Prevention of Type 1 Diabetes
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December 2019
NATURAL HISTORY OF TYPE 1 DIABETES

ENVIRONMENTAL TRIGGER

CELLULAR (T CELL) AUTOIMMUNITY

AUTOANTIBODIES
ICA, IAA, GAD$_{65}$ ICA512A

Loss of first phase insulin (IVGTT)

Glucose intolerance (OGTT)

“PRE”-DIABETES

DIABETES

BETA CELL MASS

GENETIC PREDISPOSITION

INSULITIS BETA CELL INJURY

TIME
PREDICTED TRENDS IN INCIDENCE OF TYPE 1 DIABETES IN FINNISH CHILDREN ≤ 15 YRS

Something has to be done……….
GENETICS OF TYPE 1 DIABETES

• Inheritance not explained in a Mendelian fashion
• No single gene allele always associated
• No unique DNA sequences observed (e.g., no mutations)
• Polymorphisms in multiple genes associated
• Susceptibility therefore polygenic
• HLA (DRB1, HLA-DQB1 and HLA-DQA1) alleles confer greatest risk (30-50%)
<table>
<thead>
<tr>
<th></th>
<th>DIAGNOSIS RELATIVES POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>70-80%  3-5%  0.5-5%</td>
</tr>
<tr>
<td>GADA</td>
<td>60-80%  2-4%  1-3%</td>
</tr>
<tr>
<td>IAA</td>
<td>40%     2-4%  1-3%</td>
</tr>
<tr>
<td>IA-2A</td>
<td>60%     2-3%  2-3%</td>
</tr>
</tbody>
</table>

ICA = islet cell autoantibodies
GADA = glutamic acid decarboxylase autoantibodies
IAA = insulin autoantibodies
IA-2A = autoantibodies to insulinoma associated Ag
DQB1*0402

α-chain

β-chain

DQ beta chain amino acid 57
non asp – susceptibility
Asp - protection
EVIDENCE FOR AUTOIMMUNITY

- Morphologic evidence of insulitis
- Humoral immunity
- Cell mediated immunity
- Association with other autoimmune disease
- Genetic/HLA Association
- Response to immunotherapy
Normal Islet

Insulitis
EVIDENCE FOR ENVIRONMENTAL INFLUENCE

- Increasing incidence worldwide
- No relative in 85-90% of cases
- 1 in 2-3 twins concordant
- Enormous country-country variation
- Animal studies
**DPT-1**

*(Diabetes Prevention Trial – Type 1)*

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**Purpose:**
This form requests your child’s participation in a screening for participants in a research study. This is a prospective study designed to identify individuals who are at risk of developing Type 1 diabetes. Type 1 diabetes is a chronic, lifelong condition in which the body cannot produce insulin, a hormone that helps glucose enter cells to provide energy. The test used in this study is called an ICA screening test, which measures the presence of ICA antibodies in the blood. The presence of ICA antibodies in the blood indicates an increased risk of developing Type 1 diabetes in the future.

**Sample Information:**
- Date of birth: [ ] Local lab (if applicable)

**Person Being Screened:**
- Name: [ ]
- Address: [ ]
- City: [ ]
- State: [ ]
- Zip: [ ]
- Social security number: [ ]

**Telephone:**
- Home: [ ]
- Work: [ ]
- Cell: [ ]

**Date of Last Medical Examination:**
- [ ]

**Social Security Number:**
- [ ]

**Relatives with Insulin-Dependent Diabetes (IDDM):**
- [ ]

**Type of Relation:**
- [ ]

**Seronegative for ICA:**
- [ ]

**SATellite, AFFiliate or PHYSician requesting SCREENING:**
- Name: [ ]
- Address: [ ]
- City: [ ]
- State: [ ]
- Zip: [ ]

**People to Be Notified of Screening Results:**
- [ ]

**Clinical Center:**
- [ ]

**ICA Reference Laboratory Use Only:**
- [ ]

**Signed Consent Form:**
- [ ]

**MAY NOT BE USED FOR CLINICAL PURPOSES:**
- [ ]

**Consent:**
- [ ]

**Signature of Subject Parent:**
- [ ]

**Date:**
- [ ]

**I.D.B. Approval Date:**
- [ ]

**For minors 7-17 years of age:**

I understand that my parents have given permission for me to participate in this study. I have read the protocol and procedures explained to me and agree to participate.
DPT-1

(Diabetes Prevention Trial – Type 1)

RISK/TIME TO DIABETES BY ISLET ANTIBODIES

Survival Distribution Function

Years Followed

Number at Risk

1 Ab (ICA Only)
2 Abs
3 Abs
4 Abs

P- Value < 0.001
(Log Rank Test)

STRATA:
EFFECT OF AGE
10 YEAR RISK OF DIABETES
IF CONFIRMED ICA+
RISK OF TYPE 1 DIABETES IN ISLET ANTIBODY + RELATIVES ACCORDING TO FPIR

Survival Distribution Function

FPIR > 1st % FOR AGE

FPIR < 1st % FOR AGE

Years Followed

Survival Distribution Function

0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
1
2
3
4
5
6
7

Years Followed

1
6
7
ROLE OF INTRAUTERINE/PERINATAL ENVIRONMENT

• Possible trigger/modulate immune response
• Viruses
  In-utero: Rubella
  Enterviruses
  Early exposure: Mumps, Rotavirus, CMV
• Dietary practices
  Decreased breastfeeding
  Early introduction of cow milk/cereals
  Nitrosamines
  Coffee consumption
CONGENITAL RUBELLA

- 30% develop Type 1 diabetes
- Incubation period 5-20 years
- ICA, IAA in up to 80%
- High-risk HLA DR3/4
- Associated with autoimmune thyroid disease
- Molecular mimicry with 52kDa autoantigen
- Animal model – Syrian hamster
- No diabetes post MMR vaccination
TRIGR RATIONALE
(Trial to Reduce IDDM in the Genetically at Risk)

Diabetes Incidence (%)

0 4 8 12 16 20 24 28 32 36 40 44
Weeks of Age

Standard weaning formula

Hydrolyzed weaning formula

Karges et al Diabetes: 1997
TRIGR
(Trial to Reduce IDDM in the Genetically at Risk)

- 2159 infants randomized when weaned from exclusive breastfeeding to
  - extensively hydrolyzed casein formula
  - regular intact cow’s milk based formula
- Monitored until February 2017 for appearance of diabetes predictive autoantibodies and clinical T1 diabetes
- Participants 10-14 years old at study conclusion

JAMA 2018;319(1):38-48
TRIGR
(Trial to Reduce IDDM in the Genetically at Risk)

- Did NOT result in a reduction in the incidence of Type 1 diabetes after 11.5 years of follow up
- No evidence to revise dietary recommendations for infants at high genetic risk for Type 1 diabetes

JAMA 2018;319(1):38-48
PREVENTION TRIALS

- TRIGR: Cow Milk Avoidance
- PREVEFIN: Vitamin D
- ENDIT (Europe): Nicotinamide
- DPT-1 (North America): DPT-1
- DIPP (Finland): DIPP
- INIT (Australia): INIT
- “PRE”-DIABETES: Insulin

GENETIC PREDISPOSITION

INSULITIS

BETA CELL INJURY

BETA CELL MASS

TIME
PREVENTION OF DIABETES IN NOD MICE

• More than 200 therapies !!!
• Immunosuppression
• Immunostimulation
• Diet
• Tolerance
• Hormonal manipulation
• Many others...............
LESSONS LEARNED FROM NOD PREVENTION

- Early prevention easy
- Late intervention difficult few effective agents
- Dosing is important
- Not all interventions are safe
- Humans are not mice!!!!
DEFINITIVE DETERMINATION TEDDY
THE ENVIRONMENTAL DETERMINANTS OF DIABETES IN THE YOUNG

To identify environmental factors and gene environment interactions causing autoimmunity and diabetes.
DEFINITIVE DETERMINATION TEDDY

THE ENVIRONMENTAL DETERMINANTS OF DIABETES IN THE YOUNG

Cohort of over 8000 children with 747 children with persistent confirmed autoantibodies in Finland, Germany, Sweden and the United States
Family history

- FH of Type 1 is confirmed
- FH (2nd degree relative) of Type 2 diabetes showed significantly delayed progression from islet autoimmunity to clinical T1 diabetes (all countries)
- Father or sibling with T1 more likely to develop islet autoimmunity
- Mother with T1 NOT a significant risk factor for autoimmunity
Maternal use of Vitamin D (63%) and omega-3 fatty acid (16%) during pregnancy

- NOT associated with change in persistent islet autoimmunity
- NOT associated with change in IAA as 1\textsuperscript{st} appearing autoantibody
- NOT associated with change in GAD antibodies as 1\textsuperscript{st} appearing autoantibody
Maternal infections during pregnancy
- NOT associated with change in 1st appearing islet autoantibodies
- Women with respiratory infections during pregnancy showed a protective influence on IAA and GAD antibodies
- CTLA-4, T cell regulatory protein, influence how DR4-DQ8 or DR3-DQ2 react to hypothetical trigger
• Gastrointestinal viral infections in children 4 years old and younger modulate risk for islet autoimmunity in genetically predisposed
  – WAS associated with GAD antibodies as 1st appearing autoantibody, not IAA
  – NOT associated by season, islet autoimmunity associated genes, or respiratory infection prior to seroconversion
  – WAS associated with early life respiratory infection
OPPORTUNITIES FOR INTERVENTION

THERAPY MORE LIKELY TO BE EFFECTIVE
PREDICTION LESS ACCURATE

SAFE DRUGS

PREDICTION MORE ACCURATE
THERAPY LESS LIKELY
TO BE EFFECTIVE

? MORE TOXIC
DRUGS

GENETIC PREDISPOSITION
BETA CELL INJURY

INSULITIS
BETA CELL INJURY

“PRE”-DIABETES

DIABETES
REQUIREMENTS FOR A PRIMARY PREVENTION STUDY

- Cost/benefit to individual and society  YES

- Effective methods for identifying those eligible for intervention (high sensitivity, specificity, positive predictive value, false positives)  YES

- Disease detected early enough to intervene  YES
TrialNet

• 1974 detection of islet cell specific autoantibodies
• Established 2001
• International network
• 15,000 research subjects/year
• 180,000 relatives tested overall
• ~5% have one or more antibodies: GAD 65, mIAA, IA-2A, ZnT8A and ICA
TrialNet Goals

Type 1 Diabetes TrialNet is a NIH-sponsored clinical trials network which aims to:
1) conduct studies designed to evaluate new approaches to prevent or ameliorate T1D
2) further define epidemiology, natural history, risk factors and mechanisms leading to Type 1 Diabetes
TrialNet

- Risk of clinical diabetes multiple autoantibody-positive infants followed from birth
  - 44% at 5 years
  - 70% at 10 years
  - 84% at 15 years
- Rate of 10-12% per year
Trial Net
New Staging System for Type 1 Diabetes

- Genetic Risk: the starting point
- Immune Activation: Beta cells are attacked
- Immune Response: Single autoantibody
- Stage 1: **Start of Type 1 Diabetes** 2 or more autoantibodies with normal glucose tolerance
- Stage 2: Abnormal glucose tolerance
- Stage 3: Clinical Diagnosis
Trial Net
New Staging System for Type 1 Diabetes

- Progressive nature of pre-type 1 diabetes
- Disease is present long before clinical presentation
- Onset is “the point of no return”
- Disease of islet autoimmunity
- NOT intervening in healthy people to prevent a disease
- Changes risks and benefits of clinical trials
OPPORTUNITIES FOR INTERVENTION

THERAPY MORE LIKELY TO BE EFFECTIVE
PREDICTION LESS ACCURATE

SAFE DRUGS

PREDICTION MORE ACCURATE
THERAPY LESS LIKELY
TO BE EFFECTIVE

? MORE TOXIC DRUGS

GENETIC PREDISPOSITION

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BETA CELL INJURY

“PRE”-DIABETES

DIABETES
DPT-1 Oral Study – Time to Diabetes By Treatment

Survival Distribution Function

Years Followed

0 1 2 3 4 5 6 7

186 170 137 110 85 71 40 37 23

Oral Insulin
Oral Placebo

Number at Risk

P-Value = 0.176
(Log Rank Test)

Control
Treated

STRATA:

Diabetes Care 2005; 28:1068-76
EFFECTIVENESS OF ORAL INSULIN IN AT RISK SUBJECTS WITH IAA $\geq 300$

- Proportion Free of Diabetes

- Log-rank $P=0.01$
- Peto Pr. $P=0.01$
- Hazard Ratio: 0.41 (0.21, 0.80)

N = 69

N = 63
TrialNet Interventions

• New-Onset Diabetes: Late intervention
  – Cyclosporin A (1980s): proof of concept that could prolong insulin production
  – Daclizumab and Mycophenolate Mofetil and canakinumab were negative
  – GAD-alum: Antigen-specific: no impact on C-peptide secretion
  – Anti-CD20: rituximab: slowed decline in C-peptide, lower insulin dose and lower A1c (single dose)
TrialNet Interventions

- **New-Onset Diabetes/Stage 3**
  - Abatacept (CTLA4-Ig): blocks costimulatory pathway between antigen presenting cell and T lymphocyte
    - After 2 years of treatment, 59% more C-peptide
    - C-peptide remained higher 1 year after cessation of treatment
    - Well tolerated
    - Similar response rates to rheumatoid arthritis trials
    - Trials for repeated and intermittent treatment protocols are the next steps
TrialNet Interventions

• Stage 1 and 2:
  – Abatacept (CTLA4-Ig): blocks costimulatory pathway between antigen presenting cell and T lymphocyte
  – Teplizumab (anti-CD3)
  – Oral insulin:
    • 67.5 mg daily
    • 500 mg every other week
Anti-CD3 antibody induced self tolerance in diabetic NOD mice

• Treatment with anti-CD3 mAb reversed diabetes in 80% of diabetic NOD mice

• The effect was long lasting and did not require continued treatment

• Recurrent diabetes was prevented by treatment with F(ab’)2 anti-CD3 in recipients of syngeneic islet grafts

(Chatenoud et al)
REDUCTION IN LOSS OF C-PEPTIDE

Herold et al, NEJM 2004
EFFECTS OF $\alpha$CD3 mAB ON INSULIN DOSE

Figure 2. Comparison of Individual Insulin Doses at Baseline and 18 Months in Patients with an Initial Secretory Response at or above the 50th Percentile. Blue circles represent the placebo group, and red triangles the ChAglyCD3 group.
EFFECTS OF AN ANTI-HUMAN CD3 mAB IN NEW-ONSET DIABETES

Keymeulen et al, NEJM, 2005
Anti-CD3 mAb (Teplizumab) For Prevention of Diabetes in Relatives at risk for Type 1 Diabetes Mellitus

Study Chair: Kevan Herold MD
Yale University
# Study Design and Timeline

<table>
<thead>
<tr>
<th>Study Design</th>
<th>2-arm, multicenter, randomized, double-masked, placebo-controlled clinical trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To determine whether intervention with teplizumab will prevent or delay the development of T1D in high-risk autoantibody positive non-diabetic relatives of patients with T1D.</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>A comparison of time to diagnosis of T1D after randomization to teplizumab or placebo.</td>
</tr>
</tbody>
</table>
| Secondary Outcomes | To assess the safety and mode of action of teplizumab.  
To determine whether responses to teplizumab differed in subgroups of participants.  
To analyze the effects of teplizumab on metabolic responses. |
Enrollment in the trial: N=76

Randomization:
- First Subject: July 18, 2011
- Last Subject: September 19, 2017
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Teplizumab N=44</th>
<th>Placebo N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years (IQR)</td>
<td>14 (12 - 22)</td>
<td>13 (11 – 16)</td>
</tr>
<tr>
<td>Male</td>
<td>25 (56.8)</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>Race: White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0 (0.0)</td>
<td>2 (6.2)</td>
</tr>
<tr>
<td>Glycated hemoglobin – percent</td>
<td>5.2 (4.9 – 5.4)</td>
<td>5.3 (5.1 – 5.4)</td>
</tr>
<tr>
<td>C-peptide AUC OGTT (nmol/L)</td>
<td>1.76 (1.47 – 2.18)</td>
<td>1.73 (1.44 – 2.36)</td>
</tr>
<tr>
<td>HLA alleles present – no. of subjects (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither DR3 or DR4</td>
<td>5 (11.6)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>DR3</td>
<td>10 (23.3)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>DR4</td>
<td>17 (39.5)</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Both</td>
<td>11 (25.6)</td>
<td>7 (21.9)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Teplizumab N=44</th>
<th>Placebo N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoantibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ - no. of subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-GAD65 (harmonized)</td>
<td>40 (90.9)</td>
<td>28 (87.5)</td>
</tr>
<tr>
<td>mIAA</td>
<td>20 (45.5)</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Anti-IA-2 (harmonized)</td>
<td>29 (65.9)</td>
<td>28 (87.5)</td>
</tr>
<tr>
<td>ICA</td>
<td>32 (72.7)</td>
<td>24 (75.0)</td>
</tr>
<tr>
<td>ZnT8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titer – median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-GAD65 (harmonized)</td>
<td>240 (76.8 – 464)</td>
<td>221 (42.3 – 520)</td>
</tr>
<tr>
<td>mIAA</td>
<td>0.0070 (0.0020 – 0.028)</td>
<td>0.0040 (0.0020 – 0.0168)</td>
</tr>
<tr>
<td>Anti-IA-2 (harmonized)</td>
<td>52 (0 – 310)</td>
<td>187 (26 – 253)</td>
</tr>
<tr>
<td>ICA</td>
<td>20 (0 -200)</td>
<td>80 (20 – 160)</td>
</tr>
<tr>
<td>ZnT8</td>
<td>0.157 (0.0133 – 0.496)</td>
<td>0.096 ( 0.028 – 0.386)</td>
</tr>
</tbody>
</table>

* Most recent autoantibody results prior to randomization
Teplizumab Dosing

- Teplizumab was given over 14 days, i.v.
- 93% (41/44) and 88% (28/32) of subjects randomized to the teplizumab and placebo groups, respectively, completed the 14 days of drug therapy.
- The median total dose of teplizumab was 9.14 (IQR:9.01-9.37) mg/m2.
- 3 drug-treated and 4 placebo-treated subjects did not complete treatment because of laboratory abnormalities (n=4), inability to establish intravenous access (n=2), or rash (n=1).
- Median follow-up was 745 days (range 74-2683 days). The duration of follow up was more than 3 years in 75% of subjects.
- T1D was diagnosed in 42 (55%) of the participants.
Time to T1D by Treatment Group: Primary Outcome

The hazard ratio of teplizumab to placebo was 0.412 (95% CI: 0.216, 0.783) adjusted Cox proportional hazards). P=0.006
Rate of Progression to T1D and the impact of teplizumab were greatest in the first year

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of T1D</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Teplizumab (%)</td>
<td>Placebo (%)</td>
<td>Chi-square Test</td>
<td>Hazard Ratio (95%CI)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (6.8)</td>
<td>14 (43.8)</td>
<td>15.9</td>
<td>0.129 (0.0482, 0.343)</td>
<td>0.129 (0.0482, 0.343)</td>
</tr>
<tr>
<td>2</td>
<td>8 (18.2)</td>
<td>2 (6.3)</td>
<td>7.55</td>
<td>0.372 (0.169, 0.82)</td>
<td>1.8 (0.473, 6.88)</td>
</tr>
<tr>
<td>3</td>
<td>3 (6.8)</td>
<td>3 (9.4)</td>
<td>7.77</td>
<td>0.404 (0.198, 0.825)</td>
<td>0.58 (0.11, 3.05)</td>
</tr>
<tr>
<td>4</td>
<td>3 (6.8)</td>
<td>2 (6.3)</td>
<td>7.05</td>
<td>0.447 (0.23, 0.868)</td>
<td>0.864 (0.14, 5.33)</td>
</tr>
<tr>
<td>5</td>
<td>2 (4.5)</td>
<td>2 (6.3)</td>
<td>8.24</td>
<td>0.439 (0.233, 0.828)</td>
<td>0.359 (0.039, 3.32)</td>
</tr>
<tr>
<td>Total</td>
<td>19 (43.2)</td>
<td>23 (71.9)</td>
<td>7.77</td>
<td>0.419 (0.228,</td>
<td>---</td>
</tr>
</tbody>
</table>

---
Lymphocyte Count by Treatment Group Over Time
Effects of Teplizumab (Time to T1D) by Subgroup
Summary

• A single two-week treatment with teplizumab delayed the onset of T1D in non-diabetic relatives who were at very high risk for development of clinical T1D.
• The delay in the median time to diabetes was 2 years
• 43% of teplizumab treated subjects developed T1D as compared with 72% of those receiving placebo.
• Teplizumab can be safely administered in children and adults who are at risk for T1D
• Subgroups of individuals, identified by characteristics at screening, may have particularly robust responses to teplizumab.
• This is the first trial to show that immune therapy can be used to delay T1D.
An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

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

- Biomarker of beta cell death
- Beta cell-derived insulin encoding DNA ($INS$ DNA)
- Only source of non-methylated $INS$ DNA is the beta cell
- Level of $INS$ DNA in circulation reflects active rate of beta cell death
TrialNet
Beta Cell Death

• Beta cell death found before the onset of Type 1 diabetes
• Tempo of the disease
  • Decline in the prediabetes period
  • Dramatic increase in killing in peridiagnosis period
• Surrogate marker to monitor beta cell “health status” during prevention and intervention studies
Pathway to Prevention

Mechanistic Studies

Genetic Risk

Immune Activation

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

Immune Response

Beta cells are attacked

Immune Response

Development of single autoantibody

Normal Glucose Tolerance
≥ 2 Autoantibodies
START OF T1D

Abnormal Glucose Tolerance
≥ 2 Autoantibodies

Clinical Diagnosis
≥ 2 Autoantibodies

STAGE 1

STAGE 2

STAGE 3

STAGE 4

NIP

Oral Insulin

Teplizumab

Immune Effects of Oral Insulin

Abatacept

Hydroxychloroquine

Methyldopa

Rituximab/Abatacept

LIFT

ATG/GCSF

Tocilizumab*

Alefacept*

Canakinumab

Metabolic control**

GAD-alum

Abatacept

IL-2/Rapamycin*

Thymoglobulin*

Rituximab

Teplizumab*

MMF/DZB

* With ITN
** With DirectNet

*   With ITN
** With DirectNet