Presenter Disclosure Information

Peter A. Gottlieb, MD

Advisor: Takeda, Viacyte

Research Support: Bayhill Therapeutics, Inc. Diamyd, Macrogenics, Novartis, Omni, Pfizer Helmsley Foundation, JDRF, NIH
Main Points

• What have we learned?
• What are we learning about the disease pre- and post-diagnosis?
• How do we put this together?
Lobular Beta Cell Destruction

ALL ISLETS WITH BETA CELLS

ALL ISLETS NO BETA CELLS

nPOD (Atkinson)
Genome-wide Associations in Type 1 Diabetes

Concannon et al NEJM
T1D incidence is rising 3-5% per year

Due to environmental cause(s)

Incidence /100,000/ yr in children aged 0-14
DPT-1 – Time to Diabetes
By Number of Antibodies

P- Value< 0.001
(Log Rank Test)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>24151</th>
<th>22297</th>
<th>17049</th>
<th>11807</th>
<th>9052</th>
<th>7439</th>
<th>6198</th>
<th>3524</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</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>1</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>2</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>3</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>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

n = 26799

Years Followed
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)
- **CLINICAL ONSET**
- **BETA CELL INJURY**
- **“PRE”-DIABETES**
- **DIABETES**

**TIME**

**BETA CELL MASS**

- **GENETIC PREDISPOSITION**
- **INSULITIS**

**PRE-DIABETES**

**DIABETES**
Strategies to prevention and cure

• The balance of autoreactive T cells and regulatory T cells is important to disease development.

• Antigen presentation and innate immunity play a role in the disease process
  – B lymphocytes, Macrophages and Dendritic Cells

• New trials based on these concepts may impact disease progression.
What have we learned?

1980-2001

Slow down Diabetes

• Cyclosporine
• High Dose Insulin

Don’t Work

• Low Dose Insulin (DPT-1)
• Nicotinamide (ENDIT)
• BCG
Effect of Anti-CD3 on MMTT at 12 months


**Monoclonal-Antibody Group**

**Control Group**
Follow-up: Anti-CD3 preservation of C-peptide out to 24 months

Herold, Diabetes, 2005
What have we learned?

2002-2014

Don’t Work

• MMF/DZB
• GAD in Alum
• Canakinumab/Anakinra (Anti-IL-1)
• IL-2/Rapamycin
• Low dose anti-CD3
• ATG (high dose)
What have we learned?

2002-2014

*Slow down Diabetes*

- Anti-CD3
- Oral Insulin (?)
- Anti-CD20 (Rituximab)
- Abatacept (CTLA4-Ig)
- Alefacept (anti-CD2)
- ATG/GCSF (ADA last month)
- Myeloablation with Stem Cells
C-PEPTIDE PRESERVATION

OVER 1 YEAR

2-hour C-peptide AUC

P=0.05
C-PEPTIDE PRESERVATION

OVER 1 YEAR

2-hour C-peptide at baseline

2-hour C-peptide at month 3

2-hour C-peptide at month 6

2-hour C-peptide at month 12
What have we learned?

2002-2014

Maybe Slow down Diabetes

• DiaPep277
• Insulin (DNA vaccine or peptides)
• Etanercept (Anti-TNF)
• AAT
Where are we going?

- Define disease pathways
- Define responders from non-responders
- Tailor trials to fix those pathways
  - Reduce autoreactive cells
  - Increase regulatory cells
  - Reduce inflammation
  - Restore immune balance
  - Improve islet function
Natural History of T1D - How does this data fit in?

Phase 1
Genetic Risk
Ab- Relatives

Phase 2
Environmental Factors
Pre-Clinical Autoimmunity
Failed tolerance
Ab- → Ab+

Phase 3
Clinical Disease
T1D
Ab+ non-progressors
Ab+ → T1D

↓ IL-2 signaling
↑ Teff resistance
↑ Transitional B cells

BCR p-PLCγ

Jane Buckner
Natural History of T1D-
How does this data fit in?

Phase 1
HLA/INS Genetic Risk
Ab- Relatives
Ab- \rightarrow Ab+

Phase 2
Environmental Factors
Pre-Clinical Autoimmunity
Ab+ non-progressors
Ab+ \rightarrow T1D

Phase 3
Clinical Disease
T1D

Virus/nutrients/inflammation

↑IL-1 signature in monocytes/DC’s

IL-2R
↓IL-2 signaling and ↓Treg act.

BCR p-PLCγ

PTPN22

↑Th1 IFN-γ cells

↑Th17 cells

↑Teff resistance

↑Transitional B cells

Loss of anergic B cell population

Adapted from Jane Buckner
Teplizumab (Anti-CD3 mAb) Treatment Preserves C-Peptide Responses in Patients With New-Onset Type 1 Diabetes in a Randomized Controlled Trial

Metabolic and Immunologic Features at Baseline Identify a Subgroup of Responders

Kevan C. Herold,¹ Stephen E. Gitelman,² Mario R. Ehlers,³ Peter A. Gottlieb,⁴ Carla J. Greenbaum,⁵ William Hagopian,⁶ Karen D. Boyle,⁷ Lynette Keyes-Elstein,⁷ Sudeepa Aggarwal,⁸ Deborah Phippard,⁸ Peter H. Sayre,³ James McNamara,³ Jeffrey A. Bluestone,² and the AbATE Study Team⁶
Responder vs. Non-Responder in ABATE Anti-CD3 Trial

Baseline A1c and Insulin Use Define Responder Group for Anti-CD3

Decrease Autoreactive T and B cells

• Anti-CD3 – activated T cells
• Alefacept (Anti-CD2) – T effector memory cells
• Anti-CD20 – B cells
• Abatacept – Decrease Central Memory CD4 T cells
• Anti-IL-6 – T and B cells?
• Anti-CD127R – T effector cells?
• Antigen – Insulin and Small Molecules – T and B cells?
Increase Regulatory Cell Function and Number

- Anti-CD3 – CD8CD25 Treg?
- GCSF? - preserve or increase CD4CD25 Treg
- ATG - decrease
- DZB – decrease
- IL-2/Rapamycin – increased # and function
- Low Dose IL-2
- Non-specific Treg (POC)
- Insulin- or GAD-specific Treg
- Dendritic Cells – induce Treg
- Antigen – IBC/MAS-1, insulin peptides
- Anti-IL6 or Anti-CD127R
Reduce Inflammation

- AAT – multiple cytokines (IL-1)
- Canakinumab/Anakinra (IL-1)
- Etanercept (anti-TNF)
- Anti-IL6
- HDAC inhibitors
- Medium Chain Fatty Acids (Gut/Microbiome->Innate Immunity)
- ‘Probiotic’ with IL-10 gene and proinsulin peptide
Clinical Responders have Decreased IL-1b levels

Gottlieb et al. JCEM, 2014
### Ongoing and Proposed T1D Intervention Trials

<table>
<thead>
<tr>
<th>PreDM</th>
<th>New Onset</th>
<th>Recent Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIGR</td>
<td>Gleevec</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Oral Insulin</td>
<td>AAT</td>
<td>Anti-CD127R</td>
</tr>
<tr>
<td>Abatacept</td>
<td>ATG/GCSF</td>
<td>IBC/MAS-1</td>
</tr>
<tr>
<td>GAD in Alum</td>
<td>Anti-IL6</td>
<td>Anti-CD3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• We have learned a lot
• We are about to learn a whole lot more
• Smaller and smarter trials
• Combination therapy
• Earlier treatment