Immunotherapy Trials in Type 1 Diabetes

Peter A. Gottlieb, MD
Barbara Davis Center
University of Colorado Health Sciences Center
Denver, CO

Keystone, CO 7/19/09
Main Points

• Type 1 diabetes is an autoimmune disease.
• It is a predictable disease with different phases.
• Maintaining beta cell function at time of diagnosis is a goal.
• Combination therapy targeting multiple pathways may hold the greatest hope for prevention and cure.
Natural History of Type 1 Diabetes

- **PUTATIVE ENVIRONMENTAL TRIGGER**
  - **CELLULAR (T CELL) AUTOIMMUNITY**
    - HUMORAL AUTOANTIBODIES (ICA, IAA, Anti-GAD65, IA2Ab, etc.)
    - LOSS OF FIRST PHASE INSULIN RESPONSE (IVGTT)
    - GLUCOSE INTOLERANCE (OGTT)

- **BETA CELL MASS**
  - GENETIC PREDISPOSITION
  - INSULITIS BETA CELL INJURY

- **“PRE”-DIABETES**

- **DIABETES**

**TIME**

**CLINICAL ONSET**
TrialNet Sites in North America

+ 117 North American Affiliates
TrialNet International Sites

+ 25 International Affiliates

Melbourne, Australia
Turku, Finland
Malmo, Sweden
Bristol, UK
Milan, Italy
Munich, Germany
TrialNet Natural History Study and Oral Insulin Trial
Enrollment in Natural History Study

March 31, 2008

Number of Participants Enrolled

Study Period

n=60,007

n=54,076

Expected

Enrolled

<table>
<thead>
<tr>
<th>Year</th>
<th>Screenings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>3773</td>
</tr>
<tr>
<td>2005</td>
<td>8995</td>
</tr>
<tr>
<td>2006</td>
<td>12420</td>
</tr>
<tr>
<td>2007</td>
<td>15948</td>
</tr>
</tbody>
</table>
Enrollment in Oral Insulin Study

March 31, 2008

**Subjects Enrolled**

- Expected
- Enrolled

- n = 79
Effects of Oral Insulin in Relatives of Patients With Type 1 Diabetes

The Diabetes Prevention Trial–Type 1

THE DIABETES PREVENTION TRIAL–TYPE 1
STUDY GROUP

Diabetes Care 28:1068–1076, 2005
Oral Tolerance: Mode of Action

Oral Antigen

Regulatory (Th2 / Th3) Lymphocytes Producing Protective Cytokines

Insulin Producing \(\beta\)-cells

Autoimmune Lymphocytes

Inhibition of \(\beta\)-Cell Autoimmunity and Prevention of Diabetes

Protective Cytokines
DPT-1 Oral Study – Time to Diabetes By Treatment

Survival Distribution Function

Years Followed

P- Value= 0.176 (Log Rank Test)

Number at Risk

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 1 2 3 4 5 6 7

STRATA: Oral Insulin Oral Placebo

Diabetes Care 2005; 28:1068-76
DPT-1 Oral Study - Time to Diabetes - By Treatment Subset: IAA Confirmed > 80 nU/ml

Survival Distribution Function

Years Followed

Number at Risk

P- Value = 0.015 (Log Rank Test)

Projected 4.5 – 5 year delay

Treated

Control

STRATA: Oral Insulin Oral Placebo

Diabetes Care 2005; 28:1068-76
Insulin Effect Most Evident in Subjects with Baseline IAA ≥ 300

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

Proportion Free of Diabetes

Years

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

Projected 10 year delay
DPT-1/TrialNet

• 22 papers to date
  – Trial results
  – Genetics particularly HLA region
  – Antibody markers
  – Metabolic abnormalities
  – Prediction
  – Refinement of risk
DPT-1 – Time to Diabetes By Number of Antibodies

Survival Distribution Function

P-Value < 0.001 (Log Rank Test)

Number at Risk

<table>
<thead>
<tr>
<th>Years Followed</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24151</td>
<td>22297</td>
<td>17049</td>
<td>11807</td>
<td>9052</td>
<td>7439</td>
<td>6198</td>
<td>3524</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1718</td>
<td>1401</td>
<td>1045</td>
<td>743</td>
<td>557</td>
<td>457</td>
<td>371</td>
<td>199</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>405</td>
<td>297</td>
<td>229</td>
<td>163</td>
<td>118</td>
<td>91</td>
<td>66</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>378</td>
<td>255</td>
<td>192</td>
<td>130</td>
<td>78</td>
<td>49</td>
<td>31</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td>95</td>
<td>61</td>
<td>40</td>
<td>30</td>
<td>22</td>
<td>16</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

n = 26799
Ongoing Prevention Trials

- **TRIGR** - Casein Hydrolysate – finished recruitment (Cow’s Milk Elimination)
  - finished recruitment

- **NIP** - Nutritional Intervention to Prevent T1D
  - Ongoing since late 2006

- **DIPP** - Nasal Insulin – no effect (Finland)

- **INIT** - IntraNasal Insulin Trial (Australia)

- **PrePoint Study** – Oral Nasal Insulin in genetically high risk subjects (Aug, 2009)

- **TrialNet** – Oral Insulin – 137 subjects, since 4/07

- **TrialNet** – SQ GAD in alum – Summer, 2010

- **TrialNet** – Anti-CD3 and Byetta - Fall, 2009
Ongoing Prevention Trials

- **TRIGR** - Casein Hydrolysate – finished recruitment (Cow’s Milk Elimination)
  - Recruitments finished
- **NIP** - Nutritional Intervention to Prevent T1D
  - Ongoing since late 2006
- **DIPP** - Nasal Insulin – no effect (Finland)
- **INIT** - IntraNasal Insulin Trial (Australia)
- **PrePoint Study** – Oral Nasal Insulin in genetically high risk subjects (Aug, 2009)

- **TrialNet** – Oral Insulin – 137 subjects, since 4/07
- **TrialNet** – SQ GAD in alum – Summer, 2010
- **TrialNet** – Anti-CD3 and Byetta - Fall, 2009
Tertiary Prevention (early in clinical disease)

- Preserve Beta cells
- STOP complications

Clinical onset of disease
Treatment

- Intensive Insulin Therapy
- Antigen specific interventions
- Non-antigen-specific interventions (anti-CD3 monoclonal antibodies)
- Regenerative Therapies
Treatment

- Intensive Insulin Therapy

- **Antigen specific interventions**

- **Non-antigen-specific interventions (anti-CD3 monoclonal antibodies)**

- Regenerative Therapies
BENEFITS OF β-CELL PRESERVATION

DCCT Intensive Therapy Group

3+ Step Retinopathy Progression

Risk Reduction: 58% (CI: 27, 76)  
$p < 0.001$

Non-responders  
Responders

Year of Follow-up

Non-Resp, N: 276  
Respond, N: 138

Diabetes 53: 250-264, 2004
T-cell Activation: Potential Targets

Potential Therapies

- Anti-CD25 mAb
- Sirolimus, Everolimus
- Anti-CD154 mAb
- Interleukin-2
- JAK3 inhibitor
- MPA
- FK778
- Anti-CD52 mAb
- FTY720
- Cyclosporine, Tacrolimus
- Azathioprine
- Costimulation
- CD25
- CD28
- CD154
- PI-3K
- mTOR
- Cell cycle
- NFAT
- AP-1
- NF-κB
- Signal 1
- Signal 2

Antigen Specific Therapy

- Magic bullet Approach
- Targets autoreactive cells
- Generates protective cells
- Spares rest of immune system
- Minimal Toxicity
- Timing and route may be critical to efficacy
Insulin

- Beta Cell Specific
- Predominant T-cell reactivity - islets NOD
- Insulin expressed in lymphoid tissue by dendritic and macrophage-like cells
- Thymic messenger RNA for insulin related to “protective” insulin allele
- Proinsulin expression in thymus prevents NOD diabetes
Core technology: antigen specific immune suppression
DNA plasmid platform
Two plasmid products
- BHT-3009 for MS
- BHT-3021 for Type 1 diabetes
**BHT-3021 MOA**

- **Pancreas**: Insulin pieces and other cell protein fragments taken to lymph nodes.
- **Lymph node**: Autoreactive T cells attack islet cells, causing islet cells to be killed.
BHT-3021 MOA

Pancreas

Islet cells killed

Insulin pieces and other cell protein fragments taken to lymph nodes

Autoreactive T cells attack islet cells

Lymph node

APC

BHT-3021
Bayhill Therapeutics: Phase I

- Pro-Insulin Antigen (BHT) administered as a vaccination
- Double-Blind, Placebo-Controlled, dose finding, randomized (3:1)
- Administered Intramuscularly:
  - 12 weekly shots
  - Participants randomized to control will be treated with BHT medication after first year of follow-up
Bayhill HbA1c

Study Duration

HbA1c (%)

Age:32 DM:2yrs*
Age:26 DM:2yrs*
Age:32 DM:18yrs
Age:31 DM:1yr
Age:39 DM:2yrs*
Age:18 DM:6 mo
Age:35 DM:11 yrs

* = un-blinded; patient received treatment
Bayhill Therapeutics Insulin Use

Units of Insulin/kg

Study Duration

Baseline  Mo 3  Mo 6  Mo 9  Mo 12  Mo 18

* = un-blinded; patient received treatment

- **Age:** 32 DM: 2yrs*
- **Age:** 26 DM: 2yrs*
- **Age:** 32 DM: 18yrs
- **Age:** 31 DM: 1yr
- **Age:** 39 DM: 2yrs*
- **Age:** 28 DM: 6 mo
- **Age:** 18 DM: 6 mo
- **Age:** 35 DM: 11 yrs
- **Age:** 38 DM: 6 mo
C-peptide Preservation by BHT-3021

Mean C-pep (AUC) in pmol/L:

- **PBO**
  - Week 0: n=13
  - Month 6: n=13
  - Month 12: n=4

- **1 mg (n=7)**
  - Week 0
  - Month 6
  - Month 12

(n=6, one pt. withdrew)
C-peptide Preservation by BHT-3021

Mean C-peptide (AUC) across different dosages and time points:
- **PBO**:
  - Week 0: n=13
  - Month 6: n=13
  - Month 12: n=4
- **1 mg (n=7)**:
  - Week 0
  - Month 6
  - Month 12 (n=6, one pt. withdrew)
- **0.3 mg (n=6)**:
  - Week 0
  - Month 6
- **3 mg (n=7)**:
  - Week 0
  - Month 6
- **6 mg (n=8)**:
  - Week 0
  - Month 6 (n=7, one pt. missed visit)
GAD-65 vaccination preserves residual insulin secretion in children and adolescents with recent onset type 1 diabetes; results of a randomized controlled Phase II trial.


Linköping, Sweden
Fasting and Stimulated C-Peptide

Significant difference in Fasting C-peptide after 30 months follow up

Less decline in stimulated C-peptide

A. Change in Fasting C-peptide, Means ± SEM

B. Change in Stim. C-pept. (AUC, MMTT), Means ± SEM

Efficacy and Duration of T1DM

Change in C-peptide (AUC) MMTT, Means ± SEM

A 0-3; B 3-6; C 6-12; D 12-18 months duration

![Graph A](image1.png)

![Graph B](image2.png)

![Graph C](image3.png)

![Graph D](image4.png)
Safety

- No treatment related SAE in any Diamyd study
- No neurologic sequelae
- No injection related problems
GAD: Phase III

• Double-blind, placebo controlled, randomized (2:1)
• Administered subcutaneously:
  – 3 shots, administered once a month for three months
• Eligibility:
  – Within 12 weeks post diagnosis
  – Males & females ages 3-45 yrs* (staggered enrollment; >16 year old first)
  – Weight ≥20 kg
  – Detectable C-peptide
  – Presence of GAD65 auto-antibodies
  – Enrollment – 20 patients July 17, 2009

• GAD combination trial: David Harlan, NIH
  – GAD vaccine +
  – Proton pump inhibitor and DPP4 inhibitor to stimulate islet regeneration
Possible Mechanisms of ATG (Thymo)
What is rationale for Thymo?

• Clinical Studies
  – Transplant
    • “Partial” tolerance in Starzl studies *(Lancet 2003, 361: 1502-10)*
  – Autoimmune conditions, alone or in combination
    • Aplastic anemia
      – 40-70% remission with single course of ATG
    • Diabetes
      – Early ATGAM study in new onset T1DM *(Eisenbarth, 1985)*
        • 4 of 5 required < 0.2 units/kg/d of insulin for 250 days or longer
        • 2 did not require any exogenous insulin for > 8 mos
      – ATG-Fresnius study underway in Europe, promising pilot results *(Saudek et al, 2004 RDS 1: 80-88)*
What is the rationale for Thymo?

**Mechanistic Considerations**

- T-cell depletion, eliminates autoreactive, pathogenic T cells
- Alters function of remaining cells $\rightarrow$ modulation, anergy
- Homeostatic proliferation:
  - Flip in CD4+ : CD8+ ratio
  - May induce regulatory cells, and shift balance towards Th2
    - Preliminary results from J. Williams (Genzyme), Sayegh
- May affect T-cell migration
  - Binds to leukocyte adhesion molecules
- May affect APC function
Is Thymo Safe?

• Well characterized drug, widespread use
  – During and shortly after Thymo administration
    • Cytokine release syndrome
      – Manage with pre-meds, rate of infusion
  – Transient immunosuppression
    • Careful pre-screening
    • EBV negative subjects are excluded
    • Prophylaxis per transplant and HIV guidelines
    • Surveillance, PCR screening

• Expect side effects to be minimized in this study because:
  – Will be using at a modest dose
  – Will not be using with other agents
  – Aside from DM, subjects will be otherwise well
  – Safeguards built into study, with careful surveillance
Interventions in New Onset Diabetes

- **Completed Enrollment**
  - Mycophenolate Mofetil +/- Anti-CD25 (Study Stopped due to lack of efficacy)
  - Anti-CD20 (Rituximab) (2 year end point 8/09)
  - CTLA4-Ig (Abatacept) (completed as of 1/09)
  - Anti-CD3 (ABATE – ITN) (completed as of 4/09)

- **Enrolling**
  - Thymoglobulin (ITN)
  - IL-2 plus Sirolimus – Phase 1 Safety Study (ITN)
  - GAD-Alum

- **Soon to Enroll**
  - Meticulous Metabolic Control
Anti-CD3 Trials in 2009

• **ABATE** – NIH, 2 courses of anti-CD3 at 0 and 12 months, new onset pts within 8 wks, fully enrolled 4/09

• **Protégé** – Macrogenics, 2 courses of anti-CD3 at 0 and 6 months, new onset pts. (Phase 3), 500 patients fully enrolled 6/09 (Protégé Encore in Fall, 2009)

• **TTEDD** – TolRx, Dose finding study in recent onset patients, >18 with detectable c-peptide

• **DEFEND**, Phase 3 – TolRx, new onset patients, >18 years old 105 pts (7/6/09)

• **DELAY** – Anti-CD3 to Recent onset patients 8-35, 4-12 months from diagnosis, still enrolling

• **Anti-CD3 in Prediabetes** – TrialNet/ITN, one course of antibody to high risk prediabetic patients (multiple antibodies and decreased insulin production), Fall 2009
Current Studies

• Proinsulin DNA Vaccine
• GAD Vaccine +/- combination tx
• ATG
• Anti-CD3 Monoclonal Antibodies
• Mesenchymal Stem Cells
Future Studies

- Anti-IL1RA and other IL-1 inhibitors
- Alpha1-antitrypsin (AAT)
- Insulin B chain in IFA
- Anti-CD3 Ab in Prediabetes
- T regulatory cell therapy
- Transduced Dendritic Cells
**Summary**

- Antigen specific therapy trials in new onset subjects are being undertaken.
- Immunomodulatory trials with anti-CD3, other biologics and GAD vaccination are encouraging.
- Level of C-peptide may be an important indicator of potential response.
- Multicenter trials and networks will help us find effective therapies during the next decade.
- Combination therapy targeting multiple pathways may hold the greatest hope for prevention and cure.
Acknowledgements

Laurie Weiner, Lisa Meyers and Debbie Lehr
Ray Gutin, Mary Voelmle, Aaron Michels, Meyer Belzer

• Natural History: Vicky Gage and Pat Burdick
• Oral Insulin: Leah Briggs
• T&B Cell: Rachael Jenison
• AbATE: Amy Wallace
• TTEDD: Susan George
• BHT: Amy Wallace

• CTLA4-Ig: Whitney Kastelic
• ATG: Amy Wallace
• Protégé: Susan George
• GAD: Susan George
• DEFEND: Whitney Kastelic
• DELAY: Whitney Kastelic

And the Denver Type 1 Diabetes Referral Network