Defence against Pathogens and Tolerance of Commensal Microbiota as well as of Dietary Antigens in the Early Stage: Challenging Steps to avoid Immune Deviances Later on.

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The Bacterial Colonisation and the Feeding in the Early Stage: Why it matters ?

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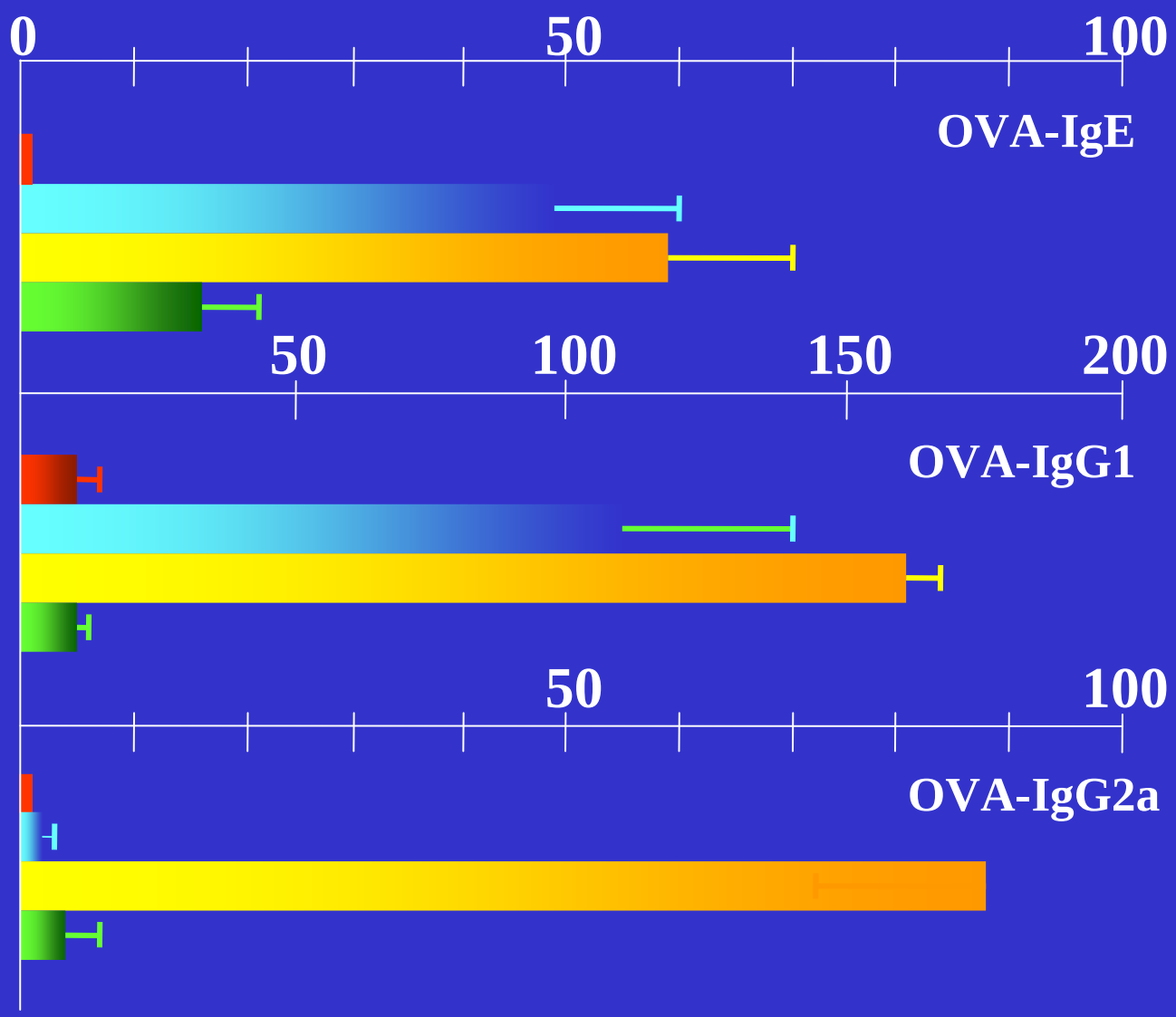
- It initiates the mucosal immune system rendering it able to favour the HOST DEFENCE but in the same time the DIETARY ANTIGEN TOLERANCE

The Bacterial Colonisation and the Feeding in the Early Stage: Why it matters ?

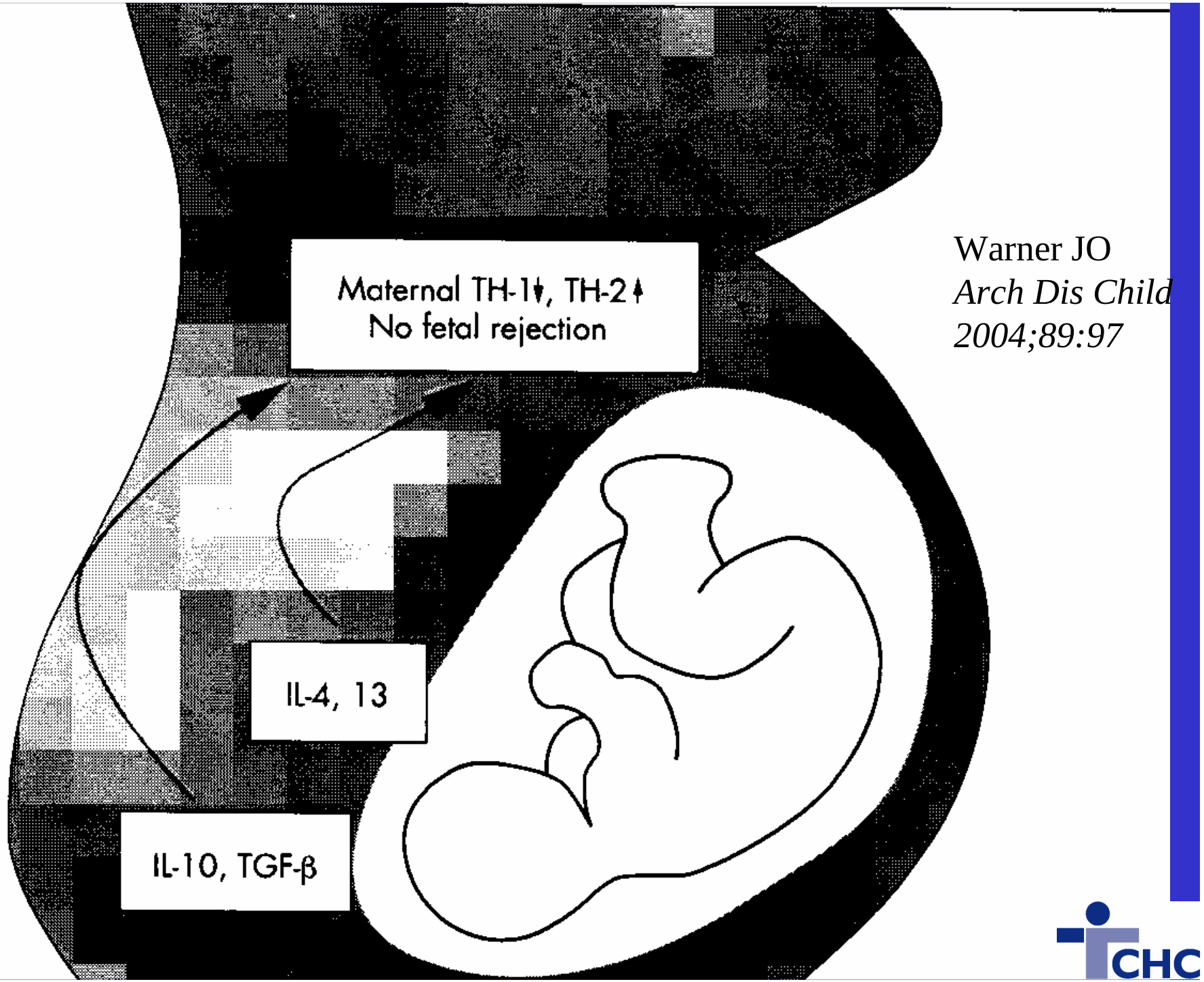
- It initiates the mucosal immune system rendering it able to favour the HOST DEFENCE but in the same time the DIETARY ANTIGEN TOLERANCE
- An adequate presentation of the dietary antigen to the mucosa in the early stage is likely to be a CRUCIAL STEP in optimising this tolerance to the DIETARY ANTIGEN.

The Bacterial Colonisation of the Neonatal Intestine is mandatory to get Diet Antigen Tolerance

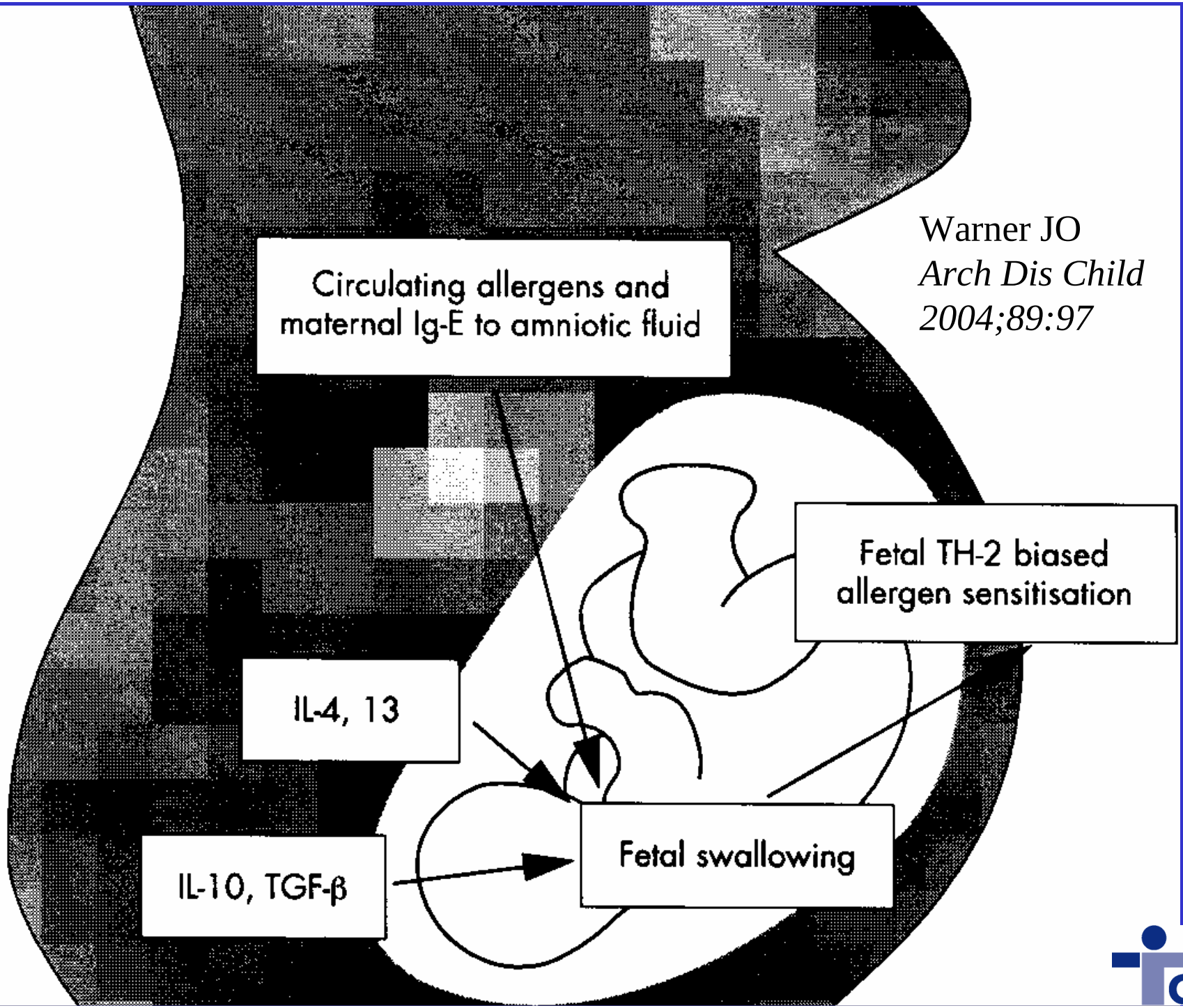


From Sudo et al J Immunol 1997;159:1739.

The Fetus and its Immunological protection….



Warner JO
Arch Dis Child
2004;89:97

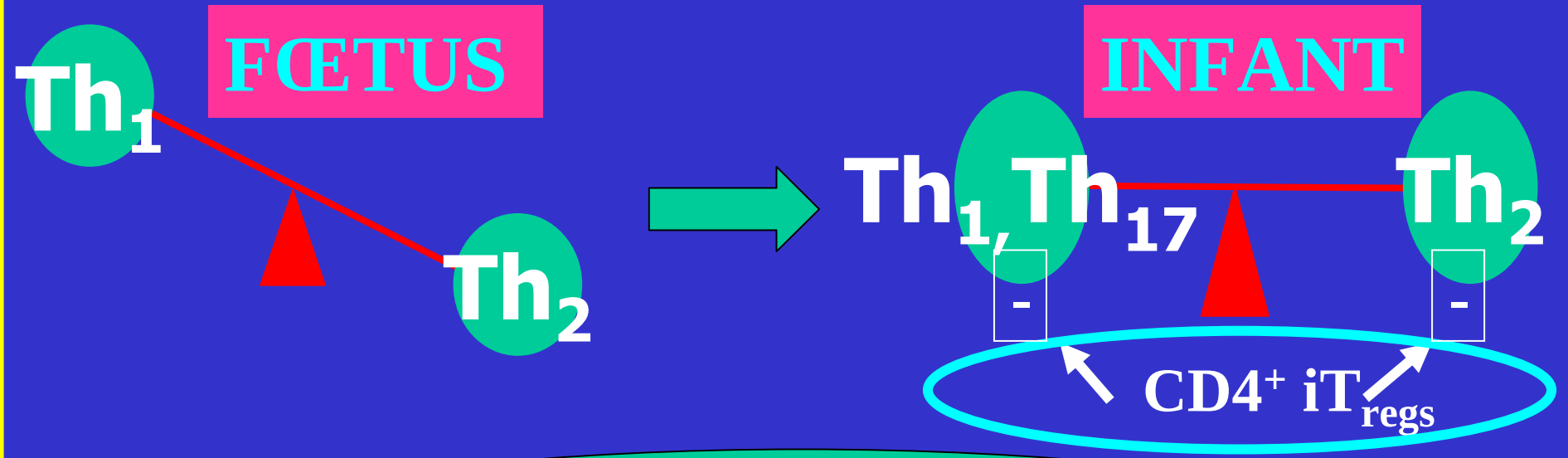


Warner JO
Arch Dis Child 2004;89:97

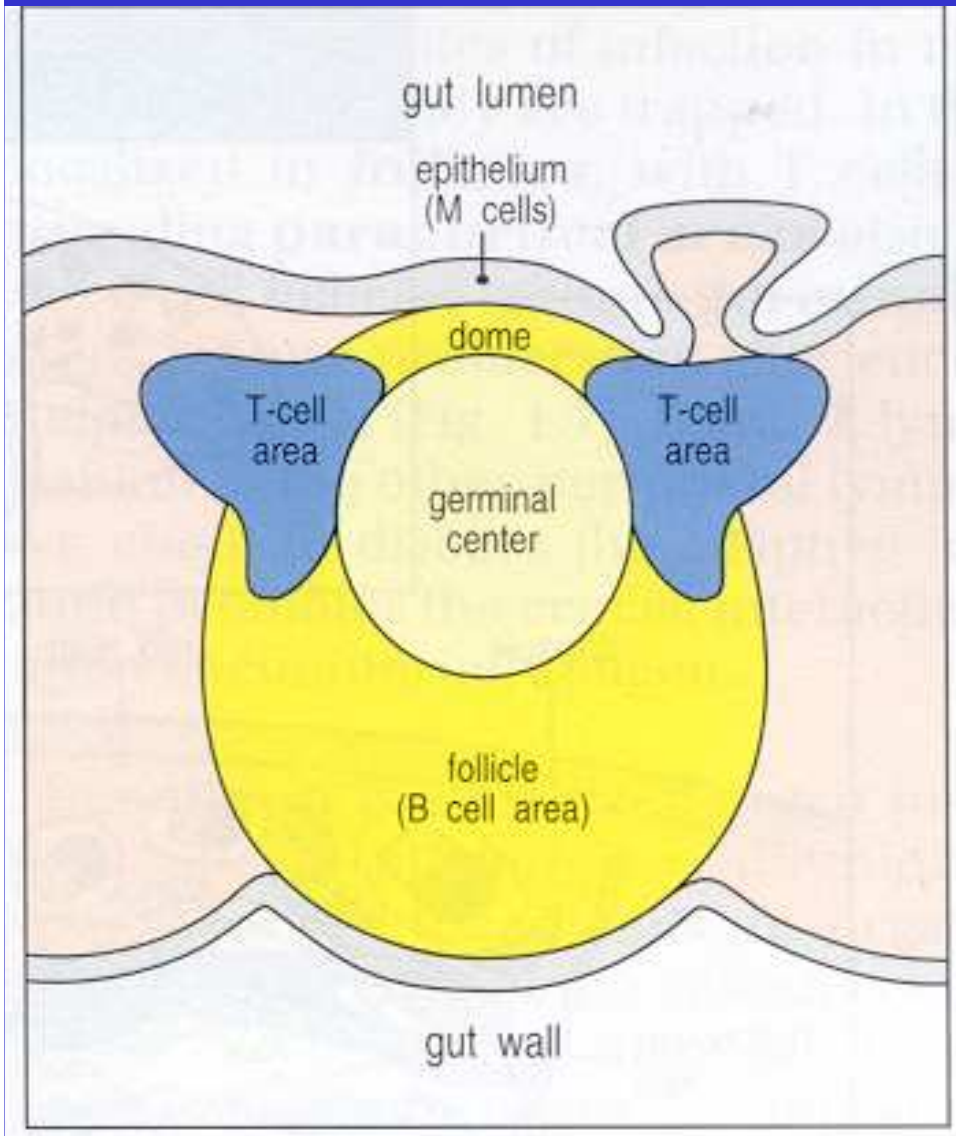
The Process of Birth triggers a dramatic Immune Induction at the Sterile Intestine Mucosal level…

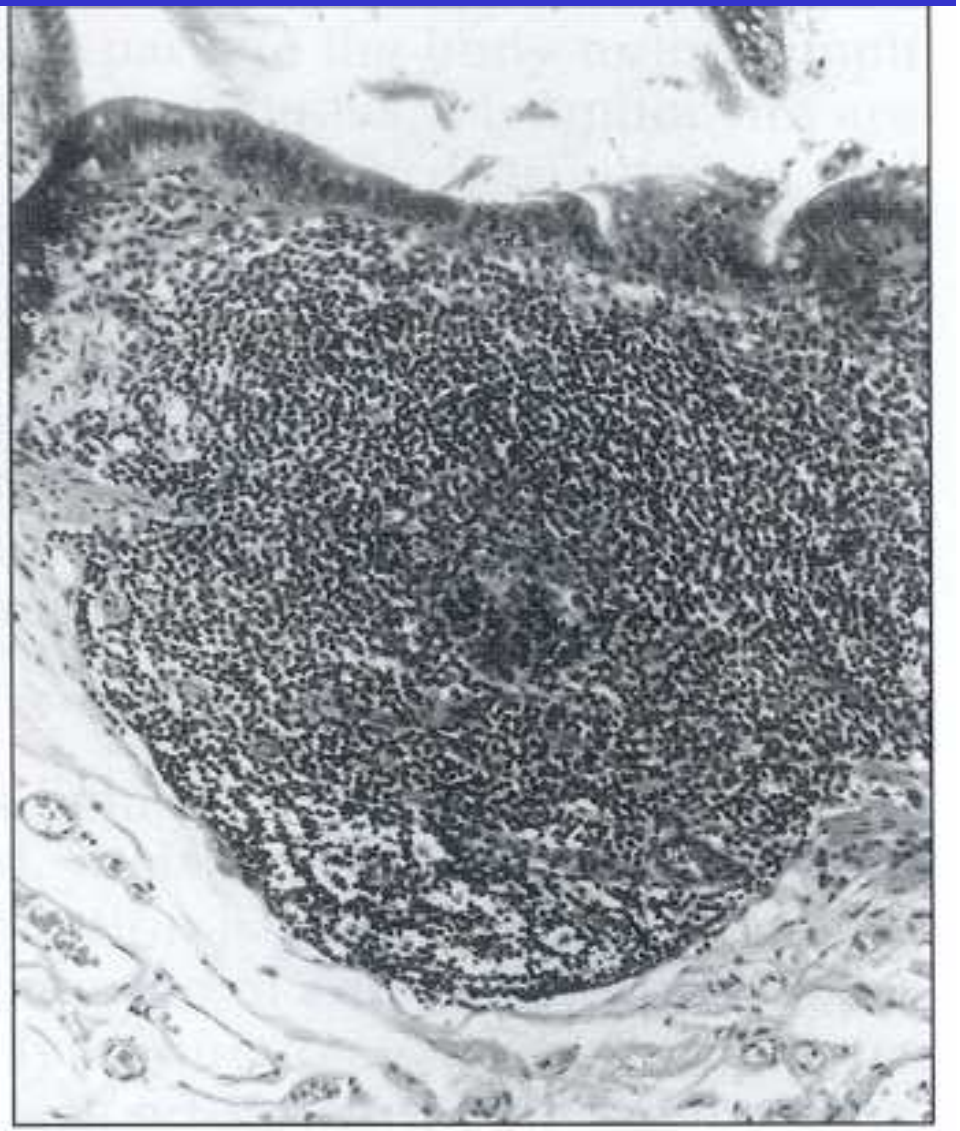
….a challenging step initiated by the Invasive Microbiotia….

Physiological Fetal Immune Imbalance to be corrected by invasive bacteria in the Early Stage



Th1,Th17 impulse and up-regulation of $CD4^+$ iT_{reg} cells (Bystander Suppression) in a progressively increased TGF-β immune climate.


gut lumen
epithelium
(M cells)
dome
T-cell
area
T-cell
area
germinal
center
follicle
(B cell area)
gut wall



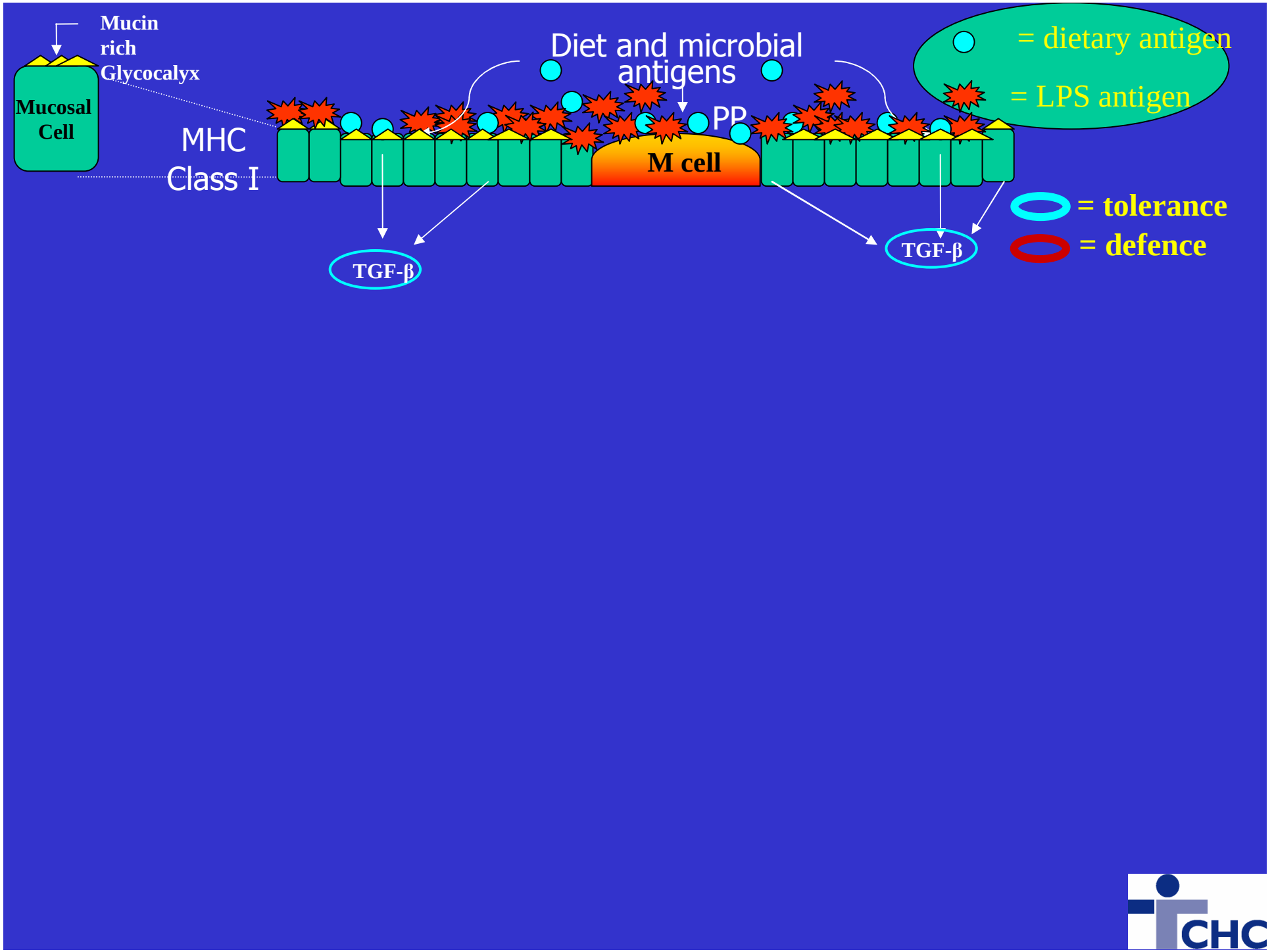
Crucial role of bacteria to induce **HOST DEFENCE** but also in the same time to get **DIET ANTIGEN TOLERANCE**……

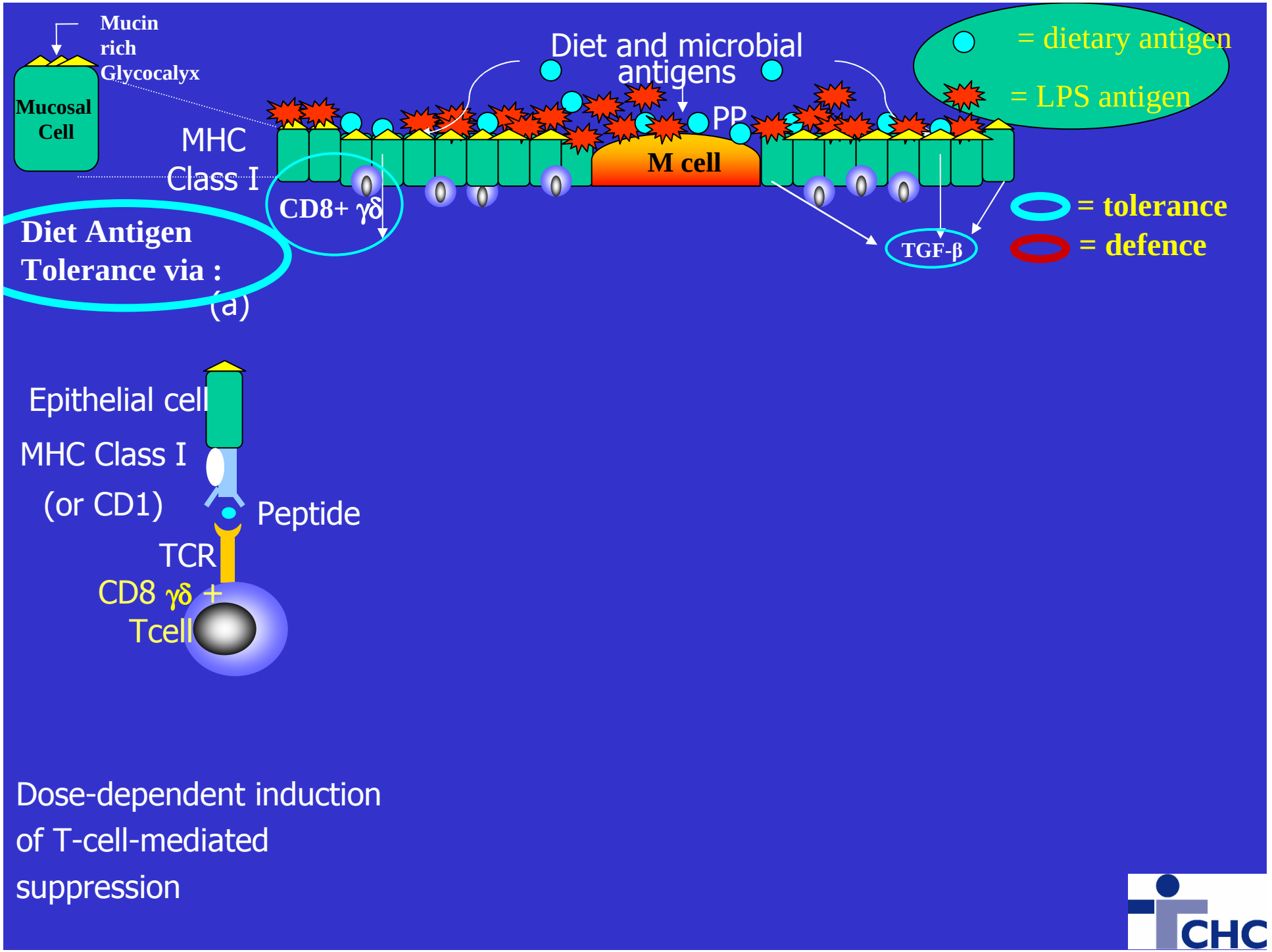
……but, how can it be possible to get this opposite effect at the mucosal level ….

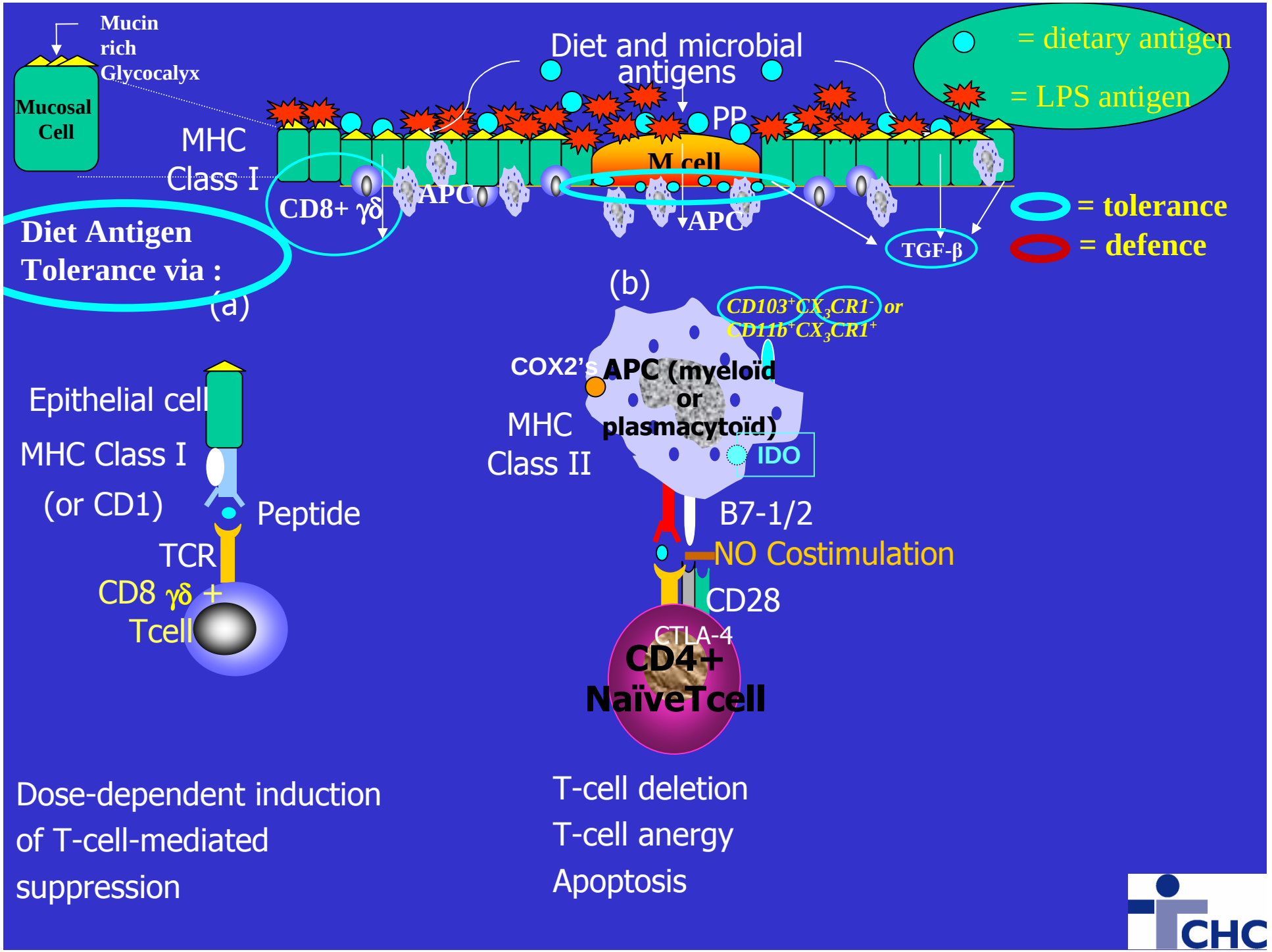
….how does it work ?
which Actors are involved in the process of the dietary antigen tolerance ?

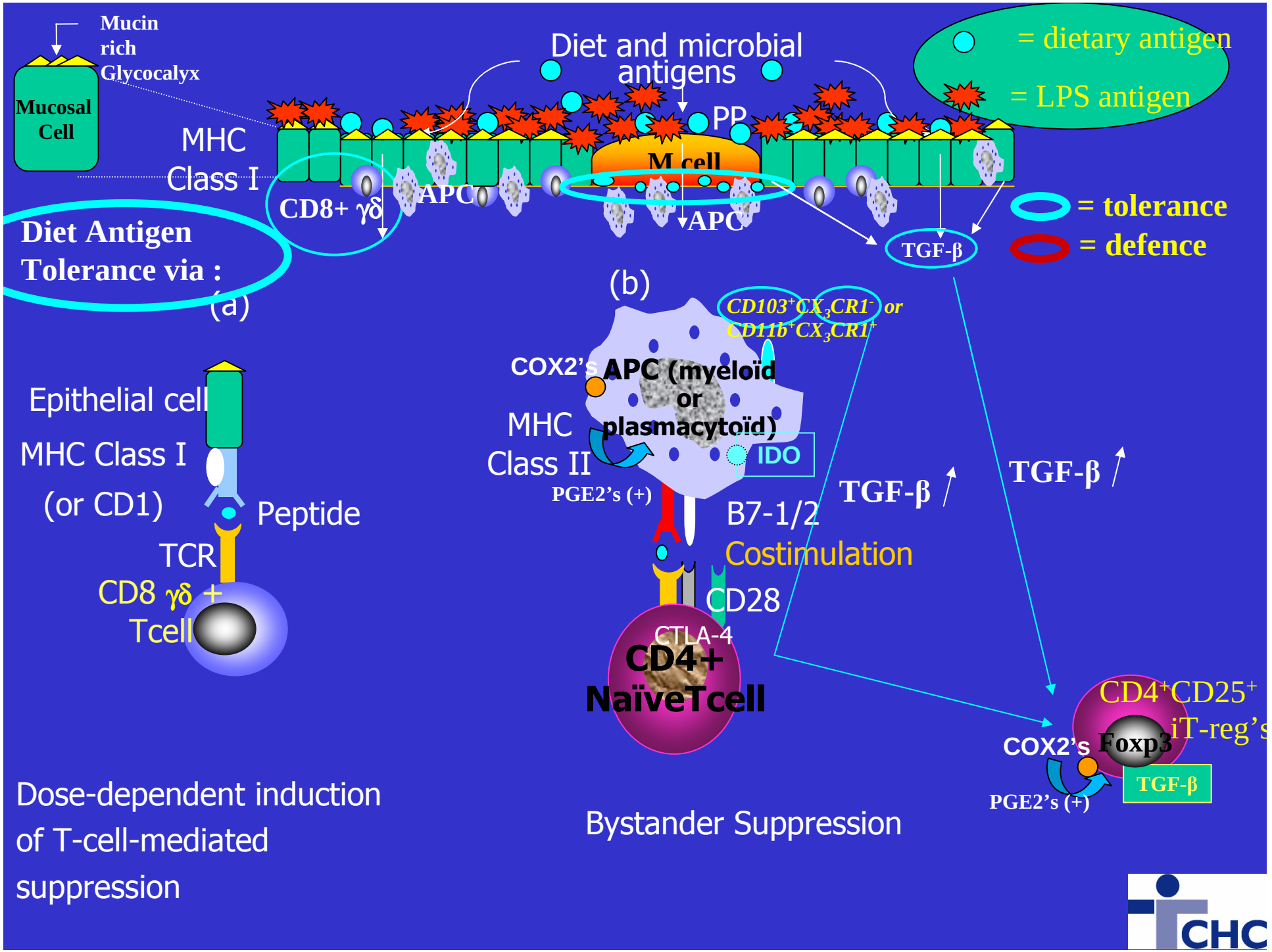
From experimental studies but which tend to be recently confirmed in HUMANS ……..

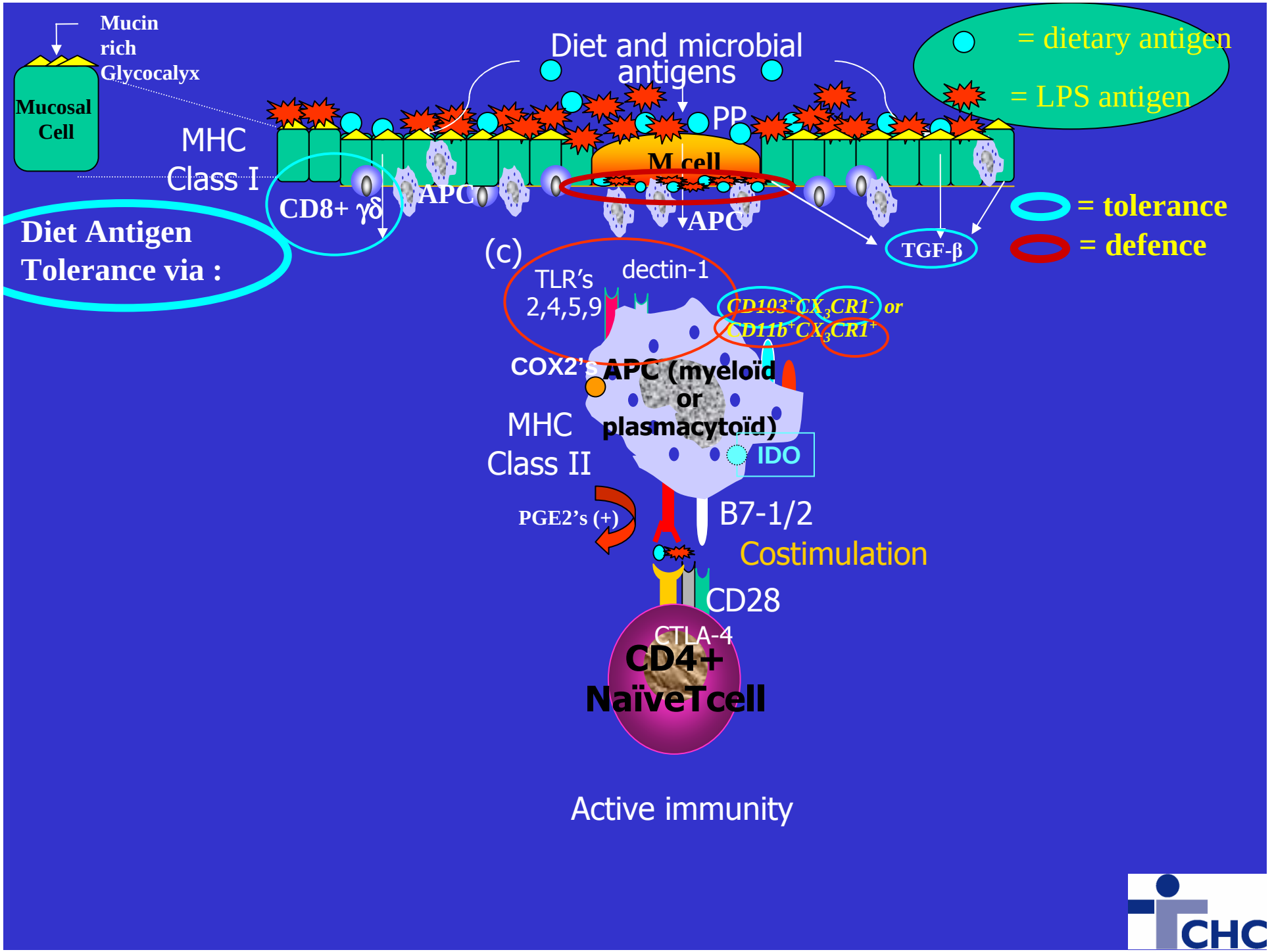
…….. 3 Challenging Steps (a, b, c) to Get the Dietary Antigen Tolerance……


Mucin
rich
Glycocalyx
Mucosal
Cell
MHC
Class I
Diet and microbial
antigens
PP
M cell
TGF-β
TGF-β
= dietary antigen
= LPS antigen
= tolerance
= defence


Mucin rich Glycocalyx
Mucosal Cell
MHC Class I
Diet and microbial antigens
PP
M cell
= dietary antigen
= LPS antigen
CD8+ γδ
Diet Antigen Tolerance via :
(a)
TGF-β
= tolerance
= defence
Epithelial cell
MHC Class I
(or CD1)
Peptide
TCR
CD8 γδ +
Tcell
Dose-dependent induction of T-cell-mediated suppression


Mucin rich Glycocalyx
Mucosal Cell
MHC Class I
Diet and microbial antigens
PP
M cell
APC
CD8+ γδ
APC
= dietary antigen
= LPS antigen
= tolerance
= defence
TGF-β
Diet Antigen Tolerance via :
(a)
Epithelial cell
MHC Class I
(or CD1)
Peptide
TCR
CD8 γδ +
Tcell
(b)
CD103+CX3CR1- or CD11b+CX3CR1+
COX2's
APC (myeloïd or plasmacytoïd)
MHC Class II
IDO
B7-1/2
NO Costimulation
CD28
CTLA-4
CD4+ NaïveTcell
Dose-dependent induction of T-cell-mediated suppression
T-cell deletion
T-cell anergy
Apoptosis


Mucin rich Glycocalyx
Mucosal Cell
MHC Class I
Diet and microbial antigens
PP
M cell
APC
CD8+ γδ
APC
= dietary antigen
= LPS antigen
= tolerance
= defence
TGF-β
Diet Antigen Tolerance via :
(a)
(b)
CD103+CX3CR1- or CD11b+CX3CR1+
COX2's
APC (myeloïd or plasmacytoïd)
MHC Class II
IDO
PGE2's (+)
B7-1/2
Costimulation
CD28
CTLA-4
CD4+ NaïveTcell
TGF-β
TGF-β
Epithelial cell
MHC Class I
(or CD1)
Peptide
TCR
CD8 γδ + Tcell
CD4+CD25+ iT-reg's
COX2's
Foxp3
TGF-β
PGE2's (+)
Dose-dependent induction of T-cell-mediated suppression
Bystander Suppression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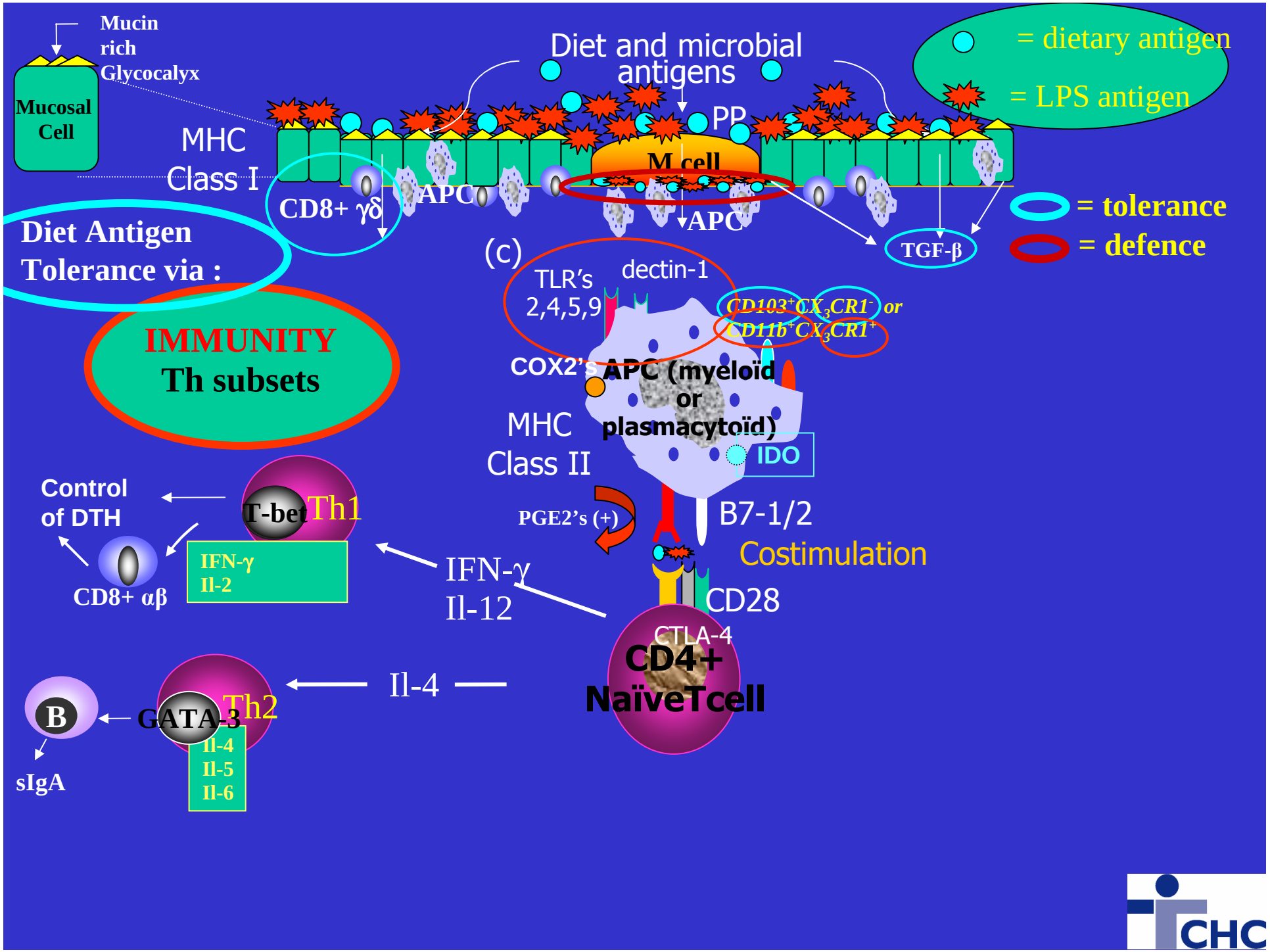
Diet Antigen Tolerance via :
TGF-β
(c)
TLR's 2,4,5,9
dectin-1
CD103+CX3CR1- or CD11b+CX3CR1+
COX2's
APC (myeloïd or plasmacytoïd)
MHC Class II
IDO
PGE2's (+)
B7-1/2
Costimulation
CD28
CTLA-4
CD4+ NaïveTcell
Active immunity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M cell
APC
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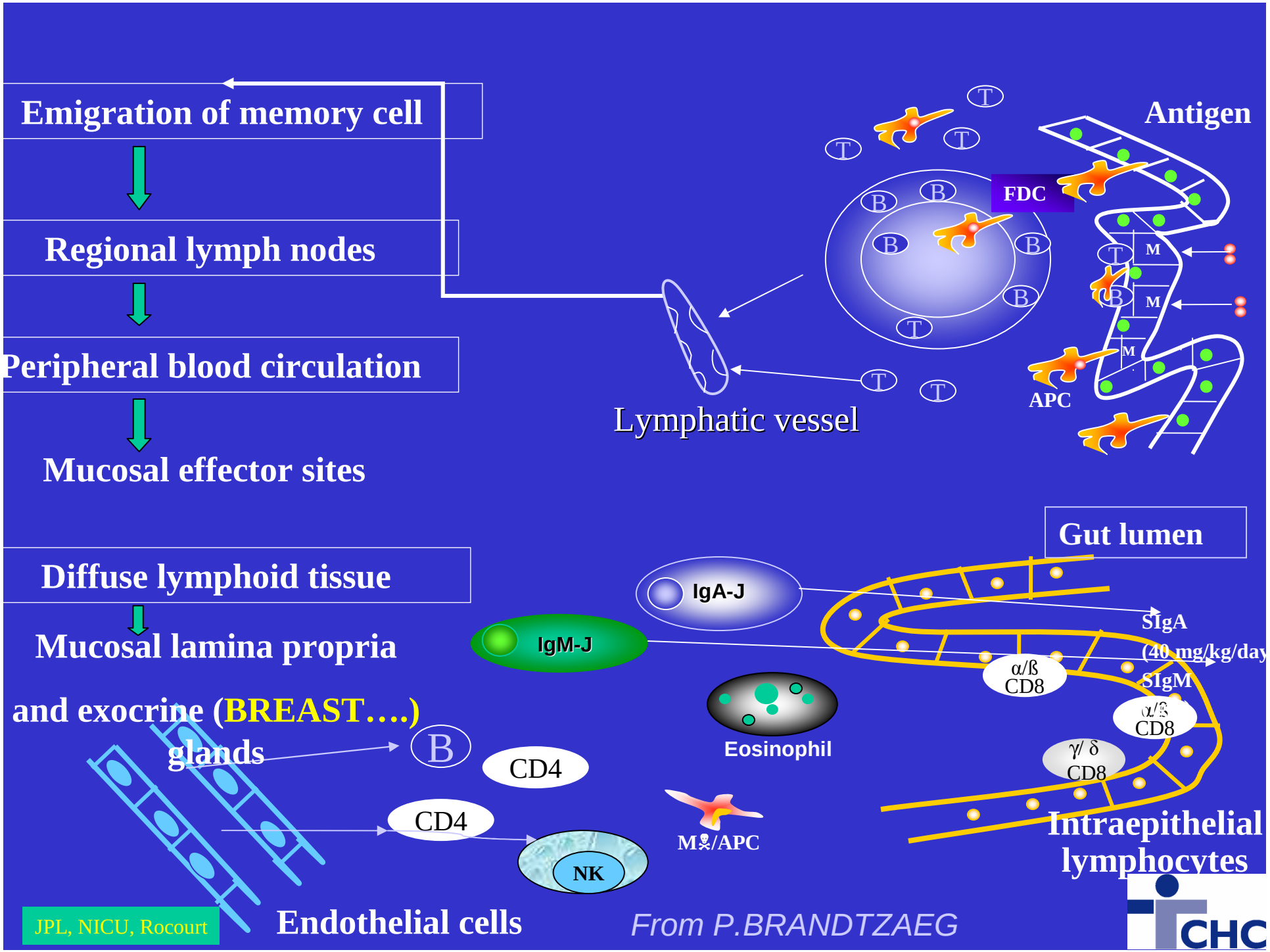
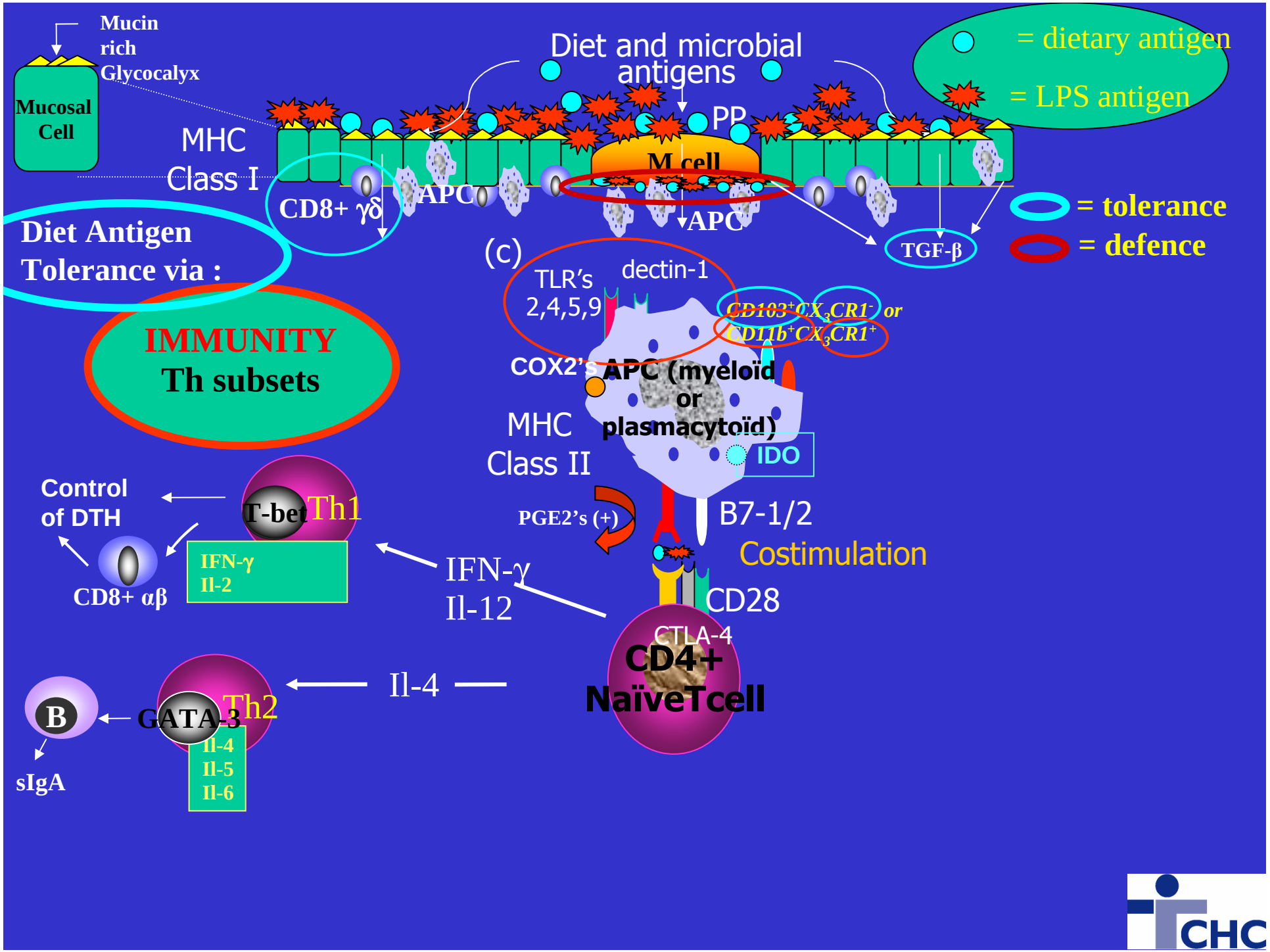
CD8+ γδ
TGF-β
= tolerance
= defence
Diet Antigen Tolerance via :
IMMUNITY
Th subsets
(c)
TLR's 2,4,5,9
dectin-1
CD103+CX3CR1- or CD11b+CX3CR1+
COX2's
APC (myeloïd or plasmacytoïd)
MHC Class II
IDO
PGE2's (+)
B7-1/2
Costimulation
CD28
CTLA-4
CD4+ NaïveTcell
Control of DTH
T-bet
Th1
IFN-γ Il-2
CD8+ αβ
IFN-γ Il-12
Il-4
B
GATA-3
Th2
Il-4 Il-5 Il-6
sIgA


Emigration of memory cell
Regional lymph nodes
Peripheral blood circulation
Mucosal effector sites
Diffuse lymphoid tissue
Mucosal lamina propria
and exocrine (BREAST….)
glands
Endothelial cells
Lymphatic vessel
Antigen
FDC
APC
M
T
B
Gut lumen
IgA-J
IgM-J
SIgA
(40 mg/kg/day
SIgM
α/ß
CD8
α/ß
CD8
γ/ δ
CD8
Eosinophil
CD4
CD4
NK
M/APC
Intraepithelial
lymphocytes
JPL, NICU, Rocourt
From P.BRANDTZAEG
CHC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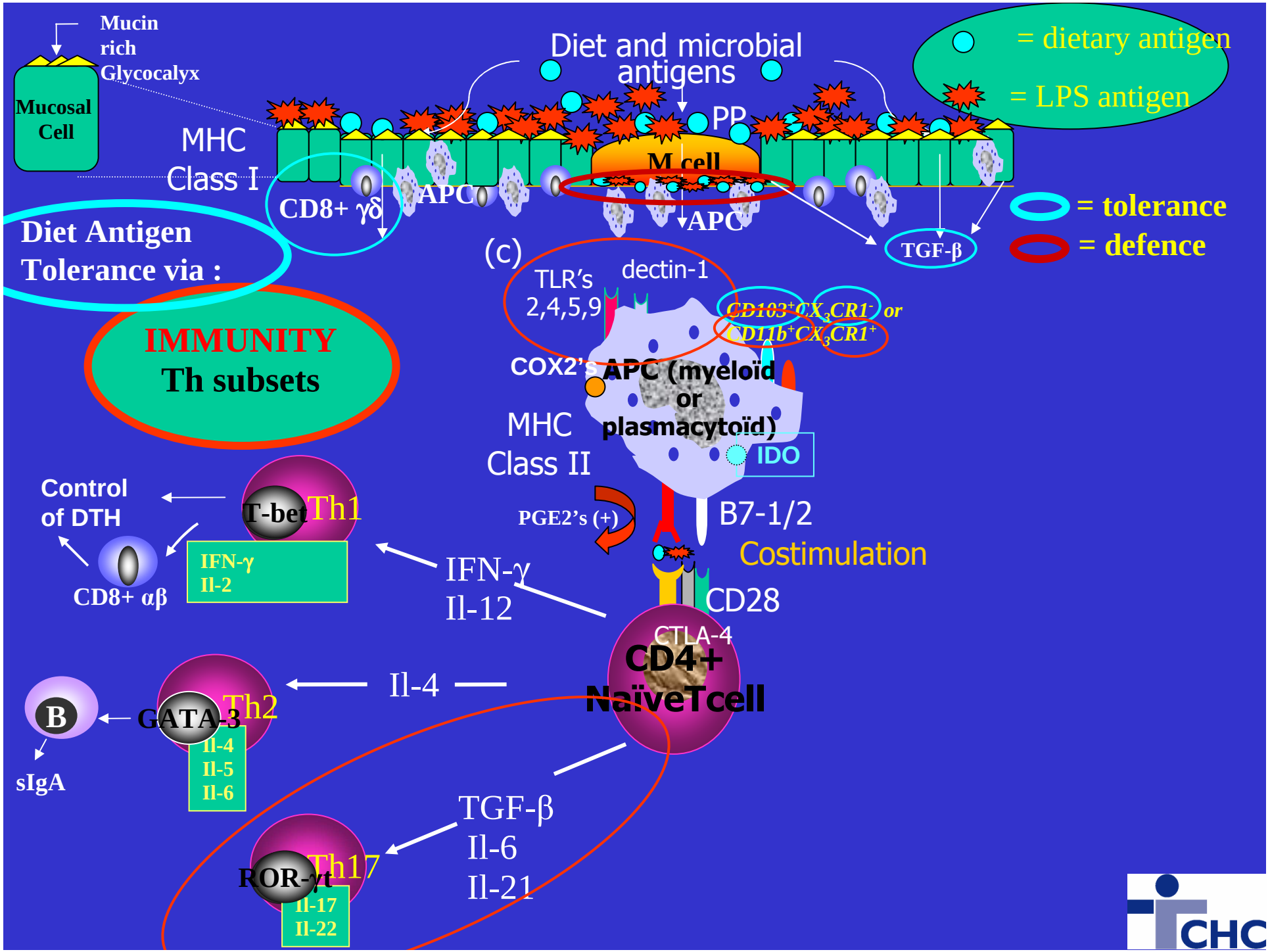
Mucosal Cell
Diet and microbial antigens
= dietary antigen
= LPS antigen
MHC Class I
PP
M cell
CD8+ γδ
APC
APC
= tolerance
= defence
Diet Antigen Tolerance via :
TGF-β
(c)
TLR's 2,4,5,9
dectin-1
CD103+CX3CR1- or CD11b+CX3CR1+
IMMUNITY
Th subsets
COX2's
APC (myeloïd or plasmacytoïd)
MHC Class II
IDO
Control of DTH
T-bet
Th1
PGE2's (+)
B7-1/2
Costimulation
IFN-γ
Il-2
IFN-γ
Il-12
CD8+ αβ
CD28
CTLA-4
CD4+ NaïveTcell
Il-4
B
GATA-3
Th2
Il-4
Il-5
Il-6
sIgA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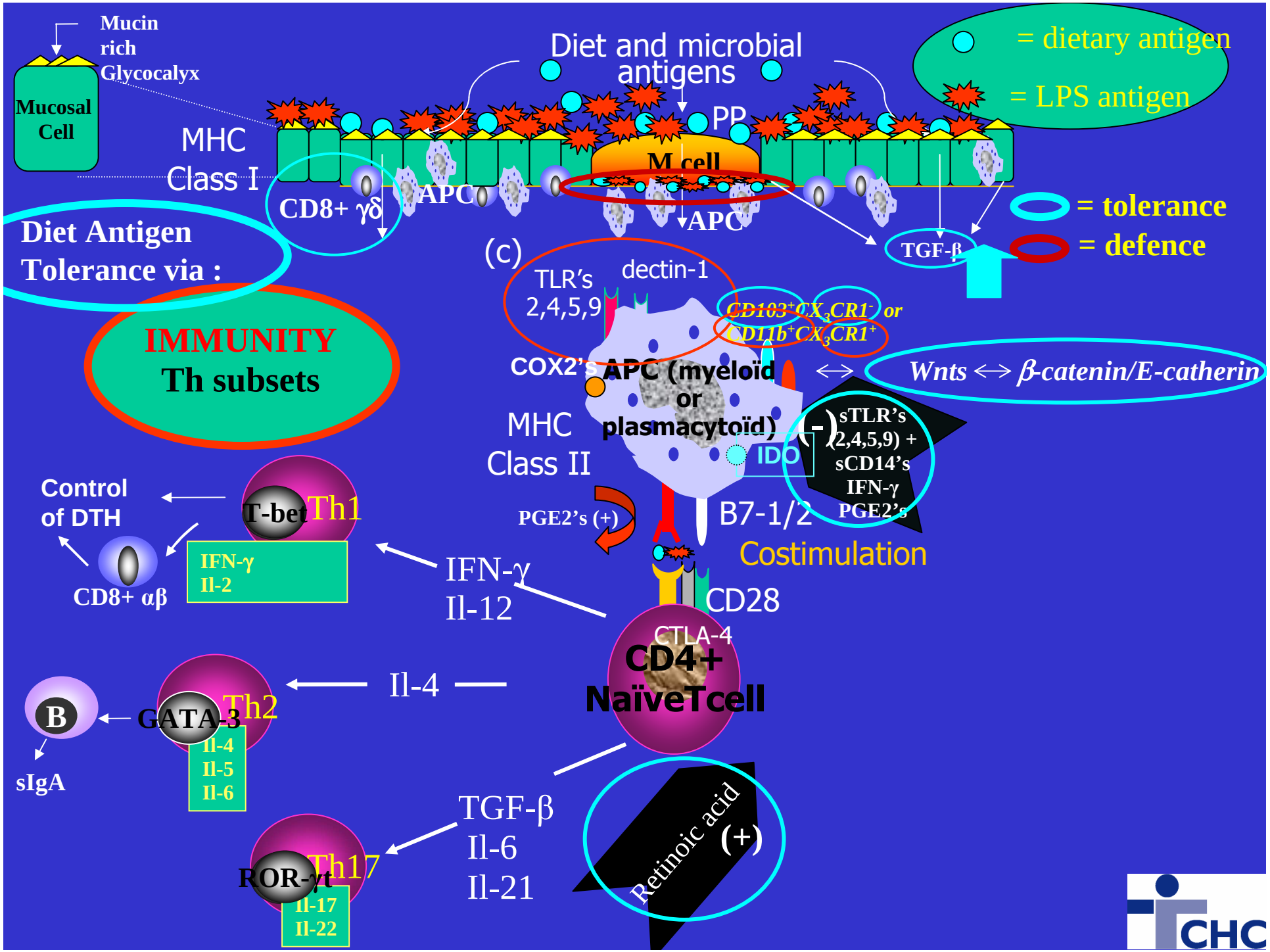
IFN-γ
Il-12
Il-4
B
GATA-3
Th2
Il-4
Il-5
Il-6
sIgA
TGF-β
Il-6
Il-21
ROR-γt
Th17
Il-17
Il-22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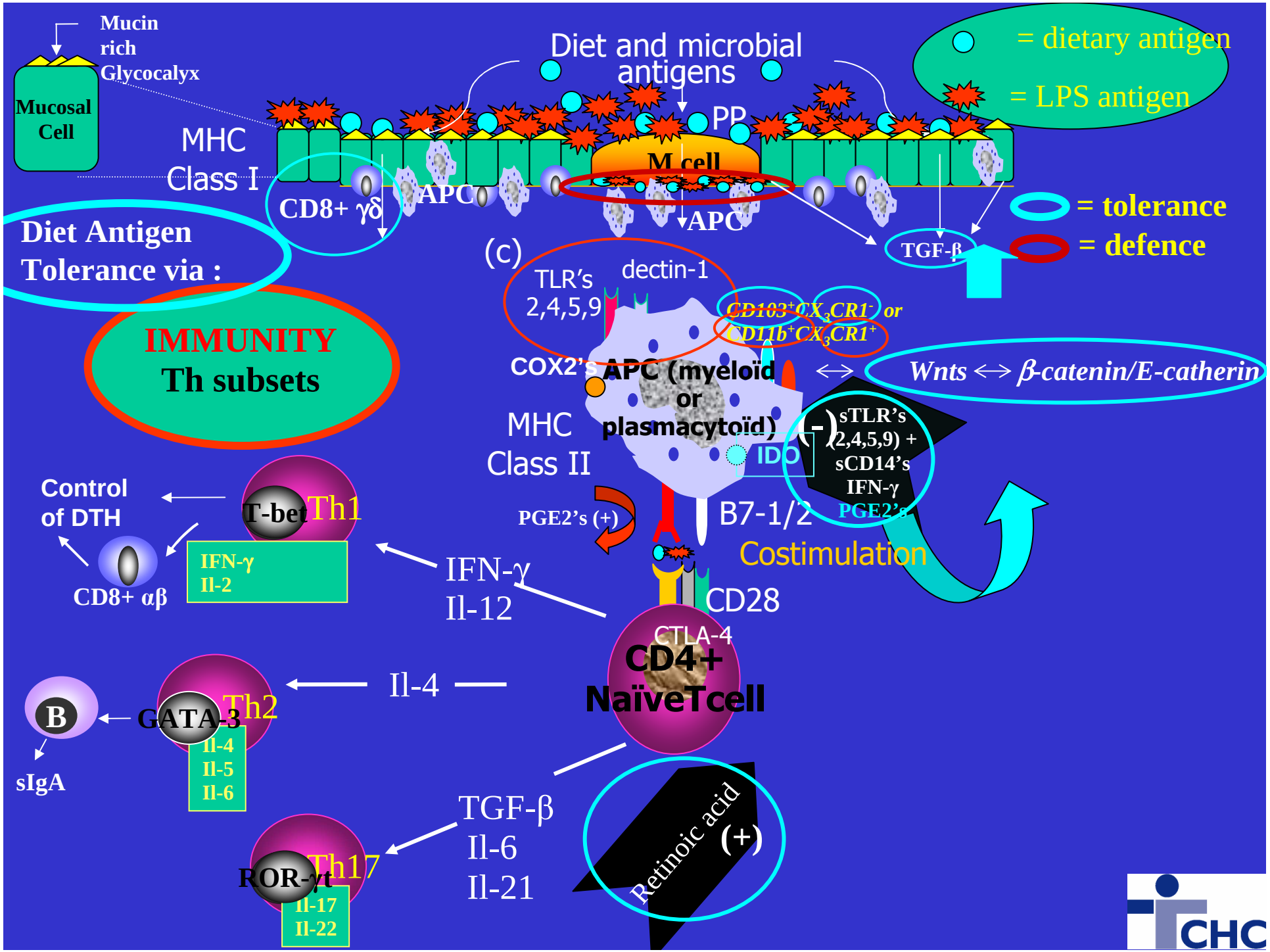
CD103+CX3CR1- or CD11b+CX3CR1+
COX2's
APC (myeloïd or plasmacytoïd)
Wnts ↔ β-catenin/E-catherin
MHC Class II
IDO
(-)
sTLR's (2,4,5,9) + sCD14's IFN-γ PGE2's
PGE2's (+)
B7-1/2
Costimulation
CD28
CTLA-4
CD4+ NaïveTcell
Control of DTH
T-bet
Th1
IFN-γ Il-2
CD8+ αβ
IFN-γ Il-12
Il-4
B
GATA-3
Th2
Il-4 Il-5 Il-6
sIgA
TGF-β Il-6 Il-21
Retinoic acid
(+)
ROR-γt
Th17
Il-17 Il-22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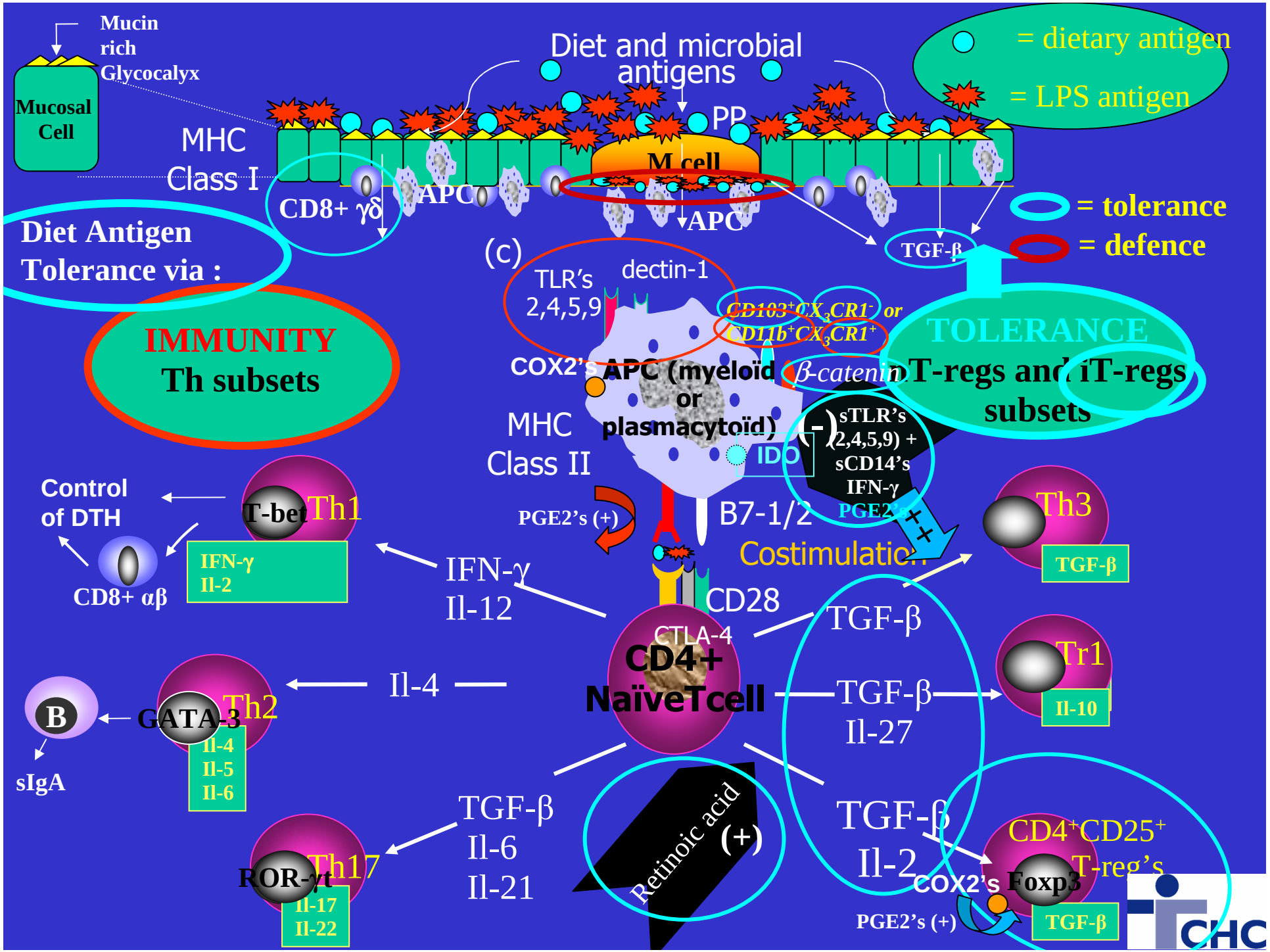
B
GATA-3
Th2
Il-4 Il-5 Il-6
sIgA
TGF-β Il-6 Il-21
Retinoic acid
(+)
ROR-γt
Th17
Il-17 Il-22
CHC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Th subsets
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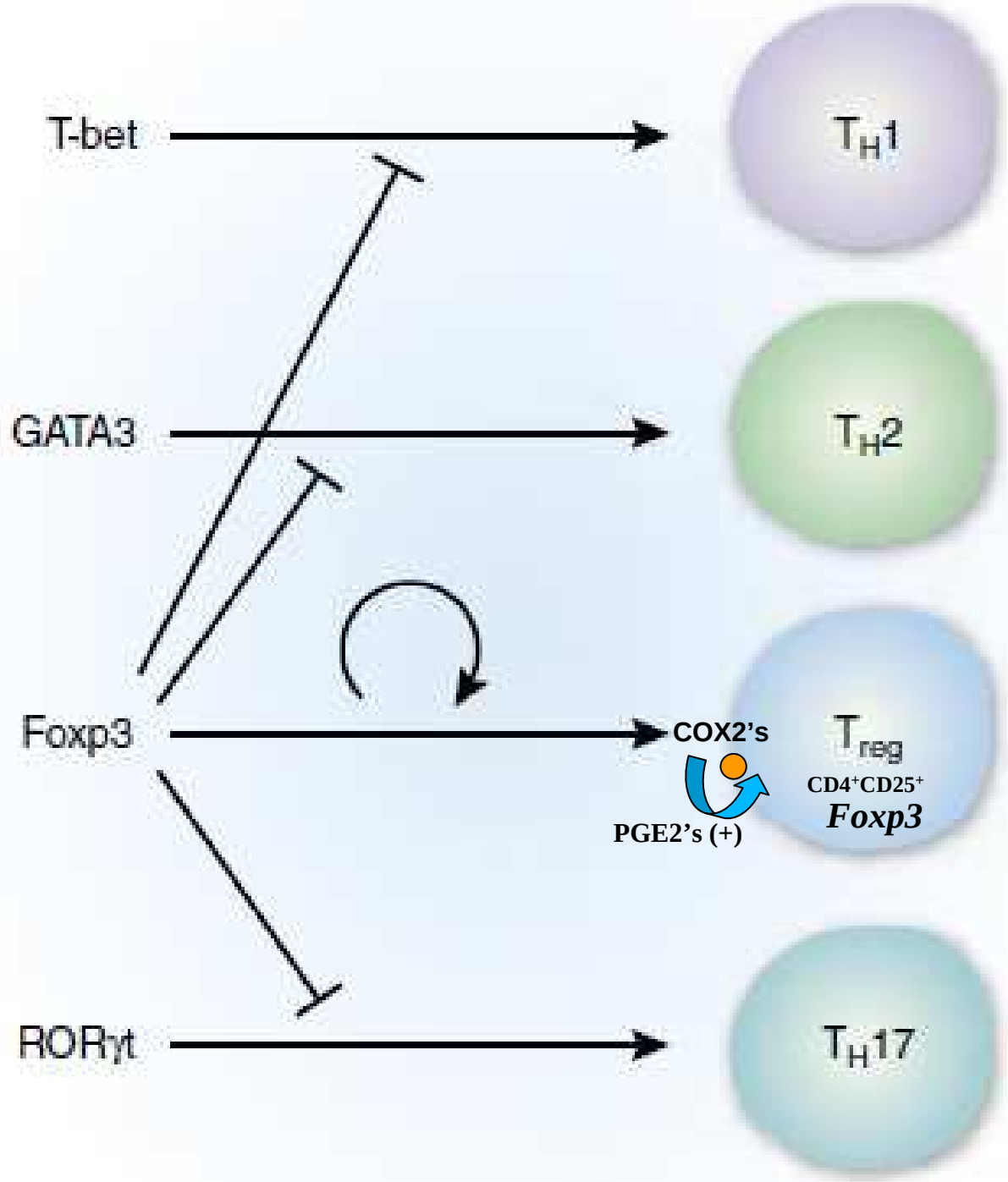
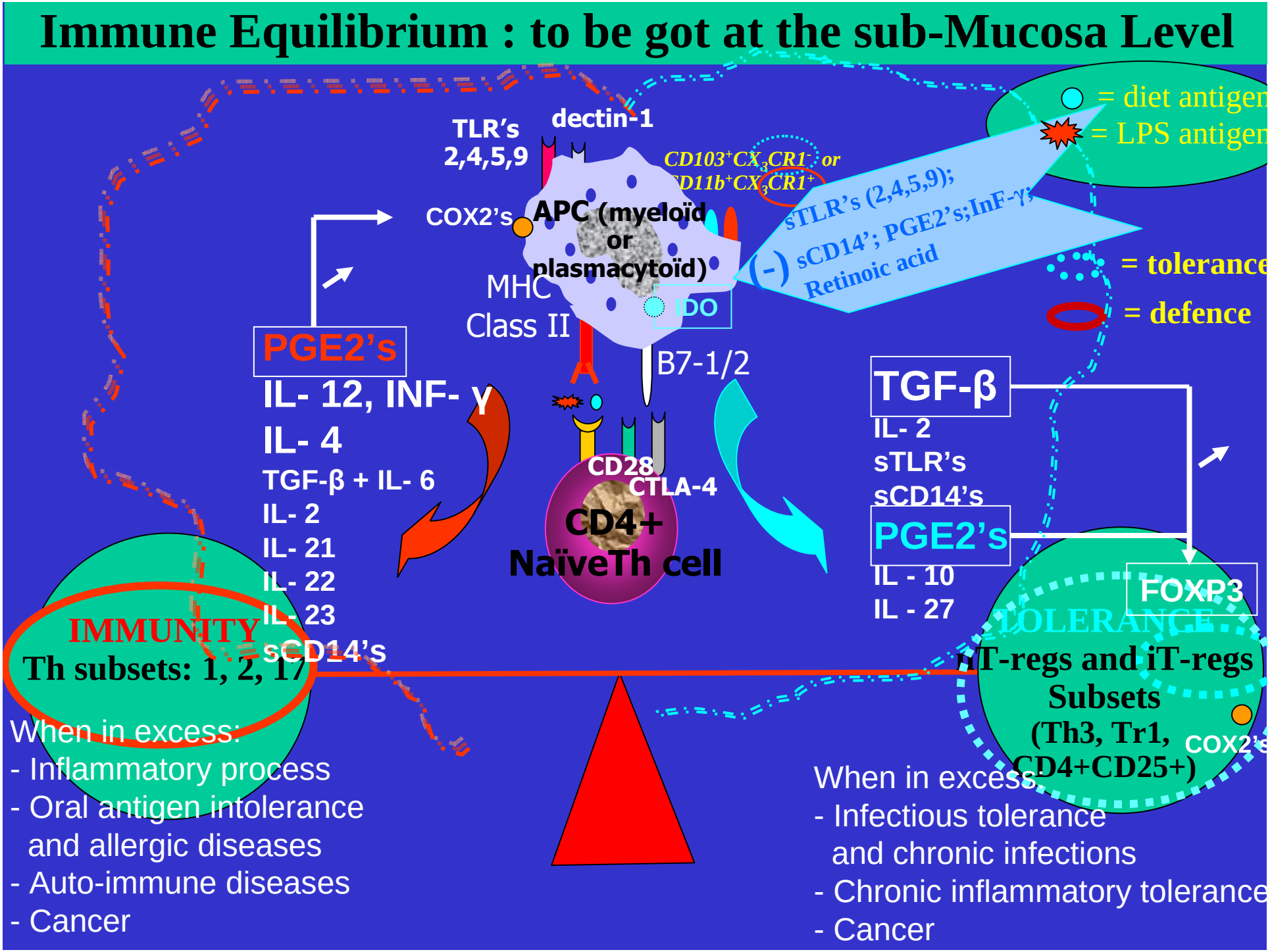
CTLA-4
CD4+ NaïveTcell
TGF-β
Th3
TGF-β
Il-4
TGF-β
TGF-β Il-27
Tr1
Il-10
B
GATA-3
Th2
Il-4 Il-5 Il-6
sIgA
TGF-β Il-6 Il-21
Retinoic acid (+)
TGF-β Il-2
CD4+CD25+ T-reg's
RORγt
Th17
Il-17 Il-22
COX2's Foxp3
PGE2's (+)
TGF-β



adapted from
Zheng Y and Rudensky AY.
Nature Immunol 2007;8:457.

Immune Equilibrium : to be got at the sub-Mucosa Level



Cyclooxygenase-2-dependent arachidonic acid metabolites are essential modulators of the intestinal immune response to dietary antigen

RODNEY D. NEWBERRY[1,2], WILLIAM F. STENSON[1,2] & ROBIN G. LORENZ[1,3]

Department of Internal Medicine[1], Division of Gastroenterology[2], Center for Immunology, Department of Pathology[3], Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110, USA

Correspondence should be addressed to R.G.L.; email: lorenz@pathbox.wustl.edu

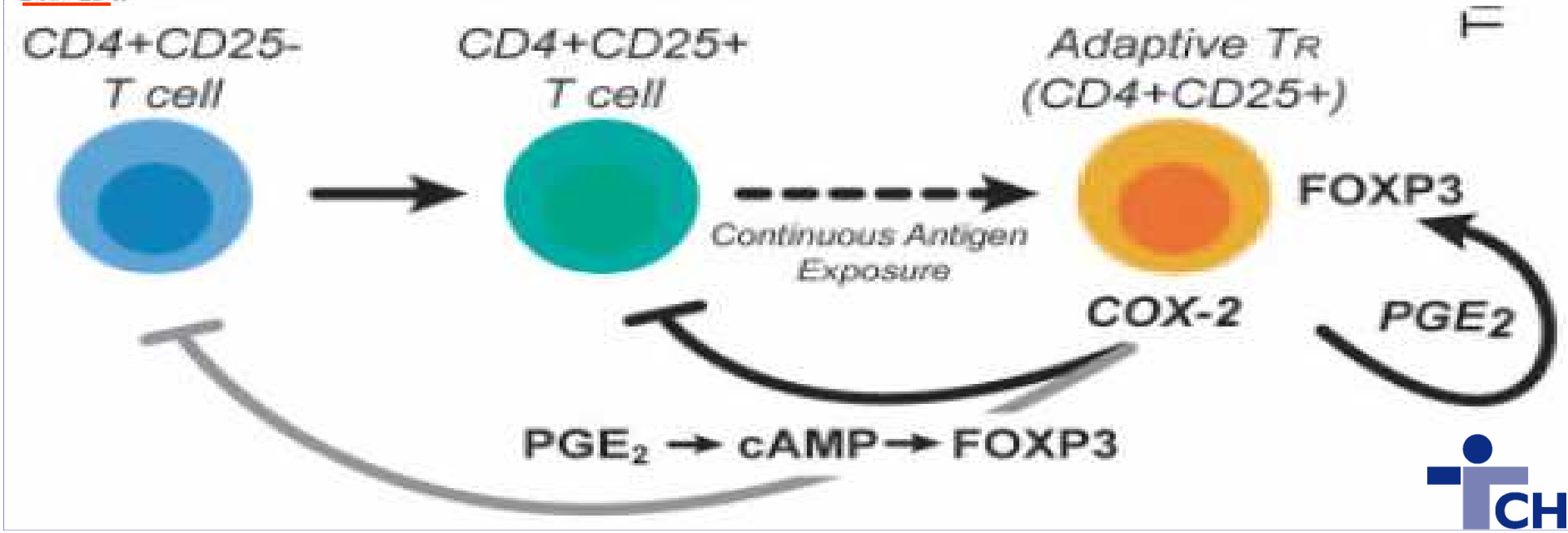
Intestinal inflammatory diseases are mediated by dysregulated immune responses to undefined luminal antigens. Feeding hen egg-white lysozyme to mice expressing a transgenic T-cell receptor that recognizes hen egg-white lysozyme peptide 46–61 resulted in no intestinal pathology; however, simultaneous administration of cyclooxygenase-2 inhibitors and dietary hen egg-white lysozyme resulted in increased proliferation of lamina propria mononuclear cells and crypt epithelial cells, crypt expansion and villus blunting. Lamina propria mononuclear cells produce high levels of cyclooxygenase-2-dependent arachidonic acid metabolites, which act as immunomodulators in the immune response to dietary antigen. These findings establish that cyclooxygenase-2-dependent arachidonic acid metabolites are essential in the development and maintenance of intestinal immune homeostasis.

Newberry et al *Nature Med* 1999; 5: 900

FOXP3$^+$CD4$^+$CD25$^+$ Adaptive Regulatory T Cells Express Cyclooxygenase-2 and Suppress Effector T Cells by a Prostaglandin E_2-Dependent Mechanism[1]

Milada Mahic,* Sheraz Yaqub,* C. Christian Johansson,[2]* Kjetil Taskén,[3]* and Einar M. Aandahl*†

CD4$^+$CD25$^+$ regulatory T (T_R) cells suppress effector T cells by partly unknown mechanisms. In this study, we describe a population of human suppressive CD4$^+$CD25$^+$ adaptive T_R (T_R^{adapt}) cells induced in vitro that express cyclooxygenase 2 (COX-2) and the transcription factor FOXP3. T_R^{adapt} cells produce PGE_2 and suppress effector T cell responses in a manner that is reversed by COX inhibitors and PGE_2 receptor-specific antagonists. In resting CD4$^+$CD25$^-$ T cells, treatment with PGE_2 induced FOXP3 expression. Thus, autocrine and paracrine effects of PGE_2 produced by COX-2-positive T_R^{adapt} cells may be responsible for both the FOXP3$^+$ phenotype and the mechanism used by these cells to suppress effector T cells. *The Journal of Immunology*, 2006, 177: 246–254.

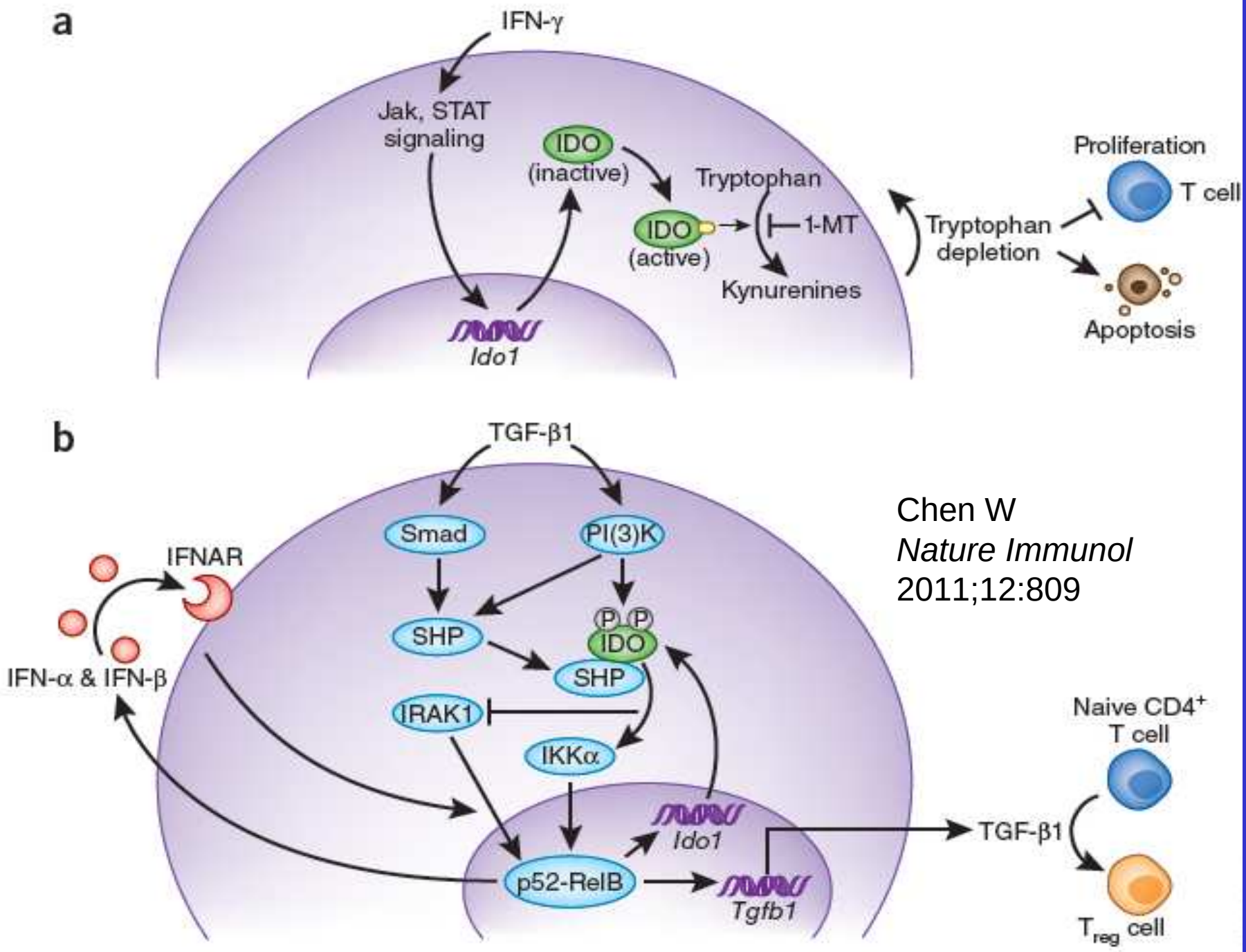


Cyclooxygenase-2 in mucosal DC mediates induction of regulatory T cells in the intestine through suppression of IL-4

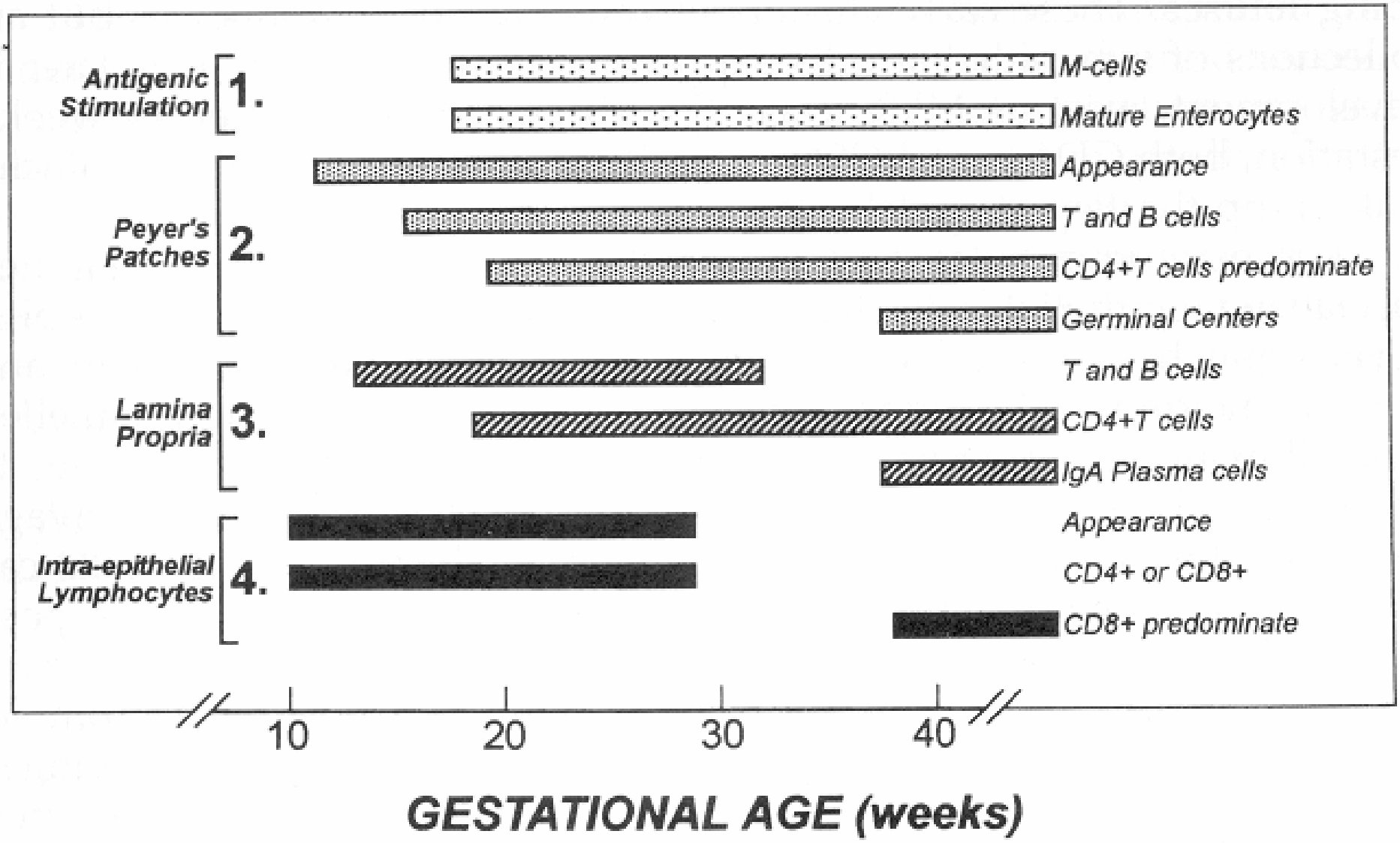
F Broere[1,7], MF du Pré[2,7], LA van Berkel[2], J Garssen[3,4], CB Schmidt-Weber[5], BN Lambrecht[6], RW Hendriks[6], EES Nieuwenhuis[2], G Kraal[1] and JN Samsom[2]

Oral intake of protein leads to tolerance through the induction of regulatory T cells (Tr cells) in mesenteric lymph nodes (MLNs). Here we show that the inhibition of cyclooxygenase-2 (COX-2) *in vivo* suppressed oral tolerance and was associated with enhanced differentiation of interleukin (IL)-4-producing T cells and reduced Foxp3$^+$ Tr-cell differentiation in MLN. As a result, the functional suppressive capacity of these differentiated mucosal T cells was lost. IL-4 was causally related to loss of tolerance as treatment of mice with anti-IL-4 antibodies during COX-2 inhibition restored tolerance. Dendritic cells (DCs) in the MLN differentially expressed COX-2 and reductionist experiments revealed that selective inhibition of the enzyme in these cells inhibited Foxp3$^+$ Tr-cell differentiation *in vitro*. Importantly, the inhibition of COX-2 in MLN-DC caused increased GATA-3 expression and enhanced IL-4 release by T cells, which was directly related to impaired Tr-cell differentiation. These data provide crucial insights into the mechanisms driving *de novo* Tr-cell induction and tolerance in the intestine.

Broere et al *Mucosal Immunology* 2009;2:254.



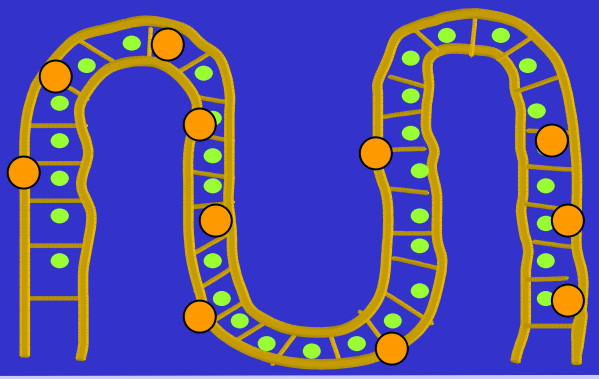
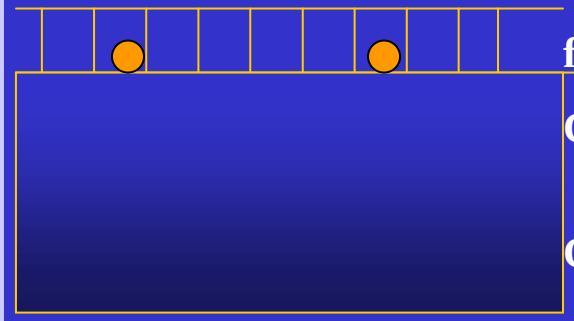
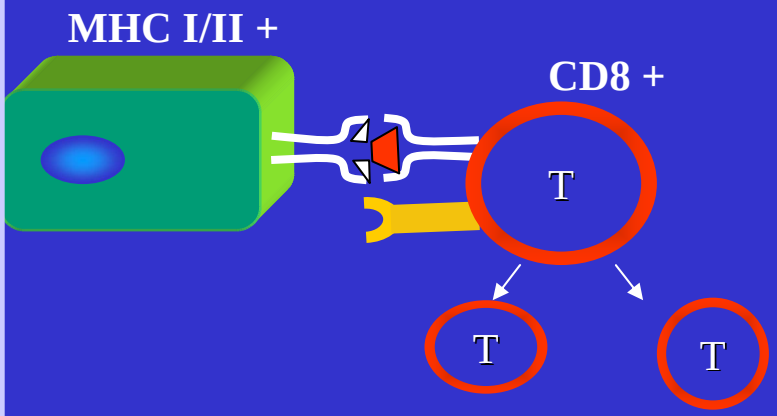
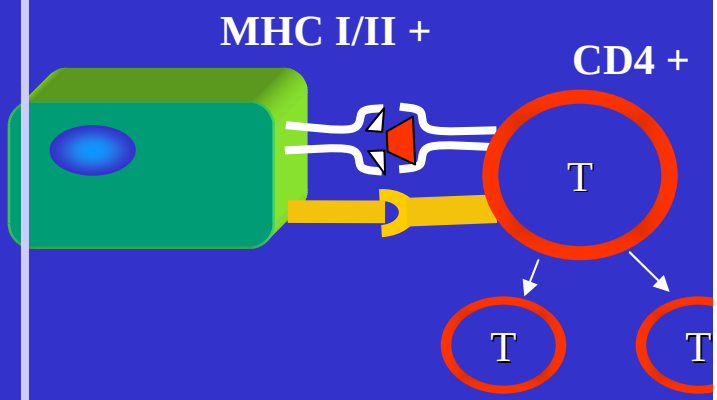
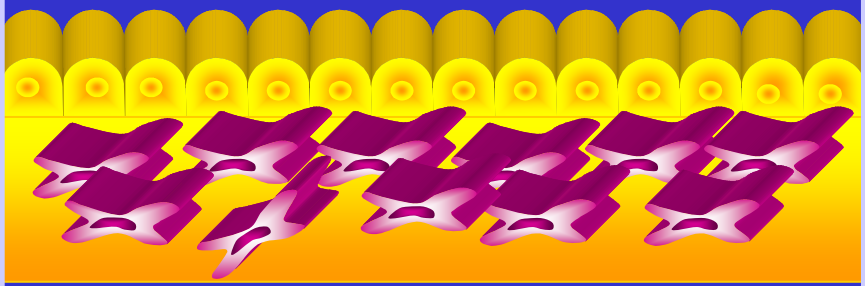
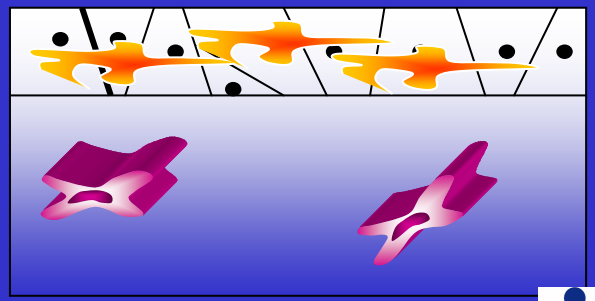
Chen W
Nature Immunol
2011;12:809



Insoft RM, Sanderson IR & Walker A
Pediatr Clin N Am 1996;43:551

Immunological Immaturity in Early Life

- **Limitations of the Innate immune response**
- **- Immature APC function** (*$CD103^+CX_3CR1^-$ or $CD11b^+CX_3CR1^+$*)
  - Adenosine antagonises TLR-mediated cytokines production
- **Limitations of early life antibody responses**
  - Limited responses to protein antg's, to PS and LPS antg's
  - Influence of maternal antibodies
- **Limitations of T cell responses**
  - Reduced expression of MHC class II
- **- Defective IFN-gamma secretion** and low Th-17 activation
- **- $CD4^+/CD25^+$ T reg's fully functional and abundant**
- **Limitations in mucosal immunity**
  - Deficiency in BPI (bactericidal/permeability-increasing protein)
- **- Limited sIgA's synthesis in the first months (IgM's)**

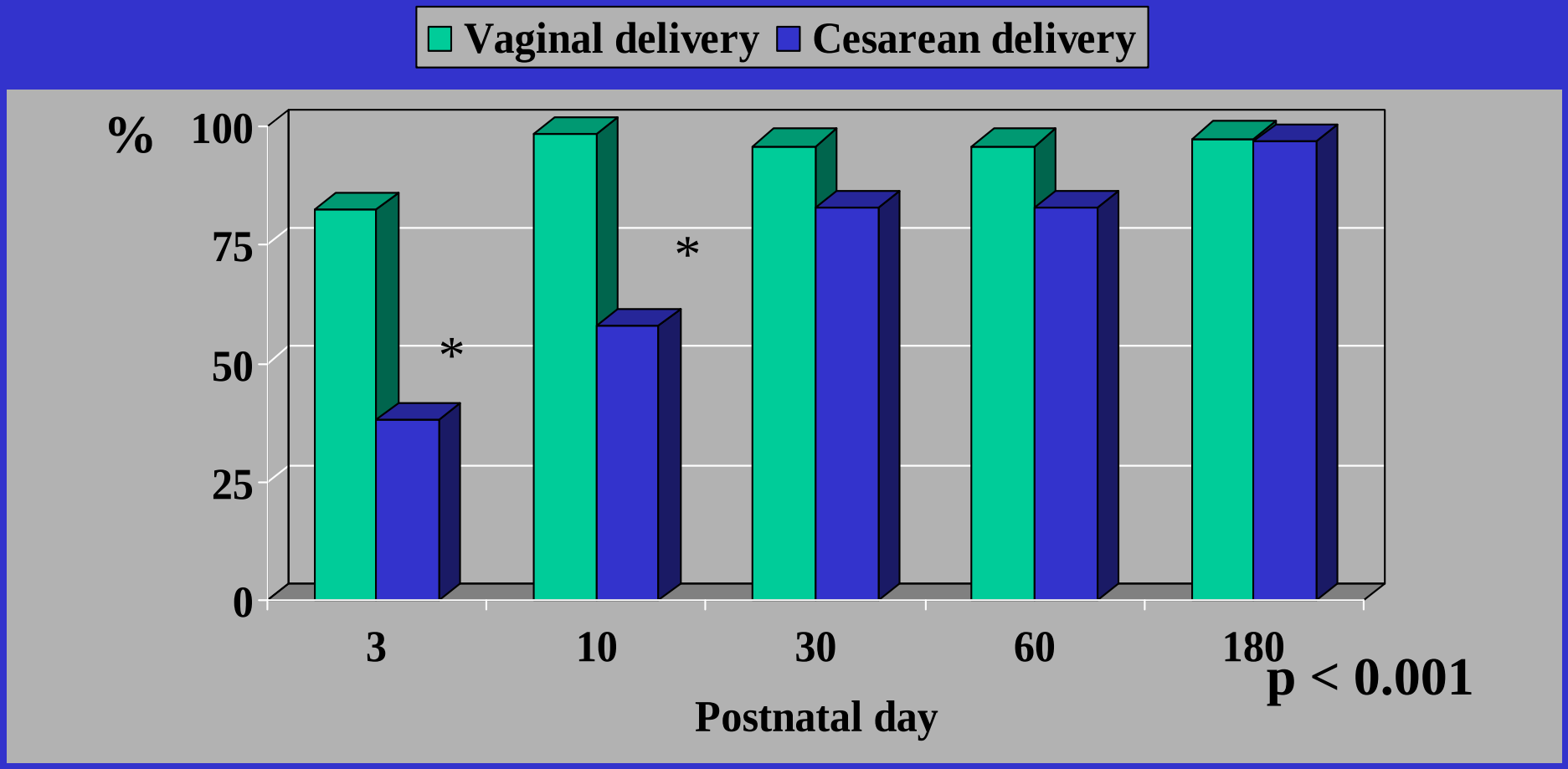
Variable	Gut	Airway
IEL	 many CD8 + >> CD4 +	 few CD8 + > < CD4 +
Epithelial cell	 MHC I/II + CD8 + T T T suppression	 MHC I/II + CD4 + T T T help
Professional MHC class I/II Positive APC	 From P.BRANDTZAEG, 1996	

JPL, NICU, Rocourt

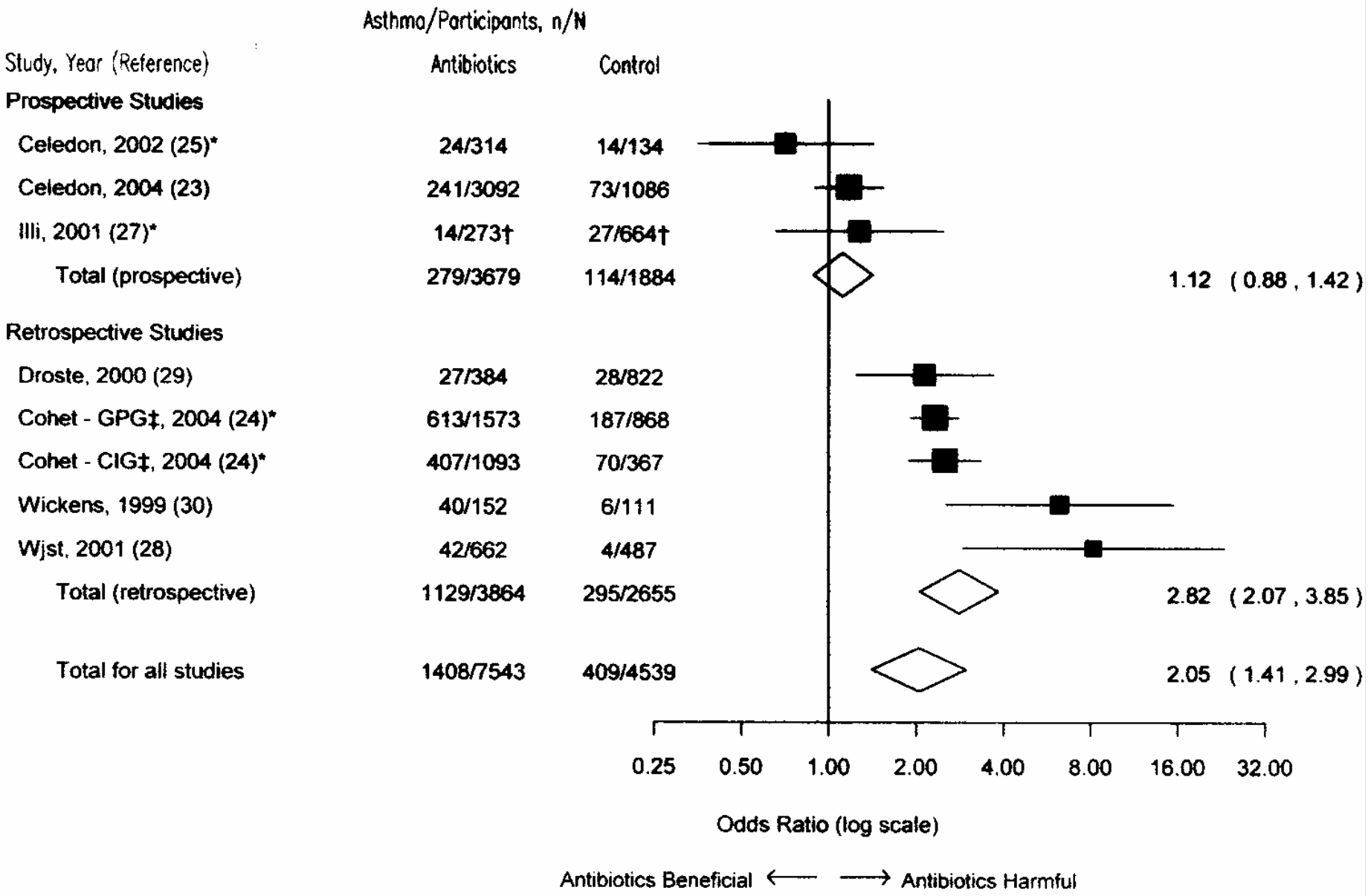
CHC

Our modern perinatal ways of care badly interfere with the bacterial colonisation at birth….. and could favour immune deviances….

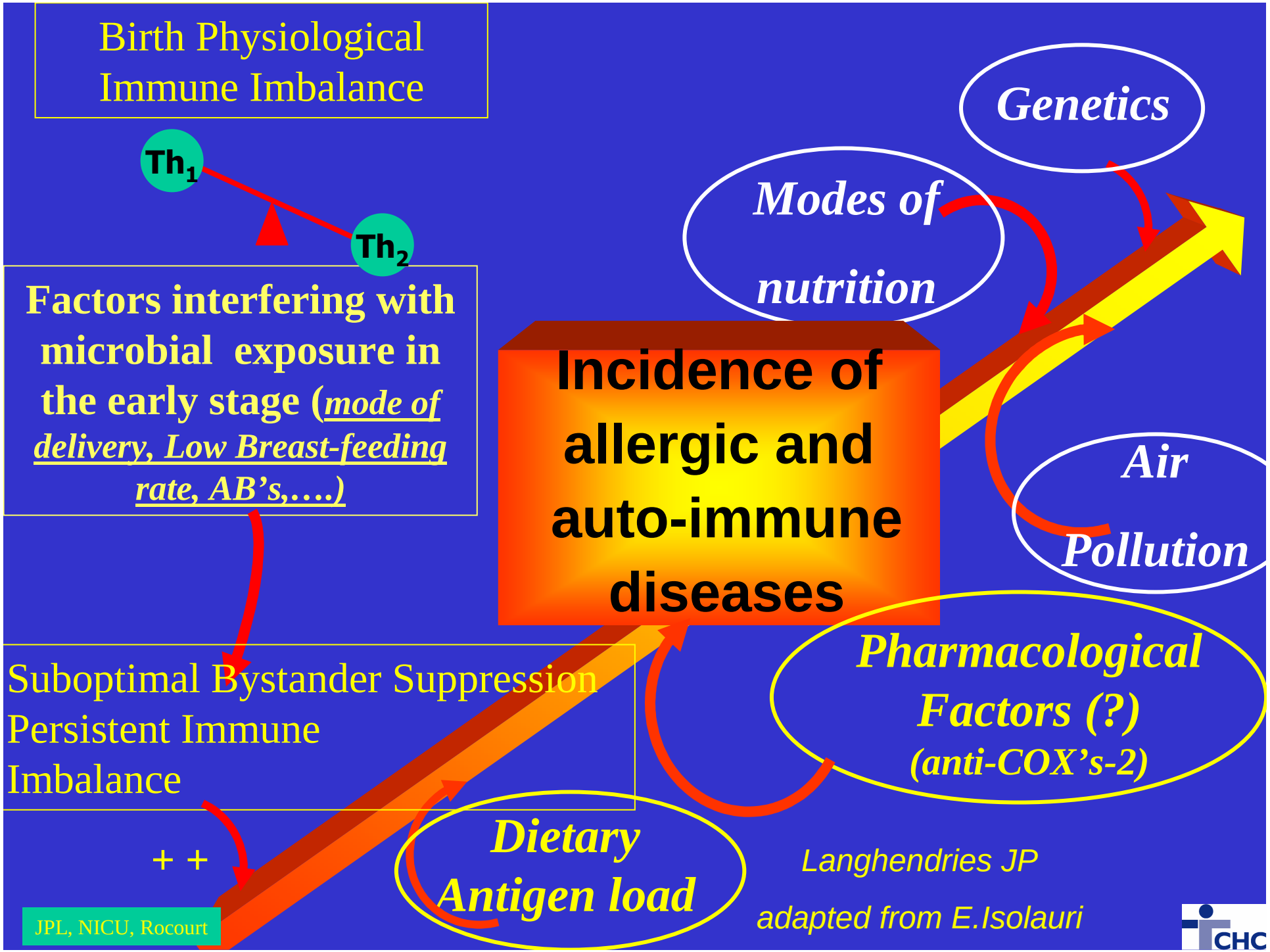
Percentage of *Bifidobacterium-like bacteria (BLB)* colonization in infants



Gronlund et al J Pediatr Gastroenterol Nutr 1999; 28:19-25



Marra et al, *Chest* 2006;129:610.


Birth Physiological Immune Imbalance
Th1
Th2
Factors interfering with microbial exposure in the early stage (mode of delivery, Low Breast-feeding rate, AB's,….)
Suboptimal Bystander Suppression Persistent Immune Imbalance
+ +
JPL, NICU, Rocourt
Genetics
Modes of nutrition
Air Pollution
Incidence of allergic and auto-immune diseases
Pharmacological Factors (?) (anti-COX's-2)
Dietary Antigen load
Langhendries JP
adapted from E.Isolauri
CHC

Exclusive Breast-Feeding : Optimising Bacterial/Mucosal Interface

Bifidogenic Factors

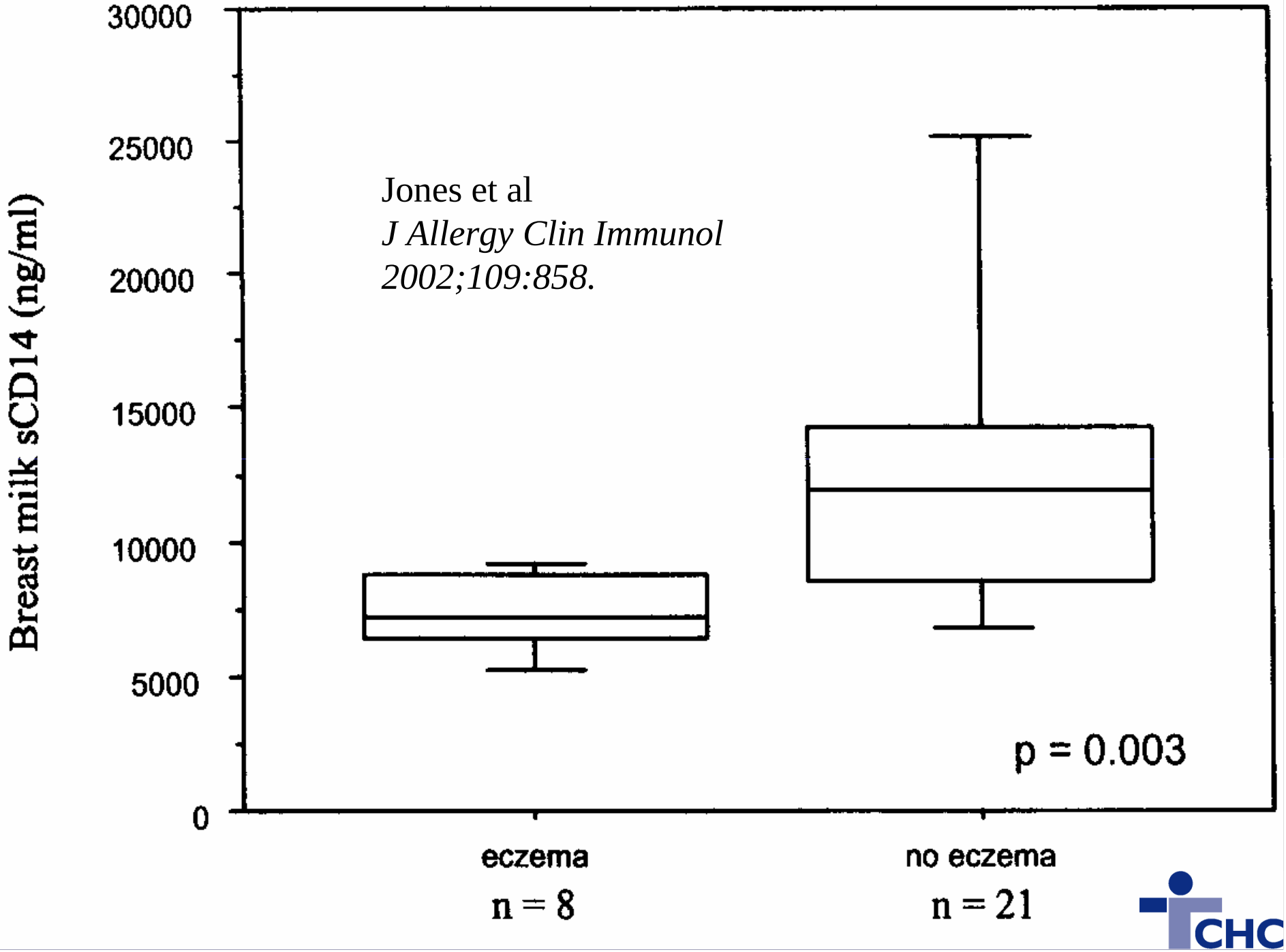
- Glycoproteins {κ Casein (N-Acetyl-Glucosamine)}
- Mono-oligosaccharides, GOS, ….
- Low protein level
- High lactose concentration
- Low phosphate concentration

Immunomodulating Components

- Virtually all known immune components/nutriments found in HM are relevant for specific protective action on the epithelial cell
- Of outstanding interest: sCD14, Il-10, TGF-β, (S)IgA.

Biologically active Components

- Whey proteins (Lactoferrin, Lysozyme, Defensins, EGF, PAF-AH..
- Osteoprotegerin, adiponectin,
- PUFA's


Breast milk sCD14 (ng/ml)
30000
25000
20000
15000
10000
5000
0
Jones et al
J Allergy Clin Immunol
2002;109:858.
p = 0.003
eczema
n = 8
no eczema
n = 21

THE BEST WAY TO PROGRESS WITH THE INFANT FEEDING IN ORDER TO FAVOUR THE DIETARY ANTIGEN TOLERANCE: NEW DATA FROM EXPERIMENTAL STUDIES

Breast milk–mediated transfer of an antigen induces tolerance and protection from allergic asthma

Valérie Verhasselt[1], Valérie Milcent[1], Julie Cazareth[2], Akira Kanda[3], Sébastien Fleury[3], David Dombrowicz[3], Nicolas Glaichenhaus[1] & Valérie Julia[1] *Nature Immunol* 2008; 14: 170.

- **Exclusive Breast-feeding is the best way by which the Antigen Epitopes are presented to the infant intestinal mucosa (Verhasselt et al, *Nature Immunol* 2008;14:170)**

- **Whatever the postnatal age (preferably not before 4 months), the dietary diversification should progress ahead according to the 4 points rule: 1) antigen in very slow amount; 2) daily repeated; 3) increased; 4) very progressively (Friedman A. *Ann NY Acad 1996;778:103;* Williamson et al *J Immunol 2002;169:3606;* Mahic et al *Eur J Immunol* 2008;38:640)**

CHC

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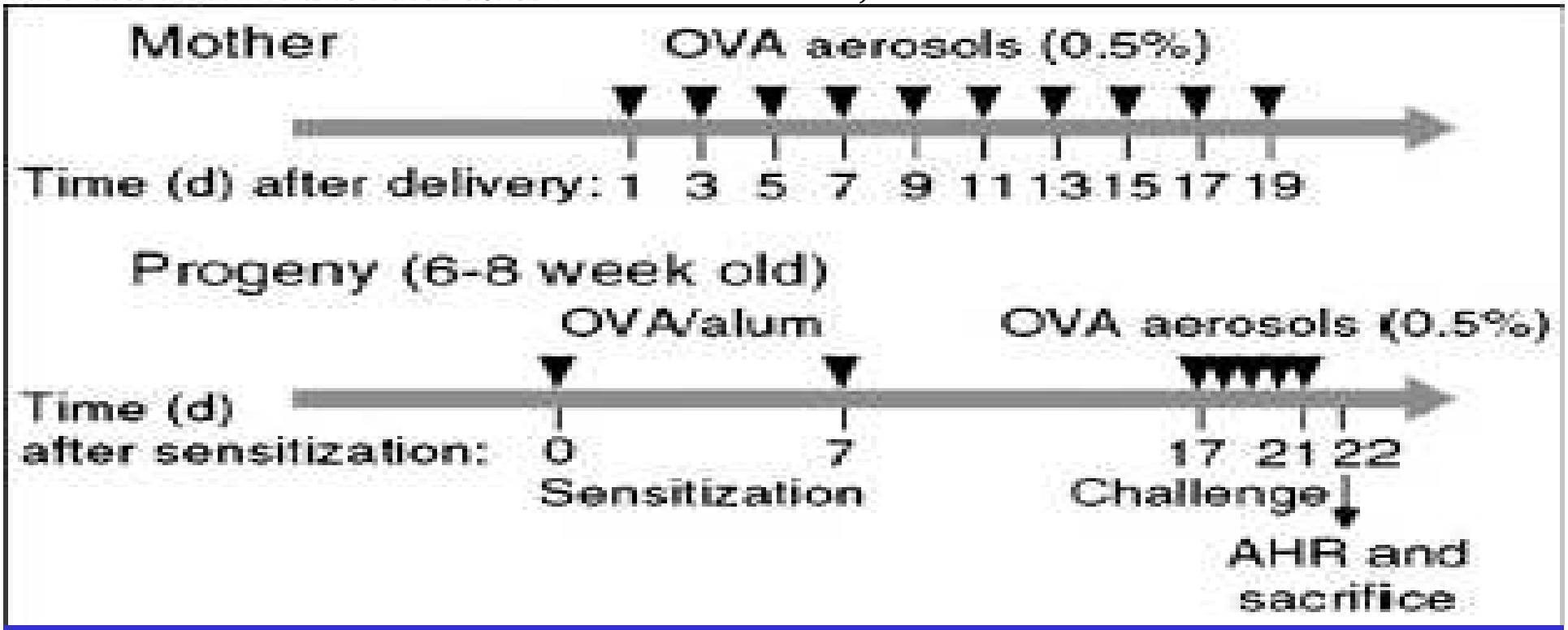

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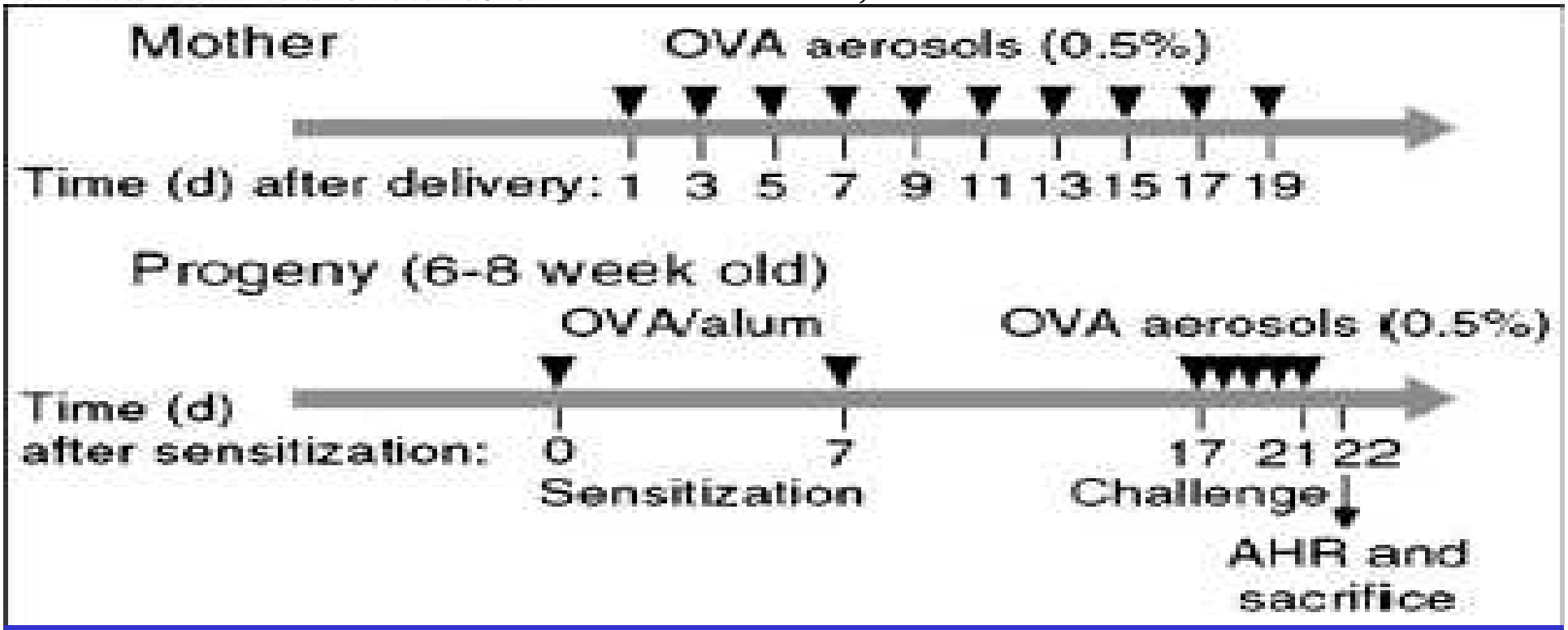

Breast milk-mediated transfer of an antigen to the neonate results in oral tolerance induction leading to antigen-specific protection from allergic airway disease.

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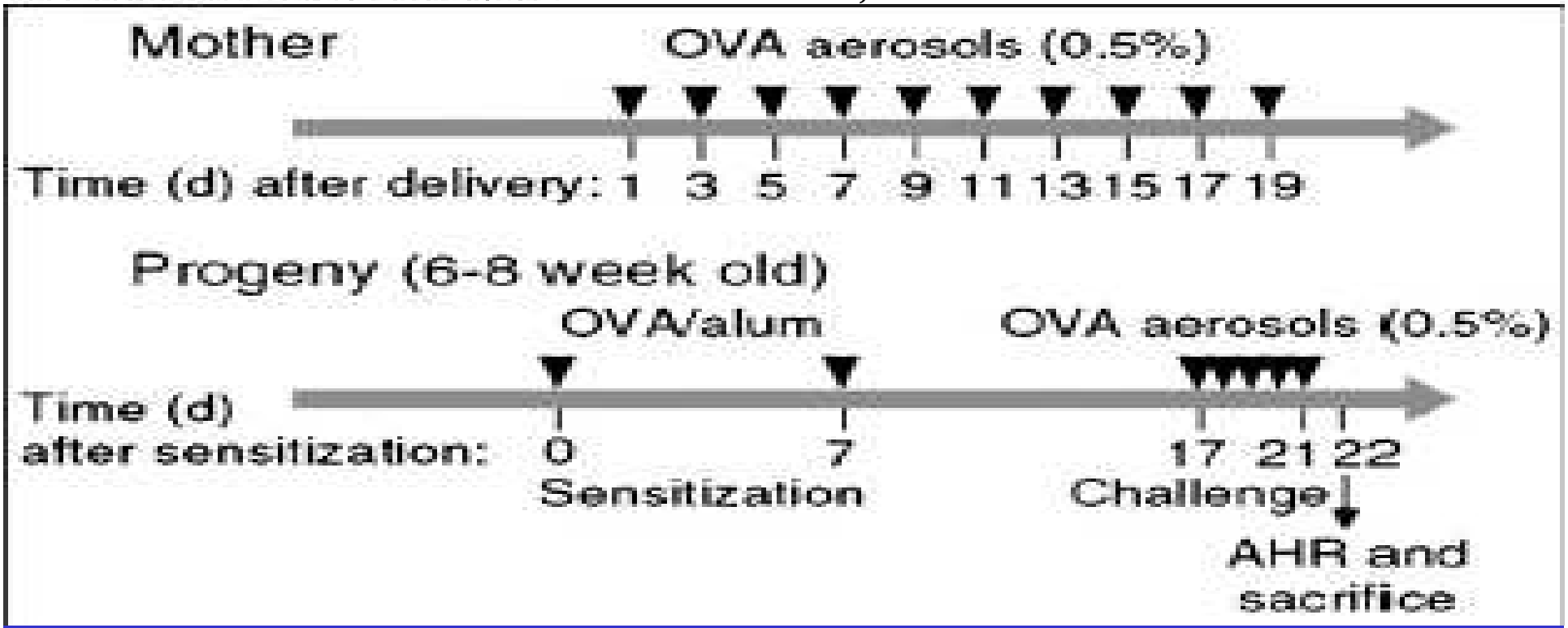
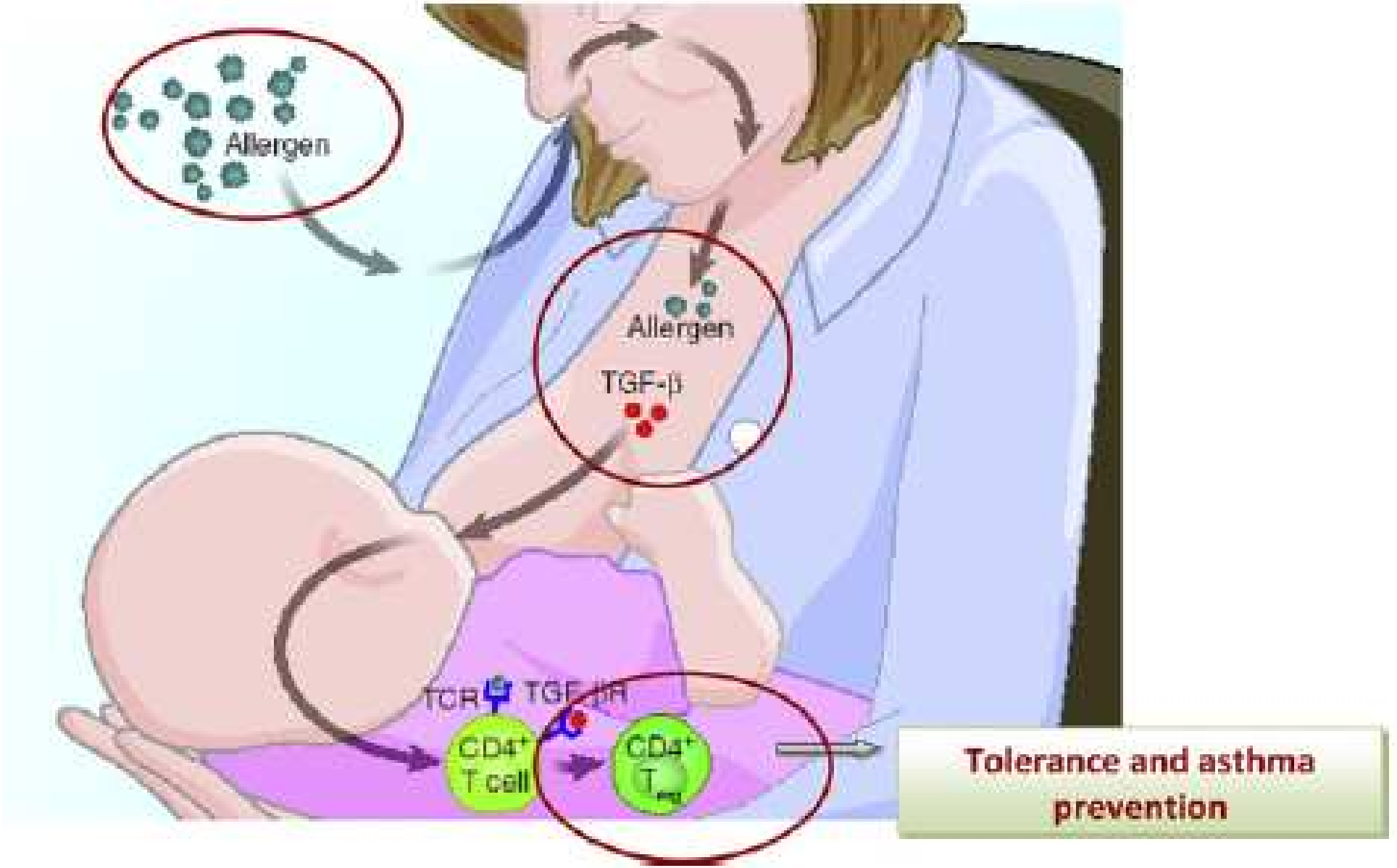


Breast milk-mediated transfer of an antigen to the neonate results in oral tolerance induction leading to antigen-specific protection from allergic airway disease. The presence of TGF-β in breast milk together with the antigen was needed and mandatory to get this tolerance .

Hypothesis emerging from Verhasselt's studies: to be confirmed in humans



Verhasselt et al *J Pediatr 2010; 156: S16.*

Author's sentence :

« This study may pave the way
for the design
of new strategies to prevent
the development of allergic diseases…… such as
deliberate exposure of mothers to allergens
during breastfeeding …. {to try enhancing their tolerance to the progeny}. »

Verhasselt et al *J Pediatr 2010; 156: S16.*

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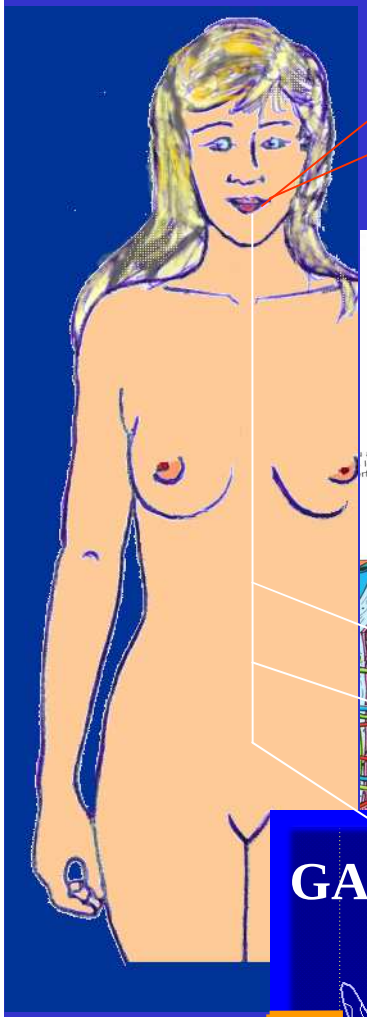
CHC

Mother

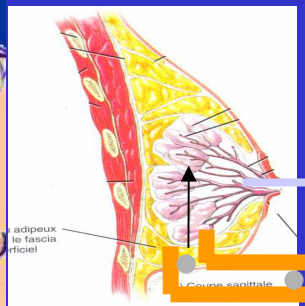
Protection of upper respiratory tract mucosa and gastrointestinal mucosa, oral dietary antigen tolerance

Child



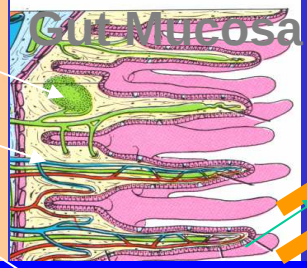
Microbes

Food antigens

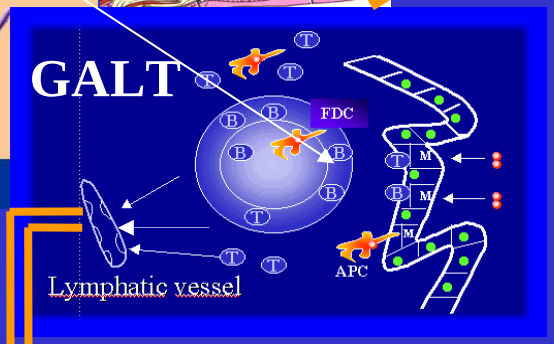


Breast milk

Gut Mucosa



Peripheral blood



* sIGA, sIgM
* Natural defense factors (lactoferrin,..
* Controlled Bacterial translocation
* Maternal Dietary Atg Epitopes
* Immuno regulatory factors (TGF-β,..)

Mesenteric lymph node

Thoracic duct

adapted from P.BRANDTZAEG, 1996

CHC

Recommendations are needed to ameliorate Infant Bacterial Colonisation of the Intestine as well as the Mode of Presentation of the Dietary Antigen to the Intestine Mucosa = PUBLIC HEALTH IMPACT IN ALLERGY PREVENTION

- **Prefer vaginal delivery when possible**
- **Exclusive breast feeding as long as possible**

⇒ optimal immune response after optimal mucosal microbial stimulation

⇒ allows low early diet antigen stimulation on immature mucosa

- **Progressive introduction of complementary foods**

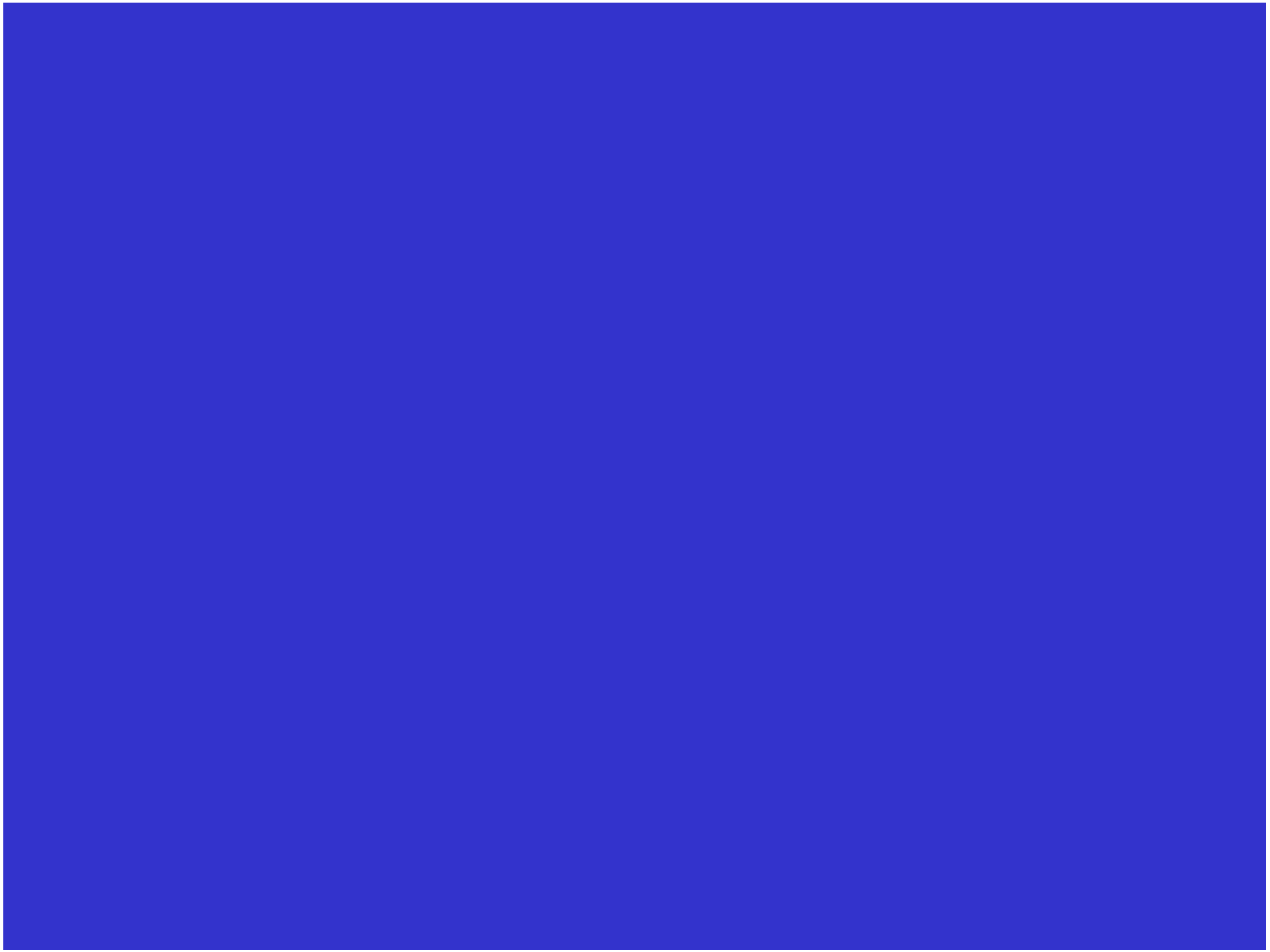
= not before four or six months = according to the 4 points rule

- **Rationale use of antibiotics and anti-COX's:**

⇒ restriction in the early stage when possible

⇒ avoid excessive use of broad spectrum AB (esp. in prophylaxis)

CHC



Factors interfering with microbial exposure in the early stage (*mode of delivery, mode of feeding, AB's,….)*

→ **Suboptimal Tregs Suppression Function in the Early Stage**

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Dietary Factors (low Breast-feeding habits, inadequate diversification,…) in the Early Stage

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Dietary Factors (low Breast-feeding habits, inadequate diversification,…) in the Early Stage

- **Genetics**
- **Air pollution**
- **Allergic load**
- **AB's overuse and modification of microbial pressure on the submucosa area**
- **Pharmacological factors (anti-COX 's overuse) (??)**

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EPIGENETIC MODIFICATIONS (GENE EXPRESSION) in the EARLY STAGE

EPIGENETIC MODIFICATIONS

(GENE EXPRESSION)

INCREASE INCIDENCE OF IMMUNE DEVIANCES LATER ON

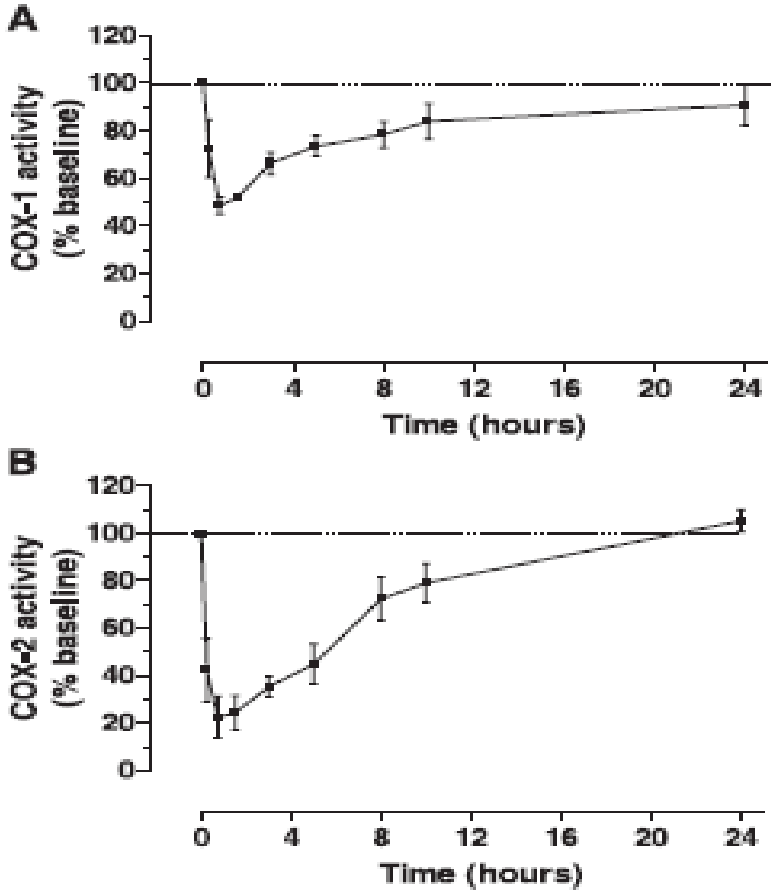
The FASEB Journal • Research Communication

FASEB J. 22, 383–390 (2007)

Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man

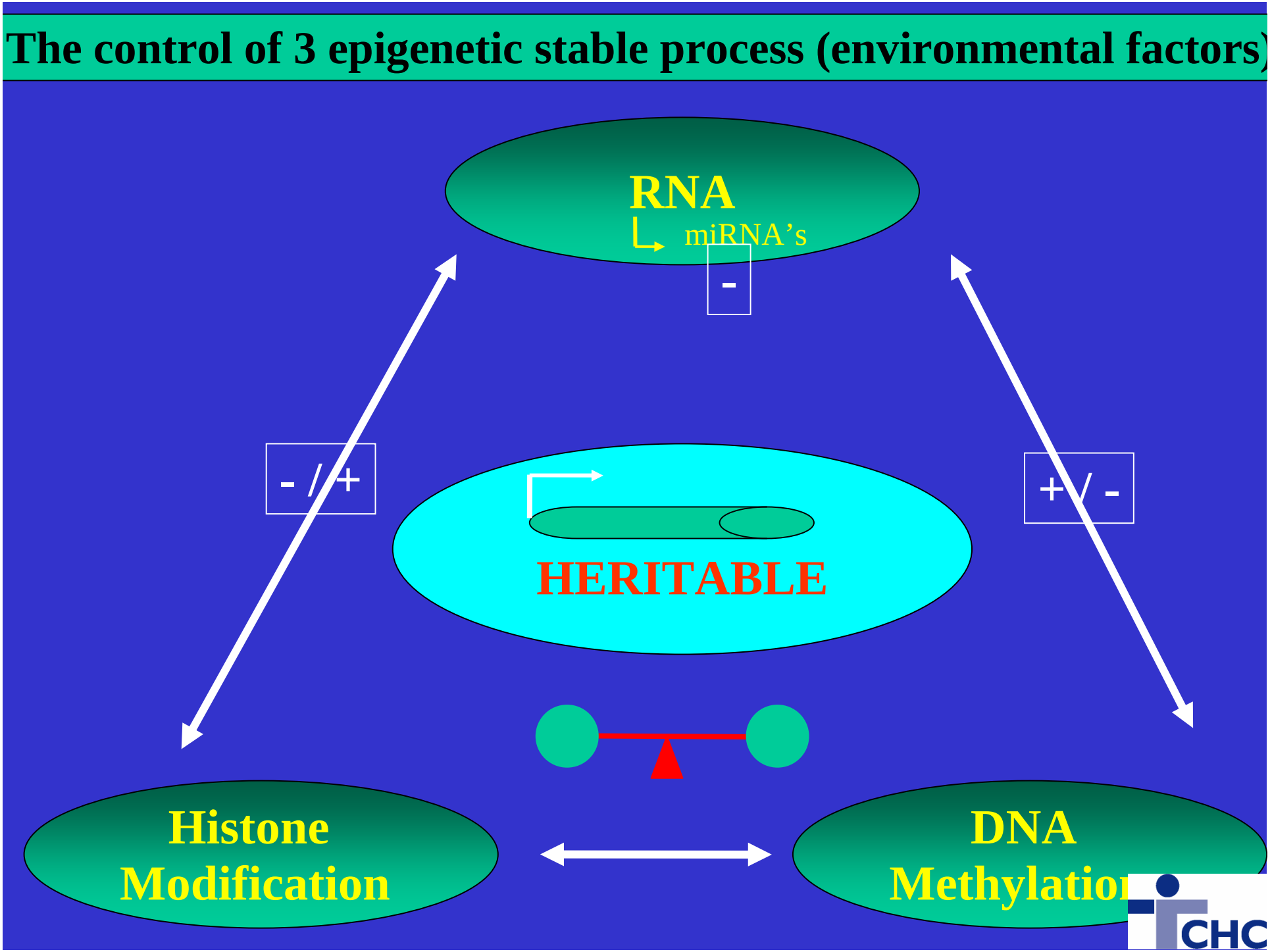
Burkhard Hinz,*,[1] Olga Cheremina,[†] and Kay Brune[†]

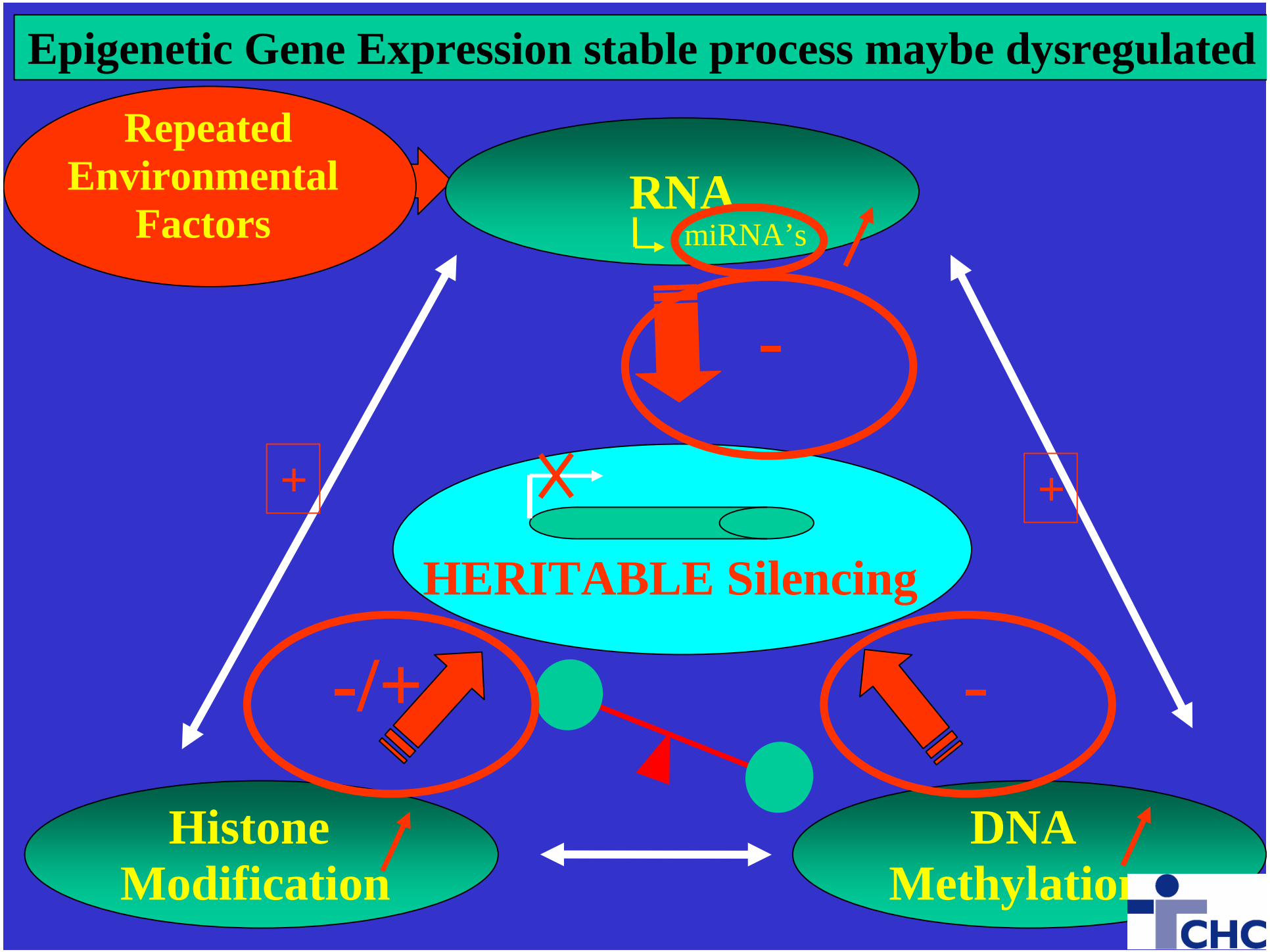
*Institute of Toxicology and Pharmacology, University of Rostock, Rostock, Germany; and [†]Institute of Experimental and Clinical Pharmacology and Toxicology, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany



Epigenetics can be defined as mitotically and meiotically heritable changes in gene expression that do not involve a change in the DNA sequence.

The control of 3 epigenetic stable process (environmental factors)




Epigenetic Gene Expression stable process maybe dysregulated
Repeated Environmental Factors
RNA
miRNA's
-
+
+
HERITABLE Silencing
-/+
-
Histone Modification
DNA Methylation
CHC

Early life environment

↓

“Stress” response signaling

↓

Epigenetic changes

↓

Inter-individual epigenetic

↓

Gene expression programming variation

↓

Phenotypic variation

Health disease and behavioral pathologies

Szyf M. Acta Paediatrica 2009;98:1082.

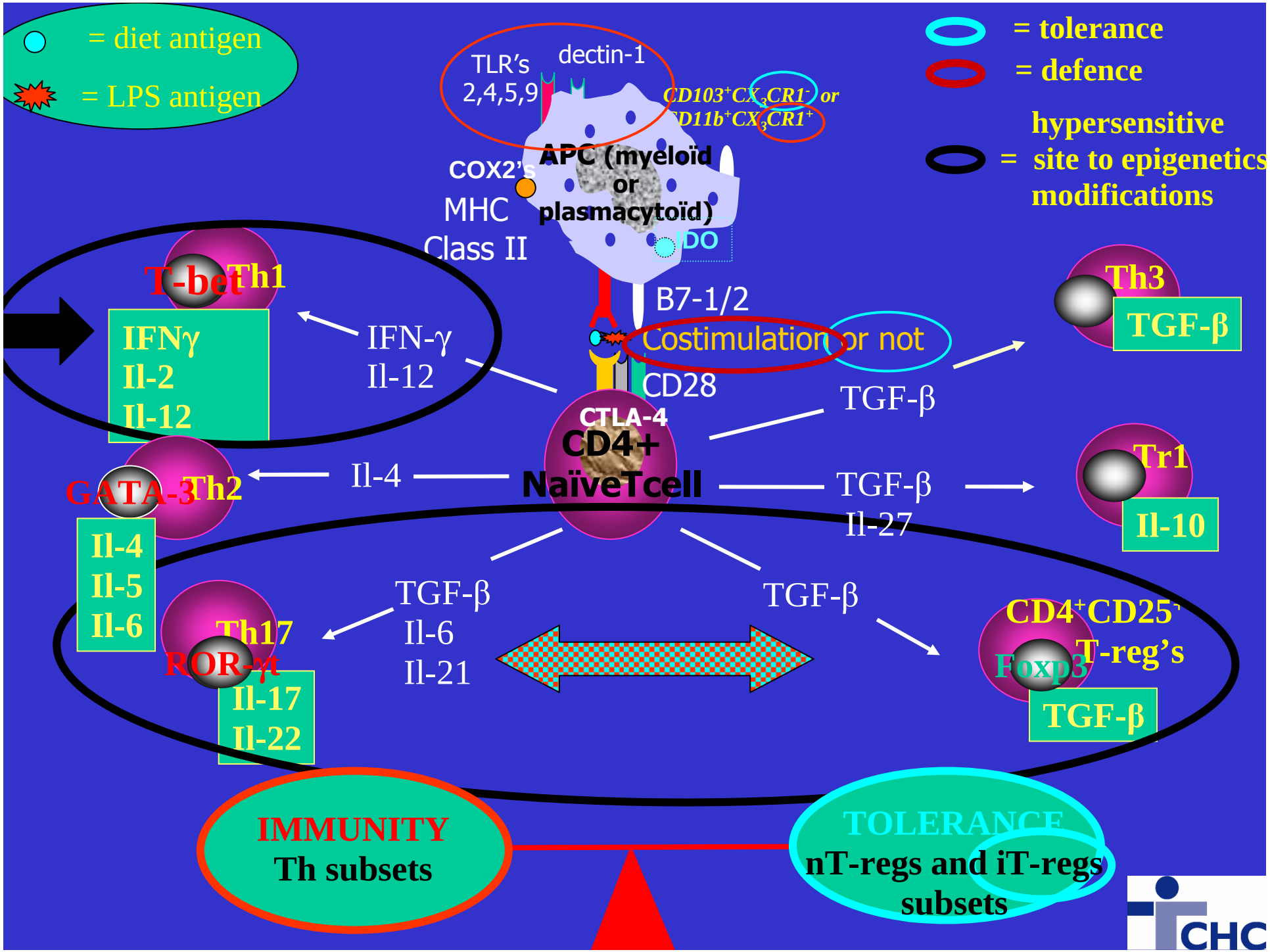
EPIGENETIC MODIFICATIONS

could be issued from

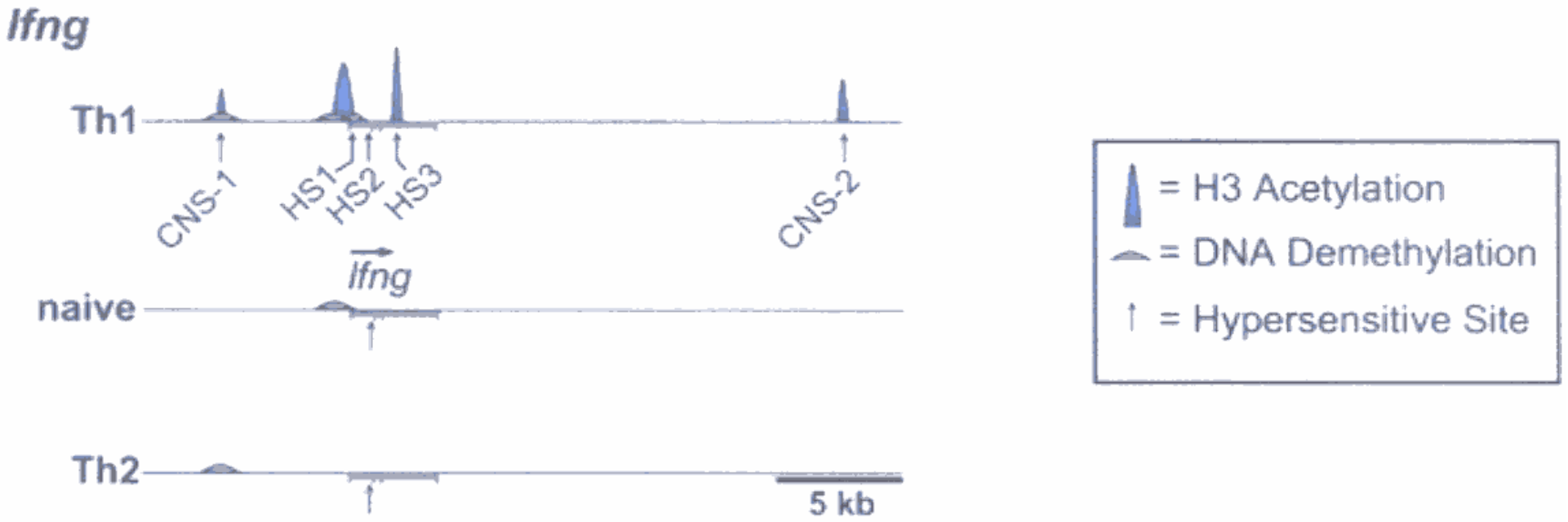
an inadequate bacterial interface and/or diversity at the intestinal sub-mucosal level in the early stage .....

.....leading to

IMMUNE DEVIANCES later on.

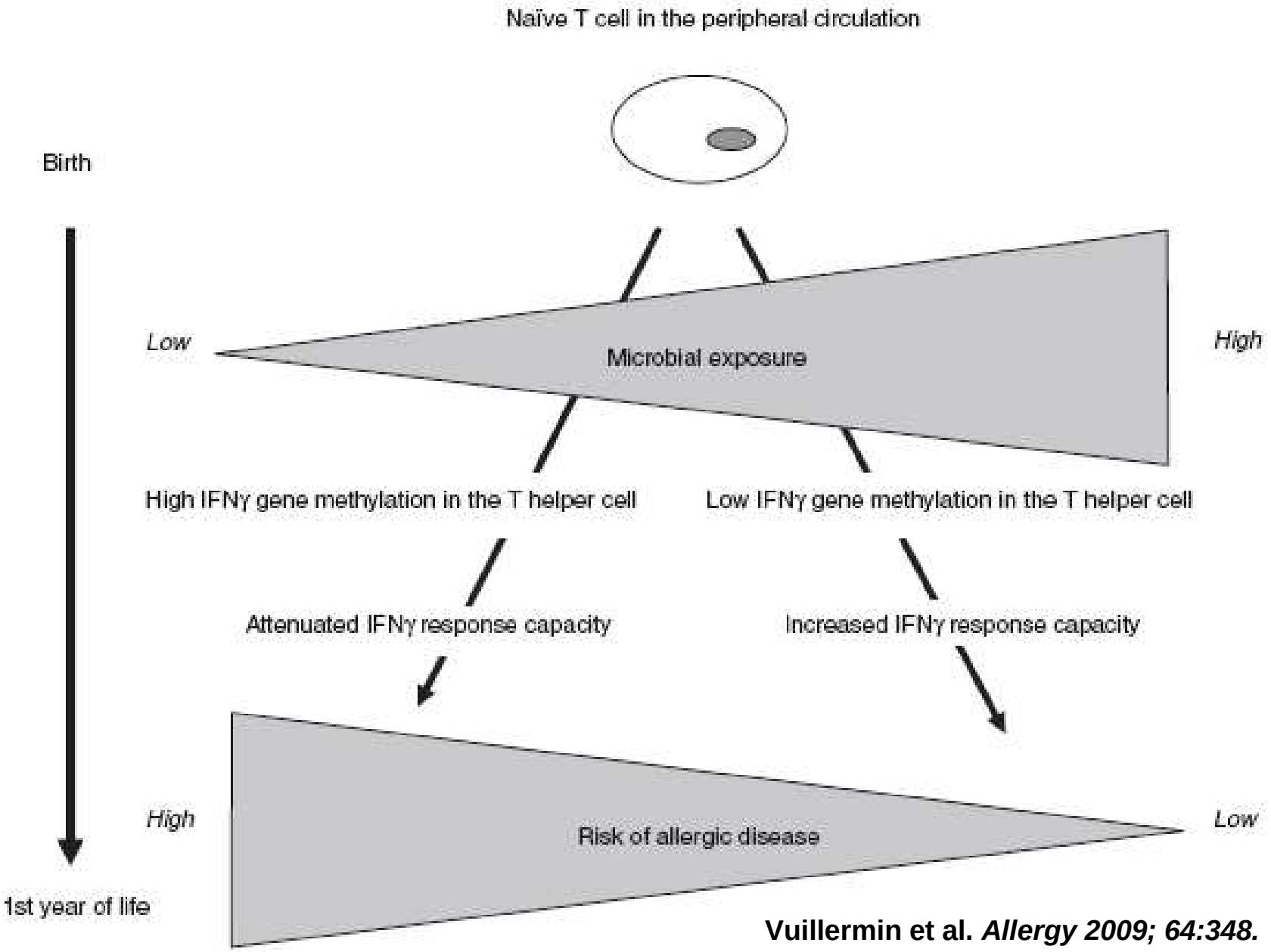

= diet antigen
= LPS antigen
= tolerance
= defence
hypersensitive
= site to epigenetics modifications
TLR's 2,4,5,9
dectin-1
CD103+CX3CR1- or CD11b+CX3CR1+
APC (myeloïd or plasmacytoïd)
COX2's
MHC Class II
IDO
B7-1/2
Costimulation or not
CD28
CTLA-4
CD4+ NaïveTcell
T-bet Th1
IFNγ
Il-2
Il-12
IFN-γ
Il-12
Th3
TGF-β
TGF-β
GATA-3 Th2
Il-4
Il-5
Il-6
Il-4
TGF-β
Il-27
Tr1
Il-10
TGF-β
Il-6
Il-21
TGF-β
Th17
RORγt
Il-17
Il-22
CD4+CD25+
Foxp3
T-reg's
TGF-β
IMMUNITY
Th subsets
TOLERANCE
nT-regs and iT-regs subsets

Hypersensitive sites to Epigenetic modifications in the Interferon *gamma* gene



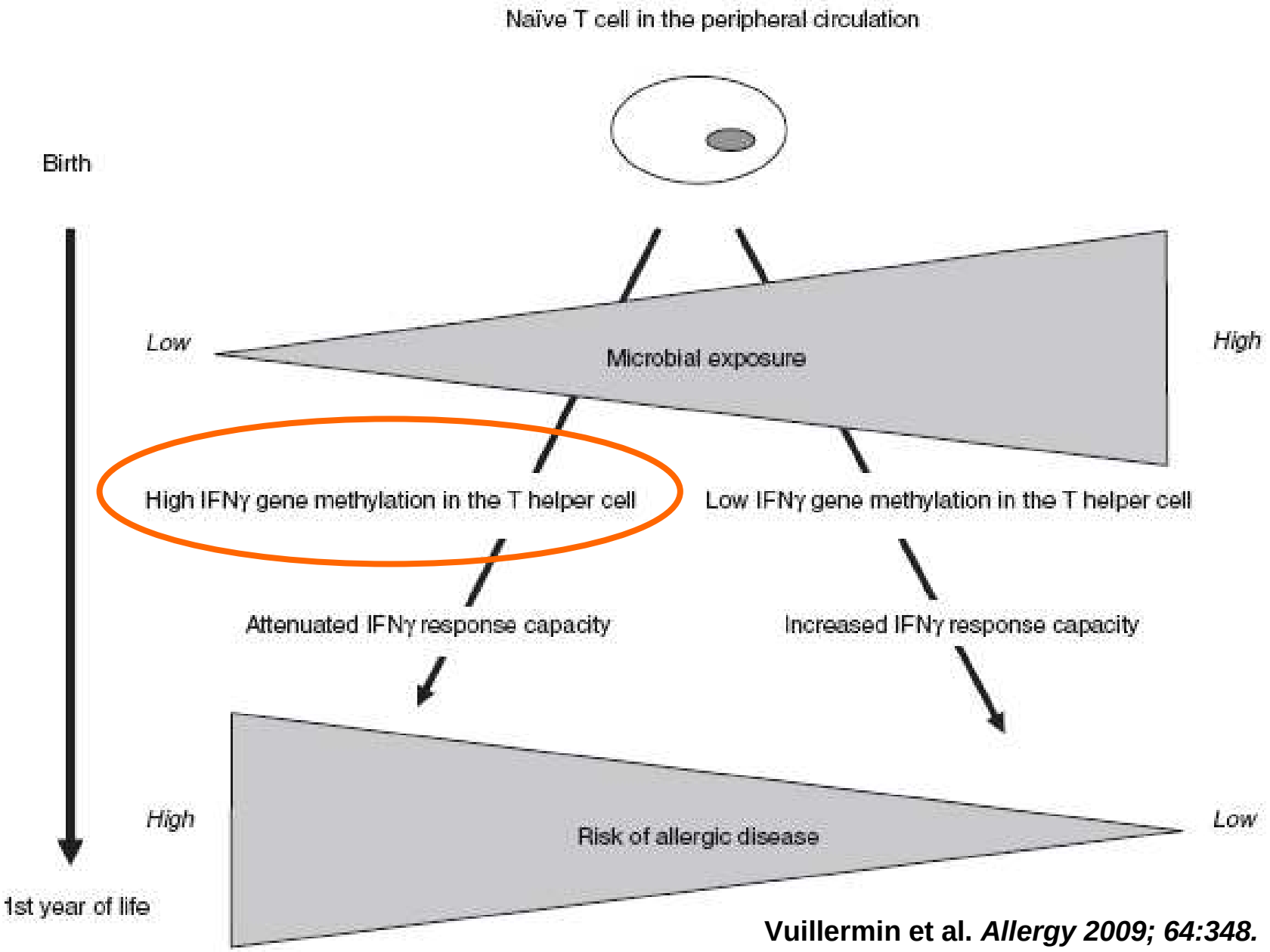
Lee et al *Immunology* 2006;24:369.

Naïve T-cell IFNγ gene demethylation and allergic disease



Vuillermin et al. *Allergy 2009; 64:348.*

Naïve T-cell IFNγ gene demethylation and allergic disease



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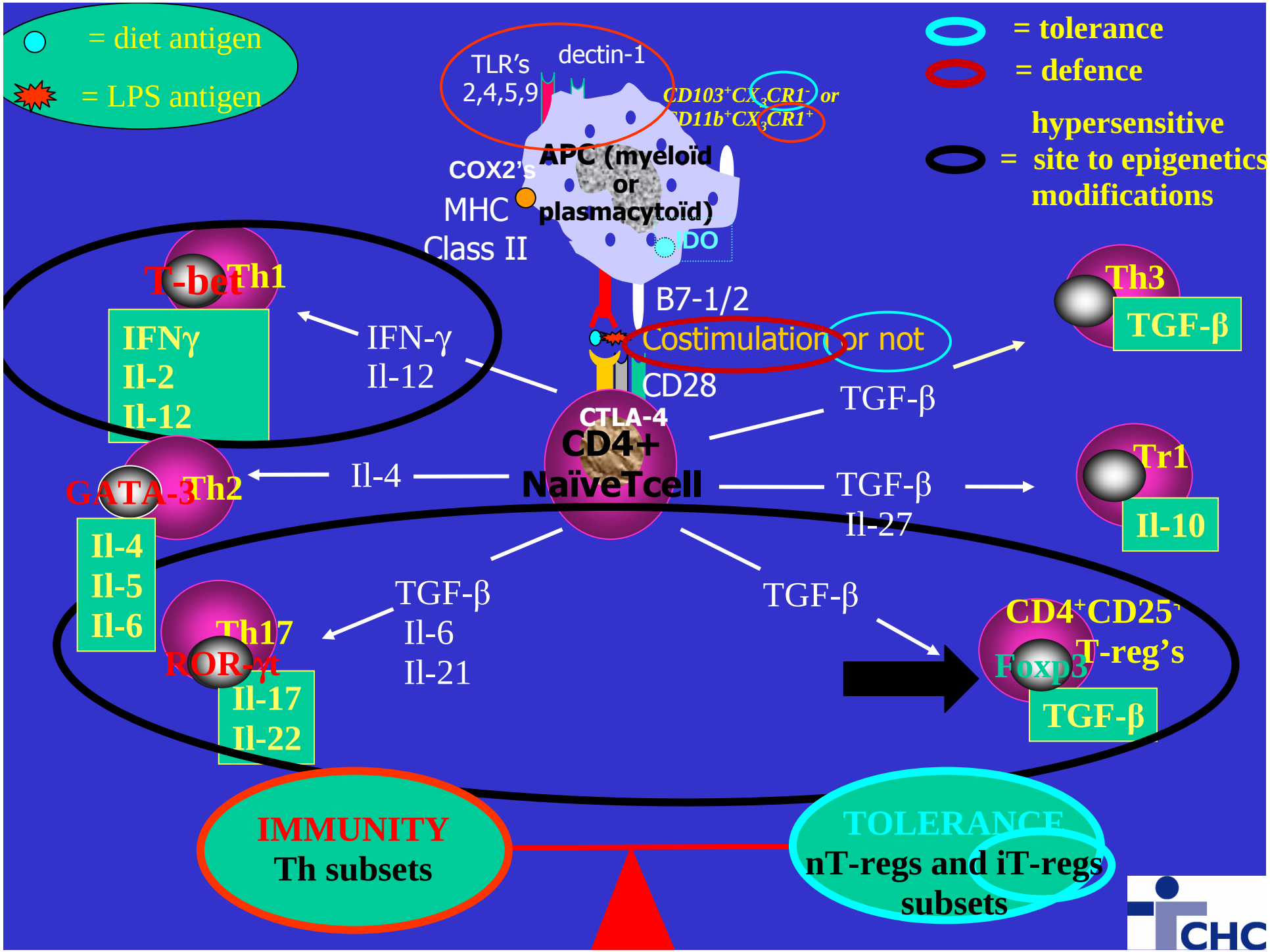
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TLR's 2,4,5,9
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COX2's
MHC Class II
IDO
B7-1/2
Costimulation or not
CD28
CTLA-4
CD4+ NaïveTcell
T-bet Th1
IFNγ
Il-2
Il-12
IFN-γ
Il-12
Th3
TGF-β
TGF-β
GATA-3 Th2
Il-4
Il-5
Il-6
Il-4
TGF-β
Il-27
Tr1
Il-10
Th17
RORγt
Il-17
Il-22
TGF-β
Il-6
Il-21
TGF-β
CD4+CD25+
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Th subsets
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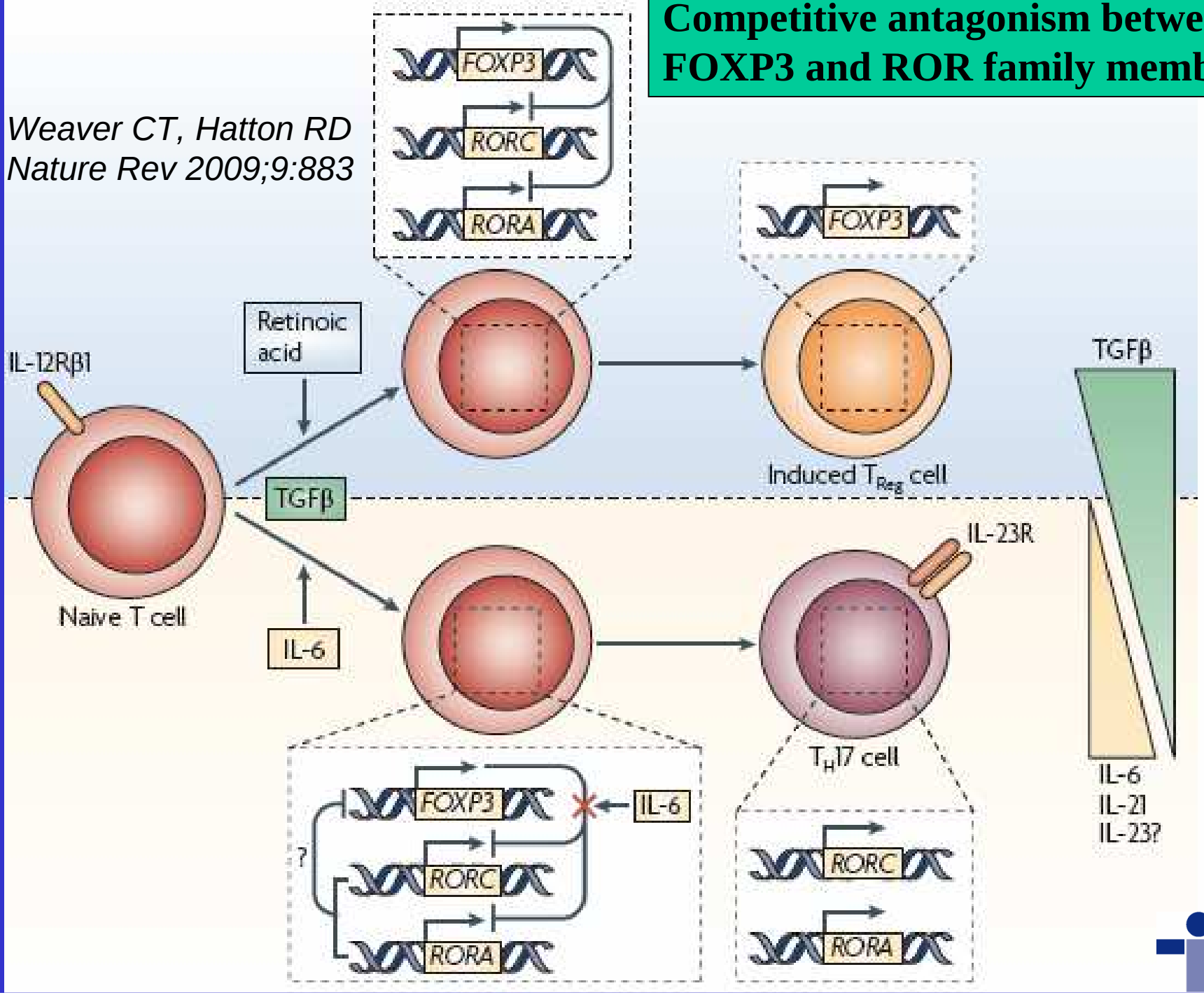
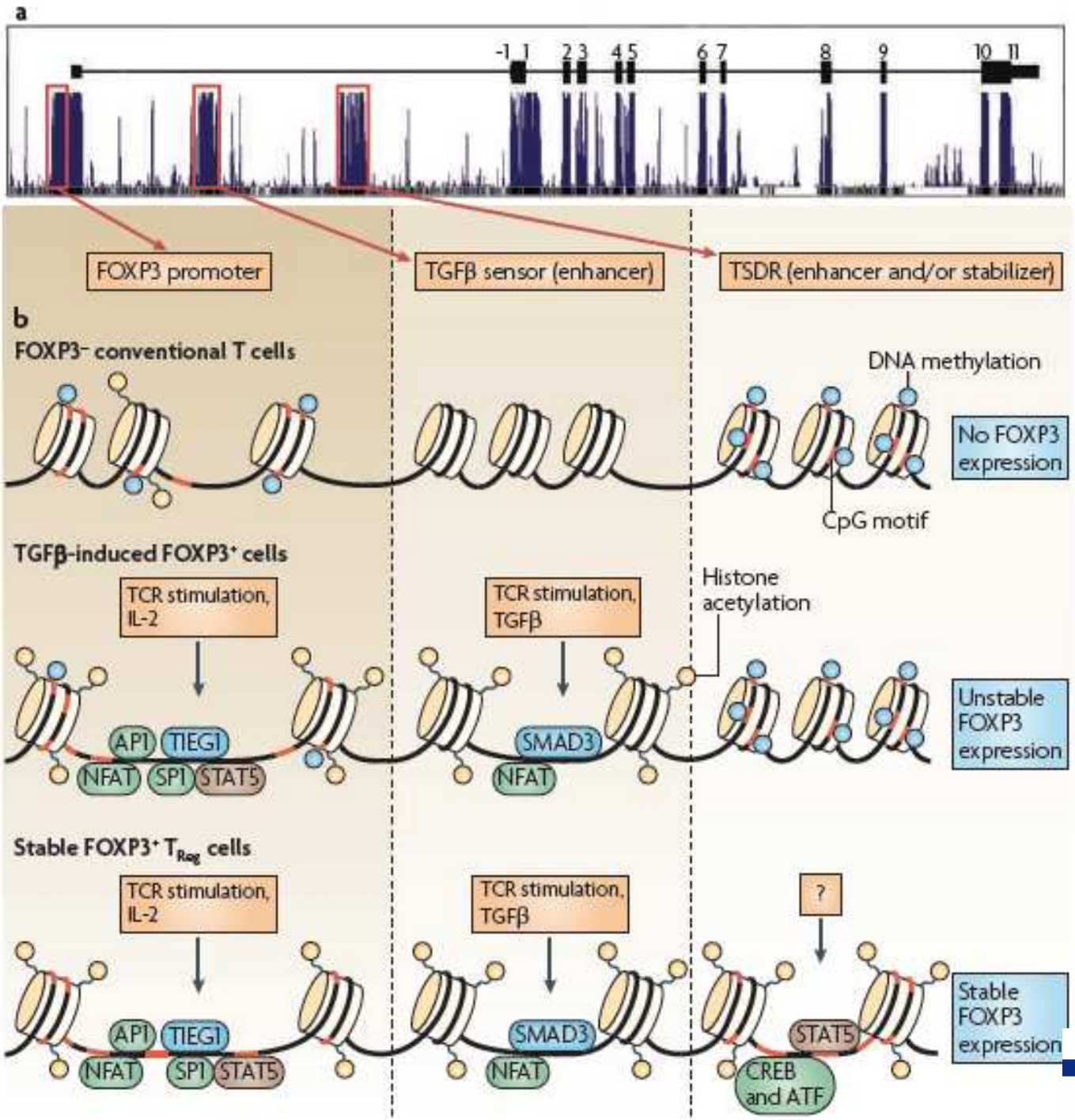
nT-regs and iT-regs subsets
CHC

Competitive antagonism between FOXP3 and ROR family members

Weaver CT, Hatton RD
Nature Rev 2009;9:883



The FOXp3 locus subjected to epigenetic control



Huehn et al
Nat Rev Immunol 2008.

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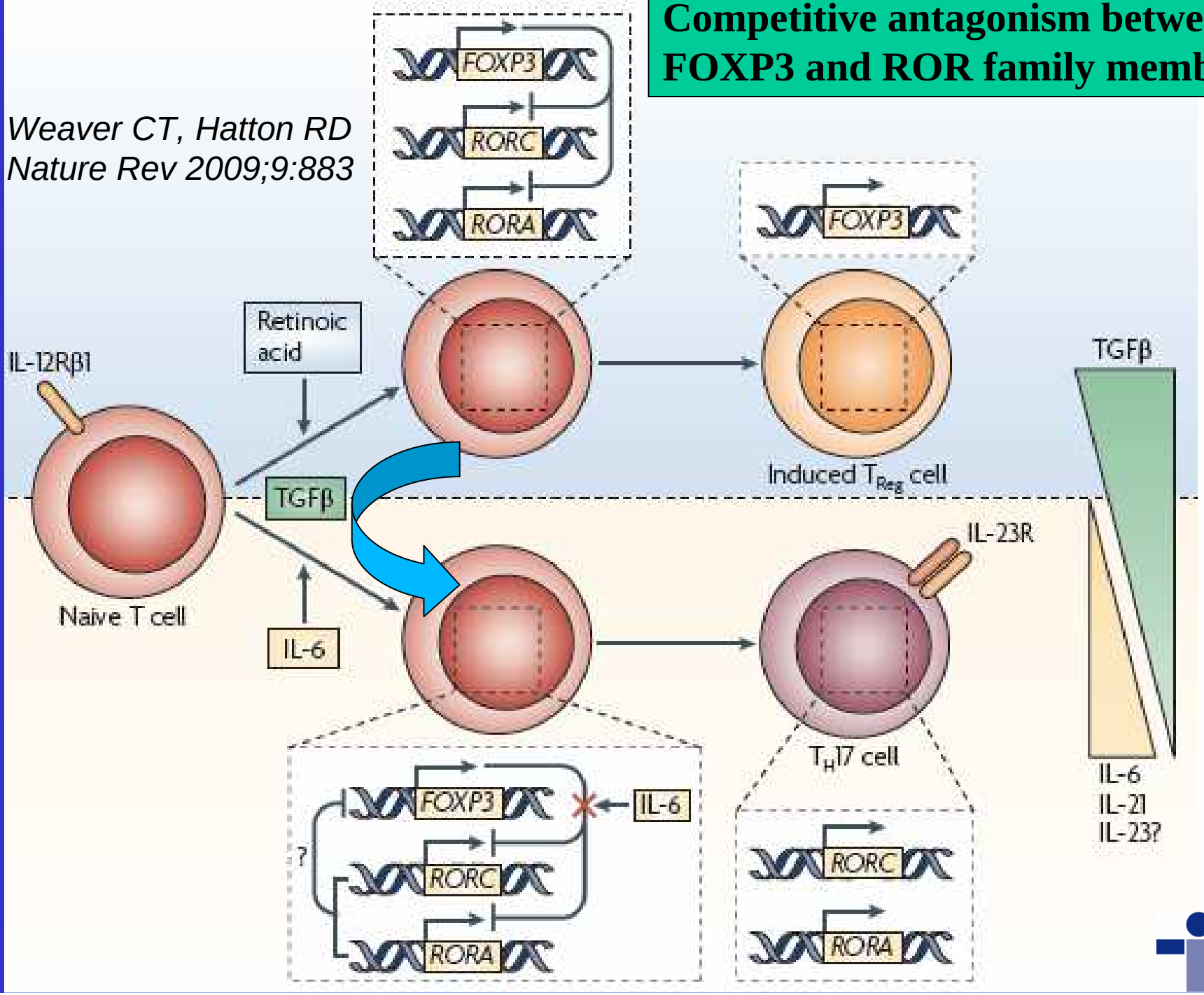
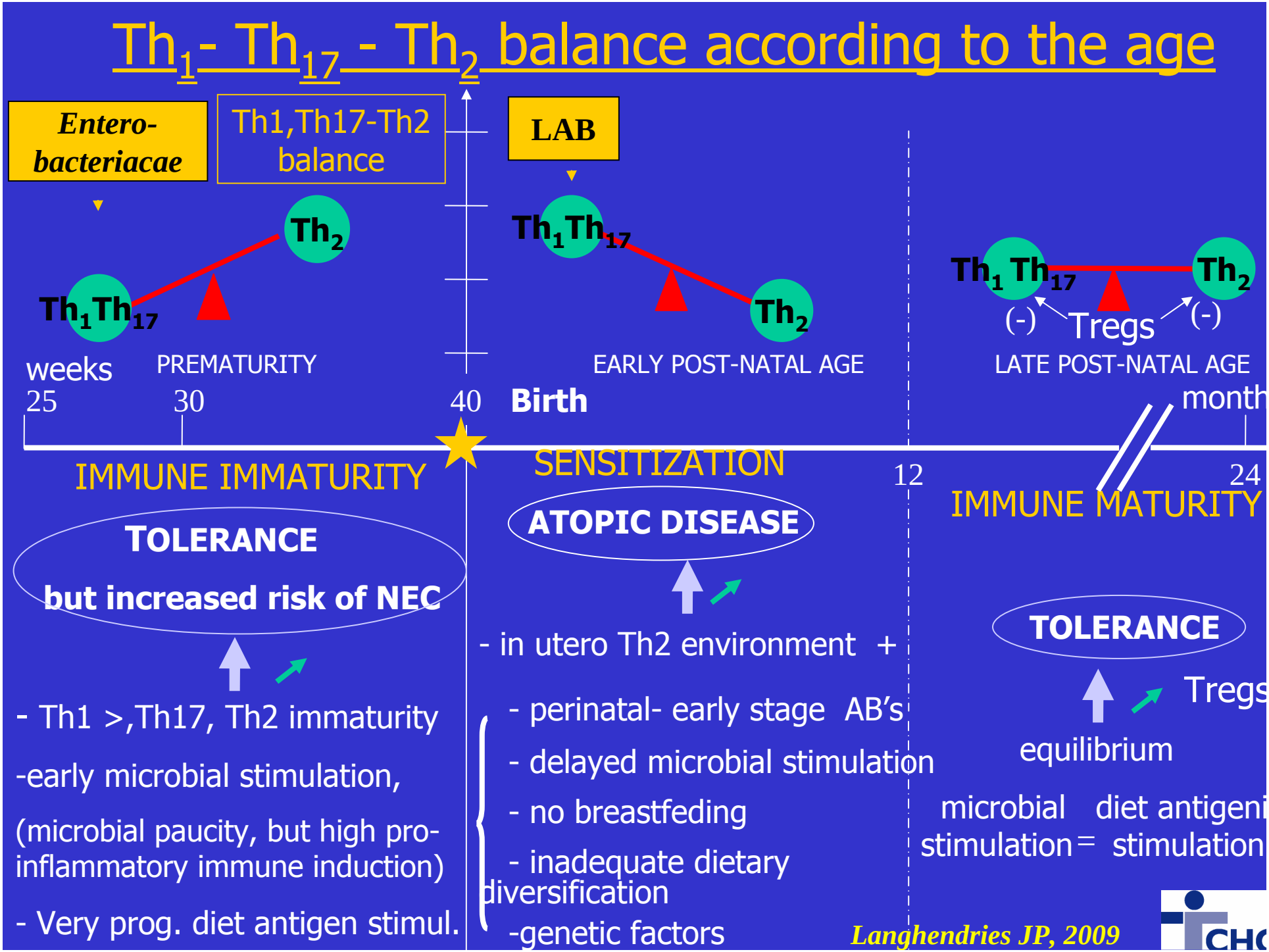


Th_1- Th_{17} - Th_2 balance according to the age



Langhendries JP, 2009

The oral administration of bacterial extracts prevents asthma via the recruitment of regulatory T cells to the airways

S Navarro[1,2], G Cossalter[1,2], C Chiavaroli[3], A Kanda[4,5,6], S Fleury[4,5,6], A Lazzari[1,2], J Cazareth[1,7], T Sparwasser[8], D Dombrowicz[4,5,6], N Glaichenhaus[1,2] and V Julia[1,2]

The prevalence of asthma has steadily increased during the last decade, probably as the result of changes in the environment, including reduced microbial exposure during infancy. Accordingly, experimental studies have shown that deliberate infections with live pathogens prevent the development of allergic airway diseases in mice. Bacterial extracts are currently used in children suffering from repeated upper respiratory tract infections. In the present study, we have investigated whether bacterial extracts, commercially available as Broncho-Vaxom (BV), could prevent allergic airway disease in mice. Oral treatment with BV suppressed airway inflammation through interleukin-10 (IL-10)-dependent and MyD88 (myeloid differentiation primary response gene (88))-dependent mechanisms and induced the conversion of FoxP3 (forkhead box P3)$^-$ T cells into FoxP3$^+$ regulatory T cells. Furthermore, CD4$^+$ T cells purified from the trachea of BV-treated mice conferred protection against airway inflammation when adoptively transferred into sensitized mice. Therefore, treatment with BV could possibly be a safe and efficient strategy to prevent the development of allergic diseases in children.

Navarro et al *Mucosal Immunol* 2011;4:63