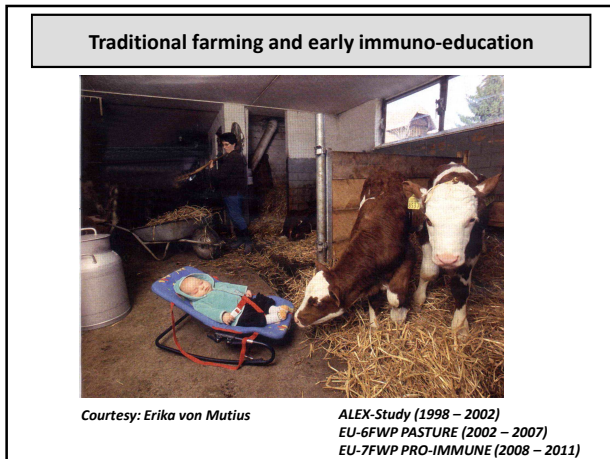


Loss of clinical and immunological tolerance

◆ Hygiene hypothesis

- Lack of infectious microbes in early childhood
- Altered exposure to environmental microbes
- Examples:
 - having older siblings
 - frequent viral infections
 - anthroposophical life style
 - early day care
 - traditional farming

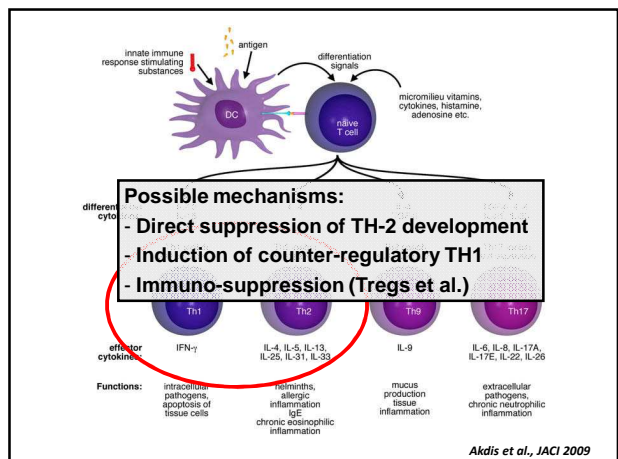
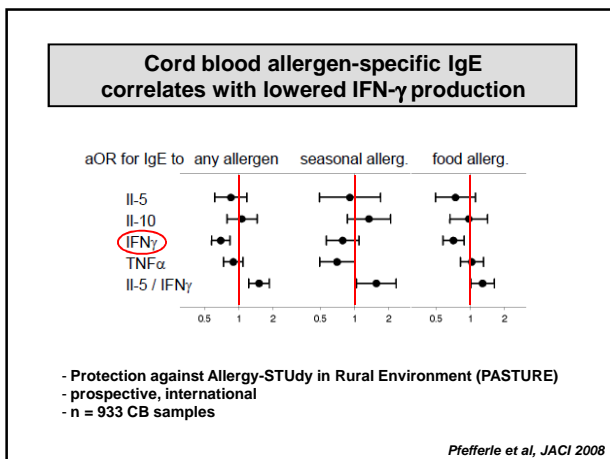


Effect of childhood farm exposure on allergic phenotypes

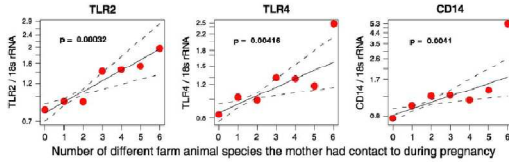
Protective effect	Phenotype	Number of studies (n =)	Risk reduction	
			Significant (n =) %	Trend (n =) %
▲	rhinitis/ conjunctivitis	16	(12) 75 %	(4) 25 %
	atopic sensitization	14	(10) 71 %	(4) 29 %
	asthma	28	(18) 64 %	(10) 36 %
	wheezing	17	(9) 53 %	(7) 41 % *
	atopic dermatitis	14	(3) 21 %	(10) 72 %

Total study number : n = 33
* In one study a slight increase in risk was observed

von Mutius and Vercelli, 2010;
Rodiut et al., 2010



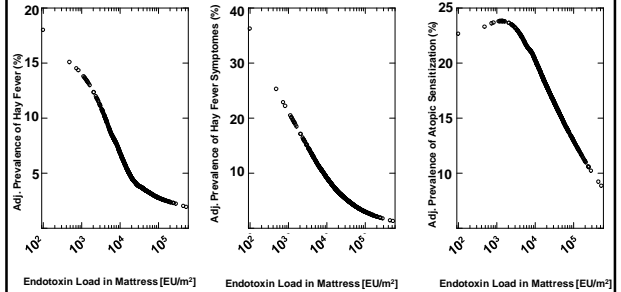
Prenatal farm exposure relates to the expression level of TLRs at school age



- cross-sectional (PARSIFAL)
- subsample of n = 322 children
- adjusted for age, sex, family history of atopy, parental education, environmental tobacco smoking, maternal smoking during pregnancy, number of older siblings, contact with pets ever, child's current exposure to a farming lifestyle, child's exposure to farm animals, and predominant farm milk consumption of the child

Ege et al, JACI 2006

Inverse relationship between endotoxin-load and atopic phenotypes



Braun-Fahrlander et al. NEJM, 2002

Gene-by-environment interaction Model situation: (Traditional) farming and endotoxin exposure

Gene	Allele (homozygous)	phenotype	
CD14	-159 TT	risk of allergic rhinitis, atopy ↓	Leynaert et al, JACI 2006
CD14	-260 CC	total and specific IgE: if regular contact with pets ↑ if contact with stable animals ↓	Eder et al, JACI 2005
CD14	-159 TT -1619 G	lung function, wheeze ↑	Le Van et al, AJRCCM, 2005
CD14	-159 CC	sensitization ↓	Simpson et al, AJRCCM, 2006
TLR2	-16934 TT	asthma	Eder et al, JACI, 2004

PAMPs with allergy-protective activities

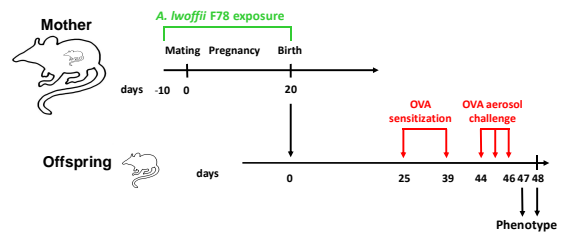
TLR 2	Lipopeptide	TH1	Patel, J Immunol 2005
TLR 2/ 4	Peptidoglycan	TH1	Velasco, Am J Respir Cell Mol Biol 2005
TLR 4	Lipopolysaccharide	TH1	Gerhold, J Allergy Clin Immunol 2003 Blümer, Clin Exp Allergy 2005
TLR 3	poly (I:C)	IL-12	Sel, J Immunol 2008
TLR 7	R848	IL-10	
TLR 9	DNA from <i>Bordetella pertussis</i>	TH1	Kim, Immunology 2004

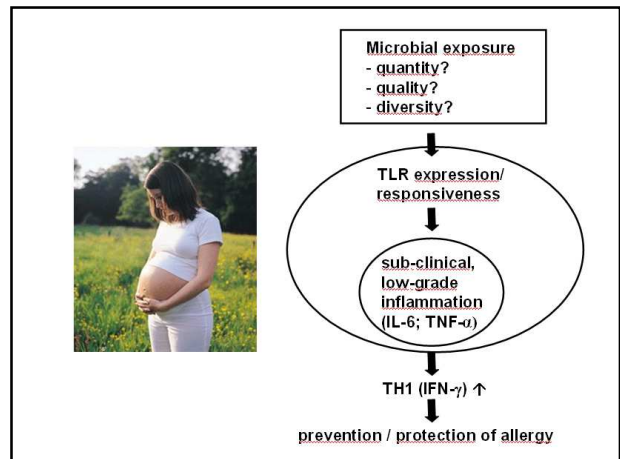
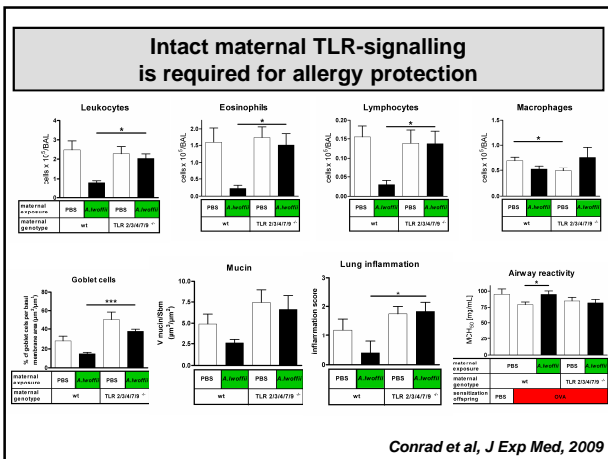
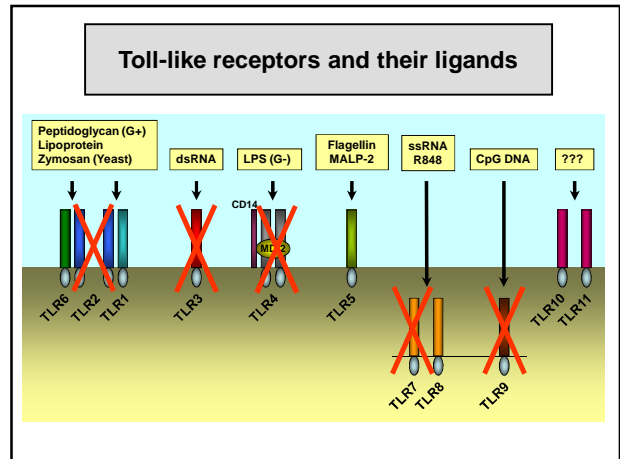
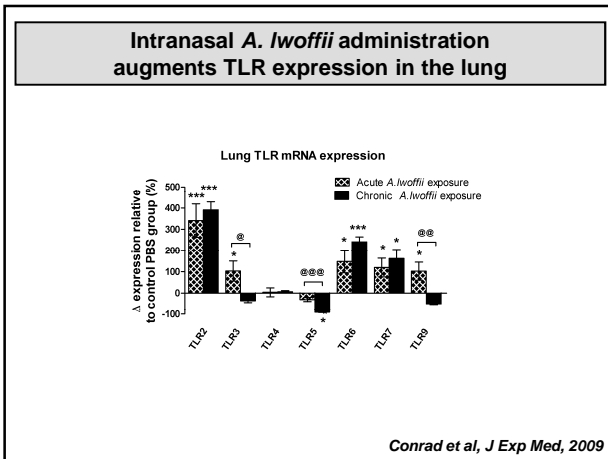
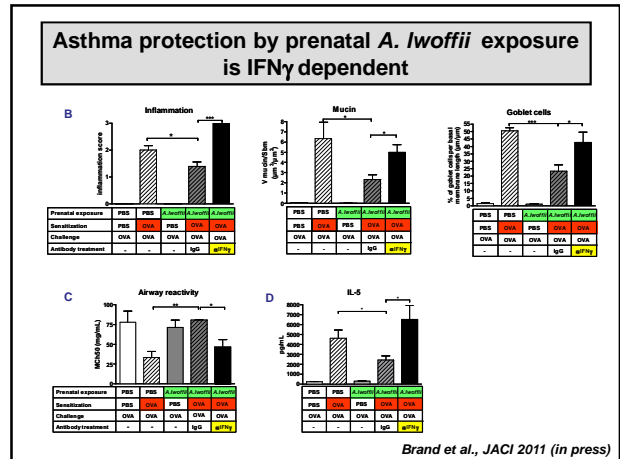
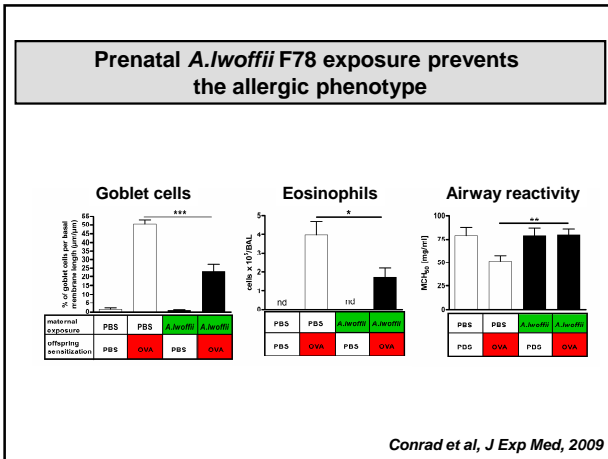
Environmental microbes with asthma protective properties

Acinetobacter lowffii	-	TH1 / IEN γ ↑	1)
Staphylococcus sciuri	+	T-cell activation ↓	2)
Lactococcus lactis	+	TH2 ↓ (IEN γ) ↑	3)
Bacillus licheniformis	+	TH1 pathology	4)
Lactobacillus GG	+	(T-cell activation) ↓	5)
LPS	-	IL-12 ↑ / TH1 ↑	5)

1. Conrad et al, JEM 2009
2. Hagner-Benes et al, submitted
3. DeBarry et al, JACI 2007
4. Vogel et al, JACI 2008
5. Bluemel et al, Clin Exp Res, 2007

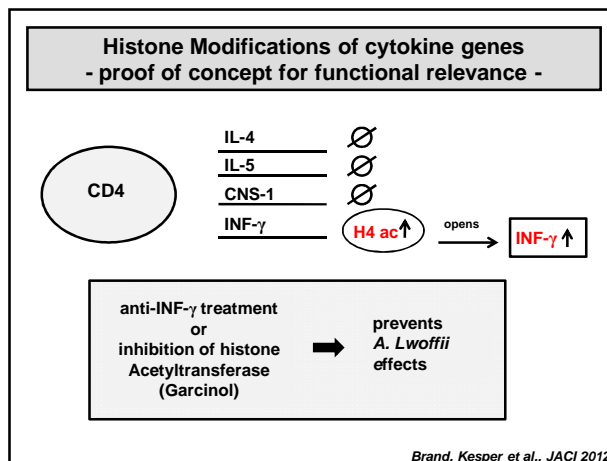
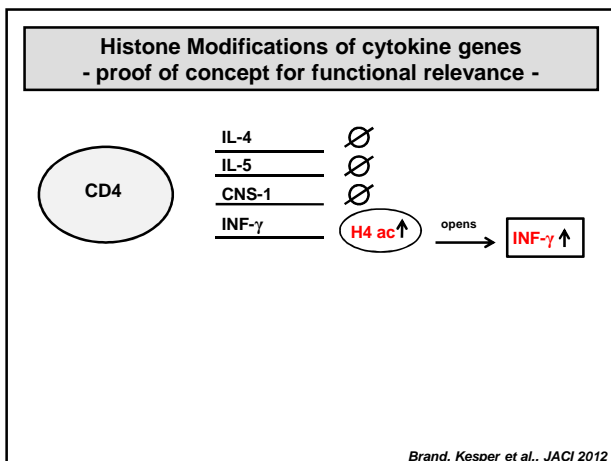
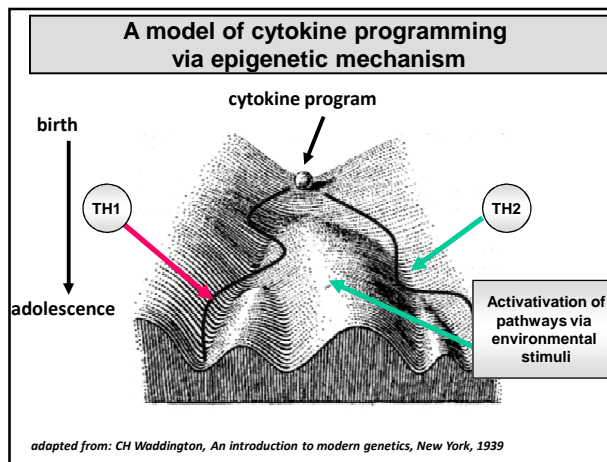
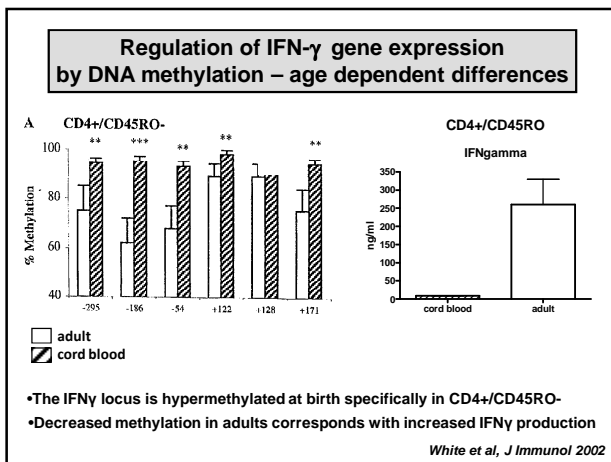
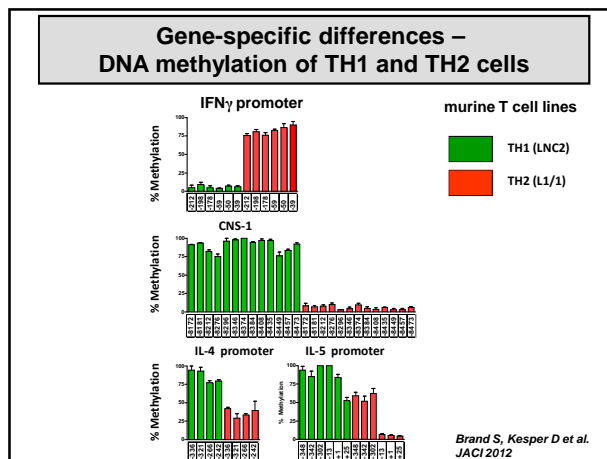
Mouse model of prenatal immuno-modulation - proof of principle -



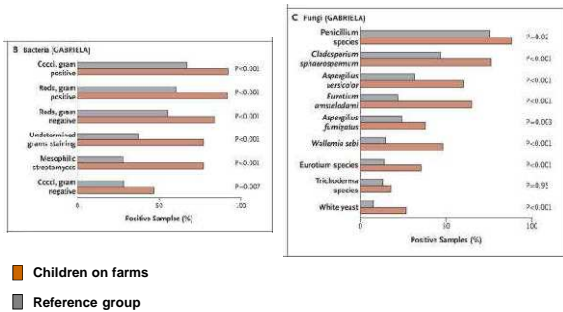


The genetic and the epigenetic code

Genetic Code	Epigenetic Code
DNA sequence	<ul style="list-style-type: none"> Chromatin remodelling DNA methylation histone modification histone variants high-order chromatin organization
fixed	Plasticity <ul style="list-style-type: none"> heritable, but potentially reversible cell-type specific dynamic changes throughout life

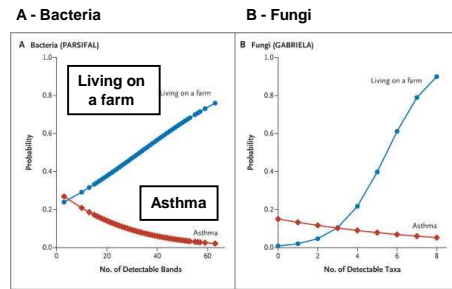


Higher load of environmental microorganisms in dust samples from farms



Ege et al, NEJM, 2011

Inverse relationship between microbial exposure and probability of asthma

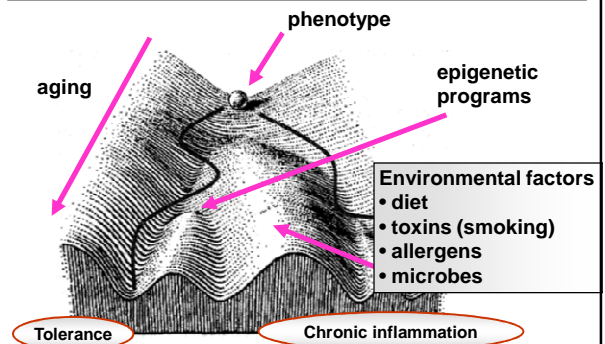


Ege et al, NEJM, 2011

Loss of clinical and immunological tolerance

- ➔ Microbiota hypothesis
 - modern/ industrialized life style
 - > altered microbial diversity
 - > loss of ancient co-evolved microbes
 - > altered immune response
 - > disease
 - (organized) microbial colonization of skin and mucosal surfaces
- ➔ Biodiversity Hypothesis

A model of chronic inflammatory disease and epigenetic programming



adapted from CH Waddington, An introduction to modern genetics, New York, 1939

The Team

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