Altering The Course Of Type 1 Diabetes

JDRF TypeOneNation Summit

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Today's Agenda

• My story
• The path to Type 1 Diabetes
• Prevention efforts
• New-onset studies
• Next steps
TrialNet
Type 1 Diabetes Progression
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**

**Immune Response**

- Beta cells are attacked
- Development of single autoantibody
T1D Disease Progression

Genetic Risk

Immune Activation

Immune Response

STAGE 1

STAGE 2

STAGE 3

STAGE 4

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

Starting Point
Genetic Risk

The path to T1D starts here

- Everyone who is diagnosed with T1D has the gene(s) 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
Genetic Basis Of Type 1 DM

- Complex pattern of genetic transmission, with up to 20 different loci identified

- Half of the genetic risk is from the HLA locus, the region that determines self from non-self
  - High risk genes in 95% of Caucasians with T1DM, but present in 45% of general population (DR3, DR4)
  - What about twins?
    - Concordance 33 to 50%, higher when followed long term
T1D Disease Progression

- **Genetic Risk**
- **Immune Activation**
- **Immune Response**

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

**Immune Activation**
Beta cells are attacked

**STAGE 1**
**STAGE 2**
**STAGE 3**
**STAGE 4**
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”
Figure 2. The North–South Gradient in the Prevalence of Multiple Sclerosis (Panel A) and the Incidence of Type 1 Diabetes Mellitus (Panel B) in Europe. Adapted from Kurtzke and Green and Patterson.21
Relationship between autoimmunity and infection

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000. In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussem et al. In Panel B, data on immune disorders are derived from Swarbrick et al., Dubois et al., Tuomilehto et al., and Pugliatti et al.
Increasing Incidence of T1DM

Rewers M. Ann NYAS 2008
The Hygiene Hypothesis

- Follows from pre-clinical models of diabetes
  - NOD mouse raised in clean environment is higher risk for DM than one raised in dirty one

- "Clean living" may increase risk for autoimmune diseases

- Risk is higher in urban than rural settings

- Inverse correlation with immunizations, antibiotic use

- Daycare, other early exposures, lower risk for DM
Farming Lifestyle, the Activation of Innate Immunity, and Protection against Asthma.

T1D Disease Progression

Genetic Risk

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
T1D Disease Progression

Development of single autoantibody

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
  - They do not cause the destruction of beta cells
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
Beta cells are attacked

Development of single autoantibody

STAGE 1

STAGE 2
T1D Disease Progression

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

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 Response

Type 1 Diabetes
DPT-1 – Time to Diabetes
By Number of Antibodies

P- Value < 0.001
(Log Rank Test)

Number at Risk

Survival Distribution Function

Years Followed

n = 26799

STRATA:

n = 26799
Multiple Autoantibodies strongly predicts development of T1D

>80% progression over 15 years

No differences between Europe/USA or high/low risk countries

Ziegler, et al, JAMA, 2013:309(23) 2473-2479
Stage 1 T1D
Normal Blood Sugar

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

T1D Disease Progression

STAGE 1
Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D

STAGE 2

STAGE 3
Abnormal Blood Sugar
≥ 2 autoantibodies

STAGE 4
T1D Disease Progression

Stage 2 T1D
Abnormal Blood Sugar

≥ 2 autoantibodies

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

STAGE 1 STAGE 2 STAGE 3
T1D Disease Progression

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

**Genetic Risk**

**Immune Activation**

**Immune Response**

**Stage 1**
- Beta cells are attacked

**Stage 2**
- Development of single autoantibody

**Stage 3**
- Normal Blood Sugar: ≥ 2 autoantibodies
- Abnormal Blood Sugar: ≥ 2 autoantibodies

**Stage 4**
- Clinical Diagnosis: ≥ 2 autoantibodies

START OF T1D
T1D Disease Progression

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
### The Stages to Type 1 Diabetes

#### Genetic Risk

- **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

- 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
T1D Disease Progression

Stage 4 T1D
Long-Standing T1D

Post diagnosis

- Continued loss of beta cells over time
- Research outside of TrialNet
  - Engineer’s approaches
    - Closed loop systems
  - Beta cell replacement
    - Whole pancreas transplant
    - Islets
    - Stem cell derived beta cells
## T1D Disease Progression

### The impact of AGE on disease progression & beta cell decline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Autoantibodies</th>
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<tbody>
<tr>
<td>Stage 1 (Start of T1D)</td>
<td>≥ 2 autoantibodies</td>
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<tr>
<td>Stage 2</td>
<td>≥ 2 autoantibodies</td>
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<tr>
<td>Stage 3 (Clinical Dx)</td>
<td>≥ 2 autoantibodies</td>
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<tr>
<td>Stage 4</td>
<td>Long-standing T1D</td>
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<table>
<thead>
<tr>
<th>Age Group</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
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<tr>
<td>Age &lt;5</td>
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<td>Age 10-14</td>
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<td>Age 15-19</td>
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<td>Age ≥ 20</td>
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T1D Disease Progression

SUMMARY POINTS

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 after diagnosis is also faster the younger you are and continues through stage 4
T1D Disease Progression

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

Genetic Risk

Screen / Predict → Prevent

Immune Activation

Immune Response

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

Immune Activation
Beta cells are attacked

Immune Response
Development of single autoantibody

Screen / Predict

Prevent

Preserve

Replace
Prevention Trials
Considerations For Selecting Agents For Prevention And New Onset Trials

- Benefit suggested by:
  - Animal models
  - Human trials in related autoimmune disease, or transplant

- Mechanism likely to be effective
  - Targets T-cells

- Safety of intervention established

- Ideal therapies are those that do not require continuous use, are tolerizing
Dilemma For DM Interventions

• Attempts at early prevention
  – Less likely to predict who will ultimately get DM
    • Larger studies conducted over longer time period
  – Less aggressive intervention, such as dietary manipulation or antigen-based therapy, more likely to be efficacious

• Later stages of intervention
  – Greater likelihood of predicting who will get DM
    • Smaller studies conducted over shorter time
  – Later intervention may require more aggressive and potentially toxic agents to have efficacy
TRIGR: Avoidance of Cow’s Milk  
NIP: Omega 3 Fatty Acids  
POINT: Insulin Antigen  
BabyDiet: Gluten avoidance  
Vitamin D

**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

Immune Response

Beta cells are attacked

Development of single autoantibody

Normal Blood Sugar: ≥ 2 autoantibodies

Abnormal Blood Sugar: ≥ 2 autoantibodies

Clinical Diagnosis: ≥ 2 autoantibodies

Long-standing T1D
The Stages to Type 1 Diabetes

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Immune Response

- Development of single autoantibody

The Antigen: Insulin, GAD

T cell blockade: CTLA4 Ig
Oral Tolerance: Mode of Action

Oral Antigen

Insulin Producing β-cells

Autoimmune Lymphocytes

Regulatory T cells

Protective Cytokines

Inhibition of β-Cell Autoimmunity and Prevention of DM
Effect Of Oral Insulin On Progression To T1DM

Skyler et al, Diabetes Care 2005, 28: 1068
Effect Of Oral Insulin On Progression To T1DM

*Only subjects with IAA > 80*

Oral insulin may delay DM onset ~ 4.5 yrs

Skyler et al, Diabetes Care 2005, 28: 1068
Insulin Effect Most Evident in Subjects with Baseline IAA ≥ 300

N=63 (Ins.) and 69 (Plac.)

- Oral Insulin
- Placebo

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

Projected 10 year delay

Ann NY Acad Sci 2009; 1150:190-196
Immune Effects of Oral Insulin

• Results for the follow-up study (TN-07) will available in Summer 2017 (7.5 mg daily)
• Evaluate other doses and intervals of oral insulin (TN20)
  • 2 arms
    • One dose per day (67.5 mg daily)
    • One dose every 2 wks (500 mg every 2 wks)
• Evaluate effects on immune response, beta cell function
T1D Tertiary Prevention

The Stages to Type 1 Diabetes

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**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

**Anti-CD3 mAb**
TrialNet Screening

P2P
Pathway to Prevention

Determine where you are on the path

- No cost
- 1st and 2nd degree relatives
- Screens for autoantibodies
- Based on results
  - Can enroll in a prevention trial to preserve beta cell function
  - Or monitor for disease progression

Scott & Adam
Pathway to Prevention Participants

Keilyn
Pathway to Prevention Participant

Brooke, Emily & Ava
Pathway to Prevention Participants
TrialNet Screening

P2P
Pathway to Prevention

Eligibility Requirements

- Anyone between age 1 and 45 with a sibling, child or parent with type 1
- Anyone between age 1 and 20 with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with T1D
- Those under 18 who do not have autoantibodies can be retested every year
- We try to make screening easy and accessible,
  - at events,
  - via telephone consent and bring a kit to a local Quest lab, or
  - www.pathway2prevention.org

Tracy Rodriguez
TrialNet Coordinator, UCSF
• This approach only targets those with an affected family member

  – but 90% of new onset occurs in families unaffected by type 1 DM

  – Need to move to general population screening
Newly Diagnosed Interventions

Stage 3
The Honeymoon

• At diagnosis, 15-40% of beta cell function remains

• Past studies suggest inevitable decline of beta cell function following diagnosis, with rapid progression to complete loss

• More recent studies suggest beta cell function can persist
  • DCCT, Medalist studies, Butlers, T1D Exchange, TrialNet
  • Significant heterogeneity, driven in part by age of onset

• Beta cell function can serve one well while it lasts...even if on supplemental insulin
  - Better overall glucose control
    • lower HbA1C, less glycemic excursion, lower risk for severe hypoglycemia, lower risk for complications
Prolonging the honeymoon

• Immunotherapy works
  – Cyclosporine experience from the ’80s
    • Requires continuous immunosuppression
    • Not all respond
    • Potential toxicities
EXTREME COMBO THERAPY

BRAZILIAN COCKTAIL

1. Stem Cell Mobilization
   - Cyclophosphamide
   - G-CSF
   - CD34+ cells harvested

2. Non-myeloablation
   - Cyclophosphamide
   - ATG

3. Transplant / Mobilization
   - Infuse CD34+ cells
   - G-CSF

4. Prophylaxis / Support
   - Hospitalization
   - Antibiotics

Slide courtesy of M. Haller

Voltarelli et al JAMA, 297:1568-76, 2007
EXTREME COMBO THERAPY

BRAZILIAN COCKTAIL

Couri et al JAMA, 301:1573-9, 2009

PARTICIPANTS

New onset T1D < 6 week Dx GAD+
13-31 years (mean 19.2)

RESULTS

20 of 23 became INSULIN FREE > 1 month
12 INSULIN FREE > 14 months (mean 31)
A1c < 7% + C-peptide INCREASE at 24 mo
BUT … short and long term concerns

LOGICAL to study lower risk components of therapy ... “BRAZIL-LITE”

Slide courtesy of M.Haller
Deconstructing the Brazilian Cocktail

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
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<tbody>
<tr>
<td>ATG + GCSF + Cyclophosphamide</td>
<td>+++</td>
</tr>
<tr>
<td>ATG</td>
<td>+/-</td>
</tr>
<tr>
<td>G-CSF</td>
<td>-</td>
</tr>
<tr>
<td>ATG + G-CSF</td>
<td>?</td>
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</table>
ATG/GCSF Combo Pilot:
Established Type 1 Diabetes (Helmsley)

- Established Diabetes (4 months – 2 years)
- ATG - 2.5 mg/kg over 2 days (6.5 mg in START)
- GCSF - 6 mg q 2 weeks for 12 weeks

- 25 subjects, Single Blinded
- 2:1 Randomized Combo:Placebo
- Ages 12 years – 45 years within 4 mos to 2 yrs of diagnosis

Haller, J Clin Invest 2015
ATG/GCSF Combo Pilot Study
Data Summary

AUC c-peptide

Treated
Placebo

p = 0.050

AUC (ng/ml/min)

Months post-treatment

n = 17
n = 8

17
8
17
8
16
8

Haller et al. *Journal of Clinical Investigation* 2015
Autoreactive cells

Healthy
Disease

Regulatory T cells
Human Treg Expansion In Vitro

CD4+CD127lo/-CD25+

αCD3/αCD28 beads (1:1 ratio)
IL-2 (300U/ml)

FOXP3 analysis
Functional analysis

Expansion Curve

Cell Number

Time (d)

Treg Trial

• Phase 1 study with infusion of autologous Tregs expanded in vitro
  – First effort in autoimmunity

• Subjects 18-45 yrs old, within 2 yrs of dx and with measurable C-peptide

• Dose escalation

• Fully enrolled
  – Safe, well tolerated

<table>
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<tr>
<th>Cohort</th>
<th>Subjects</th>
<th>Cell dose (x 10^8)</th>
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<tr>
<td>1</td>
<td>3</td>
<td>0.05</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>26</td>
</tr>
</tbody>
</table>

C-peptide AUC Change Over Time

Next Steps With Tregs

**Treg expansion (Trex, Caladrius)**
- Phase 2 study for adolescents
  - Within 3 mos of dx

**TILT**
- Phase 1 study for adults
  - Tregs + IL-2
  - Within 2 yrs of dx
Potential Role For Gleevec In T1DM (Imatinib / Glivec, Novartis)

• Discovered from a high-throughput screen of chemical libraries
  – goal of identifying a tyrosine kinase inhibitor for Bcr-Abl fusion protein to treat CML
  – Specific inhibitor of Abl protein TKs, but inhibits others

• Can improve autoimmunity
  – Prevents and reverses DM in NOD mouse
  – Improves insulin sensitivity
  – Related approach FDA approved for RA

• Multiple possible mechanisms for its effects
  – T cell migration to islets
  – Lowers ER stress
Endoplasmic Reticulum (ER) Stress
Role Of ER Stress In Diabetes

- Autoimmune attack on β cells (type 1)
- Peripheral insulin resistance (type 2)
- β cells overworked

ER stress

- Homeostasis
- β cell dysfunction/death
- Diabetes
- Apoptosis
- Oxidative damage (ROS)/inflammation (IL-1β)

Unfolded protein response (UPR)
Gleevec Study Overview
(NCT01781975 )

- Multi-center 2 arm, 2:1 randomization, double blinded phase II trial
  - 66 subjects, ages 18-45 with recent onset T1DM
  - Treatment with 400 mg study drug or matching placebo for 6 months
  - Primary outcome: 2 hr stimulated C-peptide AUC in response to MMTT at 12 mos

- Secondary outcome measures will include:
  - Efficacy: C-peptide AUC at 2 and 4-hrs out to 24 mos, insulin use, hypoglycemia, HbA1C
  - Safety: frequency and severity of AEs
  - Mechanistic studies
Summary

• T1DM is a challenge
  – Risk is increasing
  – Current management is sub-optimal
  – Those with residual beta cell function do better

• Series of promising trials to
  – Prevent or delay DM onset
  – Preserve beta cell function in those recently diagnosed

• Gaining insights into how and what we need to accomplish for robust success
  – Resetting Treg balance

• New onset trials will inform our attempts at DM prevention and transplantation
Potential Type 1 DM Interventions

Modified from Matthews et al, Clin Exp Immunol 2010
What can we do to get there sooner?

• More efficient means of conducting studies
  • Multiple arms to a study,
    • Evaluate different doses of a drug
    • Evaluate different drugs
  • Evaluate a cocktail of drugs that work by different mechanisms

• Better means to study the outcome
  • Need to understand changes to T-cells, in pancreas
  • Way to visualize pancreas would be helpful

• Most studies are now limited to adults, or to adolescents
  • Ultimately, T1DM is mainly a disease of children
  • Need to find means to move these therapies to younger children
Acknowledgements

• UCSF
  - Jeff Bluestone
  - Mark Anderson
  - Chris Ferrara
  - Srinath Sanda
  - Hilary Thomas

• Yale
  - Kevan Herold
Help Us Cure Type 1 DM!

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- [http://www.diabetes.ucsf.edu](http://www.diabetes.ucsf.edu)