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Immune regulation at the fetal maternal interface

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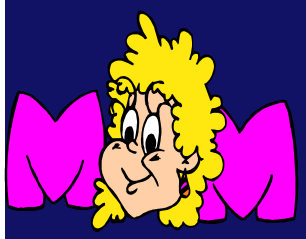
Immunological paradox of pregnancy

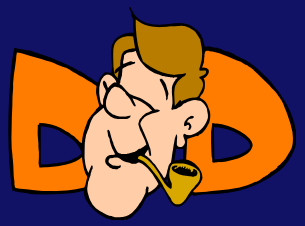


A1 Cw7 B8 DR3

A2 Cw4 B12 DR4

A3 Cw6 B7 DR2

A9 CW3 B60 DR5

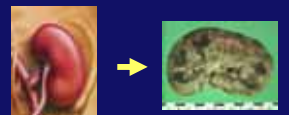


A1 Cw7 B8 DR3

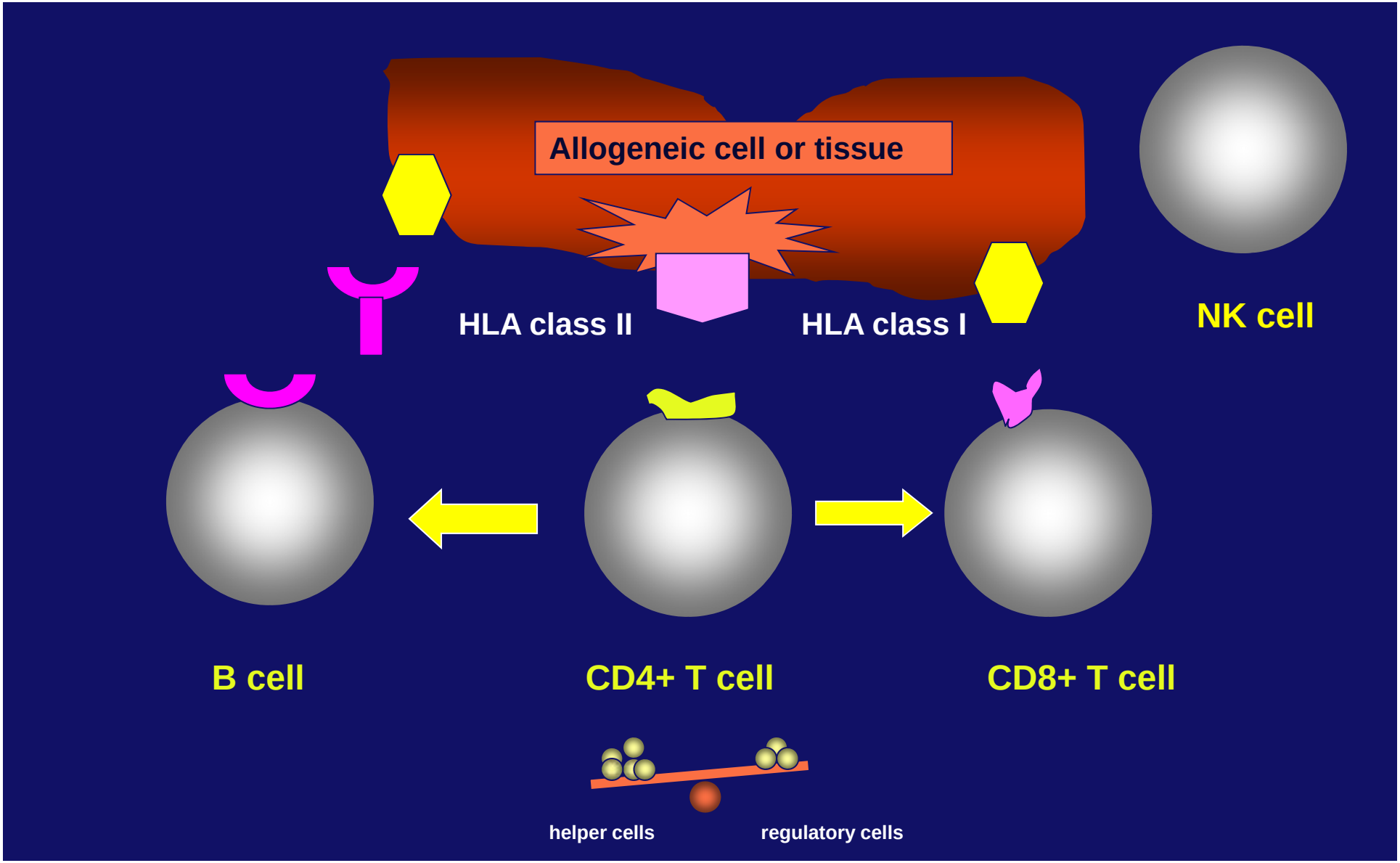
A3 Cw6 B7 DR2

Foetus is semi-allogeneic for the mother: matched for maternal- and mismatched for paternal HLA antigens.

Foetus is tolerated by the immune system of the mother but , in the absence of immunosuppressive drugs, a kidney graft from child to mother will be rejected.



Kidney graft rejection mainly due to immune response to foreign HLA



Explanation immunological paradox of pregnancy

Peter Medawar 1953:

The fetus is an allograft which is not rejected because of:

- Anatomical separation
- Immaturity of fetal antigens
- Maternal immune suppression/tolerance

Immunological paradox of pregnancy

The fetus is indeed an allograft which is not rejected but for other reasons

As maternal immune system recognizes fetal antigens:

- Maternal antibodies to fetal HLA *(van Kampen 2002)*
- Fetus specific CTLs to fetal HLA and minor Ags *(van Kampen 2001; Verdijk 2004)*
- Normal MLC response of mother to fetal umbilical cord blood cells

→ Importance of local immune regulation?

Trophoblast, the fetal tissue in direct contact with the maternal immune system, has an aberrant HLA expression.

- No expression of the classical HLA-class I (HLA-A and –B) and HLA class II antigens: **prevents immune response by alloreactive T cells.**

- Expression of non-classical HLA class I (HLA-G,HLA-E) and HLA-C*: **prevents response by NK cells**

However, HLA-C is able to induce T cell responses:

.

Why does T cell mediated rejection not occur during pregnancy?

Close collaboration with Sicco Scherjon, dept of Obstetrics

Maternal T cells were characterized at 3 fetal-maternal interfaces:

Decidua Basalis

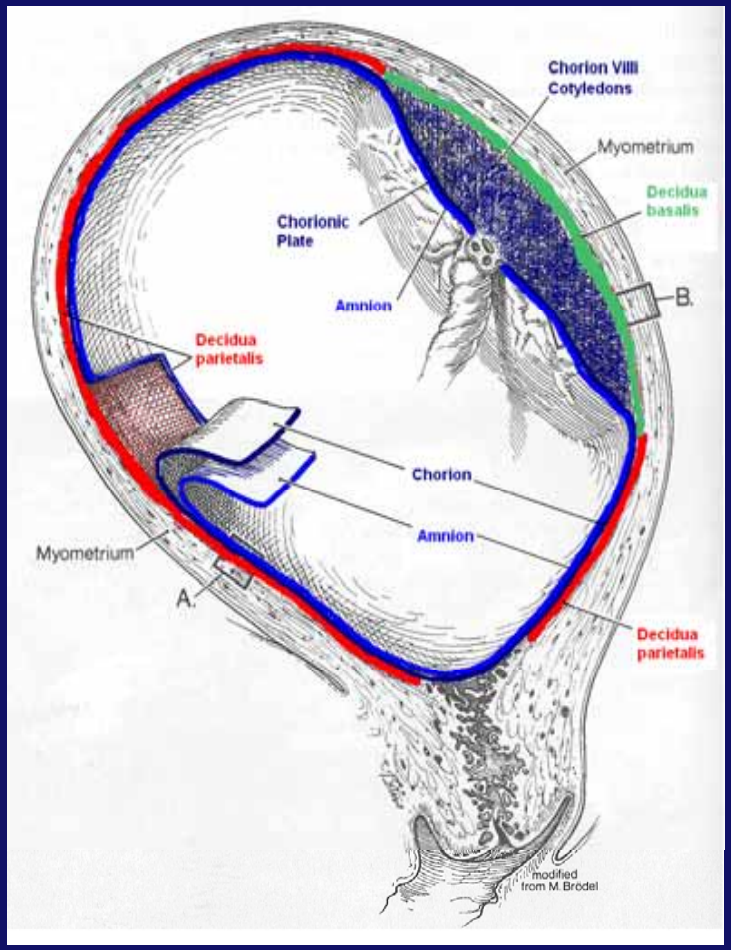
- side of implantation
- contacts the invading interstitial trophoblasts

Decidua Parietalis

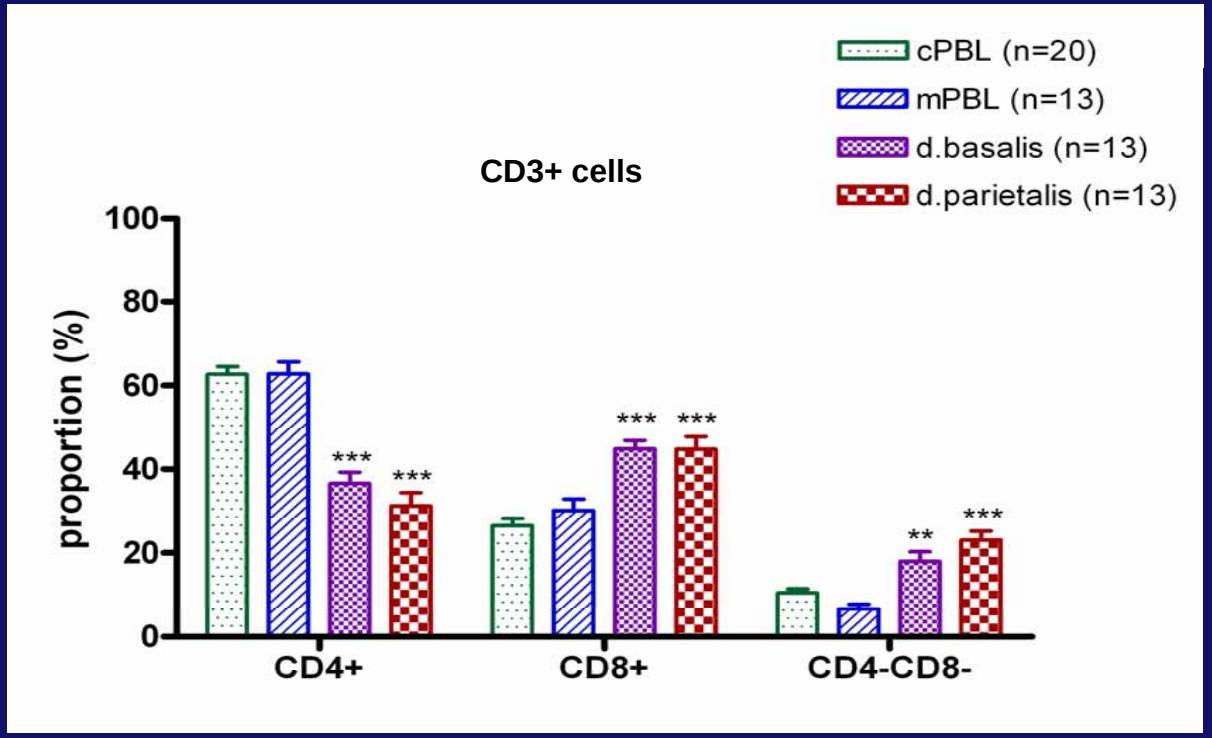
- lining the remainder of the uterine cavity
- connected to the non-invasive trophoblasts of chorion

Maternal Peripheral Blood

- contacts syncytiotrophoblast layer during utero-placental circulation
- contains circulating syncytiotrophoblast micro particles and chimeric cells.



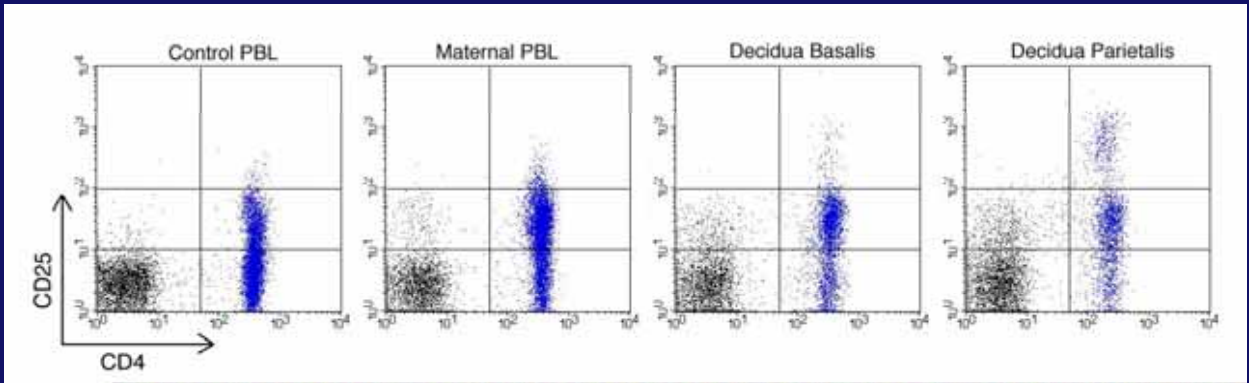
Differential distribution of T subpopulations in human pregnancy

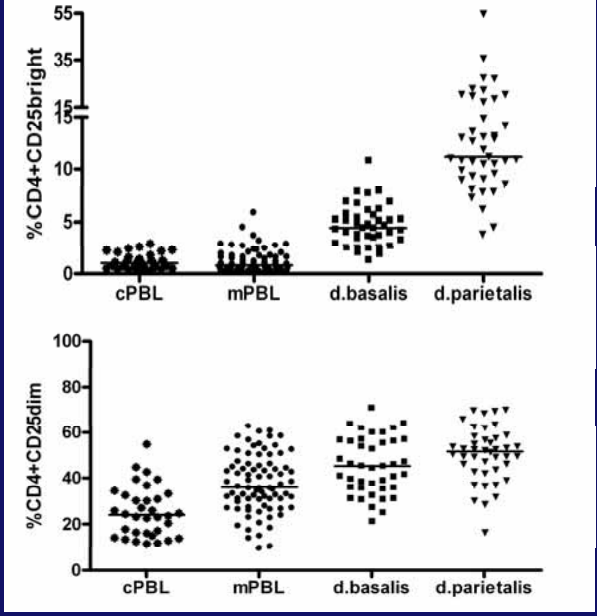


Reverse CD4/CD8 ratio in decidua compared to peripheral blood.

Sindram-Trujillo et al. 2004

Increased CD 25 expression on decidual CD4+ T cells





High % of CD4+CD25^{bright} cells in d.parietalis

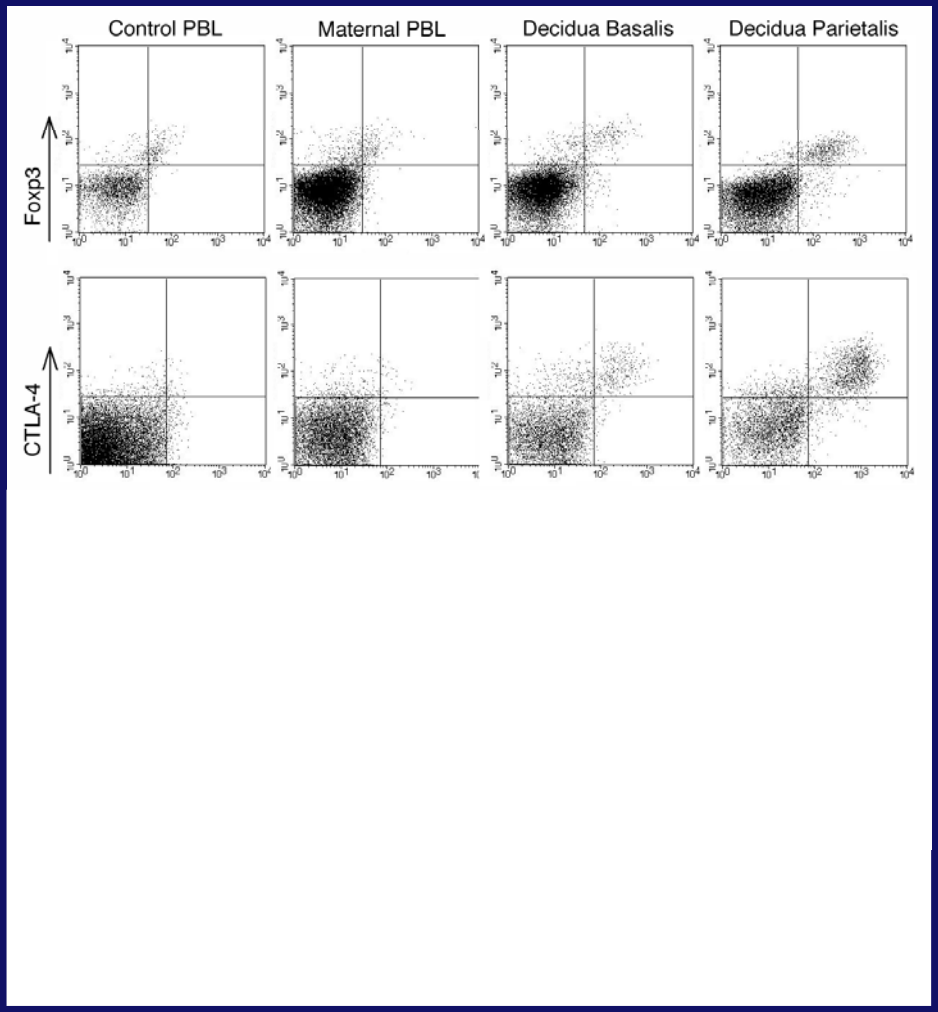
Regulatory T cells?

High % of CD4+CD25^{dim} cells in decidua

Activated helper T cells?

Tilburgs et al. Placenta 2006

Phenotypic analysis of CD4+CD25+ T cells suggests presence of both activated and regulatory CD4+ T cells.



CD4+CD25^{bright} cells

- FOXp3+, CTLA-4+, HLA-DR+, CD69-
- Regulatory phenotype

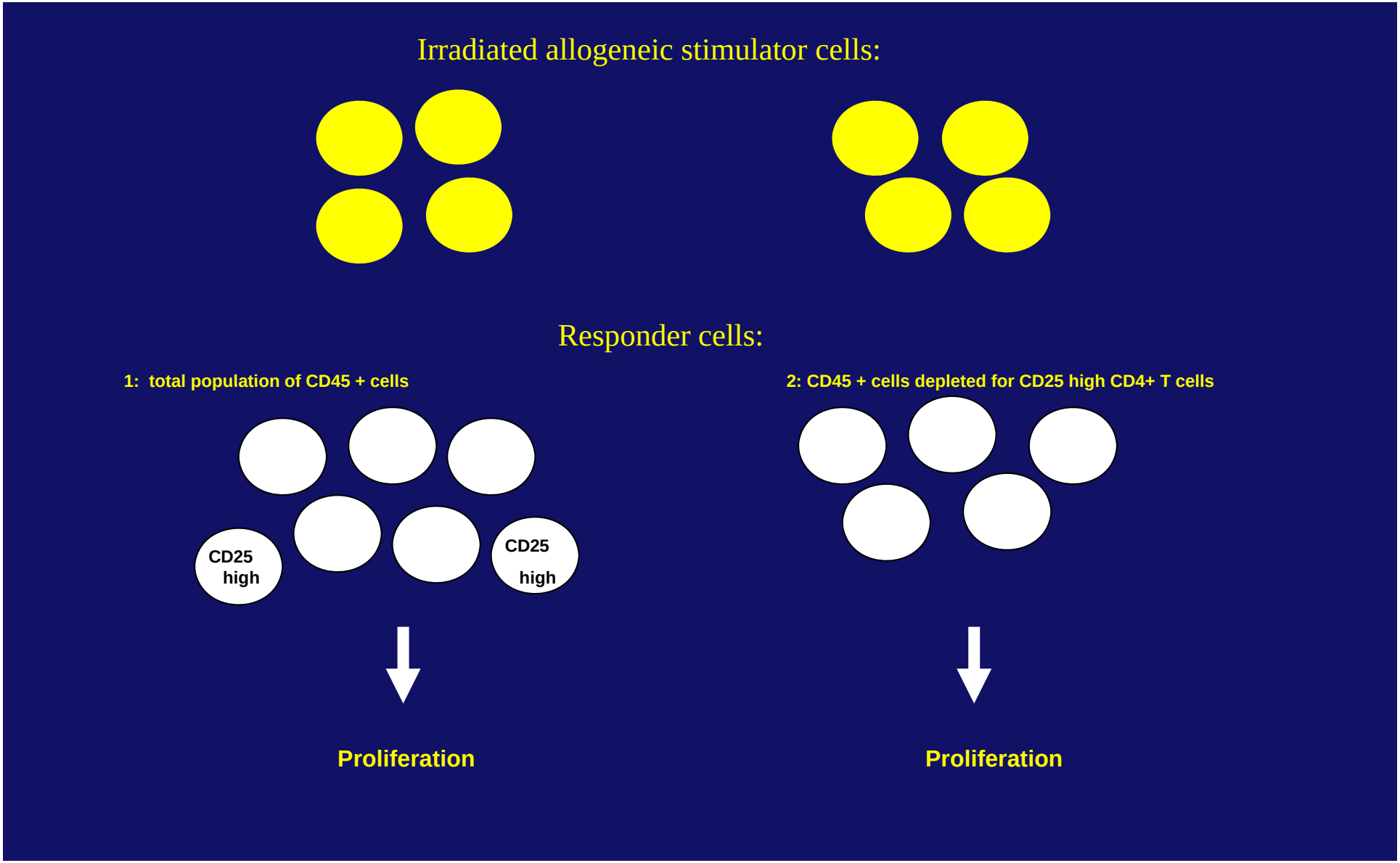
CD4+CD25^{dim} cells

- FOXp3-, CTLA-4-, HLA-DR+, CD69+
- Activated phenotype

→ Functional analysis !

Tilburgs et al. J.Immunol. 2008

MLR in the presence and absence of CD25 bright (regulatory) CD4 +T cells

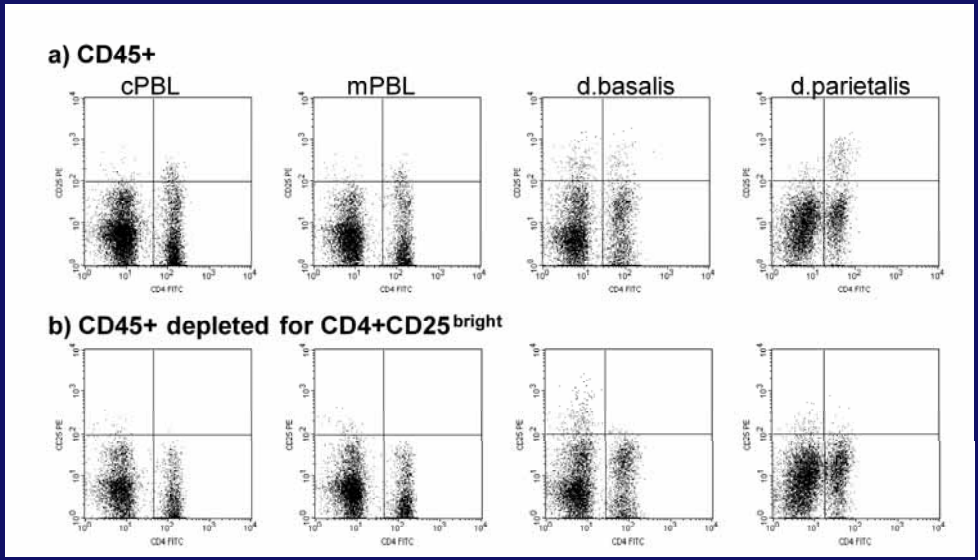


Function of CD4+CD25+ T cells in human pregnancy

→ **Functional analysis of the alloimmune response.**

1. Responder cells: FACSsort for CD45+ lymphocytes

   Comparison CD45+ fraction and the $CD25^{bright}$ depleted fraction

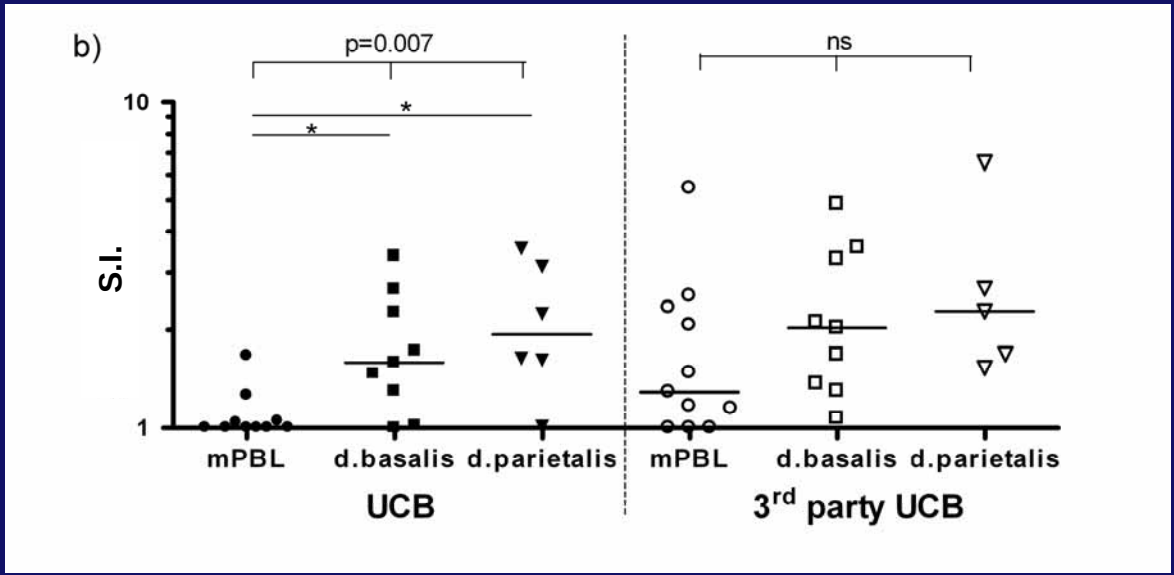


2. Stimulator cells:

   - Umbilical cord blood cells of the own child (specific)
   - 3rd party umbilical cord blood (non-specific)

Tilburgs et al J.Immunol. 2008

CD4+CD25^{bright} regulatory T cells in human pregnancy



Suppression Index (S.I.) = Ratio: $\frac{\text{CD25}^{bright}\text{ depleted fraction}}{\text{CD45+ fraction}}$

In maternal PBL: → no suppression to UCB of her own child

→ suppression to a 3rd party UCB

In decidua: → suppression to UCB and 3rd party UCB

Tilburgs et al J.Immunol. 2008

Summary CD4+ T cells

High percentage of CD4+CD25^{bright} regulatory T cells in decidua.

(FOXP3+, CTLA-4+, HLA-DR+, CD69+)

Depletion of CD4+CD25^{bright} T cells shows that they are functional:

1. Suppression of immune response to UCB of own child and to 3rd party UCB by decidual T cells

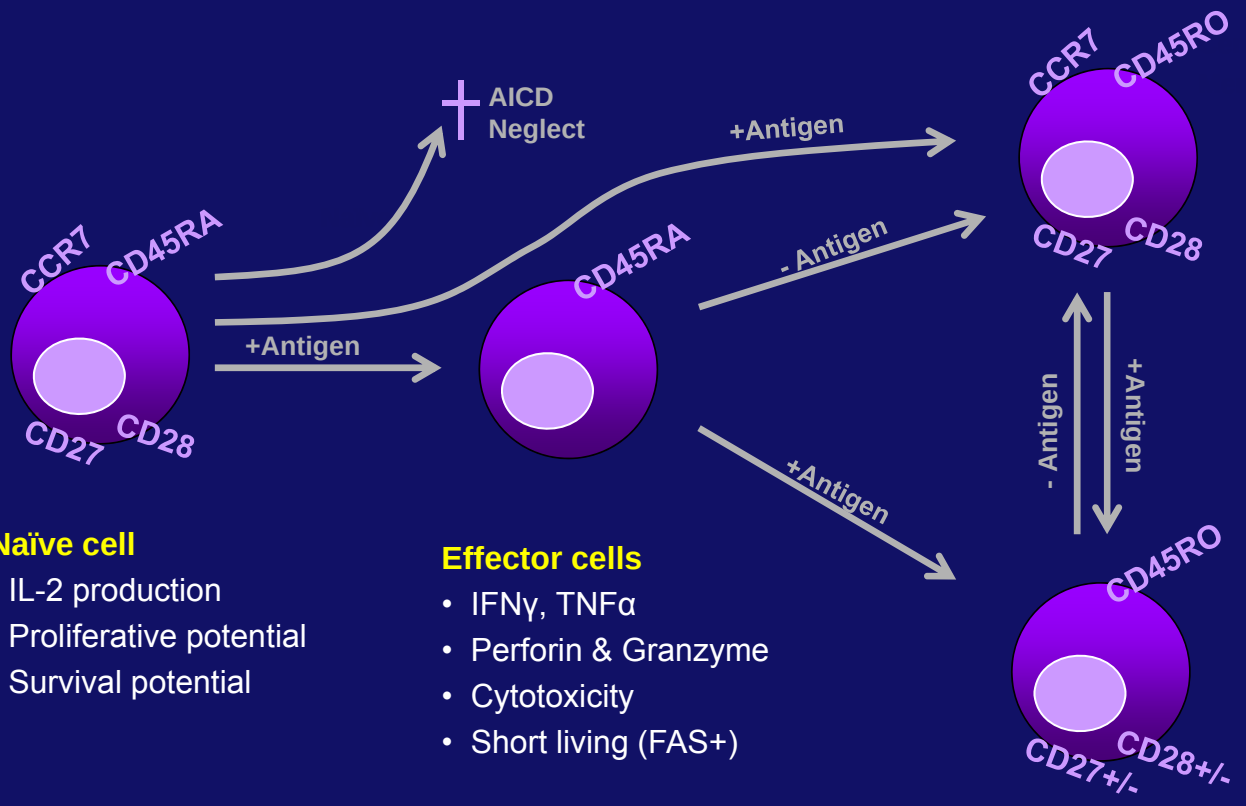
2. Suppression of immune response to 3rd party UCB but not to UCB of the own child by T cells derived from maternal peripheral blood.

   → absence of fetus specific Treg in maternal PBL

Fetus specific Treg cells seem to migrate from peripheral blood to decidua and may control the local immune response to the fetus in the placenta.

CD8+ T cell differentiation

Different CD8+ T cell populations are identified:



Naïve cell
- IL-2 production
- Proliferative potential
- Survival potential

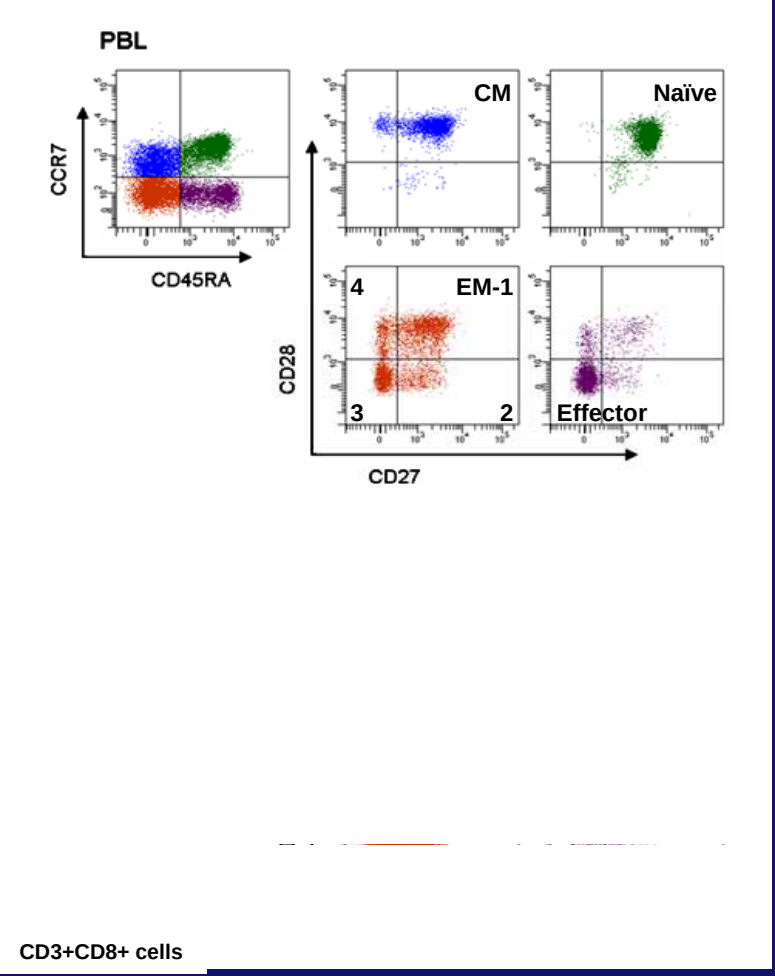
Effector cells
- IFNγ, TNFα
- Perforin & Granzyme
- Cytotoxicity
- Short living (FAS+)

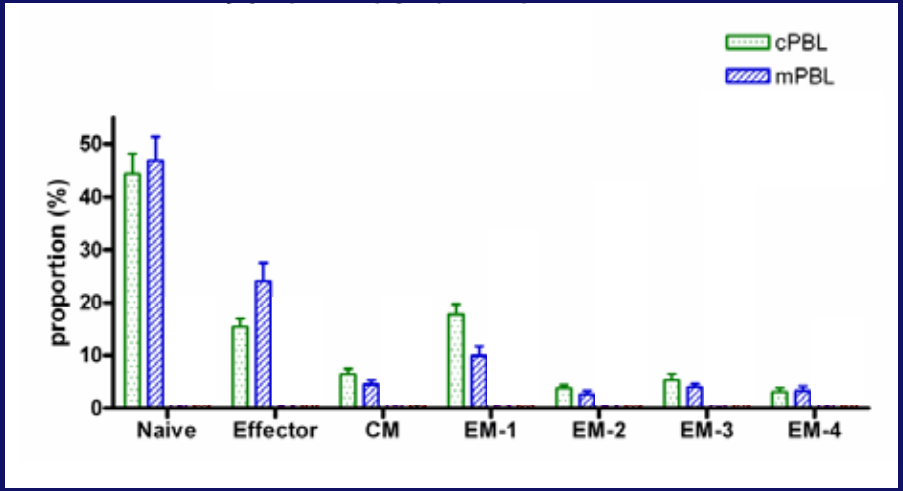
Central-Memory cells
- Proliferation to recall Ag
- IL-2, IL-4
- IFNγ, TNFα
- Survival potential

Effector-Memory cells (4 types)
- EM-1 (27+28+) → CM like
- EM-2 (27+28-) → partial effector
- EM-3 (27-28-) → effector like cells
- EM-4 (27-28+) → CM like

Romero et.al. J.Immunol 2007

Phenotypic analysis of CD8+ T cells in human pregnancy





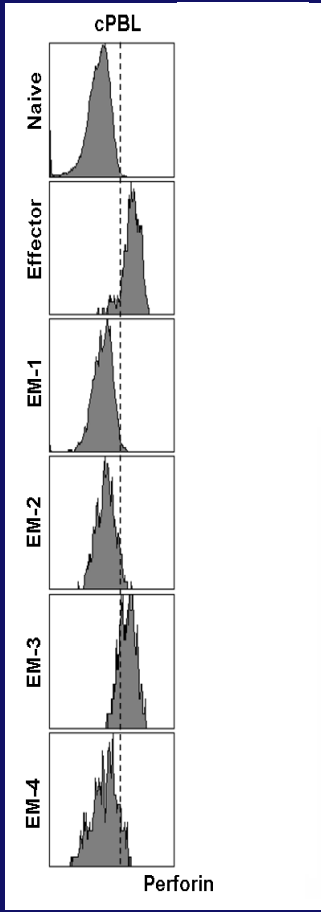
PBL contain mainly naïve, effector and EM-1 cells

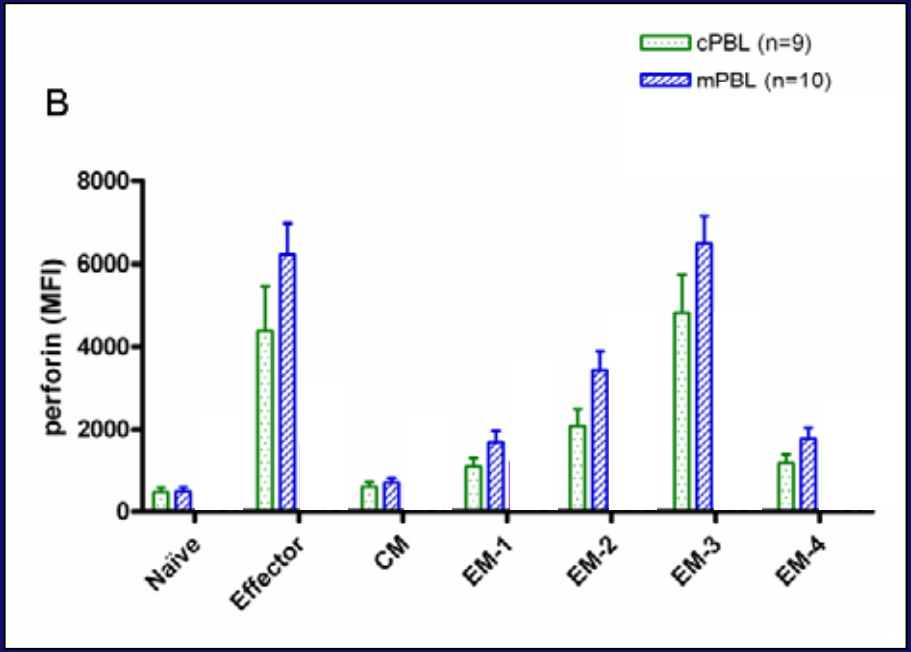
- No difference control PBL and maternal PBL

Decidua contain
a significant reduced percentage naïve cells
a significant increased percentage of EM-2, EM-3 and (EM-4) cells

Lack of perforin expression in decidual CD8+ T cells

Perforin expression:





- In PBL Effector, EM-2, and EM-3 cells express perforin.
- In decidua no expression of perforin in effector, EM-2 and EM-3 cells (also lower expression of granzyme B).

Tilburgs et al. J.Immunol. 2010

Summary CD8+ T cells.

- Decidual CD8+ T cells are differentiated cells
- Decidual effector- and EM-cells do not acquire full effector functions (perforin negative, and reduced granzyme expression)

→Next step functional assays to determine the specificity of these CD8+ T cells: do they recognize HLA-C?

Individual variation of T cell subsets distribution in decidua.

CD4+CD25^{bright} non-specific regulator cells

CD4+CD25^{dim} activated T cells

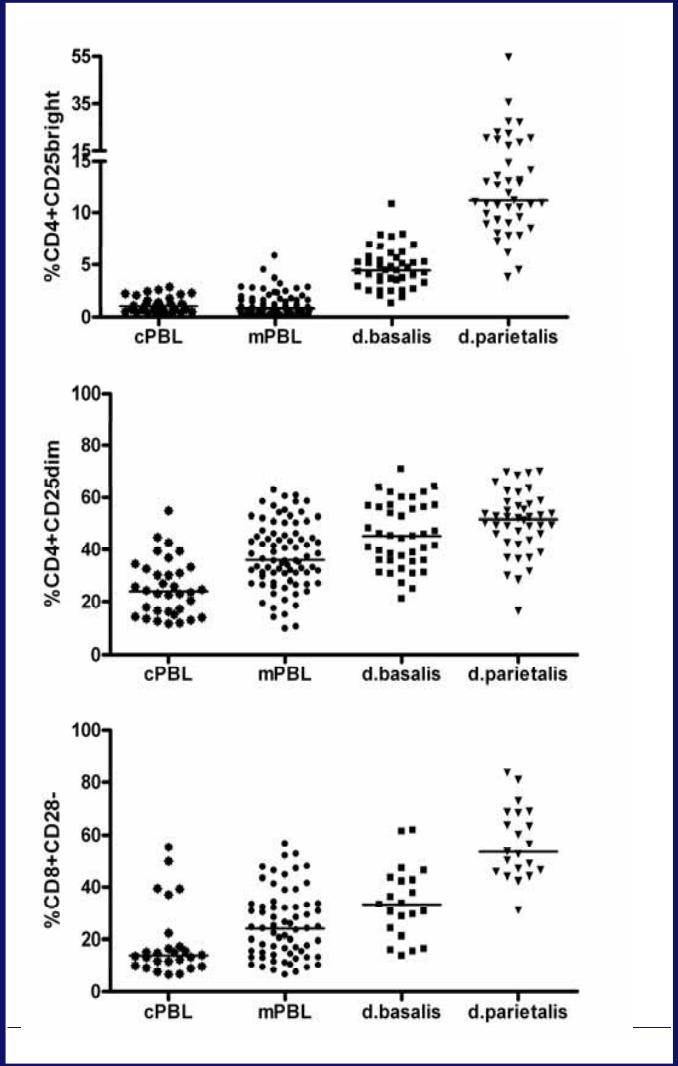
CD8+ perforin- Effector-Memory cells

→ High variation between individuals

- All normal pregnancies
- >37 weeks
- Healthy mother and child

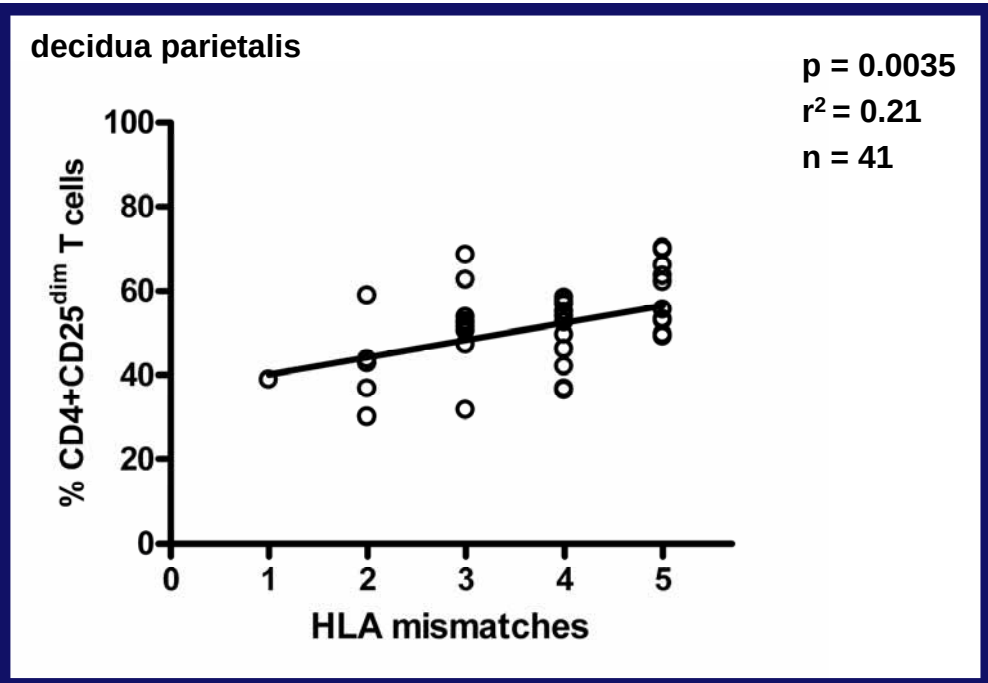
Question:

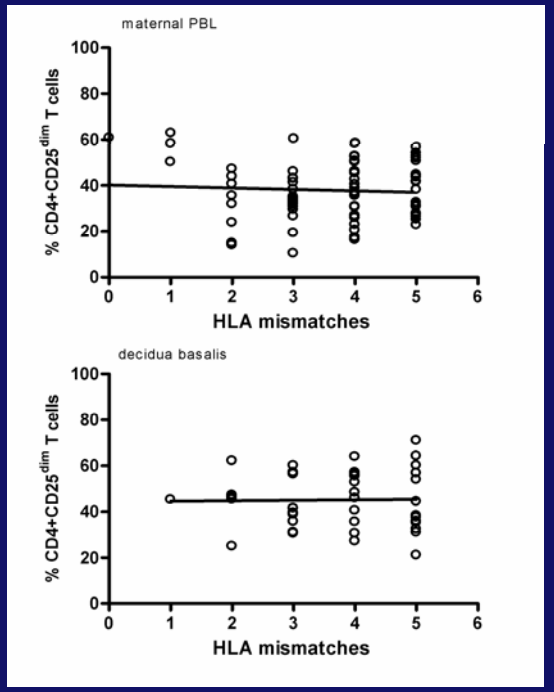
→ Do the number or the kind of HLA mismatches between mother and child play a role in this variation?



Tilburgs et al. J. Reprod. Immunol. 2009

A higher number of fetal-maternal HLA mismatches is associated with a higher % of CD4+CD25^{dim} (activated) T cells in decidua parietalis





Fetal maternal HLA mismatches:

5 loci: HLA-A, -B, -C, -DR, -DQ

No correlation in mPBL and d.basalis

No correlation with CD4+CD25^{bright} and CD8+CD28-T cells

Tilburgs et al. J. Reprod. Immunol. 2009

An HLA-C mismatch is crucial for decidual T cell activation

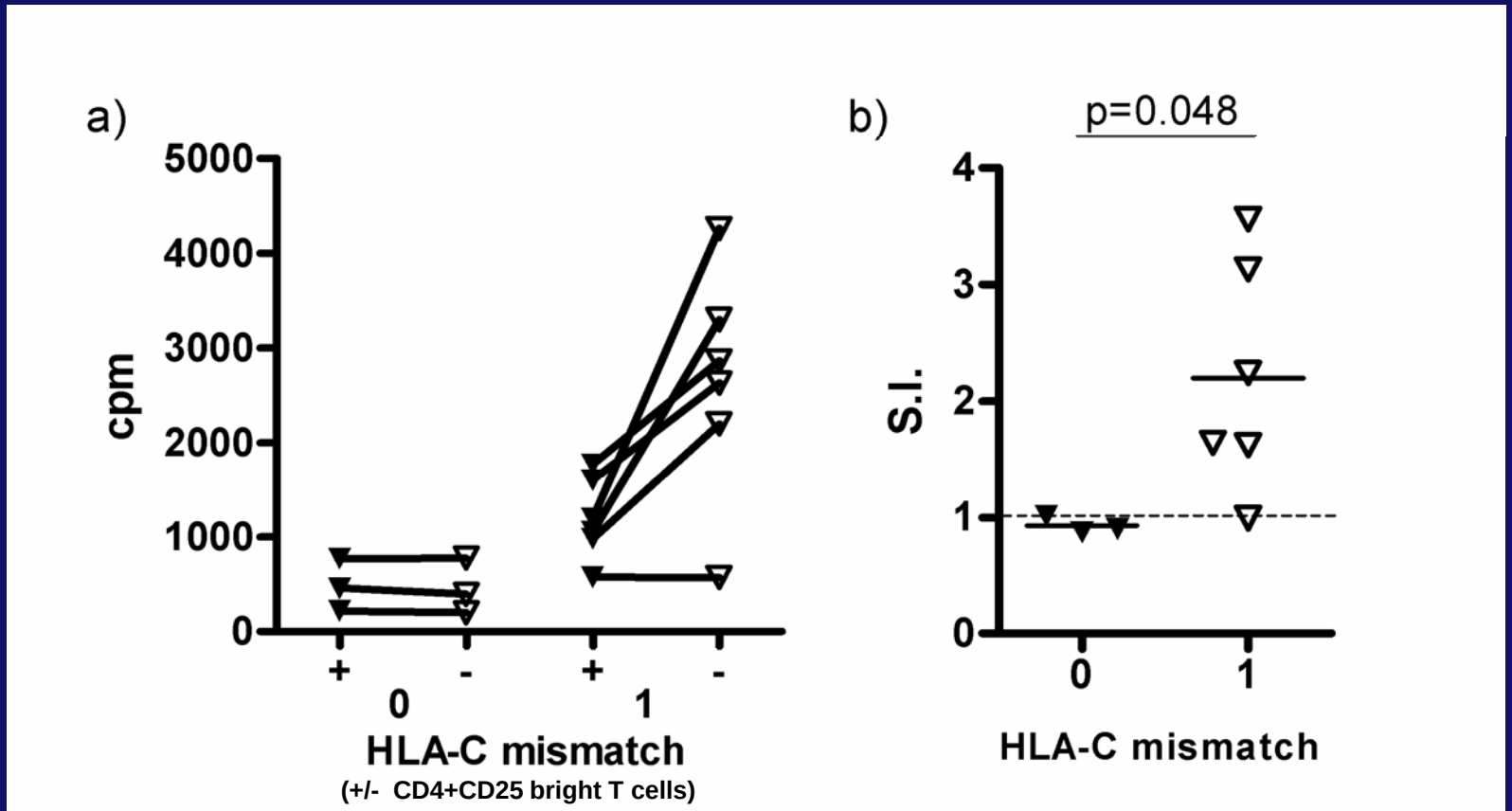
In order to determine which HLA mismatches are associated with the higher percentage of activated CD4+ T cells : HLA-A, -B, -C, -DR, -DQ mismatches were tested separately in a multivariate model

	Significance
HLA-A mismatch	ns
HLA-B mismatch	ns
HLA-C mismatch	0.030
HLA-DRB1 mismatch	ns
HLA-DQB1 mismatch	ns

Only significant for HLA-C antigen mismatches as recognized by TCR , no effect of C1 or C2 match/mismatch as ligand for KIRs on NK cells.

Tilburgs et al. J. Reprod. Immunol. 2009

A fetal-maternal HLA-C antigen mismatch is also associated with induction of functional regulatory T cells in decidua parietalis.



Tilburgs et al. J. Reprod. Immunol. 2009

Crucial role of HLA-C in immune recognition and regulation at the fetal-maternal interface.

1) NK cells can recognize HLA-C1 and C2 using KIR.

2) Indirect allorecognition of fetal HLA-C by decidual CD4+ T cells.

3) Direct allorecognition of HLA-C by decidual CD8+ T cells

4) Subsets of decidual T cells express KIR and may interact with HLA-C1 and C2

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