Type 1 Diabetes Research Advances

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JDRF Type 1 Nation Chicago 2017
Overview

• T1D Basics
  o Immune Mechanisms

• Type 1 Diabetes TrialNet
  o Current findings
  o Associated Studies

• Other research
T1D is Increasing

T1D Incidence (# new cases/yr) is doubling every 20 yrs

Cases/100,000/yr in children 0-14 yr

New Ideas about T1D

- While peak onset is in youth, T1D can happen at any age
- Anti-beta cell antibodies are variable
- C-peptide may be high early on, then low
- **Incidence in first degree family members is about 5%**
- Efforts to halt progress of type 1 diabetes have been disappointing
- Is it one disease? Many? Is the beta cell the problem?
- Incidence is increasing world-wide, about 8% of all cases in the U.S.
GWAS and Type 1 Diabetes – Lots of Genes
What Have We Learned from Genetic Studies of Type 1 Diabetes?

• Susceptibility highest by a major gene or genes in the HLA region of chromosome 6.

• Effect of HLA region gene(s) modified by at least 40 genes with only a small effect on risk - genetic background.

• Genetics alone is not useful in identifying those at risk of developing type 1 diabetes - presence of autoantibodies to β-cell proteins are more predictive.
T1D Disease Progression

The Stages to Type 1 Diabetes

STAGE 1
- Normal Blood Sugar
- ≥ 2 autoantibodies
- START OF T1D

STAGE 2
- Abnormal Blood Sugar
- ≥ 2 autoantibodies

STAGE 3
- Clinical Diagnosis
- ≥ 2 autoantibodies

STAGE 4
- Long-standing T1D

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

Genetic Risk

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

Immune Activation

Normal Blood Sugar
≥ 2 autoantibodies

Abnormal Blood Sugar
≥ 2 autoantibodies

Clinical Diagnosis
≥ 2 autoantibodies

Long-standing T1D
What do we know about treating T1D?

- Importance of blood sugar control to prevent complications and prolong healthy life
- Basal / bolus dosing
- Insulin pumps
- Glucose sensors
- Closed loop systems
- Beta cell replacement

- Blood Pressure
- Cholesterol: low LDL, high HDL
- Stop Smoking
- Aerobic Exercise
- Weight loss if high
- Eye care, foot care, dental care

- hypoglycemia
What about preventing T1D?
TrialNet

• An international network of 21 leading academic institutions, physicians, scientists and healthcare teams with over 200 affiliates throughout the United States, Canada, Finland, the United Kingdom, Italy, Germany, Australia, and New Zealand at the forefront of type 1 diabetes research.

• Using knowledge gained through clinical research, the mission is to prevent type 1 diabetes and stop disease progression by preserving insulin production
TrialNet

Funded by the National Institutes of Health
we offer risk screening for relatives of people with type 1 diabetes and
innovative clinical studies to preserve insulin production
TrialNet

- Family members of those with T1D have a 15 times greater risk of developing the disease than the general population (0.03 vs 5%)

- At least 90% of people diagnosed with T1D have diabetes-related autoantibodies. Autoantibody status may change, so we recommend retesting youth annually.
Any individuals with 2 or more autoantibodies have a **50-90% risk** of developing diabetes in the next 5 years- **and a near 100% lifetime risk**

Those with autoantibodies who are not eligible for a clinical trial will be closely monitored. **Monitored participants who develop Type 1 are typically diagnosed prior to any clinical symptoms of diabetes**
TrialNet: Eligibility

- Anyone between 1 and 45 years of age, with 1st degree relative (a sibling, child, or parent) with T1D

- Anyone between 1 and 20 years of age, with a 2nd or 3rd degree relative (cousin, aunt, uncle, niece, nephew, grandparent, or half-sibling) with T1D
Sign Up Today

If you have a relative with type 1 diabetes (T1D), you’re in a unique position to help us learn more about the disease and how to stop it. The first step is to sign up for screening through the TrialNet Pathway to Prevention Study.

Take your first step on the Pathway to Prevention!

The Pathway to Prevention Study starts with a simple blood test that can detect your risk of developing T1D years before symptoms appear. Detecting the disease at its earliest stage is super important. If you are in the early stages of T1D, you may be able to join a research study looking for ways to slow down or stop the disease. We invite you to join our TrialNet family and help find a way to prevent T1D.

1. Sign Up Today!
   Pathway to Prevention screening is free to relatives of people with type 1 diabetes. Get started by answering a few simple questions and selecting the screening option that works best for you.

2. Get Screened!
   The first step on the Pathway to Prevention is to sign up for screening. It’s easy and convenient. Pick the best option for you:
   - Make an appointment at one of 200 TrialNet locations

3. Your Results
   Your screening results will be ready in 4 to 6 weeks. They will be made available only to you. If your test results show you are in the early stages of T1D, the next step will be to go to a TrialNet location for follow-up. You may qualify for participation in a prevention study or
TrialNet: Sign Up

Online

Have questions? Contact your closest TrialNet Clinical Center with any questions you may have.

At your local Quest

Ready to get started? Click here to sign up for TrialNet Pathway to Prevention type 1 diabetes risk screening.

Capillary Kits returning soon

Screen at your local center
GOT BLOOD DRAWN TODAY

DIDN'T CRY

memegenerator.net
TrialNet: Monitoring

Annual Monitoring
Individuals with one positive autoantibody will have an Oral Glucose Tolerance Test (OGTT) and HbA1c at the first monitoring visit to determine their monitoring plan (annual or semi-annual).

Semi-annual Monitoring
Individuals with a higher 5-year risk of diabetes. Those with two or more autoantibodies during screening, or who were identified as higher risk from a first annual monitoring visit.
**TrialNet**

**Scientific Statement from JDRF, Endocrine Society, ADA**

**Staging Pre-symptomatic Type 1 Diabetes**

- In the January 2016 issue of Diabetes Care, the JDRF, American Diabetes Association (ADA), and Endocrine Society recommend adoption of a new type 1 diabetes staging classification.

- The recommendation is largely based on an immense amount of data collected from TrialNet research spanning two decades and involving more than 150,000 relatives of people with type one diabetes.
  - Type one diabetes can now be most accurately understood as a disease that progresses in **three distinct stages**.
T1D Disease Progression

**Genetic Risk**

**Immune Activation**

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

**Immune Response**

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

**STAGE 1**
Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

**STAGE 2**
Abnormal Blood Sugar
≥ 2 autoantibodies

**STAGE 3**
Clinical Diagnosis
≥ 2 autoantibodies

**STAGE 4**
Long-standing T1D

The Stages to Type 1 Diabetes

- Normal Blood Sugar
- Abnormal Blood Sugar
- Clinical Diagnosis
- Long-standing T1D

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal Blood Sugar (≥ 2 autoantibodies)</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal Blood Sugar (≥ 2 autoantibodies)</td>
</tr>
<tr>
<td>3</td>
<td>Clinical Diagnosis (≥ 2 autoantibodies)</td>
</tr>
<tr>
<td>4</td>
<td>Long-standing T1D</td>
</tr>
</tbody>
</table>

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

Genetic Risk:

Immune Activation:
Beta cells are attacked.

Immune Response:
Development of single autoantibody.

Stage 1:
Normal Blood Sugar (≥ 2 autoantibodies)

Stage 2:
Abnormal Blood Sugar (≥ 2 autoantibodies)

Stage 3:
Clinical Diagnosis (≥ 2 autoantibodies)

Stage 4:
Long-standing T1D

**Legend:**
- START OF T1D
- ≥ 2 autoantibodies
T1D Disease Progression

Starting Point
Genetic Risk

The path to T1D starts here

- Everyone who is diagnosed with T1D has the genes associated with T1D
  - General population risk is 1 in 300
- Family members are at 15x greater risk to develop T1D
  - Relative risk is 1 in 20
T1D Disease Progression

Immune system is activated

Immune Activation

Immune system attacks beta cells

• Likely a common event
• Research taking place to identify the possible “event” or combination of “events”
Immune Response

- Immune system responds to beta cells being attacked
- Results in the development of autoantibodies
- Autoantibodies are a “visible” signal that the immune system is activated
T1D Disease Progression

Progression by Population:
- Everyone who goes onto develop T1D has a genetic risk
- Immune system will be activated in some of those people
- Even fewer will go on to develop an autoantibody

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

Genetic Risk → Immune Activation → Immune Response → STAGE 1 → STAGE 2 → STAGE 3

Immune Activation
Beta cells are attacked

Immune Response
Development of single antibody

Immune Response
Development of single antibody
Genetic Risk

Immune Activation

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

Immune Activation
Beta cells are attacked

Immune Response
Development of single antibody

Type 1 Diabetes

Progression by Population:
• Essentially everyone with 2 or more autoantibodies will continue to progress towards clinical symptoms
• T1D starts when you develop two or more autoantibodies

T1D Disease Progression
T1D Disease Progression

Stage 1 T1D
Normal Blood Sugar

≥ 2 autoantibodies

- START of T1D
- Two or more autoantibodies
- Normal blood sugar
- Lots of beta cells that are able to maintain blood sugar
- No symptoms
T1D Disease Progression

Stage 2 T1D
Abnormal Blood Sugar

- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
- No symptoms
Stage 3 T1D
Clinical Diagnosis

- Marked by clinical diagnosis (Dx)
- Formerly known as “start of T1D”
- Even fewer beta cells
- Symptoms of high blood sugar

≥ 2 autoantibodies
Stage 4 T1D
Long-Standing T1D

Post diagnosis

- Continued loss of beta cells over time
- Research outside of TrialNet is working to replace or replenish beta cells
## T1D Disease Progression

The impact of AGE on disease progression & beta cell decline

<table>
<thead>
<tr>
<th>Age</th>
<th>STAGE 1 (Start of T1D)</th>
<th>STAGE 2 ≥ 2 autoantibodies</th>
<th>STAGE 3 (Clinical Dx)</th>
<th>STAGE 4 Long-standing T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td></td>
<td>≥ 2 antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td></td>
<td>≥ 2 autoantibodies</td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td></td>
<td></td>
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</tbody>
</table>
T1D Progression: Importance of Staging

1. **Accelerate the clinical development of therapies by providing a common framework for**
   - Regulators, funders, academia and industry

2. **Identification of T1D in its earliest stages can lead to a decreased risk of diagnosis in DKA**

3. **Staging diabetes allows us to treat T1D early to delay progression and ultimately prevent stage 3 (symptomatic T1D)**
   - Treating high blood pressure, allows us to treat the disease early and ultimately prevent a heart attack or stroke
1. Type 1 diabetes starts with two or more autoantibodies

2. There are three defined stages:
   - **Stage 1**: Presence of 2 or more autoantibodies with normal blood sugar
   - **Stage 2**: Presence of 2 or more autoantibodies with abnormal blood sugar
   - **Stage 3**: Clinical diagnosis (Dx) of type 1 diabetes

3. Age matters!
   1. Time from 2 or more autoantibodies to Dx is faster the younger you are
   2. Beta-cell decline is also faster the younger you are and continues through stage 4
T1D Progression Intervention

THE UNIVERSITY OF CHICAGO
KOVLER DIABETES CENTER FOR KIDS

Advocate
Children’s Hospital

Ann & Robert H. Lurie
Children’s Hospital of Chicago™

Riley Hospital for Children
Indiana University Health
Interventions Target Different Mechanisms

- Oral insulin
- GAD-vaccine
- Anti-CD3
- Thymoglobulin
- Anti-CD20
- Anti-TNFα
- Anti-IL-1β
- Anti-IL-6R

Signal 1 - TCR

Signal 2 - Co-stimulation

T-cell – B-cell help

Activated Macrophage

β-cell

β-cell apoptosis

β-cell regeneration

ISLET
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.
TrialNet Intervention

P2P
Pathway to Prevention

Determine where you are on the path

- No cost
- 1st, 2nd, 3rd degree relatives
- Screens for autoantibodies
- Based on results
  - Look to enroll in clinical trial to preserve beta cell function
  - Or monitor for disease progression
**TrialNet: Intervention at Every Stage**

<table>
<thead>
<tr>
<th>P2P Pathway to Prevention</th>
<th>TN20 Immune Effects of Oral Insulin</th>
<th>TN18 Abatacept (Anti-CD3)</th>
<th>TN19 ATG/GCSF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK SCREENING</strong></td>
<td><strong>STAGE 1</strong></td>
<td><strong>STAGE 1</strong></td>
<td><strong>STAGE 2</strong></td>
</tr>
<tr>
<td>This study screens relatives of people</td>
<td>Mechanistic study to learn how</td>
<td>This study tests whether</td>
<td>This study</td>
</tr>
<tr>
<td>with T1D to study risk and learn about</td>
<td>different doses and intervals of</td>
<td>whether abatacept helps</td>
<td>tests whether</td>
</tr>
<tr>
<td>how the disease occurs.</td>
<td>oral insulin affect immune response.</td>
<td>stop or slow beta-cell</td>
<td>ATG used</td>
</tr>
<tr>
<td><strong>• Screens for five autoantibodies</strong></td>
<td><strong>• 1st stage toward T1D</strong></td>
<td>decline in people who are</td>
<td>alone or</td>
</tr>
<tr>
<td><strong>• 1st and 2nd degree relatives</strong></td>
<td><strong>• 2 or more autoantibodies</strong></td>
<td>at high risk of</td>
<td>together with</td>
</tr>
<tr>
<td>**• First step to identify eligibility</td>
<td></td>
<td>developing T1D.</td>
<td>GCSF will</td>
</tr>
<tr>
<td>for clinical trial participation**</td>
<td></td>
<td></td>
<td>help people</td>
</tr>
<tr>
<td><strong>STAGE 1</strong></td>
<td></td>
<td></td>
<td>continue to</td>
</tr>
<tr>
<td><strong>STAGE 2</strong></td>
<td></td>
<td></td>
<td>produce their</td>
</tr>
<tr>
<td><strong>STAGE 3</strong></td>
<td></td>
<td></td>
<td>own insulin.</td>
</tr>
<tr>
<td><strong>STAGE 2</strong></td>
<td></td>
<td></td>
<td><strong>3rd stage</strong></td>
</tr>
<tr>
<td><strong>STAGE 3</strong></td>
<td></td>
<td></td>
<td>diagnosis of</td>
</tr>
<tr>
<td>**Combination therapy using two</td>
<td></td>
<td></td>
<td>T1D</td>
</tr>
<tr>
<td>medications**</td>
<td></td>
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</table>
Your Participation is Impactful

How to participate

• Visit [www.diabetestrialnet.org](http://www.diabetestrialnet.org)
• Or contact the Diabetes TrialNet Recruitment Hub: [hub@benaroyaresearch.org](mailto:hub@benaroyaresearch.org)
Multiple Approaches to T1D:

• Decrease stress to the beta cell
• Early intensive insulin therapy

• Combinations with immune suppression
• Role of gut flora
• GLP-1 agonists
• SGLT-2 inhibitors
TrialNet Conclusions

- Type 1 diabetes is highly linked to HLA genes that control autoimmunity
- The immune system attack does not fully explain type 1 diabetes
- Targeting the immune system alone has not been successful in slowing or preventing t1D
- Future studies are aimed to better understand that role of the islet and the beta cell in the start and progress of T1D
- New studies to begin at the end of 2017
Other Research

- T1GER-Simponi (Janssen)
- WISDM (T1D Registry)
- Cell Level Research (ADA)
  - Autologous Stem Cell transplantation
  - Pig Islet Xenotransplantation
T1GER, Simponi

- Goal to arrest Beta cell loss in patients with new onset T1D

- Eligibility: Age 6-21, enrollment within 100 days of diagnosis of T1D

- Double blinded, placebo controlled with 2:1 placement (For every two individuals getting Simponi (Golimumab), one received placebo)
WISDM

- Determine if CGM use can reduce hypoglycemia and improve quality of life in older adults with T1D.

- Inclusion criteria
  - Current age >60.0 years
  - Clinical diagnosis of T1D at >6 months and <10 yrs of age
  - HbA1c <10%
  - Insulin regimen requiring multiple injections per day
  - No use of CGM in the last 3 months
Cell Level Research

• Autologous transplantation of induced pluripotent stem cells
  o Work being done to turn inducible cells into insulin producing beta cells
  o Need to find a way to bypass the immune system

• Pig islet cells as substitutes for human pancreatic islet cells
  o Research has been conducted in Monkeys with diabetes receiving pig islet transplants
  o Requires immunosuppressant drug therapy
  o Survival rates of more than one year without needing insulin injections
Thank you.