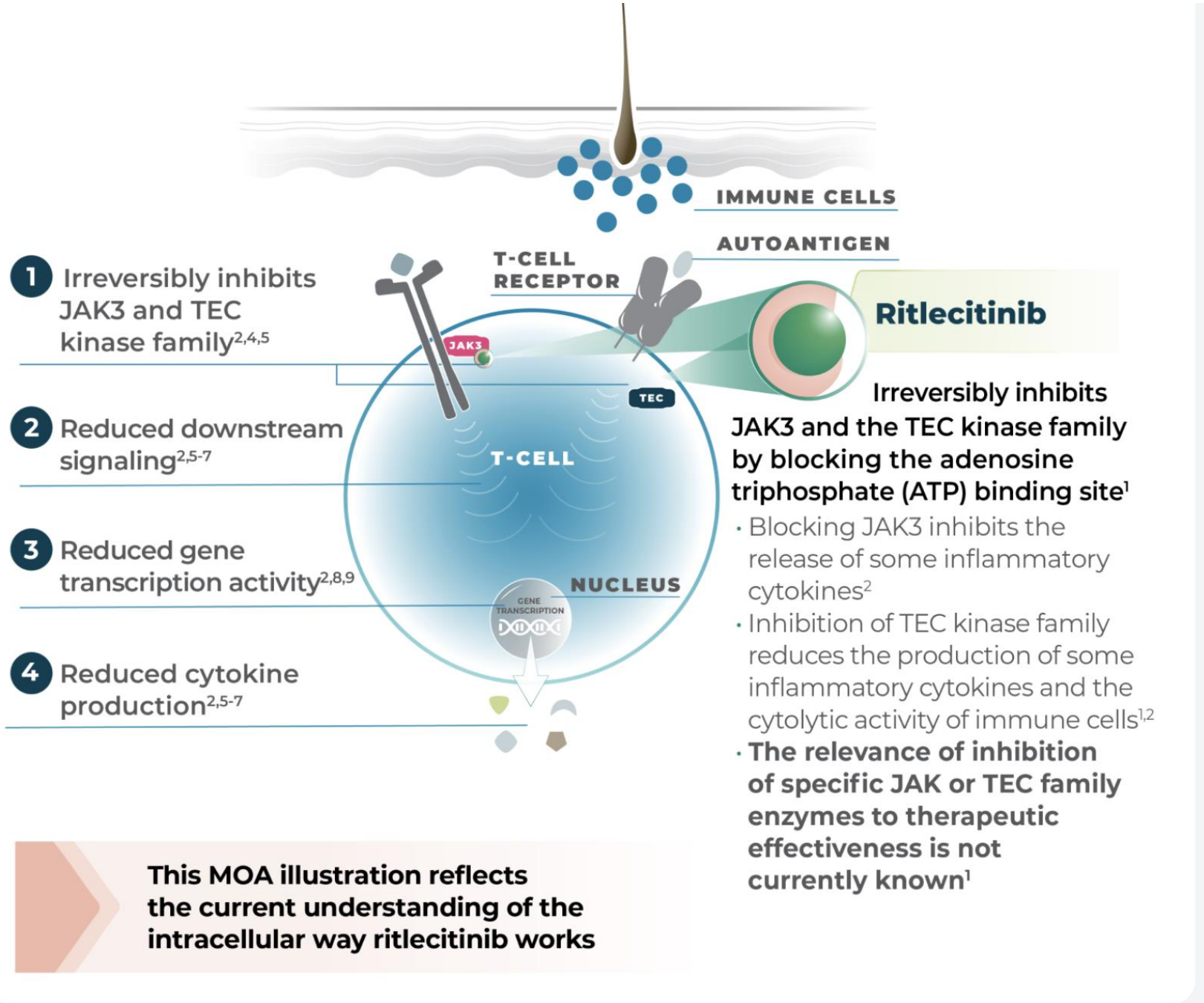
https://cibinqo.pfizerpro.com/about-cibinqo/mechanism

Abrocitinib,

- is a selective inhibitor of the enzyme janus kinase 1 (JAK1). It inhibits JAK1 by 28 fold of selectivity over JAK2 and more than 340 fold of selectivity over JAK3.

- Two mechanisms are involved in atopic dermatitis, one involves epidermal barrier disruptions, and the other one is cutaneous inflammation due to the immune system over response.
- Acute inflammation in AD typically involves IL-13, IL-4, and IL-33.[
- Consequently, inhibiting JAK1 results in suppressing the signaling cytokines IL-4, IL-3, and IL-31. Many other cytokines are involved in AD and mediated by JAK1 such as type II cytokine receptors for IL-22, IL-19, IL-10, IL-20 and glycoprotein 130 (gp130) including IL-6 and IL-12 which are also associated with JAK2 and TYK2; IFN-α and INF-β signal.

LITFULO is a kinase inhibitor—it inhibits JAK3 and the TEC kinase family pathways



https://litfulo.pfizerpro.com/about/moa

TN31 JAKPOT Study: abrocitinib and ritlecitinib

Cathleen Mulcahy RN APN

JAK Inhibitors to Preserve C-Peptide Production in New Onset T1D

- This phase 2 trial is a double-blind, randomized, placebo-controlled clinical trial in male and female adolescent and adult participants (ages 12-35 years) with newly diagnosed Stage 3 T1D (within 100 days of diagnosis). Enrollment into abrocitinib and ritlecitinib arms and the shared placebo arm will occur in a 1:1:1 allocation with a planned enrollment of 26 participants in each arm. Participants will receive 12 months of active treatment with abrocitinib, ritlecitinib, or placebo with up to 12 months of additional follow-up. A total sample size of 52 participants will receive active treatment, and a total of 26 participants will receive placebo.
- Oral administration of either 200 mg abrocitinib, 100 mg ritlecitinib, or matching placebo administered daily.

Major Inc Exc-

- age 12-35
- Diagnosis of T1D within 100 days of the baseline visit (V0).
- Positive for at least one islet cell autoantibody; GAD65A, mIAA (if obtained within 10 days of the onset of insulin therapy), IA-2A, ICA, or ZnT8A 5.
- Stimulated C-peptide of ≥0.2 pmol/mL measured during mixed-meal tolerance test (MMTT) conducted at least 21 days from diagnosis of diabetes
- HbA1c ≤ 10 % 7. Body weight ≥ 35kg at screening
- Willing to comply with intensive diabetes management and wear a CGM .
- Be up to date on recommended immunizations

Regulatory Updates (CIRB24-0507) - IRB startup is complete

Action Items:

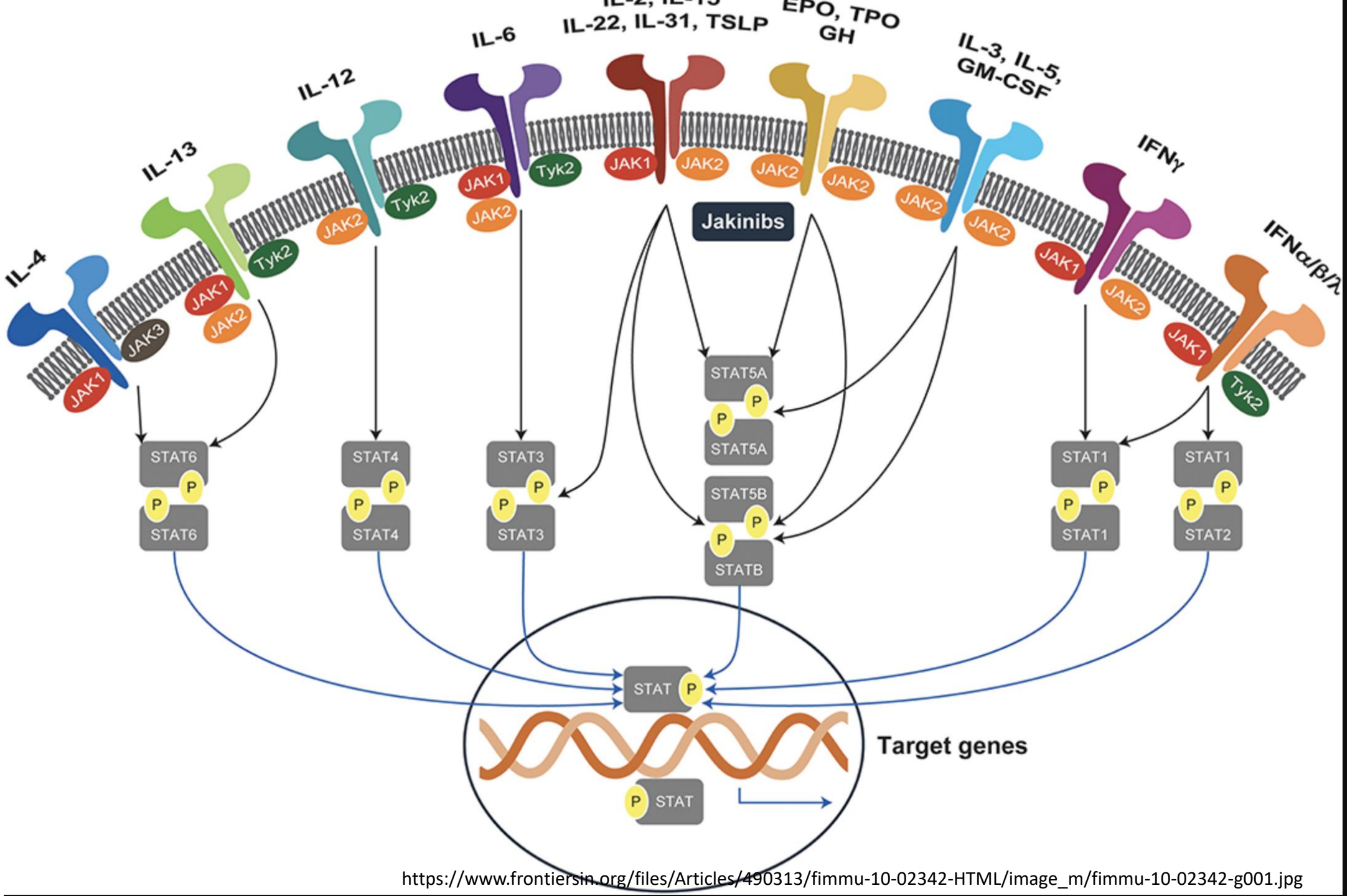
- **Pharmacy SIV and need drug order, scheduled for NOV 13, pharmacy may be able to do October**
- Drug reaction protocol-none
- CRC inservice 9/9/2024, done
- audiology inservice completed
- lab supplies will be ordered once activated

Janus Kinase (JAK) **Inhibitors to Preserve C-Peptide Production in New Onset** Type 1 Diabetes (T1D)

- A multi-center, placebo-controlled, double blind, 1:1:1 randomized control clinical trial testing two different JAK Inhibitors abrocitnib, ritlecitinib, and placebo in subjects with recent onset Stage 3 Type 1 Diabetes **within 100 days of diagnosis**.

Outcome Measure	Measure Description	Time Frame
The area under the stimulated C-peptide curve (Y_AUC)	The primary outcome of interest is the area under the stimulated C-peptide curve over the 2-hour mixed meal glucose tolerance test conducted at the 12-month visit (Y_AUC) over the 2-hour mixed meal glucose tolerance test conducted at the 12-month visit.	12 Months

Primary Outcome Measures



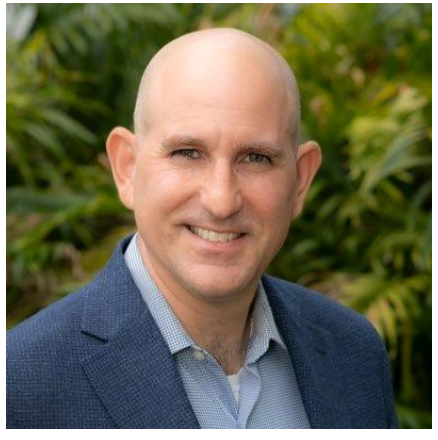
https://www.frontiersin.org/files/Articles/490313/fimmu-10-02342-HTML/image_m/fimmu-10-02342-g001.jpg

JAKPOT-TrialNet

- **JAK inhibitors** are being used and studied in other autoimmune diseases. **Abrocitinib** is approved by the U.S. Food and Drug Administration (FDA) to treat eczema. **Ritlecitinib** is being studied as a treatment for several autoimmune diseases, including alopecia, ulcerative colitis, Crohn's disease, vitiligo and rheumatoid arthritis.

- The TrialNet study is the first to test whether either treatment can preserve insulin production in people newly diagnosed with T1D.
- JAK inhibitors may be able to "calm the immune system response" that harms insulin-making beta cells.
- Continuing to make even a small amount of insulin helps keep blood glucose levels in the normal range, lowering the risk of the long-term complications of diabetes.

TN28 Protocol
STOP-T1D
Low-dose ATG to Delay or Prevent Progression to Stage 3 T1D
Currently not enrolling



Study Chair: Michael Haller, MD

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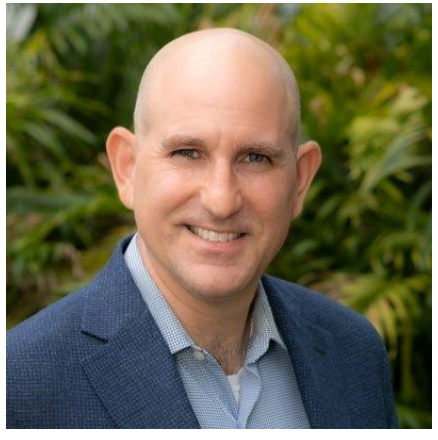


Study Chair: Michael Haller, MD

TN-19: Low-dose Anti-thymocyte Globulin (ATG) in Stage 3 T1D

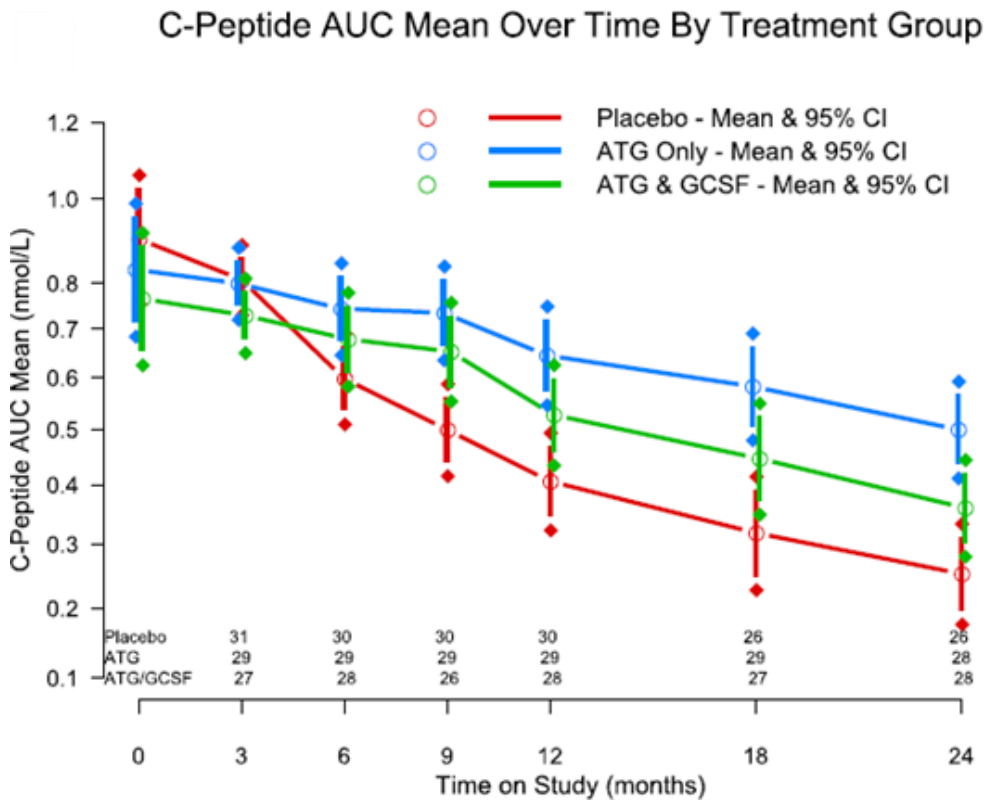
Low-Dose Anti-Thymocyte Globulin Preserves C-Peptide, Reduces HbA_{1c}, and Increases Regulatory to Conventional T-Cell Ratios in New-Onset Type 1 Diabetes: Two-Year Clinical Trial Data

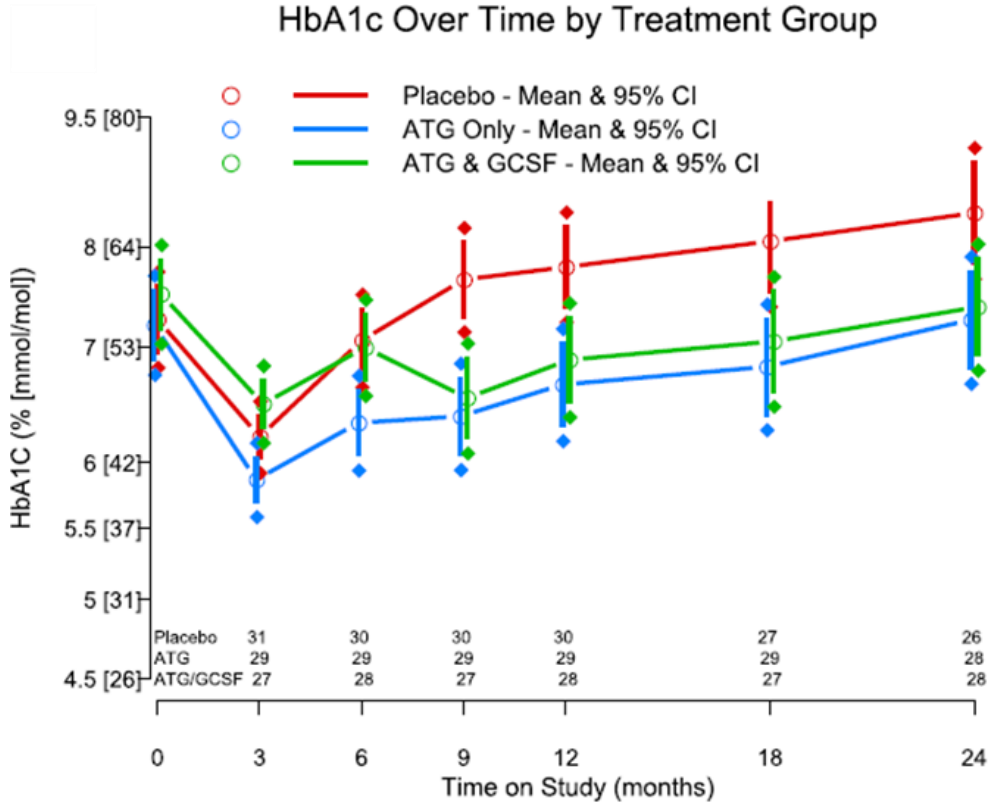
Michael J. Haller,[1] S. Alice Long,[2] J. Lori Blanchfield,[2] Desmond A. Schatz,[1] Jay S. Skyler,[3] Jeffrey P. Krischer,[4] Brian N. Bundy,[4] Susan M. Geyer,[4] Megan V. Warnock,[4] Jessica L. Miller,[4] Mark A. Atkinson,[1] Dorothy J. Becker,[3,5] David A. Baidal,[3] Linda A. DiMeglio,[6] Stephen E. Gitelman,[7] Robin Goland,[8] Peter A. Gottlieb,[9] Kevan C. Herold,[10] Jennifer B. Marks,[3] Antoinette Moran,[11] Henry Rodriguez,[4] William E. Russell,[12] Darrell M. Wilson,[13] and Carla J. Greenbaum,[2] for the Type 1 Diabetes TrialNet ATG-GCSF Study Group*

Diabetes Care 2018, Diabetes 2019

TN19 – Trial Outcome

- As with other TrialNet studies, the positive outcome in the new onset T1D study (TN19) gave way to the development of the TN28 study.
  - At 1 year after study entry, the ATG treated group (2.5 mg/kg) showed significant improvement in the c-peptide response (mean AUC to MMTT) and reduced HbA1c vs. placebo.
  - At 2 years after study entry, the HbA1c levels were significantly lower and the AUC of c-peptide were significantly greater in ATG vs placebo group.





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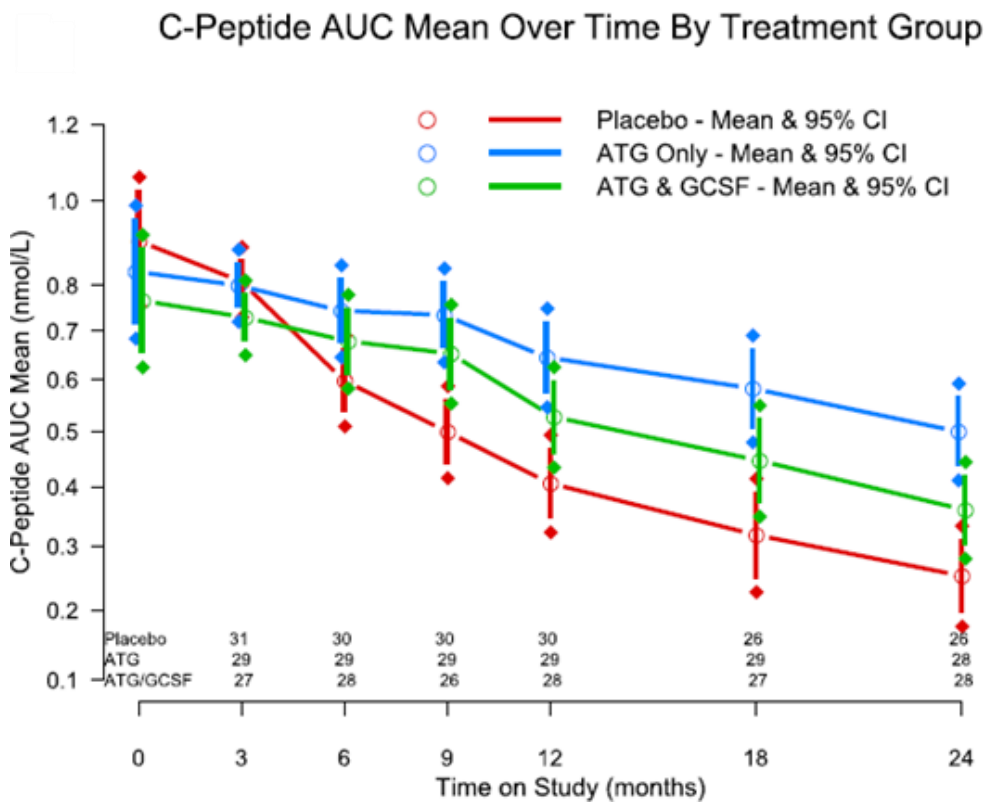

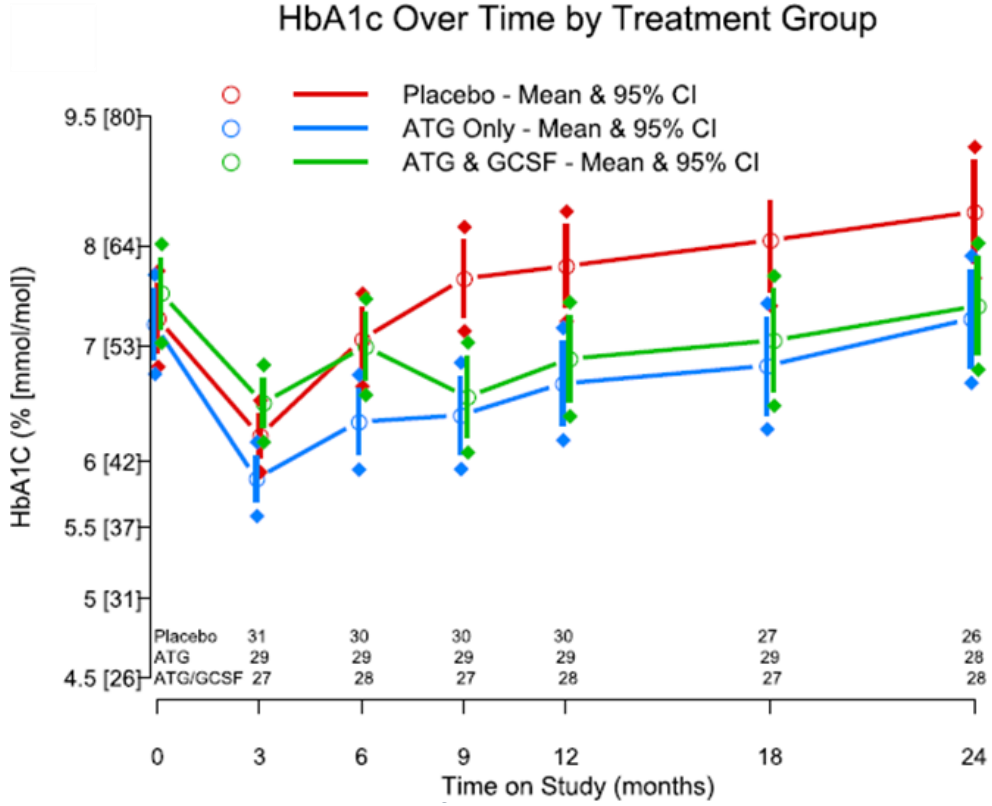

TN28: Prevent Progression to T1D from Stage 2 using Low-dose ATG

- Trial of persons with Stage 2 T1D at high risk (i.e., 50% 2-year risk) for progression to Stage 3 T1D.
- Primary outcome is diagnosis with Stage 3 T1D in participants with Stage 2 T1D with a 50% 2-year risk of diagnosis.
- The protocol received FDA approval, IRB approval, and was opened for enrollment on December 5, 2022

Overview of TN28 Protocol

Accrual Target = 114 participants

Key Eligibility Criteria

- Age ≥ 12 and < 35 years
- 2 or more diabetes-related BAA+
- ADA Stage 2 criteria* AND at least one high-risk marker (HbA1c, DPTRS or Index60)

The inclusion criteria extend the criteria originally used in the TN10 anti-CD3 extension trial: 2+ autoantibodies and:

Dysglycemia
HbA1c ≥ 5.7% and < 6.5%
Index60 ≥ 1.4
DPTRS ≥ 7.4

- Up-to-Date on Vaccinations, including COVID-19 and Influenza
- Negative COVID-19 PCR Test w/in 3 days of first study drug treatment

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Siplizumab: anti-CD2 monoclonal Ab in new onset type 1

- Designate

Why Siplizumab?

- “ has been used in conditioning regimens for hematopoietic cell transplantation and tolerance induction with combined kidney-bone marrow transplantation.
- Siplizumab-based tolerance induction regimens deplete T cells globally while enriching regulatory T cells (Tregs) early posttransplantation…. siplizumab may have immunomodulatory functions that may contribute to its success in tolerance-inducing regimens. ”

Siplizumab:
anti-CD2 monoclonal Ab in new onset type 1

Siplizumab is similar to to alefacept: both target the CD2-LFA-3 co-stimulatory pathway on memory T cells. Siplizumab is a humanized, anti-CD2 monoclonal antibody (Ab) of the IgG1κ class.

CD2: extracellular surface marker expressed on almost all human T-lymphocytes, and natural killer (NK) cells and thymocytes.

The natural ligand of CD2 is LFA-3, or CD58.

CD58 is a cell adhesion molecule expressed on antigen presenting cells (APCs), and the CD2-CD58 complex stabilizes and enhances lymphocyte interactions and co-stimulation necessary for immune activation.

CD2 is up-regulated on activated T cells and memory T cells.

Podestà MA, et al Siplizumab selectively depletes effector memory T cells and promotes a relative expansion of alloreactive regulatory T cells in vitro. Am J Transplant. 2020 Jan;20(1):88-100.

DESIGNATE- Sippluzimab

- **The primary objective is to identify a safe, metabolically favorable, dosing regimen for siplizumab in patients with type 1 diabetes that induces changes in T cell phenotypes observed with alefacept therapy in new-onset T1DM.**
- The secondary objectives are to:

Assess the safety profile of siplizumab in recently diagnosed T1DM.

Assess the effects of siplizumab on residual beta cell function in recently diagnosed T1DM participants.

CIRB22-1955 Designate

RB of Record: Advarra

A T cell phenotype signature driven dose finding study with siplizumab in type 1 diabetes mellitus

ITN funded by NIAID “DESIGNATE” Phase 1b n= 120-160 1:1:1:1 52 weeks

1st cohort adults randomized w/ 18 months

This is a multicenter, Phase Ib, open-label, siplizumab dose-finding study in individuals aged 8-45 years with a **Type 1 diabetes mellitus (T1DM) diagnosis within 18 months of onset.**
Participants will be randomized 1:1:1:1 to one of four possible siplizumab dosing arms.

DESIGNATE: A T Cell Phenotype Signature Driven Dose Finding Study With Siplizumab in Type 1 Diabetes Mellitus (ITN095AI)

https://clinicaltrials.gov/study/NCT05574335?term=designate&rank=1

- All dosing arms will receive weekly siplizumab doses for a total of 12 weeks.
- After the completion of treatment, participants will undergo follow-up visits at weeks 12, 24, 36 and 52 which include longitudinal MMTTs. Blood samples for mechanistic analyses will be obtained during the treatment phase and thereafter.
- Adults aged 18- 45 will be enrolled initially at the study sites.

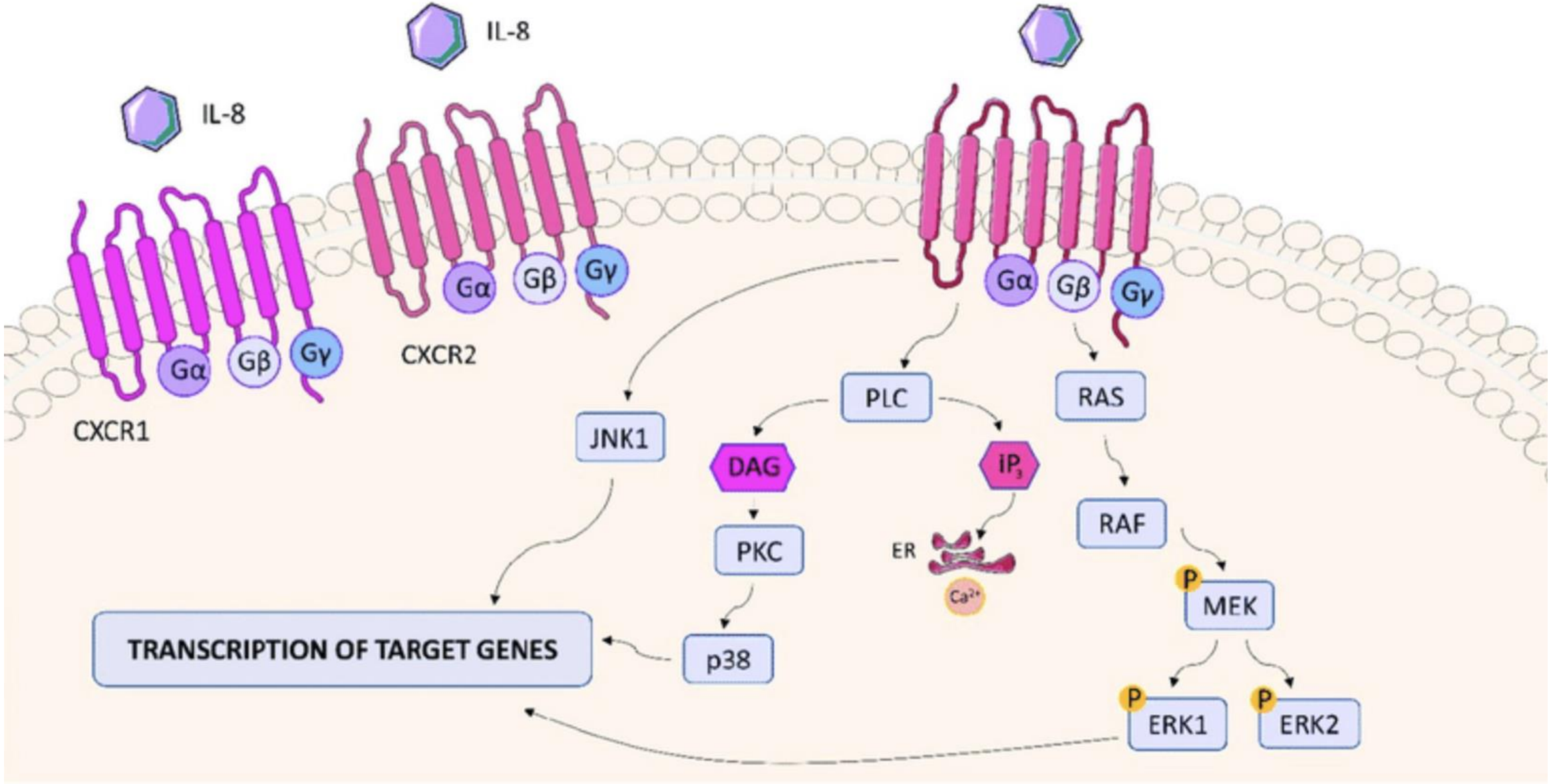
Ladirixin – Dompe, IL-8 CXCR1/2 inhibition

- IL-8 important mediator in the progression of type 1 diabetes.
- Production and secretion of pro-inflammatory IL-8 has been demonstrated from human pancreatic islets upon enterovirus infections, and
- LPS-induced production of IL-8 by neutrophils is increased in type 1 pre-diabetic and diabetic patients.
- Circulating levels of IL-8 were elevated in children with T1D compared to non-diabetic controls.
- Levels of IL-8 correlate with glycemic control, higher level being associated to poorer or unfavorable glucose control.

Ladarixin

Therefore - the modulation or inhibition of IL8 activity is a valid target for the development of innovative treatments to control the progression of T1D.

- Results obtained with ladarixin in reversal of ”T1D diabetes" in NOD mice, showed the ability of this CXCR1/2 inhibitor to protect β-cells and either prevent or delay the progression of hyperglycaemia.
- The positive effects of ladarixin, coupled with the safety shown in phase 1 studies, provided a sound rationale for a clinical study aimed at evaluating the effect of ladarixin in patients with new onset diabetes.



https://www.researchgate.net/profile/Sebastian-Wawrocki/publication/357994686/figure/fig7/AS:1121120782696465@1644307432634/CXCR1-and-CXCR2-structure-and-signaling-The-interaction-of-IL-8-with-CXR1-CXCR2.png

Ladarixin

- **A Study of Oral Ladarixin in Recent Onset Type 1 Diabetes and a Low Residual β-cell Function**
- **ClinicalTrials.gov ID** NCT04628481
- **Sponsor** Dompé Farmaceutici S.p.A
- **Information provided by** Dompé Farmaceutici S.p.A (Responsible Party)
- **Last Update Posted** 2024-11-07

- Current Trial Completed, not recruiting

Early treatment to Delay or Prevent T1DM?

- Many studies have been proposed, completed, underway, or about to be underway
- Positive signals from Rituxamab, Tepluzimab, ATG, Abatacept and others
- Combination or multiple dose studies needed
- **T1D Relay**: rituximab-pvvr and abatacept, one after the other, to learn if using both treatments extend insulin production in people (ages 8-45) who were newly diagnosed with type 1 diabetes (T1D).

T1D Relay: New onset

- 19 centers open, closest is IU
- The study is a two-arm, multicenter, double-blinded clinical trial testing sequential therapy with rituximab-pvvr followed by abatacept versus rituximab-pvvr alone in new onset T1D.
- The primary objective: test whether the C-peptide response to a 2-hour mixed meal tolerance test will be improved
- Treatment with Abatacept after Rituximab-pvvr compared to those treated with Rituximab-pvvr and placebo 24 months after enrollment.

Other studies at the University of Chicago

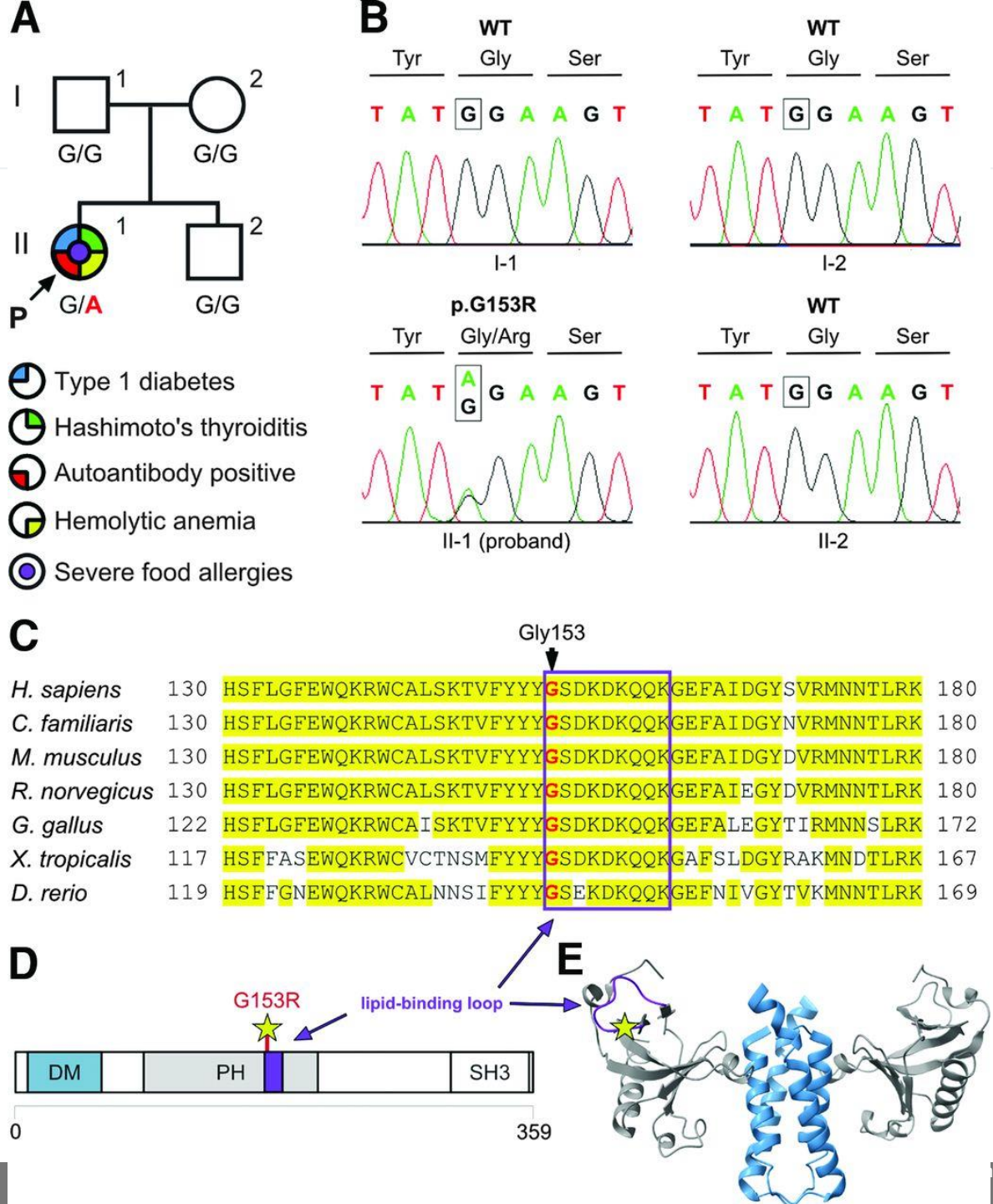
- T1DM plus multiple autoimmunities/allergies in individuals and families
- High resolution pancreas imaging – Dr Greeley/ Vanderbilt
- Fine-One – finerenone in t1D with microalbuminuria
- Diasome – insulin delivery to the liver
- Vertex -

American Diabetes Association®

Diabetes With Multiple Autoimmune and Inflammatory Conditions Linked to an Activating SKAP2 Mutation

Niklas Rutsch; Chester E. Chamberlain; Wesley Dixon; Lauren Spector; Lisa R. Letourneau-Freiberg; Wint W. Lwin; Louis H. Philipson; Alexander Zarbock; Karline Saintus; Juehu Wang; Michael S. German; Mark S. Anderson; Clifford A. Lowell

Diabetes Care. 2021;44(8):1816-1825.
doi:10.2337/dc20-2317



Precision Genetics for T1D

https://precisiont1d.uchicago.edu/

people who have T1D and other features that suggest a strong underlying genetic cause to their disease

IRB19-0834 MAP-T1D- Dr. Greeley/Demetra

Pancreas MRI in PWD **ages 7+**

Enrollment: 2aab+: 9 Monogenic: 7 Other: 2

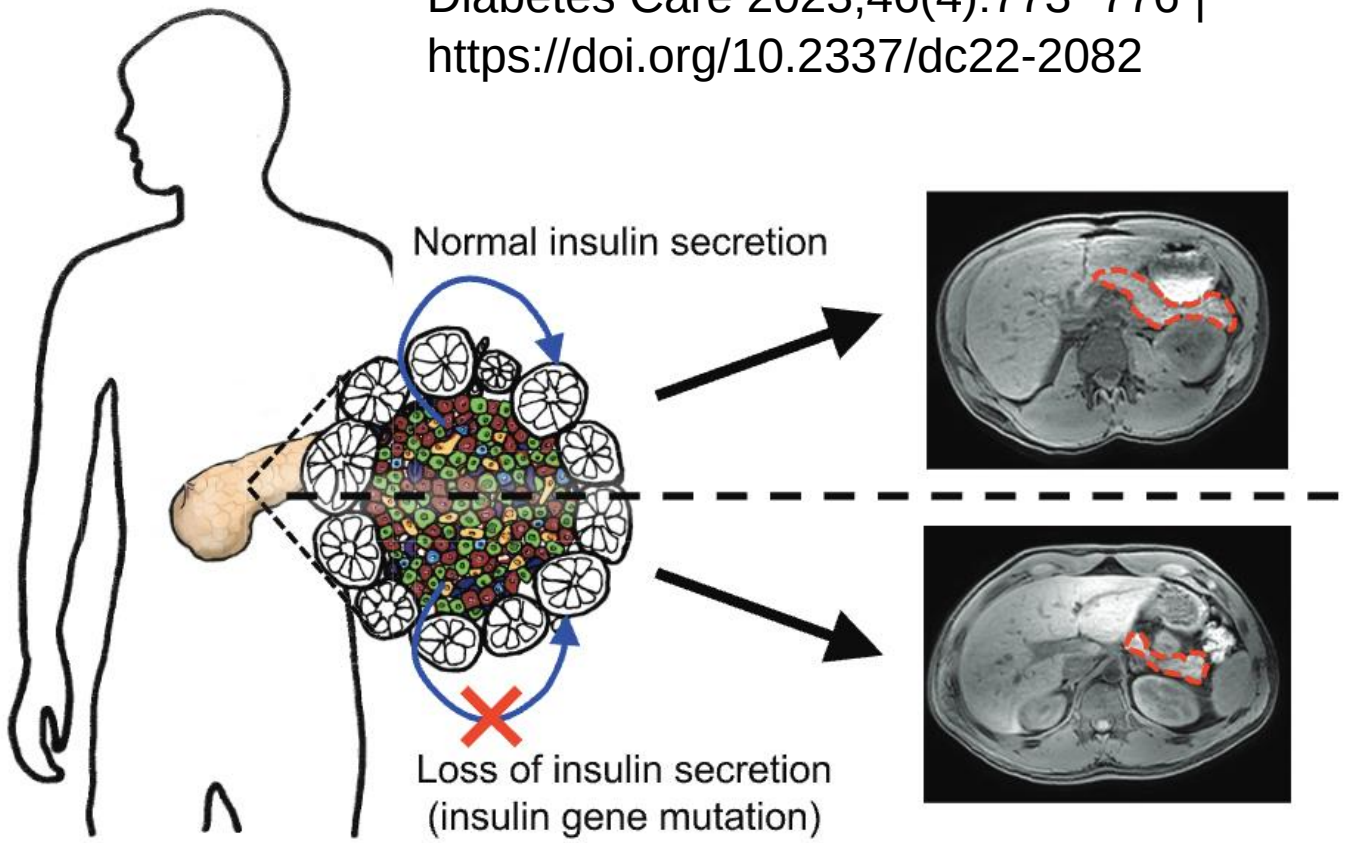
Recruitment:

- Stage 2 (follow-up only)
- Special cases require approval by Vanderbilt
- General population (Aab+ w/o T1D proband)

- Virostko, J. *et al.* Longitudinal Assessment of Pancreas Volume by MRI Predicts Progression to Stage 3 Type 1 Diabetes. *Diabetes Care* (2023) doi:10.2337/dc23-1681.
- Wright, J. J. *et al.* Insulin Deficiency From Insulin Gene Mutation Leads to Smaller Pancreas. *Diabetes Care* **46**, 773–776 (2023).
- Remedios, L. W. *et al.* Influence of Early through Late Fusion on Pancreas Segmentation from Imperfectly Registered Multimodal MRI. *arXiv* (2024).
- TRIOLO, T. M. *et al.* 1453-P: Islet Autoantibody–Positive General Population Individuals Have Smaller Pancreas Volume Compared with Control Individuals. *Diabetes* **73**, (2024).
- Wright, J. J. *et al.* Longitudinal MRI Shows Progressive Decline in Pancreas Size and Altered Pancreas Shape in Type 1 Diabetes. *J. Clin. Endocrinol. Metab.* **108**, 2699–2707 (2023).
- Virostko, J. *et al.* Development of a standardized MRI protocol for pancreas assessment in humans. *PLoS ONE* **16**, e0256029 (2021).

Insulin Deficiency From Insulin Gene Mutation Leads to Smaller Pancreas

Diabetes Care 2023;46(4):773–776 | https://doi.org/10.2337/dc22-2082



ARTICLE HIGHLIGHTS

- Individuals with type 1 diabetes and those at risk for type 1 diabetes have a smaller pancreas size than individuals without diabetes, but it is not known whether insulin deficiency or autoimmune involvement of the exocrine pancreas causes the reduction in size.
- In individuals with monogenic diabetes that causes insulin deficiency without autoimmunity, MRI pancreas imaging showed reduced size and altered shape similar to those seen in type 1 diabetes.
- Insulin is trophic for acinar cells, and insulin deficiency, without islet-directed autoimmunity, causes a reduction in exocrine pancreas size.

BAYER Fine-One TID-

US PI – Dr Janet McGill, Wash U

https://clinicaltrials.gov/study/NCT05901831

Clinical Trial > Diabetes Res Clin Pract. 2023 Oct:204:110908.

doi: 10.1016/j.diabres.2023.110908. Epub 2023 Oct 5.

Rationale and design of a randomised phase III registration trial investigating finerenone in participants with type 1 diabetes and chronic kidney disease: The FINE-ONE trial

Name: Bayer Clinical Trials Contact
Phone Number:(+)1-888-84 22937
Email: clinical-trials-contact@bayer.com

Inclusion

Age 18+,
T1D continuously treated with insulin, within 1 year of dx
A1C <10,
eGFR 25 to <90,
Potassium <4.8mmol/L,
stable ACEI or ARB,
UCAR 200mg/g to <5000mg/g

Exclusion

1. Participant with T2D.
2. Participant with other known causes of CKD than T1D.
3. Participant with kidney transplantation.
4. Known hypersensitivity to the study intervention
5. hepatic insufficiency classified as Child-Pugh C
6. Participant with mean BP higher than 160/100 mmHg or mean systolic BP lower than 90 mmHg at the Screening visit (Section 8.3.2).
7. Participant hospitalized due to a CV event within 4 weeks
8. Participant with acute kidney injury requiring dialysis
9. Symptomatic heart failure with reduced ejection fraction
10. Participant with Addison's disease.
11. Any other history, condition, therapy or uncontrolled intercurrent illness which would make the participant unsuitable

Diasome Pharmaceuticals -OPTI-2

https://www.diasome.com/

A Phase 2b Randomized, Double-blind Trial Comparing HDVInsulin Lispro Versus Insulin Lispro Alone in Adults with Type 1 Diabetes Receiving Insulin Degludec

- Adults 18 to <80
- Clinical diagnosis of T1D with measured C-peptide <0.6 nmol/L and using insulin for at least 6 months
- MDI insulin regimen for at least 28 days prior to entering study.
- Screening A1C ≥6.5% and ≤9.0%

- Officially Selected as a site 6/12
- ICF Status: Assigned to IRB Meeting 9/10
- CRC Status: Application submitted to CRC
- IRB submission: Pre-review comments received
- **SIV scheduled for 9/30**

Vertex (VX880-101)- Dr Witkowski = Phase 1,2,3

UChicago Medicine is participating in a new clinical research study of an investigational infusion of islets in individuals who have been diagnosed with type 1 diabetes with low blood sugar and impaired hypoglycemic awareness. In this study, islets manufactured from stem cells are infused into the liver with a goal of providing replacement cells producing insulin for cells that have been lost.

Contact: Lindsay Basto, RN MSN Lindsay.Basto@uchospitals.edu for more information.

VERTEX- VX22-264 Phase 1-2

- **Primary Objective:** Evaluate the safety, tolerability and function of VX-264 in participants with Type 1 diabetes mellitus (T1D)
- **Study design:** Single-arm, open-label, multi-part study
- **Sample Size:** up to approximately 16 adult subjects (18 to 65 y/o) with T1D
- **Study Endpoints**

  Primary Outcome Measures *(Selected)*
  - Safety and Tolerability as assessed by number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)
  - Change from baseline in peak C-peptide during a mixed meal tolerance test (MMTT) at Day 90

  Secondary Outcome Measures *(Selected)*
  - Proportion of Participants who are Insulin Independent at any time between 6 and 12 months after VX-264 implant
  - HbA1c change from baseline
  - CGM-derived metrics (e.g. time in range)
- **Study Duration (U.S.A)**: 5 years (+ 5 year long term follow-up)

Vertex studies – Forward and Upward

On November 4th, 2024, Vertex Pharmaceuticals **made an important announcement** that their Phase 1/2 clinical trial for their stem cell therapy VX-880 is converting into a Phase 1/2/3 pivotal trial following successful Phase 2 review by regulatory bodies. A pivotal trial gathers the data required for a regulatory submission to bring the therapy to the market. This will build upon the ongoing international trial (including 4 Canadian sites) and increase the number of participants from 37 to 50.

https://clinicaltrials.gov/study/NCT04786262?cond=type%201%20diabetes&term=Vertex&rank=7

https://clinicaltrials.gov/study/NCT05791201?cond=type%201%20diabetes&term=Vertex&rank=2

Diabetes – An Opportunity for Precision Medicine: Type and Stage

Atypical "Type 1"

- **Diabetes <6-12 months**
- **Family History**
- **Detectable C-peptide levels**
- **Negative for antibodies**
- **Extrapancreatic features**

Atypical "Type 2"

- Hyperglycemia <30 yrs
- Not obese
- **No signs of insulin resistance**
- **>2 generation linear family history**

Monogenic Diabetes Registry at the University of Chicago
http://monogenicdiabetes.org

Acknowledgements

Thanks to all the participants, patients and their families

Funding Sources

NIH/NIDDK

JDRF – Jaffe Family

Lewis – Sebring Foundation

Kovler Diabetes Center

American Diabetes Association

Helmsley Trust

Thanks to all the participants

and their families.

http://monogenicdiabetes.uchicago.edu/

THE UNIVERSITY OF CHICAGO
KOVLER DIABETES CENTER