New targets for prevention of type 1 diabetes

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WEB BOOK: Immunology of Type 1 Diabetes
HTTP://WWW.BARBARADAVISCENTER.ORG
• Board Member/Advisory Panel/Consulting
  Medimmune
• Grants
  Novartis
• Patents
  Electrochemiluminescent Islet Autoantibody Assays
  Therapeutic Targeting anti-Islet T cells
• University Service Center CLIA LAB:
  ZnT8, GAD65, IA-2, and Insulin Autoantibodies
“Type 1A Diabetes”

• Chronic progressive “lobular” autoimmune disease.

• We can predict/diagnose Type 1A diabetes (e.g. autoantibodies to insulin, GAD, IA-2, ZnT8).

• We cannot safely prevent.

• Insulin is primary target NOD mouse and very likely man.

• MHC Trimolecular recognition complex key to pathogenesis and potentially prevention
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- **New Onset Patients**
  - Anti-Islet Autoantibodies
    - ½ Hispanic/African American Children not 1A

- **All type 1A patients**
  - periodic TSH, transglutaminase and 21-OH Abs

21-OH autoantibody positive: Annual ACTH, cortrosyn
Tg+: Biopsy when level >0.5: Diet Rx if + Biopsy
Major Islet Autoantigens

- ICA
- ZnT8
- IA-2 (ICA512BDC)
- GAA (GAD$_{65}$)
- IAA
- Insulin autoantibodies
Progression to Diabetes Among Children Positive for Anti-Islet Autoantibodies

% NOT DIABETIC

YEARS SINCE INITIAL AB+ TEST

1 Ab
2 Ab
3 Ab

Steck et al Diabetes Care 2011
AGE FIRST ISLET AUTOANTIBODY POSITIVE VERSUS AGE ONSET

AGE FIRST Ab POS (YEARS)

AGE ONSET

P = 0.0002
R² = 0.26
N = 48
Mean and initial mIAA levels correlate with years to diabetes (N=47)

Update Steck et al Diabetes Care 2011
GAD65, IA2 and ZnT8 levels do not correlate with years to diabetes

- First Positive GAD Levels (Log10) vs. Time to Diabetes: $P = 0.42$, $r = 0.12$
- Mean GAD Levels (Log10) vs. Time to Diabetes: $P = 0.53$, $r = 0.095$
- First Positive IA2 Levels (Log10) vs. Time to Diabetes: $P = 0.94$, $r = 0.012$
- Mean IA2 Levels (Log10) vs. Time to Diabetes: $P = 0.53$, $r = 0.054$
- First Positive ZnT8 Levels (Log10) vs. Time to Diabetes: $P = 0.67$, $r = 0.063$
- Mean ZnT8 Levels (Log10) vs. Time to Diabetes: $P = 0.47$, $r = 0.11$
Estimated age of onset according to age of first Ab+ and mean log mIAA

diabetes predicted age=2.62-1.91*\log(\text{meanIAA})+0.77*\text{agefirstAb+}

Update Steck et al Diabetes Care 2011
DASP 2010 IAA Lab-Reported Sensitivity and Specificity with Kits (140 Samples)

ELECTROCHEMILUMINESCENCE (ECL-IAA)

MSD COUNTER

% Sensitivity

% Specificity

In-house RIAs
MSD Assay
RIA Kits
RIA Kit
ELISA Kits

Current MSD-IAA Assay with acid treatment

Yu et al Diabetes 2012
nPOD 6052-02 Tail: 12 yo 1 year diabetes
-Lobular Pseudoatrophy Islets

Glucagon/anti-CD3 Staining

Insulin and Ki67 Staining
Brief Status Report Prevention Trials

- Antigen Specific Prevention
- Intensive Insulin Therapy
- Immunosuppression/Immunomodulatory
Oral Tolerance: Mode of Action

Oral Antigen

Regulatory (Th2) Lymphocytes Producing Protective Cytokines

Protective Cytokines

Inhibition of β-Cell Autoimmunity & Diabetes Prevention

Insulin Producing β-cells

Autoimmune Lymphocytes
DPT-1 Oral Study – Time to Diabetes By Treatment

Survival Distribution Function

Number at Risk

Years Followed

STRATA:
Oral Insulin
Oral Placebo

Oral Insulin
Oral Placebo

P-Value = 0.176
(Log Rank Test)

Diabetes Care 2005; 28:1068-76
ORAL Insulin TO INDUCE MUCOSAL “TOLERANCE”

Effect Most Evident in Subjects with IAA>300

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

Tertiary Prevention (early in clinical disease)

- Beta cell function
- Time

- 100%
- 20%

Preserve Beta cells
STOP complications
Clinical onset of disease
Intensive Insulin Therapy

Continuous Glucose Monitoring Systems

Continuous Subcutaneous Insulin Infusion

Insulins
Effect of Intensive vs Conventional Therapy on β-Cell Function

N = 303 With 1 – 5 y duration and C-Peptide 0.2 – 0.5 pmol/mL

Risk Reduction 57% (CI: 39, 71%)  P < 0.0001

Number of patients in each treatment group who were evaluated

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Herold et al
Anti-CD3 in new onset T1DM

Also Transient Protection: Anti-CD20, CTLA4-Ig


*A p<0.02
Where Next?

- Build on current successful trials (combination Rx?) to extend, and with luck, permanently arrest beta cell destruction.
- For the long-term utilize knowledge of the trimolecular complex to develop more specific therapies (remove need for “luck”).
T cell Recognition of Antigen on an APC

Antigen

Endocytosis

APC

MHC II

Peptide

Trimolecular Complex

CD4+ T cell

T Cell Receptor
The Trimolecular Complex

- MHC
- PEPTIDE
- TCR
- INS B:9-23
Identifying a Swarm of T cells Targeting B:9-23 Insulin Peptide?
Mutating One Amino Acid of Insulin Prevents (B16:A) All NOD Diabetes

Crystal Structure of I-A$^g_7$

- ARG(22)
- GLU
- GLY
- CYS
- VAL
- LEU
- LEU
- ALA(14)
Screen, *in silico*, large chemical libraries of drug-like small molecules for their abilities to interact with I-A\(^{g7}\) structural pockets by high-throughput molecular docking.

**Molecular Docking**

**High-Throughput Screening**

No MHC specific compounds identified to date by conventional high throughput screening.

Rapid and economical

Expensive, false positives
Glyphosine in Pocket 9 (amino acids in yellow form p9)
Glyphosine only enhances stimulation of the T-cell hybridoma 8-1.1\(\alpha_1\) when insulin B:9-23 peptide is present.
Early Prevention Study with Glyphosine

% Without Diabetes

Weeks of Age

- Control, n=12
- Glyphosine, n=17

P<0.001
DQ8 Screening with B:9-23 & Clone 5

Pocket 1

Pocket 9
In vivo data - Prevention Study with TATD

Female Jax NOD mice.
Received TATD 20mg/kg/day IP from 4 to 12 weeks of age.
Trialnet/Immune Tolerance Network

NEW ONSET TRIALS

RELATIVES of PATIENTS TYPE 1 DM

1-800-HALT-DM1
TRIMOLECULAR
• Li Zhang
• Aaron Michels
• Maki Nakayama
• John Kappler
• David Ostrov
• Mark Atkinson
• Brian Stadinski

PREDICTION
• Liping Yu
• Andrea Steck
• Kelly Johnson
• Dongmei Miao
• Marian Rewers
• Kathy Barriga
• Pam Fain
• Sunanda Babu