Altering The Course Of Type 1 Diabetes

UCSF Diabetes Update 4.29.15

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Disclosures

• Sanofi Advisory Board
• DSMB for Novo Nordisk
• Consultant for NeoStem
• Overview of the challenge
• Prevention efforts
• New onset trials
• Limitations and opportunities

Report Card From The Trenches

• Near normal glycemic control prevents or delays complications but...
• Not consistently achieving glycemic goals
  • ~20% of adolescents and 30% of adults reaching expected targets
• Still see burden of long term complications
• Toll on mental health
  • Depression
  • Eating disorders
• Mortality
**Type 1 Diabetes – a progressive disease that develops over years**

Considerations For Selecting Agents For 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

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**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
**Prevention Of Type 1 DM**

- All are large, well conducted trials
- None have shown efficacy

**Primary Prevention Of Type 1 DM**

- No AutoAbs

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

- Oral Insulin
- Placebo

Proportion Free of Diabetes

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

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

Projected 10 year delay

- Control
- Treated

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
- Dysglycemia

Genetic Predisposition

Environmental

Loss of First Phase Insulin Response

β-cell mass

Hyperglycemia

Honeymoon phase

Modified from von Herrath et al. Nat Rev Immunol. 2007

Diabetes Center

Ann NY Acad Sci 2009; 1150:190-196
**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 OGTT
Why Participate In Screening?

- May help the medical community understand diabetes better
- May benefit patient’s 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 → prolong honeymoon
- Eligible for intervention studies
  - Oral insulin, Abatacept, anti-CD3 mAb
- How to get patients screened?
  - Consider joining our affiliate network
  - UCSF can do a telephone consent and send out a kit directly to your family for testing in a local Quest lab, or
  - www.pathway2prevention.org

Type 1 Diabetes – New Onset Trials

[Diagram showing the relationship between genetic predisposition, environmental factors, and the progression of diabetes.]
By the time of diagnosis, is it too late to make a difference?

The Honeymoon

• At diagnosis, 15-40% of beta cell function remains

• Past studies suggest inevitable decline of beta cell function following diagnosis, with progression to complete loss

• However, if present, beta cell function 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
  - Examples of extended honeymoons
### 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**

- 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.

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

Keymeulen et al NEJM 2005; Keymeulen et al, Diabetologia 2010
**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

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**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
  – Differences in baseline CD4 and CD8 T cell subsets

• 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

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”

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### Study To Arrest Type 1 DM (START Trial):

**2 year Data**

![Graph showing 2-hour C-peptide AUC change from baseline over 24 months.](image)

Bars represent 95% confidence intervals. Lines connect the mean values across visits for each treatment arm.

\[ P = 0.380 \]

Gitelman et al, manuscript in preparation
What happened?

- Based on investigations performed to date, several mechanisms might be contributing for those who had decline in β-cell function:
  - Milieu surrounding CRS, serum sickness, steroid use, with immune activation

Effect of ATG Treatment on Lymphocyte Subsets

CD3

CD4

CD8

Values are mean and error bars are SD.

*P < 0.05

Changes In T cell Subsets following ATG Treatment
(% change from baseline)

CD4

Naive CD45RA+

CD8

Central Memory CD45RO+CD62Lhigh

P < 0.05

Persistence Of Effector Memory T cell Subsets Following ATG Treatment

CD45RO+CD62Llow

CD4

CD8

ATG

Placebo

What happened?

- Based on investigations performed to date, several mechanisms might be contributing for those who had decline in β-cell function:
  - Milieu surrounding CRS, serum sickness, steroid use, with immune activation
  - Persistence of effector memory T cells following ATG
  - Decrease in Treg number and Treg/Tem in 1st 6 months in ATG participants
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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</tbody>
</table>

ATG/GCSF Combo Pilot: Established Type 1 Diabetes (Helmsley)

- Established Diabetes (4 months - 2 years)
- ATG - 2.5 mg/kg over 2 days (low dose)
  - 6.5 mg/kg in prior START Trial (ATG alone)
- GCSF - 6 mg q 2 weeks for 12 weeks
- 25 subjects, Single Blinded
- 2:1 Randomized Combo: Placebo
- Ages 12 years - 45 years within 4 mos to 2 yrs of diagnosis
  - Within 100 days of dx for START
**ATG/GCSF Combo Pilot Study**

**Data Summary**

<table>
<thead>
<tr>
<th>Months post-treatment</th>
<th>Treated</th>
<th>Placebo</th>
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<td>17</td>
<td>8</td>
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<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

AUC (ng/ml/min)

- **AUC c-peptide**
  - Treated
  - Placebo

*Haller et al. Journal of Clinical Investigation 2015*

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**ATG vs ATG + GCSF**

- For ATG + GCSF trial, used lower ATG dose
  - Less cytokine release syndrome, serum sickness, glucocorticoid use

- Differences in changes in T cells
  - Less nadir in T cells, more rapid recovery
  - Tregs not as impacted
    - Do not see same extent and duration of depletion
    - Increase in Treg/Tem ratio

- Larger Phase 2 study just launching with TrialNet
  - ATG + GCSF vs ATG vs Placebo
  - Ages 12-45 within 100 days of dx
**Tregs - police of the immune system**

- 2-5% of lymphocytes
- Suppress responses of other immune cells
  - CD4$^+$ CD25$^+$CD127$^{lo}$
  - Require the transcription factor Foxp3 for development and function
- Foxp3 deficiency leads to
  - multi-organ autoimmunity and early lethality in animal models
  - IPEX (Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) in man
**Human Treg Expansion In Vitro**

- CD4+CD127lo/CD25+
- αCD3/αCD28 beads (1:1 ratio)
- IL-2 (300U/ml)

**Expansion Curve**

- **Time (d)**
- **Cell Number**
- **Percent**

- **Average FOXP3 at day 14**
  - (range) 55.3 (89.3 to 98.3)

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**Treg Trial**

- **Phase 1 study with infusion of autologous Tregs expanded in vitro**
  - First effort in autoimmunity

- **Subjects** 18-45 yrs old, within 2 yrs of dx and with measurable C-peptide

- **Dose escalation**

- **Fully enrolled**
  - Safe, well tolerated

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<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subjects</th>
<th>Cell dose (x 10^6)</th>
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<tbody>
<tr>
<td>1</td>
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<tr>
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</tbody>
</table>

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**Diabetes Center**

**UCSF Benioff Children's Hospital San Francisco**
**C-peptide AUC Change Over Time:** enrolled 3 mos -2 yrs from dx

![C-peptide AUC Change Over Time](image)

**Administration of CD4⁺CD25
highCD127⁻ Regulatory T Cells Preserves β-Cell Function in Type 1 Diabetes in Children**

- Phase 1 trial
  - 10 Subjects, 8-16 yrs, within 2 mos since dx
    - 4 pts @10x10⁶ cells/kg, 6 pts @20x10⁶/kg
  - Infusions well tolerated
  - Metabolic data at 4-5 months:
    - 2 subjects off insulin, 8 subjects <0.5 units of insulin/kg/d
    - Plans for Phase 2 new onset study in adolescents
  - Fasting C-peptide data (not stimulated) > than comparator
  - FDA has approved plans for phase 2 study in adolescents

Diabetes Care 2012
Complexities Of The Autoimmune Response:
Multiple Cell Types And Pathways Involved

Innate Immunity

Adaptive Immunity

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
    - Prevents and reverses DM in NOD mouse
  - Clinically, case reports and small series show benefit in autoimmunity
  - Related drug approved for RA treatment

Imatinib Study Overview

www.gleevec1d.com

- Multi-center, 2-arm, 2:1 randomized, placebo-controlled, double blinded phase II trial

  - 66 subjects, ages 12-45, with recent onset T1DM
    - Starting with adults first
  - Treatment with 400 mg of drug or matching placebo for 6 months
    (260 mg/m^2 in children)
  - Primary outcome: 2 hour stimulated C-peptide AUC in response to MMTT at 12 months

  - Secondary outcome measures will include:
    - Other metabolic measures of efficacy: insulin use, HbA1C
    - Safety: frequency and severity of adverse events
    - Mechanistic studies

- 30 subjects enrolled to date, favorable safety profile
Summary

- Current management of T1DM is problematic
  - Those with residual beta cell function do better

- Series of promising trials to prevent T1DM and preserve beta cell function in those recently diagnosed

- Gaining insights into how and what we need to accomplish for robust success
  - Resetting Teff-Treg balance

- New onset trials will inform our attempts at DM prevention and transplantation

Potential Type 1 DM Interventions

Modified from Matthews et al, Clin Exp Immunol 2010
Limitations and Opportunities

• Further analysis of what we have done to date
  – Responders vs non-responders
• Back to drawing board
  – Use of animal models
  – Human samples, nPOD
• Need surrogate measures to assess treatment efficacy
  – Currently rely on change in C-peptide
    • Indirect measure, requires 6-12 months
  – What about an immune measure?
    • Change in AutoAbs not helpful
    • Ideally track T-cell changes
      – Difficult assays, peripheral changes may not be relevant to pancreas
      – No current means for direct visualization

Acknowledgements

• UCSF
  – Jeff Bluestone
  – Mark Anderson
  – Saleh Adi
  – Stephen Rosenthal
  – Srinath Sanda
  – Hilary Thomas
• Yale
  – Kevan Herold
Help Us Cure Type 1 DM!

Contacts For Research Studies

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- clinicalresearch@diabetes.ucsf.edu
  844-T1D-UCSF (813-8273)

- http://www.diabetes.ucsf.edu
Alefacept Rationale

- CD2 - LFA3 is involved with T cell co-stimulation
  - expressed on the majority of human T cells
    - effector-memory T cells > central-memory > naive T cells
- Alefacept (LFA3-Ig) binds to CD2+ T cells
  - Deactivates and depletes T cells which most highly express CD2
- Approved for use in plaque psoriasis

Effect of alefacept on CD4+ T cell subpopulations

Rigby et al, Lancet DE 2013
**Efficacy Data At 2 yrs**

A. 4-hr C-peptide AUC

![Graph showing efficacy data at 2 yrs](image)

Rigby et al, submitted

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**Trial To Reduce T1DM In The Genetically At Risk**

- Can avoidance of early cow's milk exposure prevent DM?
- Hypothesis: with early exposure to cow’s milk
  - immature gut mucosa allows passage of antigenic proteins
  - cross-react with beta cell antigens
  - Supported by animal models, epidemiological studies
- Design: randomized, double blind trial
  - Enroll 2800 infants of 1st degree relatives with high risk HLA types
  - After usual initial breast feeding in first 2-3 months of life, randomized to casein hydrolysate vs cow's milk formula
  - Follow subjects prospectively until age 10
**Trial To Reduce T1DM In The Genetically At Risk**

**Does avoidance of cow’s milk proteins lower risk?**

**Cumulative Incidences of > 1 AutoAb In Pilot**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Casein hydrolysate</th>
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<td>10</td>
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</table>

*P=0.02*

Knip M et al. NEJM 2010;363:1900-1908

**Less Hypoglycemia in those with Residual β Cell Function (0.2 pM to 0.5 pM C-peptide)**

DCCT 62% Risk Reduction

Conventional Intensive Intensive

With β cell function Without β Cell Function

Diabetes 53:250-264, 2004
Less Retinopathy in those with Residual β Cell Function (0.2 pM to 0.5 pM C-peptide)

Risk Reduction: 79%
(CI: 9, 95) \( p < 0.012 \)

DCCT Intensive Therapy Group
Sustained 3+ Step Retinopathy Progression

Diabetes 53: 550-264, 2004

% Of Subjects With Detectable Random C-peptide

% Of Subjects with Random C-peptide \( \geq 0.2 \) nmol/L

AK Davis et al, Diabetes Care 2014
• NIDDK sponsored international consortium of 18 clinical centers
  – Charged with better understanding natural history of type 1 DM, and conduct prevention and new onset trials to prevent or preserve beta cell function

• Several new onset T1DM intervention trials have been conducted with 24 months or longer follow-up
  – Standardized entry criteria, DM management protocols, and beta cell assessment with serial MMTTs

• Evaluate change in beta cell function in placebo group, and treatment groups that had no effect

  Greenbaum et al, Diabetes 2012

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**Individual Trajectories In C-peptide AUC Over Time**

- 17% retained C-peptide from baseline to 12 months, and 11% from baseline to 24 mos
- Increased likelihood with age

  Greenbaum et al, Diabetes 2012
Heterogeneity of T1D amongst recently diagnosed children and adolescents with HLA-DRB1*301 and/or HLA-DRB1*401

<table>
<thead>
<tr>
<th>“Pro-inflammatory”</th>
<th>“Partially-regulated”</th>
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<tbody>
<tr>
<td>Peripheral blood</td>
<td></td>
</tr>
<tr>
<td>Multi-autoantibody positivity</td>
<td>Less &quot;pauci&quot;-autoantibody positivity</td>
</tr>
<tr>
<td>IFNγ–dominated CD4-T-cell response</td>
<td>IL-10–dominated CD4-T-cell response</td>
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</tbody>
</table>

Based on data from Arif et al. Diabetes 2014; 63:3835–3845

Decline In Beta Cell Function By Age

Greenbaum et al., Diabetes 2012

Months from diagnosis
### Multivariable Analysis of Baseline Factors Associated With AUC C-peptide Change Over Time

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Relationship with covariate across time</th>
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<tr>
<td>Age (continuous), years</td>
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<td>0.0024</td>
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<tr>
<td>Ethnicity (not Hispanic or Latino is reference)</td>
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<tr>
<td>Race (white is reference)</td>
<td>-0.00251</td>
<td>0.5079</td>
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<tr>
<td>BMI z score</td>
<td>-0.00247</td>
<td>0.0152</td>
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<tr>
<td>ICA512 positivity</td>
<td>0.00447</td>
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<td>Diabetic ketoacidosis (absent is reference)</td>
<td>0.00430</td>
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<td>HbA1c</td>
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<td>Insulin (per kg)</td>
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<td>Autoimmune disease history</td>
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<td>Platelet count</td>
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<tr>
<td>Basophils</td>
<td>0.00516</td>
<td>0.0123</td>
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</table>

**Greenbaum et al, Diabetes 2012**

NA, not applicable.
Impact Of Diabetes On Society

- Currently affects ~29 million in USA
  - ~10% have type 1 DM

- Aside from asthma, DM is most common chronic disease of childhood

- Concern regarding long term complications
  - Leading cause of blindness in 20 to 74 year olds
  - Most frequent cause of end stage renal disease
  - Most common reason for non-traumatic limb amputation
  - Five fold increase in coronary artery disease
  - Shortened life span by 10 to 20 years

- DM accounts for $246 billion in total health care related costs in USA
  - Up 41% in 5 yrs
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

The Honeymoon

- Re-visitation of natural history studies given
  - Improvement in glycemic control over time
  - Change in HLA distribution
  - Increase in BMI

- Recent studies suggest slower decline with measureable C-peptide long after diagnosis
  - 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 autopsy studies
### Comparison Of Anti-CD3 Dose Regimens Across Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Anti-CD3 Dose</th>
<th>Dosing Duration</th>
<th>Achieve Primary Outcome</th>
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<tbody>
<tr>
<td>Phase 1/2 Herold, 2005 Diabetes</td>
<td>17 mg teplizumab</td>
<td>Single 14-day course</td>
<td>Yes</td>
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<tr>
<td>Phase 2 AbATE Herold, 2013 Diabetes</td>
<td>17mg teplizumab x 2</td>
<td>Two 14-day courses 12 months apart</td>
<td>Yes</td>
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<tr>
<td>Phase 3 Protégé Sherry, 2011 Lancet</td>
<td>17mg teplizumab x 2</td>
<td>Two 14-day courses 6 months apart</td>
<td>No • Primary Endpt • Pt population</td>
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<tr>
<td>Phase 2 Keymulen, NEJM 2008</td>
<td>48 mg otelixizumab</td>
<td>Single 8-day course</td>
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<tr>
<td>Phase 3 DEFEND Aronson, 2014 Diabetes Care</td>
<td>3.1 mg otelixizumab</td>
<td>Single 8-day course</td>
<td>No • Used 1/15th dose</td>
</tr>
</tbody>
</table>

### Study To Arrest Type 1 DM (START Trial): ATG Alone

![Graph showing C-Peptide AUC (nmol/L) over time](image)

- **Treatment Group:**
  - ATG
  - Placebo

- **C-Peptide AUC (nmol/L):**
  - Screening
  - Month 6
  - Month 12

- **P-value:** 0.59

*Gitelman et al. Lancet D&E 2013; 1:306-316*
Study To Arrest Type 1 DM (START Trial): ATG Alone

![Graph showing C-Peptide AUC (nmol/L) over time for ATG and Placebo groups.]

- ATG alone:
  - Screening
  - Month 6
  - Month 12

The Balance of Pathogenic Effector T Cells and Regulatory T Cells in Healthy Persons versus Imbalances in Persons with Pathologic Conditions.


> IL-2 is vital for Tregs generation and survival, means to boost Tregs in vivo

The Balance of Pathogenic Effector T Cells and Regulatory T Cells in Healthy Persons versus Imbalances in Persons with Pathologic Conditions.
Augmenting Tregs

- ITN Phase 1 study with IL-2 plus Rapamycin in recent onset T1DM
  - Supported by NOD mouse studies
  - IL-2 can induce Tregs, but also Teffectors, NK and eosinophils
  - Rapamycin can keep effectors in check
  - Phase 1 trial for adults with longer standing type 1 DM

Change in β-cell function with rapamycin/IL-2 combination therapy.

• Not clear if IL-2 dosing +/- Rapamycin that caused issues
• Attempts to use lower dose IL-2, or mutants
  – Trials from Klatzmann, Waldrup-Lynch