Staging of Type 1 Diabetes: Clinical Implications
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BRI’s major contributions to type 1 diabetes research

• Identified type 1 diabetes susceptibility genes
• Developed tetramer technology to find cells that destroy insulin producing cells
• NIH TrialNet Hub and clinical center for Pacific NW for T1D studies
• JDRF Biomarker Translational Research Center
• Immune Tolerance Network (ITN) director
• T1D Exchange Biobank Coordinating Center
• T1DGC Coordinating Center
Eisenbarth Model-T1D Natural History

1986

- Genetic Predisposition
- Overt Immunologic abnormalities
- Normal insulin release
- Progressive loss insulin release
- Glucose normal
- Overt diabetes
- C-peptide present
- No C-peptide

Age (years+)

Beta cell mass

(?Precipitating Event)
Type 1 Diabetes Genetic Consortium (2004-2010)

- Established in 2004 to discover genes that effect the risk of T1D
  - 9,976 subjects from 2,321 T1D sibling pair families

- 40-50 genes identified as T1D risk locations of the immune system
  - Affect function of immune cells
  - Regulate cellular responses that lead to autoimmunity
  - Rate or pattern of beta cells loss is variable
50% of the risk for T1D determined by genetic factors

- HLA region, chromosome 6 – encode antigen-presenting molecules (50%)
  - Haplotypes DR3-DQ-2 and DR4-DQ8
  - Occurs in 2.3% of the white population
  - Associated with 5% risk of T1D
  - 55% risk for T1D for child with sibling with T1D with same haplotype
  - 75% of people with T1D have this haplotype
Genetics of Type 1 Diabetes

• ~40 genes outside the HLA – affect immune system T cell activation
  • PTPN22 – influences signaling from the T cell receptor
    • Assoc. with risk for other autoimmune diseases (RA, SLE, Grave’s disease)
  • Gene for insulin
  • CTLA4 – T cell development
  • IL2RA – associated with MS
Immune cell activation and inflammation causes an insulitis causing destruction of the beta cells.
Type 1 diabetes is an immune disease

"insulitis"

1970’s

Normal islet

Islet missing insulin producing beta cells
Lots of immune cells

2014’s

Insulitis not seen in every islet
Type 1 Diabetes starts at two antibodies and the rate of progression before and after clinical disease onset is highly age dependent.
When do autoantibodies occur? (How soon does “diabetes” start?)

Antibodies develop very early

95% of children who developed T1D before puberty had antibodies by age 5

Parikka et al; Diabetologia (2012) 1936
Multiple Aab+ in genetically at risk babies = T1D

Ziegler, et al, JAMA, 2013:309(23) 2473-2479

~11% per year
T1D starts at two or more antibodies: Progression to clinically overt disease by age
Impact of age at clinical diagnosis on change in C-peptide first two years post diagnosis

Greenbaum et al, Diabetes 2012
Many people with T1D still make insulin (at least a little bit) many years after diagnosis 
(particularly if diagnosed with T1D as an adult)
% of people still making some insulin years after diagnosis

- Diagnosed ≤18 years old
- Diagnosed >18 years old

### Duration, yrs

**3-5 yrs**
- N=122 N=83
  - 78% Detectable C-Peptide (≥0.017 nmol/L)

**6-9 yrs**
- N=93 N=67
  - 60% Detectable C-Peptide

**10-19 yrs**
- N=104 N=93
  - 35% Detectable C-Peptide

**20-40 yrs**
- N=103 N=95
  - 19% Detectable C-Peptide

**>40 yrs**
- N=103 N=56
  - 16% Detectable C-Peptide
Less Hypoglycemia in those with Residual β Cell Function (0.2 pM to 0.5 pM C-peptide)

Diabetes Control and Complications Trial

62% Risk Reduction

Hypoglycemia Rate per 100 pt years

Conventional | Intensive with β cell function | Intensive without β Cell Function

Diabetes 53:250-264, 2004
Less Retinopathy in those with Residual β Cell Function (0.2 pM to 0.5 pM C-peptide)

Risk Reduction: 79%
(CI: 9, 95) \( p < 0.012 \)

DCCT Intensive Therapy Group
Sustained 3+ Step Retinopathy Progression

Diabetes 53: 550-264, 2004
EDIC Study: HbA1c Matters Today, Tomorrow and 20 Years On

- EDIC is measuring the ongoing impact on control in the initial 10 years of the study.

- Control in EDIC for 2 groups was same after the DCCT: HbA1c was 8%.

- At 18 years of follow-up, the overall prevalence of complications is 50% lower in DCCT intensive treatment group.

- Metabolic Memory”
Goals

- **Save** beta cells
- **Maintain** insulin secretion
- **Prevent** recurrence
Type 1 Diabetes TrialNet

- International Consortium of diabetes clinical researchers – 17 U.S. & 6 international centers with multiple affiliates
- Carla Greenbaum MD – Chair
- Cutting edge researchers in academic centers, scientists, nurses and coordinators
- Benaroya Research Institute – the clinical network Hub
Using knowledge gained through clinical research, TrialNet’s mission is to prevent type 1 diabetes and stop disease progression by preserving insulin production before and after diagnosis.
Why Save Beta Cells?

• Lower risk of short-term complications such as severe hypoglycemia/ seizure

• Lower risk of long-term complications such as retinopathy

• If we can prevent beta cell destruction, we can improve the likelihood that beta cell replacement therapies (such as transplantation) will be successful long term.
Most Therapies Interrupt Immune Cell Signaling

- Different dosing schedules
- Different mechanisms of action
Abatacept

Anti CD3 – Teplizumab

Effects all occurring at the same time

Rituximab

Placebo

*p < 0.020

Time in months

0.4 0.5 0.6 0.7

0 3 6 12
What does all this mean and what is next?

Biggest effects in recently diagnosed patients appear to be early:

**Hypothesis:** there is a more aggressive beta cell destructive process in the first year after diagnosis

Drugs with different mechanisms have similar effects

**Question:** Is there a mechanism in common that helps us explain the common outcomes?
What does all this mean and what is next?

• There are several drugs that likely do save beta cells at least for a while!

• How long will the effect of therapy last?

• Is there a way to prolong the effects of therapy?

• Is there a long term benefit on complications or control?

➢ Continue to study subjects in trials even once their participation in the trial is complete (LIFT Trial)
Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association


The Adoption of the Staging Classification System Is Endorsed by the American Association of Clinical Endocrinologists, the International Society for Pediatric and Adolescent Diabetes, and The Leona M. and Harry B. Helmsley Charitable Trust
Type 1 Diabetes Stages

• Stage 1: Autoimmunity + / Normoglycemia / Presymptomatic Type 1 Diabetes *

• Stage 2: Autoimmunity + / Dysglycemia / Presymptomatic Type 1 Diabetes *

• Stage 3: Autoimmunity + / Dysglycemia / Symptomatic Type 1 Diabetes

* Lifetime risk approaches 100 %

FAMILY MEMBERS

• 15x greater risk to develop T1D
IMMUNE SYSTEM ACTIVATION

• Likely a common event
IMMUNE SYSTEM RESPONSE

• Development of autoantibodies

• Immune system’s signal that beta-cells are being attacked
PROGRESSION BY POPULATION

- Large numbers with genetic risk
- Many likely with activated immune system
- Fewer with immune system response
T1D STARTS with two or more autoantibodies

Stage 1: NORMAL BLOOD SUGAR
Stage 2: ABNORMAL BLOOD SUGAR
Stage 3: DIAGNOSIS
Type 1 Diabetes Disease Progression
TrialNet intervention on Disease Progression
Future of TrialNet
Screening for type 1 diabetes recommendations

• “Consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study.”
PATHWAY TO PREVENTION

• 1st and 2nd degree relatives
• Screen for five autoantibodies
• Based on autoantibody status we look to enroll in clinical trials or monitoring
ORAL INSULIN

• 1st stage towards T1D
• Two or more AAB’s
• DPT1
  • Must have mIAA

• Delay conversion to abnormal blood sugar
• Maintain current level of beta-cell function
ABATACEPT

- 1st stage towards T1D
- Two or more autoantibodies (excluding mIAA)
- Approved and efficacious for treatment of:
  - Adult Rheumatoid Arthritis (moderate to severe)
  - Juvenile Idiopathic Arthritis (JIA/JRA) (Children 6-17 years old)
- Effective in TrialNet Abatacept New Onset Trial

Delay conversion to abnormal blood sugar
Current & Future Status of Stage 1 Trials

• This is when T1D starts

Oral Insulin

• Enrollment closed Dec 2015; Results expected—2017
  • New Study! Results expected 2017
  • Mechanistic study to help us learn for the future; everyone receives active drug

Abatacept

• Two or more autoantibodies, normal glucose tolerance
• Currently enrolling
• Ages 6-45
TEPLIZUMAB (ANTI-CD3)

Stage 2 T1D

• Most at-risk population for developing T1D

• Two or more autoantibodies with ABNORMAL glucose tolerance

• Delay conversion from abnormal blood sugar to diagnosis of T1D

• Anti-CD3 has been shown to improve the decline in insulin production in patients in numerous clinical trials
Current & Future Status of Stage 2 Trials

- Second stage in development of T1D
- Population most at risk for diagnosis of T1D

**Teplizumab**
- Two or more autoantibodies, abnormal glucose tolerance
- Currently enrolling
- Ages 8-45
ATG/GCSF

Stage 3 T1D – Clinical Diagnosis

• Combination therapy—intervention using two medications
• Benefit to maintaining beta-cell function at anytime pre or post diagnosis
• Pilot study suggests benefit

Diagram:
- Genetic Risk
- Activation
- Immune System Response
- Normal Blood Sugar
- Abnormal Blood Sugar
- Diagnosis
- Post Diagnosis
Current & Future Status of Stage 3 Trials

- Clinical diagnosis
- Benefit to maintaining beta-cell function even after clinical diagnosis

ATG/GCSF
- Randomized within 100 days from diagnosis
- Currently enrolling
- Ages 12-45
ATG-GCSF: Thymoglobulin (ATG) and Neulasta (GCSF) for New-Onset T1D

- At least 28 subjects will receive active ATG-GCSF
- At least 28 subjects will receive ATG alone
- At least 28 subjects will receive placebo alone

- **ATG**: Rabbit anti-human antibody to T cells
- **Induces T cell depletion** Currently used daily for transplant pre-treatment

- **GCSF**: Mobilizing Agent, favors Treg development
- **Currently in use for neutropenic patients**
Pilot trial of Randomized (2:1) 25 subjects: 17:8

AUC c-peptide

Treated
Placebo

Months post treatment

AUC (ng/ml/2 hr)

p = 0.05

Current Stage 3 Trial – Immune Tolerance Network

- Clinical diagnosis
- Benefit to maintaining beta-cell function even after clinical diagnosis
- EXTEND (Tocilizumab)
  - Randomized within 100 days from diagnosis
  - Currently enrolling
- Ages 18-45
EXTEND: Tocilizumab

• 2:1 randomization of 108 participants

• Seven infusions over six months (infusions last ~1-2 hours)

• Tocilizumab: an FDA-approved drug for treatment of RA in patients as young as 2yrs who have systemic JIA; has not yet been tested in T1D.

• Tocilizumab blocks the receptor for a molecule called IL-6.

• IL-6 is thought to contribute to inflammation in type 1 diabetes leading to destruction of beta cells.
TrialNet Impact on Post Diagnosis
What about all those people living with T1D?

- Type 1 diabetes starts with two or more antibodies:
- Save beta cells at stage 1: Stop abnormal blood sugar
- Save beta cells at stage 2: Stop clinical diagnosis
- Save beta cells at stage 3: Make diabetes easier and less complications

Cure Type 1 Diabetes
Immunotherapy is needed to induce remission and to prevent disease progression and irreversible tissue damage in many autoimmune diseases.
Alopecia areata
Ankylosing spondylitis
Addisons disease
Hemolytic anemia
Autoimmune Hepatitis
Thrombocytopenic purpura
Behcets disease
Pemphigus
Crohns disease
Dermatomyositis
Lupus
Graves disease
Hashimotos Thyroiditis
Autoimmune Diabetes
Multiple sclerosis

Myasthenia gravis
Pernicious anemia
Polyarteritis
Polychondritis
Polymyositis
Psoriasis
Rheumatoid arthritis
Scleroderma
Sjogren’s syndroms
Stiff man syndrome
Giant cell Arteritis
Ulcerative colitis
Vasculitis
Uveitis
Vitiligo
Key points

• There is a significant role for disease-modifying therapy in T1D
• Type 1 diabetes starts when two or more antibodies are present
• The disease course and response to Rx differs for adults and children
• Therapies with different mechanisms of action have been effective and safe in disease modification soon after diagnosis
• Disease modifying therapies are currently being tested in placebo controlled, randomized trials earlier in the disease process and in those after diagnosis
For more information:

• Call 800-888-4187

• Email diabetes@BenaroyaResearch.org

• Visit: www.TrialNet.org