The challenges for neonatal immunization

Induction of early protection in spite of :

- –lower antibody responses
- –inhibitory influence of maternal antibodies

Extracellular pathogens

- –limited IFN-γ responses
- –limited cytotoxic responses (?)

Intracellular pathogens

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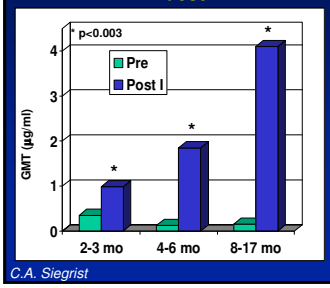
Immune immaturity limits infant antibody responses to vaccines

PRP-OMC immunization
1 dose



No clinical relevance because of the unique immunogenicity of HIB vaccines... but several doses needed !

Einhorn MS, Lancet. 1986

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Immune immaturity limits early life antibody responses to vaccines

- Responses to a single dose of measles vaccine (seronegative infants)

	GMT	> NT level
@ 12 mo :	972	100%
@ 9 mo :	578	100%
@ 6 mo :	27	36%

Gans HA JAMA 1998

Similar for mumps

Gans HA JID 2001

- Novel OMV vaccine against group B meningococcus

Brazil, Chile

Field efficacy	
Adults :	74%
Toddlers :	47%
Infants :	0%

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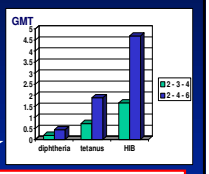
Immune immaturity limits early life antibody responses to vaccines

- Antibody responses to current vaccines schedules appear influenced by :
  - –Vaccine type
  - –Interval bwn doses
  - –Age at priming
  - –Age at last dose



May infant immunogenicity predict neonatal responses ?

Does this pattern reflect the prenatal development or the postnatal maturation of the immune system ?

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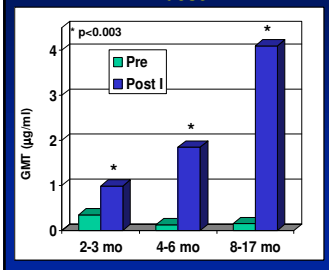
Immune immaturity limits early life antibody responses to vaccines

PRP-OMC immunization
1 dose



PRP-OMC elicits the strongest responses in infants.... but was not successful in neonates

Other HIB vaccines such as **PRP-T** did successfully prime neonatal responses

Einhorn MS, Lancet. 1986

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Prenatal development of the immune system or postnatal immune maturation ?

Preterm infants :

1. *Limited birth responses - GA*
2. *Significant responses after 8 weeks, which remain lower than in term infants if birth < 32 wks (1500g)*

- Hepatitis B vaccine given at birth (0-1-6 mo)
  - – seroresponse <1000g: 55%, 1000-1500g: 71%, >1500g: 96%
  - ➡ limited immune capacity at birth
- Hepatitis B, HIB, DTPa vaccines given at 8 weeks of age
  - –seroresponses similar to those of term infants (>32 wks)
  - ➡ essential role of the post-natal maturation

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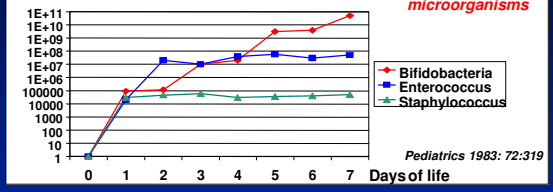
Neonatal exposure to the microbial world…

Neonatalcolonisation of the intestinal tract : *From zero to 10^{13} microorganisms*



A strong role for postnatal maturation?

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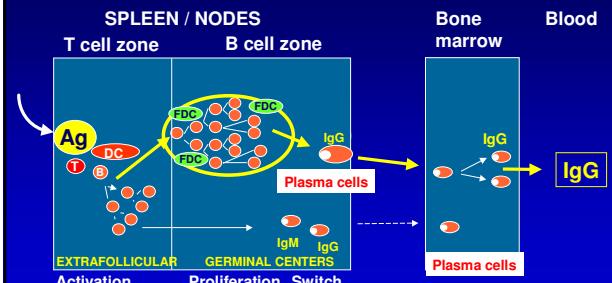
Which limitations of early life antibody responses ?



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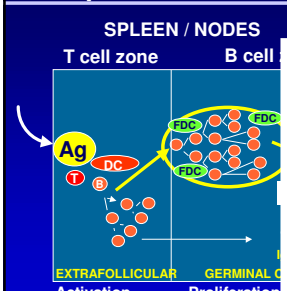
Which limitations of early life antibody responses ?



Bone marrow

Extrafollicular reaction :
1. Limited DC activation ?
2. Limited CD4 T cell help ?
3. Limited B cell activation / prolif. ?

Germinal center reaction :
1. Limited induction of GC (…) ?
2. Limited GC B cell activation +/- differentiation ?

Antibody persistence :
1. Limited bone marrow homing ?
2. Limited differentiation / survival ?
3. Limited memory B cell diff. ?

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Limitations of early life antibody responses

	age-dependent lower IgG + IgM much lower IgG2 low resp. to most PS short-term persistence	age-dependent lower IgG + IgM much lower IgG2a low resp. to most PS short-term persistence
Magnitude		
Avidity	lower avidity (??) repertoire ?	lower avidity (Ag dep) hypermutation ?

Organogenesis → Cellular ontogeny → Immune maturation

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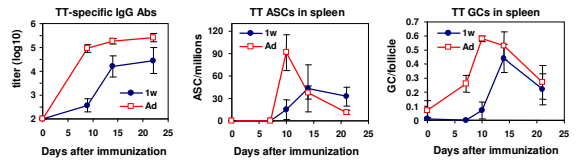
Ab titers and Ab secreting cells following early life and adult immunization

B cell responses to alum-adsorbed tetanus toxoid (1 dose)



Limitations of early life Ab responses reflect a delayed and limited induction of ASC and Germinal Center responses

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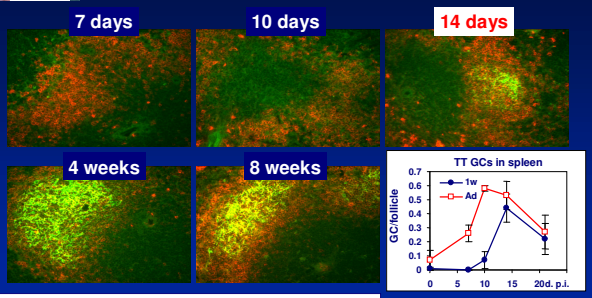
Pihlgren M et al, JI 2003

The age-dependent capacity of inducing GC correlates with presence of FDC at immunization



FDC function : antigen trapping, enhancement of B cell activation, protection against apoptosis

Pihlgren M et al, JI 2003

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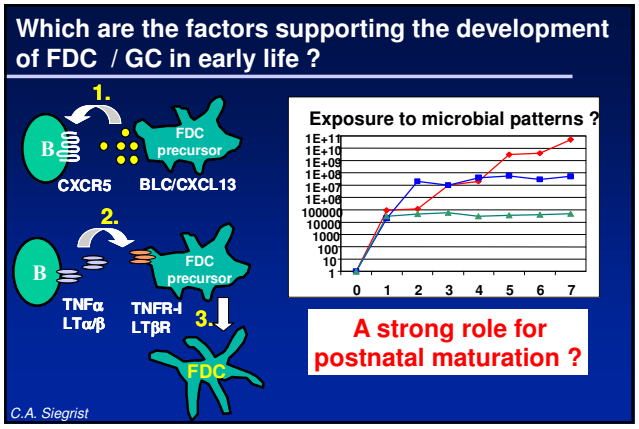

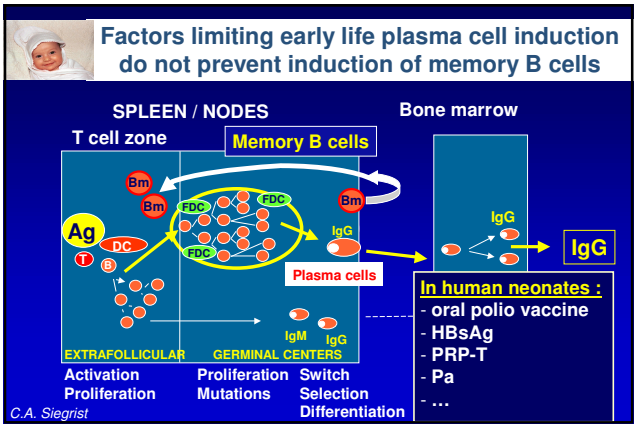

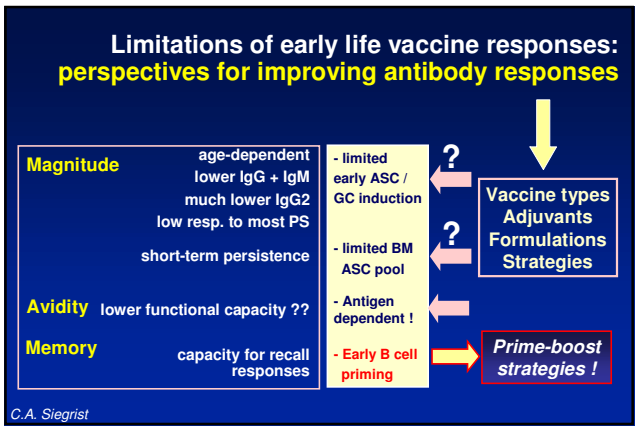

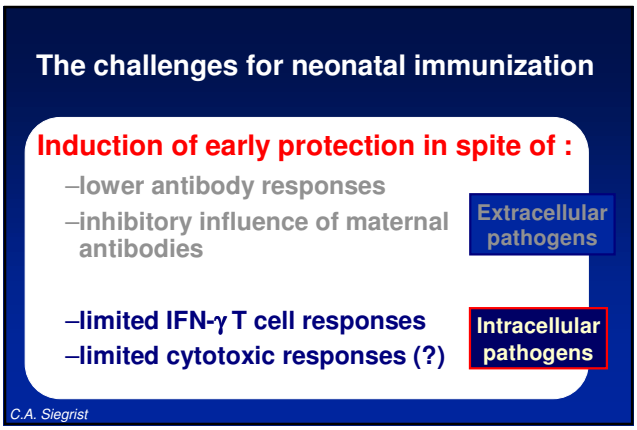

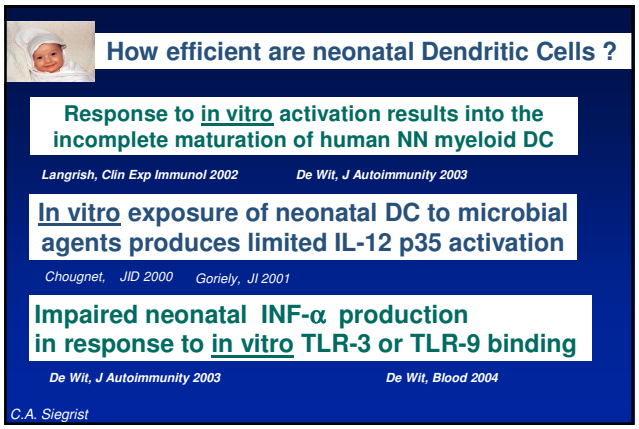

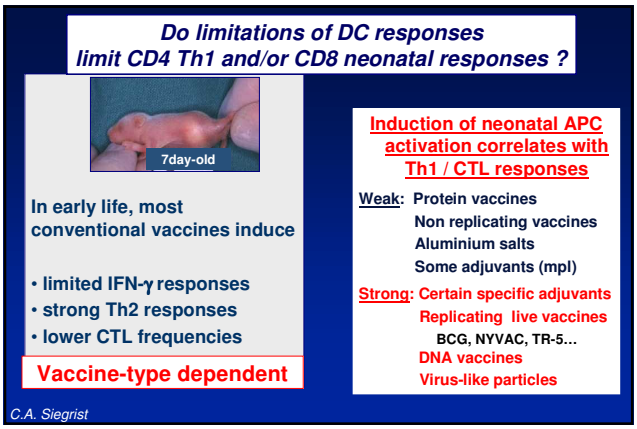

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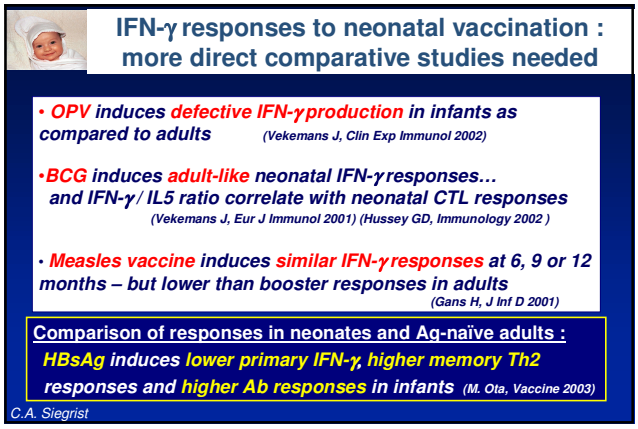

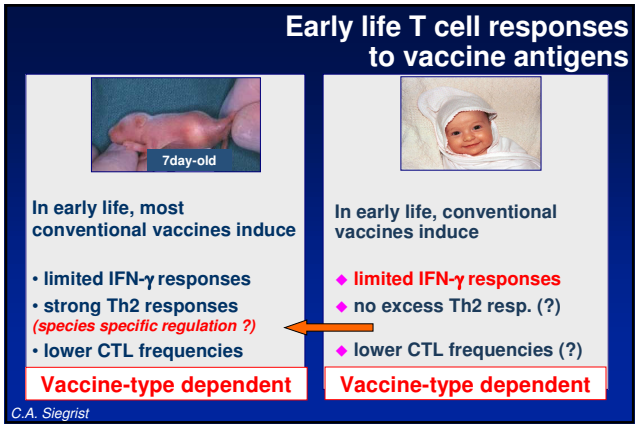

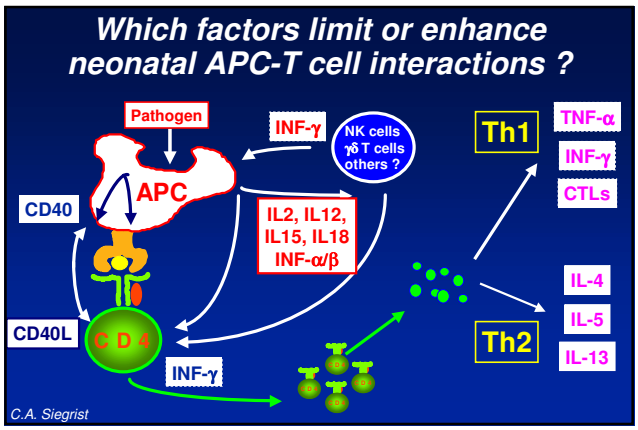

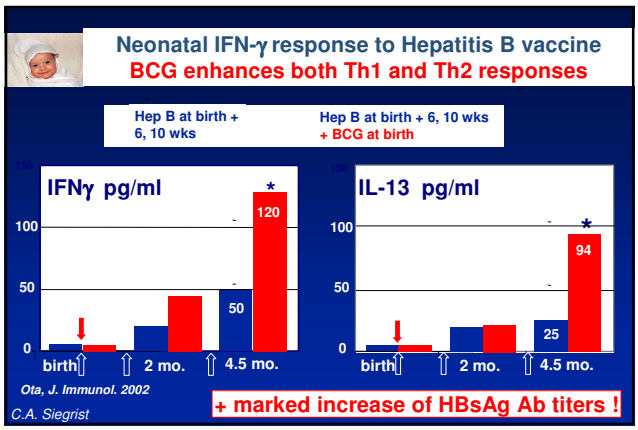

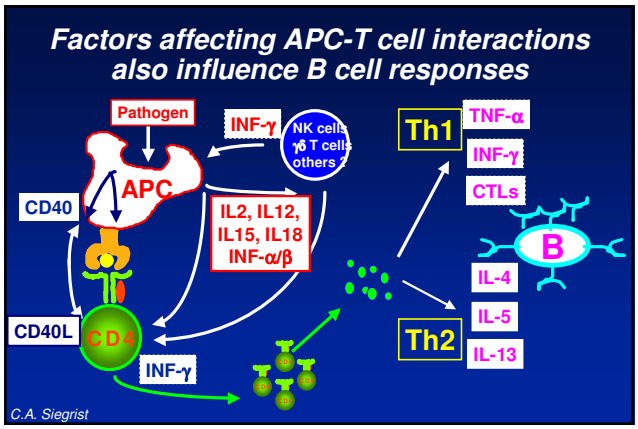

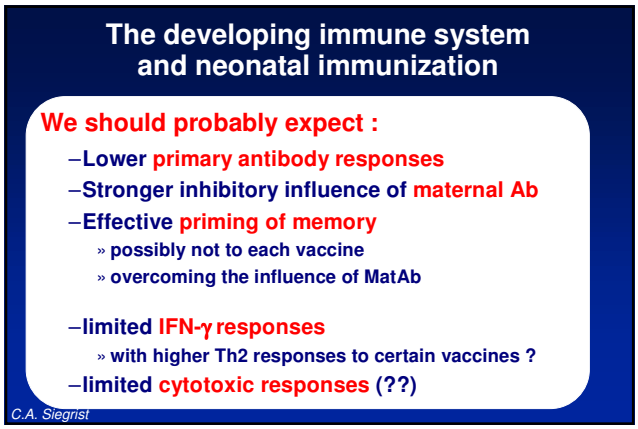

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