Purpose of the Workshop

- Discuss the current understanding of the natural history of type 1 diabetes (T1D) prior to the onset of symptomatic disease
- Inform clinical trial design for interventions in early stages of T1D
- Encourage product development for early stages of T1D
- Aid regulatory decision-making
T1D is Growing Significantly in the United States

**T1D PREVALENCE ROSE 21%**
**AGES <20 YEARS, 2001-2009**

**T1D INCIDENCE INCREASED 2.6% PER YEAR**

T1D UNMET NEED

With Current Tools, Most Not Meeting A1C Targets

Source: T1D Exchange
Rates of DKA and Severe Hypo Are Too High

12 MONTH FREQUENCY OF DKA

12 MONTH FREQUENCY OF SEVERE HYPO

Source: T1D Exchange
Objectives of the Workshop

- Garner common understanding of current data on T1D risk detection, staging, and progression
- Discuss the design and optimization of intervention trials in the early stages of T1D
- Identify tools to improve staging and predict progression of T1D
- Discuss approaches to validate existing tools and develop new tools
Scientific Framework of the Workshop

- T1D is a disease continuum that begins prior to its phenotypic, symptomatic disease
- Risk of developing T1D can be identified and quantified
- T1D has well-defined, reproducible early stages that reach a point of inevitability of symptomatic T1D
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy
- The ability to screen for risk and stage T1D prior to symptomatic T1D has benefit today, and in the future, will provide a unique opportunity to intervene to delay, and ultimately prevent, the onset of clinical symptoms and life-long insulin dependence
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia-/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Overview of Workshop Agenda

- State of Type 1 Diabetes Today
- Screening, Natural History and Risk Detection of the Early Stages of Type 1 Diabetes
- Biomarkers in the Early Stages of T1D
- Recommendation for Classification of Early Stages of Type 1 Diabetes
- Opportunities for Future T1D Prevention Research
- Conclusions and Next Steps
Desired Outcomes of the Workshop

- Provide a new standardized taxonomy and staging approach for human T1D
- Accelerate clinical development of therapies to prevent symptomatic T1D
- Aid design of clinical trials through use of risk profiles, subject stratification, and stage-specific trial endpoints
- Promote precision medicine: Tailoring of optimal therapies to specific individuals at specific stages of T1D
- Provide an approach for the benefit/risk framework in the early stages of T1D
Epidemiology of Type 1 Diabetes

Dana Dabelea, MD, PhD
Professor of Epidemiology and Pediatrics
University of Colorado Denver
Start of 20\textsuperscript{th} century – T1D was rare and rapidly fatal
Youth were thin, usually white race/ethnicity
Incidence in 1900 ~ 2/100,000 rising to 7/100,000 by 1920 (Norway)
International rise in incidence began in mid-20\textsuperscript{th} century
Incidence from 1960-1996 increased in 24/37 studies averaging 2-4\% per year; recent levelling off in Scandinavia countries
Limited US data- SEARCH registry

Gale EA:. *Diabetes* 51(12):3353-3361, 2002
Burden of Type 1 Diabetes Worldwide and in the US
Incidence of T1D, by Age and Race/Ethnicity

2002-2003

- NHW
- AA
- H
- API
- AI

SEARCH Study Group, JAMA 297(24), 2716, 2007

2008-2009

SEARCH Study Group, JAMA 297(24), 2716, 2007
Trends in Incidence of T1D Among NHW Youth, 2002-2009

Average annual percent increase:
Males: 2.84% (1.12-4.58%)
Females: 2.57% (0.68-4.51%)

Lawrence, et al. Diabetes 2014, in press
Trends in T1D Prevalence, 2001-2009, by Sex, Age, and Race/Ethnicity

21.2% relative increase

Dabelea & Mayer-Davis, et al., *JAMA*, 311 (17), 1778, 2014
Trends in High and Moderate/Low Risk HLA Alleles
Colorado 1978 - 2004

Vehik et al., *Diab Care: 31 (7), 2008*
# Estimated Number of T1D cases in the US, by Race/Ethnicity, 2009

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>N of US Population &lt; 20 yrs. In 2009</th>
<th>Type 1 Diabetes N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83,280,391</td>
<td>166,984</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>46,859,149</td>
<td>119,387</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18,609,959</td>
<td>23,915</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>12,791,402</td>
<td>20,887</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>4,158,522</td>
<td>2,493</td>
</tr>
<tr>
<td>American Indian</td>
<td>861,359</td>
<td>303</td>
</tr>
</tbody>
</table>

Pettitt et al., *Diabetes Care*: 37(1), 402, 2014
Projections of future burden
Projected Number of Youth < 20 Years With T1D: Increased Incidence Scenario

- Number of US youth with T1D projected to increase 3.3-fold by 2050
- Highest among NHW youth (7.04/1000 in 2050)
- Largest relative increase among Hispanic youth (6.6-fold increase)
- US health care systems need to be prepared

Presentation and Definition of Diabetes Type

With increasing obesity, youth with T1D are increasingly overweight or obese, causing confusion about the correct diagnosis.
Classification of Diabetes Type based on Autoimmunity and Insulin Sensitivity

Autoimmunity

DA +

DA -

Insulin Sensitivity*

Sensitive
IS ≥ 8.15
(54.5%)

Resistant
IS < 8.15
(19.5%)

Sensitive
IS ≥ 8.15
(10.1%)

Resistant
IS < 8.15
(15.9%)

DA+  Positive for IA2 or GAD65 autoantibody

* Insulin Sensitivity = \exp [4.64725 - 0.02032*(\text{waist, cm}) - 0.09779*(\text{HbA1c, %}) - 0.00235*(\text{TG, mg/dl})];

Resistant = IS index below the 25th percentile for NHANES youth

Sensitive = IS index ≥ the 25th percentile for NHANES youth

Algorithm for Classification of Pediatric Diabetes

Diabetes

Autoantibodies present (GADA, IA-2A, ZnT8, IAA, etc.)

No Autoantibodies

Insulin Sensitive (Normal waist)

Insulin Resistant (Large waist)

Additional Testing

Type 1 Diabetes

MODY

Secondary Diabetes

Type 2 Diabetes

Other Genetic
### Baseline FCP and Estimated Decline in FCP According to Etiologic Diabetes Type

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Baseline FCP (ng/ml) [median (IQR)]</th>
<th>FCP Decline (% per month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune + insulin sensitive</td>
<td>688</td>
<td>0.5 (0.7)</td>
<td>4.0 (3.8-4.3)%</td>
</tr>
<tr>
<td>Autoimmune + insulin resistant</td>
<td>212</td>
<td>0.8 (1.3)</td>
<td>4.2 (3.8-4.7)%</td>
</tr>
<tr>
<td>Non-Autoimmune + insulin sensitive</td>
<td>122</td>
<td>0.7 (1.0)</td>
<td>2.4 (1.8-2.9)%</td>
</tr>
<tr>
<td>Non-Autoimmune + insulin resistant</td>
<td>189</td>
<td>3.4 (2.9)</td>
<td>0.7 (0.3-1.2)%</td>
</tr>
</tbody>
</table>

Dabelea et al., *Diabetologia*, 2012
Risk Factors for Poor Prognosis
Prevalence of DKA at Onset with T1D Over Time, by Age and Race- No Trends Over Time

- 31% Prevalence overall
- 39% Prevalence in children 0-4 yrs

12-month Frequency of Diabetic Ketoacidosis*
According to Age

*1 or more events in 12 months

Age (years)

- <6: 8%
- 6-<13: 6%
- 13-<18: 10%
- 18-<26: 10%
- 26-<31: 5%
- 31-<50: 5%
- 50-<65: 4%
- ≥65: 4%
12-month Frequency of Severe Hypoglycemia* According to Age

* Seizure or LOC: 1 or more events in 12 months
ADA HbA1c Target Met

A1c Goal = <7.5%

Current

Age (years)

<6  21%
6-<13 21%
13-<18 17%
18-<26 13%
26-<50 32%
≥50 29%

A1c Goal = <7.0%
Disparities in Prevalence of Poor Glycemic Control (A1c ≥ 9.0%)

**Race/Ethnicity**
- NHW
- AA
- HISP
- API
- AI

**Parental Education**
- < H.S.
- H.S. Grad
- Some College
- B.A./B.S. or more

**Family Income**
- <$25K
- $25-49K
- $50-74K
- $75+K

**Insurance Type**
- None
- Medicaid
- Other
- Private

Prevalence of Cardiovascular Risk Factors in Youth with Diabetes

MetS: > 2 CVD risk factors

Complications patterns
Elevated Albumin/Creatinine Ratio* by Race/Ethnicity Among Youth with T1D

*ACR ≥ (30 g albumin/mg creatinine)  All p>0.4 vs. NHW

Maahs et al., *Diab Care* 30(10):2593-2598, 2007
Prevalence of Diabetic Retinopathy Among Youth with T1D: Pilot Study

Mayer-Davis et al., *Diabetic Med* 29(9):1148-1152, 2012

Average duration 6.8 years

Any Retinopathy = 17% (n=222)
## Complications by Diabetes Duration in adults with T1D

Type 1 Diabetes Exchange

<table>
<thead>
<tr>
<th>Complication</th>
<th>&lt;20 yrs (n=1554)</th>
<th>20-&lt;40 yrs (n=2269)</th>
<th>≥40 yrs (n=817)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for Retinopathy(a)</td>
<td>2.9%</td>
<td>19%</td>
<td>36%</td>
</tr>
<tr>
<td>Nephropathy(b)</td>
<td>5.8%</td>
<td>16%</td>
<td>25%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6.2%</td>
<td>16%</td>
<td>29%</td>
</tr>
<tr>
<td>Myocardial Infarction (MI)</td>
<td>1.0%</td>
<td>1.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.3%</td>
<td>0.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Coronary Artery Disease, no MI</td>
<td>2.2%</td>
<td>6.7%</td>
<td>23%</td>
</tr>
</tbody>
</table>

\(a\)Known laser, injection therapy, or vitrectomy in either eye

\(b\)Micro or macroalbuminuria, renal failure (dialysis or post-kidney transplant)

Weinstock, RS, ADA 2012
Trends in childhood-onset T1D: Mortality and life expectancy

**Alleghany County, PA**

All cause mortality / 100,000/ yr

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>1965-69</th>
<th>1970-74</th>
<th>1975-79</th>
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</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>800</td>
<td>676</td>
<td>531</td>
</tr>
</tbody>
</table>

**Pittsburgh, PA EDC**

Life expectancy (yrs) by birth cohort

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>1950-64</th>
<th>1965-80</th>
<th>1965-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td>53.4</td>
<td>68.8</td>
<td>67.1</td>
</tr>
</tbody>
</table>

Secrest et al., Diabetes, 59, 3216, 2010

Miller et al., Diabetes, 61, 2987, 2012
Conclusions

- Increasing numbers of youth with T1D, especially among minorities
- T1D now more difficult to diagnose due to increasing obesity, especially among minorities – diabetes autoantibodies are needed
- High burden of risk factors for future complications, worse in minority youth with T1D
- Subclinical complications present at young age, increasing with age and diabetes duration
- Limited data on complications & mortality in contemporary, diverse cohorts – major research need
- Shifts suggest that higher costs and greater societal burden are very likely in the next 20-30 years
Overview of Natural History of Type 1 Diabetes: Lessons for Staging

Mark Atkinson, PhD
The Departments of Pathology and Pediatrics
The University of Florida
Classic Model of Type 1 Diabetes Pathogenesis

Eisenbarth, NEJM 1986
Natural History Biomarkers Derived from the Classic Model of T1D Pathogenesis

![Diagram of T1D pathology with key stages: Genetic Predisposition, Autoantibodies, Glucose Tolerance, Beta cell mass, Age (years+), etc.]

Eisenbarth, NEJM 1986
Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

1. Precipitating events might occur in utero
2. Genetic predisposition probably the key driver or linkage to immune abnormalities
3. Beyond precipitating, environment might influence entire natural history
4. Although overall loss of β cells is potentially linear, it could show a relapsing or remitting pattern
5. Presence of two or more islet autoantibodies might represent asymptomatic type 1 diabetes
6. Increasing glucose excursions as individual approaches symptomatic onset
7. Some patients produce low concentrations of C-peptide long after onset
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Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
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Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Biomarkers to Refine Type 1 Diabetes Staging

- **Patient Stratification**
  - Distinguish healthy, at-risk from not at-risk

- **Heterogeneity of T1D disease**
  - Distinguish healthy, at-risk from pre-symptomatic diabetes

- **Stratification & Response to Specific Therapy**
  - Define “Degree” of Disease
  - Quantify functional beta cell mass
  - Detect on-going autoimmunity and beta-cell regeneration

---

- **Disease Staging**
  - Pre-Symptomatic
  - At Risk
  - Recent Onset
  - Established Diabetes

- **Beta Cell Mass**
  - 100% at Risk
  - 0% Established Diabetes

---

**Time**
Practical Evolution of Biomarkers for Type 1 Diabetes

“Something is Wrong”
- Genetic Susceptibility
- Autoantibodies
- Declining Metabolic Status

“This is What is Wrong”
- Mechanistic Insights that Guide:
  - Disease State
  - Pathogenesis

“This is How we will Respond to the Wrong”
- Improved Prediction
- Therapies for Prevention/Cure
- Better Treatment Modalities
Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Potential “Future” Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Maternal Factors

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Precipitating Events Might Begin In-Utero

- Born to diabetic fathers vs. mothers
- Diabetic mother diagnosed less than 8 years of age vs later age
- First born
- Increased maternal enterovirus infections
- ABO incompatibility
- Increasing maternal age at delivery
- Season of delivery
- Early cessation of breast feeding
Potential “Future” Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

1. Precipitating events might occur in utero
2. Genetic predisposition probably the key driver or linkage to immune abnormalities
(Precipitating event)
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8. β-cell mass not always zero in longstanding patients

Genotype/Phenotype	Epigenetics

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Genetic Linkage to T1D

The Evolution of Type 1 Diabetes Genetics

1980’s to Present – Biomarkers that Define Risk for Type 1 Diabetes

Note: Too many; Too little OR; Notions of GWAS “Bust”

Future – Genotype/Phenotype Studies in Type 1 Diabetes

Concannon P, Rich S, Nepom GT
Genetic Linkage to T1D Abnormalities

**Compartment #1**
Bone Marrow / Thymus Contributions
- Defective thymic selection (positive/negative)
- Potential for self-antigens presented in incorrect register of MHC binding
- Influence of Aire and VNTR expression in thymus
- Mobilopathy
- Intrinsic defects in lymphocyte precursors
- Inherited genetic susceptibility
- “Niche” for persistent autoreactive lymphocytes

**Compartment #2**
Immune Contributions
- Defective immune regulation (e.g., Teff resistance to Treg, Treg abnormalities, etc.)
- Chronic APC activation
- Autoantibody production
- Self-antigens with low affinity epitopes recognized by low avidity autoreactive TCRs
- Failure to resolve autoreactive immune memory
- Abnormal cytokine production/regulation
- Cellular trafficking/adhesion defects

**Compartment #3**
Beta Cell Contributions
- Expression of Class I MHC
- Production of cytokines and chemokines
- Free radical sensitivity
- Sensitivity to stress protein response
- Potential to present high quantities of self-antigen via Class II MHC
- Susceptibility to viral tropism/inability to resolve inflammation
- Limited replication potential
- Rate of immune destruction influenced by metabolic activity

Atkinson, Eisenbarth, Michaels 2014 Lancet
Potential “Future” Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Beyond Triggering, Environment Likely Contributes throughout Natural History of T1D
Potential “Future” Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Not All Humans are “Created Equal”, in terms of Beta Cell Mass nor in Their Ability to Replicate Beta Cells

$r = 0.02$

$p = 0.9$
Smaller Pancreas in the Natural History of T1D

Campbell-Thompson, JAMA. 2012
Beta Cell Mass may be a Key Risk Factor in Time of Development of Symptomatic T1D – A Current Hypothesis

Battalia M. & Atkinson M. (submitted)
Are Early Stages of T1D Associated with a Relapsing/Remitting Pattern?

Type 1 Diabetes – Vitiligo of the Pancreas?

• Sporadic islet destruction (lobular)
• Perhaps a disease of relapse/remission?

Pancreatic pathology suggests:

Eisenbarth, Diabetes 2010; Atkinson, nPOD Unpub.

Insulin and Ki67 Staining

CD45 Glucagon PanTail

6197-06
Are Early Stages of T1D Associated with a Relapsing/Remitting Pattern?

Von Herrath, 2014, Diabetologia
Beta Cell Destruction may be Homicide, Suicide, or Failed Mechanisms of Self-Protection

Disease Progression

- Glut 2 Receptor
- Empty Beta cells
- mRNA abberancies
- ER Stress
- UPR

Potential “Future” Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Multiple Autoantibodies are Associated with Faster Progression to Symptomatic T1D in T1D Relatives

Numbers 1–4 are number of autoantibodies at screening. Curves indicate occurrence of type 1 diabetes over follow-up (n = 29,035). DPT-1 = Diabetes Prevention Trial–Type 1

Potential “Future” Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Increased Glucose Intolerance (Dysglycemia) with Loss of Functional Beta Cell Mass

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Rising HbA1c Can Precede Symptomatic T1D

Stene et al DAISY. Pediatr Diab 2006
Potential “Future” Biomarkers Derived from Current Model for Improved Staging of Type 1 Diabetes

Maternal Factors  Epigenetics  Genotype/Phenotype

- Pancreatic Volume
- Genetic predisposition
- (Precipitating event)
- 1. Precipitating events might occur in utero
- 2. Genetic predisposition probably the key driver or linkage to immune abnormalities
- 3. Beyond precipitating, environment might influence entire natural history
- Inflammatory Signatures
- Micro RNAs
- Overt immunological abnormalities
- Normal insulin release
- Progressive loss of insulin release
- Glucose normal
- Overt diabetes
- C-peptide present
- No C-peptide
- CGM
- Markers of B Cell Death
- Improved C-Peptide Assays
- Beta Cell Imaging

1. Precipitating events might occur in utero
2. Genetic predisposition probably the key driver or linkage to immune abnormalities
3. Beyond precipitating, environment might influence entire natural history
5. Presence of two or more islet autoantibodies might represent asymptomatic type 1 diabetes
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4. Although overall loss of β cells is potentially linear, it could show a relapsing or remitting pattern

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Overview of Natural History of Type 1 Diabetes: Lessons for Staging

Thank You
Assessment of T1D Risk in Newborns

Marian Rewers, MD, PhD
Barbara Davis Center for Childhood Diabetes
University of Colorado
## Risk of Type 1 Diabetes by Age 20 Years

<table>
<thead>
<tr>
<th>Category</th>
<th>T1 DM risk by age 20 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>1:250</td>
</tr>
<tr>
<td>Offspring of women with T1D</td>
<td>1:50</td>
</tr>
<tr>
<td>Offspring of men with T1D Siblings</td>
<td>1:15</td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>1:3</td>
</tr>
<tr>
<td>No family history of T1D HLA-DR3/4,DQB1*0302 genotype</td>
<td>1:15</td>
</tr>
</tbody>
</table>
Prediction of T1D under age 30 years in the U.S. (n= 25,000/yr)

Cases per year

- All T1D cases
- T1D in 1st degree relatives

0.4% of the general population

PPV <5%

Se <10%

Age (Yrs)

0-4 5-9 10-14 15-19 20-24 25-29
Genome-wide Associations in T1D

Concannon et al, NEJM 2009
Genetic markers and the Risk of T1D
Adjusting for sex, ethnicity, family history of T1D

- **HLA-DR3/4, DQ8**
- **PTPN22 R620W**
- **INS -23Hph1**
- **CTLA-4 T17A**
- **IFIH1 rs1990760**
- **SLC30A8 R325W**
- **UBASH3A rs11203203**
- **CCR5 Δ32**
- **HLA-DPB1*0402**
- **HLA-DRB1*0403**

DAISY, 2011
### DAISY Strip (18 BSA-SSO probes) for **DRB1** and **DQB1**

#### Epitopes:

<table>
<thead>
<tr>
<th>DAISY Strip (18 BSA-SSO probes) for DRB1 and DQB1</th>
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#### DR Type

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<table>
<thead>
<tr>
<th>IDDM risk by age 20</th>
<th>HLA-DR</th>
<th>DQB1</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>High 1:15</td>
<td>3/4</td>
<td>0201/0302</td>
<td>2.4</td>
</tr>
<tr>
<td>Moderate 1:60-1:200</td>
<td>4/x</td>
<td>0302/</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>4/4</td>
<td>0302/</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3/3</td>
<td>0201/0201</td>
<td>1.4</td>
</tr>
<tr>
<td>Average 1:300</td>
<td>3/x</td>
<td>0201/</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>0201/not 0302</td>
<td>1.0</td>
</tr>
<tr>
<td>Lower than 1:300</td>
<td>4/x, 4/4</td>
<td>/not 0302</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>2/x</td>
<td>0602</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td>others</td>
<td></td>
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</tbody>
</table>
DAISY Newborn HLA Screening for Genetically High-risk Children

~10% of children with the highest T1D risk

<table>
<thead>
<tr>
<th>Genotype frequency</th>
<th>General Population</th>
<th>T1D &lt;15 yrs of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-301-302 / 3-501-201</td>
<td>2.3%</td>
<td>32.7%</td>
</tr>
<tr>
<td>4-301-302 / 4-301-*</td>
<td>3.0%</td>
<td>10.4%</td>
</tr>
<tr>
<td>4-301-302 / 8-401-402</td>
<td>1.5%</td>
<td>7.0%</td>
</tr>
<tr>
<td>4-301-302 / 1-101-501</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>4-301-302 / 9-301-303</td>
<td>0.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>3-501-201 / 3-501-201</td>
<td>1.3%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10.7%</strong></td>
<td><strong>61.2%</strong></td>
</tr>
</tbody>
</table>
Islet Autoantibodies

1st generation assays

2nd generation RIA, ELISA

3rd generation ECL ElectroChemiLuminescent

ICA

ZnT8A

IA-2A

GADA

mIAA

Insulin autoantibodies

ECL-IA-2A  ECL-GADA  ECL-IAA
Clinical Centers

★ Colorado
★ Finland
★ Georgia/Florida
★ Germany
★ Sweden
★ Washington

★ Data Coordinating Center, Tampa, FL
TEDDY Newborn HLA Screening for Genetically High-risk Children 2004-2010

<table>
<thead>
<tr>
<th>General Population n= 418,709</th>
<th>First-Degree Relatives n= 6,417</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1-DQA1-DQB1/DRB1-DQA1-DQB1</td>
<td>DRB1-DQA1-DQB1/DRB1-DQA1-DQB1</td>
</tr>
<tr>
<td>4-301-302 / 3-501-201</td>
<td>4-301-302 / 3-501-201</td>
</tr>
<tr>
<td>4-301-302 / 4-301-302</td>
<td>4-301-302 / 4-301-302</td>
</tr>
<tr>
<td>4-301-302 / 8-401-402</td>
<td>4-301-302 / 8-401-402</td>
</tr>
<tr>
<td>3-501-201 / 3-501-201</td>
<td>4-301-302 / 1-101-501</td>
</tr>
<tr>
<td>4-301-302 / 13-102-604</td>
<td>4-301-302 / 13-102-604</td>
</tr>
<tr>
<td>4-301-302 / 9-301-303</td>
<td>3-501-201 / 3-501-201</td>
</tr>
<tr>
<td>3-501-201 / 9-301-303</td>
<td>3-501-201 / 9-301-303</td>
</tr>
</tbody>
</table>

5% of the population 50% of T1D cases

22% of the FDRs 70% of T1D cases
Development of islet autoimmunity and T1D among TEDDY participants

N=8677

August 2014

1st Primary endpoint

Confirmed persistent islet autoimmunity:
IAA, GADA, IA-2A or ZnT8A at least twice 3 months apart & confirmed in the second laboratory

2nd Primary endpoint

Clinical diabetes
ADA / WHO

n=603
n=191

Expected by age 15 y:
n~800
n~400
Clinic visits every 3 months (including ab+ children older than 4):

**Blood** for: GADA, IAA, IA-2A, ZnT8; DNA, mRNA, infectious agents, HbA1c, PBMC, erythrocytes, storage plasma/serum;

**Nasal** swabs, tap water, toenail clippings, and **salivary** cortisol.

**urine** samples; DNA from FDRs

**Interviews:** medications, immunizations, infections, family history;

**Diet:** maternal pregnancy diet; child’s 24 hr recall, 3 day FFQ;

**Physical activity** quest., accelerometer;

Negative life events, parental anxiety, depression.
Summary:

• No simple ‘genetic screening’ for T1D
  – Polygenic disease
  – HLA region explains >50% of familiar clustering
  – HLA-DR,DQ-based newborn screening is 50-65% sensitive, but positive predictive value only 2-3%
  – Non-HLA markers may slightly improve prediction
  – Ethnic differences in HLA markers of T1D risk

• Islet autoantibody screening in combination with HLA pre-screening:
  – Sensitivity: ~60%
  – Specificity: ~35% (x2); up to ~50% (x3-4 tests)
Should gene-environment interactions be accounted in T1D risk prediction?

- HLA-DR3, DQB1*0201
- DR4, DQB1*0302
- DPB1
- MICA
- UBD

- HLA-DR3, DQB1*0201
- DR4, DQB1*0302
- DPB1
- MICA
- UBD

- INS
- PTPN2
- UBASH3A
- IL2RA

- IFIH1
- PTPN22
- VDR
- CYP27B1
- PPARG2

- IL-4R
- cow's milk
- CRS
- enterovirus

- vit. D
- cereal
- cow's milk
- Ω-3 FA

M Rewers 2013
Extreme Risk for Diabetic Autoimmunity in DR3/4 Siblings

- % Autoantibody Positive
  - Siblings at high risk (Share 2)
  - Siblings at low risk (Share 0 or 1)

- % With Diabetes

Aly et al, PNAS 2006
Questions?

Barbara Davis Center for Childhood Diabetes
www.bardaviscenter.org
marian.rewers@ucdenver.edu
Public Health Screening for Early Type 1 Diabetes

Anette-Gabriele Ziegler
Helmholtz Zentrum München
Klinikum rechts der Isar
Technische Universität München
Children with Multiple Islet Autoantibodies Progress to Symptomatic Diabetes

Also in General Population Children
5- and 10-Year Risk of Progression to Symptomatic T1D with Multiple Islet Autoantibodies ≤ Age 5 Years is 51% and 75%

And the Lifetime Risk Approaches 100%

George Eisenbarth „The clock to T1D has started when islet antibodies are first detected”. Paradigm shift for staging of type 1 diabetes before clinical onset
Is Early Staging of T1D on a Public Health Level Feasible?

When?
What test?
Expected prevalence?
Expected sensitivity?
Multiple Islet Autoantibodies Are Detected Early in Life

Incidence of islet autoantibodies in cases that become multiple Abs amongst unselected FDRs

Ziegler, Bonifacio, Diabetologia 2012
Also In The General Population

Finland

TEDDY
(Finland, Sweden, Germany, USA)

Parikka et al, 2012

TEDDY study, IDS, 2013
Age 3 and 4 years may be an optimal age for early staging

Incidence of islet autoantibodies in cases that become multiple Abs amongst unselected FDRs

Compulsory Preventive Check-ups in Germany
U1-U6 age 0 to 12 months
U7 age 21-24 months
U7a age 34-36 month
U8 age 46-48 month
U9 age 60-64 month
U10 age 7-8 years
U11 age 9-10 years

2/3 of multiples islet autoantibodies occur before age 4 years (JAMA).

11 % of youth T1D is before age 3 years

Ziegler, Diabetologia 2012
Validated Assay for Early Staging
(screening for multiple islet autoantibodies)

Capillary blood (200 µl) for combined measurement ELISA (RSR Ltd.):

- GAD65 antibody
- IA-2 antibody
- ZnT8 antibody

Positive (1%)

Test IAA, GADA, IA-2A, ZnT8A in single assays*

*(Bonifacio et al., J Clin Endocrinol Metab 2010; Achenbach et al., Diabetologia 2009; Ziegler et al., Diabetes 1999).
Assay Performance of ELISA (RSR Ltd) for Combined Detection of GADA and IA2A (DASP/IASP workshops 2012)
Estimated Prevalence of Multiple Islet Autoantibodies in General Population

Estimated prevalence at age 3-4 years:

0.3% or 300 children from 100,000 screened

Basis for estimate:

0.45% of children with diabetes between 3 and 20 years
2/3 are positive for multiple islet autoantibodies by age 3-4

0.0045*100,000*0.667 = 300
Estimated Progression to Symptomatic T1D
Risk is persistently around 11% per year

Diabetes incidence per 100 per year

Year of follow-up after seroconversion

Follow-up (years)

Number Diabetes-free
Design of Model Project Diabetes 2015

**Information for pediatricians and parents:**
Flyer, Public announcements, Bavarian Pediatric Convention

**Screening:** offered to all children in Bavaria at their U7a (age 3 years) und U8 (age 4 years) check-ups
Offered to 200,000 children in total (100,000 at U7a and 100,000 at U8)

**Inclusion criteria:**
- Children living in Bavaria
- Written informed consent of one parent
- Capillary blood 200 μl
- Questionnaire (1 page)

**Estimated participation rate:** 50% at U7a; 50% at U8
100,000 children (50,000 at U7a; 50,000 at U8)
- Microvette and questionnaire
- Shipment to IDF, HMGU
- Islet autoantibody testing

**Islet autoantibody negative:** Ca. 99,000 children
**Positive in screening ELISA:** Ca. 1,000 children

- Separate measurement of IAA, GADA, IA2A, and ZnT8 by RBA in remaining serum
- Negative or positive for only one antibody
- Multiple islet autoantibodies: Ca 330

**Offer participation in Natural history and Prevention studies**

- No written report will be sent
- Confirmation sample requested (contact with pediatrician)

- Separate measurement of IAA, GADA, IA2A, and ZnT8 by RBA
- Ca 300: OGTT, HbA1c, Education and teaching, stress assessment, Check-up plan, comprehension test
Impact of Early Staging of T1D on a Public Health Level

- prevent diabetic ketoacidosis on a population level, reducing family burden and health care cost
- help set new standards for early diagnosis of T1D and teaching
- assess the impact of environmental determinants for pre-T1D for which a population based approach is most suitable (air pollution, population density)
- provide a validation cohort for findings from other cohorts such as TEDDY
- provide an unprecedented opportunity to design secondary prevention studies to prevent insulin dependence on a broad population based level and with relatively rapid recruitment capacity.
Summary:
Population Based Screening for Multiple Islet Autoantibodies at Age 3 or 4 years

100,000 children screened ➔ 500 with T1D by age 20 years

300 detected positive

133 (44%) would develop T1D prior to age 8 – 9 years
(5 years of follow-up)
206 (69%) would develop T1D prior to age 13 – 14 years
(10 years of follow-up)
255 (85%) would develop T1D prior to age 20 years
(= 50% of all cases developing T1D before age 20 years)
Dimelli and DPV Diabetes Register in Bavaria

>95% of all diabetes cases before age 20 years in Bavaria are captured by Dimelli or DPV registers

Allows:
• validation of estimates
• Comparisons between screened and followed vs non-screened and non followed diabetes cases
What about children with single islet autoantibodies?

Certain single Ab positives have a risk

What about children with single islet autoantibodies?

Certain single Ab positives have a risk

Follow-up after seroconversion

- Multiple at seroconversion (SC)
- IAA at SC, multiple later
- GADA at SC, multiple later
- High risk single (high affinity, trunc GAD, ELISA GAD, IA2)
- Low risk single (low affinity or wrong epitope)

% with symptomatic t1D

defining the early stages of type 1 diabetes T1D
Pre-selection by genetic testing?
Feature Ranking of Type 1 Diabetes Susceptibility Genes For Improved Risk Prediction

HLA + 40 non-HLA SNPs \[\rightarrow\] multivariable logistic regression and Bayesian feature selection

<table>
<thead>
<tr>
<th>T1DGC cohort (training cohort)</th>
<th>Training cohort</th>
<th>German validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n=4574</td>
<td>Controls n=1207</td>
<td>Patients n=765</td>
</tr>
</tbody>
</table>

Winkler, Krumsiek, Diabetologia 2014
Prediction of type 1 diabetes using HLA class II genotypes and 40 minor susceptibility genes

Higher discrimination when SNP genotyping of the 40 minor susceptibility genes was added to the HLA risk model (p value of increase: $2.6 \times 10^{-11}$)

<table>
<thead>
<tr>
<th>Model</th>
<th>T1DGC cohort (Training)</th>
<th>10-fold cross-validation</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA</td>
<td>0.82</td>
<td>0.81</td>
<td>0.78</td>
</tr>
<tr>
<td>HLA + 40 SNPs</td>
<td>0.87</td>
<td>0.87</td>
<td>0.84</td>
</tr>
</tbody>
</table>

AUC
Selection of a reduced set of SNPs with comparable prediction quality

Feature ranking

Top 10

Top 10 model: *HLA, PTPN22, INS, IL2R, ERBB3, ORMDL3, BACH2, IL27, GLIS3, RNLS*
Population Based Screening
Application of the Top 10 Model

10 SNP set: HLA, PTPN22, INS, IL2R, ERBB3, ORMDL3, BACH2, IL27, GLIS3, RNLS

Screening with the top 10 model

100,000 children screened
(99,500 no diabetes, 500 develop diabetes)

At threshold selecting 0.5% of controls (risk score of >0.97)
618 selected

120 (19.5%) would develop T1D prior to age 20 years

24% of all cases

72 will develop islet antibodies by age 3 years

defining the early stages of type 1 diabetes
Population Based Screening
Application of the Top 10 Model

10 SNP set: HLA, PTPN22, INS, IL2R, ERBB3, ORMDL3, BACH2, IL27, GLIS3, RNLS

**Screening with the top 10 model**

100,000 children screened
(99,500 no diabetes, 500 develop diabetes)

At threshold selecting 2.5% of controls (risk score of >0.95)
2654 selected

167 (6.3%) would develop T1D prior to age 20 years

33% of all cases

100 will develop islet antibodies by age 3 years
Helmholtz Zentrum Munich /Forschergruppe Diabetes eV
Peter Achenbach
Christiane Winkler
Andreas Beyerlein
Florian Haupt
Ramona Puff
Jan Krumsiek
Fabian Theis

Center for Regenerative Therapies Dresden
Ezio Bonifacio
Anne Eugster

Collaborators
Marian Rewers and DAISY team
Olli Simell and DIPP team
John Todd
Screening for Risk of T1D:
Relatives of Individuals with T1D

Carla Greenbaum
Diabetes TrialNet and Benaroya Research Institute
Agenda

- Rational for testing relatives
- Historical perspective: Diabetes Prevention Trial
  - Primary results
  - Key information about Natural History of Disease
- Current screening for risk: Diabetes TrialNet
  - Scope of screening effort
  - Algorithm to determine risk
  - Clinical Trial Enrollment
Why Test Relatives?

- Comprehensive “genetic” screening
  - Assumption that T1D genes are enriched in families, both those we know and don’t know
- Knowledge and experience about living with T1D
  - Assumption that family members are most committed to finding a cure and prevention strategy
- Several decades of robust data about the pre-clinical natural history of disease
- Relative risk of disease ~15X higher than risk in general population
RATIONALE FOR TESTING RELATIVES

T1D non-HLA Genetic Associations
Why NOT test relatives?

~85-90% of those who will get T1D do NOT have a relative with T1D
RATIONALE FOR TESTING RELATIVES

Families with diabetes

\[ \sim 5\% \]

15x

Families without diabetes

0.3%

100 Newly diagnosed patients with type 1 diabetes

10

90
HISTORICAL PERSPECTIVE: DIABETES PREVENTION TRIAL

Diabetes Prevention Trial (DPT-1)

- AIM: Identify relatives at risk for T1D to enroll in one of two randomized clinical trials testing:
  - Can parenteral insulin delay or present the onset of T1D in those at high risk of disease?
  - Can oral insulin delay or prevent the onset of T1D in those at intermediate risk of disease?
Begun in early 1990’s using “state of the art” antibody testing
- Islet cell antibodies (ICA)
- Insulin autoantibodies (IAA)

Tested 103,391 relatives over 8 years for presence of ICA and IAA → Antibody positive: 3,483

N= 339 (high 5 year risk >50%) randomized in Parenteral Insulin Trial and N=372 (intermediate 5 year risk 25-50%) randomized in Oral Insulin Trial

Primary Results: Neither Parenteral or Oral Insulin delayed or prevented onset of disease
HISTORICAL PERSPECTIVE: DIABETES PREVENTION TRIAL

Diabetes Prevention Trial (DPT-1)

- Increased knowledge despite negative trials: Laying the groundwork for future studies
5-year risk estimates

ICA+, IAA+ relatives
ICA+ relatives

<25%
25-50%
>50%

LOW
INTERMEDIATE
HIGH

ICA+, IAA+ relatives with low beta cell function or IGT

HISTORICAL PERSPECTIVE: DIABETES PREVENTION TRIAL: KEY INFORMATION ABOUT NATURAL HISTORY
5-year risk estimates vs actual results

ICA+, IAA+ relatives

ICA+ relatives

25-50%

35%

>50%

60%

ICA+, IAA+ relatives with low beta cell function or IGT
TYPE 1 DIABETES TRIALNET
TrialNet Goals

- Delay, prevent, or modify the course of T1D
  - Explore new therapies in:
    - Secondary prevention – antibody-positive relatives “at risk” of T1D
    - Primary prevention – high genetic risk infants
    - New-onset T1D

- Further define epidemiology, natural history, and risk factors of T1D
- Advance translational science to lay groundwork for future generations of trials and future clinical use
CURRENT SCREENING FOR RISK: DIABETES TRIALNET: SCOPE OF SCREENING EFFORT

NORTH AMERICA

FINLAND + Sweden

UNITED KINGDOM

AUSTRALIA

ITALY + Germany
PREVENTION
TrialNet Prevention Studies

TrialNet Pathway to Prevention Study

- TrialNet Oral Insulin Study
- TrialNet Abatacept Study
- TrialNet Teplizumab Study
CURRENT SCREENING FOR RISK: DIABETES TRIALNET: ALGORITHM TO DETERMINE RISK

1\textsuperscript{st} and 2\textsuperscript{nd} degree relatives

Screening sample to measure autoantibodies

0 antibodies (~95%)

Rescreen annually until age 18

1 antibody

Baseline monitoring
HbA1c, OGTT, Antibodies

≥ 2 antibodies OR Abnormal glucose tolerance OR Risk score ≥ 6.5 OR HbA1c ≥ 6.0%

≥ 2 antibodies OR HbA1c ≥ 6.0% OR Hba1c ≥ 0.5% increase from last test

No

Annual Monitoring
HbA1c, Antibodies

Yes

Semi-annual monitoring
HbA1c, OGTT, Antibodies
TNNHS: Cumulative Ab seroconversion by annual rescreen number by age (A) and cost of rescreening by age at initial screen (B).
Consensus Conference

Exploring the Drug Development Pathway for Type 1 Diabetes in the Pediatric Population

Co-Chairs: Carla Greenbaum, MD and Diane Wherrett, MD, FRCPC

STATEMENT OF NEED

Despite medical advances, type 1 diabetes (T1D) remains a significant burden on individuals with T1D and their families; thus, there is need for disease modifying therapy. While autoimmune diabetes occurs in all age groups, emerging data highlights important differences in pathophysiology and clinical course according to age at diagnosis. Consequently, the effectiveness of disease modifying treatments is expected to be different between children and adults. Understanding the development and regulatory pathways for T1D disease modifying therapies according to age will enable industry, academia, funders, advocacy organizations, and regulators to collectively translate new science to clinical care.

OBJECTIVES

The objectives for this Consensus Conference are to characterize the fundamental differences in T1D between children and adults and to propose a thoughtful approach for developing disease modifying therapeutics in children before or after the onset of clinical T1D; encompassing a development and regulatory pathway considering both safety and efficacy. It is the intent that the Consensus Conference Report will be published in Diabetes Care and notable pediatric journals.

WHEN:
January 14, 2015
8:30 am - 4 pm EST

LOCATION:
Hilton Mark Center
5000 Seminary Road
Alexandria, VA 22311

OPEN REGISTRATION:
To register, please contact Sonya Pendleton at spendleton@diabetes.org or 703.549.1500 ext. 2311 by December 1, 2014.
## TrialNet Pathway to Prevention

<table>
<thead>
<tr>
<th>Group</th>
<th>Five-year risk of T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ab+</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>1 ab+, NGT</td>
<td>3%</td>
</tr>
<tr>
<td>≥ 2ab+, NGT</td>
<td>35%</td>
</tr>
<tr>
<td>≥ 2ab+, AGT (dysglycemia)</td>
<td>75-80%</td>
</tr>
</tbody>
</table>
# TrialNet Pathway to Prevention

<table>
<thead>
<tr>
<th>Group</th>
<th>Five-year risk of T1D</th>
<th>Prevention Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ab+</td>
<td>&lt; 1%</td>
<td>Not currently eligible; rescreen until age 18</td>
</tr>
<tr>
<td>1 ab+, NGT</td>
<td>3%</td>
<td>Not currently eligible; annual monitoring</td>
</tr>
</tbody>
</table>
# TrialNet Pathway to Prevention

<table>
<thead>
<tr>
<th>Group</th>
<th>Five-year risk of T1D</th>
<th>Prevention Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2ab+, NGT</td>
<td>35%</td>
<td>Oral Insulin (if mIAA+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abatacept</td>
</tr>
<tr>
<td>≥ 2ab+, AGT (dysglyceremia)</td>
<td>75-80%</td>
<td>Teplizumab</td>
</tr>
</tbody>
</table>
Screening for Risk of T1D: Relatives of Individuals with T1D

Thank You
Predicting Rate of Progression to Type 1 Diabetes

Jeffrey Krischer
University of South Florida
Why predict rates of progression?

- Identifying a population with elevated rate of progression allows the test of interventions to alter disease progression.

Need to identify **high risk** population to justify **high risk** interventions.

- It is easier to measure the effect of an intervention in a higher risk population.
But we already know how to predict who is susceptible to get T1D

- Genetics: Human leukocyte antigen (HLA) class II genes
- Age: 4-7 and 10-14 years
- Family History
- Geography
Biomarkers

- Immunologic: ICA, GAD, IA2, IA, ZnT8

- Metabolic: Insulin, glucose, C-peptide, HbA1c

The appearance of these markers, either singly or in combination predicts the risk and the rate of T1D development.
The problems of sensitivity and specificity

- Markers that are more specific, $P(D|M)$, are generally less sensitive: $P(M|D)$ is low.

- Is this a generalizability problem?
The problem of sensitivity and specificity

- Markers that are more specific, $P(D|M)$, are often less frequent: $P(M)$ is low.

$$P(D|M) = \frac{P(M|D) P(D)}{P(M)}$$

as $P(D|M) \rightarrow 1$, then $P(M) \rightarrow P(D)$

- This is a cost problem requiring screening large numbers.
An Example from TEDDY

Human leukocyte antigen eligibility for First Degree Relatives (FDR) and General Population (GP) newborns:

<table>
<thead>
<tr>
<th>Haplotype genotypes</th>
<th>Abbreviation</th>
<th>FDR</th>
<th>GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR4-DQA1<em>030X-DQB1</em>0302/DR3-DQA1<em>0501-DQB1</em>0201</td>
<td>DR3/4</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DR4-DQA1<em>030X-DQB1</em>0302/DR4-DQA1<em>030X-DQB1</em>0302</td>
<td>DR4/4</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DR4-DQA1<em>030X-DQB1</em>0302/DR8-DQA1<em>0401-DQB1</em>0402</td>
<td>DR4/8</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DR3-DQA1<em>0501-DQB1</em>0201/DR3-DQA1<em>0501-DQB1</em>0201</td>
<td>DR3/3</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DR4-DQA1<em>030X-DQB1</em>0302/DR4-DQA1<em>030X-DQB1</em>020X</td>
<td>DR4/4b</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>DR4-DQA1<em>030X-DQB1</em>0302/DR1-DQA1<em>0101-DQB1</em>0501</td>
<td>DR4/1</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>
An Example from TEDDY

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR 3/4 or DR 4/4</td>
<td>97%</td>
<td>39%</td>
</tr>
<tr>
<td>9 TEDDY Genotypes (FDR)</td>
<td>90%</td>
<td>69%</td>
</tr>
<tr>
<td>4 TEDDY Genotypes (GP)</td>
<td>94%</td>
<td>50%</td>
</tr>
</tbody>
</table>
### An Example from TEDDY

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>P(M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR 3/4 or DR 4/4</td>
<td>97%</td>
<td>39%</td>
<td>2.9%</td>
</tr>
<tr>
<td>9 TEDDY Genotypes (FDR)</td>
<td>90%</td>
<td>69%</td>
<td>22%</td>
</tr>
<tr>
<td>4 TEDDY Genotypes (GP)</td>
<td>94%</td>
<td>50%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
## Markers of Diabetes Risk

<table>
<thead>
<tr>
<th>Family history</th>
<th>Risk</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.3%</td>
<td>85%</td>
</tr>
<tr>
<td>Some</td>
<td>3-5%</td>
<td>15%</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple affected</td>
<td>20-50%</td>
<td></td>
</tr>
<tr>
<td>Sib</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Identical Twin</td>
<td>30-70%</td>
<td></td>
</tr>
<tr>
<td>Offspring</td>
<td>3-5%</td>
<td></td>
</tr>
</tbody>
</table>
Immune Markers of Symptomatic Diabetes Risk in First Degree Relatives

5-Year Risk  Prevalence

- Single antibody  <10%  3.1%
- Multiple antibodies  30-50%  2.2%
Even in the presence of other risk markers, age is important. T1D-free curves by age categories among first degree relatives with multiple autoantibodies.
Metabolic Markers of Symptomatic Diabetes Risk in Multiple Antibody Positive, First Degree Relatives

- Abnormal Oral Glucose Tolerance Test

<table>
<thead>
<tr>
<th>5-Year Risk</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>75-80%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
Again, age is a modifying factor.
# HbA1c vs. T1D

## Is HbA1c 6.5% a good threshold?

<table>
<thead>
<tr>
<th></th>
<th>T1D+ by OGTT</th>
<th>T1D- by OGTT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;=6.5</td>
<td>32</td>
<td>11</td>
<td>23.7%</td>
<td>97.6%</td>
<td>0.74</td>
</tr>
<tr>
<td>HbA1c &lt;6.5</td>
<td>103</td>
<td>441</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>135</td>
<td>452</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=587

## Type 1 Diabetes TrialNet

<table>
<thead>
<tr>
<th></th>
<th>T1D+ by OGTT</th>
<th>T1D- by OGTT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;=6.5</td>
<td>18</td>
<td>2</td>
<td>26.4%</td>
<td>99.7%</td>
<td>0.90</td>
</tr>
<tr>
<td>HbA1c &lt;6.5</td>
<td>50</td>
<td>664</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>666</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=734

## TRIGR

<table>
<thead>
<tr>
<th></th>
<th>T1D+ by OGTT or Physician</th>
<th>T1D- by OGTT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;=6.5</td>
<td>5</td>
<td>0</td>
<td>38.5%</td>
<td>100.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>HbA1c &lt;6.5</td>
<td>8</td>
<td>413</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>413</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=426*  

* Control arm only
## HbA1c vs. T1D

### Is HbA1c 5.7% a good threshold?

<table>
<thead>
<tr>
<th></th>
<th>T1D+ by OGTT</th>
<th>T1D- by OGTT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;=5.7</td>
<td>99</td>
<td>209</td>
<td>73.3%</td>
<td>53.8%</td>
<td>0.32</td>
</tr>
<tr>
<td>HbA1c &lt;5.7</td>
<td>36</td>
<td>243</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>135</td>
<td>452</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=587

<table>
<thead>
<tr>
<th></th>
<th>T1D+ by OGTT or Physician</th>
<th>T1D- by OGTT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;=5.7</td>
<td>6</td>
<td>46</td>
<td>64.7%</td>
<td>90.5%</td>
<td>0.41</td>
</tr>
<tr>
<td>HbA1c &lt;5.7</td>
<td>7</td>
<td>367</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>413</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=734

<table>
<thead>
<tr>
<th></th>
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<th>T1D- by OGTT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;=5.7</td>
<td>44</td>
<td>63</td>
<td>46.2%</td>
<td>88.9%</td>
<td>0.12</td>
</tr>
<tr>
<td>HbA1c &lt;5.7</td>
<td>24</td>
<td>603</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>666</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=426*  

* Control arm only
A confession.....

- Much of the data available on risk markers has been obtained from studies of first degree relatives.
- Much of that data is available only on antibody positive individuals.
- Much of that data is from cross-sectional studies.
- So it is natural to ask, what about combinations of markers?
DPTRS risk score derived from DPT-1 by Sosenko et al.

DPTRS = \(1.569 \times \text{log(bmi)} - 0.056 \times \text{age} + 0.00813 \times \text{sumglu}^\uparrow + 0.476 \times \text{log(fastcpep)} - 0.0848 \times \text{total c-peptide}^\uparrow\)

\(^\uparrow\) sum from 30 to 120 minutes/100 from an OGTT

<table>
<thead>
<tr>
<th>DPTRS</th>
<th>T1D Risk</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.50</td>
<td>0.09</td>
<td>56%</td>
</tr>
<tr>
<td>≥ 6.50 and ≤ 7.50</td>
<td>0.40</td>
<td>27%</td>
</tr>
<tr>
<td>&gt; 7.50</td>
<td>0.77</td>
<td>18%</td>
</tr>
</tbody>
</table>
DPTRS risk score derived from DPT-1 by Sosenko et al.

The DPTRS is a continuous measure of risk and exhibits the same trade-off between sensitivity and specificity.
Combinations of Diabetes Risk Markers: Recursive partitioning

Subjects in Control Groups only (N=356), IVGTT Measurements Excluded

- Node 1: $\text{glu2h, } p < 0.001$
  - $\leq 127$
  - $> 127$

- Node 2: $\text{randage, } p = 0.003$
  - $\leq 19.825$
  - $> 19.825$

- Node 3: $\text{basehb, } p = 0.015$
  - $\leq 5.1$
  - $> 5.1$

- Node 5: $\text{peacpcep, } p = 0.001$
  - $\leq 4.6$
  - $> 4.6$

- Node 4 (n = 64)
- Node 6 (n = 78)
- Node 7 (n = 83)
- Node 8 (n = 41)
- Node 9 (n = 90)
Recursive Partitioning Risk Groups

Low risk: (Five-year risk=2.5%)
  Two hour glucose <=127 mg/Dl and age >19.8 years

Moderate Risk: (Five-year risk= 29%)
  Two hour glucose <=127 mg/Dl and age <19.8 years and either (HbA1c>5.1% and peak C-peptide>4.6 nmol/L) or HbA1c<=5.1%.

High risk: (Five-year risk: 74.8%)
  Two hour glucose >127 mg/Dl or
  (Two hour glucose <=127 mg/Dl and age <19.8 years and HbA1c>5.1% and peak C-peptide<=4.6 nmol/L)
RPA classification is based on 2-hour glucose (127 mg/DL), age at baseline (19.825 years), HbA1c (5.1%) and Peak C–peptide (4.6) derived from DPT-1.
Relative Comparison of the DPTRS and RPA Analyses

**DPTRS**

<table>
<thead>
<tr>
<th>T1D Risk</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.50</td>
<td>0.09</td>
</tr>
<tr>
<td>≥ 6.50 and ≤ 7.50</td>
<td>0.40</td>
</tr>
<tr>
<td>&gt; 7.50</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**RPA classification**

<table>
<thead>
<tr>
<th>T1D Risk</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>0.03</td>
</tr>
<tr>
<td>Medium Risk</td>
<td>0.29</td>
</tr>
<tr>
<td>High Risk</td>
<td>0.75</td>
</tr>
</tbody>
</table>
The Effect of Time
Diabetes Risk Markers

- Risk based upon baseline or screening
The Effect of Time
Diabetes Risk Markers

- Diabetes risk is not static
The Effect of Time
Diabetes Risk Markers

- What we observe is consequence of cross-sectional screening
Future Directions

- Identify markers with higher specificity and prevalence
  - Limited by underlying incidence of T1D

- Markers that are more homogeneous – $p=.5$ has highest s.d., moving to the extremes reduces sample size.

- Markers that are easier to screen for – e.g. HbA1c vs. IGT
Future Directions

- Expanding/testing generalizability to the larger cohort of individuals that will develop T1D
  - If an intervention works/doesn’t work in a particular risk group what does this tell us about whether it will work in another risk group? E.g., anti-CD3 or antigen therapy going in either direction.
Where we are

- Use risk markers as eligibility criteria for prevention studies
  - 1 ab – none yet
  - 2 ab – oral insulin, abatacept
  - IGT – anti CD-3
- Now beginning to use risk markers as surrogate end points
  - abatacept
The end

Grateful acknowledgements:
The DPT-1 Study Group
The TrialNet Study Group
Use of risk detection and staging for design of prevention clinical trials

Carla Greenbaum
Diabetes TrialNet and Benaroya Research Institute
Agenda

- Current Prevention Trials: Rationale, planning parameters
  - Oral Insulin
  - Abatacept
  - Teplizumab

- Additional Planned Prevention Trials: Rationale, planning parameters
  - Silent Diabetes

- Newer Considerations
  - Other intermediate risk parameters
  - Risk beyond 5 years
    - Islet autoimmunity as a disease
    - Islet autoimmunity prevention trial
## TrialNet Pathway to Prevention

<table>
<thead>
<tr>
<th>Group</th>
<th>Five-year risk of T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ab+</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>1 ab+, NGT</td>
<td>3%</td>
</tr>
<tr>
<td>≥ 2 ab+, NGT</td>
<td>35%</td>
</tr>
<tr>
<td>≥ 2 ab+, AGT (dysglycemia)</td>
<td>75-80%</td>
</tr>
</tbody>
</table>
Current TrialNet Prevention Protocol
Considerations

• Population to be included
• Primary outcome
• Planning parameters
• Choice of Intervention
• Current status
• Summary
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
ORAL INSULIN PREVENTION TRIAL
Oral Insulin Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- 5-year risk of T1D: 35%
- Relative with T1D
- mIAA+ and at least one other antibody
- Normal Glucose Tolerance
Oral Insulin Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Primary stratum
  - mIAA+, ICA+, NGT, nl insulin secretion*
  - mIAA+, ICA512ab+, GAD65ab+, NGT, nl FPIR

- Other stratum
  - Same antibodies, NGT, below threshold FPIR
  - mIAA+, ICA512ab+ OR GADab+; NGT, nl FPIR
  - mIAA+, ICA512ab+ OR GADab+; NGT, below threshold FPIR

*above threshold first phase insulin release (FPIR)
35% 5-year risk in those with 2 or more antibodies and normal glucose tolerance
Oral Insulin Prevention Trial

• Why mIAA+?
  – Original insulin autoantibody assay (IAA) used in Diabetes Prevention Trial.
  – Post-hoc analysis of that trial identified that those with high levels of IAA had an apparent benefit of treatment: 4-year delay in diabetes
  – Next generation of insulin autoantibody assay (mIAA); only included those with post-hoc benefit
HISTORICAL PERSPECTIVE: DIABETES PREVENTION TRIAL: KEY INFORMATION ABOUT NATURAL HISTORY

A Subset with IAA Confirmed > 80 nU/ml
Suggested Potential 4.5-5-year Delay of T1D

Survival Distribution Function

Years Followed

P-Value = 0.015
(Log Rank Test)

Number at Risk

Treated

Control

Oral Insulin
Oral Placebo

Diabetes Care 2005; 28:1068-76
Delay in T1D was Most Evident in Subjects with Baseline IAA ≥ 300: Up to 10 years

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

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

Ann NY Acad Sci 2009; 1150:190-196
Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

Development of T1D (ADA criteria)
Two of the following on separate days
- OGTT on two separate days*
  - Fasting ≥ 126 mg/dl
  - 2 hour ≥ 200 mg/dl
OR
- Clear symptoms and random glucose ≥ 200 mg/dl

*~2/3 of those diagnosed with T1D was from two OGTTs
Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Maximum Information Trial: subjects are recruited and followed until the required amount of information is achieved.
  - If 50/year...duration of ~8 years

- Effect size: 40% risk reduction
- Power: 85%; one-sided test
Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Safety
  - Dose ranging test study in healthy humans – no effect on glycemia
  - Prior exposure DPT-1 oral insulin trial, same population and age range – no associated AE

- Efficacy
  - Animal models suggestive of efficacy
  - Primary endpoint DPT-1 negative, post hoc analysis of high IAA subgroup suggestive of significant effect (4 to 10 year delay in onset)
Oral Insulin Prevention Trial

- Study start 2007
- N=436 randomized; – 304 to primary stratum
- No therapy related AEs
Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- High benefit if efficacy demonstrated
- Strong pre-clinical and clinical data with above average likelihood of efficacy
- Minimal risk to all age groups
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Oral Insulin Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
ABATACEPT PREVENTION TRIAL
Abatacept Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- 5-year risk of T1D: 35%
- Relative with T1D
- 2 or more ab+, not mIAA
- Normal Glucose Tolerance
35% 5-year risk in those with 2 or more antibodies and normal glucose tolerance
Abatacept Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

Development of Abnormal glucose tolerance or T1D

**Abnormal Glucose Tolerance**
- OGTT on two separate days*
  - Fasting ≥ 110 mg/dl and <126 mg/dl
  - 2 hour ≥ 140 mg/dl and <200 mg/dl
  - 30, 60, 90 min ≥ 200 mg/dl

*~2/3 of those diagnosed with T1D was from two OGTTs

OR

**Diabetes**
- T1D by ADA criteria
Abatacept Prevention Trial

- Effect size: 40% risk reduction
- Power: 80%; two-sided test at 0.05
- N= 206; randomized 1:1
- Estimated enrollment 50/year; recruitment 4 years – outcome at 6 years

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary
Abatacept Prevention Trial

- Safety
  - FDA approved in kids (age 6+) and adults for Adult RA, Juvenile RA; >60,000 total person/years of exposure
  - Prior exposure in 112 T1D new onset subjects ages 6-45; no significant treatment related AE
  - Expected AEs = infusion reactions; infections; not expected with limited duration of therapy (12 months)

- Efficacy
  - Animal models suggestive of efficacy
  - New onset trial with positive result
Abatacept (CTLA4-Ig) (co-stimulation blockade)

Treatment period

Figure 2: Population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group. The estimates are from the ANCOVA model adjusting for age, sex, baseline value of C-peptide, and treatment assignment. Y-axis is on a log(y + 1) scale. Error bars show 95% CIs. AUC = area under the curve.

Moran, Lancet 2012
**Abatacept Prevention Trial**

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Study start 2013
- N=65 randomized;
- No therapy related AEs
Abatacept Prevention Trial

- High benefit if efficacy demonstrated
- Strong clinical data in other diseases and initial data in T1D with above average likelihood of efficacy
- Slightly greater than minimal risk to all age groups
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Teplizumab Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- 5-year risk of T1D: 78%;
  - Varies by age
- Relative with T1D
- 2 or more ab+, Abnormal glucose Tolerance
Risk of T1D in ab+ relatives with abnormal glucose tolerance

75-80% 5-year risk with Impaired glucose tolerance
Teplizumab Prevention Trial

- Development of T1D (ADA criteria)
  Two of the following on separate days
  - OGTT on two separate days*
    - Fasting $\geq 126$ mg/dl
    - 2 hour $\geq 200$ mg/dl
  OR
  - Clear symptoms and random glucose $\geq 200$ mg/dl

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary
Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Effect size: 60% risk reduction
- Power: 80%; two-sided test at 0.05
- N= 71; randomized 1:1
- Complete recruitment within 3 more years and follow for an additional 4 years
Teplizumab Prevention Trial

- **Population to be included**
- **Primary outcome**
- **Planning parameters**
- **Choice of Intervention**
- **Current status**
- **Summary**

- **Safety**
  - Prior exposure in >600 T1D subjects ages 8-45;
  - Expected AEs = transient lymphopenia, cytokine release syndrome, infections, rash

- **Efficacy**
  - Animal models suggestive of efficacy
  - New onset trials with positive result (and one with negative result overall)
Teplizumab (hOKT3γ1 (ala-ala): AbATE

Change in C-peptide over time (primary endpoint)*

*Solid lines connect mean values; stars denote medians. Bars represent 25th and 75th percentile.

Herold, Lancet Endo
Teplizumab Prevention Trial

- Study start 2011
- N=41 randomized;
Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- High benefit if efficacy demonstrated
- Clinical data in T1D suggestive of above average likelihood of efficacy
- Greater than minimal risk to all age groups
Proposed Stages of Type 1 Diabetes

**Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D**
Multiple T1D-associated islet autoantibodies with normal glycemic control

**Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D**
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Teplizumab Prevention Trial

**Stage 3: Symptomatic T1D**
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
PLANNING STAGES; NEW PREVENTION TRIAL
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control
- Oral Insulin Prevention Trial
- Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia
- Teplizumab Prevention Trial

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Progression to Type 1 diabetes: DPT-1

- Asymptomatic "silent" diabetes
- Overt Diabetes

- NGT
- IGT
- IFG

Fasting glucose mg/dl

2 hour glucose mg/dl

100 126

140 200
**New therapy Prevention Trial**

- Population to be included
  - Risk estimate
  - Entry criteria

- Primary outcome
- Planning parameters
- Choice of Intervention

- OGTT = Diabetes
- HbA1c <6.5%
- No insulin therapy

Kevan Herold, Jeff Krischer
New therapy Prevention Trial

- Population to be included
- Primary outcome

Proportion of participants who revert to non-DM OGTT at 6 months

Kevan Herold, Jeff Krischer
PREVENT ISLET AUTOIMMUNITY
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control
   Oral Insulin Prevention Trial
   Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia
   Teplizumab Prevention Trial

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Risk of T1D with ≥ 2 antibodies does not appear to level off

Babies: multiple antibodies – 85% risk over 15 yrs
Risk and Benefit Considerations

• Current evidence supports the concept that essentially ALL relatives with two or more antibodies will develop clinical diabetes at some time.

• Thus, islet autoimmunity could be considered a disease like hypertension.
What defines a disease to be treated? 
First, give it a name

<table>
<thead>
<tr>
<th></th>
<th>Lab results</th>
<th>Clinical signs and symptoms</th>
<th>Later consequences</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Clinical presentation of hyperglycemia and symptoms</td>
<td>Abnormal HbA1c. Fasting and 2 hour elevated</td>
<td>YES</td>
<td>YES: complications</td>
</tr>
<tr>
<td>2.</td>
<td>&quot;Silent&quot; diabetes</td>
<td>Normal HbA1c, Normal fasting 2 hour ≥ 200</td>
<td>NO</td>
<td>YES: Symptomatic DM</td>
</tr>
<tr>
<td>3.</td>
<td>Abnormal glucose tolerance</td>
<td>Normal HbA1c, Normal fasting 2 hour 140-199</td>
<td>NO</td>
<td>YES: 85% with clinical T1D in 3-5 years</td>
</tr>
<tr>
<td>Disease</td>
<td>Hypertension*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequence within 4-5 years</td>
<td>2.4/100 get coronary heart disease (CAD) and 1.9/100 have stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction (effect size) of treatment</td>
<td>Treating HTN reduces CAD by 16% and stroke by 40% (relative risk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute benefit of treatment</td>
<td>Treating 100 HTN patients prevents 2 people from getting CAD or stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proposed Stages of Type 1 Diabetes

Single T1D-associated islet autoantibody

Prevent Islet Autoimmunity

**Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D**
Multiple T1D-associated islet autoantibodies with normal glycemic control
- Oral Insulin Prevention Trial
- Abatacept Prevention Trial

**Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D**
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia
- Teplizumab Prevention Trial

**Stage 3: Symptomatic T1D**
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
FUTURE THINKING: OTHER ENDPOINTS TO BE EXPLORED
Other potential endpoints?

- 2-hr plasma glucose (mmol/L)
- Glucose sensitivity (pmol·min⁻¹·m⁻²·mM⁻¹)
- Fasting insulin secretion (pmol·min⁻¹·m⁻²)
- Insulin sensitivity (mL·min⁻¹·m⁻²)

Ferrannini et al. Diabetes 2010; 59:679-685
Summary

- **Current Prevention Trials:** Rationale, planning parameters
  - Oral Insulin
  - Abatacept
  - Teplizumab
- **Additional Planned Prevention Trials:** Rationale, planning parameters
  - Silent Diabetes
- **Newer Considerations**
  - Other intermediate risk parameters
  - Risk beyond 5 years
    - Islet autoimmunity as a disease
    - Islet autoimmunity prevention trial
Use of risk detection and staging for design of prevention clinical trials

Thank You
Benefits of Screening/Risk Detection

Desmond Schatz MD
Professor of Pediatrics
University of Florida College of Medicine
We Cannot Afford to do Nothing
Current Status Quo in 2014 Unacceptable

- Epidemic worldwide
- Increasing burden to individual and society
- No reduction in acute complications
- Potential benefits of improved glycemic control reaching a minority of patients
- Even current `successful’ immune interventions after diagnosis are of questionable translation
Burden of Diabetes in USA (2012)

**Diabetes Rising**

- **Prevalence/Incidence:**
  - 24.9 million Americans (29 million 2014)
  - 6.3 million undiagnosed
  - 1.6 million cases/year
  - 10% type 1 (1/300)
    - 2 million

**Morbidity/Mortality**

- **High rate as evidenced by:**
  - > 246,000 deaths/ > 600/day
  - Shortened life span
  - 2-4x risk MI, stroke
  - 75% hypertensive
  - 47,000 new cases RD/yr
  - 12,000 – 24,000 new cases blindness/yr
  - >82,000 amputations/yr

**Economic Burden**

- **2012 Medical costs:**
  - $245 billion
  - ~ 1/8 health care dollars
  - 27% of all medications ($77 billion of $286 billion)
  - Type 1 disproportionately ↑

Diabetes Care 36: 1033-1046, 2013
Falling Short of Target: HbA1c ≤7.5% by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>HbA1c ≤ 7.5%</th>
<th>Mean A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5 yrs</td>
<td>31%</td>
<td>8.1%</td>
</tr>
<tr>
<td>6–12 yrs</td>
<td>30%</td>
<td>8.2%</td>
</tr>
<tr>
<td>13–17 yrs</td>
<td>25%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

Wood JR et al Diabetes 2013 Jul;36(7):2035-7
Ultimate Goal........
Public Health Screening

Identification of a burdensome disease with the long-term goal of reducing the incidence and mortality for that disease in the subjects being examined.
Does T1D Fulfill Requirements for a Public Health Screening Program?

- Cost/benefit to individual and society: YES
- Disease detected early enough to intervene: YES
- Effective method for identifying those eligible for intervention (sensitivity, specificity, positive predictive value): YES
- Credible intervention must be available, i.e., safe/efficacious: NOT YET

Current `Screening` = Risk Detection
Why Screen in 2014?

- Better understanding of natural history of pre-diabetes
- Gain insight into immunopathogenesis
- Make early diagnosis (decrease morbidity/mortality)
- Identify individuals for prevention trials

Without prevention there will NEVER be a cure....
Screening Enables Earlier “Diagnosis” 

...........Decreases Prevalence of DKA

NEWBORN GENETIC SCREENING

- Barker et al Diabetes Care 27 1399-1404, 2004
- Winkler et al Pediatr Diabetes 13 308-13, 2012
- Larsson et al Diabetes Care 34 2347-52 2011

ISLET AUTOANTIBODY SCREENING

- Greenbaum et al Diabetes 2001; 50:470-476
DKA Morbidity and Mortality = Cerebral Edema

- UK study of DKA (Edge et al 2001 Arch Dis Child)
  - CE: 1.19%, 24% mortality, 35% morbidity. N= 2,940
- Canadian Study – Case:Control (Lawrence et al. J Peds 2005)
  - CE: 0.51% (13 cases). 23% mortality, 15% morbidity
- Swedish Study of DKA (Hanas et al. Diabet Med 2007)
  - CE: 0.68% (2 cases). No mortality, 1 neuro sequelae, n = 292
# Newborn TEDDY Screening Reduces DKA Rates in < 2 year olds

<table>
<thead>
<tr>
<th>Study</th>
<th>Total DKA</th>
<th>Under 2 years</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEDDY</td>
<td>16.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden Registry</td>
<td>39.5%</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>SEARCH</td>
<td>50.0%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Finland Registry</td>
<td>44.8 %</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>German Registry</td>
<td>54%</td>
<td></td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Larsson et al Diabetes Care 34, 2347-52 2011
Newborn TEDDY Screening Reduces DKA Rates in < 5 year olds

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<td>13.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden Registry</td>
<td>16.9%</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>SEARCH</td>
<td>36.4%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Finland Registry</td>
<td>18.7%</td>
<td></td>
<td>&lt;0.11</td>
</tr>
<tr>
<td>German Registry</td>
<td>32.2%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Larsson et al. Diabetes Care 34, 2347-52 2011
Prevention of hospitalization at T1 DM onset

*DAISY, Denver, children, ages 0-11, 1999-2002*

Barker J, et al. Diabetes Care 2004

- all newborns
  - HLA-DR, DQ genetic screening

- children with high-risk genotypes (<10%)
  - follow-up for islet autoantibody
  - anticipatory diabetes education
  - free glucometer, strips
  - referral to a tertiary care center

Hospitalization rate

Denver community cases
n=101

DAISY cases
n=30

p < 0.0001
HbA1c At Diagnosis and First 2 Years in DiPiS

Pediatric Diabetes 2014 doi: 10.1111/pedi.12151
Will earlier diagnosis and onset of insulin replacement therapy in T1D lead to greater preserved functional beta cell mass and decreased insulin dose requirements over time and decreased risk of hypoglycemia and long-term diabetic complications?
DCCT: Impact of Preserved C-Peptide on Hypoglycemia & Retinopathy

C-Peptide at entry

- positive
- negative

Hypoglycemia (seizure/coma)

Retinopathy

CONCLUSION

Screening should be performed in the context of defined research questions

Diabetes Care 37 (Suppl), 1 S18, 2014.

As soon as an intervention is shown to be safe and efficacious in slowing progression of Type 1 diabetes, wide-scale screening should begin.
Biomarkers in the Early Stages of T1D

Åke Lernmark, Professor
Department of Clinical Sciences
Lund University/CRC, Malmö, Sweden
Proposed Stages of Type 1 Diabetes

- **Stage 1: Autoimmunity+/Dysglycemia-/Asymptomatic T1D**
  Multiple T1D-associated islet autoantibodies with normal glycemic control

- **Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D**
  Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

- **Stage 3: Symptomatic T1D**
  Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Current and Candidate Biomarkers: Risk Detection

1: Sensitivity, specificity and predictive value

2: **Metabolomics:** cord blood biomarkers

3: **Systems Biology:** will it define seroconversion to yield new biomarkers

4: **Genomics:** HLA and Non-HLA genetic factors

5: **Autoimmunity:** next generation cellular and humoral tests

6: Summary
Sensitivity and specificity: Will “omics” do the trick?

Screening strategy:  Step One: inclusive – false positives accepted.  
Step Two: selective – false positives ruled out.
METABOLOMICS IN THE CORD BLOOD—LOW PHOSPHOLIPIDS INCREASED THE RISK FOR T1D
CORD BLOOD LIPIDOMICS: Low phospholipids a biomarker for increased T1D risk.

The future of phospholipids as a biomarker:
Recommendations to pregnant mothers to take folic acid should perhaps be complemented also to take phospholipids (lecithin)?
SYSTEMS BIOLOGY – WILL IT DETECT THE TRIGGER OF ISLET AUTOIMMUNITY?
Systems Biology Approach to detect trigger of seroconversion and beyond.

Analyses applicable to:
- Pre-Stage I
- Stage I
- Stage II
GENOMICS— IS THERE ROOM FOR INCREASED SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE?
NEXT GENERATION SEQUENCING (NGS) — DO WE UNDERSTAND ALL VARIANTS? — WHAT IS THE ROLE OF NON-CODING SEQUENCES?

NGS may reduce the frequency of low risk individuals to be randomized to follow up for the risk of either T1D Stage I or II.
Non-HLA genetic factors for type 1 diabetes

Concannon et al. 2009
Combining HLA with non-HLA genotypes for studies of seroconversion, Stage I or Stage II.

**HLA AND 40 SNP**


*Feature selection identified HLA plus nine SNPs from the PTPN22, INS, IL2RA, ERBB3, ORMDL3, BACH2, IL27, GLIS3 and RNLS genes that could achieve similar prediction accuracy as the total SNP set.*

**T1DGC & DAISY**


*Genotyping data sufficient to tag DR3, DR4-DQB1*03:02, CTLA4, and INS were shown to distinguish between subjects with type 1 diabetes and their unaffected siblings.*
AUTOIMMUNITY– WHAT ARE THE NEXT GENERATION CELLULAR AND AUTOANTIBODY BIOMARKERS?
Stage I: Islet Autoantibodies

- Number
- Specificity (IA-2, ZnT8)
- Titer (IAA)
- Affinity (GAD)

**ISLET AUTOANTIBODY STANDARDIZATION PROGRAM**

| 1986 IMMUNOLOGY OF DIABETES WORKSHOPS (IDW) |
| WHO STANDARD: ICA, GADA AND IA-2A (JDF Units) |
| DIABETES AUTOANTIBODY STANDARDIZATION PROGRAM (DASP) |
| NIDDK STANDARD: GADA AND IA-2A (DK UNITS) |
| ISLET AUTOANTIBODY STANDARDIZATION PROGRAM (IASP) |
Stage I and II Biomarker Challenge

- Biomarker that would predict seroconversion:
  - Antigen presentation
  - CD4+ T cell responses
  - CD8+ T cell activation
  - B cell activation – islet autoantibodies

Stage I and II likely differ in cellular responses.

Wong S, Diabetes 83: 1855-1857, 2014
The age distribution for the appearance of the first autoantibody in the group of children with advanced β-cell autoimmunity (left panels) compared with the age distribution for the secondary autoantibodies appearing after the first autoantibody (right panels).

# Possible next generation biomarkers for T1D Stage I and II

## Autoantibody Markers

### High Density Protein Arrays


and others........

## Biomarkers of Islet Autoimmunity

### Reporter Assays

- **Chen et al.** Molecular signature differentiate immune states in Type 1 diabetes families. Diabetes. 2014 Apr 23.

### Gene Expression

**INDIVIDUAL CELLS NEEDED FOR STAGE I AND II**


## Biomarkers of Beta-Cell Function

### Urine C-PEPTIDE

- **Oram et al.** The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. Diabetologia. 57:187-91, 2014.

### Discharge of Intracellular Markers

- Proinsulin, GAD65 and others

- miRNA
Next generation biomarkers for T1D Stage I and II: Will they pass the acid tests?

<table>
<thead>
<tr>
<th>ISLET AUTOANTIBODY STANDARDIZATION PROGRAM</th>
<th>NEWBORN SCREENING STUDIES</th>
<th>FDA REQUIREMENTS OF BIOMARKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986 IMMUNOLOGY OF DIABETES WORKSHOPS (IDW)</td>
<td>DiPP</td>
<td>INTEGRATION OF BIOMARKERS IN GLOBAL DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT</td>
</tr>
<tr>
<td>WHO STANDARD: ICA, GADA AND IA-2A (JDF Units)</td>
<td>BABYDIAB</td>
<td>GENOMIC BIOMARKERS</td>
</tr>
<tr>
<td>DIABETES AUTOANTIBODY STANDARDIZATION PROGRAM (DASP)</td>
<td>DAISY</td>
<td>DIFFERENTIAL GENE EXPRESSION SIGNATURE</td>
</tr>
<tr>
<td>NIDDK STANDARD: GADA AND IA-2A (DK UNITS)</td>
<td>DiPiS</td>
<td>FACILITATE DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT</td>
</tr>
<tr>
<td>ISLET AUTOANTIBODY STANDARDIZATION PROGRAM (IASP)</td>
<td>TEDDY</td>
<td></td>
</tr>
</tbody>
</table>

FDA REQUIREMENTS OF BIOMARKERS:
- INTEGRATION OF BIOMARKERS IN GLOBAL DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT
- GENOMIC BIOMARKERS
- DIFFERENTIAL GENE EXPRESSION SIGNATURE
- FACILITATE DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT
Conclusion: Biomarkers in the Early Stages of T1D

1: Sensitivity, specificity and predictive value should improve above existing assays

2: **Metabolomics**: cord blood biomarkers – low level phospholipids

3: **Systems Biology**: will it yield novel biomarkers of the events leading to seroconversion?

4: **Genomics**: HLA and Non-HLA genetic factors show promise

5: **Autoimmunity**: next generation cellular and humoral tests will be needed for Stage I and II

6: **Stage I and II defined on autoantibodies**: what are the next generation assays?
THANK YOU
Current and Candidate Biomarkers for Staging of Progression in Early Stages of Type 1 Diabetes

Kevan C. Herold, MD

Departments of Immunobiology and Internal Medicine
Yale University
Biomarkers in At-Risk Setting of T1D

- Identification, validation, and use of biomarkers in the at-risk setting to understand the progression of Type 1 diabetes and identify subjects for clinical trials. Biomarker development will need to go hand-in-hand with characterizing the heterogeneity and pathogenesis of the disease that may improve selection of subjects for prevention studies.
Outline

- Current biomarkers of dysglycemia
- Can beta cell stress and beta cell death be detected in at-risk individuals with normal glucose tolerance?
- Analysis of glucose tolerance in the prediabetic period. What accounts for the heterogeneity of progression?
- Can the cellular immune process that leads to T1D be identified?
- What other modalities may be useful for evaluating individuals at risk?
Natural History of Type 1 Diabetes

Beta cell stress, and death

Herold, Vignali, Cooke, Bluestone, NRI, 2013
Dysglycemia in the prediabetes setting:

- **OGTT**
  - 120 min plasma glucose: $\geq 140$ mg/dL ($\geq 7.8$ mmol/L)
  - 30, 60, or 90 min plasma glucose: $>200$ mg/dL ($\geq 11.1$ mmol/L)

- **IVGTT**: FPIR, other

- **Fasting plasma glucose**: $>110$ mg/dL ($\geq 6.1$ mmol/L)

- **HbA1c**
  - Rising - 10% change
  - Absolute level
Patterns of Metabolic Progression to Type 1 Diabetes in the Diabetes Prevention Trial- Type 1

Jay M. Sosenko, MD1  Jerry P. Palmer, MD2  Carla J. Greenbaum, MD3  Jeffrey Mahon, MD4  Catherine Cowie, PhD5  Jeffrey P. Krischer, PhD6  H. Peter Chase, MD7

Diabetes Care 2006; 29:643-649

Glucose and C-Peptide Changes in the Perionset Period of Type 1 Diabetes in the Diabetes Prevention Trial-Type 1

Jay M. Sosenko, MD1  Jerry P. Palmer, MD2  Lisa Rafkin-Mervis, MS, CDE2  Jeffrey P. Krischer, PhD7  David Cuthbertson, MS4  Della Matheson, RN2  Jay S. Skyler, MD1

Diabetes Care 2008; 31:2188-2192

The Metabolic Progression to Type 1 Diabetes as Indicated by Serial Oral Glucose Tolerance Testing in the Diabetes Prevention Trial-Type 1

Jay M. Sosenko,1  Jay S. Skyler,1  Kevan C. Herold,2  Jerry P. Palmer,3 and the Type 1 Diabetes TrialNet and Diabetes Prevention Trial-Type 1 Study Groups

Diabetes 2012; 61:1331-1337
Key features of metabolic progression in individuals at-risk for T1D

- Glucose levels are increasing at least 2 years before dx
- Despite increasing glucose levels, fasting and overall measures of C-peptide change little until 6 mos before dx
- Peak C-peptide is delayed at least 2 years before dx. It occurs even later as diagnosis approaches.
- Although glucose levels increase during

Sosenko et al, Diabetes 2012
C-Peptide AUC Is Relatively Flat for the Period Up to 6 months Prior to Diagnosis

C-peptide AUC from OGTT

Sosenko et al. Diabetes Care 2006; 29:643-649
Functional Beta Cell Mass is Better Preserved in New Onset T1D Adults vs. Children

A: 7.7-12.3 yrs
B: 12.4-14.7 yrs
C: 14.8-21.2 yrs
D: 21.4-46.1 yrs

Model-based estimates of average slopes of AUC C-peptide over time according to age quartiles

. Diabetes 2012;61:2066-2073
-cell Glucose Sensitivity Decreases Earlier than Other Parameters

In progressors 2 hr glucose levels changed little until 0.78 yrs before dx and glucose sensitivity declined significantly beginning 1.45 yrs before dx.

At baseline, insulin sensitivity and insulin secretion were similar in progressors and non-progressors.

Ferrannini et al. Diabetes 2010; 59:679-685
The need for a direct measurement of beta cell killing: Problems with existing approaches

- Glucose and HbA1c levels normal until close to diagnosis (Sosenko et al, Diabetes Care 2006; Sosenko et al, Diabetes 2012)

- Elevated glucose levels may only occur after extreme beta cell loss.

- Autoantibodies do not provide direct information on the pathologic process.

- T-cell assays can differentiate patients with T1D from HC, not all labs can perform these and the relationship between the appearance of these cells and beta cell killing has not been evaluated. (Herold et al, Diabetes 2012)
Rationale for an Assay to Measure Beta Cell Death In-Vivo

- Beta cell function affected by environmental factors
- Beta cell death is a silent event
- Methylation is one epigenetic control mechanism that can affect gene transcription.
- When cells die, they release their DNA into the bloodstream.
- The only source of unmethylated insulin DNA should be dead beta cells. This assay is based on the detection of unmethylated INS DNA in the serum. Two methods have been used: nested PCR (“delta”) and droplet digital PCR.

Akirav PNAS, 2011; Lebastchi Diabetes 2013; Usmani-Brown Endocrinology, 2014
Identification of beta cell death following autologous islet transplants or successful immune therapy

Anti-CD3 (teplizumab) treatment of recent onset T1D

(Lebastchi Diabetes 2013)
Outline

- Current biomarkers of dysglycemia
- Can beta cell stress and beta cell death be detected in at-risk individuals with normal glucose tolerance?
- Analysis of glucose tolerance in the prediabetic period. What accounts for the heterogeneity of progression?
- **Can the cellular immune process that leads to T1D be identified?**
- What other modalities may be useful for evaluating individuals at risk?
Cellular assays: T cell immunoblot and T cell proliferation assays

Sensitivity and specificity of the assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>n</th>
<th>Sensitivity</th>
<th>Composite 95% CI</th>
<th>Specificity</th>
<th>Composite 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell proliferation</td>
<td>52</td>
<td>0.58</td>
<td>0.37–0.79</td>
<td>0.91</td>
<td>0.79–1.0</td>
</tr>
<tr>
<td>Immunoblot</td>
<td>47</td>
<td>0.94</td>
<td>0.83–1.0</td>
<td>0.83</td>
<td>0.69–0.97</td>
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<tr>
<td>GAD65</td>
<td>62</td>
<td>0.74</td>
<td>0.57–0.91</td>
<td>0.85</td>
<td>0.72–0.95</td>
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<tr>
<td>ICA512</td>
<td>62</td>
<td>0.52</td>
<td>0.30–0.74</td>
<td>0.97</td>
<td>0.92–1.0</td>
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</tbody>
</table>

Seyfert-Margolis, Diabetes, 2006
TrialNet Analysis of Immune Cellular Studies

<table>
<thead>
<tr>
<th>Autoantibodies (one or more)</th>
<th>Specimens evaluable</th>
<th>Indeterminant</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Correct classification</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Odds ratio</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Anti-GAD65</td>
<td>296 (99.7)</td>
<td>—</td>
<td>68</td>
<td>98</td>
<td>83</td>
<td>91</td>
<td>84</td>
<td>56.9</td>
<td>&lt;0.0001</td>
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<tr>
<td>Anti-ICA512</td>
<td>296 (99.7)</td>
<td>—</td>
<td>58</td>
<td>99</td>
<td>78</td>
<td>98</td>
<td>76</td>
<td>124.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-ICA</td>
<td>296 (99.7)</td>
<td>—</td>
<td>59</td>
<td>94</td>
<td>76</td>
<td>91</td>
<td>69</td>
<td>22.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cellular immunoblot</td>
<td>122 (68.2)</td>
<td>6 (4.9)</td>
<td>74</td>
<td>88</td>
<td>81</td>
<td>86</td>
<td>77</td>
<td>21.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T-cell proliferation</td>
<td>151 (84.4)</td>
<td>0</td>
<td>60</td>
<td>69</td>
<td>64</td>
<td>66</td>
<td>63</td>
<td>3.36</td>
<td>0.0041</td>
</tr>
<tr>
<td>Tetramer</td>
<td>117 (76.5)</td>
<td>32 (27.4)</td>
<td>46</td>
<td>72</td>
<td>59</td>
<td>63</td>
<td>57</td>
<td>2.10</td>
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<tr>
<td>U.S.-ELISPOT</td>
<td>87 (56.8)</td>
<td>0</td>
<td>35</td>
<td>65</td>
<td>50</td>
<td>51</td>
<td>50</td>
<td>1.09</td>
<td>0.95</td>
</tr>
<tr>
<td>U.K.-ELISPOT</td>
<td>109 (100)</td>
<td>8 (7.3)</td>
<td>61</td>
<td>69</td>
<td>65</td>
<td>66</td>
<td>64</td>
<td>3.44</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

Herold et al, Diabetes 2009
Insulitis May be Visualized by MRI

Imaging beta cell mass with $^{18}$F-fluoropropyl-Dihydrotetrabenazine and PET

Conclusions

- Increased levels of unmethylated $INS$ DNA (reflecting beta cell death) can be detected about 1 ½-2 yrs before the diagnosis of T1D.

- Insulin secretory dysfunction corresponds to episodes of increases in levels of unmethylated $INS$ DNA in at-risk subjects.

- Individuals at very high risk for T1D have elevated levels of unmethylated INS DNA in their serum.

- Insulin secretory dysfunction is the feature that distinguishes individuals who meet diagnostic laboratory criteria of “diabetes” from those who do not.
What else do we need?

- The reason for the delayed insulin secretion is not known. This is associated with an increase in unmethylated INS (beta cell death) but there is a reversible component.

- Additional measures of beta cell stress may identify more frequent episodes that warrant interventions with cellular protective agents.

- The relationship between cellular immune assays and beta cell killing and stress are under investigation.

- Insulitis imaging and quantitative measurement of
Acknowledgements

- Jeff Bluestone
- Eitan Akirav
- Sahar Usmani-Brown
- Michel Ledzet
- Jasmin Lebastchi
- Nicole Sherry
- Jake Kushner
- Craig Beam

Funding

- ITN
- TrialNet
- NIDDK
- NIAID
- JDRF
- Brehm Coalition
- Howalt family
Early Stages of T1D

Richard Insel

JDRF
Scientific Framework of the Workshop

- T1D is a disease continuum that begins prior to symptomatic disease ✓
- Risk of developing T1D can be identified and quantified ✓
- T1D has well-defined, reproducible early stages that reach a point of inevitability of symptomatic T1D ✓
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy ✓
- The ability to screen for risk and stage T1D prior to symptomatic T1D has benefit today, and in the future, will provide a unique opportunity to intervene to delay, and ultimately prevent, the onset of clinical symptoms and life-long insulin dependence ✓
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Proposed Stages of Type 1 Diabetes

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Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Children with Multiple Islet Autoantibodies Progress to Symptomatic Diabetes

Children with Multiple Islet Autoantibodies Progress to Symptomatic Diabetes

Also in General Population Children

![Graph showing the probability of progression to diabetes stratified by study site, with data points for Finland, Colorado, and Germany. The graph includes a table with the number of participants at risk for each location and follow-up period.]

JAMA. 2013;309(23):2473-2479
5- and 10-Year Risk of Progression to Symptomatic T1D with Multiple Islet Autoantibodies ≤ Age 5 Years is 51% and 75%

And the Lifetime Risk Approaches 100%

George Eisenbarth „The clock to T1D has started when islet antibodies are first detected“. Paradigm shift for staging of type 1 diabetes before clinical onset
Estimated Progression to Symptomatic T1D
Risk is persistently around 11% per year
Multiple Islet Autoantibodies Are Detected Early in Life

Incidence of islet autoantibodies in cases that become multiple Abs amongst unselected FDRs

Ziegler, Bonifacio, Diabetologia 2012
Immune Markers of Symptomatic Diabetes Risk in First Degree Relatives

5-Year Risk  Prevalence

- **Single antibody**<br>  <10%  3.1%
- **Multiple antibodies**  30-50%  2.2%
Even in the presence of other risk markers, age is important. T1D-free curves by age categories among first degree relatives with multiple autoantibodies.
What about children with single islet autoantibodies?

Certain single Ab positives have a risk

- Multiple at seroconversion (SC)
- IAA at SC, multiple later
- GADA at SC, multiple later
- High risk single (high affinity, trunc GAD, ELISA GAD, IA2)
- Low risk single (low affinity or wrong epitope)
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

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Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Metabolic Markers of Symptomatic Diabetes Risk in Multiple Antibody Positive, First Degree Relatives

- Abnormal Oral Glucose Tolerance Test

5-Year Risk: 75-80%
Prevalence: 0.7%
Again, age is a modifying factor.
## Early Stages of Type 1 Diabetes: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage #1</th>
<th>Stage #2</th>
<th>Stage #3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autoimmunity + Dysglycemia – Asymptomatic</td>
<td>Autoimmunity + Dysglycemia + Asymptomatic</td>
<td>New Onset Symptomatic T1D</td>
</tr>
<tr>
<td>Diagnostic Criteria</td>
<td>▪ Multiple AutoAbs ▪ No impaired glucose tolerance or impaired fasting glucose</td>
<td>▪ Multiple AutoAbs ▪ Dysglycemia: Impaired Glucose Tolerance and/or Impaired Fasting Glucose• FPG &gt;100 mg/dL • OGGT: 2h PG ≥140mg/dL; 30, 60, 90 min PG ≥200 mg/dL • Random plasma glucose &gt;200 mg/dL • HbA1c &gt;5.7% • Increasing HbA1c</td>
<td>▪ Clinical Symptoms</td>
</tr>
</tbody>
</table>
# Early Stages of Type 1 Diabetes: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage #1</th>
<th>Stage #2</th>
<th>??Stage #2A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autoimmunity + Dysglycemia – Asymptomatic</td>
<td>Autoimmunity + Dysglycemia + Asymptomatic</td>
<td>Autoimmunity + Diabetic IGT +/- Diabetic OGT Asymptomatic</td>
</tr>
</tbody>
</table>

### Diagnostic Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
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<tbody>
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<td></td>
<td>Multiple AutoAbs</td>
</tr>
<tr>
<td></td>
<td>No impaired glucose tolerance or impaired fasting glucose</td>
</tr>
<tr>
<td>Stage #1</td>
<td>Multiple AutoAbs</td>
</tr>
<tr>
<td></td>
<td>Dysglycemia: Impaired Glucose Tolerance and/or Impaired Fasting Glucose</td>
</tr>
<tr>
<td></td>
<td>• FPG &gt;100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• OGGT: 2h PG ≥140mg/dL; 30, 60, 90 min PG &gt;200 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Random plasma glucose &gt;200 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• HbA1c &gt;5.7%</td>
</tr>
<tr>
<td></td>
<td>• Increasing HbA1c</td>
</tr>
<tr>
<td>??Stage #2A</td>
<td>Multiple AutoAbs</td>
</tr>
<tr>
<td></td>
<td>“Diabetic” Impaired Glucose Tolerance and/or Impaired Fasting Glucose</td>
</tr>
<tr>
<td></td>
<td>• FPG ≥126 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• OGGT: 2h PG ≥200mg/dL</td>
</tr>
<tr>
<td></td>
<td>• HbA1c ≥6.5%</td>
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</tbody>
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Early Stages of Type 1 Diabetes: Diagnostic Criteria

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</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
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<td>Diagnostic</td>
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<td>Criteria</td>
<td>Multiple AutoAbs</td>
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<td>Dysglycemia: Impaired Glucose</td>
<td>Clinical Symptoms</td>
</tr>
<tr>
<td></td>
<td>or impaired fasting glucose</td>
<td>Tolerance and/or Impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fasting Glucose</td>
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</tr>
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<td></td>
<td></td>
<td>• FPG &gt;100 mg/dL</td>
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<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increasing HbA1c</td>
<td></td>
</tr>
</tbody>
</table>
Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia−/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control
- Oral Insulin Prevention Trial
- Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia
- Teplizumab Prevention Trial

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
### Early Stages of Type 1 Diabetes: Potential Clinical Trial Endpoints

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage #1</th>
<th>Stage #2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autoimmunity + Dysglycemia – Asymptomatic</td>
<td>Autoimmunity + Dysglycemia + Asymptomatic</td>
</tr>
</tbody>
</table>
|       | • Dysglycemia prevented  
       | • Autoimmunity regulated  
       | • Symptoms delayed, Insulin dependence delayed, prevented |
|       |          | • Dysglycemia reversed  
       |          | • FPG normalized |
|       |          | • IGT fails to progress to IFG |
|       |          | • HbA1c restored to normal levels; Increasing HbA1c reversed |
|       |          | • Autoimmunity regulated |
|       |          | • Symptoms delayed; Insulin dependence delayed, prevented |

**Potential Endpoints of Clinical Trials**
Desired Outcomes of the Workshop

- Provide a new standardized taxonomy and staging approach for human T1D
- Accelerate clinical development of therapies to prevent symptomatic T1D
- Aid design of clinical trials through use of risk profiles, subject stratification, and stage-specific trial endpoints
- Promote precision medicine: Tailoring of optimal therapies to specific individuals at specific stages of T1D
- Provide an approach for the benefit/risk framework in the early stages of T1D