Altering The Course Of Type 1 Diabetes

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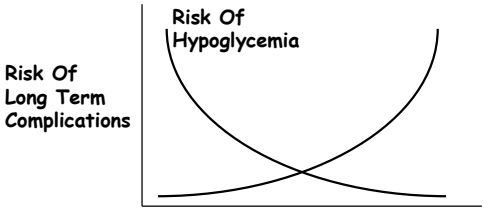
- **Overview of current therapy**
- **Places for intervention**
  - **Established diabetes**
  - **Prevention**
  - **New Onset**

Before and After

One of the first patients to ever receive insulin therapy

DCCT Findings: *Glycemic Control Matters*

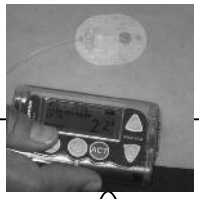


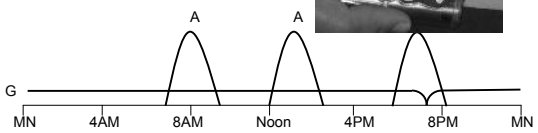
N Engl J Med 329: 977-86, 1993

Current Gold Standard For Care: Intensive DM Management

- Patient needs to see a diabetes team
  - dietitian, RN / CDE, counselor, and diabetologist
- Monitor blood sugar 4 or more times per day
- Must follow a meal plan, count carbohydrates
- Need to become adept at complex insulin regimens
  - more frequent insulin injections, or use of pump
  - increase insulin to correct high glucoses
  - adjust insulin for variation in CHO intake, exercise
- Frequent follow-up in and out of clinic
  - telephone, FAX, e-mail

"Basal + Bolus" regimen





Life In The Post-DCCT Era

- Not consistently achieving glycemic goals
- Still see burden of long term complications
- Toll on mental health
  - Depression
  - Eating disorders
- Mortality

Where Is The Cure?

Glucose Sensor

- Clinical Symptoms, Glucometer

X X

Insulin Secretion

- MDI
- Pump
- Inhaled Insulin

Where Is The Cure?
The Engineer's View

Glucose Sensor

- Clinical Symptoms, Glucometer

- Continuous Glucose Monitor

X X

Insulin Secretion

- MDI

- Pump

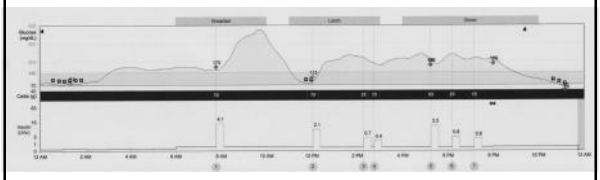
- Inhaled Insulin

Continuous Glucose Sensors

Medtronic Minimed Guardian RT

Dexcom

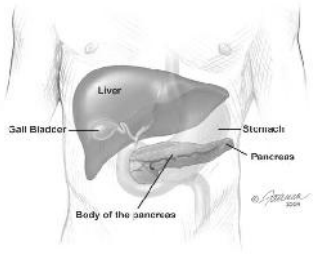
CGM/Pump recordings



Drawbacks Of Current Sensors

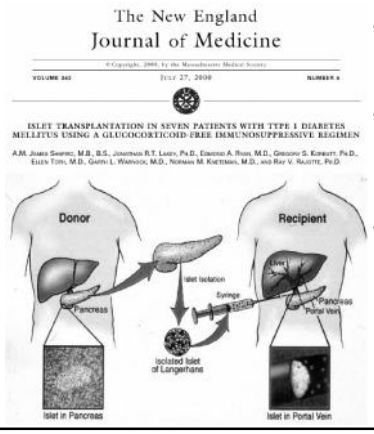
- Not covered by insurance
- Have to wear a device
- Not as accurate as we would like
  - Still have to use your glucometer to calibrate sensors, confirm values out of range
- Not a closed loop
  - Hard to mimic nature...

Where Is The Cure?
The Biologist Approach



Pancreas Transplantation

- Big procedure
- It works
  - 50-70% exogenous insulin free at 5 yrs
- Lifelong immuno-suppression



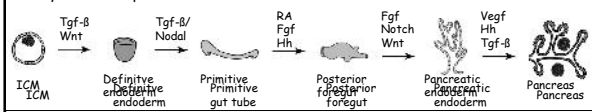
- 7 of 7 insulin independent at 1 yr!
- High quality islets
  - Usually need 2 donors
- New immuno-suppressant cocktail
  - No steroids

Islets...where do we stand?

- What are the short and long term risks?
  - Bleeding, clots from procedure
  - Long-standing immunosuppression
- How robust are the islets?
  - Only 10% remain off exogenous insulin by 5 yrs
- Can the procedure be exported to other centers?
- Can we optimize the procedure?
  - islet preparation and infusion
  - Currently need 2 or more donors
  - allo- and auto-immunity
- Do we have enough islets?
  - 3,000 cadaveric pancreases / yr
  - 35, 000 new onset Type 1 / yr, 1.8 million with established T1DM
- What about stem cells?

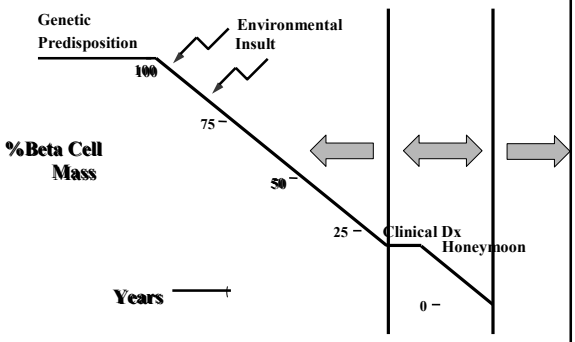
Recapitulating pancreas and ß-cell development

Embryonic development



D'Amour, '05,'06; Kroon, '08

Natural History Of Type 1 DM



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

Environment And Autoimmunity

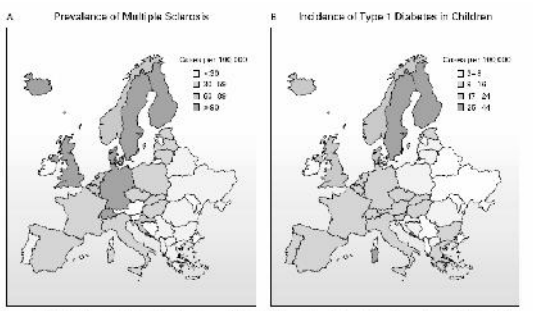


Figure 2. The North–South Gradient in the Prevalence of Multiple Sclerosis (Panel A) and the Incidence of Type 1 Diabetes Mellitus (Panel B) in Europe.
Adapted from Kurtzke[47] and Green and Patterson.[48]

JF Bach N Engl J Med 2002

Relationship between autoimmunity and infection

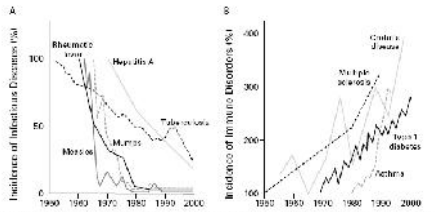
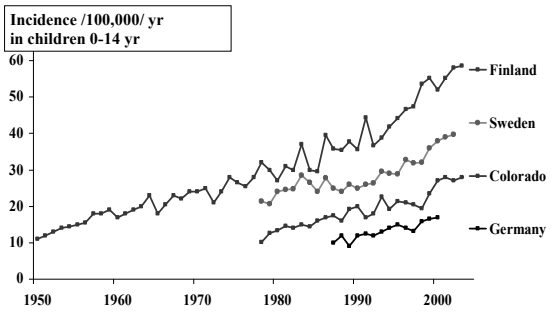


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1900 to 2000.
In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Armstrong et al.[7] In Panel B, data on immune disorders are derived from Swerdlow et al.,[8] Dubois et al.,[9] Incerpi et al.,[10] and Poglitsch et al.[11]

JF Bach, New England J of Med 2002 347:911

Increasing Incidence of T1DM

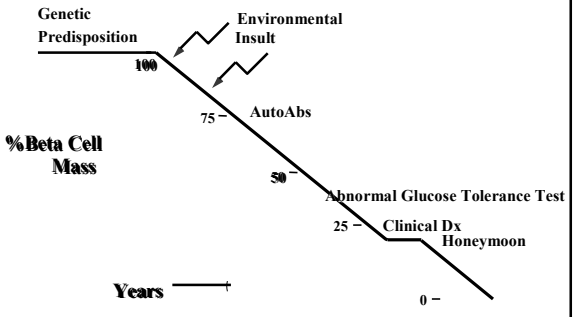


Rewers M. Ann NYAS 2008

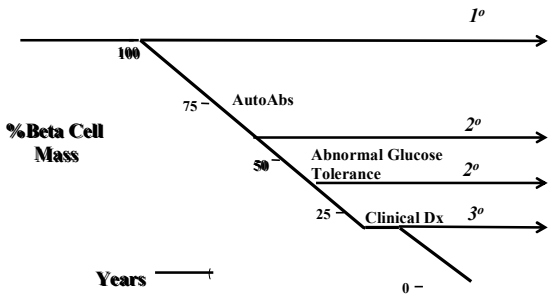
The Hygiene Hypothesis

- 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

Natural History Of Type 1 DM



Interventions For Type 1 DM



Dilemma For DM Interventions

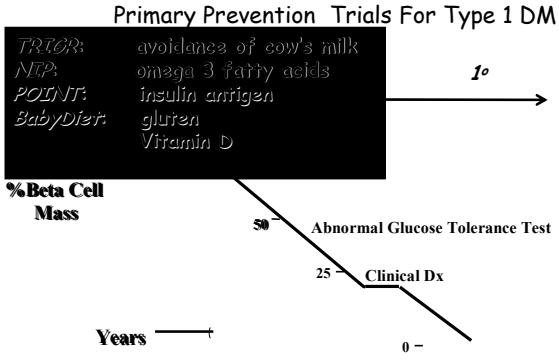
- **Attempts at early prevention**
  - Less likely to predict who will ultimately get DM
    - Larger studies conducted over longer time period
  - Less aggressive intervention, such as dietary manipulation or antigen-based therapy, more likely to be efficacious
- **Later stages of intervention**
  -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

Ongoing Or Planned

Primary Prevention Trials For Type 1 DM

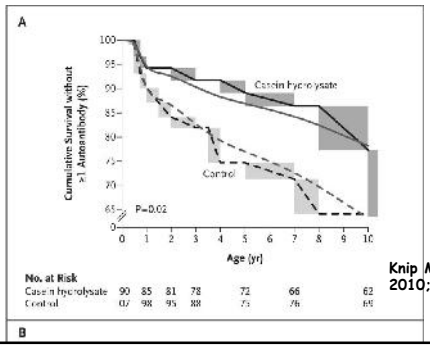


Trial To Reduce T1DM In The Genetically At Risk

TRIGR

- 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

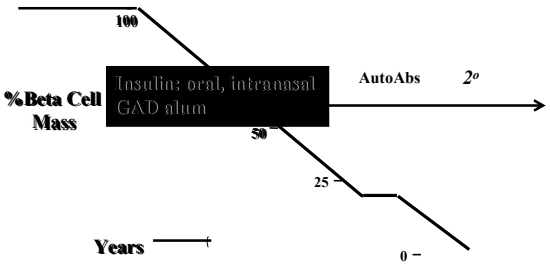
Cumulative Incidences of ≥ 1 Autoantibody in Pilot TRIGR



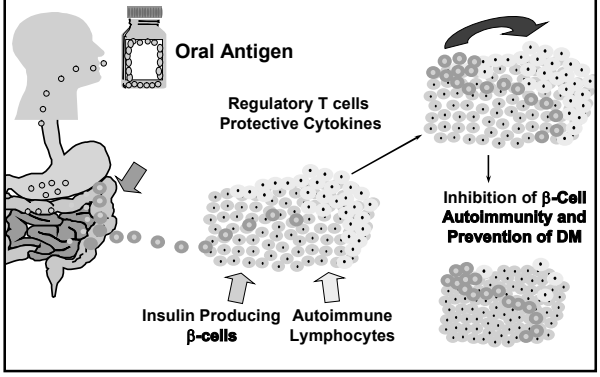
Knip M et al. NEJM 2010;363:1900-1908

Secondary Prevention Trials For Type 1 DM

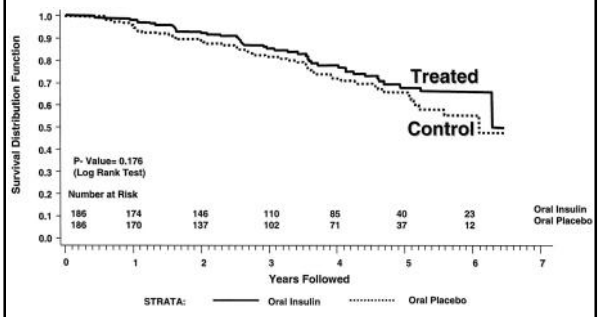
25-50% risk for DM in next 5 yrs



Oral Tolerance: Mode of Action



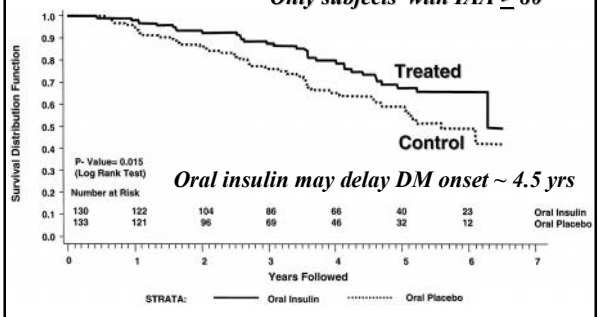
Effect Of Oral Insulin On Progression To T1DM



Skyler et al, Diabetes Care 2005, 28: 1068

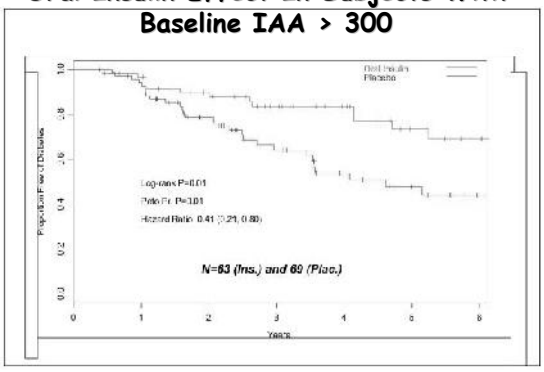
Effect Of Oral Insulin On Progression To T1DM

Only subjects with IAA ≥ 80



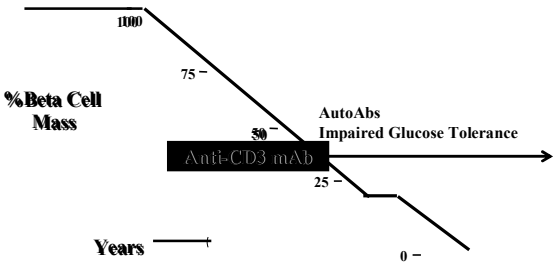
Skyler et al, Diabetes Care 2005, 28: 1068

Oral Insulin Effect In Subjects With Baseline IAA > 300



Tertiary Prevention Trials For Type 1 DM

> 50% chance of developing DM in next 5 yrs



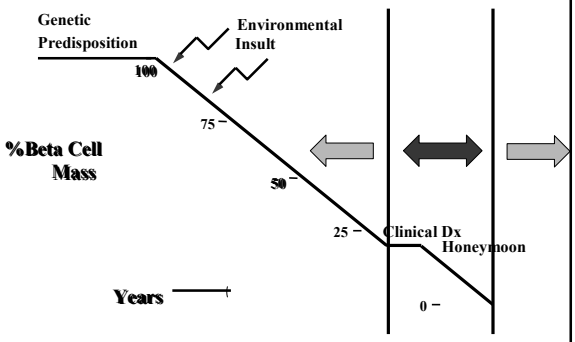
TrialNet Natural History Study

- *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
    - Insulin, GAD, IA-2, ICA, and Zinc Co-Transporter 8
    - Those who are < 18 and Ab neg can be rescreened yearly
- *What happens if they have 1 or > Abs?*
  - Staging
    - Genetic screen: HLA class II
    - Metabolic screen: Oral glucose tolerance test
  - Surveillance
    - Follow-up every 6 months with OGTT

Why Participate In Screening?

- May help the medical community understand diabetes better
- May benefit the family
  - Clarify what chances are of developing diabetes
  - Participants tend to make diagnosis of diabetes much earlier
    - Safer, avoid DKA
    - Benefit to starting insulin sooner → **prolong honeymoon**
  - **Eligible for intervention studies**
    - **Oral insulin, anti-CD3 mAb**
- **How to initiate family contact?**
  - **UCSF can do a telephone consent and send out a kit directly to the family for testing in a local lab, OR**
  - **Your group can become a TrialNet affiliate**

Natural History Of Type 1 DM



The Honeymoon

- By the time of diagnosis, up to 15-40% of beta cell function remaining
- Length of honeymoon varies
  - Inversely correlated with age
  - Gradual shift over time
  - 10-15% of teens and adults still have clinically significant insulin production ≥ 5 yrs after DM onset *(DCCT NEJM 1993)*
- 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

Prolonging the honeymoon

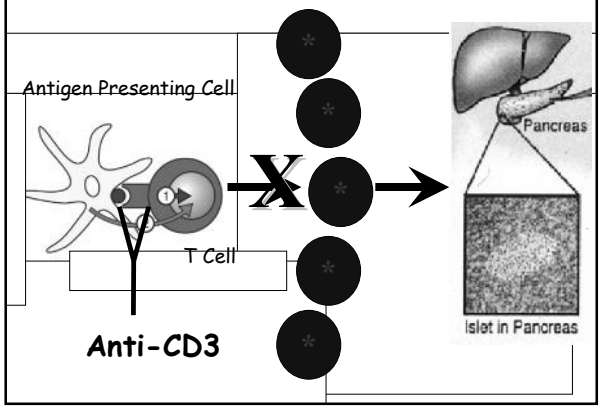
- Immunotherapy works
  - Cyclosporine experience from the '80s
    - Requires continuous immunosuppression
    - Not all respond
    - Potential toxicities

New Onset T1DM Immunotherapy Trials

Underway Or Under Consideration

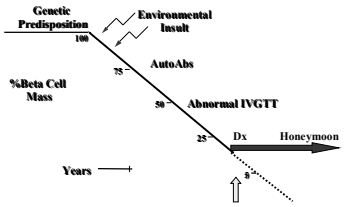
- Anti-CD3
- Anti-thymocyte globulin, +/- GCSF
- Anti-CD20
- Glutamate Decarboxylase (GAD)
- CTLA4 Ig
- Rapamycin + IL-2
- IL-1beta antagonist
- Atorvastatin
- Alpha 1 anti-trypsin
- Alefacept
- Intensive metabolic control
- GAD, Sitagliptin, Lansoprazole
- Pioglitazone
- Etanercept
- Lisofylline
- Autologous dendritic cells with AS oligo Rx
- Autologous regulatory T cells
- Imatinib

T Cell Activation



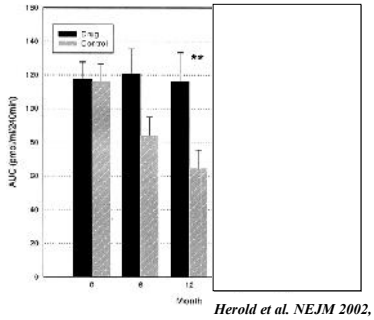
Phase 1/2 Study of Anti-CD3 In Type 1 DM

- 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.



Anti-CD3 Therapy

Preservation Of Beta Cell Function With Anti-CD3 Rx



Herold et al. NEJM 2002, Diabetes 2005

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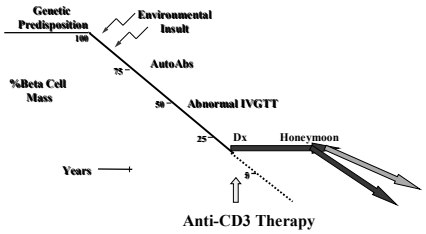
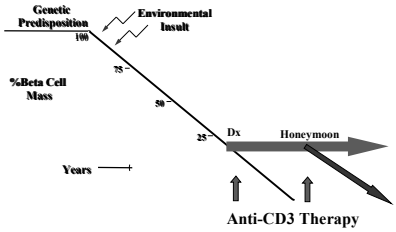


Herold et al. NEJM 2002; Herold et al. Diabetes 2005; Herold et al. Clin Immunol 2009
Keymeulen et al NEJM 2005

Hypothesis For Phase 2 Study

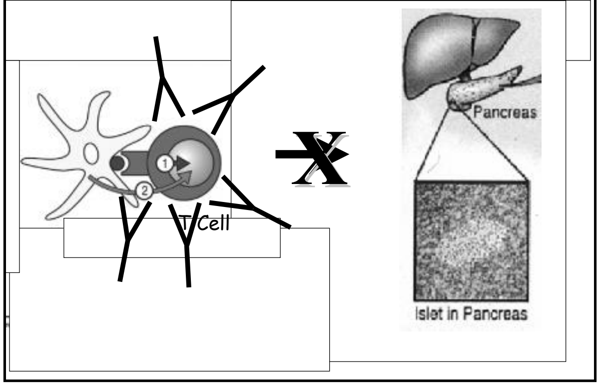
- Two courses of anti-CD3 therapy, at baseline and 12 mos, will induce tolerance and inhibit further beta cell destruction in patients with new onset Type 1 DM.



Where Do We Go From Here With Anti-CD3?

- Does therapy have to be used so early in the course…what is the window of opportunity?
  - Clinical trial with 1st dose given *4 to 12 mos from dx*
- What about the dosing?
  - Reduced total doses less effective
  - 1/15th dose
    - No side effects, no efficacy
- Can we improve efficacy if it is combined with an agent that works via another mechanism?
  - Anti-CD3 + Exenatide
  - Anti-CD3 + Antigen (insulin or GAD)
- Can it prevent type 1 diabetes? What about use in transplant?

Anti-Thymocyte Globulin



ORIGINAL CONTRIBUTION

C-Peptide Levels and Insulin Independence Following Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus

JAMA 2007, 297:1568

JAMA 2009, 301: 1573

Autologous Non-Myeloblative HSC Therapy

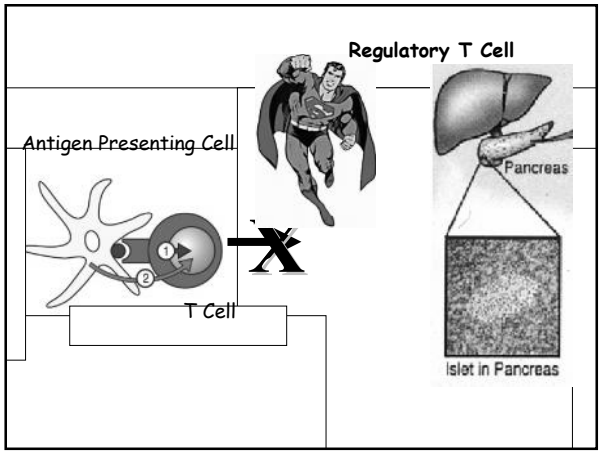
- Phase 1 study in new onset Type 1 DM
- Intervention
  - Pre-treatment
    - Cyclophosphamide + G-CSF
    - Collect CD34+ cells in periphery
  - Conditioning Rx
    - Thymo (4.5 mg/kg) + cyclophosphamide
  - Re-infuse cells
- Safety concerns: 3 wk hospitalization
  - Infusion reactions, opportunistic infection, oligospermia
- Metabolic outcome:
  - 20 of 23 pts became insulin free
    - 12 for mean of 31 mos (14-52)
- *Do we need such an aggressive cocktail? Can ATG alone suffice?*

ITN028AI
Effect Of Anti-Thymocyte Globulin On Preserving Beta Cell Function In New Onset Type 1 DM

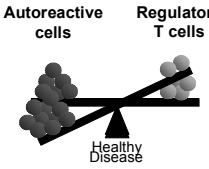
START
STUDY OF THYMOGLOBULIN TO ARREST TYPE 1 DIABETES

ATG + G-CSF

- In NOD mouse, even more robust remission rate with ATG + G-CSF than ATG alone
  - can use ~1/3rd of ATG dose
- Now conducting a phase 2 trial for subjects $\geq$ 12, 4 mos to 2 yrs from dx
  - 2.5 mg/kg ATG (2 doses)

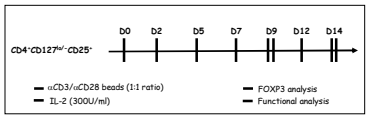


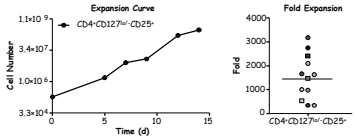
Regulatory T cells: Police of the Immune System



- Small population of CD4+CD25+ T cells
- Suppress pathogenic cells by both contact-dependent and cytokine (TGFb and IL-10)-dependent mechanisms.

Human Treg Expansion In Vitro





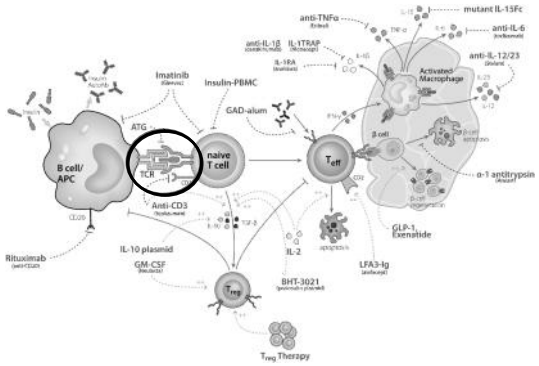
Putnam et al, Diabetes. 2009 Mar;58(3):652-62.

Diabetes Center

Treg Trial

- Phase 1 study with infusion of autologous Tregs expanded in vitro
  - First effort in autoimmunity
  - Prior trial with related cell product in GVHD *(Brunstein et al, Blood 2010)*
- Subjects ≥ 18, within 2 yrs of dx and with measurable C-peptide
- Dose escalation

Potential Type 1 DM Interventions



Why participate in new onset T1DM trials in 2011?

- Existing therapy is available, and improving
  - Not a life threatening condition
  - Usually 1 in 3 chance of randomizing to placebo group
- Intent is that all participants in NIH sponsored new onset studies will benefit from participation
  - All are offered intensive DM management with team
    - Contact from CDE at least every 2 wks to optimize regimen
    - Unlimited glucose test strips
  - Improved metabolic control in and of itself helps preserve beta cell function (DCCT, 1993)
  - Metabolic memory: tighter control early in the course of DM, even if it cannot be maintained, may have long term benefits in lowering complications risk
    - DCCT / EDIC studies
- Altruism
  - Ultimately, this is how we move the field forward!

Summary

- Current clinical care for type 1 DM is improving, but limitations remain
- Series of prevention and new onset trials launched or planned to alter the natural course of T1DM
  - Encouraging results to date
  - Await results of follow-up studies
- Many other agents to evaluate, either alone or in combination
- New onset trials will inform our attempts at DM prevention and transplantation

New Onset T1DM Studies

Ages 12-45, up to 24 months from dx

Study	*Age, yrs*	*DM Duration*	*Design*	*Rx*	*Status*
Alefacept	12-35	< 100 days	Blinded 2:1	12 wkly injection x 2	Open
Thymo + G-CSF	12-44	4 – 24 mos	Blinded 2:1	2 doses in-pt	Open
Tregs	18-35	3 – 24 mos	Open label Phase 1	1 dose in-pt	Open

Help Us Cure Type 1 DM!

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