Altering The Course Of Type 1 Diabetes

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• Overview of the challenge
• Prevention efforts
• New onset trials
• Limitations and opportunities
Progression To Type 1 Diabetes

Risk Of Developing Type 1 Diabetes

- General Population: 0.3%
- Sibling: 4%
- Mother: 2-3%
- Father: 6-8%
Genetic Basis Of Type 1 DM

- Complex pattern of genetic transmission, with up to 20 different loci identified
- Half of the genetic risk is from the HLA locus, the region that determines self from non-self
  - High risk genes in 95% of Caucasians with T1DM, but present in 45% of general population (DR3, DR4)
- What about twins?
  - Concordance 33 to 50%, higher when followed long term
Figure 2. The North–South Gradient in the Prevalence of Multiple Sclerosis (Panel A) and the Incidence of Type 1 Diabetes Mellitus (Panel B) in Europe.

Adapted from Kurtzke and Green and Patterson.

Relationship between autoimmunity and infection

**Figure 1.** Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al. In Panel B, data on immune disorders are derived from Swarbrick et al., Dubois et al., Tuomilehto et al., and Pugliatti et al.

Increasing Incidence of T1DM

Incidence /100,000/ yr in children 0-14 yr

Finland, Sweden, Colorado, Germany

Rewers M. Ann NYAS 2008
Has Type 1 Diabetes gone “viral”?
The Hygiene Hypothesis

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

• “Clean living” may increase risk for autoimmune diseases

• Risk is higher in urban than rural settings

• Inverse correlation with immunizations, antibiotic use

• Daycare, other early exposures, lower risk for DM
Stages For Intervention In The Type 1 Diabetes Continuum

Considerations For Selecting Agents For Prevention And New Onset Trials

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

- Mechanism likely to be effective
  - Targets T-cells

- Safety of intervention established

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

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

• Later stages of intervention
  – Greater likelihood of predicting who will get DM
    • Smaller studies conducted over shorter time
  – Later intervention may require more aggressive and potentially toxic agents to have efficacy
Type 1 Diabetes Prevention

- Focus has been on 1st degree relatives, at 10-fold higher risk for T1DM than general population
  - Overall risk for siblings is ~4%
  - Screened > 100,000 first degree relatives in DPT-1

- Ultimately, will need to find means to apply to general population, not just first degree relatives
  - 90% of new onset T1DM occurs in families without proband
Primary Prevention Of Type 1 DM

- **TRIGR:** avoidance of cow’s milk
- **NIP:** omega 3 fatty acids
- **POINT:** insulin antigen
- **BabyDiet:** gluten
- **Vitamin D**

No AutoAbs

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Secondary Prevention Trials For Type 1 DM

> 2 Abs, normal OGTT: 25-50% risk for DM in next 5 yrs

- **Antigen:** Insulin, GAD
- **T cell blockade:** CTLA4 Ig

Oral Tolerance: Mode of Action

Oral Antigen

Regulatory T cells
Protective Cytokines

Inhibition of β-Cell Autoimmunity and Prevention of DM

Insulin Producing β-cells
Autoimmune Lymphocytes
Effect Of Oral Insulin On Progression To T1DM

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

Only subjects with IAA > 80

Oral insulin may delay DM onset ~ 4.5 yrs

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

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

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

Projected 10 year delay

Oral Insulin
Placebo

Control

Treated

Proportion Free of Diabetes

Years Followed

Ann NY Acad Sci 2009; 1150:190-196
Type 1 Diabetes High Risk Prevention

> 2 Abs, abnormal OGTT: >50% risk for DM in next 5 yrs


Anti-CD3 mAb
TrialNet Natural History Study

- **Who is eligible for screening?**
  - Ages 1-45 and immediate family member with DM
  - Ages 1-20 for extended family

- **What is the screening test?**
  - Single blood test for panel of autoantibodies
    - Those who are < 18 and Ab neg can be rescreened yearly

- **What happens if you have 1 or > Abs?**
  - Staging
    - Genetic screen: HLA class II
    - Metabolic screen: Oral glucose tolerance test
  - Surveillance
    - Follow-up every 6-12 months with OGGT
Why Participate In Screening?

• May help the medical community understand diabetes better
• May benefit your family
  - Clarify what chances are of developing diabetes
  - Participants tend to have diagnosis of diabetes much earlier
    • Safer, avoid DKA
    • Benefit to starting insulin sooner $\rightarrow$ prolong honeymoon
  - Eligible for intervention studies
    - Oral insulin, Abatacept, anti-CD3 mAb
• How to get screened?
  - At meeting today
  - On site at UCSF, or many other sites
  - We can do a telephone consent and send out a kit directly to your family for testing in a local Quest lab, or
Type 1 Diabetes - New Onset Trials
The Honeymoon

- By diagnosis, 15-40% of beta cell function remains

- Length of honeymoon varies
  - 10-15% of teens and adults still have clinically significant insulin production > 5 yrs after DM onset (DCCT, 1993)
  - Medalist study: 2/3's with measurable insulin > 50 yrs after dx (King, Diabetes, 2010)
  - Butler studies
  - Rate of beta cell loss correlates with age
    - Younger patients lose beta cells faster

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

• Immunotherapy works
  – Cyclosporine experience from the ’80s
    • Requires continuous immunosuppression
    • Not all respond
    • Potential toxicities
New Onset T1DM Trials
Recently Reported, Underway Or Under Consideration

- MMF / daclizumab
- Anti-CD3
- Anti-thymocyte globulin +/- GCSF, cyclophosphamide
- Anti-CD20
- Glutamate Decarboxylase (GAD)
- CTLA4 Ig
- Rapamycin + IL-2
- IL-1 antagonist
- Atorvastatin
- Alpha 1 anti-trypsin
- Alefacept
- Intensive metabolic control
- Diapep 277
- Sitagliptin + Lansoprazole
- TNF blockade
- Autologous regulatory T cells
- Autologous dendritic cells with AS oligo Rx
- Imatinib (Gleevec)
- IL-6 receptor blockade
- IL-17A blockade
- IL-7 receptor blockade
Pathogenesis Of Type 1 DM

Anti-CD3 mAb
Phase 1/2 Study of Anti-CD3 In Type 1 DM

- A single 14 day course of anti-CD3 therapy will induce tolerance and inhibit further beta cell destruction in patients with new onset Type 1 DM.
Phase 1/2 Study of Anti-CD3 In Type 1 DM

- A single 14 day course of anti-CD3 therapy will induce tolerance and inhibit further beta cell destruction in patients with new onset type 1 DM.

Herold et al. NEJM 2002; Diabetes 2005
Keymeulen et al NEJM 2005
Hypothesis For Phase 2 Study

- 2 courses of anti-CD3 therapy, at baseline and 12 mos, will induce tolerance and inhibit further beta cell destruction in patients with new onset T1DM
AbATE Primary Endpoint

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

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

Herold et al, Diabetes 2013
AbATE Responders vs Non-responders

Change in C-peptide: responders vs. non-responders

*Bars represent 25th and 75th percentile.

Herold et al, Diabetes 2013
Next Steps With Anti-CD3

• Define those most likely to be responders:
  – Children (8-17)
  – Enroll < 6 wks from diagnosis
  – HbA1C < 7.5%
  – Exogenous insulin use <0.4 units/kd/d
  – Less likely to develop anti-drug Abs

• Further new onset anti-CD3 trials
  – Anti-CD3 alone or in combination with other agents
    • Antigen
    • GLP-1 agonists, DPPIV inhibitors

• Anti-CD3 prevention trial
Anti-Thymocyte Globulin
**EXTREME COMBO THERAPY**

**BRAZILIAN COCKTAIL**

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

2. Non-myeloablation
   - Cyclophosphamide
   - ATG

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

4. Prophylaxis / Support
   - Hospitalization
   - Antibiotics

*Slide courtesy of M. Haller*

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

BRAZILIAN COCKTAIL

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

**PARTICIPANTS**

New onset T1D
< 6 week Dx
GAD+

13-31 years
(mean 19.2)

**RESULTS**

20 of 23 became INSULIN FREE > 1 month

12 INSULIN FREE > 14 months (mean 31)

A1c < 7% + C-peptide **INCREASE** at 24 mo

BUT … short and long term concerns

**LOGICAL** to study lower risk components of therapy ... "BRAZIL-LITE"
Deconstructing the Brazilian Cocktail

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
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<tbody>
<tr>
<td>ATG + GCSF + Cyclophosphamide</td>
<td>+++</td>
</tr>
<tr>
<td>ATG</td>
<td>+/-</td>
</tr>
<tr>
<td>G-CSF</td>
<td>-</td>
</tr>
<tr>
<td>ATG + G-CSF</td>
<td>?</td>
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ATG/GCSF Combo Pilot Study
Data Summary

AUC c-peptide

<table>
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<tr>
<th>Months post-treatment</th>
<th>Treated (n=17)</th>
<th>Placebo (n=8)</th>
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<tbody>
<tr>
<td>0</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>1.2</td>
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<tr>
<td>6</td>
<td>1.6</td>
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<tr>
<td>12</td>
<td>1.4</td>
<td>0.8</td>
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\[ p = 0.050 \]
Autoreactive cells

Healthy

Disease

Regulatory T cells
**Human Treg Expansion In Vitro**

**Expansion Curve**

- **Time (d)**
  - 0
  - 5
  - 10
  - 15
- **Cell Number**
  - $3.3 \times 10^4$
  - $1.0 \times 10^6$
  - $3.4 \times 10^7$
  - $1.1 \times 10^9$

**CD4+CD127lo/-CD25+**

- $\alpha$CD3/CD28 beads (1:1 ratio)
- IL-2 (300U/ml)
- **FOXP3 analysis**
- **Functional analysis**

Average FOXP3 at day 14 (range) 95.3 (89.3 to 98.3)

Treg Trial

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

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

• Dose escalation

• Fully enrolled
  – Safe, well tolerated
  – Polish experience
  – Now planning Phase 2 effort
C-peptide AUC Change Over Time: enrolled 3 mos -2 yrs from dx

Cohort 1

Cohort 2

Cohort 3

Cohort 4

Gitelman, ADA 2014
Complexities Of The Autoimmune Response: Multiple Cell Types And Pathways Involved

**Innate Immunity**

- Viruses, endogenous ligands

**Adaptive Immunity**

- TLR3/4, RIG-I, MDA5, other receptors
  - \( \uparrow \) STAT-1, \( \uparrow \) NFκB, \( \uparrow \) IRF3, others (?)
  - \( \uparrow \) JunB

- ER stress
- \( \uparrow \) Apoptotic signaling
- \( \uparrow \) Chemokines, \( \uparrow \) Cytokines
- \( \uparrow \) MHC class I

- Presentation of modified antigens
- \( \uparrow \) Cell death

- Macrophage
  - IFN-α and IFN-β
  - TNF IL-1β

- IFN-γ

- T cell
  - MHC class I

- Dendritic cell
  - Apoptotic β cell

What is Gleevec?
(Imatinib / Glivec, Novartis)

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

• Specific inhibitor of Abl protein TKs
  – Inhibits many other constitutively activated TKs (but not all)
    • PDGF, c-kit, c-fms, Abl-related gene, Lck
Rationale For Gleevec In T1DM

• Initial target for CML, but expanded use
• Role as anti-inflammatory agent
• Affects various arms of immune system
  – May affect T cell trafficking to islets
• Lowers ER stress
  – Decrease in beta cell death, increase in regeneration
• Improves insulin sensitivity

• In autoimmunity, effective in
  – Animal models of autoimmunity
    • In NOD mouse
      – 10 wk treatment AFTER DM leads to lasting remission
  – Case reports and small clinical studies show benefit in autoimmunity
  – Related drug approved for RA treatment
Summary

- T1DM is on the rise
  - Can utilize immune, metabolic, and genetic markers to predict DM risk

- Series of exciting trials to
  - Prevent or delay DM onset
  - Preserve beta cell function in those recently diagnosed

- New onset trials will inform our attempts at DM prevention and transplantation
  - Expanding window of eligibility
    - Studies to 2 yrs or longer from diagnosis

- Gaining insights into how and what we need to accomplish for robust success
  - resetting Teff-Treg balance
Potential Type 1 DM Interventions

Modified from Matthews et al, Clin Exp Immunol 2010
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Help Us Cure Type 1 DM!

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