Can We Prevent Type 1 Diabetes?

Dr. Chantal Mathieu
Universitaire Ziekenhuizen Leuven
Belgium

The NOD mouse model

- Spontaneous diabetes
- Insulitis
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The NOD mouse model
- Spontaneous diabetes
- Insulitis
- Sex difference in diabetes incidence
- Defects in immune regulation (cytokine profile, T cell apoptosis, regulatory cells)

Other NOD characteristics
- Deficiency in CD4+CD25+ regulatory T cells
- NK T cell deficiencies (number and function)
- Impaired production of IL-4
- I-E
- Lack serum hemolytic complement activity (no C5)
- Defective NK cell activity
- Defects in differentiation and function of APCs

Adapted from T. DiLorenzo

Environment
- TNF-α, IL-1, IL-6, IFN-γ
- Free radical (O₂⁻, NO)
- Genetic predisposition

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Type 1 diabetes

- Genetic predisposition: Multigenetic
- Environmental influence: Yes
- T-cell driven insulitis: Yes
- Defective peripheral immunoregulation: Yes
- Autoantigens: GAD65, IA-2, insulin, p38
- Humoral reactivity to β-cells: Yes
- Delay-onset with immunosuppression: Yes
- Successful intervention studies: Multiple

Adapted from B. Roep, Diabetologia, 2003

Diabetes prevention in the NOD mouse: aspecific immune modulation

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Specificity</th>
<th>Animal</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Immune suppression</td>
<td>None</td>
<td>NOD and BB</td>
<td>Nonspecific suppression of cell-mediated immunity</td>
</tr>
<tr>
<td>Anti-CD4</td>
<td>CD4 T cells</td>
<td>NOD</td>
<td>Anti-CD4 mAb</td>
</tr>
<tr>
<td>Transplantation</td>
<td>None</td>
<td>NOD and BB</td>
<td>Grafts of marrow, dermato, cells, fetal liver and thymus</td>
</tr>
<tr>
<td>Anti-CD3</td>
<td>CD3 T cells</td>
<td>NOD</td>
<td>Anti-CD3 mAb reverse diabetes at onset, with long duration of effect, induction regulatory T cells</td>
</tr>
</tbody>
</table>

Anti-CD3 therapy in NOD mice

- Anti-CD3 only effective in recent-onset diabetic animals, a short therapeutic efficacy window
- Splenocytes from treated “cured” mice still transfered disease into irradiated male NODs
- Cyclophosphamide induced disease relapse in “cured” mice 10-15 weeks after anti-CD3 therapy
- Cyclosporine A administration at the time of anti-CD3 therapy prevented therapeutic effect

Chattenoud et al., J. Immunology, 1997
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### Diabetes prevention in the NOD mouse: aspecific immune modulation

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<td>None</td>
<td>NOD and BB</td>
<td>Non-specific suppression of cell-mediated immunity</td>
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<td>CD4 T cells</td>
<td>NOD</td>
<td>Anti-CD4 mAb</td>
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<td>CD3 T cells</td>
<td>NOD</td>
<td>Anti-CD3 mAb suppresses diabetes at onset with long-term effect, induction regulatory T cells</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D$_3$ and analogues</td>
<td>None</td>
<td>NOD</td>
<td>APC and T lymphocytes as targets</td>
</tr>
</tbody>
</table>

### 1,25-dihydroxyvitamin D$_3$ prevents insulitis and diabetes in NOD mice

![Graph showing % of DIABES vs. age days]

Mathieu et al., 1994, Diabetologia

### Diabetes prevention in the NOD mouse: aspecific immune modulation (Ctd)

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<td>Immune stimulation</td>
<td>None</td>
<td>NOD</td>
<td>Immune activation by agents such as BCG</td>
</tr>
<tr>
<td>Calcitriolamide</td>
<td>NK T cells</td>
<td>NOD</td>
<td>Activation CD4 restricted cells</td>
</tr>
<tr>
<td>Syntheses</td>
<td>IL-12, TNF, IL-4</td>
<td>NOD</td>
<td>Complex effect</td>
</tr>
<tr>
<td>Care therapy</td>
<td>Antigens/cytokines</td>
<td>NOD</td>
<td>Multiple potential targets</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>PPARy agonist</td>
<td>NOD</td>
<td>Suppression of IL-1 induced ICAM-1 expression</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>Beta cell protective</td>
<td>NOD</td>
<td>Prevention of disease (?)</td>
</tr>
</tbody>
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### Diabetes prevention in humans: aspecific immune modulation

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</tr>
</thead>
<tbody>
<tr>
<td>Immune suppression</td>
<td>None</td>
<td>Temporary delay in disease</td>
</tr>
<tr>
<td>Modified immune suppression</td>
<td>None</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Antibody</td>
<td>No-effect</td>
</tr>
<tr>
<td>Cytokines (oral IFNα)</td>
<td>None</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Anti-CD3</td>
<td>CD3 T cells</td>
<td>Anti-CD3 mAb preserves C-peptide in newly diagnosed children - ongoing</td>
</tr>
</tbody>
</table>

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### Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus

Kevan C. Herold, MD; William Hagopian, MD, PhD; Julie A. Auger, BA; Eva Fountain-Ruiz, BS; Leslie Taylor, BA; David Donaldson, MD; Stephen E. Gitelman, MD; David M. Harlan, MD; Danlin Xu, PhD; Robert A. Zivin, PhD; & Jeffrey A. Bluestone, PhD


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### Changes from study entry to 12 months in the total C-peptide response to mixed-meal tolerance testing

Monoclonal-antibody group  
Control group


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CD4+/CD8+ ratio in the monoclonal-antibody group according to the presence or absence of response to treatment


In a recent study, Herold K. et al. (2002) found that the CD4+/CD8+ ratio was lower in the monoclonal antibody group compared to the control group, indicating a potential role of these antibodies in preventing type 1 diabetes.


- Recent onset of type 1 diabetes
- <6 months symptoms
- <4 weeks insulin
- ICA+ or GADA+
- C-peptide > 0.2mmol/L
- Humanized monoclonal aCD3 or placebo


In the Belgian anti CD3 trial, Kemmeelen B. et al. (2005) observed that participants randomized to the CD3 antibody group had a lower incidence of type 1 diabetes compared to the placebo group, suggesting a potential therapeutic effect of CD3 antibodies.

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**Humanized anti-CD3 in T1D**

<table>
<thead>
<tr>
<th></th>
<th>USA (n = 24)</th>
<th>Belgium + Münich (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humanized anti-CD3</td>
<td>HOK15N (Ala-Ala) (n = 12)</td>
<td>Aglycosyl CD3 (n = 40)</td>
</tr>
<tr>
<td>Control group</td>
<td>Observation (n = 12)</td>
<td>Placebo (n = 40)</td>
</tr>
</tbody>
</table>

**Age (yrs)**
- USA: 7.5±3.0
- Belgium + Münich: 12±3.6

**Insulin tr. (wks)**
- USA: <6
- Belgium + Münich: <4

**Autoantib. pos.**
- USA: Yes (GAD/IA2/Ins)
- Belgium + Münich: Yes (GAD/ICA)

**C-peptide (µg/l)**
- USA: ?
- Belgium + Münich: <17.8

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- Recent onset of type 1 diabetes
  - <6 months symptoms
  - <4 weeks insulin
  - ICA+ or GADA+
  - C-peptide > 0.2mmol/L
- Humanized monoclonal aCD3 or placebo

Results: effects of treatment

HbA1c

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>ChAgly CD3</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>


C-peptide release

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.2</td>
<td>1</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>ChAgly CD3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Insulin dose

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>ChAgly CD3</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>


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**AUC C-peptide 60-140 min at baseline < P50:**

effects of treatment

Placebo: n = 16
ChAgly CD3: n = 24


**AUC C-peptide 60-140 min at baseline ≥ P50:**

effects of treatment

Placebo: n = 24
ChAgly CD3: n = 16


**Conclusion**

- Patients with higher initial beta cell function benefit the most from treatment with ChAgly CD3
- In this patient group, preservation of beta cell function is associated with lower insulin needs during at least 18 months

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Safety and immunological changes

- Safety tests
- Immunological tests
  - HLA-DQA and DQB genotyping (BDR)
  - ICA and GADA (BDR)
  - Peripheral lymphocyte subsets (Brussels-ULB – M. Goldman, L. Schandoo)
  - Cytokines (Hop Necker – L. Chatenoud, S. Candon)
  - ChAgly CD3 (TAC)
  - Antibodies to ChAgly CD3 (TAC)

"Flu-like" syndrome during treatment

<table>
<thead>
<tr>
<th>During treatment</th>
<th>ChAgly CD3</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;38°C)</td>
<td>38/40</td>
<td>1/40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>40/40</td>
<td>14/40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>29/40</td>
<td>7/40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>40/40</td>
<td>2/40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>35/40</td>
<td>8/40</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

"Flu-like" syndrome after treatment

<table>
<thead>
<tr>
<th>Onset at day 16-21</th>
<th>ChAgly CD3</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mononucleosis-like syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>30/40</td>
<td>3/40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>13/40</td>
<td>1/40</td>
<td>0.001</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>10/40</td>
<td>3/40</td>
<td>0.07</td>
</tr>
</tbody>
</table>
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Results: AUC C-peptide 60-140 min at baseline

Healthy volunteers (n = 20)
Patients (n = 80)

25% of normal

Diabetes prevention in humans: aspecific immune modulation (Ctd)

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<td>Immune stimulation (BCG vaccine, Q fever vaccine)</td>
<td>None</td>
<td>No effect</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>Beta cell protective</td>
<td>No effect</td>
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My friends, we did not prevent diabetes
E. Gale, EASD, September 2002

First-degree relatives of type 1 diabetic subjects
- ICA titre > or = 20 JDF U (n = 29,718)
- Placebo (n = 275)
- Oral high dose of NIC (1.2 g/m²) daily (n = 274)

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Diabetes prevention in the NOD mouse: antigen specific modulation

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<td>Insulin</td>
<td>NOD and BB</td>
<td>Prevention of disease - no consensus on treatment regimen</td>
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</table>

Effect of insulin on diabetes in NOD mice

1990, Atkinson: Prophylactic (zinc pork) insulin therapy (0.25 - 0.75 U)
11 female NOD mice (daily from 21 to 168 days of age)

1991, Zhang & Eisenbarth: Oral (porcine) insulin therapy (1 mg)
30 female NOD mice (twice weekly from 35 to 180 days of age and weekly thereafter till 1 year)

1994, Bergerot & Thivolet: Oral (human) insulin therapy (20 U)
15 female NOD mice (every other day from 42 to 70 days of age)

1996, Daniel: Intranasal insulin peptide B:9-23 (40 µg)
9 female NOD mice (3 consecutive days from 28 days of age)

Effect of GAD, HSP 60 and Cow’s milk proteins on diabetes in NOD mice

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<tr>
<td>GAD, HSP 60</td>
<td>NOD</td>
<td>Prevention of disease - no consensus on treatment regimen</td>
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<tr>
<td>Cow’s milk proteins</td>
<td>NOD</td>
<td>Prevention of disease by avoidance</td>
</tr>
</tbody>
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Diabetes prevention in humans: antigen specific modulation

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<tr>
<td>Insulin</td>
<td>DIPP, DPT-1</td>
<td>No effect – ongoing</td>
</tr>
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<td></td>
<td>INIT, Belgian trial</td>
<td></td>
</tr>
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DPT-1 intervention protocols

- Parenteral antigen
  - In subjects with 5 year risk of type 1 diabetes > 50%
- Oral antigen
  - In subjects with 5 year risk of type 1 diabetes = 25-50%

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DPT-1 staging scheme

ICA positive

HLA DQA1*0102/B1*0602
Not eligible

IVGTT
Low FPIR x 2
OGTT non-diabetic

Intact FPIR
Eligible parenteral

IAA positive
DGTT
IGT or IFG

Normal
Eligible oral

Parenteral antigen protocol

- Randomized, controlled, unmasked
- Experimental group:
  - 4 day's continuous IV insulin infusion
  - At baseline and yearly thereafter
  - Low dose subcutaneous insulin
    - 0.125 U/kg bid human ultralente
- Control group: close observation

DPT-1 screening results

- 89,827 relatives screened
- 3152 samples ICA+ (3.73%)
- 2103 subjects staged (70%)
- 535 low first phase insulin on IVGTT
- 372 eligible for randomization – projected 5-year risk of >50%
- 339 randomized (91% of eligible)
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DPT-1 parenteral study – time to diabetes by treatment

DPT-1 parenteral study
MMTT peak C-peptide (ng/ml) – by treatment

Oral antigen protocol
- Randomized, controlled, double-masked
- Experimental group: oral insulin
- Control group: matched placebo
- Began Sept. 1996
  - No overall effect: major subgroup high insulin autoantibodies protection  
  

Survival distribution function

PHvalue = 0.796  
(Log rank test)


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Diabetes prevention in humans: antigen specific modulation

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<tr>
<td>HSP 60</td>
<td>Elias (p277)</td>
<td>Minor protection of C-peptide loss</td>
</tr>
</tbody>
</table>

DiaPep277 trial (phase II)

Newly diagnosed type 1 diabetes subjects (<6 months)

Placebo (n = 16)
s.c. DiaPep277 (1 mg) + mannitol (40 mg)
at entry and at 1 month and 6 months (n = 15)

Lancet 2001; 358: 1749-1753

Autoantigen vaccination: risk of shock?

Overbergh et al., Diabetes
Insulin peptide induction of anaphylaxis

- Insulin B: 9-23 in saline – 7 injections = death NOD
- Anaphylaxis dependent upon both IgG and IgE antibodies; Histamine and platelet activating factor
- Anaphylaxis following subcutaneous injection prevented with addition RR to peptide to produce peptide with neutral pI while peptide able to prevent diabetes of NOD mice

Liu et al., JCI, 2002

Objectives
Autoantigen vaccination: risk for shock?
(100 µg in CFA injected in the footpads + booster 3 wks later)

<table>
<thead>
<tr>
<th></th>
<th>GAD65</th>
<th>InsB</th>
<th>hsp65</th>
<th>PLP</th>
<th>HEL</th>
<th>OVA</th>
<th>TT</th>
<th>KLH</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Balb/C</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Only hen egg-white lysozyme (HEL) induced shock exclusively in NOD mice

Incidence of HEL-induced shock: strain specific

- No shock
- Reversible shock
- Lethal shock

Overbergh et al., Diabetes, 2003
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### Diabetes prevention in humans: antigen specific modulation

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<td>Minor protection of C-peptide loss</td>
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<tr>
<td>Cow’s milk avoidance</td>
<td>TRIGR</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

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### TRIGR (trial to reduce IDDM in genetically at risk)

- First degree relatives
- No protective genotype
- Cow’s milk exclusion
- Cow’s milk
- Development of diabetes
- Development of antibodies

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Use of VD supplements in first yr of life

<table>
<thead>
<tr>
<th>Use of VD supplements</th>
<th>Type 1 diabetes</th>
<th>Incidence per 100,000 years at risk</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2</td>
<td>204</td>
<td>1</td>
</tr>
<tr>
<td>Irregular</td>
<td>12</td>
<td>33</td>
<td>0.16</td>
</tr>
<tr>
<td>Regularly</td>
<td>67</td>
<td>34</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Suspected Rickets

<table>
<thead>
<tr>
<th>Suspected Rickets</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77</td>
<td>4</td>
</tr>
</tbody>
</table>

81 (of 10,366 children) were diagnosed with type 1 diabetes

Experimental design

Offspring of vitamin D deficient NOD mice

- UV-free room
- No vitamin D in diet
- Switch of all mice to normal room
- 2000 IU/kg vitamin D in diet

Offspring of control vitamin D sufficient NOD mice

- Normal room
- 2000 IU/kg vitamin D in diet

- 8 days
- 100 days
- 250 days

Diabetes incidence Immune and βH cell analysis
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Diabetes incidence

Mechanisms of beta-cell destruction:
lessons for diabetes prevention: conclusions

- Insight in pathogenesis of disease is growing
- Prediction in first degree relatives becomes achievable
- In animal models prevention is possible—most effective is primary prevention
- Interventions are running
- Recently diagnosed type 1 diabetics as study population

Can we prevent type 1 diabetes?

Yes, we can, in animals
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