Join by Web

1. Go to **PollEv.com**
2. Enter **HONESTCOOKIE180**
3. Respond to activity

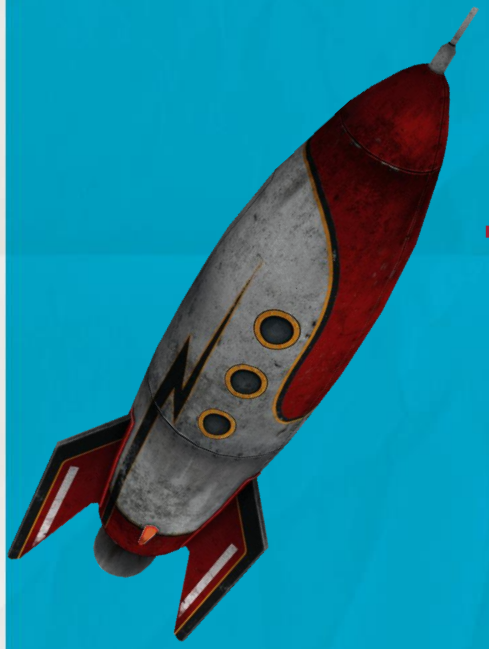
Join by Text

1. Text **HONESTCOOKIE180** to **22333**
2. Text in your message

Welcome! Please get ready to participate!

Benaroya Research Institute

To Infinity and Beyond: The Future of Type 1 Diabetes



Friends For Life Seattle

March 17, 2023

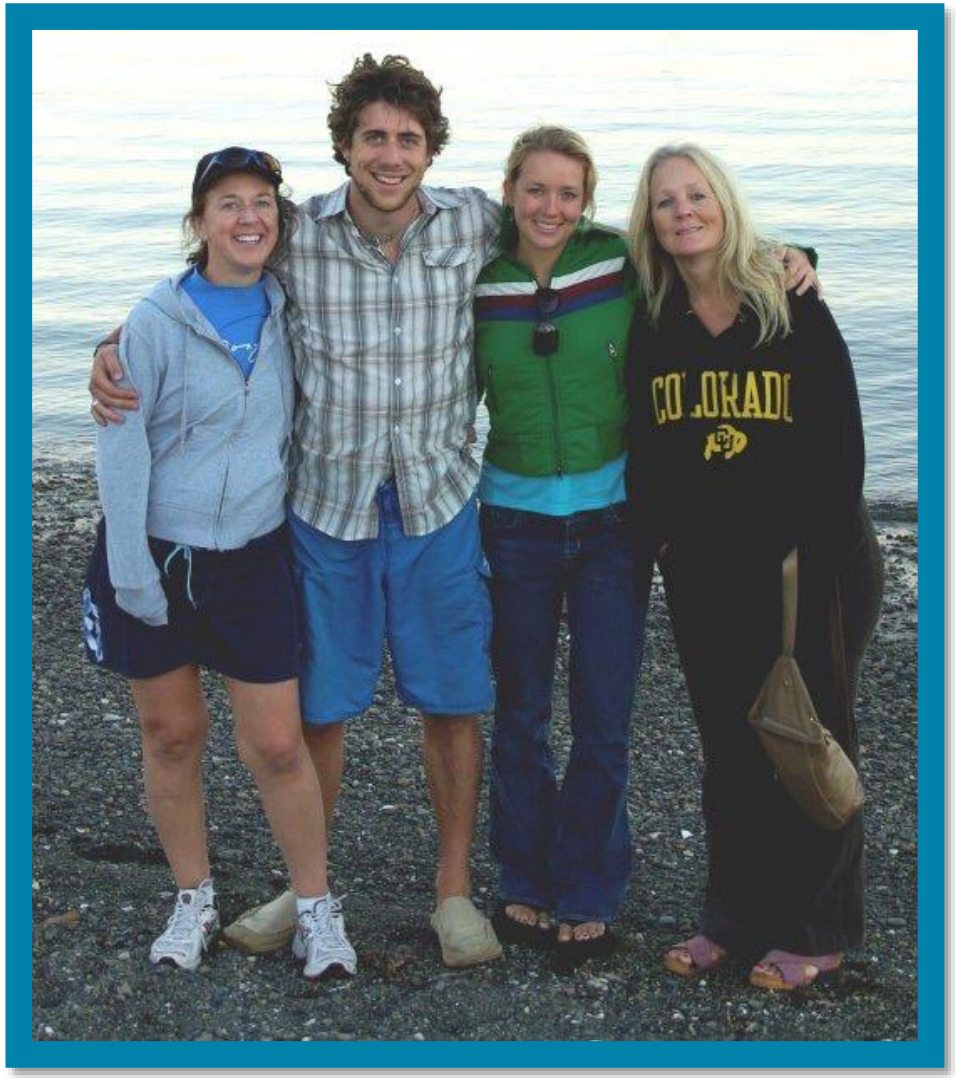
Dana VanBuecken, ARNP
Diabetes Clinical Research Program

Benaroya Research Institute
diabetes@benaroyaresearch.org

Benaroya Research Institute

Introduction

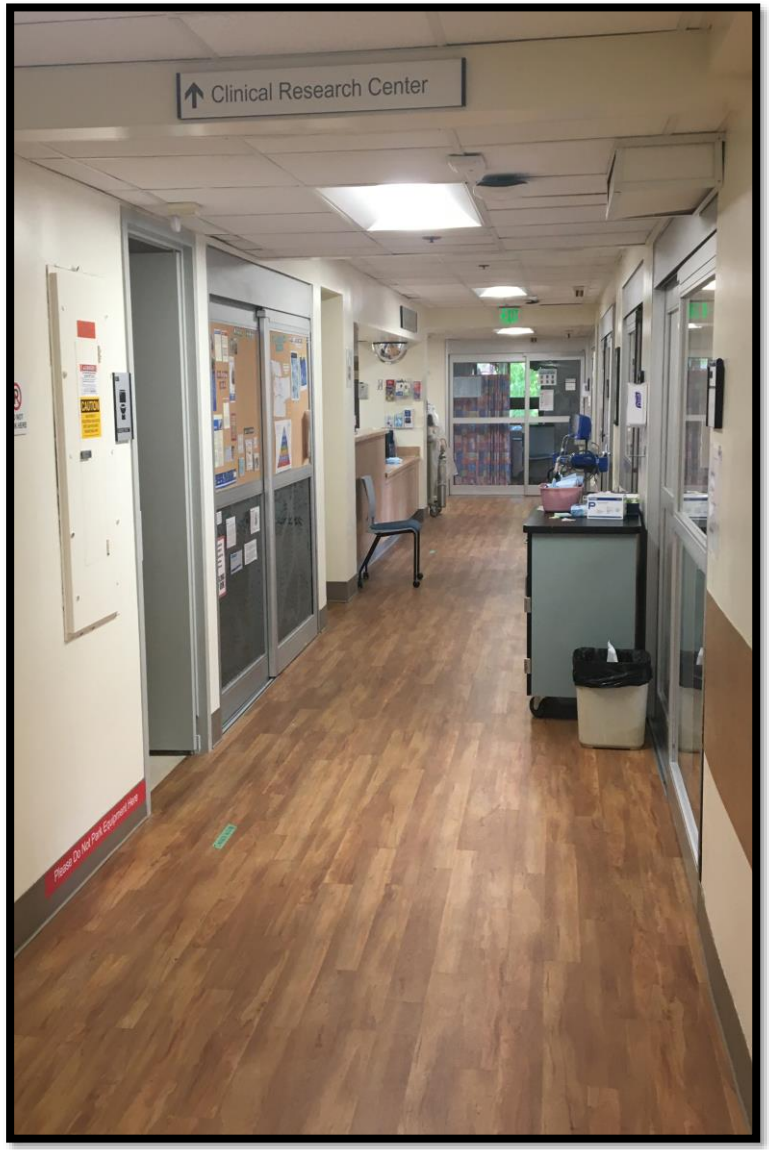
- No disclosures



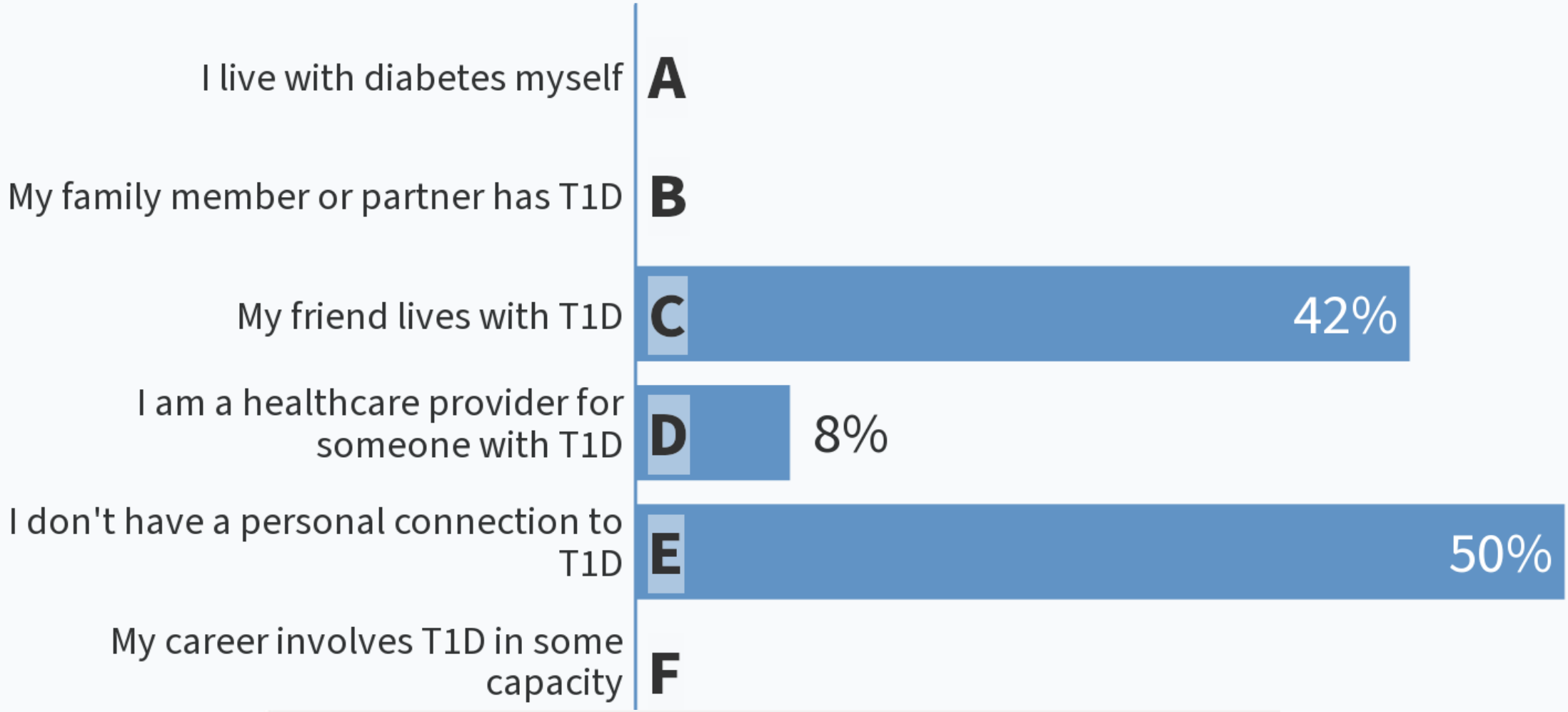
About Benaroya Research Institute

- Nonprofit biomedical research center in Seattle with a focus on understanding autoimmune/ immune diseases
- 29 different labs
- 6-bed unit located on floor 8 of Virginia Mason hospital
- Adult and pediatric clinical trials

“Progress against one autoimmune condition is progress against them all”



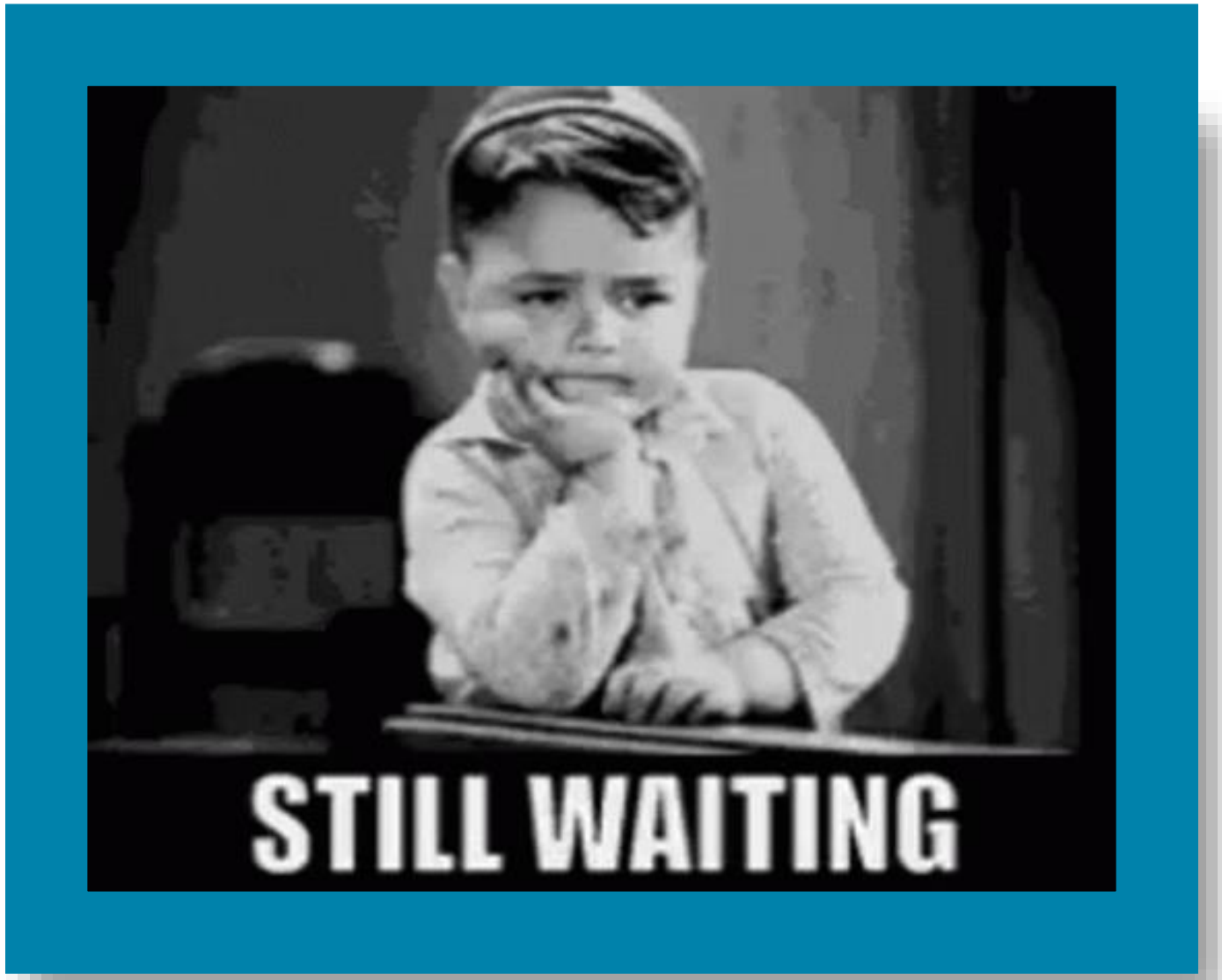
What is your connection to type 1 diabetes?



When poll is active, respond at **PollEv.com/honestcookie180**

Text **HONESTCOOKIE180** to **22333** once to join

When will there be a cure for T1D?



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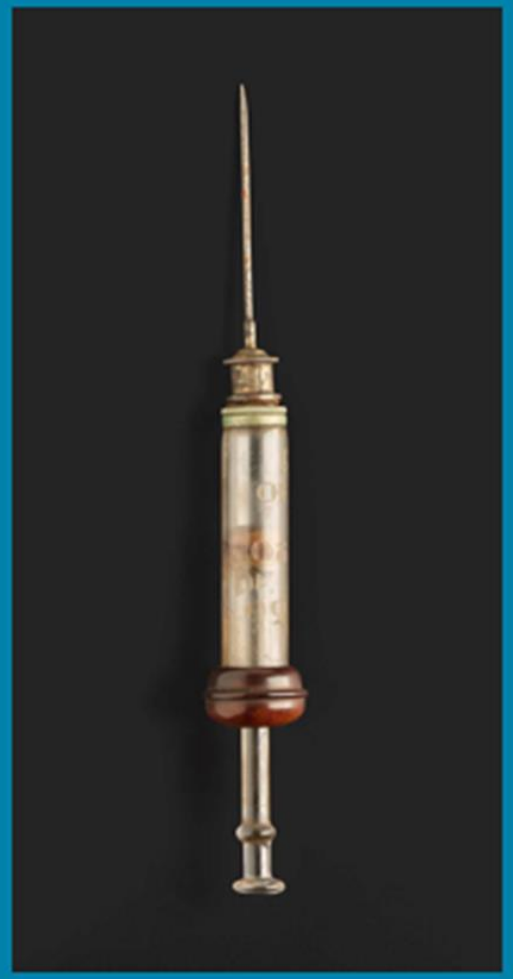
How far have we come?

3500 BC- Ancient texts describe T1D symptoms

Diagnosis made by tasting the urine to determine if it was sweet

How far have we come?



1844: First syringe is invented in Dublin, Ireland by physician Francis Rynd

How far have we come?

1899- German physician Josef von Mering finds that diabetes is a “problem of the pancreas”

How far have we come?

Teddy Ryder prior to insulin treatment

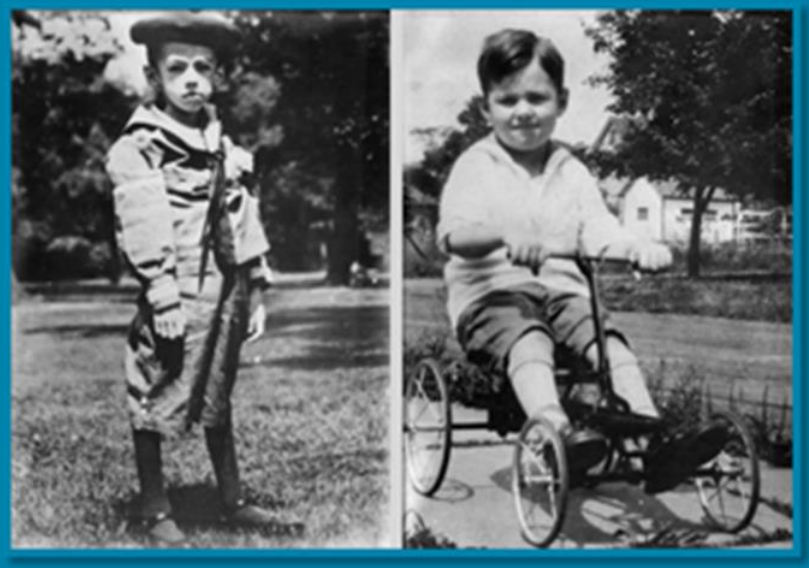
Early 1900s:

T1D treatment consists of individualized starvation diets

Allowed only ~ 400 calories/day (one PBJ sandwich)

How far have we come?

1921: Canadian doctors Frederick Banting and Charles Best discover insulin!



Teddy was one of the first 12 people to receive insulin treatment through a clinical trial run by Banting

How far have we come?

Pancreas glands examined and run through grinders

1921-1982: Insulin purified from pig/cow pancreases left over from the meat-packing industry

2 tons of pig pancreas needed to extract just eight ounces of purified insulin

Patients take just 1-2 injections /day and glucose control is generally poor

How far have we come?

1982: We successfully make human insulin in the lab and bring it to market!

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How far have we come?

1963: Dr. Arnold Kadish develops the first insulin pump

How far have we come?

1965: First blood glucose meter invented

It will not become widely available for home use until the 1980s

How far have we come?

The Lancet · Saturday 30 November 1974

ISLET-CELL ANTIBODIES IN DIABETES MELLITUS WITH AUTOIMMUNE POLYENDOCRINE DEFICIENCIES

1974: Lancet publishes evidence that T1D is an autoimmune disease!

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Where are we now and where are we headed?

Update on research progress for:

- Individuals with New-Onset T1D
- Family members of those with T1D
- Individuals with Longstanding T1D

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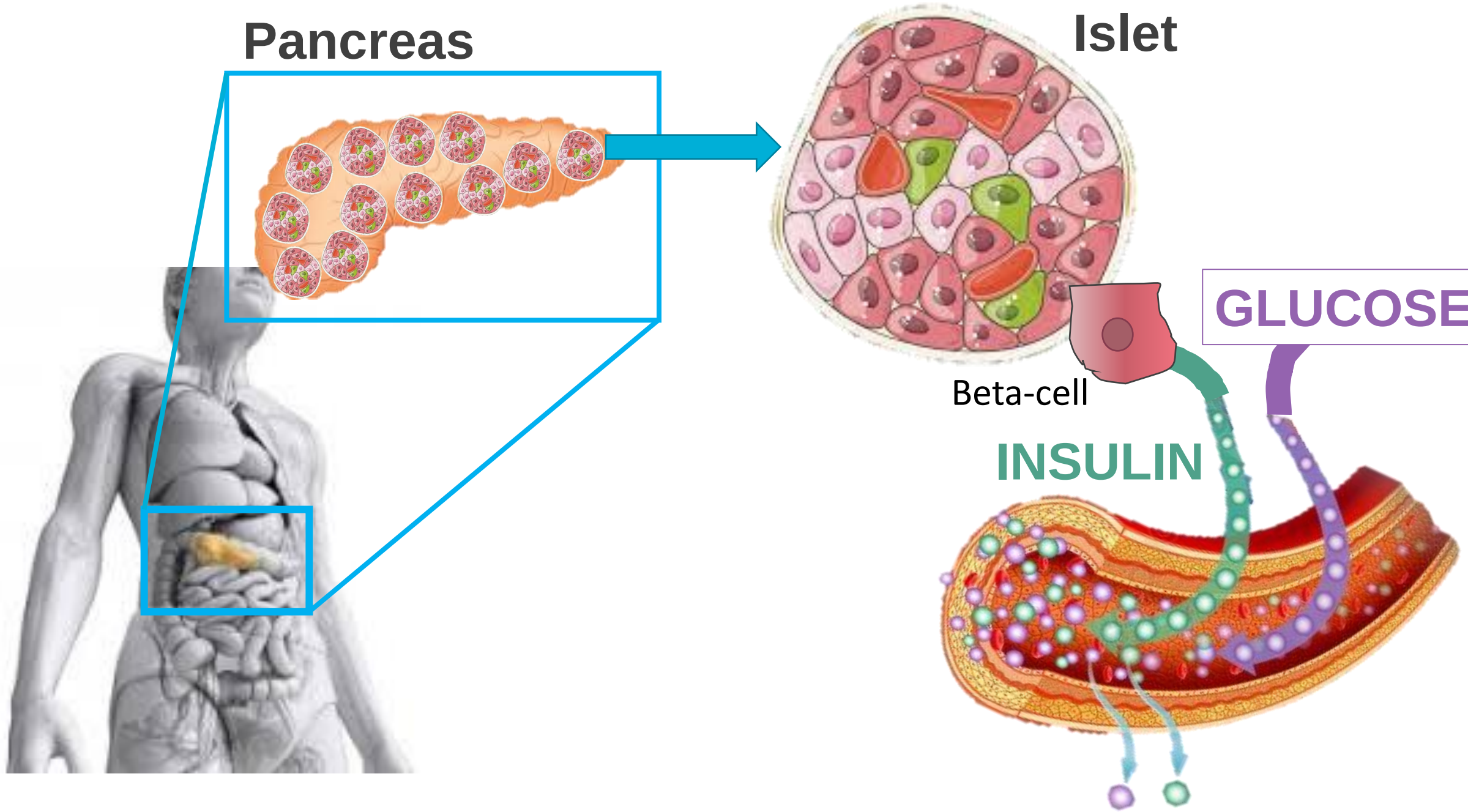
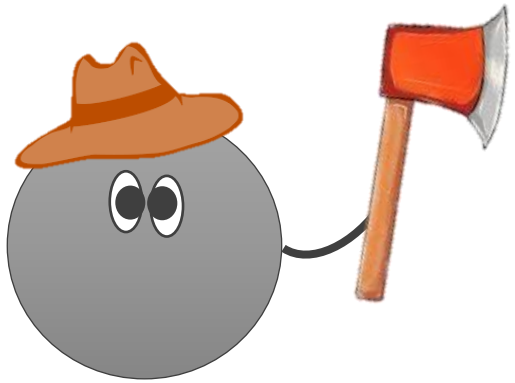
Think back to diagnosis….

What questions might someone have immediately after receiving a T1D diagnosis?

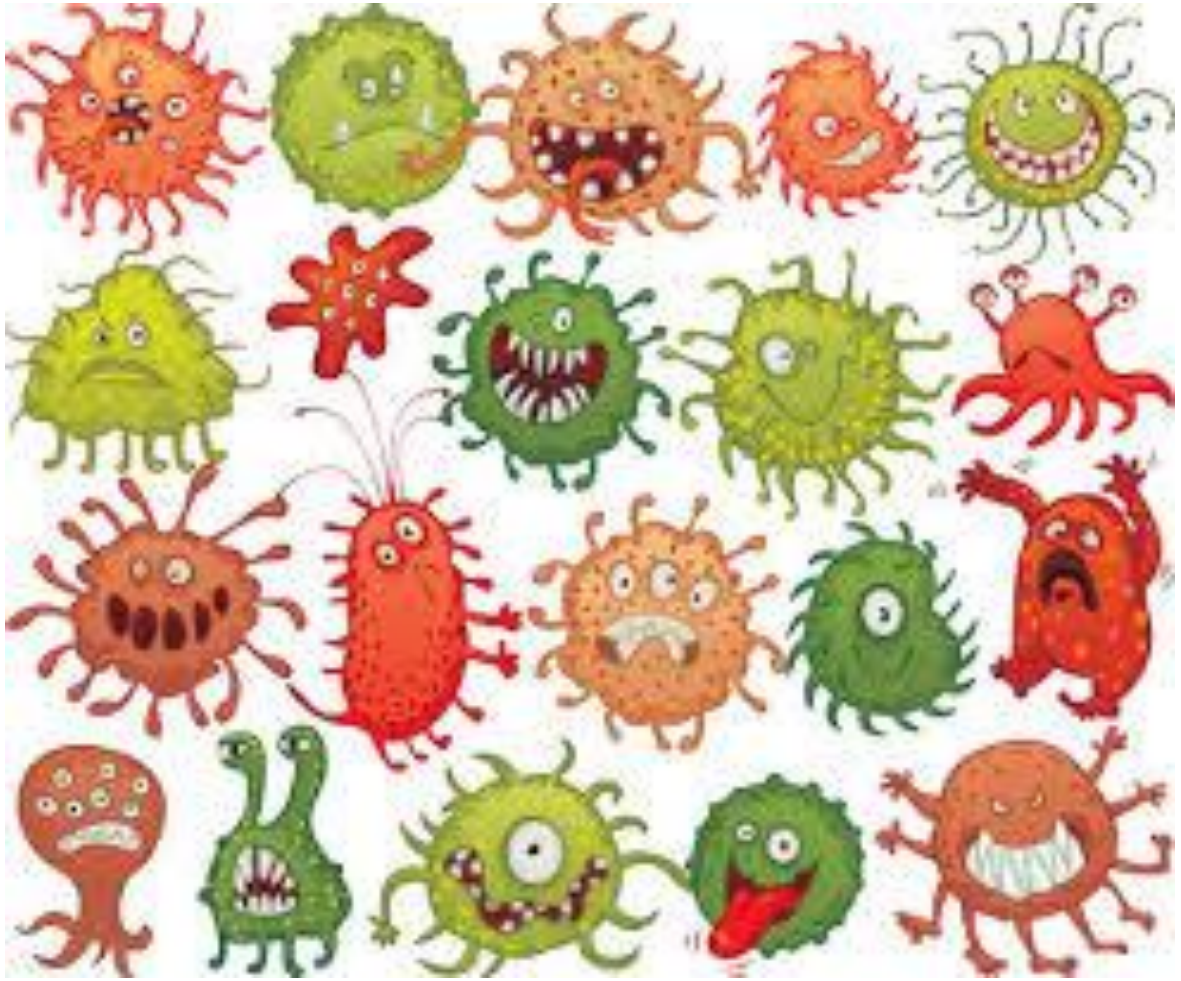
What did ***we*** do **WRONG**?


Pancreas
Islet
GLUCOSE
Beta-cell
INSULIN

T cells protect us against infections and foreign organisms



T cell



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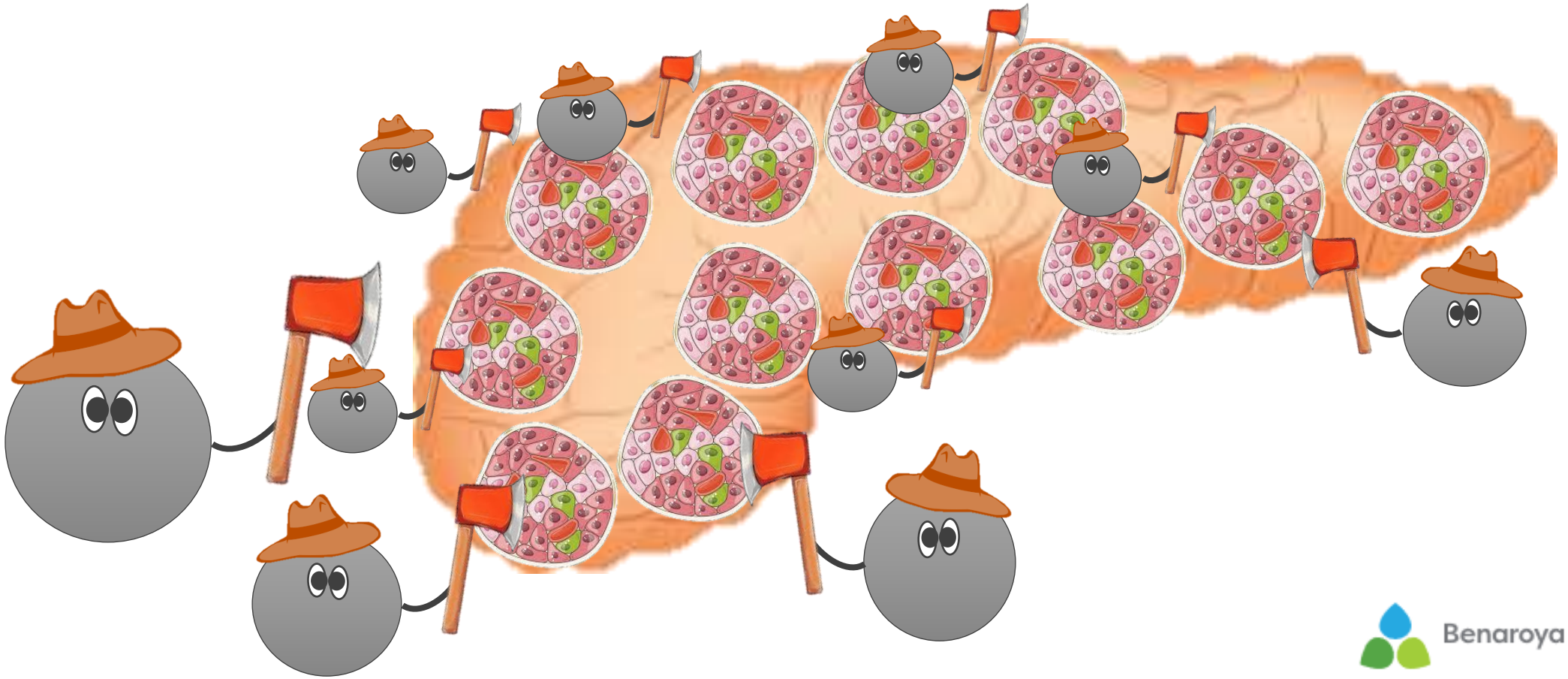
In T1D, T cells attack beta-cells as if they are foreign. This attack may begin years before symptoms develop.



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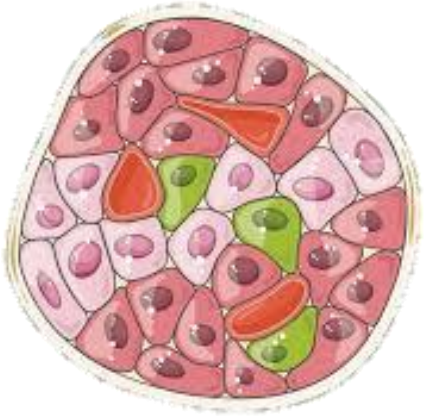
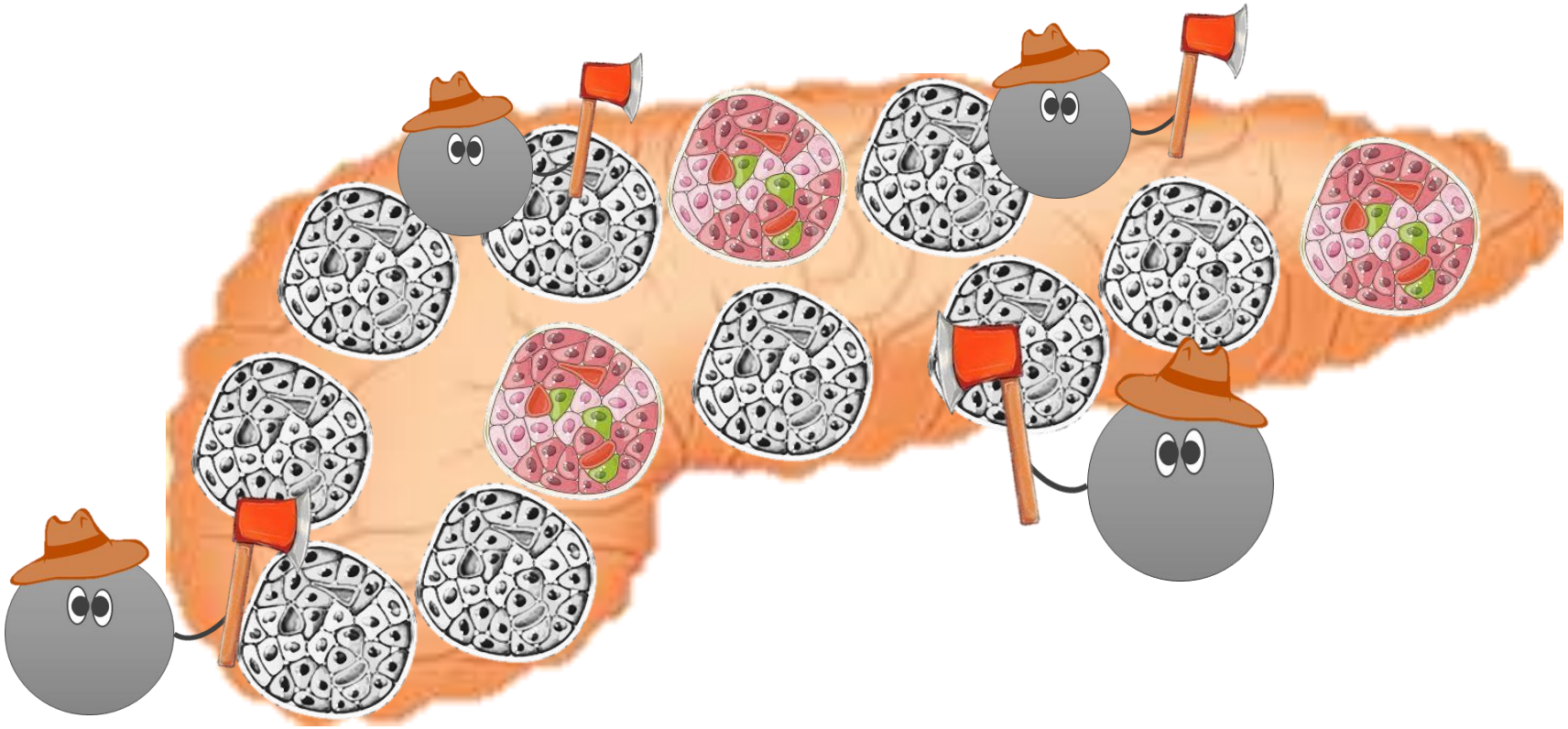


<20% functioning beta cells



At Diagnosis

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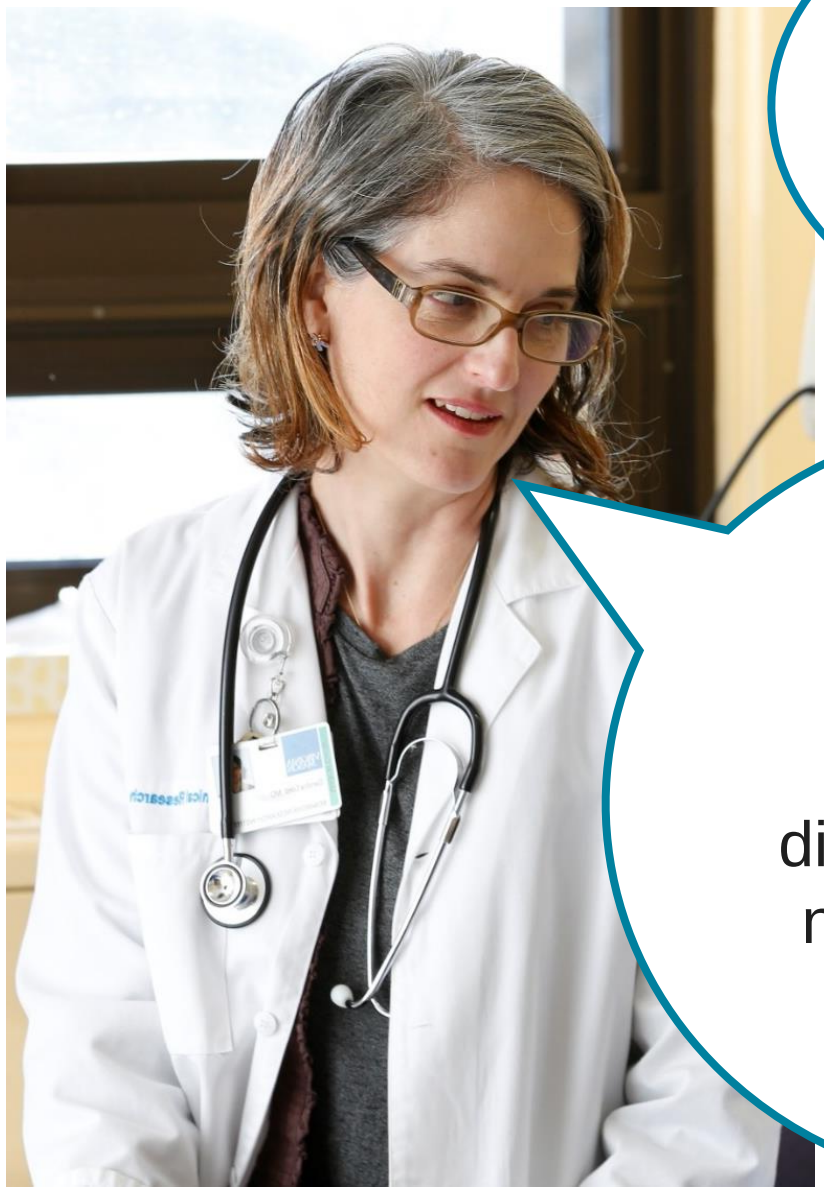

What did ***we*** do **WRONG**?

It is an autoimmune disease. You did nothing wrong.

Can we do anything to help save the beta cells she still has?

Immunotherapy trials aimed at saving beta cells in new onset T1D have been done since the 1980s

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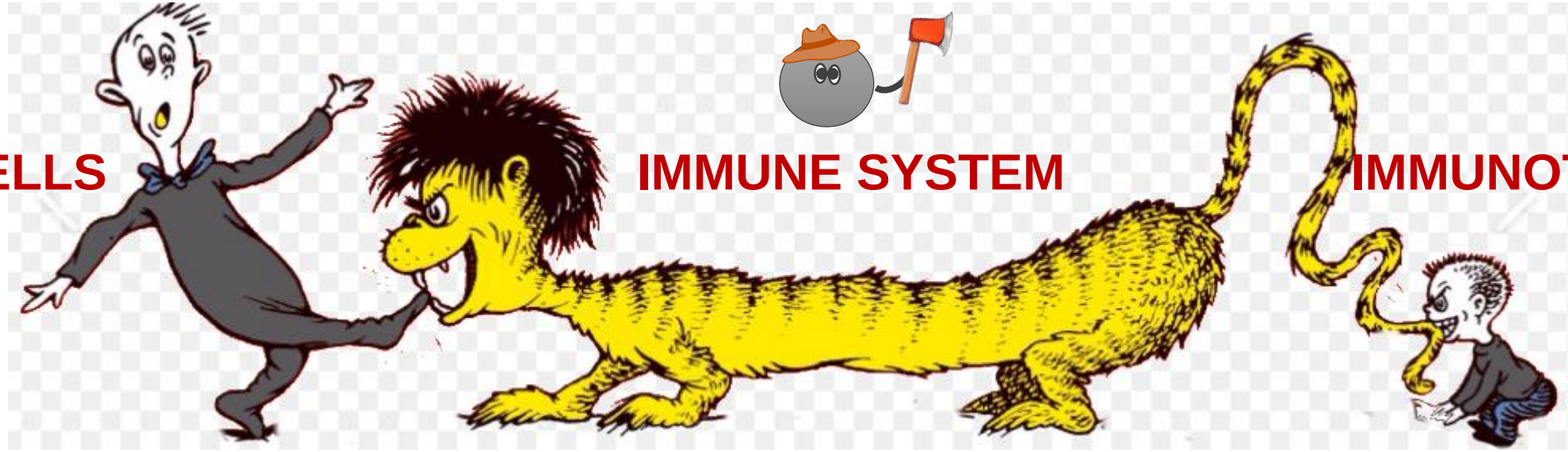
Why Immunotherapy for T1D?



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How do we select therapies to test to preserve remaining beta cells?

- Therapies that work in other autoimmune diseases
- Using known therapies in new ways (i.e. combinations)
- Novel, cutting edge therapies with strong scientific support

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Scientific support from mouse models is imperfect

- Over 700 ways to prevent or reverse diabetes in mouse models
- Immune systems of mice differ greatly from those of humans
- Efficacy does not always translate

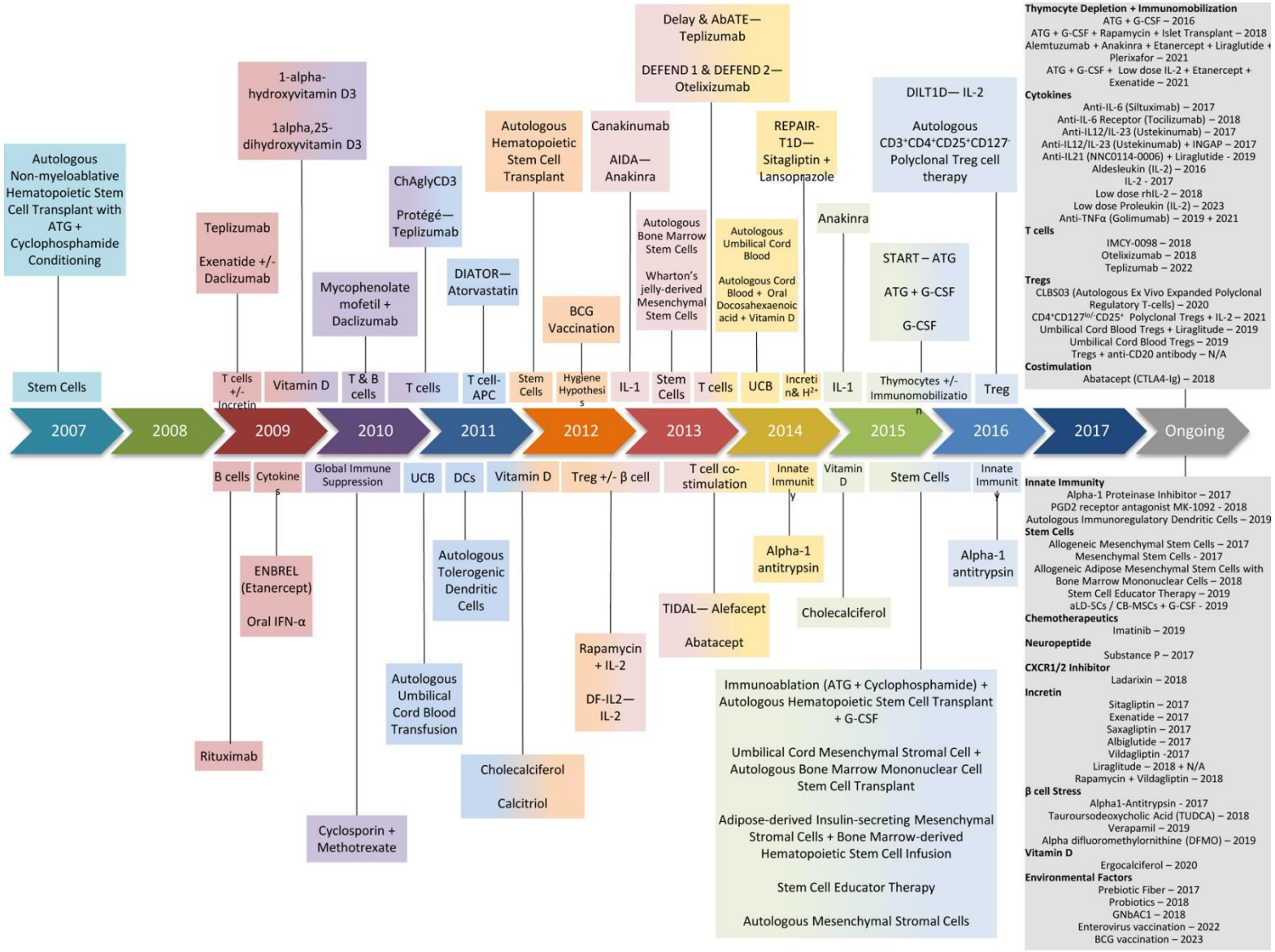
Therapies that Cure T1D in Mice:

Androgen
Anesthesia
Azathioprine
Anti-B7-1
Bacille Calmette Gue'rin (BCG)
Baculofin
β-1,6;1,3-D-glucan
Anti-β 7 integrin
Blocking peptide of MHC class II
Bone marrow transplantation
Castration
Anti-CD3
Anti-CD4
Anti-CD8
Anti-CD28
Cholera toxin-B subunit
Cold exposure
Anti-complement receptor
Complete Freund's adjuvant
Anti-CTLA-4
Cyclosporin
Cyclosporin A
Dapsome (4,4'-diaminodiphenyl sulfone)
Deflazacort
Dendritic cells from pancreatic lymph node
Deoxysperogualin
Diazoxide
1,25 dihydroxyl Vitamin D3
Elevated temperature
Encephalomyocarditis virus (ECMV)
Escherichia coli extract
Essential fatty acid-deficient diets
FK506
Galium nitrate
Glucose (neonatal)
Glutamic acid decarboxylase -intraperitoneal, intrathymic, intravenous, oral
Glutamic acid decarboxylase peptides -intraperitoneal, intrathymic, intravenous, oral
Gonadectomy
Heat shock protein 65
Heat shock protein peptide (p277)
Anti-ICAM-1
Immobilization
Immunoglobulin (IgG2a)
Anti-integrin alpha 4
Inomide
Insulin -intraperitoneal, oral, subcutaneous, nasal
Insulin B chain/B chain amino acids 9–23 -intraperitoneal, oral, subcutaneous, nasal
Insulin–metabolically inactive
Insulin-like growth factor I
Interferon-α
Anti-interferon-γ
Interferon-γ receptor
Interleukin-1
Interleukin-1 receptor
Interleukin-2
Interleukin-2 receptor fusion toxin (DAB480-IL-2)
Interleukin-3
Interleukin-4
Interleukin-10
Interleukin-12 antagonist
Islet cells–intrathymic
Lactate dehydogenase virus (LDH)
Lactobacilus casei
Lazaroid
Linomide
Lithium chloride
Anti-LFA-1
Anti-L-selectin
Lymphocyte choriomeningitis virus (LCMV)
Anti-lymphocyte serum/lymphotoxin
Lymphocyte vaccination
LZ8
MDL 29311
Melatonin
Anti-MHC class I
Anti-MHC class II
Mixed allogeneic chimerism
Monosodium glutamate
Murine hepatitis virus (MHV)
Mycobacterium
Natural antibodies
Nicotinamide
Nutramigen
OK432
Overcrowding
Pancreatectomy
Pentoxifylline
Pertussigen
Poly [I:C]
Pregestimil diet
Probucol
Prolactin
Rampamycin
Reg protein
Rolipram
Saline (repeated injection)
Semi-purified diet (AIN-76)
Silica
Sodium fusidate
Somatostatin
Non-specific pathogen free conditions
Streptococcal enterotoxins (SEA)
Superantigens
Superoxide dismutase-desferrioxamine
TGF-β
Anti-T-cell receptor
Anti-thy-1
Thymectomy (neonatal)
T-lymphocyte clones
Tolbutamide
Troglitazone
Tumor necrosis factor-α
Tumor necrosis factor-β
Vitamin E
Anti-VLA-4

*from Atkinson and Leiter, Natur Med 1999

Immunotherapy trials in humans

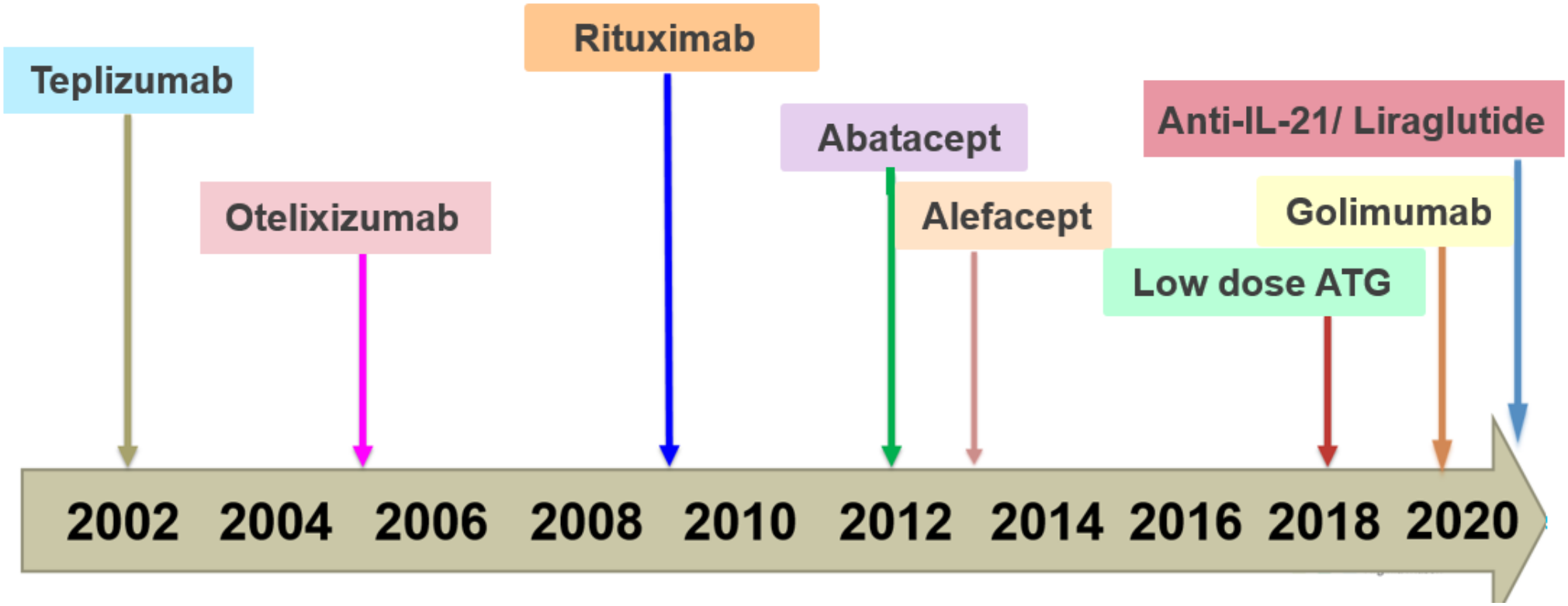
It is estimated that over
20,000 people
have participated in prevention/preservation trials since the early1980s when the first trial was done with cyclosporine



*From Atkinson et al., Lancet D & E, 2019

How many different therapies have been effective in saving beta cell function in people with newly-diagnosed T1D?

8 immunotherapies have been effective!



- All studies done in new-onset T1D
- Therapies prolonged beta cell function for 6 months to 2 years

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Trials enrolling those with new-onset T1D

CURRENTLY ENROLLING AT BRI:

DESIGNATE

Eligibility: Diagnosed within the past 18 months, Ages 18-45

Treatment: 12 weekly injections of **Siplizumab**

4 possible arms with varying doses of Siplizumab

COBRA STUDY

Eligibility: Diagnosed within the past **3 years,** Ages 18-45

Treatment: 3 infusions of **Vedolizumab** with or without 8 weekly injections of **Etanercept**

No Placebo Group

TOPPLE STUDY

Eligibility: Diagnosed within the past **4 years,** Ages 18-45

Treatment: **Plasmid Therapy** via weekly injection for 12 weeks

3:1 randomization

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Most new-onset studies pay for travel!

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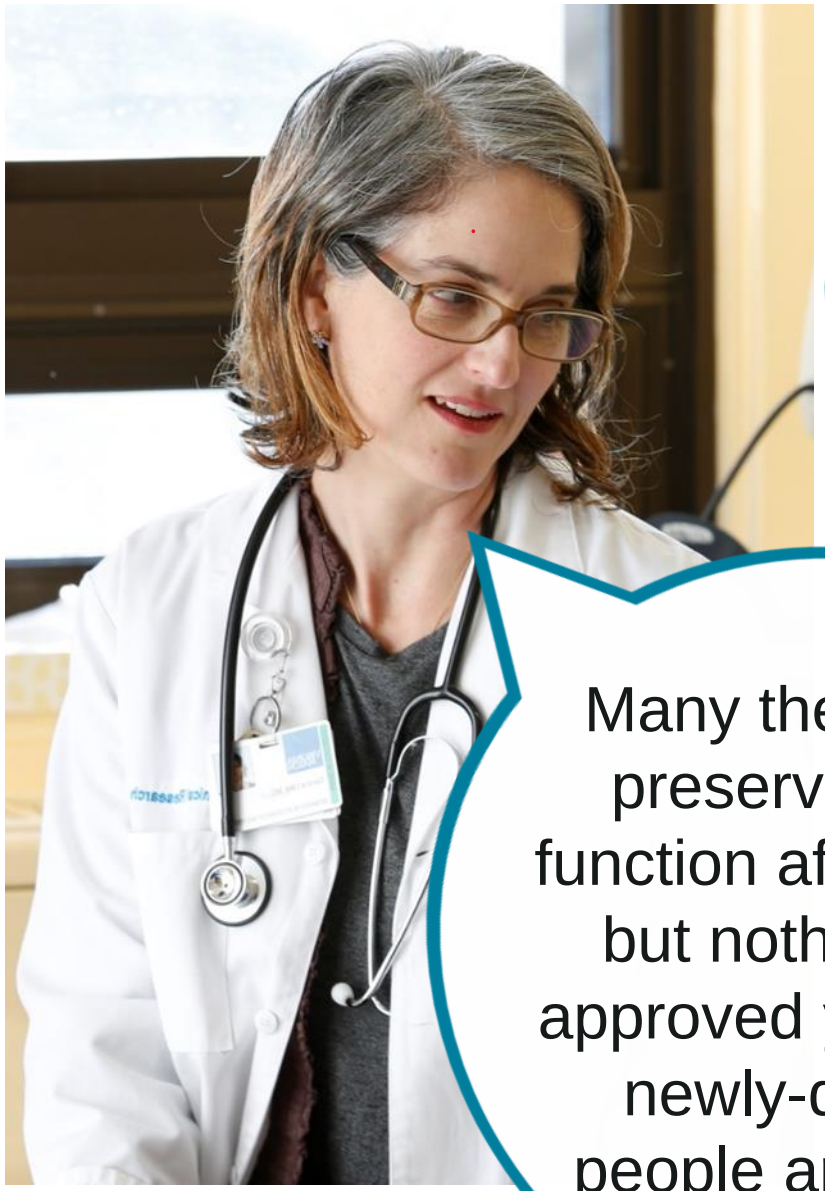

Can we do anything to help save the beta cells she still has?

Many therapies *can* preserve beta cell function after diagnosis but nothing is FDA approved yet. Trials for newly-diagnosed people are enrolling!

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Could we have known about her T1D **earlier**?

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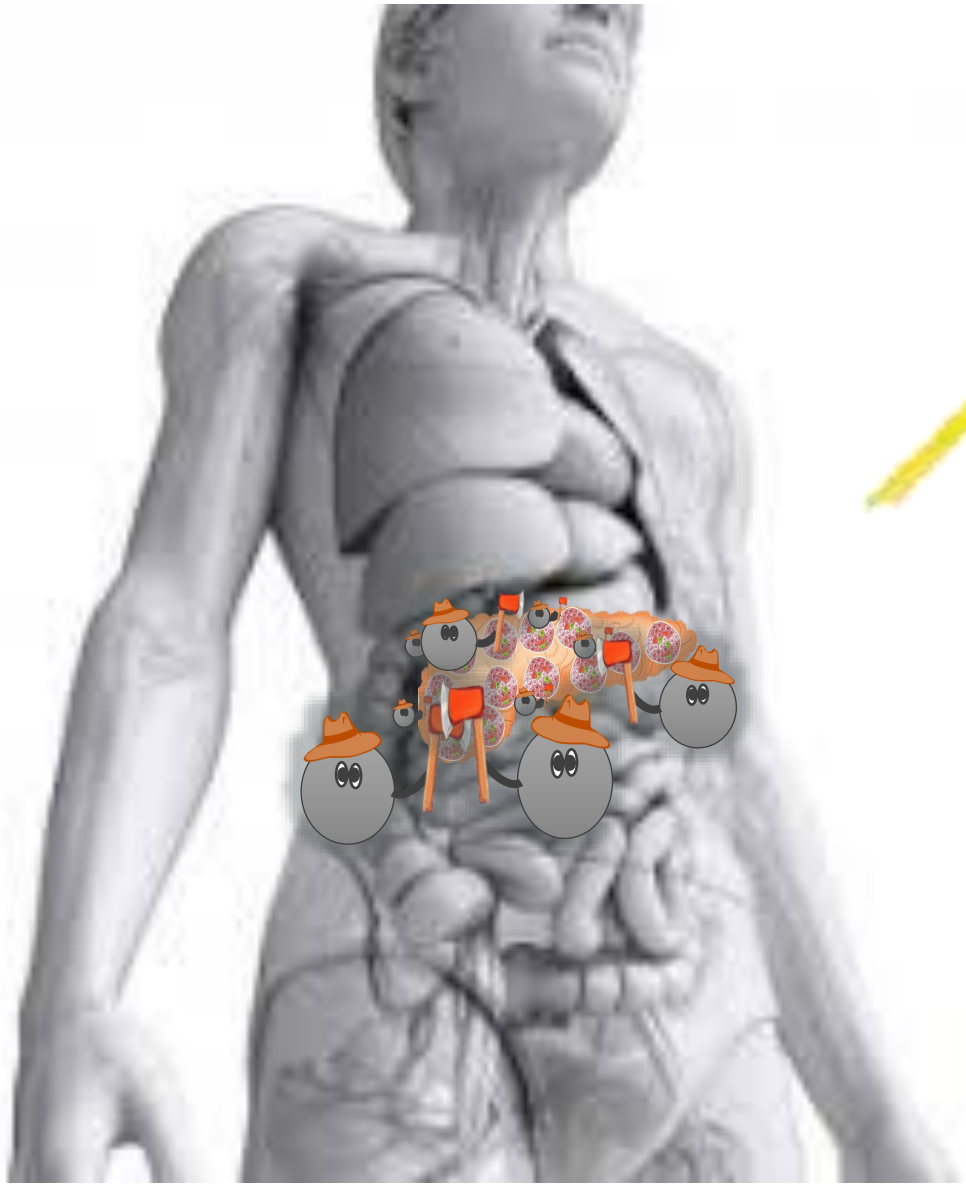

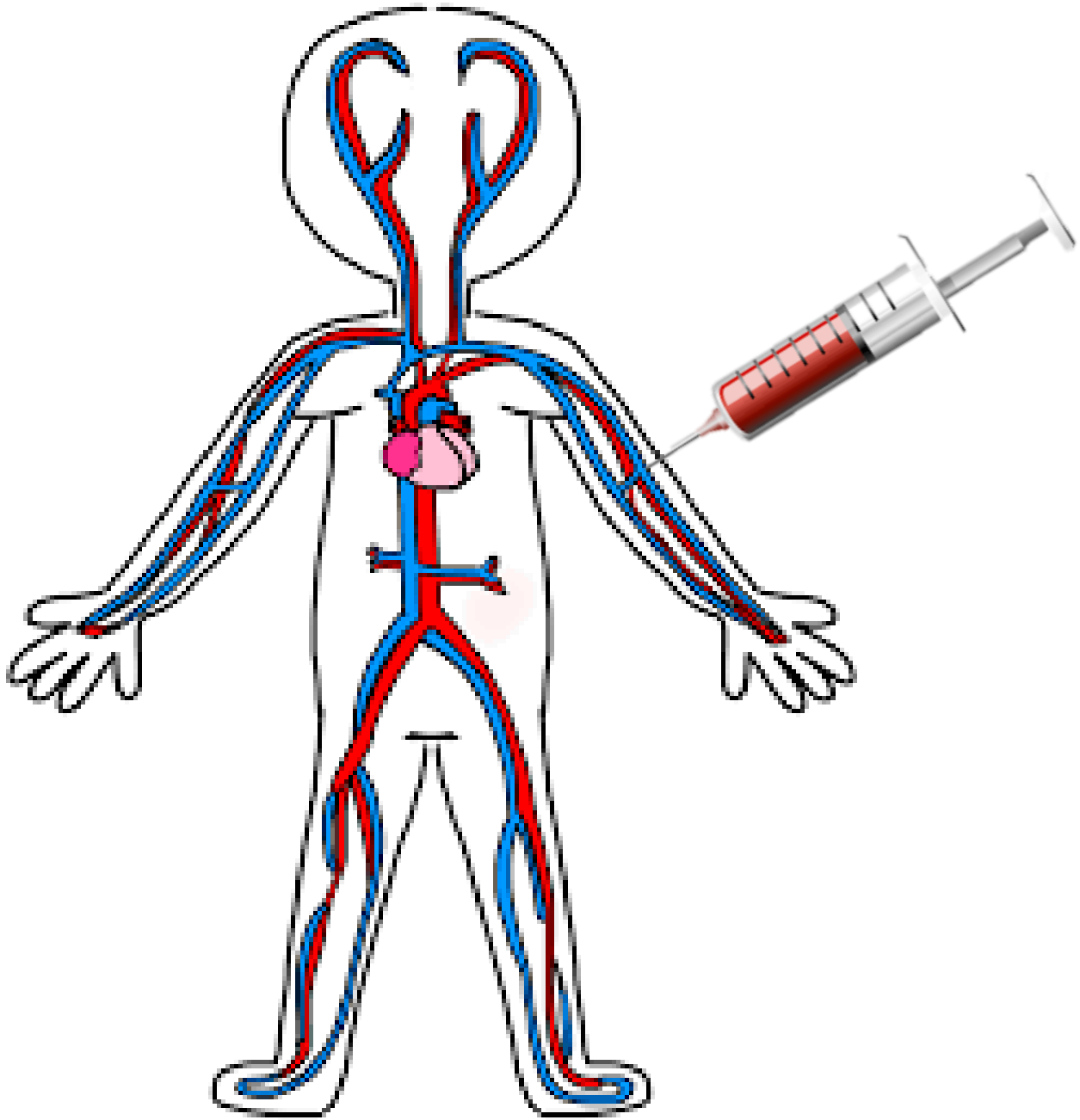

The only window we currently have into the pancreas is through a blood test.

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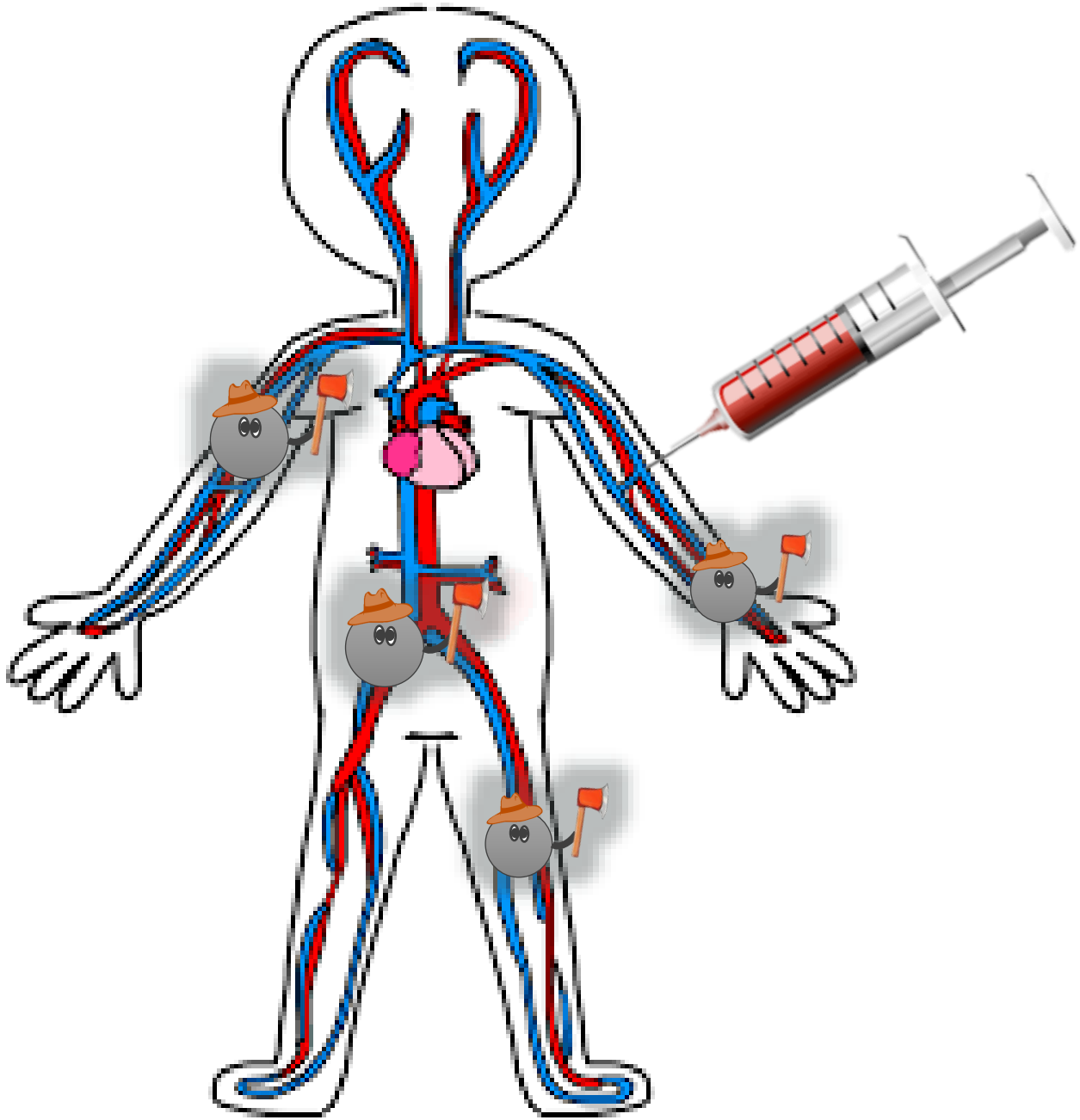

Too few circulating islet-attacking T cells to detect easily on a blood test

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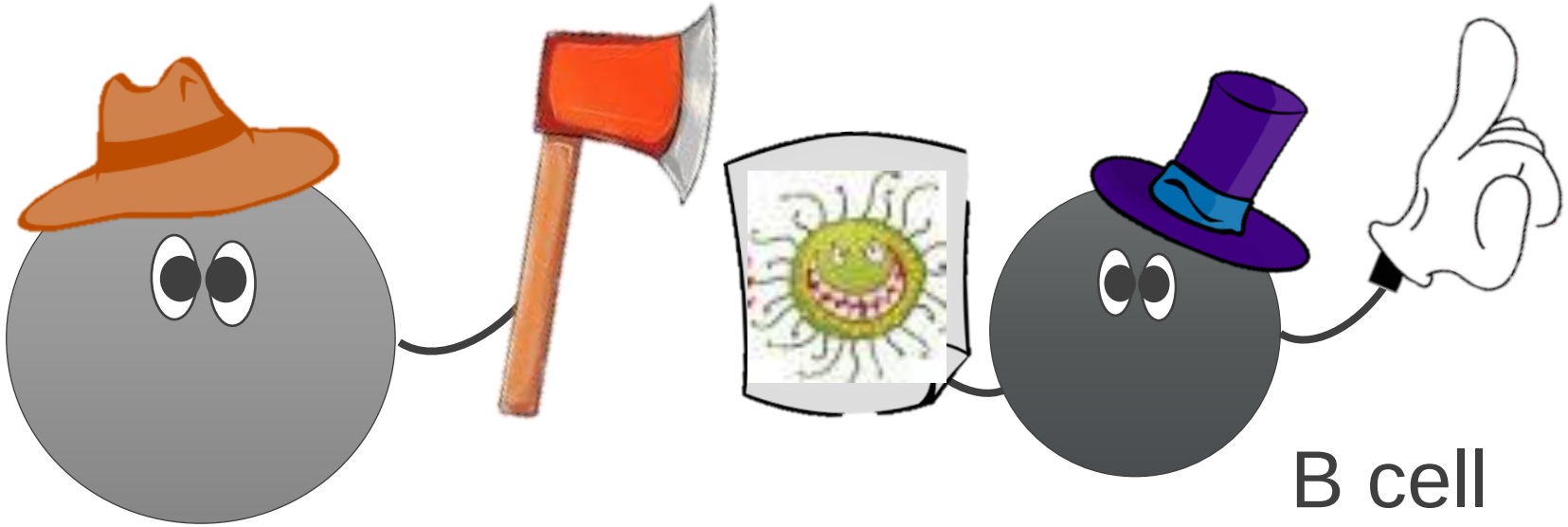
B cells help direct T cells to where they are needed



B cell

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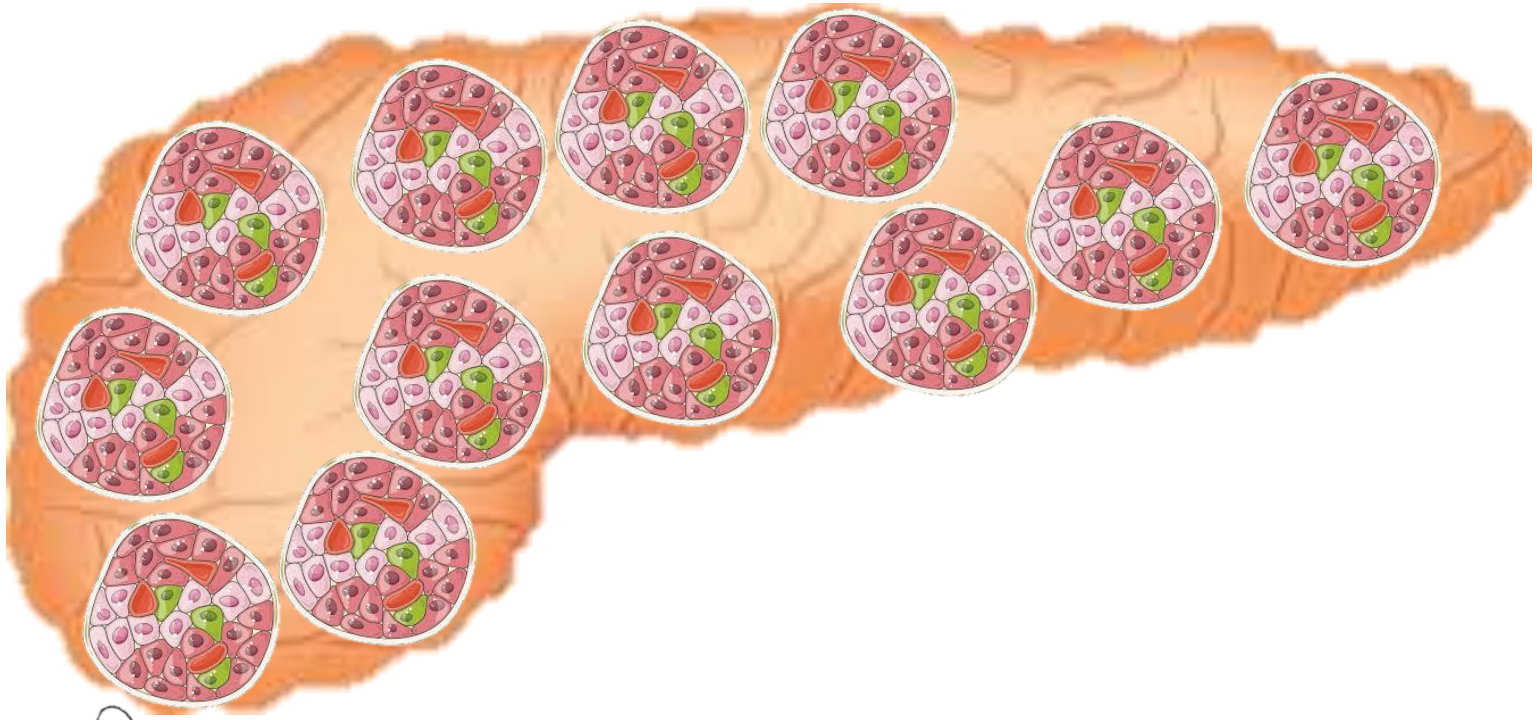
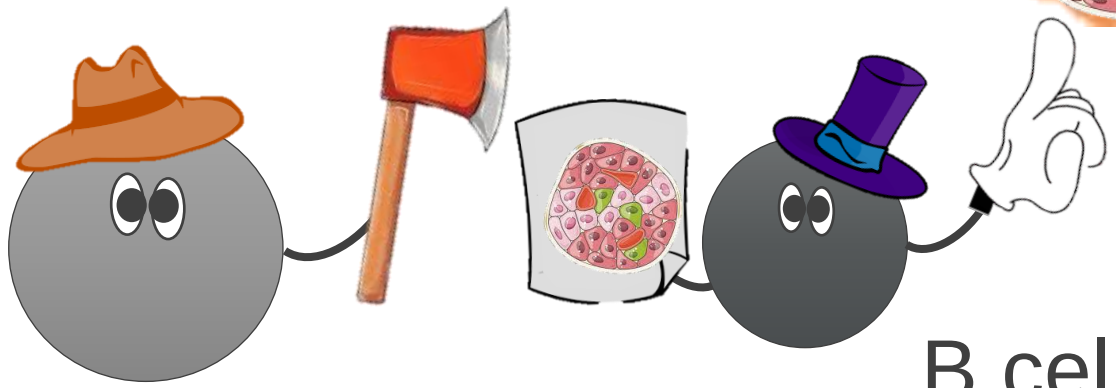
In T1D, B cells send wrong messages and direct T cells to the islets





B cell

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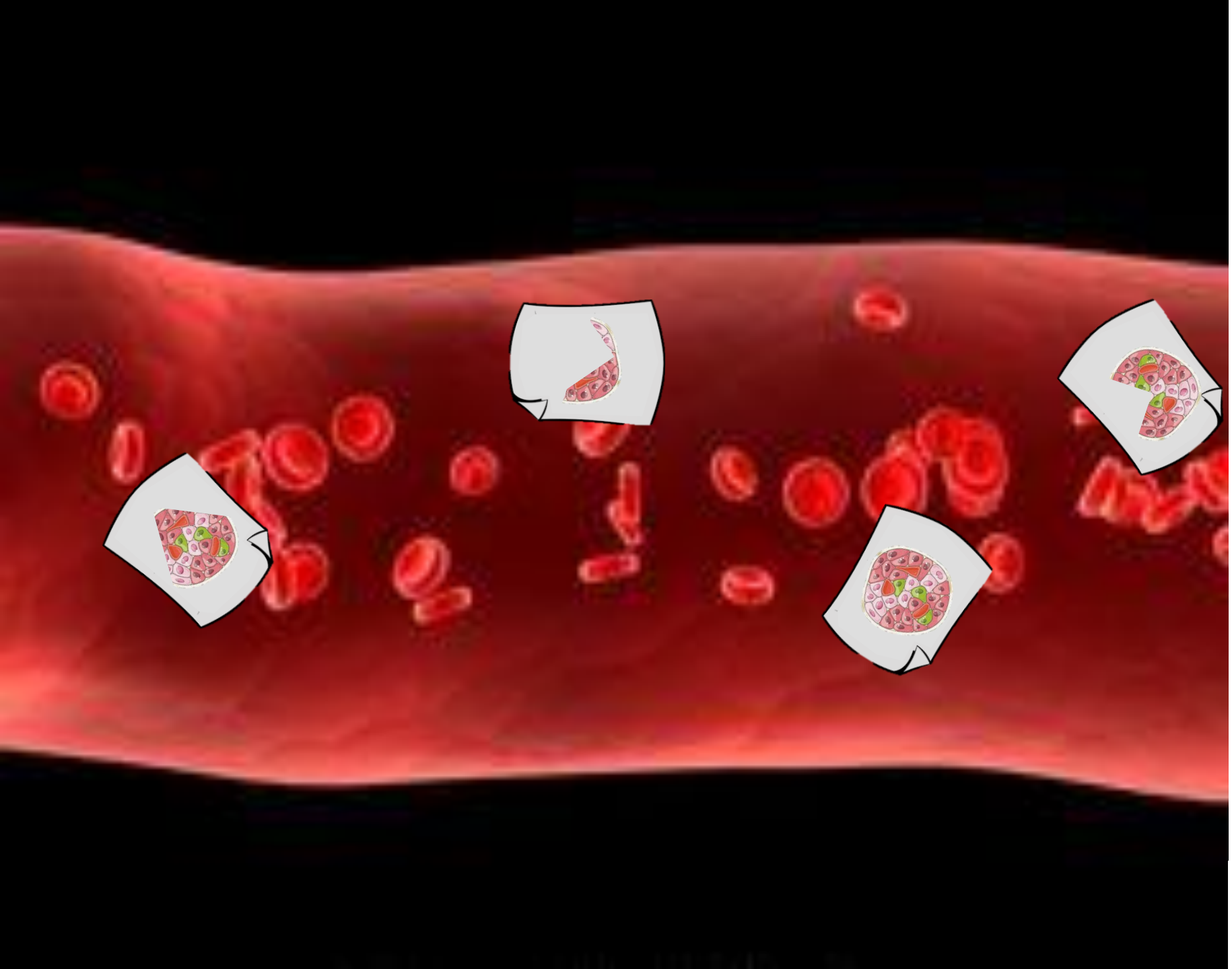

Evidence of these wrong messages can be found in the bloodstream

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What are these "wrong messages" called?

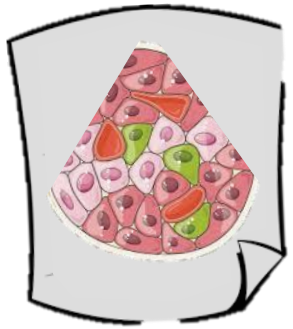
Cytotoxic T-Cells

Diabetes Autoantibodies

Immunoglobulins

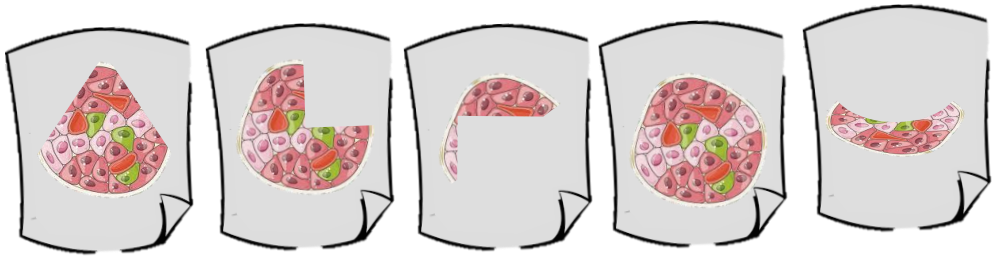
Autoimmune antigens

Bad News



= diabetes autoantibodies

95% of children who develop T1D before puberty have antibodies by age 5



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Insulin GAD IA2 ICA ZnT8

There are 5 autoantibodies associated with T1D so far

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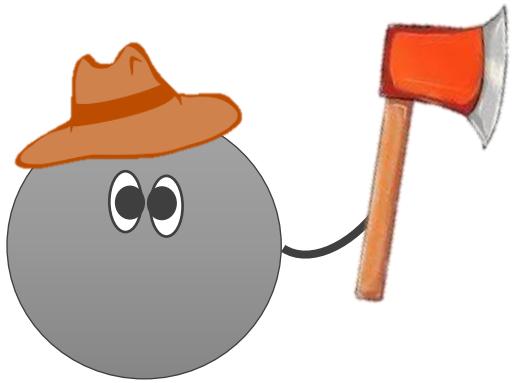
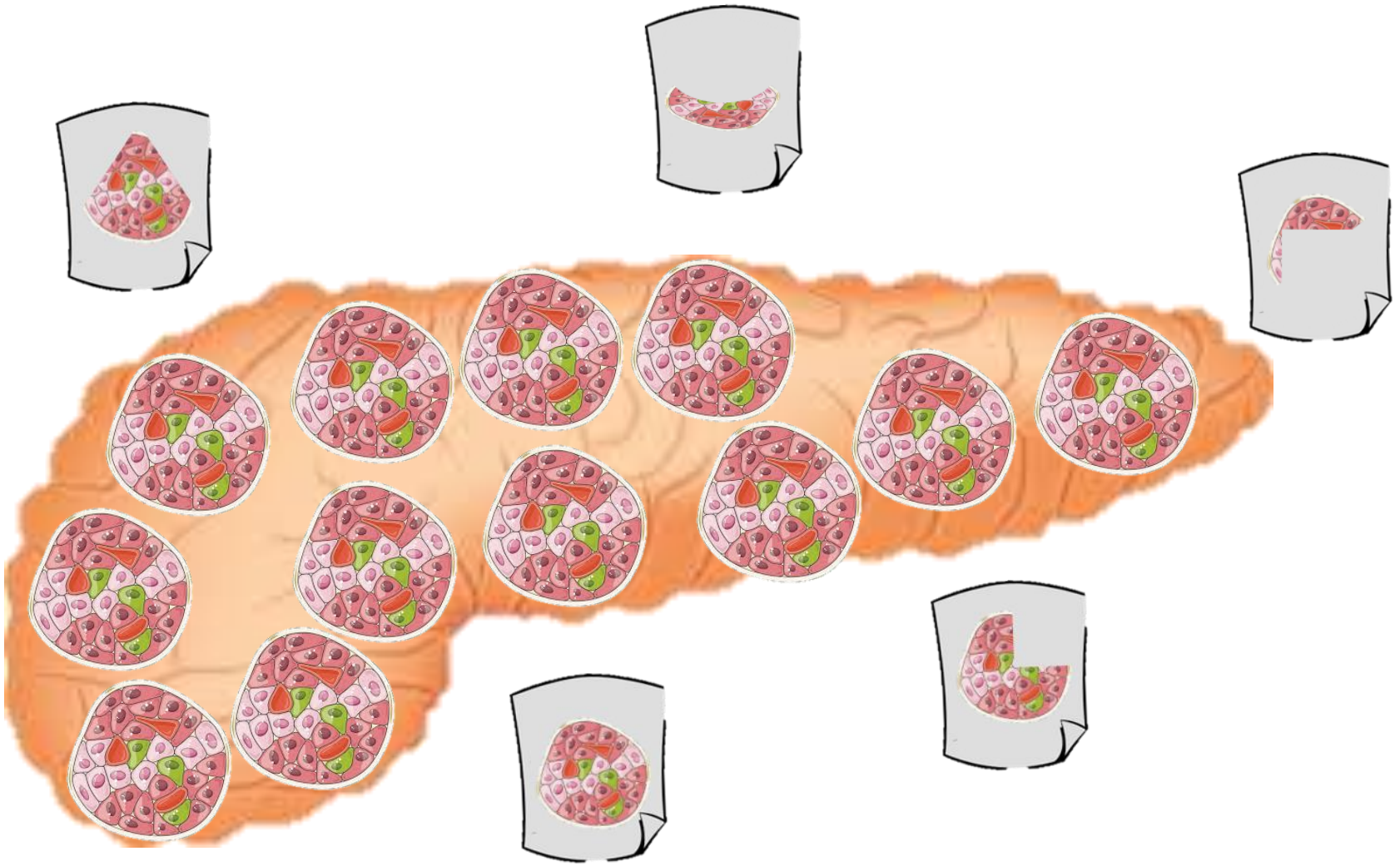
Autoantibodies appear many years before diagnosis





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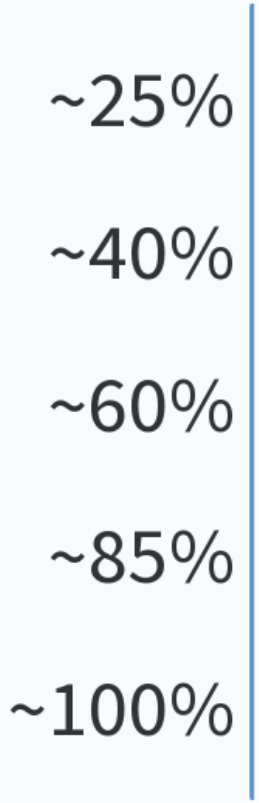
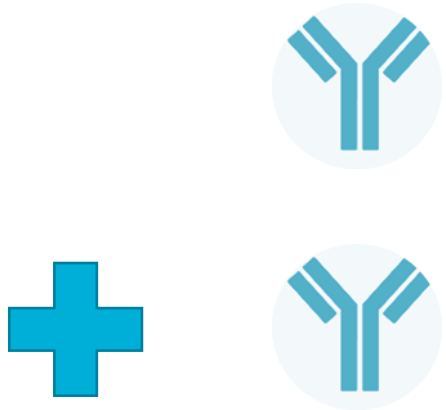
If you test positive for at least 2 autoantibodies, what is your chance of developing symptomatic T1D over the course of your lifetime?



If you test positive for at least 2 diabetes autoantibodies, you have ~100% chance of developing symptomatic T1D over the course of your lifetime



This is Stage 1 T1D!

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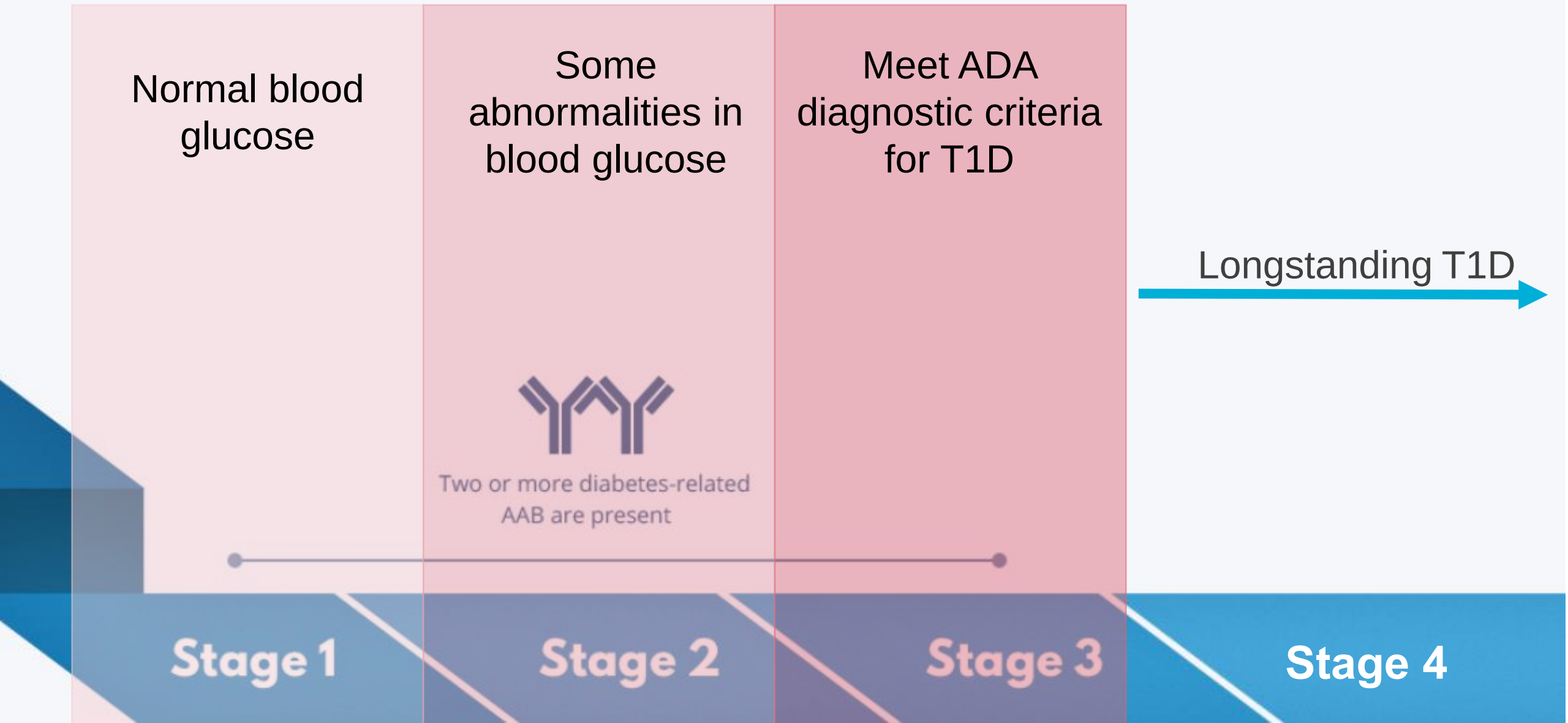
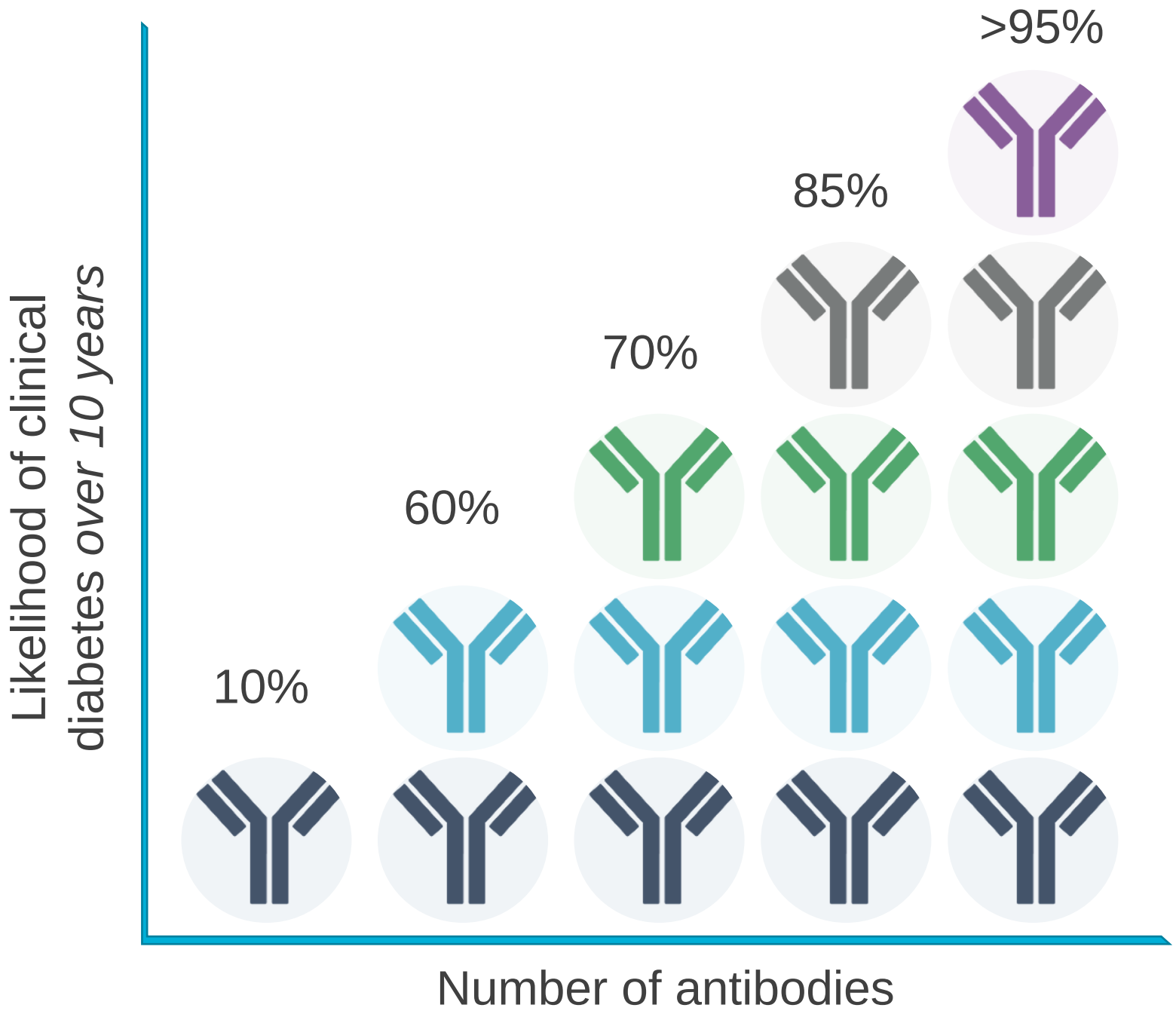
What are the stages of T1D?

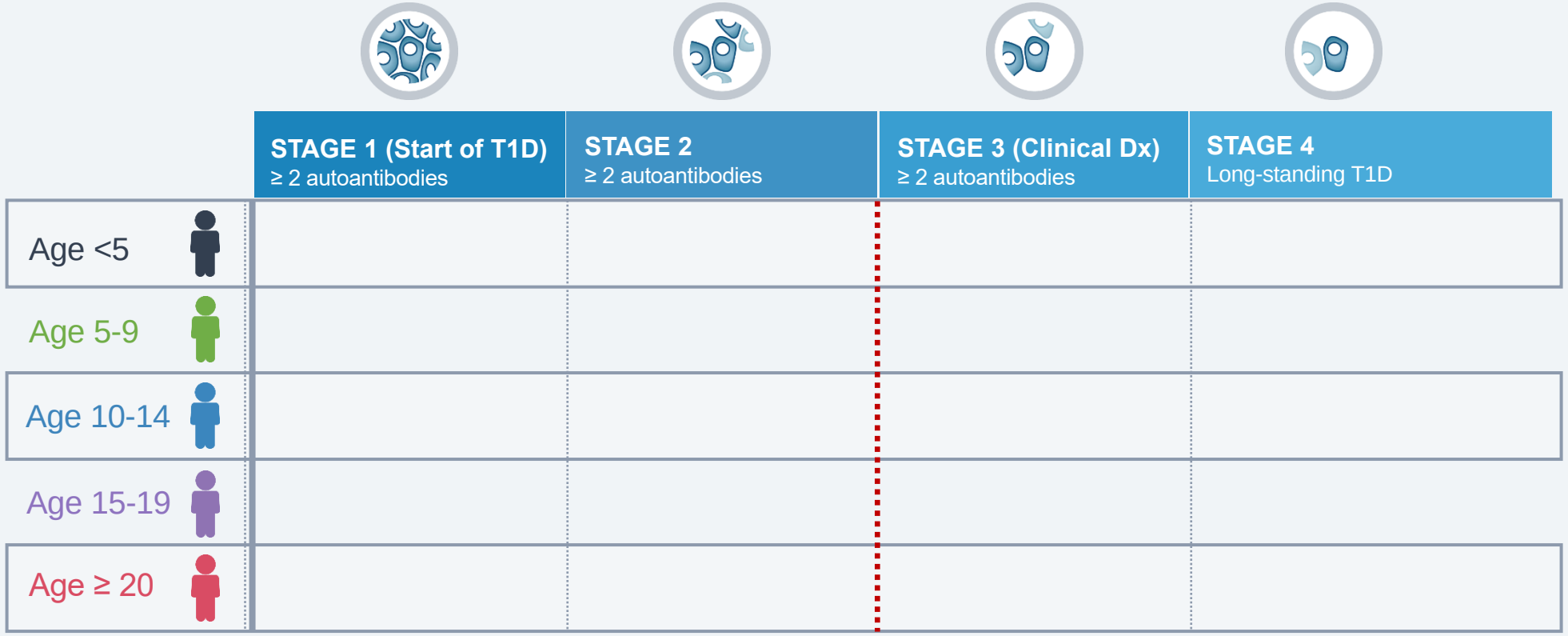


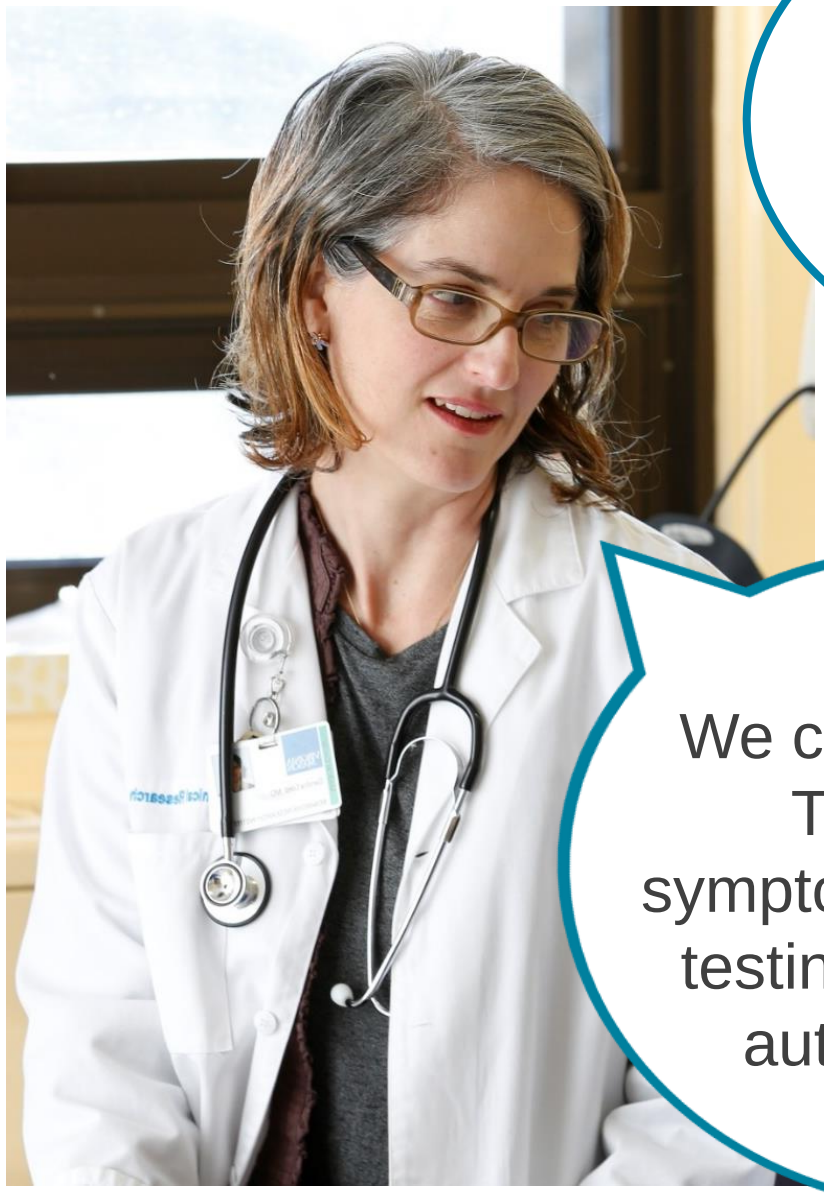


More *types* of islet autoantibodies = greater likelihood of developing clinical diabetes

Type 1 Diabetes TrialNet

Impact of AGE on Disease Progression





Could we have known this **earlier**?

We can now detect T1D before symptoms develop by testing for diabetes autoantibodies

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Since I have a child with T1D….

…are my other family members at risk??

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What is the lifetime risk of T1D in family members of those with T1D?

1 in 100

1 in 20

1 in 50

1 in 5

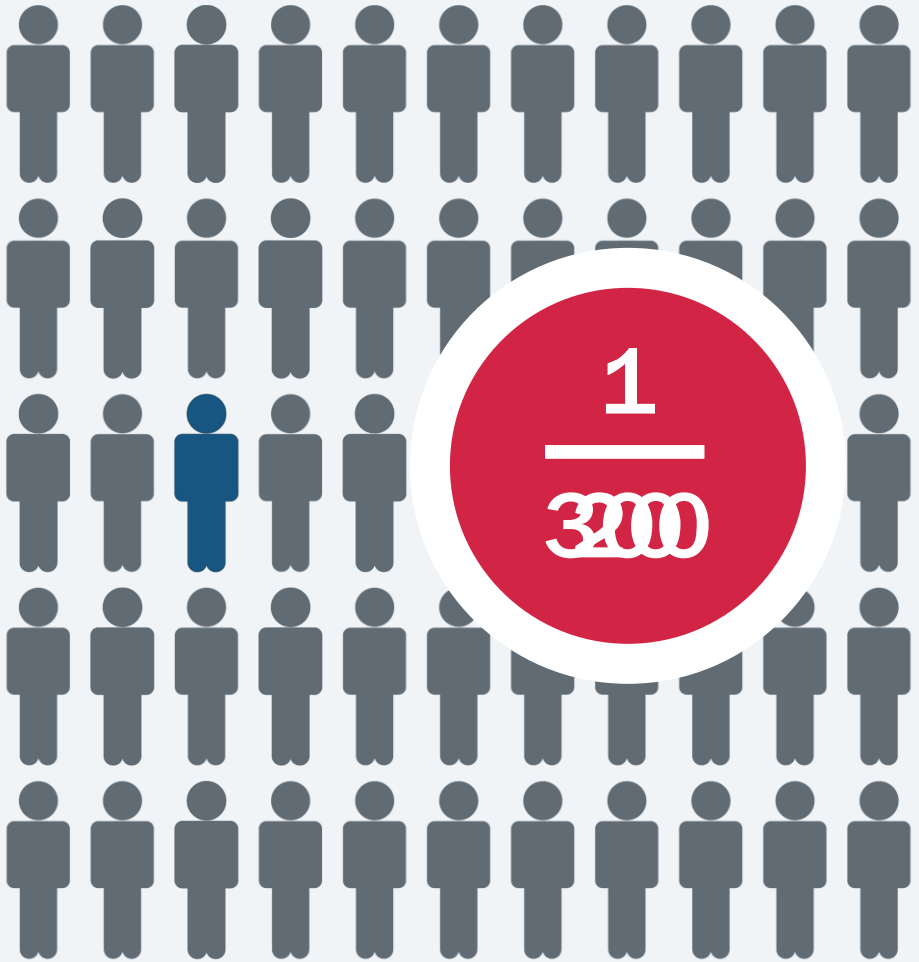
None of the above

T1D risk in family members

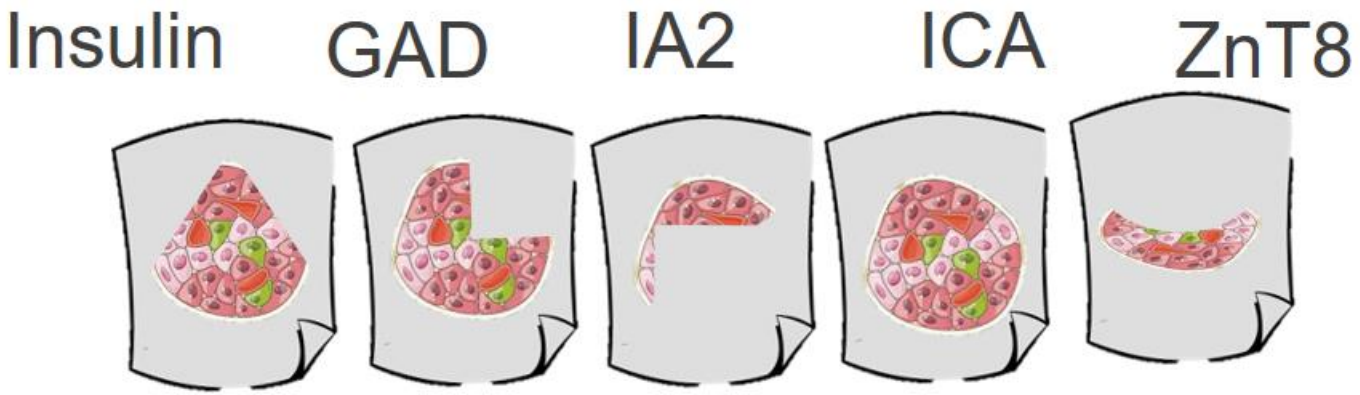
Genetic Risk

- General population risk is 1 in 300
- If you have a family member with T1D, your risk is 1 in 20

Family members are at 15x greater risk to develop T1D



Because of this elevated risk, family members are eligible for FREE autoantibody screening through TrialNet and other programs



Type 1 Diabetes TrialNet

Benaroya Research Institute

How can family members be screened?

Visit the TrialNet table!

Screening will be available until 4:00 pm TODAY ONLY

Who can be screened:

- Anyone age 2.5 through 45 years with a sibling, child or parent with T1D.
- Anyone age 2.5 through 20 years with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with T1D.

Visit www.TrialNet.org

Type 1 Diabetes TrialNet

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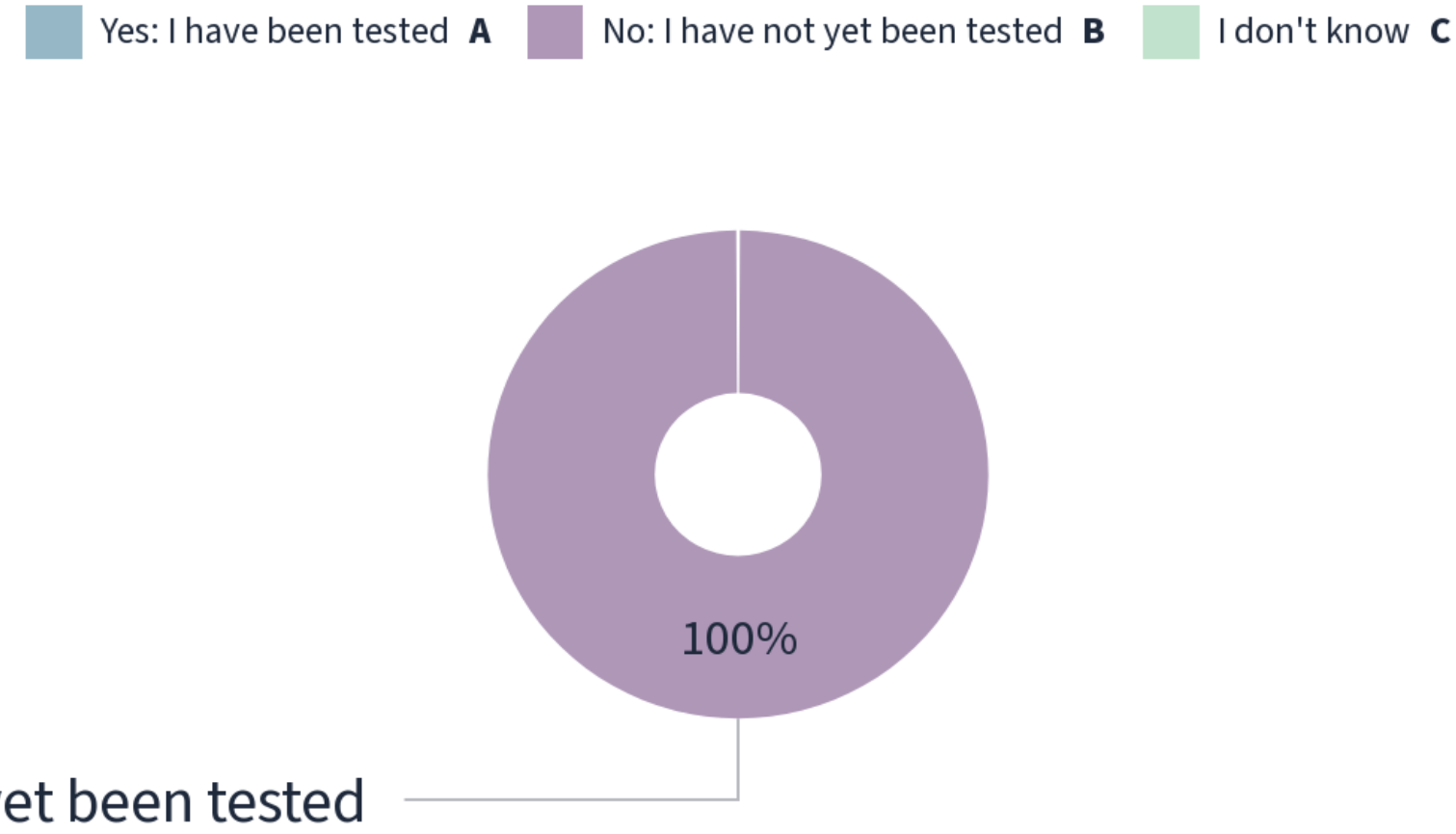
What if I test positive for autoantibodies?

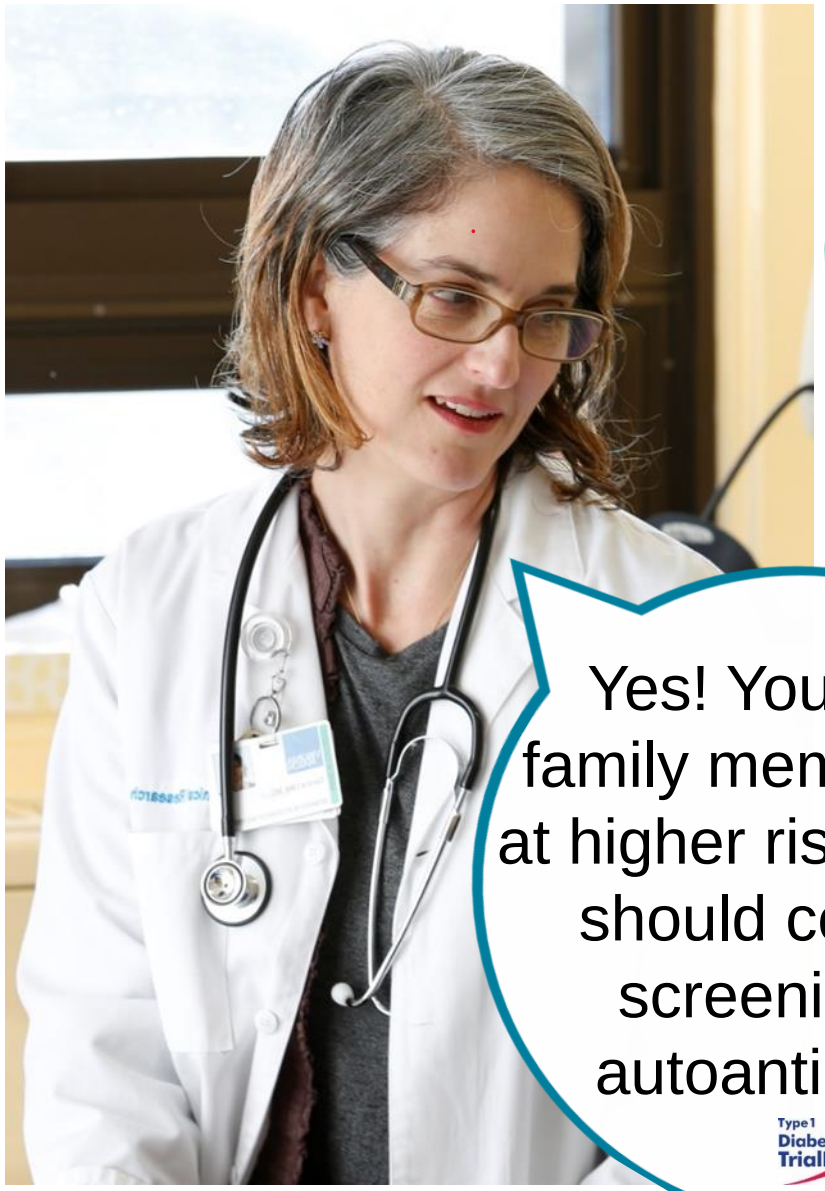
- **MONITOR CLOSELY FOR DISEASE PROGRESSION**
  - HbA1c, oral glucose tolerance test, and autoantibody testing every 6-12 months at a TrialNet clinic (BRI is one!)
  - Lowers risk of DKA at diagnosis
  - Lowers HbA1c at diagnosis
  - Decreases chance of hospitalization
- **EARLY DETECTION ALLOWS FOR EARLY INTERVENTION**
  - Refer to endocrinologist as soon as insulin is needed
  - May offer treatment with therapies aimed saving beta cell function….

Type 1 Diabetes TrialNet

Benaroya Research Institute

If you have a family member with T1D, have you been tested for autoantibodies?





Yes! Your other family members are at higher risk and you should consider screening for autoantibodies

Type 1 Diabetes TrialNet

Since I have a child with T1D….

…are my other family members at risk??

Benaroya Research Institute

If my family members test positive for antibodies, can we do anything for them to prevent T1D?

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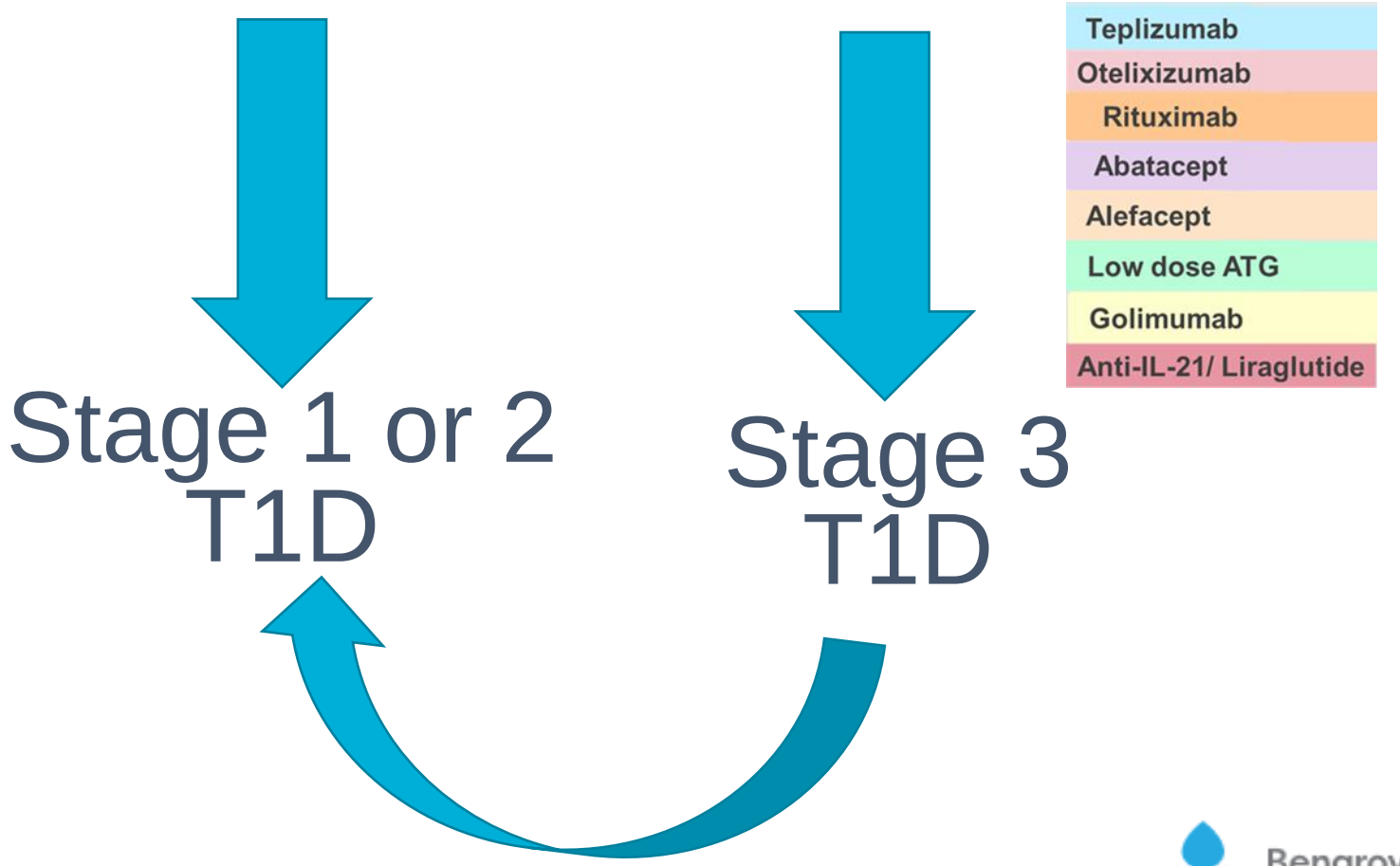
Will therapies that work in new-onset T1D be more effective if we give them before symptoms develop?

✓

✓

ENROLLING



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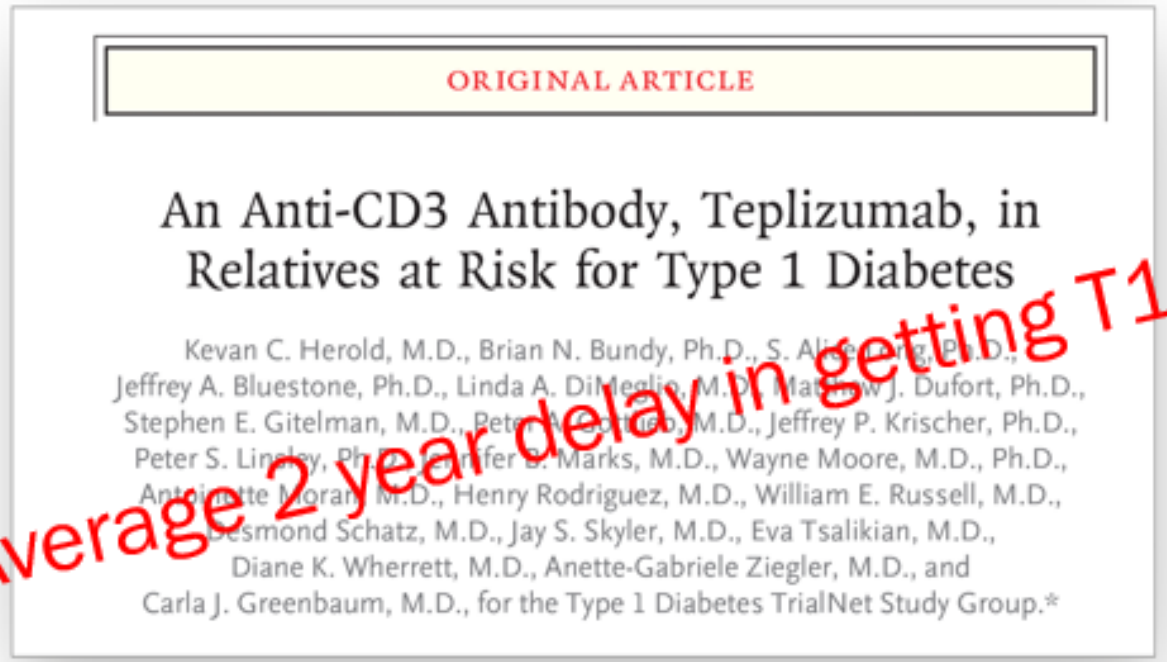
We already have an FDA-Approved drug to slow diabetes progression before symptoms develop

True

False

TRUE! We have already successfully delayed progression from Stage 2 to Stage 3 T1D



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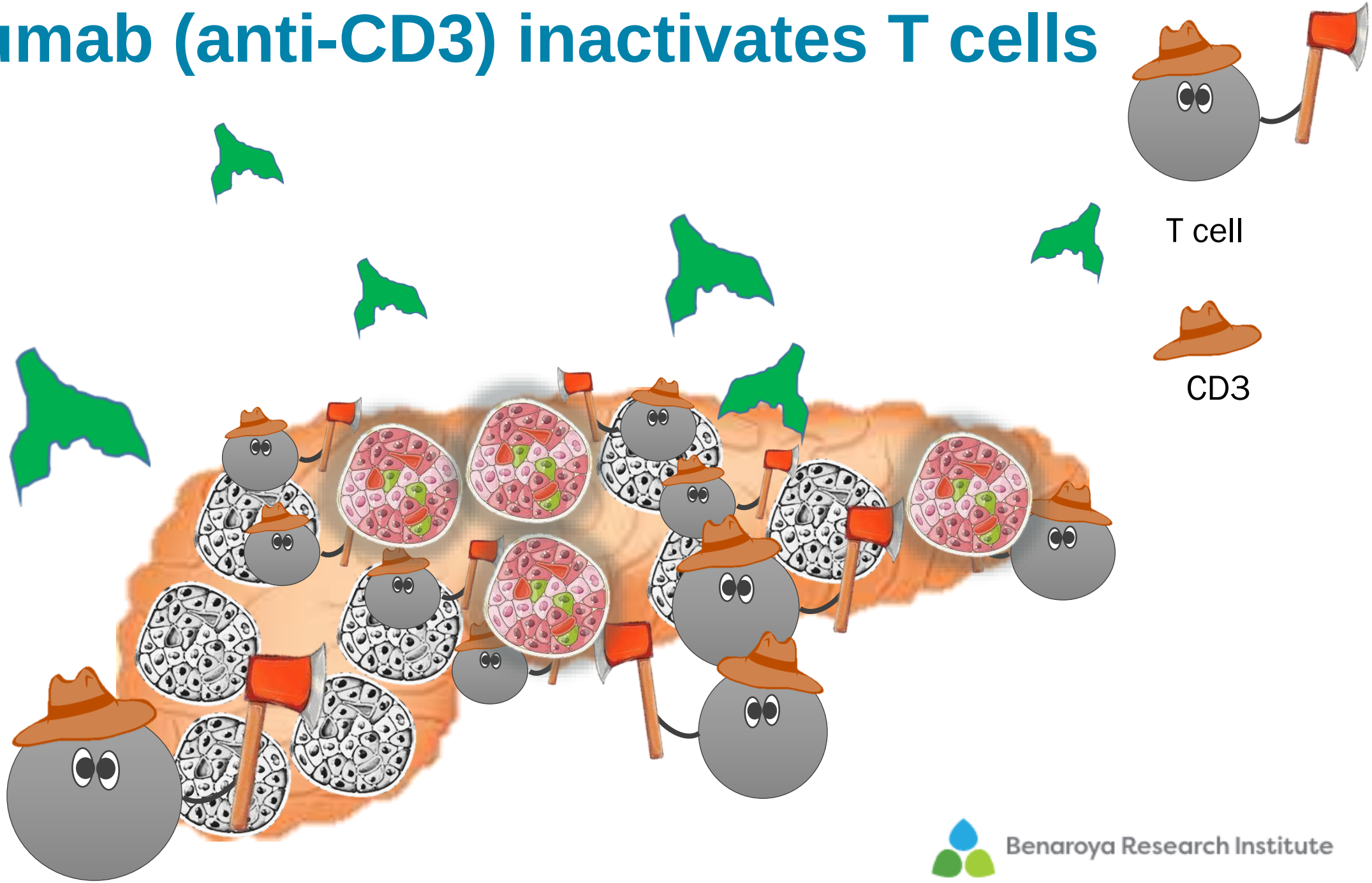
Teplizumab (anti-CD3) inactivates T cells



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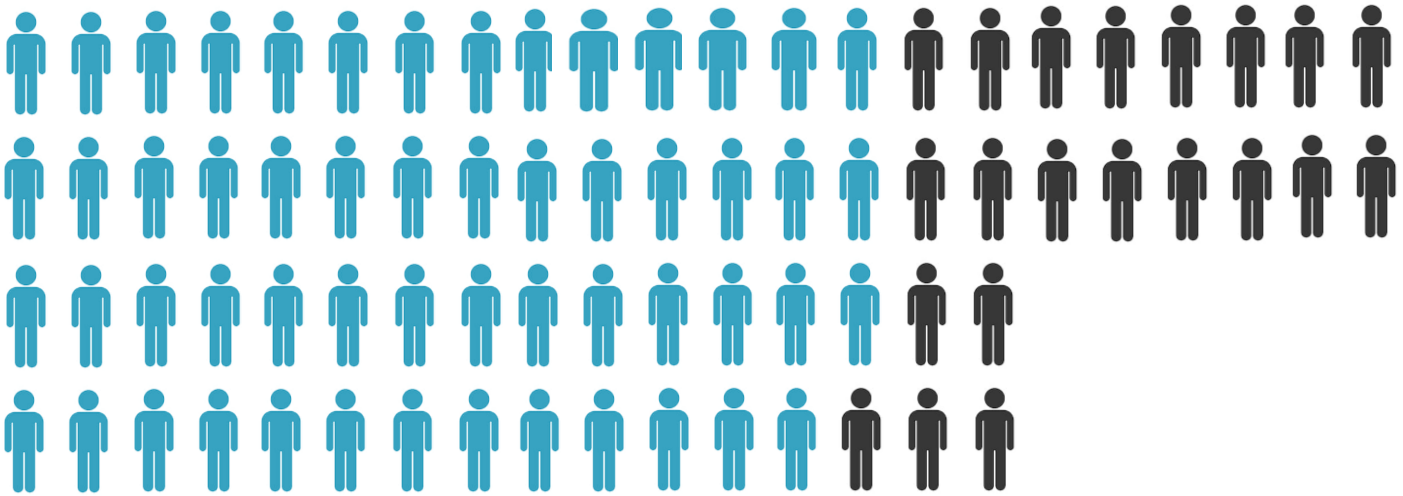
TrialNet's prevention study tested 76 people

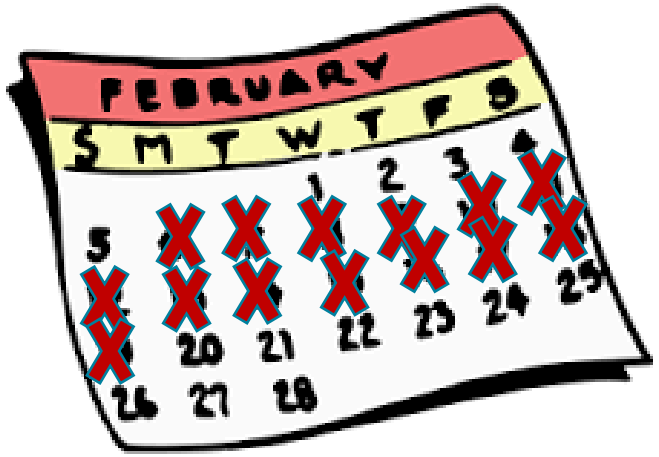


- Relatives of people with T1D
- 2 or more antibodies AND abnormal glucose tolerance

Majority (nearly ¾) were <18 years old

Slide courtesy of Michelle So, MD, PhD

Benaroya Research Institute



Participants received 14 days of infusions of Teplizumab or placebo

Follow-up for average of 2-3 years

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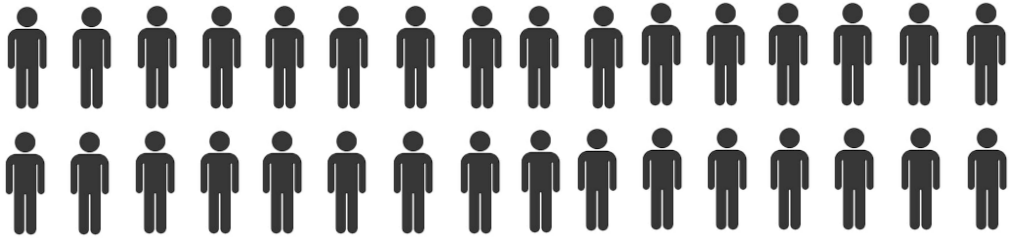
Study showed a big delay in T1D in the first year

Placebo



Clinical T1D

44%

Teplizumab

7%

Ongoing follow-up showed 3-year delay in development of T1D!

Slide courtesy of Michelle So, MD, PhD

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A Big Step

Only study ever to demonstrate that onset of T1D can be delayed

November, 2022- **FDA APPROVED Teplizumab (Tzield) for T1D prevention!**

First immunotherapy EVER approved to prevent an autoimmune condition

https://www.tzield.com/ for more information on accessing the medication

Type 1 Diabetes TrialNet

Benaroya Research Institute

New Prevention Trial Now Enrolling

STOP-T1D: ATG Prevention Study

Eligibility: Ages 12 to 35, positive for 2 or more autoantibodies, abnormal blood sugar, high risk marker such as A1c between 5.7 and 6.4%

Treatment: 2 ATG or placebo infusions over 2 consecutive days

- Each infusion will take between 6 and 10 hours
- Must stay overnight at the treatment center for observation

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If my family members test positive for antibodies, can we do anything for them to prevent T1D?

We have already delayed T1D with Teplizumab, and it is now FDA-approved! Other diabetes prevention trials are enrolling.

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My cousin Pete also has T1D, but he's had it for over 20 years. Are there any therapies that could help his body to make insulin again?

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For those in the room with T1D, how many years has it been since you were diagnosed?

- Less than 1 year
- 1-4 years
- 5-10 years
- 10-20 years
- 20-30 years
- 30-50 years
- more than 50 years

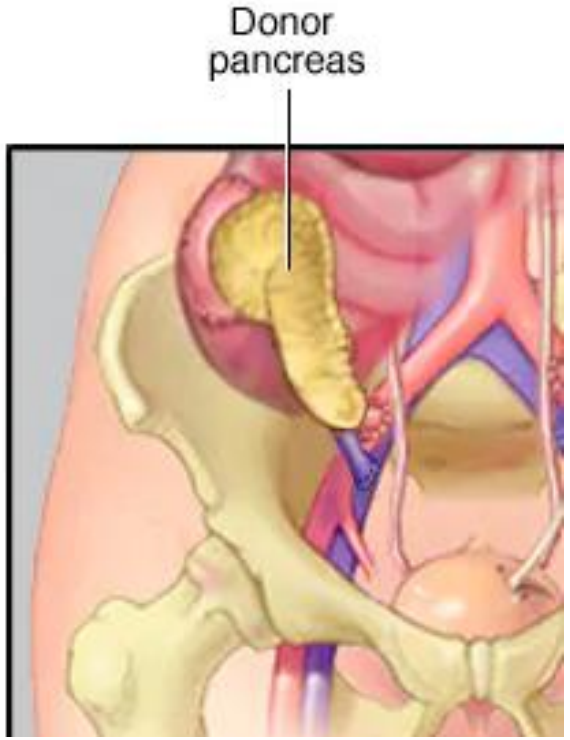
Therapeutic goals for those with longstanding T1D:

BETA CELL REPLACEMENT

BETA CELL PROTECTION

Benaroya Research Institute

Human pancreas transplants have been done since 1960s

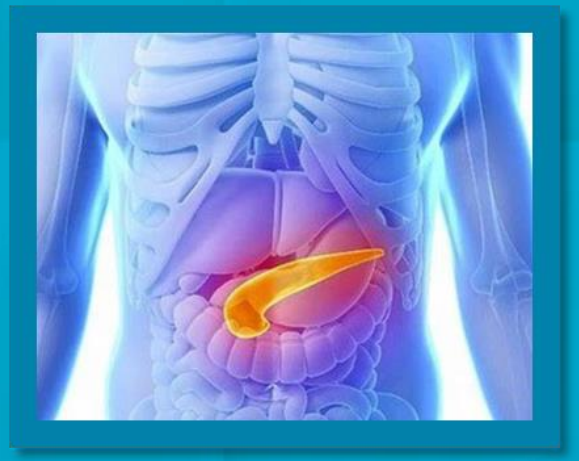


- Most patients able to stop insulin therapy immediately after transplantation
- 50-60% remain insulin-independent 10 years after transplant

- Patients require life-long anti-rejection medications which have side effects
- Surgery is not without risks
- Only~1,500 pancreases are recovered from donors each year; many aren't suitable for transplant
- Only one pancreas available per 1000 patients with T1D in the US

Supply simply cannot meet demand……

We need an unlimited source of beta cells!



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Vertex trial: Beta cells from stem cells

Douglas A Melton, PhD, along with wife Gail and children, Sam and Emma

Melton with one dose of VX-880

Stem cell-derived islet cell replacement therapy

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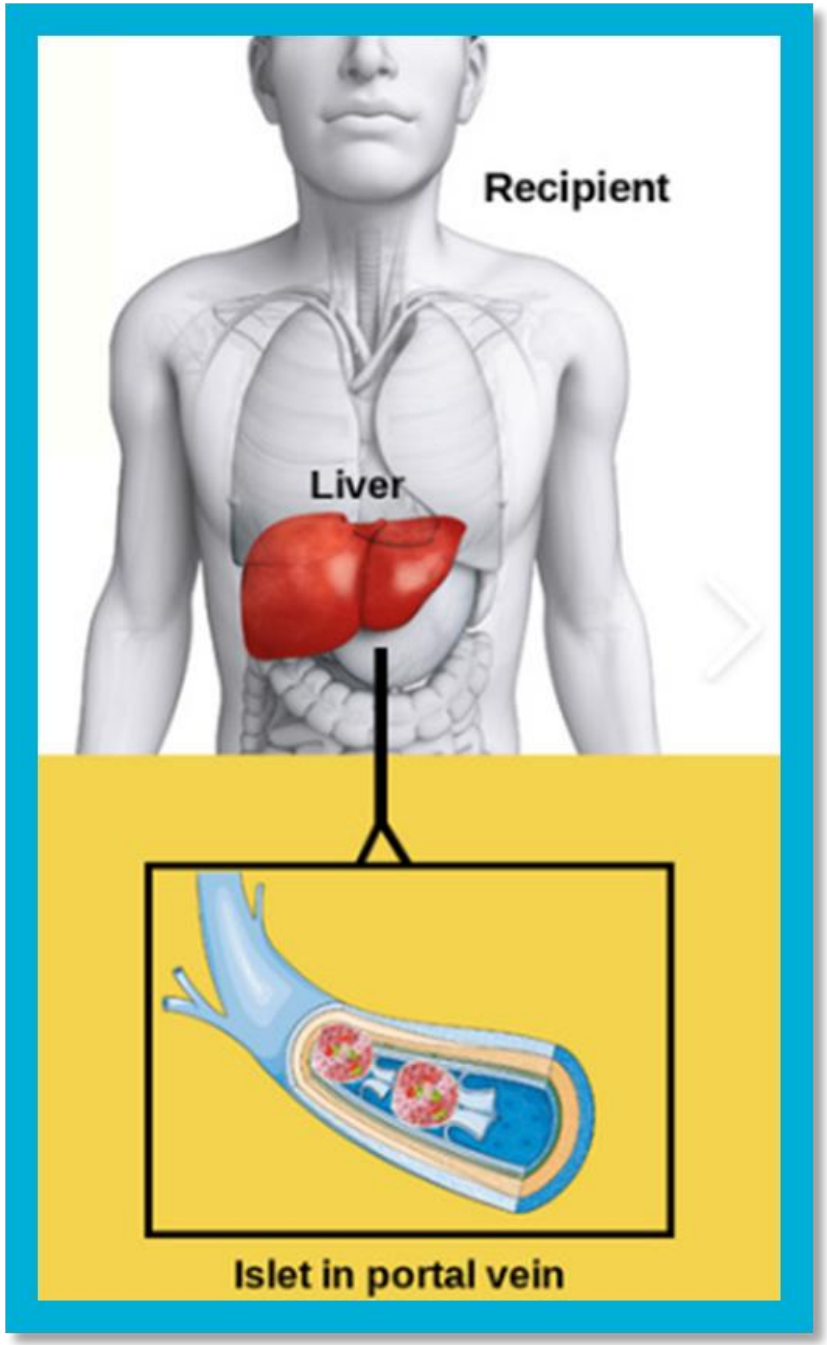
Treatment

- **VX-880 production**: stem cells are stimulated in the lab to become insulin-producing beta cells
- Human dose: 400 million beta cells (one vial)
- Treatment is infused into the portal vein and cells take up residence in the liver
- Participants remain in the hospital for 1-2 weeks for pre-treatment care, infusion, monitoring, and initiation of immunosuppressant therapy

VX-880 Beta Cell transplant recipients currently require lifelong immunosuppression to protect the cells



Results in first participant

Brian Shelton, 64, first to receive VX-880

"It's a whole new life," Mr. Shelton said. "It's like a miracle."

- So far, three patients have received infusions of VX-880
- 270 days after receiving his infusion:
  - Brian no longer required any injected insulin
  - His HbA1c dropped from 8.6% to 5.2%
  - His insulin production levels were in the non-diabetic range

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VX-880 Beta Cell transplant recipients currently require lifelong immunosuppression to protect the cells

Would you trade the need for lifelong insulin therapy for the need for lifelong immunosuppression?

Yes

No

How else can we protect transplanted cells?

Encapsulation

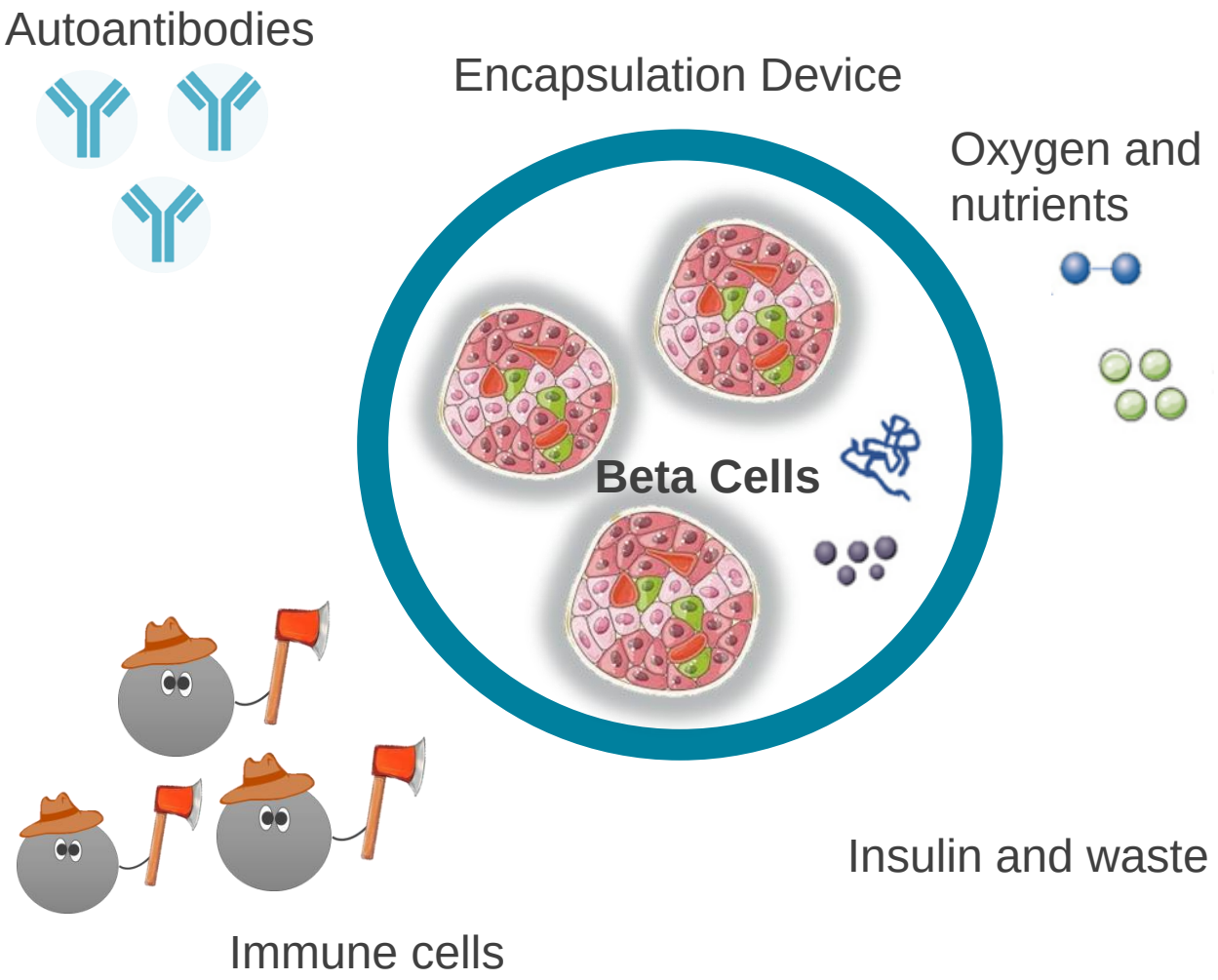
We can put the cells in a device that will protect them from the immune system

Gene Editing

We can edit the beta cells' DNA so that they will be unrecognizable by the immune system

How does encapsulation work?

- Islet encapsulation provides a selectively permeable barrier between host and beta cells
- Device is surgically implanted
- No concomitant systemic immunosuppression
- Some of the devices provide localized immunosuppression



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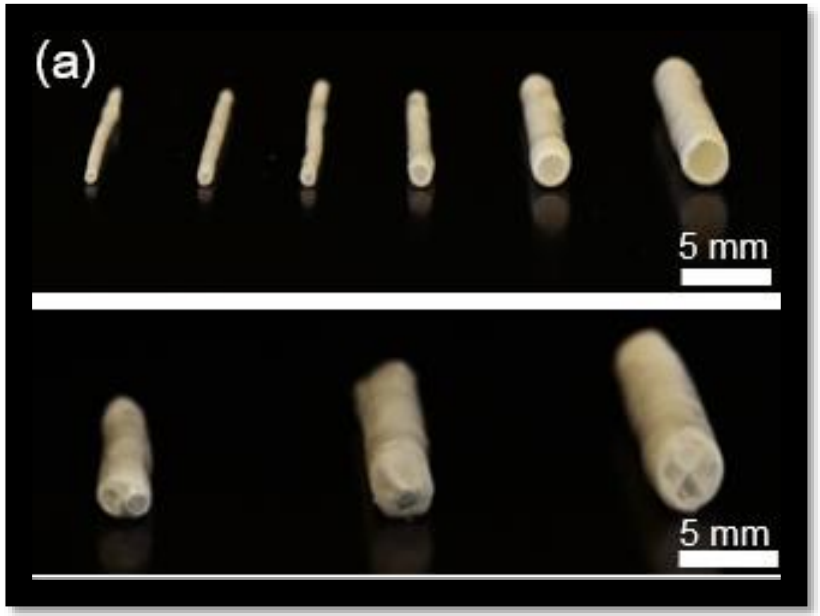
Many groups developing encapsulation devices

Sernova

Viacyte

Cornell's NEED device



- Implanted under the skin in the fat tissue
- Beta cells may be introduced before or after the device is implanted and vascularized
- Some devices have wells for localized immunosuppressants

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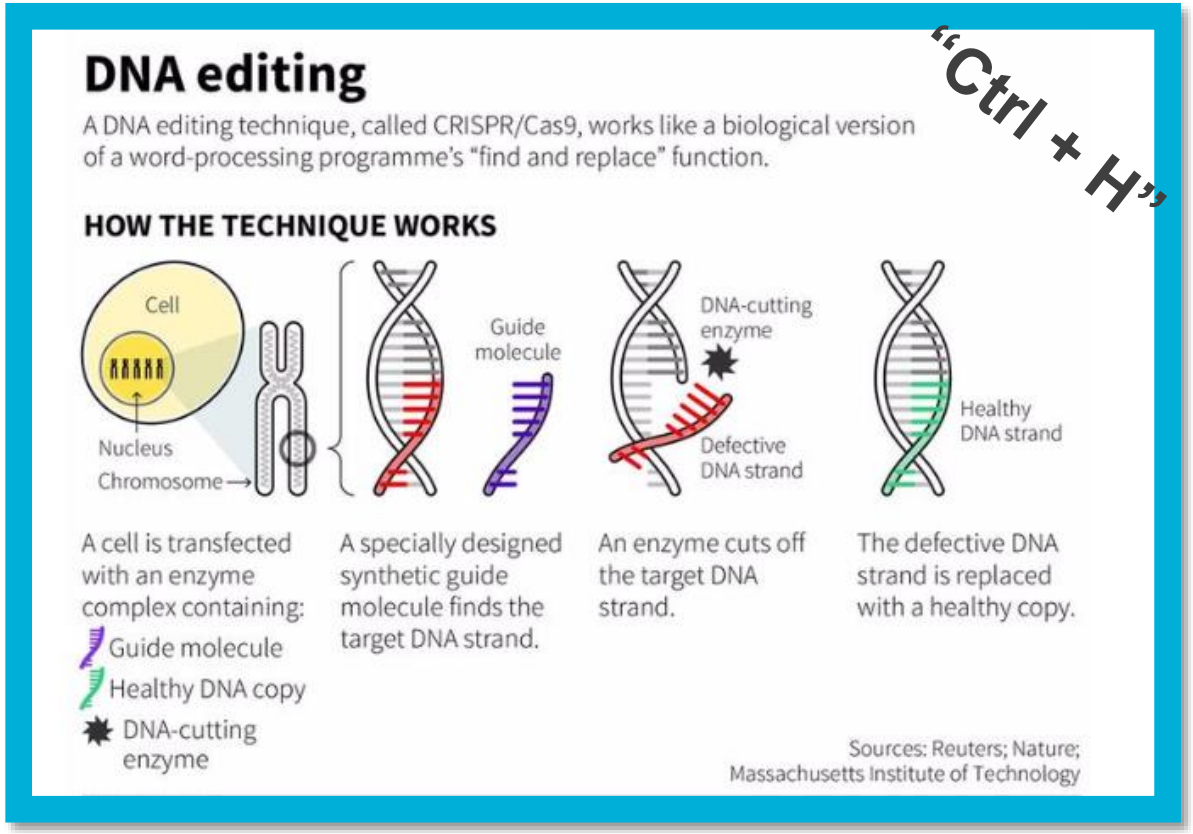
Cell protection: Gene-editing



- Can we edit genes in manufactured beta cells to make them "invisible" to the immune system?
- Clinical trial of gene-edited stem cell therapy product, VCTX-210, started this year in Canada
- Therapy is intended to be used **without** immunosuppressive therapies

VIACYTE

CRISPR THERAPEUTICS

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Other Ideas: Beta Cell Proliferation or Xenotransplantation

Maike Sander, M.D., UCSD

- Dr. Maike Sander has developed an agent that can make beta cells proliferate
- Working on a targeted drug delivery system technology that can deliver therapies directly to human beta cells
- Currently being tested in mouse models of T1D

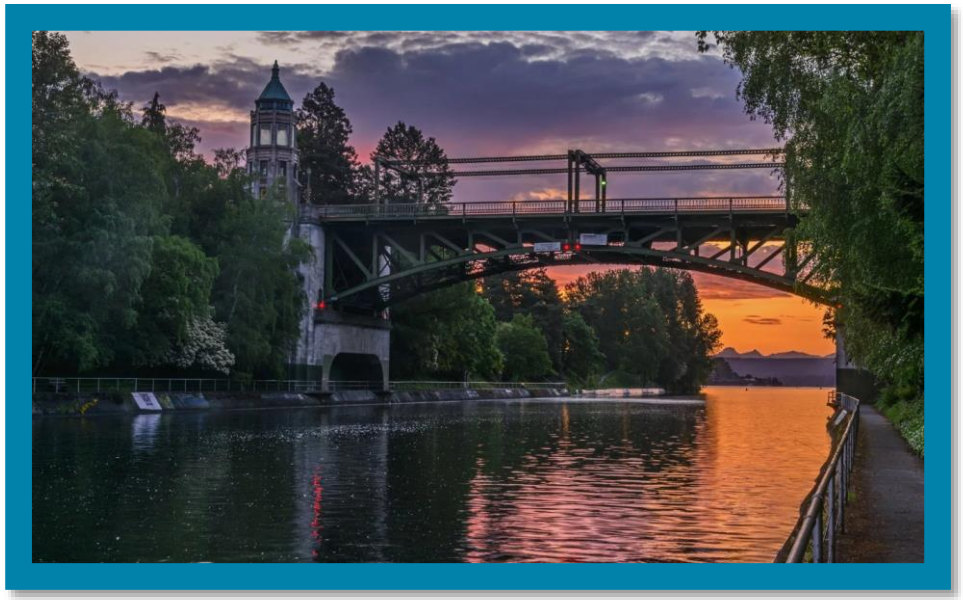
University of Alberta

- Attempts at full pancreas xenotransplantation have not been successful throughout history (cows, pigs, sheep, rabbits, fish have been trialed…)
- Team can successfully isolate beta cells from human pancreases and transplant them into people with T1D
- Team working on developing a safe source of islets from neonatal pigs

BRIDGE Study

For **ANYONE** with a T1D diagnosis

- Initial blood sample drawn:
  - checked for genes associated with T1D
  - Autoantibodies measured
  - Participant may be asked to return when a scientist needs more blood from someone who matches his/her/their profile



To schedule an appointment,
Email: **diabetes@benaroyaresearch.org**

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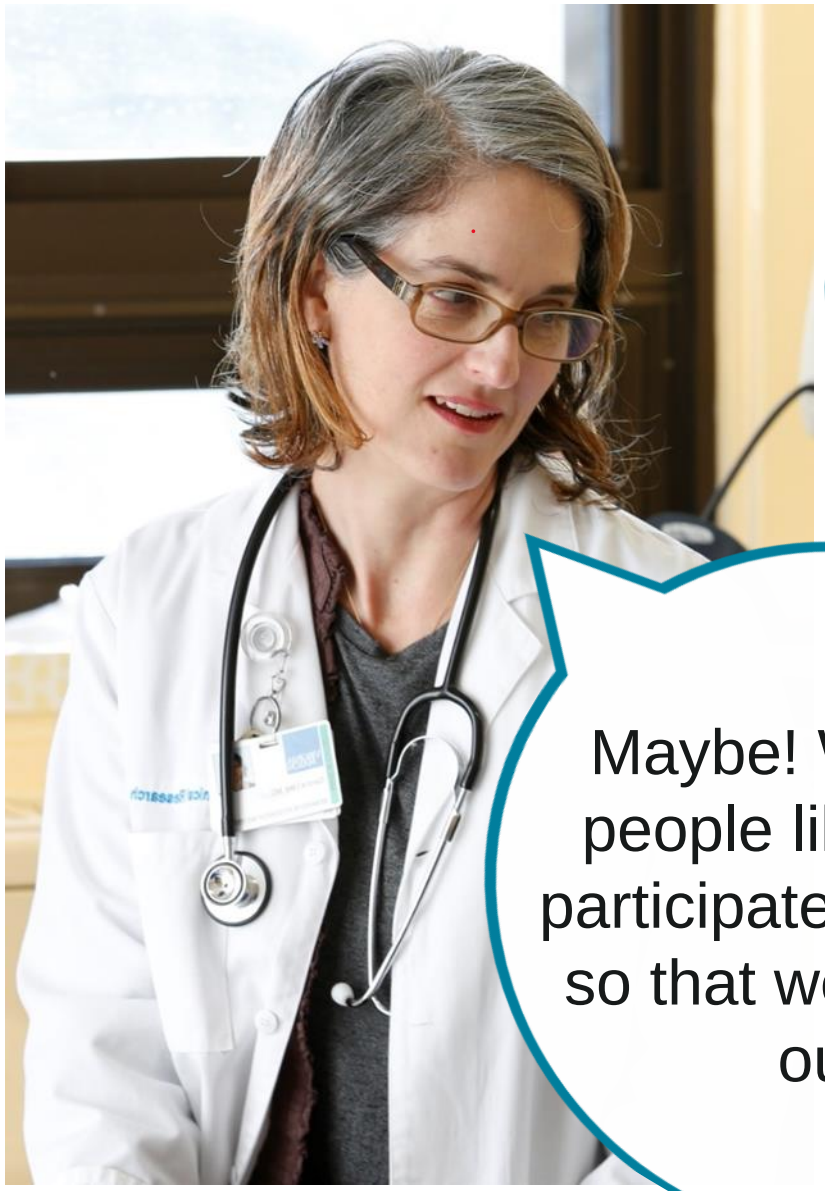

My cousin has had T1D for over 20 years. Are there any therapies that could help his body to make insulin again?

Maybe! We need people like him to participate in studies so that we can find out!

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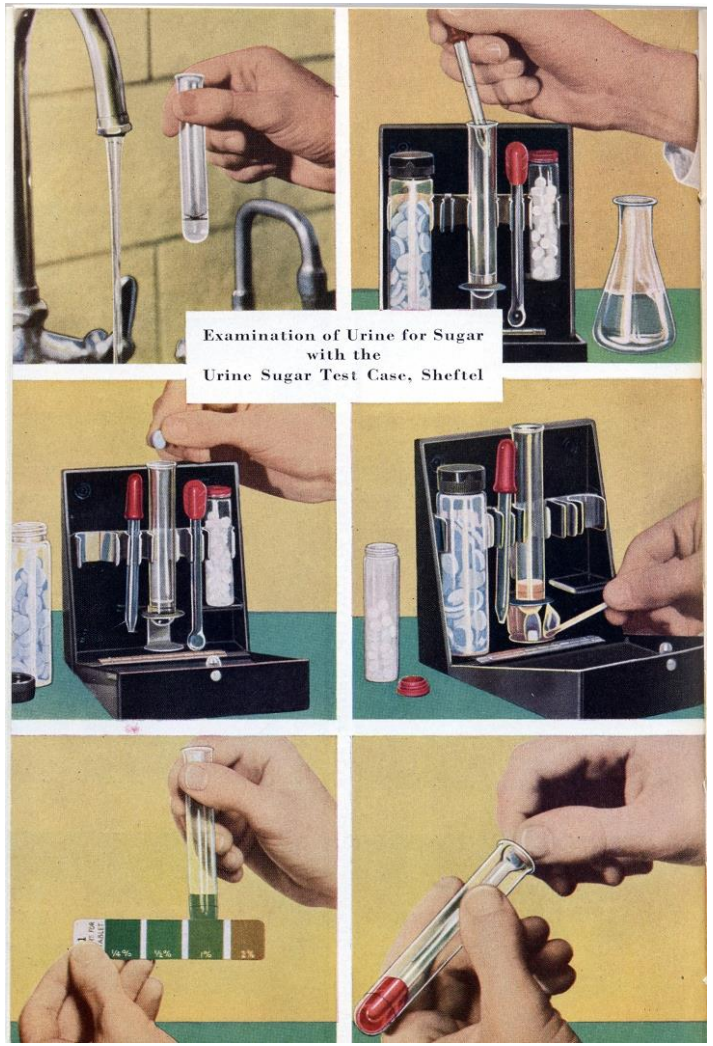
It’s been slow, but let’s reflect



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zak.huber. (2016). *Dexcom Products | Continuous Glucose Monitoring* [Photo of Dexcom G6]. https://www.dexcom.com/products

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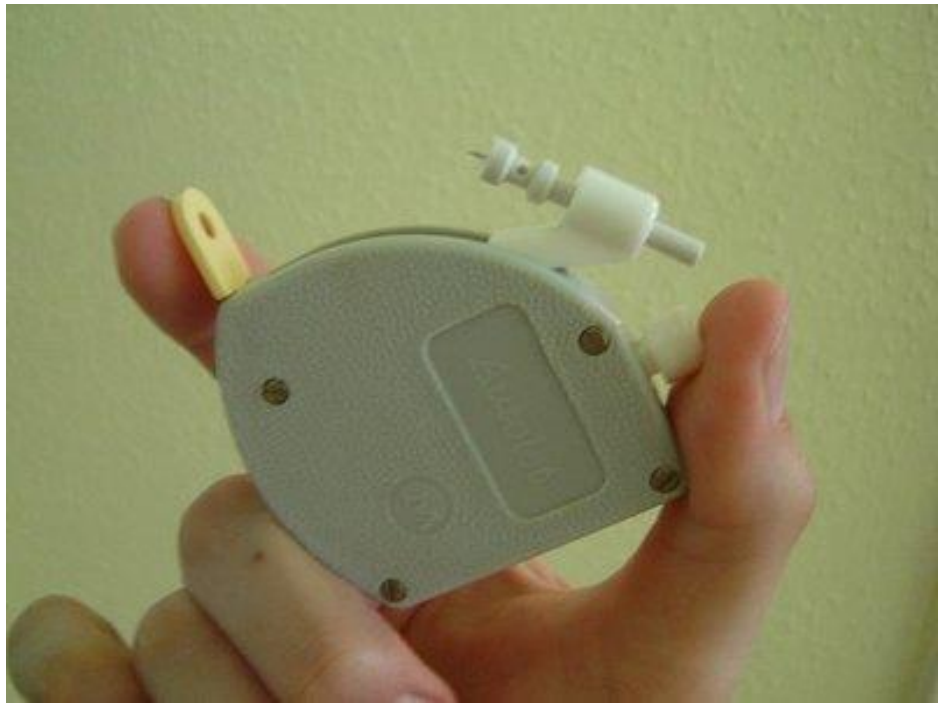
It’s been slow, but let’s reflect



Scott. (2013). *Cutting it short* [Photo of lancet]. https://rollinginthed.wordpress.com/2013/07/23/cutting-it-short/

One Drop Blood Glucose Monitoring Kit. (n.d.). [Photo of One Drop]. Retrieved March 12, 2021, from https://www.apple.com/shop/product/HMN02LL/A/one-drop-chrome-blood-glucose-monitoring-kit

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It’s been slow, but let’s reflect

Alsaleh, F. M., Smith, F. J., Keady, S., & Taylor, K. M. G. (2010). *Insulin pumps: From inception to the present and toward the future* [Photograph of insulin pump]. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2710.2009.01048.x

jwskks5786. (n.d.). *Free Image—Insulin Pump*. Retrieved March 12, 2021, from https://pixabay.com/photos/diabetes-insulin-pump-diabetic-2102239/

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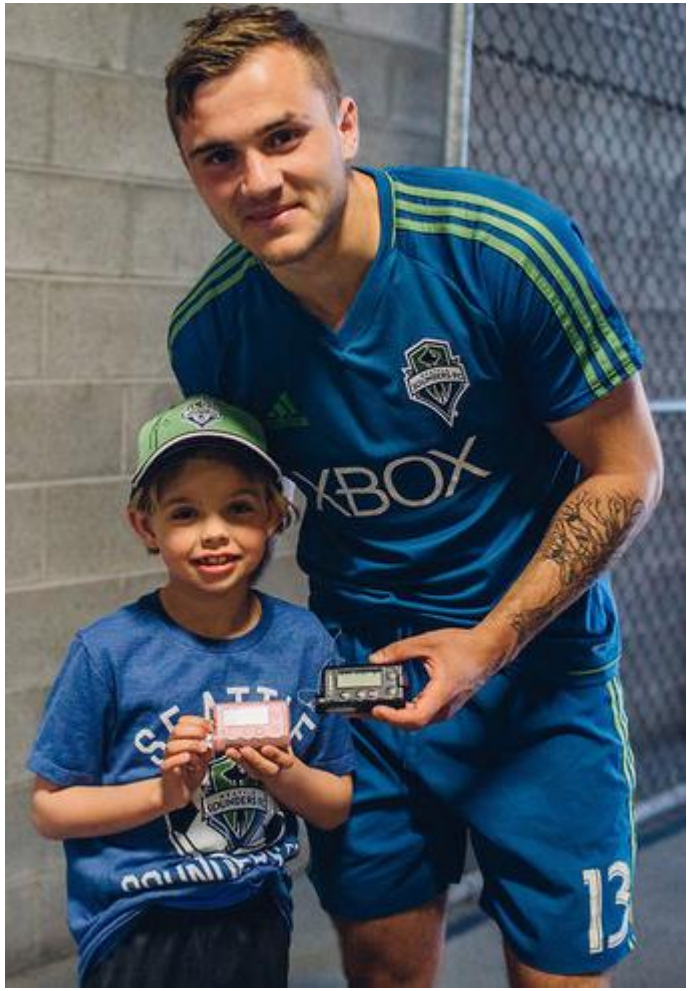
It’s been slow, but let’s reflect



New-York Historical Society | Breakthrough: The Dramatic Story of the Discovery of Insulin. (n.d.). [Photo of mother and child]. Retrieved March 12, 2021, from https://www.nyhistory.org/exhibitions/breakthrough-dramatic-story-discovery-insulin

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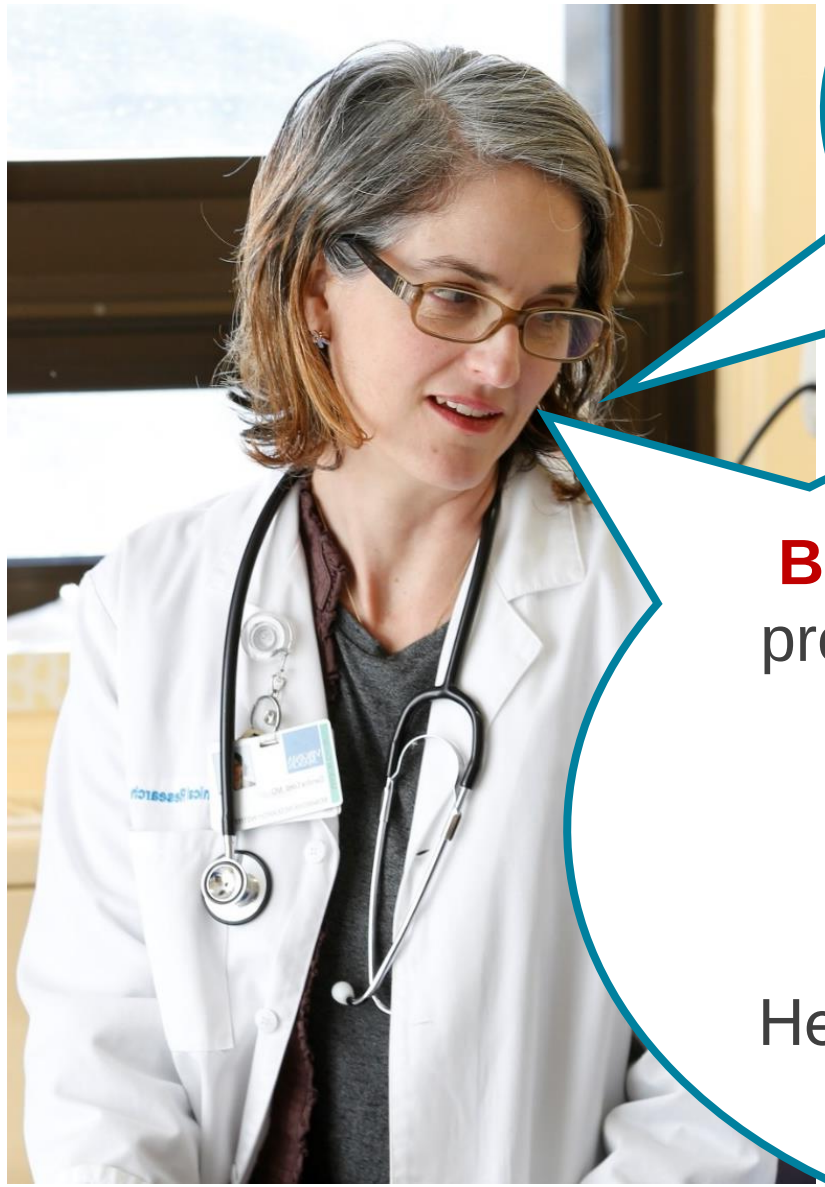


Your child has type 1 diabetes

But, we have therapies to preserve the beta-cells she still has *and* we can consider beta cell transplantation or proliferation therapies. Here is what we're going to do next…

We have research participants to thank for ALL of these advances! Friends for life changing lives…

Studies available at Benaroya Research Institute

- TRIALNET AUTOANTIBODY SCREENING AND MONITORING (AVAILABLE TODAY)

RECRUITING

Type 1 Diabetes TrialNet

ATG PREVENTION STUDY (STOP-T1D)

RECRUITING

COBRA

RECRUITING

TOPPLE (TN27)

RECRUITING

DESIGNATE

RECRUITING

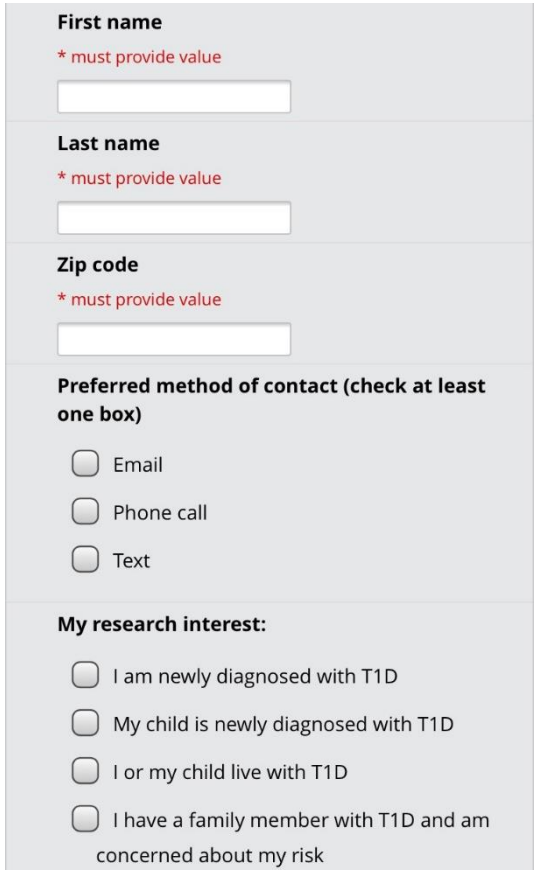
BRIDGE STUDY

RECRUITING

STAGE 1	STAGE 2	STAGE 3	LONGSTANDING T1D
Normal blood sugar	Abnormal blood sugar	Clinical diagnosis	
≥ 2 autoantibodies	≥ 2 autoantibodies	≥ 2 autoantibodies	

FOR MORE INFORMATION,
CALL: 1-800-425-8361
Or email
diabetes@benaroyaresearch.org

QR code for those interested in research!



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Benaroya Research Institute:
BenaroyaResearch.org
800-888-4147
diabetes@benaroyaresearch.org

Benaroya Research Institute

"Life doesn't always get better. But you do. You get stronger. You get wiser. You get softer. With tattered wings you rise. And the world watches in wonder at the breathless beauty of a human who survived life."

--L.R. Knost

Taylor Adams, pediatric ICU nurse, person with T1D!

FAMILY SCIENCE DAY

Saturday, April 22
9am - 1pm
Benaroya Research Institute

Come and meet a real scientist!
Fun hands-on activities for kids, hosted by youth leaders who are living with type 1 diabetes (T1D).

A chance for adults to talk with local researchers and ask your questions about T1D and research.

TrialNet risk screening for families who want to know their risk of developing T1D. This test is free for eligible family members.

For more info, call 800-888-4187 or email diabetes@benaroyaresearch.org

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