# NEONATAL VACCINATION AND AUTOIMMUNITY

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# IMMUNOLOGICAL SAFETY OF NEONATAL VACCINATION

**In a context of neonatal immunological immaturity, is there a risk that**

- **non-specific bystander effects of vaccination or**
- **specific vaccine-induced responses**

**would trigger or induce autoimmune diseases?**

# SOME AUTOIMMUNE DISEASES CAN HAVE AN EARLY ONSET (< 12 MONTHS)

# SOME AUTOIMMUNE DISEASES CAN HAVE AN EARLY ONSET (< 12 MONTHS)

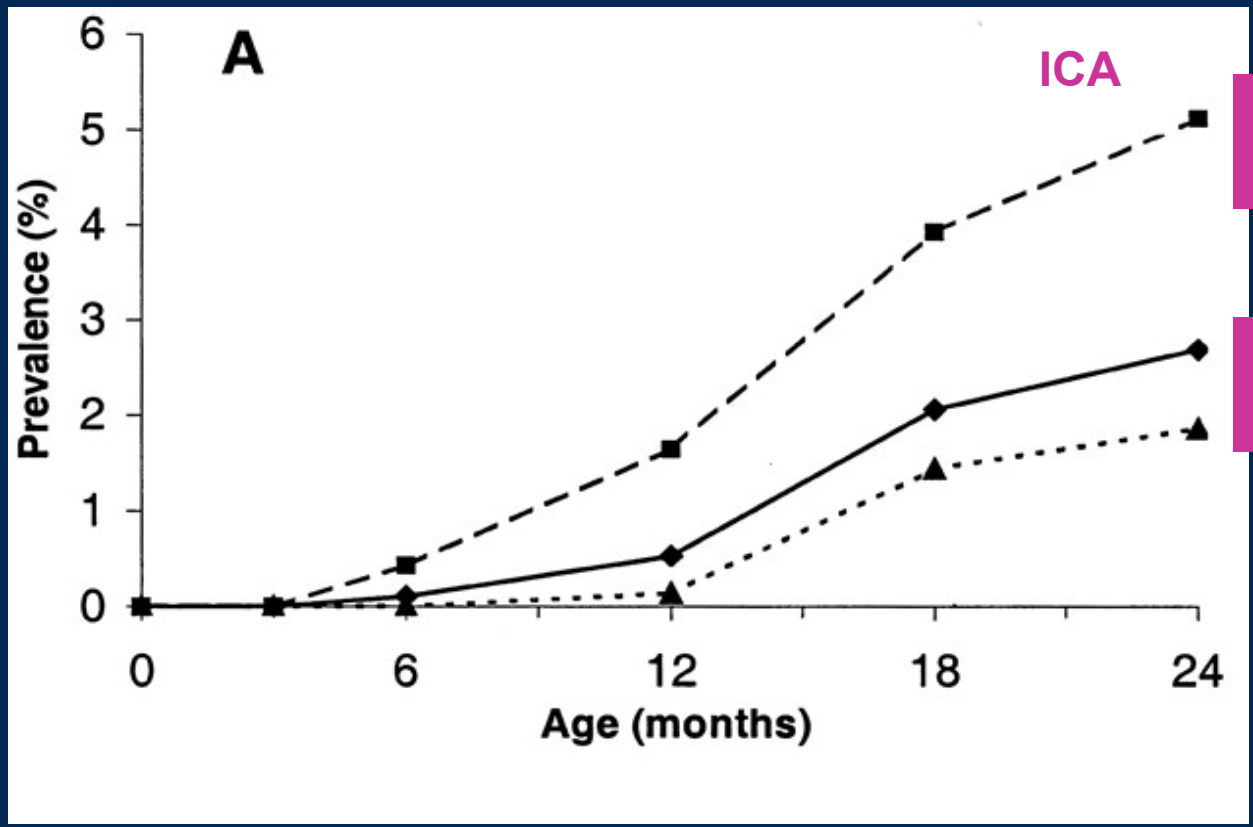
- **TYPE 1 DIABETES**

# Type 1 diabetes
# importance of genetic background

| | Risk of diabetes |
|---|---|
| Monozygotic twin of patient with type 1 DM | 1/2 |
| DR3/IDDM 17 homozygote | 1/3 |
| DQ8/DQ2 sibling type 1 DM | 4/10 |
| DQ8/DQ2 general population | 1/20 |
| Dizygotic twin of patient with type 1 DM | 1/20 |
| Sibling of patient with type 1 DM | 1/20 |
| US population | 1/300 |

*Robles DT & Eisenbarth GS., J Autoimmun 2001 May;16(3):355-62*

# Frequency of Islet Cell Antibodies from 0-2 yr (Finland)




high-risk genotype (HLA-DQB1*02/*0302

moderate-risk genotypes

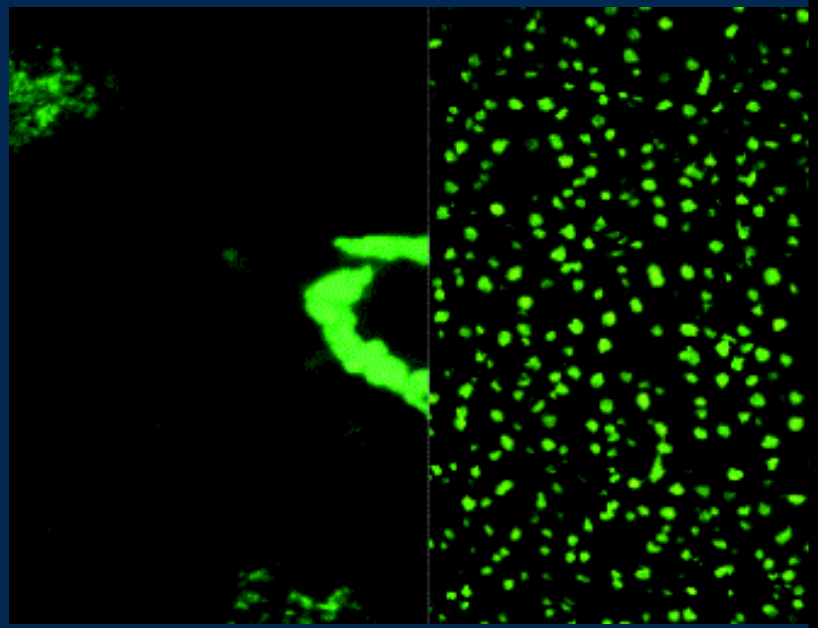
*Kimpimäki T., 2002, Journal of Clinical Endocrinology & Metabolism. 87: 4572-4579*

# SOME AUTOIMMUNE DISEASES CAN HAVE AN EARLY ONSET (< 12 MONTHS)

- TYPE 1 DIABETES
- **AUTOIMMUNE HEPATITIS – (AIH)**

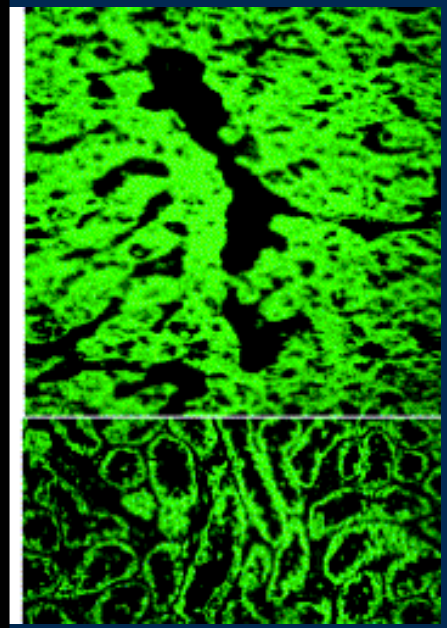
# AUTO-IMMUNE HEPATITIS (AIH)

## TYPE 1



anti- smooth muscle &
antinuclear antibodies

## TYPE 2



antibodies to cytochrome
CYP450-2D6
role of HCV? of HSV?

# SOME AUTOIMMUNE DISEASES CAN HAVE AN EARLY ONSET (< 12 MONTHS)

- TYPE 1 DIABETES
- AUTOIMMUNE HEPATITIS – TYPE 2 (AIH)
- **IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)**

# Idiopathic Thrombocytopenic Purpura (ITP) in infancy

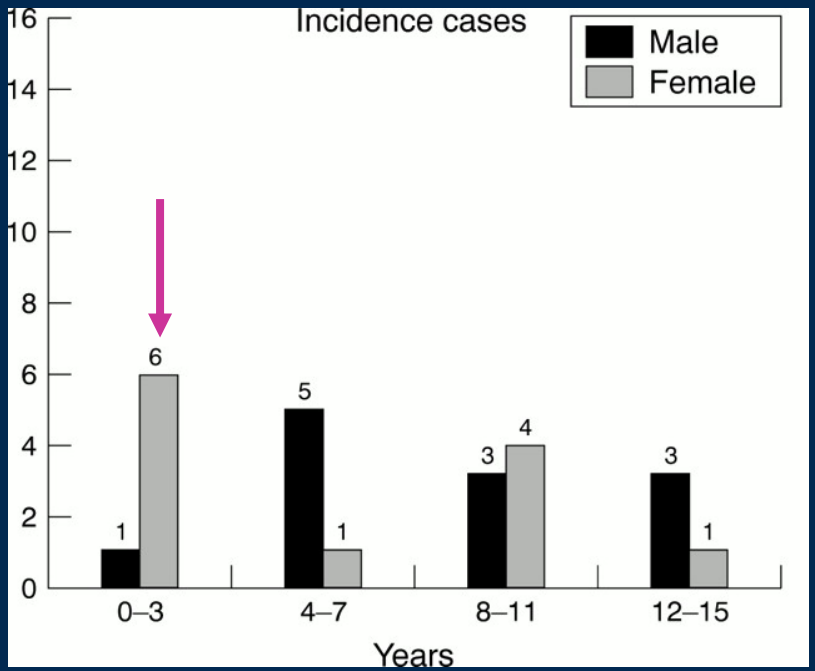
| Age Distribution of 79 Infants With ITP | |
|---|---|
| **Age range (months)** | **No. (%)** |
| 2–6 | 11 (14) |
| 7–12 | 15 (19) |
| 13–18 | 30 (38) |
| 19–24 | 23 (29) |

*Sandoval C, Pediatr Blood Cancer 2004;42:109–112*

# SOME AUTOIMMUNE DISEASES CAN HAVE AN EARLY ONSET (< 12 MONTHS)

- TYPE 1 DIABETES
- AUTOIMMUNE HEPATITIS – TYPE 2 (AIH)
- IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)
- JUVENILE CHRONIC ARTHRITIS (JCA)

# Juvenile Chronic Arthritis




**Norway 1985-94**
**Annual incidence of JCA: 22.6/100,000 children < 16 yr (42% HLA-B27 positive)**

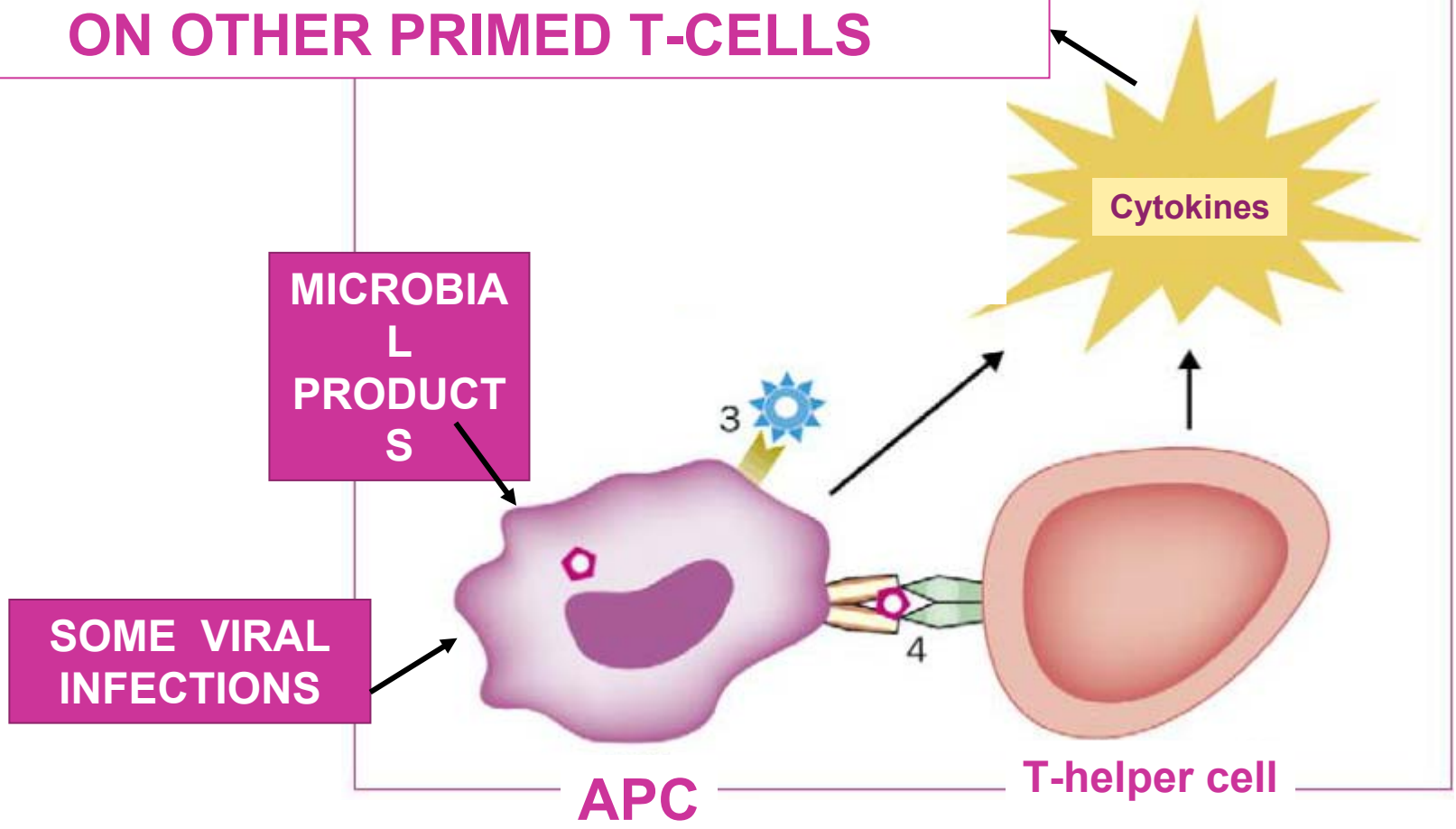
*Moe N, Clin Exp Rheumatol. 1998;16:99-101*

**JCA in relation to age and sex in Southern Germany**
*von Koskull et al., Ann Rheum Dis* 2001;60:940

**In a context of neonatal immunological immaturity,**
**is there a risk that vaccines would trigger an autoimmune disease through**

- **BYSTANDER ACTIVATION?**

# BYSTANDER EFFECTS ON OTHER PRIMED T-CELLS



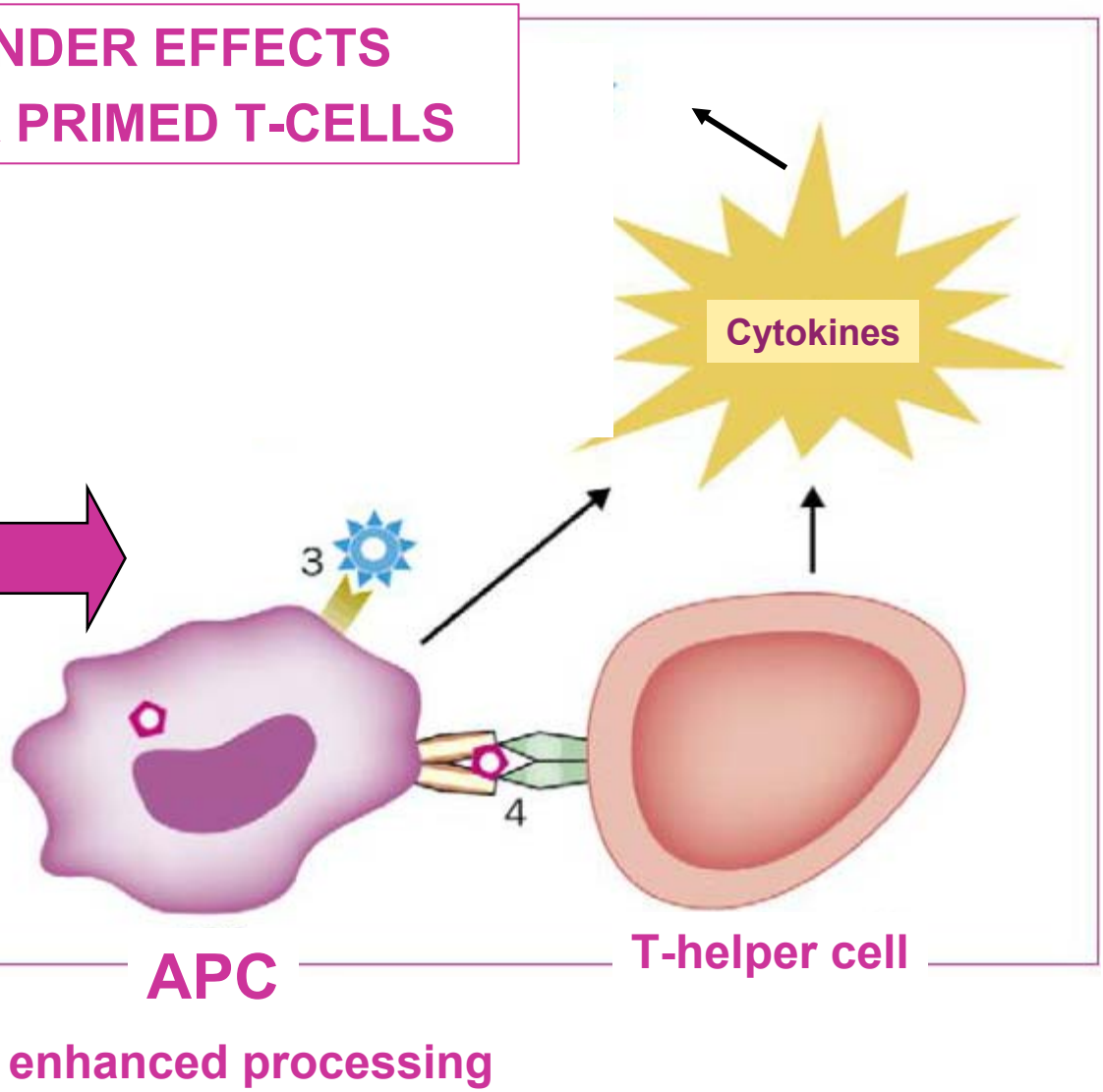

enhanced processing

# BYSTANDER EFFECTS ON OTHER PRIMED T-CELLS

**New adjuvants**
MPL, LTm, QS21, CpG, …

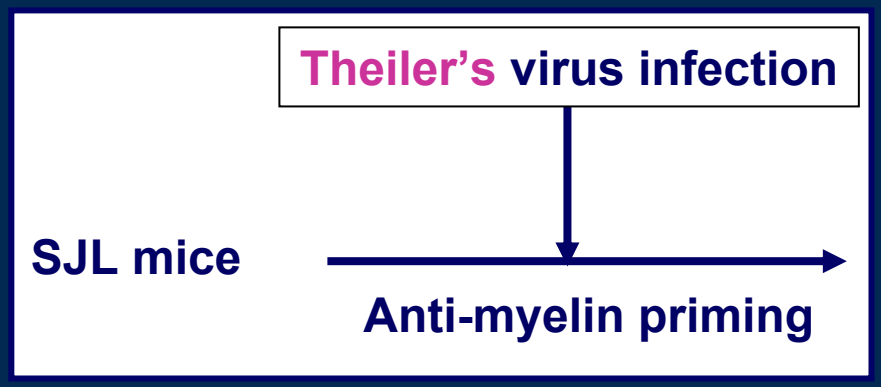
**DNA vaccines**

**Live attenuated**
viruses (IL-12 inducers), engineered BCG



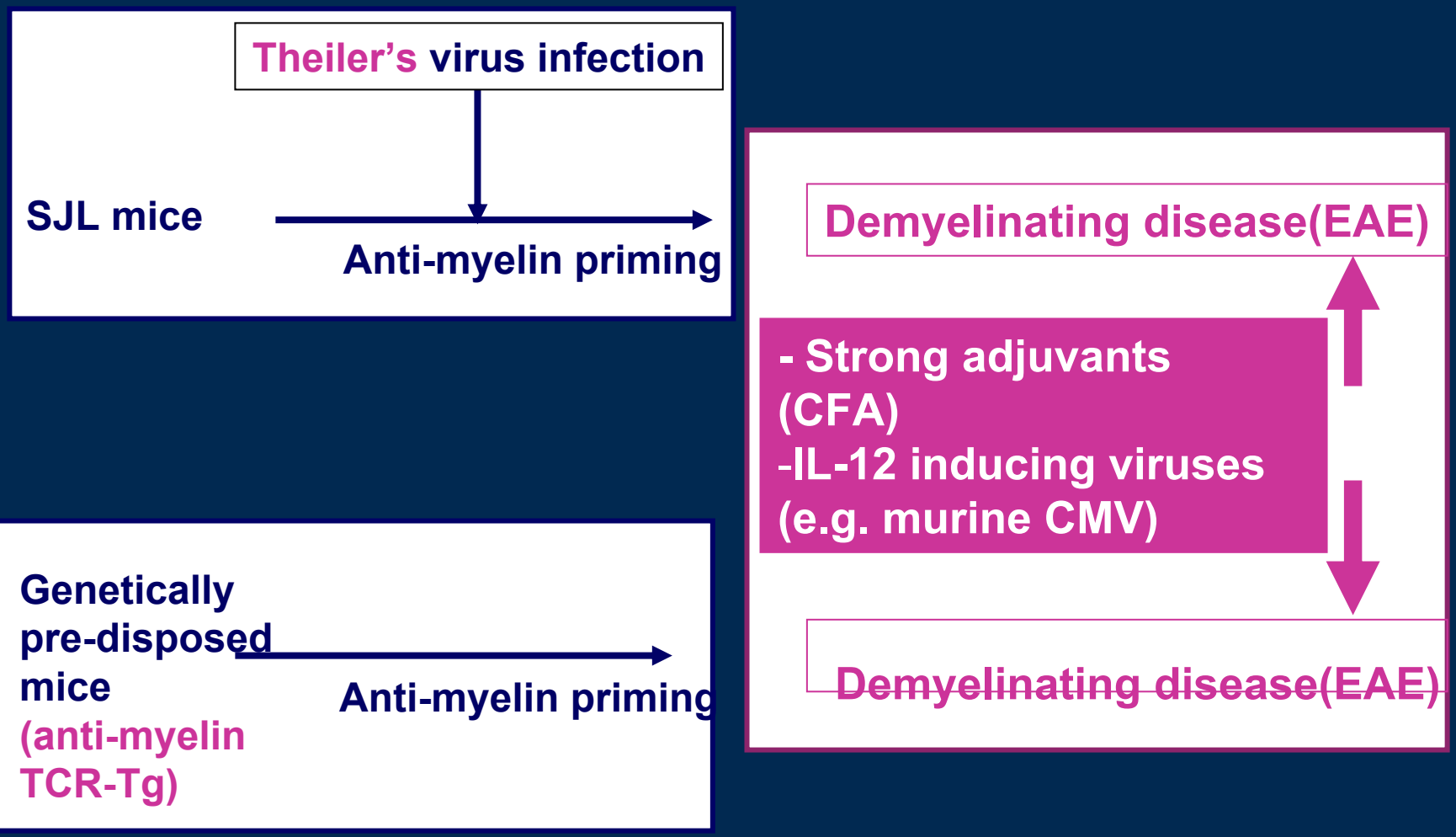

enhanced processing

# Autoimmune experimental encephalitis (EAE): silent priming




no clinical disease

# Autoimmune experimental encephalitis (EAE): triggering




*Theil DJ, Tsunoda I, Rodriguez F, Whitton JL, Fujinami RS, J Neurovirol 2001; 7:220-227.*
*Segal BM, Chang JT ,Shevach EM., J Immunol 2000; 164:5683-5688.*

# SOME INFECTIONS CAN TRIGGER AN UNDERLYING SILENT AUTOIMMUNE DISEASE

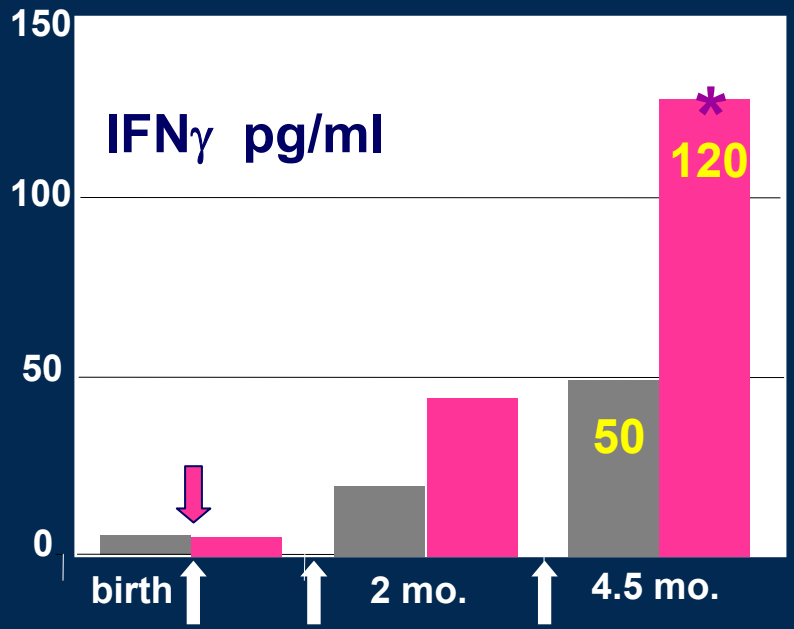
**Human Influenza infection**
**in adults**
**Triggering of exacerbations of relapsing Multiple Sclerosis in 33% of patients, within the following 6 weeks**

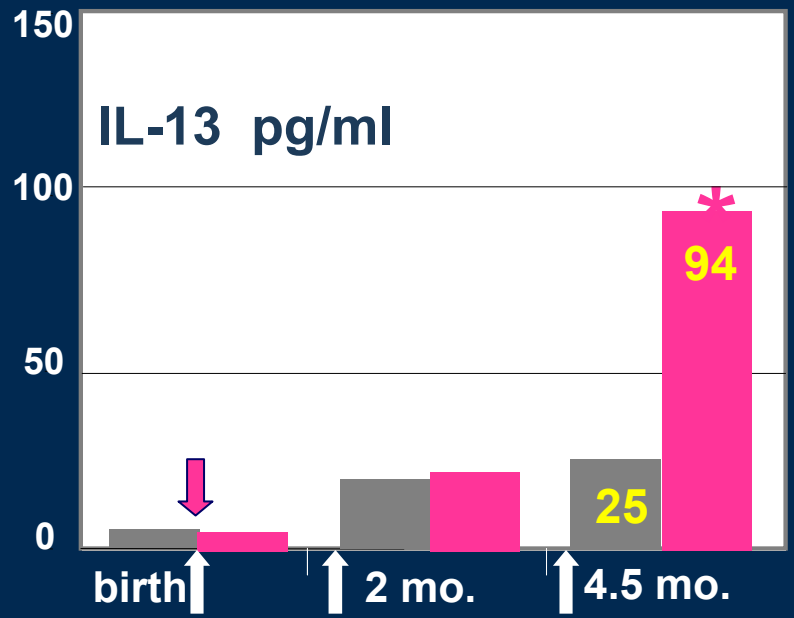
***De Keyser J, Zwanikken C, Boon M., J Neurol Sci 1998 ;159:51-3***

# Effect of neonatal BCG on Hepatitis B vaccine response

Hep B at birth + 6, 10 wks

Hep B at birth + 6, 10 wks + BCG at birth




Age at sampling

*Ota, M. et al., J. Immunol. 2002. 168: 919-925*

***+ 3X increase of anti-HB antibodies***

# NEONATAL VACCINATION AND AUTOIMMUNE DISEASES

## NO SIGNIFICANT EFFECT OF BCG AT BIRTH ON EPIDEMIOLOGY OF TYPE 1 DIABETES

- The cumulative incidence of childhood diabetes mellitus in Sweden is unaffected by BCG-vaccination.
  Dahlquist G, et al., 1995;38:873-4

- Bacille Calmette-Guerin vaccination and incidence of IDDM in Montreal, Canada
  Parent ME,etal., Diabetes Care. 1997;20:767-72.

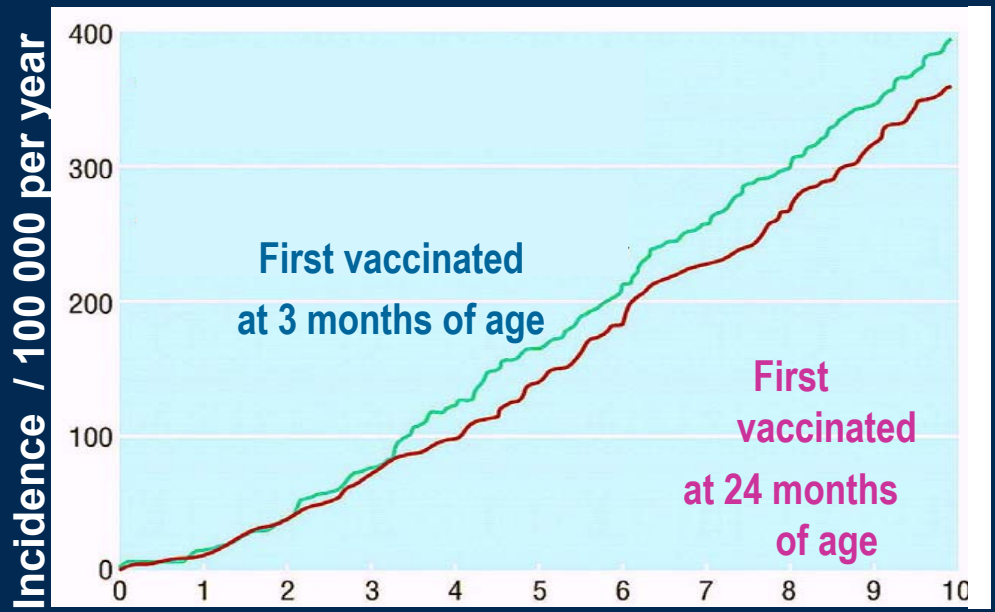
# Childhood vaccinations, vaccination timing, and risk of type 1 diabetes

**No significant association between childhood vaccines and risk of type 1 diabetes**

**DTP, DTaP, HepB, Hib, MMR, varicella**

*DeStefano F, et al., Pediatrics 2001;108:E112*

Type 1 Diabetes and Hib Vaccination (Finnish Birth Cohort Study)




*Karvonen M, et al., BMJ, 1999; 318:1169-72*

**Non antigen-specific effects of live or adjuvanted vaccines:**

- **usually time-limited**
- **often localised to regional lymph nodes**
- **negatively influenced by regulatory mechanisms (e.g. $CD4^+$ $CD25^+$ T cells)**

# NEONATAL VACCINATION AND AUTOIMMUNE DISEASES

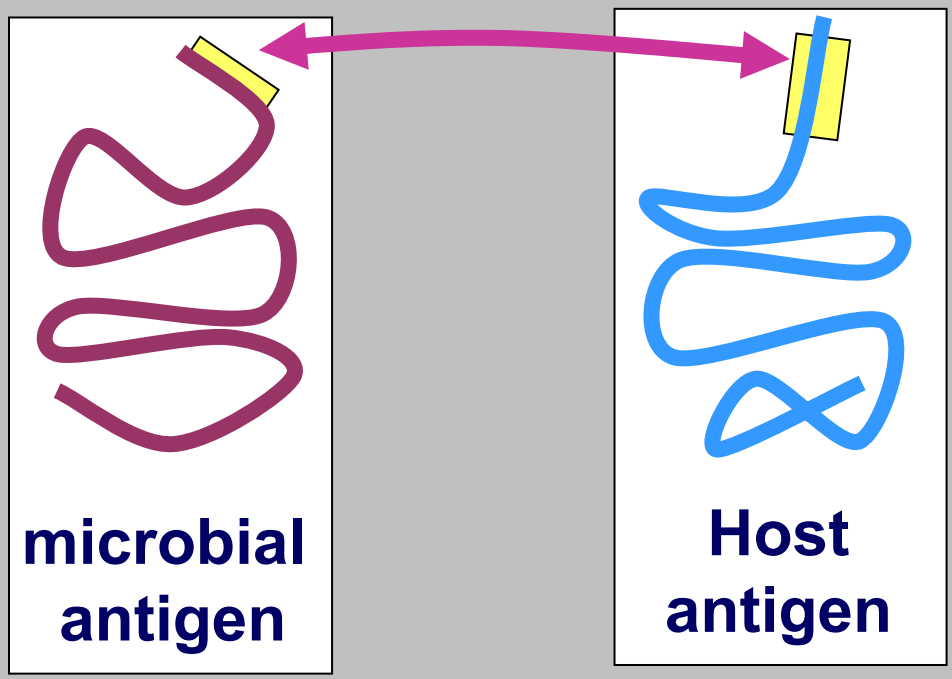
**The potential risk of triggering an underlying autoimmune disease through non-specific bystander effects (new adjuvants, some live vaccines) is very limited**

**… but should not be ignored during vaccine development.**

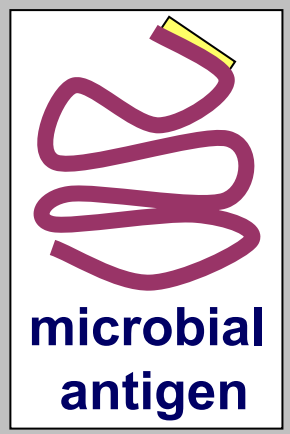
**In a context of neonatal immunological immaturity, is there a risk that vaccines would trigger an autoimmune disease through**

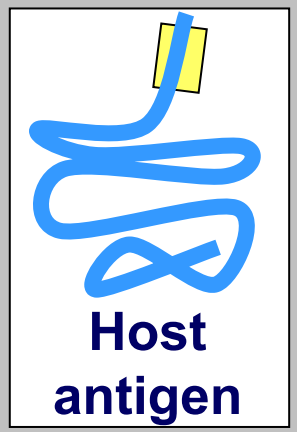
- **MOLECULAR MIMICRY?**

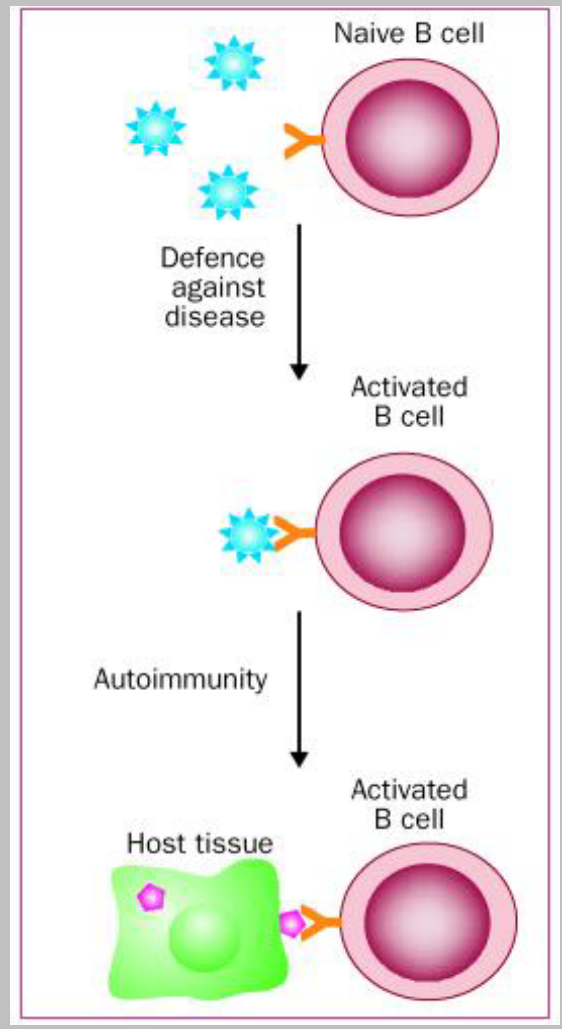
# B-CELL EPITOPE MIMICRY

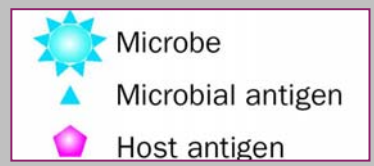


# B-CELL EPITOPE MIMICRY



# B-CELL EPITOPE MIMICRY

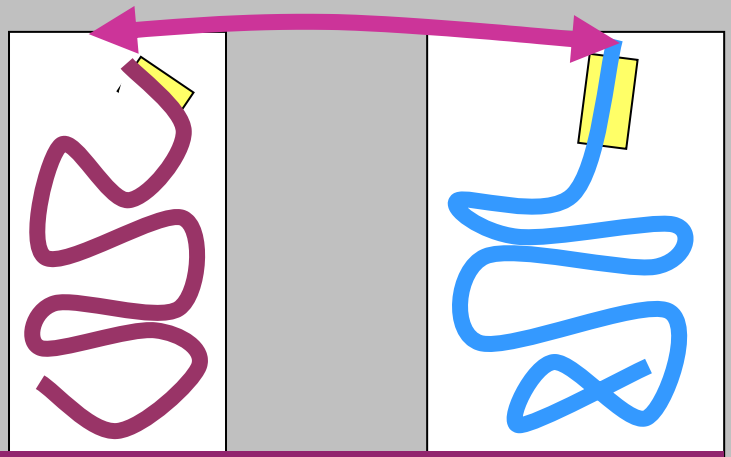
**Particular importance for polysaccharide vaccines**

Structural homologies involving oligosaccharide (repetitive epitopes) can be sufficient to select out a vaccine antigen

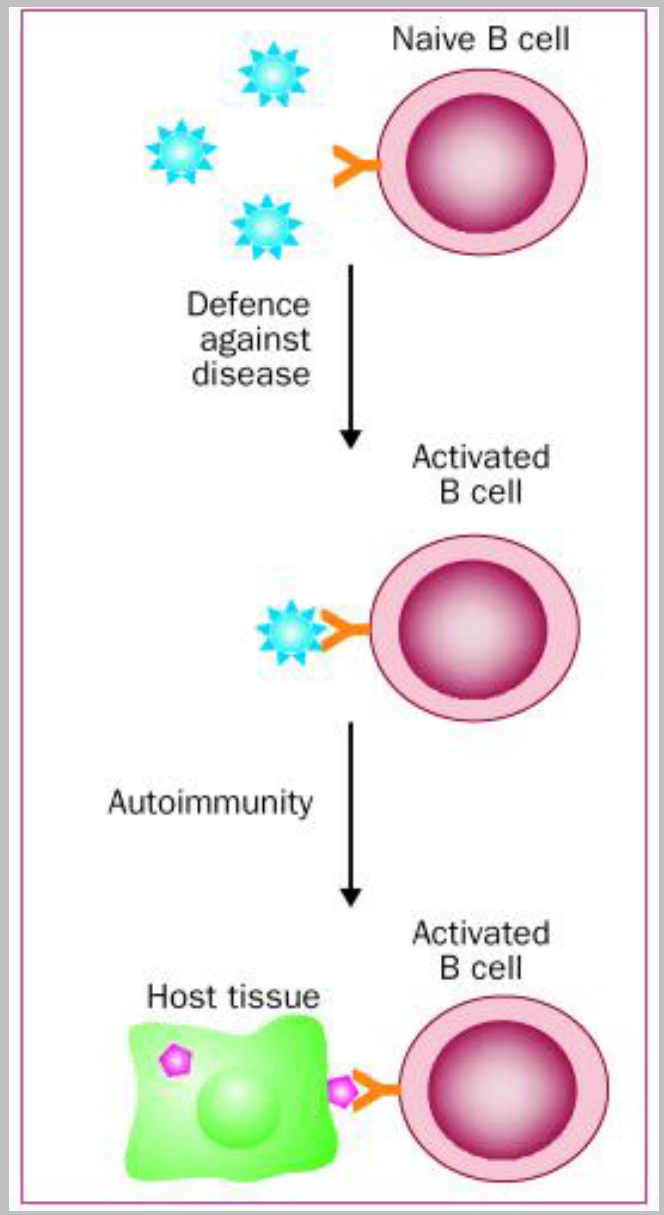
e.g.

- Group B mening.: capsular PS & NCAM-poly-alpha-2,8-NeuAc
- Campylobacter LPS and gangliosides

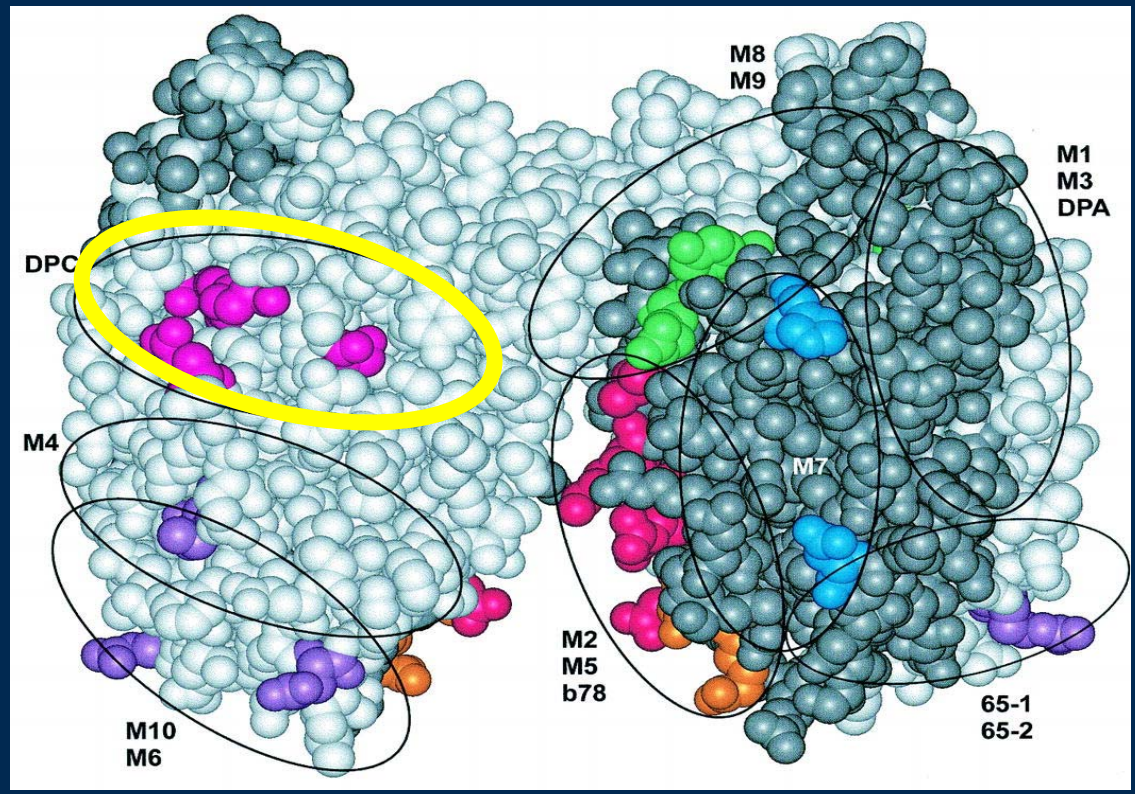
# B-CELL EPITOPE MIMICRY



<u>for peptidic antigens</u>
extensive sequence homology and/or conformation similarity are required



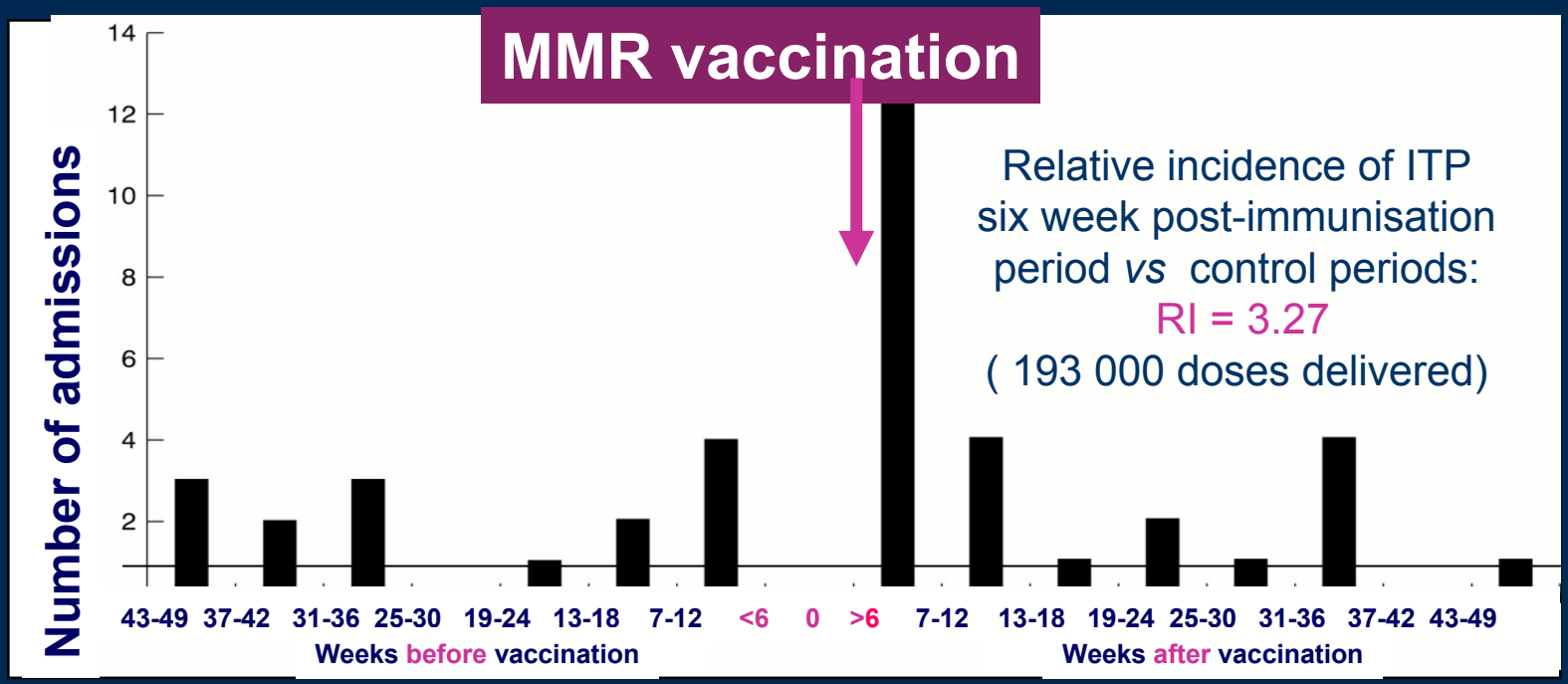
GAD65 islet cell antigen mapped with antibodies from type I diabetes patients




Schwartz H.L. et al., J. Mol. Biol. (1999) 287, 983

B-cell epitopes seen by auto-antibodies are surface exposed, conformational, discontinuous

# Idiopathic Thrombocytopenic Purpura and MMR




*E Miller, et al., Arch Dis Child 2001;84:227-229*

# ITP and MMR

-Increase in platelet-associated immunoglobulin (2/3 pt)
-Circulating antiplatelet autoantibodies against glycoprotein IIb/IIIa (1/3 pt)

*Nieminen U, Peltola H, Syrjala MT, Makipernaa A, Kekomaki R. , Acta Paediatr 1993; 82(3):267-70*

**Post-MMR vaccination**

**1 / 22 300 to**
**1 / 100 000 doses**

**Post-infection**

**Rubella 1 / 3000**
**Measles 1 / 6000**

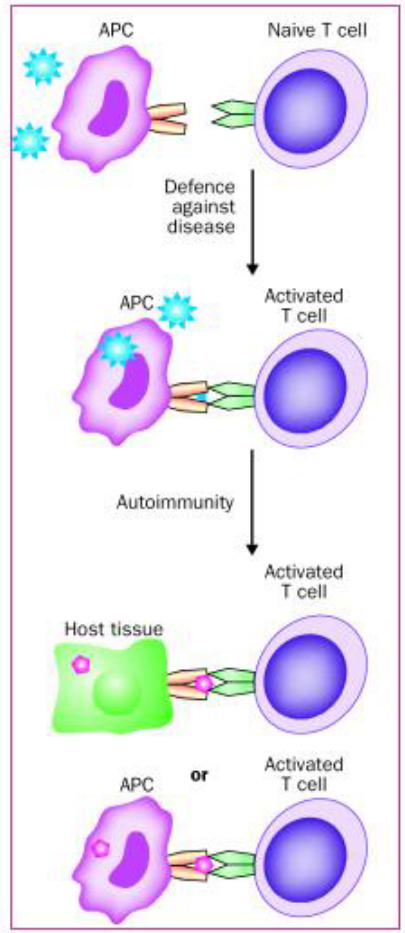
**Peltola H, Heinonen OP, Valle M, Paunio M, Virtanen M, Karanko V, Cantell K., N Engl J Med. 1994;331:1397-402; *Jonville-Bera AP, Autret E, Galy-Eyraud C, Hessel L., Pediatr Infect Dis J. 1996;15:44-8*

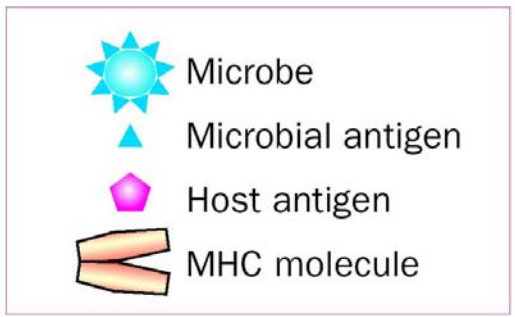
# T-CELL EPITOPE MIMICRY

**Small linear peptides**

CD4$^{+}$ : 11-20 AA peptides with 9-mer core binding peptide (HLA-class II)

CD8$^{+}$ : 8-10 AA peptides with 2 main anchor residues (HLA class I binding)



# NEW VACCINES AND T-CELL EPITOPE MIMICRY

**Sequence homologies (6-9 mer peptides) with human proteins can be extremely frequent**

# Tetanus Toxin *vs* 15,000 Human Proteins

| Peptide size | Matching level (common aa) | Hu. proteins with pept. similarity |
|---|---|---|
| 6-mer | 6/6 | 209 |
| | 5/6 | >11,000 |
| 7-mer | 7/7 | 9 |
| | 6/7 | 758 |
| 8-mer | 8/8 | 0 |
| | 7/8 | 95 |
| 9-mer | 8/9 | 8 |
| | 7/9 | 434 |

***J. Thonnard 2002, pers. communic.***

# NEW VACCINES AND T-CELL EPITOPE MIMICRY

1. Sequence homologies with human proteins? (data bank, 6-9 mer peptides)

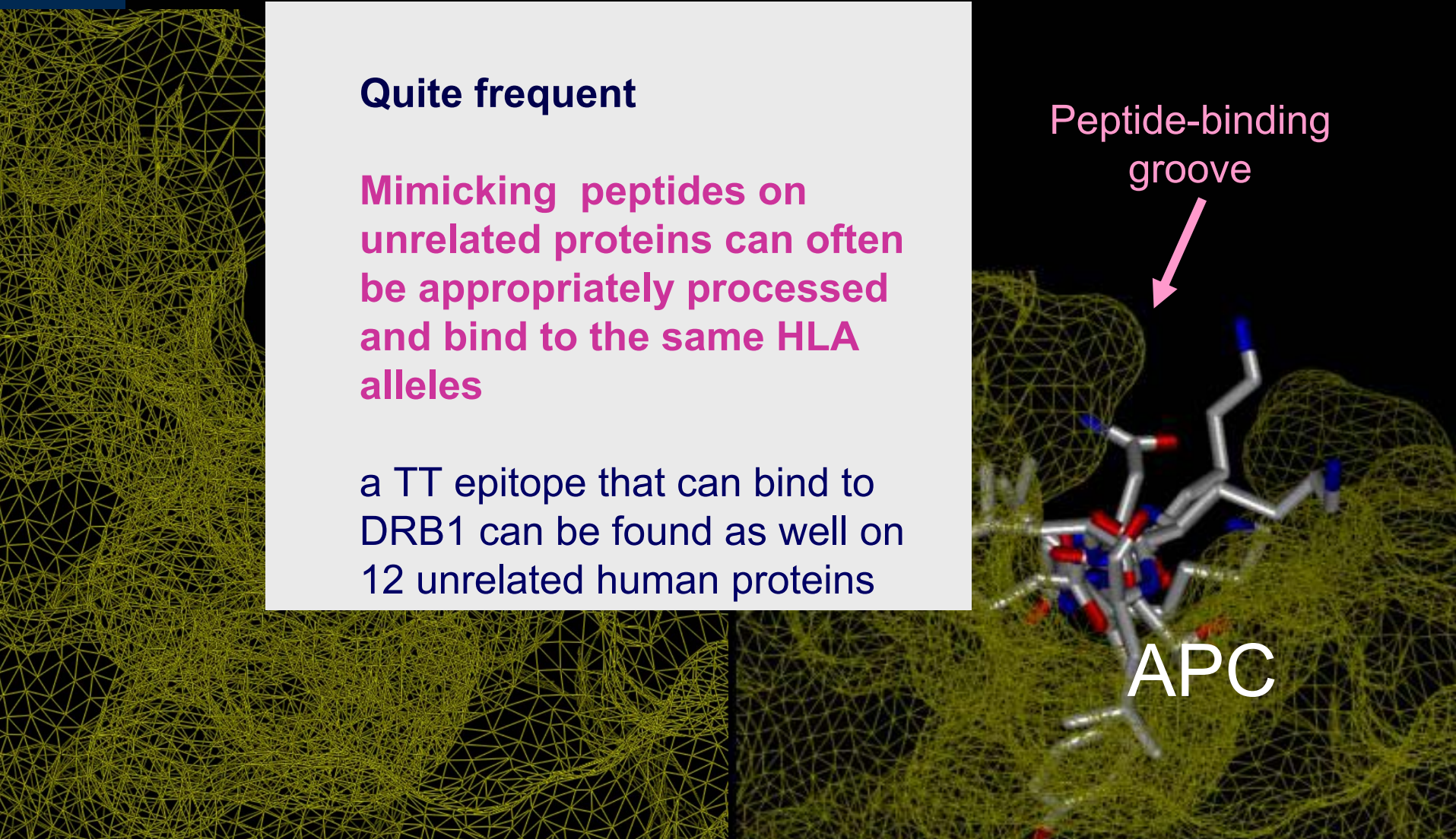
2. **Common T cell epitopes?, using epitope prediction methods (algorithms, structural modeling)**

# Common T cell epitopes?

**Quite frequent**

**Mimicking peptides on unrelated proteins can often be appropriately processed and bind to the same HLA alleles**

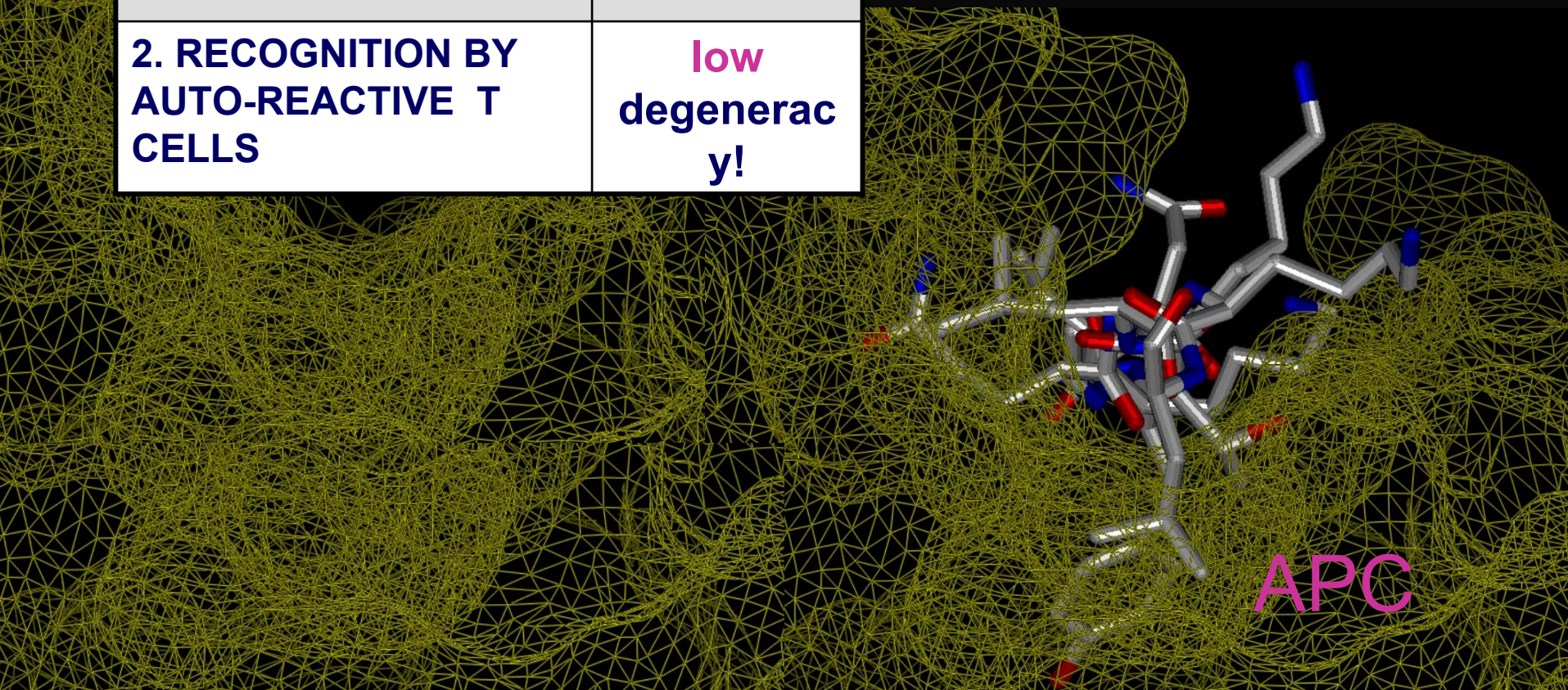
a TT epitope that can bind to DRB1 can be found as well on 12 unrelated human proteins



# FROM MIMICKING T CELL EPITOPES TO AUTOIMMUNE DISEASES: WHAT IS NEEDED?

| LIMITING FACTORS | STRINGENCY |
|---|---|
| 1. APC- MHC BINDING | low |
| 2. RECOGNITION BY AUTO-REACTIVE T CELLS | low degeneracy! |

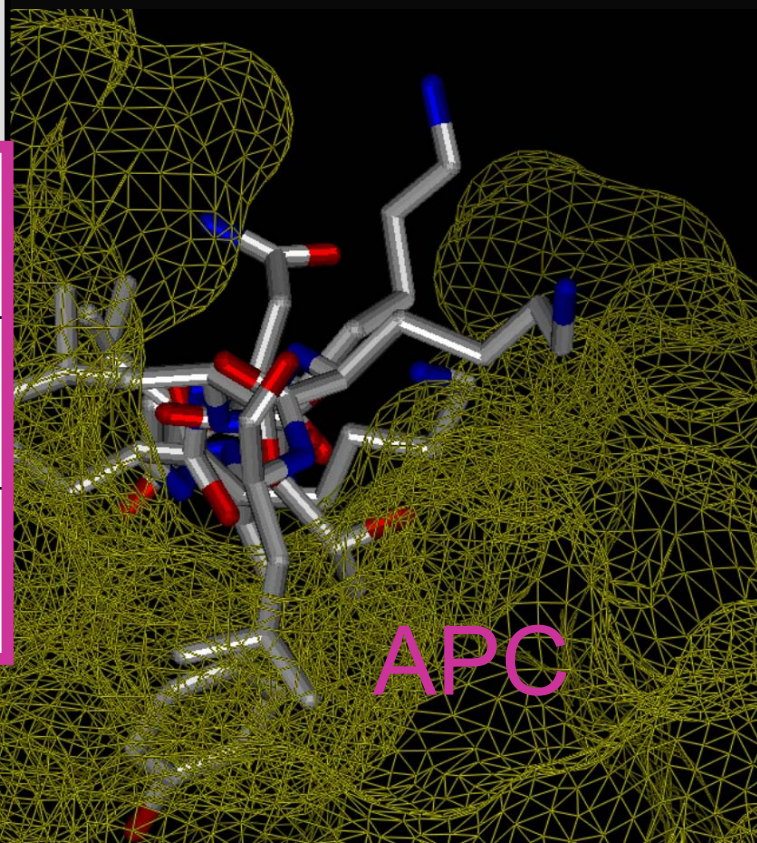
**Mimicry is everywhere …**



# FROM MIMICKING T CELL EPITOPES TO AUTOIMMUNE DISEASES: WHAT IS NEEDED?

| LIMITING FACTORS | STRINGENCY |
|---|---|
| 1. APC- MHC BINDING | low |
| 2. RECOGNITION BY AUTO-REACTIVE TCR | low<br>**degeneracy!** |
| **3. CO-STIMULATORY SIGNALS** | +++ |
| **4. OVERPASSING REGULATORY MECHANISMS** (e.g. CD4+CD25+) | +++ |
| **5. LOCAL INFLAMMATION IN TARGET ORGAN** | +++ |

**Mimicry is everywhere …**



# FROM MIMICKING T CELL EPITOPES TO AUTOIMMUNE DISEASES: WHAT IS NEEDED?

| LIMITING FACTORS | STRINGENCY | | RISK IN NEONATES |
|---|---|---|---|
| 1. APC- MHC BINDING | low | | |
| 2. RECOGNITION BY AUTO-REACTIVE TCR | low<br>**degeneracy!** | | |
| **3. CO-STIMULATORY SIGNALS** | +++ | | LOWER |
| **4. OVERPASSING REGULATORY MECHANISMS** (e.g. CD4+CD25+) | +++ | | ? |
| **5. LOCAL INFLAMMATION IN TARGET ORGAN** | +++ | | LOWER |

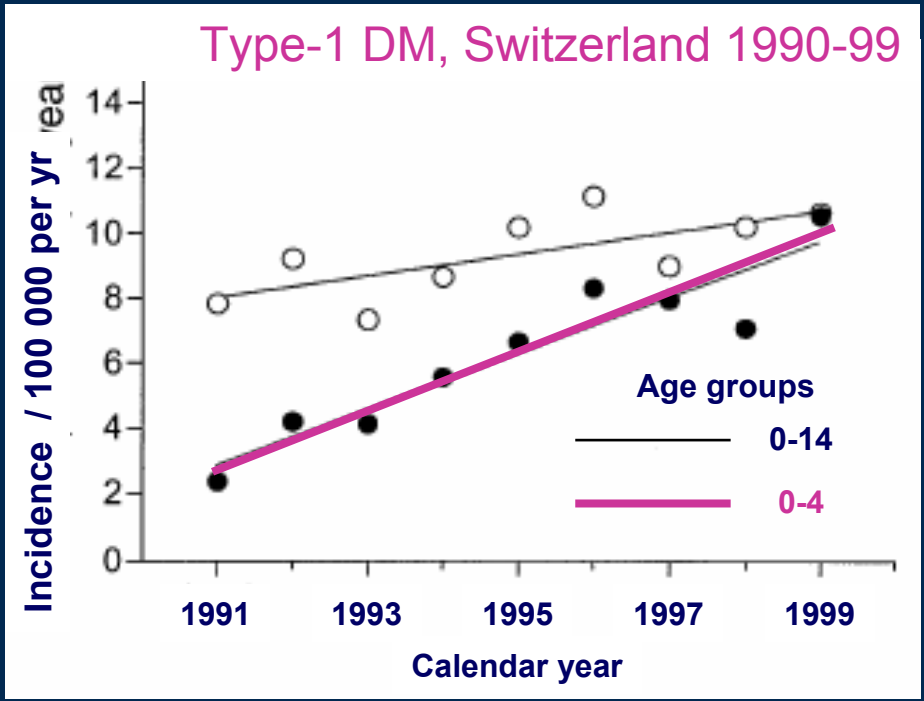
APC

# NEONATAL VACCINATION AND AUTOIMMUNE DISEASES

- **RISK OF COINCIDENTAL TEMPORAL ASSOCIATION**

**OF VACCINATION WITH AUTOIMMUNUNE DISEASES?**

# Rising incidence of autoimmune diseases




*Schoenle EJ et al., Diabetologia, 2001, 44:286-289*

**Rising incidence of autoimmune diseases**

X

**Increasingly crowded vaccination calendar**

**Mass vaccination in AI-susceptible age groups**

Rising incidence of autoimmune diseases

X

Increasingly crowded vaccination calendar

Mass vaccination in AI-susceptible age groups

**INCREASING RISK OF COINCIDENTAL TEMPORAL ASSOCIATION AID-VACCINATION**

# RISK OF AUTOIMMUNE DISEASE AFTER NEONATAL VACCINATION?

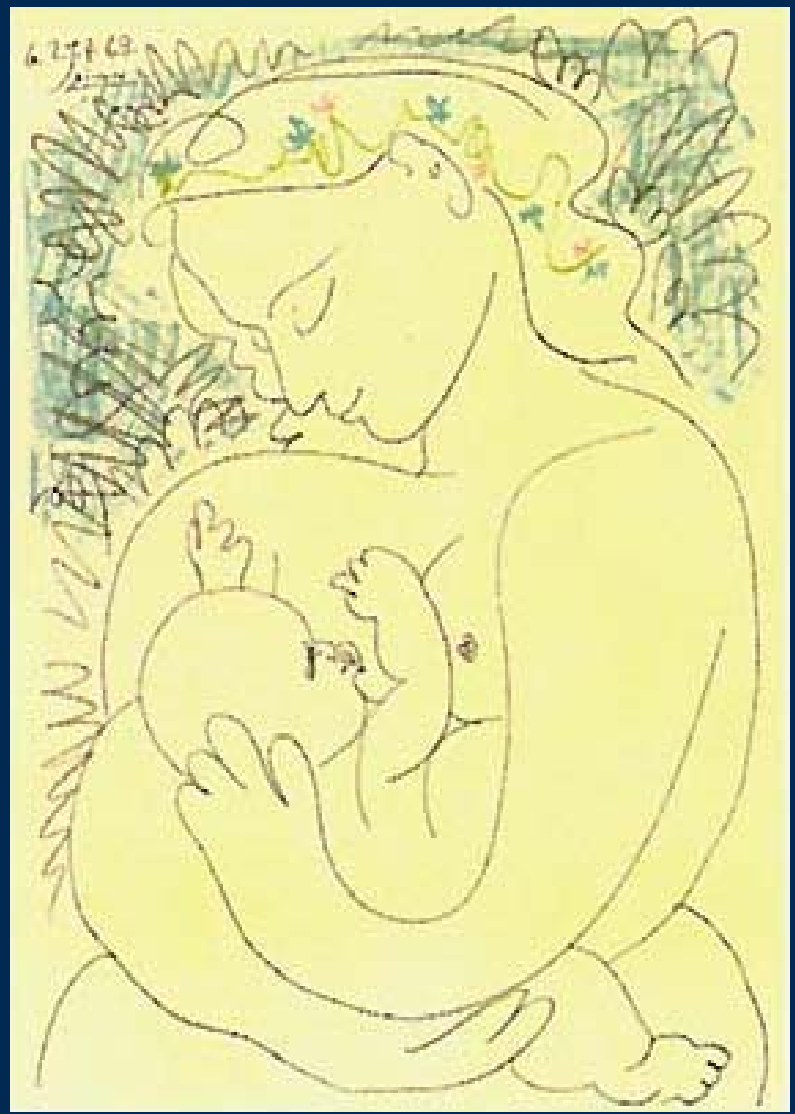
- **Probably lower than at 3 months if same vaccine is used:**
  - **lower APC responses to innate immunity signals**
  - **thymic maturation OK (repertoire), regulatory responses?**
  - **lower antibody responses can be expected**

# RISK OF AUTOIMMUNE DISEASE AFTER NEONATAL VACCINATION?

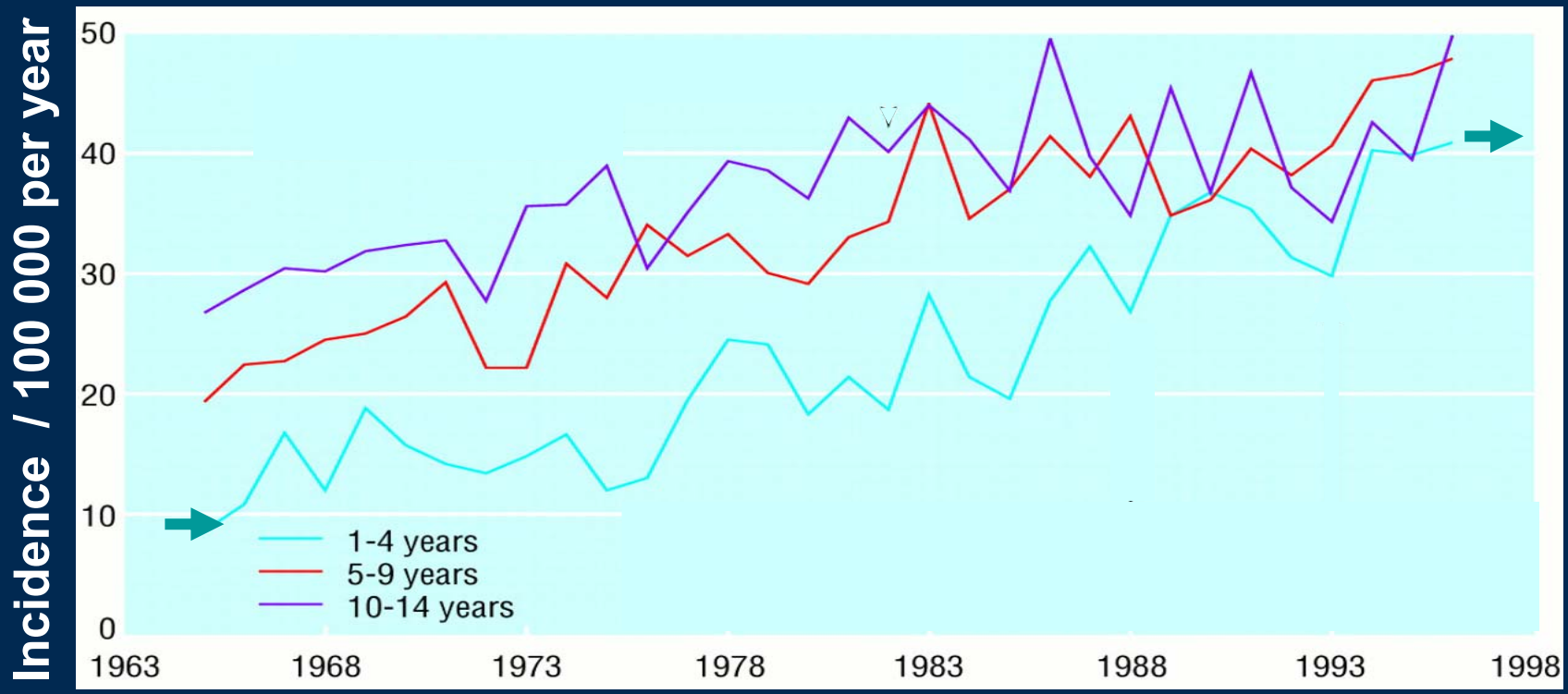
- Probably lower than at 3 months if same vaccine is used
- If « stronger » adjuvants have to be used, it is wise to monitor
  - clinical signs of diabetes, arthritis, liver disease and ITP
  - markers (at 6 & 12 mo.) of type-1 DM (ICA, AAI) and type 2 AHI (anti-CYP2B6); platelet count
  - if suspicion, assess genetic background (e.g. high risk type-1 DM genotypes, HLA-B27)

# NEONATAL VACCINATION IS FEASIBLE

**It may even be safer …**



# THE INCIDENCE OF SOME AUTOIMMUNE DISEASES IS RISING




*From: Karvonen M, Cepaitis Z, Tuomilehto J., BMJ, 1999; 318:1169-72*

# Comparison of peptide sequences in human myelin proteins and HBsAg

Tsuchida et al (1994);
Pelfrey et al (1993).

| PEPTIDE (amino acid position) | % SIMILARITY / % IDENTITY | AMINO ACID POSITION IN HBsAg |
|---|---|---|
| $PLP_{40-60}$ | 75 / 35 | 116-165 |
| $PLP_{80-88}$ | 75 / 63 | 83-90 |
| $PLP_{253-261}$ | 89 / 33 | 171-185 |
| $MAG_{8-16}$ | 78 / 44 | 11-30 |
| $MAG_{406-414}$ | 71 / 57 | 162-168 |
| $MAG_{509-517}$ | 89 / 44 | 175-190 |
| $MAG_{556-564}$ | 78 / 33 | 190-200 |
| $MBP_{110-118}$ | 100 / 67 | 31-45 |
| $MOG_{7-15}$ | 88 / 50 | 87-94 |
| $MOG_{133-141}$ | 75 / 25 | 21-28 |
| $MOG_{157-165}$ | 78 / 22 | 24-32 |
| $MOG_{164-172}$ | 71 / 43 | 203-209 |
| $MOG_{221-229}$ | 71 / 57 | 204-212 |
| $MOG_{240-248}$ | 75 / 25 | 15-24 |
| $MOG_{422-430}$ | 78 / 33 | 13-21 |

***All peptides bind to HLA-A2***

*PLP = Proteolipid protein;*
*MAG = Myelin-associated glycoprotein*
*MBP = Myelin basic protein;*
*MOG = Myelin oligodendrocyte glycoprotein*

# The example of Lyme vaccine

- In Lyme Disease, the natural infection (Borrelia sp) can be complicated by a chronic antibiotic-resistant arthritis.

  This arthritis is considered as an AI complication due to recognition of a microbial T cell epitope (Osp-A) that is mimicking an epitope of human lymphocyte protein LFA-1 (A Steere et al.)

- A registered Lyme vaccine does contain Osp-A: risk of AI arthritis?
  No joint disease nor other AI side effects observed after vaccination.

  *Importance of infection-induced local inflammation?*

- **Mimicry of host antigens is not sufficient to induce AID.**
  **This would particularly require:**
  **- co-stimulatory signals,**
  **- escaping normal regulatory mechanisms,**
  **- local inflammation in target organ**

- **Most often, occasional vaccine-induced auto-immune responses do not lead to any disease (differing from infection-induced responses)**

# IMMUNOLOGICAL SAFETY OF NEONATAL VACCINATION?

Could neonatal vaccination lead to:

1. inappropriate responses to the targeted pathogen: disease enhancement (RSV?) / tolerance? *not seen with Polio/HepB*

2. modified responses to other antigens- *as seen with BCG*

3. immunological overload? *no evidence*

4. **induction or triggering of an autoimmune disease?**