Programming of Autoimmunity Before and After Birth

Mikael Knip, M.D., Ph.D.
AGENDA

- Ontogeny of the human immune system
- What is autoimmunity?
- Role of thymus in central tolerance
- Primary immune deficiencies and autoimmunity
- Role of exogenous factors in the programming of the immune system
TIME SCHEDULE FOR THE DEVELOPMENT OF CELLS IMPORTANT IN THE IMMUNE SYSTEM DURING HUMAN GESTATION

- Thymic $\gamma\delta$ T cells
- Thymic $\alpha\beta$ T cells
- T-cell response to mitogens
- T reg cells
- B cells in fetal liver
- B cells in bone marrow
- Functional NK cells
CD4CD25high T cells are abundant in fetal, but not in adult lymphoid tissue.

Michaelson et al. *J Immunol* 2006;176:5741-48
Frequency of CFSElow CD4 (f) and CD8 T cells (g) in unstimulated cultures of unseparated fetal MLN cells (left) and MLN cells depleted of CD25 cells (right).

Fetal CD69CD25 T cells proliferate and produce IFN-γ in the absence of CD4CD25high T-Reg cells

Michaelson et al. *J Immunol* 2006;176:5741-48
CONCLUSIONS I

- All essential cells of the immune system are present and functional by the end of the first pregnancy trimester.

- The weak immune responsiveness of the fetus seems to be due to an effective suppression by regulatory T cells, the number of which appears to be four times higher in fetal peripheral lymph nodes compared to postnatal numbers.
Possible events following the encounter between antigen and the immune system

Schematic representation of the development of clinical tolerance through the pre- and postnatal periods

AUTOIMMUNITY =

BREAKING OF TOLERANCE

TO SELF-ANTIGENS
PLAYERS IN TOLERANCE INDUCTION

- CENTRAL TOLERANCE
  - negative selection in the thymus
  - the autoimmune regulator (AIRE) protein
  - dendritic cells

- PERIPHERAL TOLERANCE
  - regulatory T cells
  - dendritic cells
Representation of different tissues by promiscuous gene expression in thymic medullary epithelial cells

Mechanisms of central B-cell tolerance.

Mechanisms of central T-cell tolerance.

BREAKING OF SELF-TOLERANCE

CONCLUSION II

- BOTH CENTRAL AND PERIPHERAL MECHANISMS ARE IMPORTANT FOR THE INDUCTION AND MAINTENANCE OF TOLERANCE
INITIATION OF AUTOIMMUNITY

PATHOGENESIS OF TYPE 1 DIABETES

1. Genetic susceptibility
2. Beta-cell autoimmunity
3. Driving antigen
4. Clinical diabetes

Insulin secretory capacity, %

II. Trigger

Modyfying factors

Clinical diabetes

2 months - >20 years

I. Genetic susceptibility
II. Trigger
III. Beta-cell autoimmunity
IV. Driving antigen
CUMULATIVE INCIDENCE OF ICA, IAA, GADA AND IA-2A FROM BIRTH TO 2 YEARS OF AGE

DIPP

Kimpimäki et al. J Clin Endocrinol Metab 2002; 87: 4572-4579
CONCLUSION III

- AUTOIMMUNITY MAY BE INDUCED VERY EARLY AFTER BIRTH BUT THERE IS A HIGHLY INDIVIDUAL TIME LAG FROM THE INDUCTION TO CLINICAL DISEASE PRESENTATION
PRIMARY IMMUNODEFICIENCIES (PID)

- In most cases monogenic
- Result in a lacking or dysfunctional immune system
- More than 100 PIDs have been identified
<table>
<thead>
<tr>
<th>Primary immunodeficiencies</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Systematically associated</td>
<td>&gt;80</td>
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<tr>
<td>IPEX (immunodysregulation polyendocrinopathy</td>
<td>100</td>
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<tr>
<td>enteroopathy X-linked syndrome)</td>
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</tr>
<tr>
<td>Omenn syndrome (OS)</td>
<td>100</td>
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<tr>
<td>APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)</td>
<td>Almost 100</td>
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<tr>
<td>ALPS (autoimmune lymphoproliferative syndrome)</td>
<td>More than 80</td>
</tr>
<tr>
<td>C1q deficiency</td>
<td>93</td>
</tr>
</tbody>
</table>
AIRE GENE AND PROTEIN

- The gene is located on the long arm of chromosome 21.
- The gene encodes a protein comprising 545 amino acids.
- Molecular weight 58 kDa.
- Human AIRE protein structure and disease-causing missense mutations.

# APECED OR APS-1

## Table 1 Diagnostic criteria of APS-I

**Definite diagnosis**

- One of the following three criteria:
  - Presence of at least two of the major components chronic mucocutaneous candidosis, hypoparathyroidism or adrenal insufficiency
  - One of the major components if a sibling has definite APS-I
  - Disease-causing mutations in both AIRE genes

**Probable diagnosis**

- Presence of one of chronic mucocutaneous candidosis, hypoparathyroidism, adrenal insufficiency (before 30 years of age) and at least one of the minor components chronic diarrhoea, keratitis, periodic rash with fever, severe constipation, autoimmune hepatitis, vitiligo, alopecia, enamel hypoplasia
- Any component and anti-interferon antibodies
- Any component and antibodies against NALP5, AADC, TPH or TH

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*AIRED, autoimmune regulator; NALP5, NACHT leucine-rich repeat protein 5; AADC, aromatic L-amino acid decarboxylase; TPH, tryptophan hydroxylase; TH, tyrosine hydroxylase.*

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CENTRAL TOLERANCE AND PID

PERIPHERAL TOLERANCE AND PID

CONCLUSION IV

- MOST PIDs AFFECT BOTH CENTRAL AND PERIPHERAL TOLERANCE LEADING TO AUTOIMMUNE MANIFESTATIONS
Determinants of risk of atopy

THE HYGIENE HYPOTHESIS

Environmental changes in the developed world after World War II have led to reduced microbial exposure at an early age resulting in increasing incidence rates of immune-mediated diseases such as asthma and organ-specific autoimmune diseases.

NEW ELEMENTS IN THE HYGIENE HYPOTHESIS

- The role of the indigenous intestinal microbiota
- Regulatory and suppressive immune responses complement the Th1/Th2 paradigm
- The role of host-microbe interactions
Russian Karelia – a living laboratory
INCIDENCE OF TYPE 1 DIABETES IN CHILDREN < 15 YEARS OF AGE IN RUSSIAN KARELIA AND FINLAND IN 1990-1999


$P < 0.001$
COMPARISON BETWEEN RUSSIAN KARELIA AND FINLAND

The schoolchildren in Russian Karelia have a reduced morbidity in autoimmune diseases and a decreased frequency of allergen-specific atopy when compared to their Finnish peers:
- a 6-fold lower incidence rate of type 1 diabetes
- a 5-fold lower prevalence of celiac disease
- a 6-fold lower prevalence of thyroid autoimmunity
- a 2-6-fold lower frequency of allergen-specific IgE responses
COMPARISON BETWEEN RUSSIAN KARELIA AND FINLAND

- The schoolchildren in Russian Karelia have experienced a substantially heavier microbial load than their Finnish peers
  - a 15-fold higher prevalence of Helicobacter pylori antibodies
  - a 5-fold higher frequency of Toxoplasma gondii antibodies
  - a 12-fold higher prevalence of hepatitis A antibodies
  - a 20% higher frequency of Coxsackie virus B4 antibodies
CONCLUSION IV

- THE COMPARISON BETWEEN RUSSIAN KARELIAN AND FINNISH CHILDREN IN TERMS OF AUTOIMMUNITY AND ALLERGY SUPPORTS THE HYGIENE HYPOTHESIS
### Confirmed and Controversial Exogenous Factors in Pre- and Postnatal Programming of Autoimmunity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D supplementation during infancy</td>
<td>Protective against T1D</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Increased postnatal weight gain</td>
<td>Increases risk of T1D</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Maternal enterovirus infection</td>
<td>Increases risk of T1D</td>
<td>Controversial</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Increases risk of thyroid autoimmunity</td>
<td>Controversial</td>
</tr>
<tr>
<td>Potoranal rotavirus infection</td>
<td>Increases risk of beta-cell autoimmunity</td>
<td>Controversial</td>
</tr>
<tr>
<td>Early introduction of cow’s milk</td>
<td>Increases risk of T1D</td>
<td>Controversial</td>
</tr>
<tr>
<td>Early introduction of cereals</td>
<td>Increases risk of beta-cell autoimmunity</td>
<td>Controversial</td>
</tr>
</tbody>
</table>
Mechanisms of vitamin D immunomodulation

Enterovirus infections 0-6 months prior to appearance of autoantibodies

Lönnrot et al. *Diabetes* 2000; 49: 1314-1318
Detection of enterovirus RNA 0-6 months prior to appearance of autoantibodies

Lönnrot et al. *Diabetes* 2000; 49: 1314-1318
# ADDITIONAL CONTROVERSIAL EXOGENOUS FACTORS IN PRE- AND POSTNATAL PROGRAMMING OF AUTOIMMUNITY

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late introduction of cereals</td>
<td>Increases risk of beta-cell autoimmunity and celiac disease auto-immunity</td>
<td>Controversial</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Decreases risk of beta-cell autoimmunity</td>
<td>Controversial</td>
</tr>
<tr>
<td>Use of cod liver oil during the first year of life</td>
<td>Decreases risk of T1D</td>
<td>Controversial</td>
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### Implanted But So Far Unconfirmed Exogenous Factors in Prenatal Programming of Autoimmunity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Maternal use of vitamin D supplements</td>
<td>No effect on T1D in the offspring</td>
</tr>
<tr>
<td>Maternal use of vitamin D supplements</td>
<td>Decreases risk of beta-cell autoimmunity in the offspring</td>
</tr>
<tr>
<td>Maternal dietary vitamin D intake</td>
<td>Decreases risk of beta-cell autoimmunity in the offspring</td>
</tr>
<tr>
<td>High maternal intake of potatoes</td>
<td>Decreases risk of beta-cell autoimmunity in the offspring</td>
</tr>
<tr>
<td>High maternal intake of vegetables</td>
<td>Decreases risk of beta-cell autoimmunity in the offspring</td>
</tr>
<tr>
<td>High maternal intake of berries</td>
<td>Decreases risk of beta-cell autoimmunity in the offspring</td>
</tr>
<tr>
<td>Factor</td>
<td>Outcome</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Early enterovirus infections</td>
<td>Increases the risk of T1D</td>
</tr>
<tr>
<td>Weaning to a highly hydrolyzed formula</td>
<td>Decreases risk of beta-cell autoimmunity</td>
</tr>
<tr>
<td>Early introduction of cereals</td>
<td>Increases risk of celiac autoimmunity</td>
</tr>
<tr>
<td>Early introduction of cereals</td>
<td>Increases risk of clinical celiac disease</td>
</tr>
<tr>
<td>Late introduction of cereals</td>
<td>Increases risk of celiac autoimmunity</td>
</tr>
<tr>
<td>Intake of omega-3-fatty acids from the age of 1 to 6 years</td>
<td>Decreases risk of beta-cell autoimmunity</td>
</tr>
<tr>
<td>Circulating vitamin E concentrations</td>
<td>No effect on beta-cell autoimmunity</td>
</tr>
</tbody>
</table>
CONCLUSION V

➢ THERE IS A LONG LIST OF POTENTIAL EXOGENOUS FACTORS THAT MAY AFFECT THE PROGRAMMING OF THE PRE- AND POSTNATAL IMMUNE SYSTEM BUT SO FAR VERY FEW WITH A CONFIRMED EFFECT
THYMUS AND EARLY POSTNATAL GROWTH AND INFANT FEEDING?
Relationship between growth rate during the first year of life and plasma thymopoietin concentration in 14-15-years-old

McDade et al, J Nutr 2001;131:1225-1231
Interaction between birth weight-for-gestational age and duration of exclusive breast-feeding in predicting plasma thymopoietin concentration in 14- to 15-y olds

\[ P=0.006 \]
EARLY FEEDING AND BETA-CELL AUTOIMMUNITY

- EARLY EXPOSURE TO COMPLEX DIETARY PROTEINS MAY INCREASE THE RISK OF BETA-CELL AUTOIMMUNITY AND TYPE 1 DIABETES IN CHILDREN WITH INCREASED GENETIC DISEASE SUSCEPTIBILITY
IS IT POSSIBLE TO REDUCE THE FREQUENCY OF DIABETES-ASSOCIATED AUTOANTIBODIES BY EXCLUDING DIETARY COW’S MILK PROTEINS OVER THE FIRST 6-8 MONTHS OF LIFE IN SUBJECTS AT INCREASED RISK OF TYPE 1 DIABETES?
TWO HUNDRED THIRTY (230) INFANTS FROM DIABETIC FAMILIES:
- 85 mothers with diabetes (37%)
- 100 fathers with diabetes (43%)
- 35 siblings with diabetes (15%)
- 10 families with more than one affected family member (4%)

HLA GENOTYPES:
- DQB1*02/0302 51 (22%)
- DQB1*0302/x 92 (40%)
- DQB1*02/y 87 (38%)

FOLLOW-UP TIME: mean 7.5 years (range 3 months – 10 years)
  median 10 years

TRIGR Pilot
SEROCONVERSION TO POSITIVITY FOR AT LEAST ONE AUTOANTIBODY

Casein hydrolysate (CHF)

Regular formula (CMF)

P = 0.026
### HAZARD RATIOS (HR) FOR SEROCONVERSION TO AUTOANTIBODY POSITIVITY IN THE CASEIN HYDROLYSATE GROUP

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one autoantibody (n=50)</td>
<td>0.49 (0.26-0.87)</td>
<td><strong>0.014</strong></td>
<td>0.47 (0.25-0.84)</td>
<td><strong>0.011</strong></td>
</tr>
<tr>
<td>ICA (n=37)</td>
<td>0.38 (0.18-0.76)</td>
<td><strong>0.006</strong></td>
<td>0.37 (0.17-0.75)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>IAA (n=23)</td>
<td>0.72 (0.30-1.64)</td>
<td>0.434</td>
<td>0.64 (0.26-1.47)</td>
<td>0.292</td>
</tr>
<tr>
<td>GADA (n=23)</td>
<td>0.87 (0.37-1.98)</td>
<td>0.746</td>
<td>0.81 (0.34-1.87)</td>
<td>0.623</td>
</tr>
<tr>
<td>IA-2A (n=20)</td>
<td>0.34 (0.11-0.88)</td>
<td><strong>0.023</strong></td>
<td>0.30 (0.10-0.79)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>ZnT8A (n=14)</td>
<td>0.60 (0.18-1.74)</td>
<td><strong>0.350</strong></td>
<td>0.60 (0.18-1.75)</td>
<td><strong>0.350</strong></td>
</tr>
</tbody>
</table>

*Adjusted for exposure to study formula
TYPE 1 DIABETES

- Altogether 16 cases
  - 9/116 (7.8%) in the control group
  - 7/114 (6.1%) in the hydrolysate group
    Per protocol: 4/111 (3.6%)
    Lost to follow-up: 3/22 (13.6%)

- HAZARD RATIOS
  - Intention to treat 0.80 (95% CI 0.30-2.14)
  - Adjusted 0.48 (95% CI 0.14-1.61)
  - Per protocol 0.40 (0.11-1.51)

TRIGR Pilot
CONCLUSION V

- IT MAY BE POSSIBLE TO REDUCE THE RISK OF BETA-CELL AUTOIMMUNITY BY EARLY NUTRITIONAL INTERVENTION IN INFANTS AT RISK FOR TYPE 1 DIABETES
QUESTION IN TRIGR PROPER

IS IT POSSIBLE TO REDUCE

(i) THE FREQUENCY OF DISEASE-ASSOCIATED AUTO-
    ANTIBODIES AND/OR CLINICAL DIABETES BY THE
    AGE OF 6 YEARS AND

(ii) THE CUMULATIVE INCIDENCE OF DIABETES BY
    THE AGE OF 10 YEARS

BY WEANING TO A HIGHLY HYDROLYZED FORMULA
OVER THE FIRST 6-8 MONTHS OF LIFE?
PRESENT STATUS OF TRIGR

- 77 PARTICIPATING CENTERS FROM 15 COUNTRIES
- 2160 RANDOMIZED PARTICIPANTS REMAINED IN THE STUDY AFTER HLA GENOTYPING. THE OLDEST CHILD HAS TURNED 7 YEARS AND THE YOUNGEST WILL BE 6-YEAR-OLD IN 02/2013 AND 10-YEAR-OLD IN 02/2017
THE TYPE 1 DIABETES PREDICTION AND PREVENTION (DIPP) STUDY

- Screening of all newborn infants (n=11,000/year) in three university hospitals (Oulu, Tampere, Turku) for HLA-conferred susceptibility to type 1 diabetes from cord blood.

- Eligibility criterion
  - high risk genotype (HLA DQB1*02/0302), 7% cumulative risk of T1D by the age of 15 years
  - moderate risk genotypes [HLA DQB1*0302/x (x≠*0301, *0602), DQB1*0302/0604, DQB1*0603], 2-3% cumulative risk of T1D by the age of 15 years

- Invitation of families with a baby carrying the high risk or moderate risk genotypes: Follow-up visits at an interval of 3-12 months, screening for the appearance of beta-cell autoimmunity.
STUDY COHORT: -117 CHILDREN (50 PROGRESSORS AND 67 NON-PROGRESSORS) FROM THE TYPE 1 DIABETES PREDICTION AND PREVENTION (DIPP) STUDY -12 CHILDREN FROM THE SPECIAL TURKU CORONARY RISK FACTOR INTERVENTION PROJECT (STRIP)
DEFINITION OF METABOLOMICS

Metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind" - specifically, the study of their small-molecule metabolite profiles.

Wikipedia 2009
TOTAL PHOSPHATIDYLCHOLINE CONCENTRATIONS IN CORD BLOOD

LIPID PROFILE IN SERUM DURING PROSPECTIVE FOLLOW-UP: Progressors/non-progressors

DECREASED SERUM TRIGLYCERIDES AND ETHER PHOSPHATIDYLCHOLINES DURING PROSPECTIVE FOLLOW-UP

CONCLUSION VI

- Low serum lipids might favor the induction of beta-cell autoimmunity by predisposing to oxidative stress.

- Metabolic changes reflect both dietary intake and intestinal microflora.
THE FINNISH NETWORK ON CHILDHOOD DIABETES

AUTOIMMUNITY
- Olli Simell
- Outi Vaarala
- Hans K. Åkerblom
- Sanna Hoppu
- Taina Härkönen
- Kirsti Näntö-Salonen
- Heli Siljander
- Tuula Simell

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- Robert Hermann
- Riitta Veijola

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- Sisko Tauriainen
- Hanna Viskari
- Suvi Virtanen
- Marjaliisa Erkkola

EPIDEMIOLOGY
- Antti Reunanen
- Anita Kondrashova

SYSTEMS BIOLOGY
- Matej Oresic
- Marko Sysiaho

THE STUDY GROUPS
- DiMe
- TRIGR (MIP)
- DIPP
- DIABIMMUNE
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- Diabetes Research Foundation, Finland
- Novo Nordisk Foundation
- Sigrid Jusélius Foundation
DAILY PROBABILITY OF SEROCONVERSION FOR THE FIRST DIABETES-ASSOCIATED AUTOANTIBODY
Table 1. Frequencies of CD25$^{hi}$ Treg’s among CD3$^{hi}$CD4$^{+}$CD8$^{-}$ T cells in various organs from human fetuses

<table>
<thead>
<tr>
<th>Age</th>
<th>Thymus</th>
<th>Spleen</th>
<th>Liver</th>
<th>Bone marrow</th>
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<td>Fetus, wk</td>
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<td></td>
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<tr>
<td>13</td>
<td>26</td>
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<td>ND</td>
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<td>14</td>
<td>5</td>
<td>10</td>
<td>ND</td>
<td>ND</td>
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<td>14.5</td>
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<td>32</td>
<td>ND</td>
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<td>29</td>
<td>7</td>
<td>16.5</td>
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<tr>
<td>Mean</td>
<td>8.3</td>
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<td>SD</td>
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<td>6.3</td>
<td>7.4</td>
<td>6.4</td>
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<td>Child, mo</td>
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<tr>
<td>2</td>
<td>7</td>
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<tr>
<td>24</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

Schematic representation of factors that influence the T-cell polarizing capacity of dendritic cells (DC) that drive the development of either Th1, Th2 or Treg cells
Manifestations of proven or suspected autoimmune mechanism associated with common variable immunodeficiency

<table>
<thead>
<tr>
<th>Haematological</th>
</tr>
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<tbody>
<tr>
<td>- Autoimmune cytopenias</td>
</tr>
<tr>
<td>- Autoimmune haemolytic anemia</td>
</tr>
<tr>
<td>- Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>- Autoimmune neutropenia</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
</tr>
<tr>
<td>- Pernicious anemia</td>
</tr>
<tr>
<td>- Atrophic gastritis</td>
</tr>
<tr>
<td>- Celiac disease</td>
</tr>
<tr>
<td>- Primary biliary cirrhosis</td>
</tr>
<tr>
<td>- Inflammatory bowel disease</td>
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<tr>
<td>Rheumatological</td>
</tr>
<tr>
<td>- Sjögren syndrome</td>
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<tr>
<td>- Systemic lupus erythematosus</td>
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<tr>
<td>- Chronic juvenile arthritis</td>
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<tr>
<td>Endocrinological</td>
</tr>
<tr>
<td>- Hashimoto's thyroiditis</td>
</tr>
<tr>
<td>- Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>Dermatological</td>
</tr>
<tr>
<td>- Vitiligo</td>
</tr>
<tr>
<td>- Alopecia</td>
</tr>
<tr>
<td>Neurological</td>
</tr>
<tr>
<td>- Guillain-Barré syndrome</td>
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Bussone and Mouthon, Autoimmun Rev 2009;8: 332-6