# Microchimerism in Space and over time (Our Interstellar Movie)

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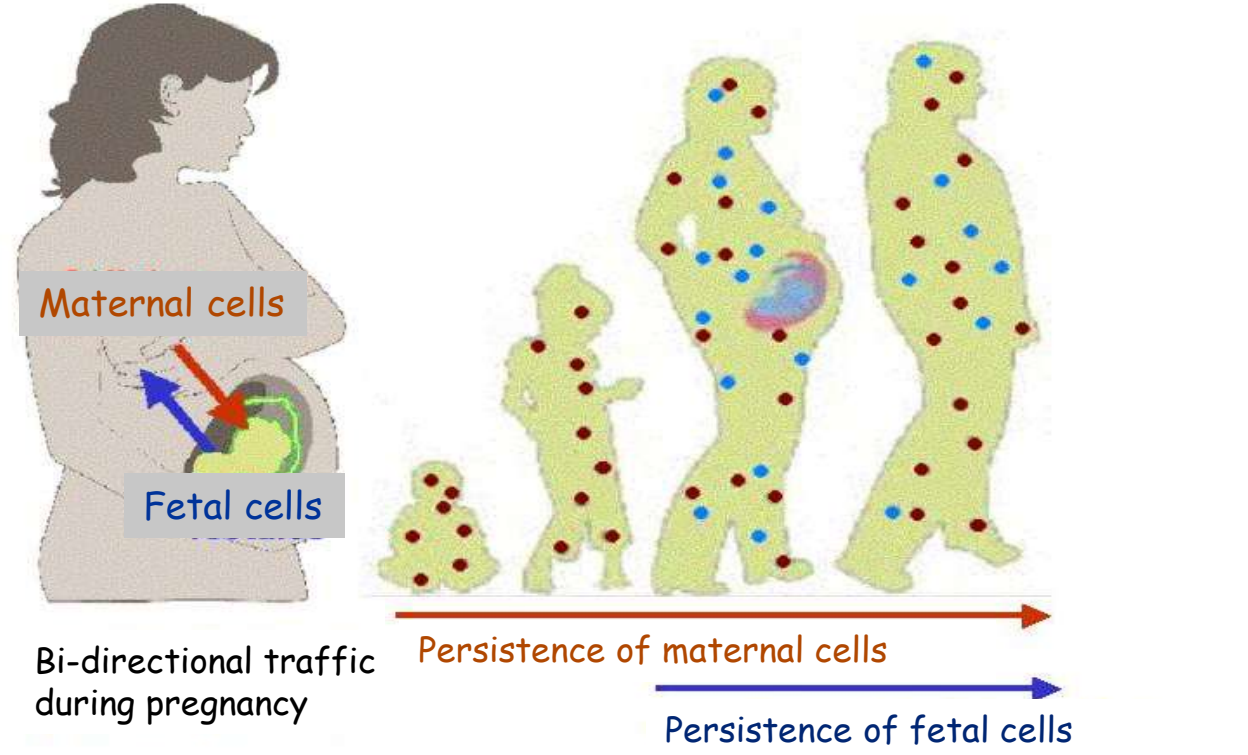
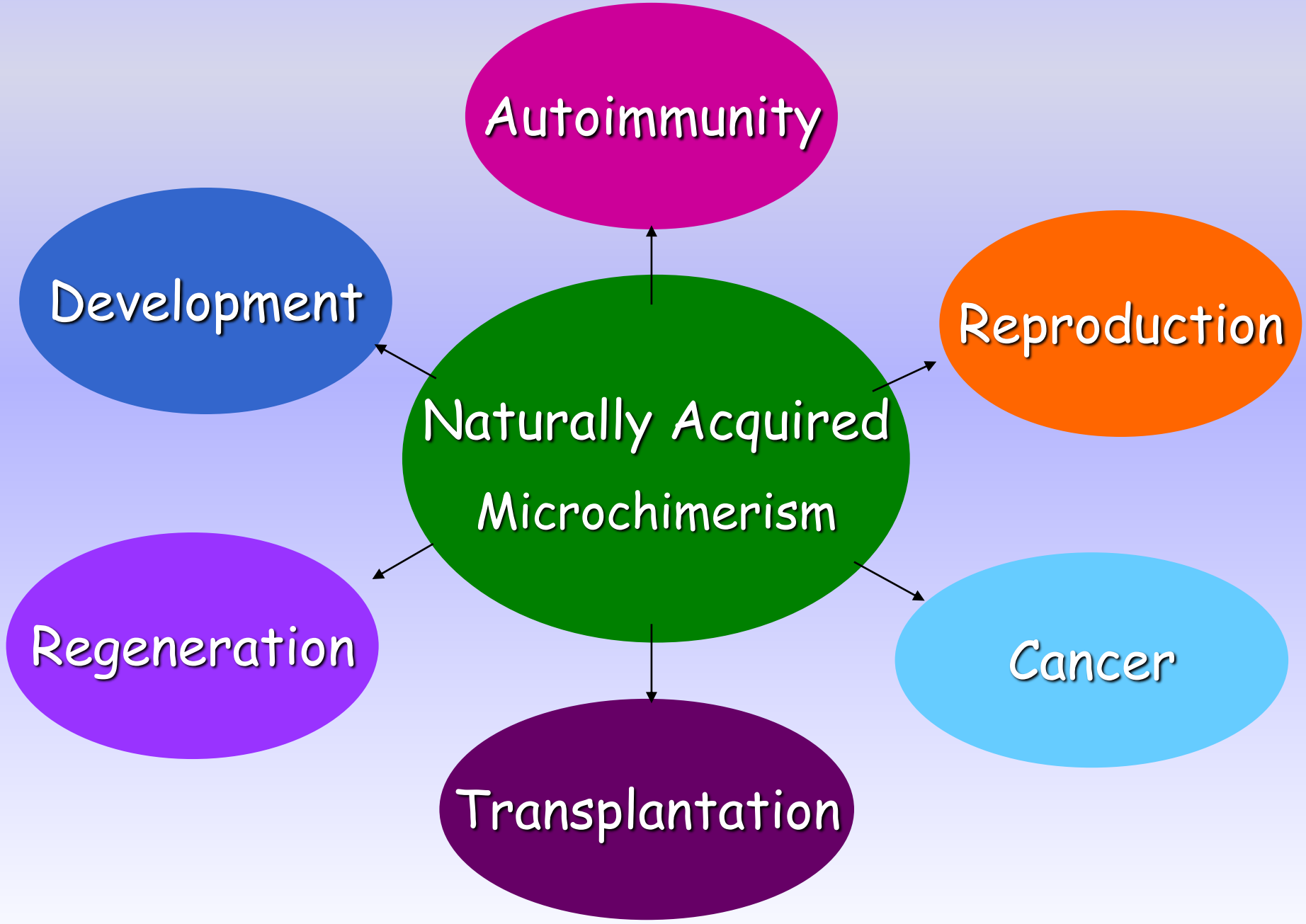
# Microchimerism (Mc): a small number of cells or DNA derived from a genetically disparate individual




## Mc of fetal and maternal origin persist for decades

*PNAS* 93:705-8,1996 *J Clin Invest* 104:41-7,1999

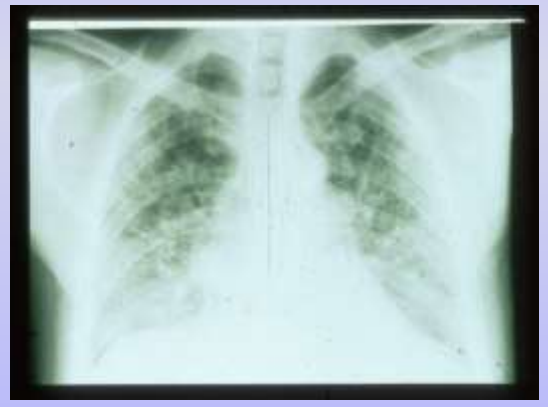
# Naturally Acquired Mc



# SOME AUTOIMMUNE DISEASES IN WHICH MC HAS BEEN INVESTIGATED

- Systemic sclerosis (scleroderma)
- Rheumatoid arthritis
- Neonatal lupus
- Type 1 diabetes
- Myositis
- Multiple sclerosis
- Autoimmune thyroid disease
- Primary biliary cirrhosis

# Mc in Systemic Sclerosis (SSc)



Hallmark feature indurated skin (scleroderma)
Death due to fibrosis of lungs, heart, gut, kidney

| | % | # | Mc/16cc | |
|---|---|---|---|---|
| Healthy mothers | 25% | 4/16 | 0-2 | |
| SSc mothers | 59% | 10/17 | 0-61 | p=0.0007 |

Women with sons tested for male DNA, Mc expressed in genome equivalents

Nelson JL et al
*Lancet* 351:559-62, 1998

# METHODS TO IDENTIFY MC

- PCR for male DNA in a female
- Fluorescence in situ hybridization (♂ in ♀ or vice versa)

➡ Quantitative PCR for a non-shared HLA allele

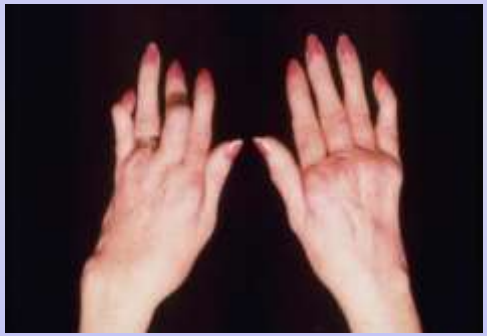
PANEL OF HLA AND OTHER POLYMORPHISM SPECIFIC qPCR ASSAYS DEVELOPED

| *HLA specificities* | | *Other polymorphisms* |
|---|---|---|
| DRB1*01 | DQA1*01 | GSTM1 |
| DRB1*15/16 | DQA1*03 | GSTT1 |
| DRB1*03 | DQA1*05 | AT3 |
| DRB1*04 | DQB1*02 | Tg |
| DRB1*12 | DQB1*0602/3 | |
| DRB1*07 | DQB1*0301/4 | |
| DRB1*08 | DRB1*04 | |
| DRB1*10 | B*44 | |
| DRB1*14 | | |

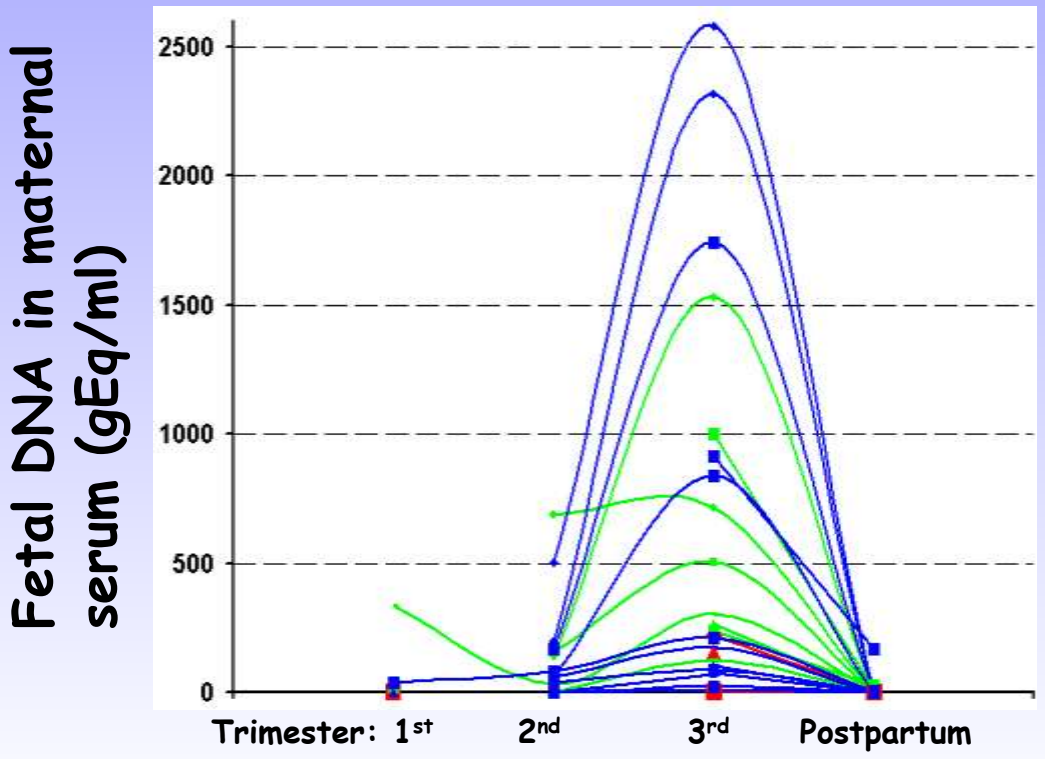
Test mother for HLA-B*44 to identify Mc from the daughter

| HLA*B genotype | | |
|---|---|---|
| Mother | 35 | 08 |
| Daughter | 35 | 44 |

# MC IN RHEUMATOID ARTHRITIS, THE GOOD AND THE BAD



Hallmark feature symmetrical polyarthritis
Pregnancy induces amelioration for most




Yan Z et al
*Arthritis Rheum* 54:2069-75,2006

# MC IN RHEUMATOID ARTHRITIS, THE GOOD AND THE BAD

*Natural "mini-gene transfer hypothesis":*
A person without genetic (HLA) risk of RA, can develop risk by acquiring Mc that has the HLA RA-risk allele

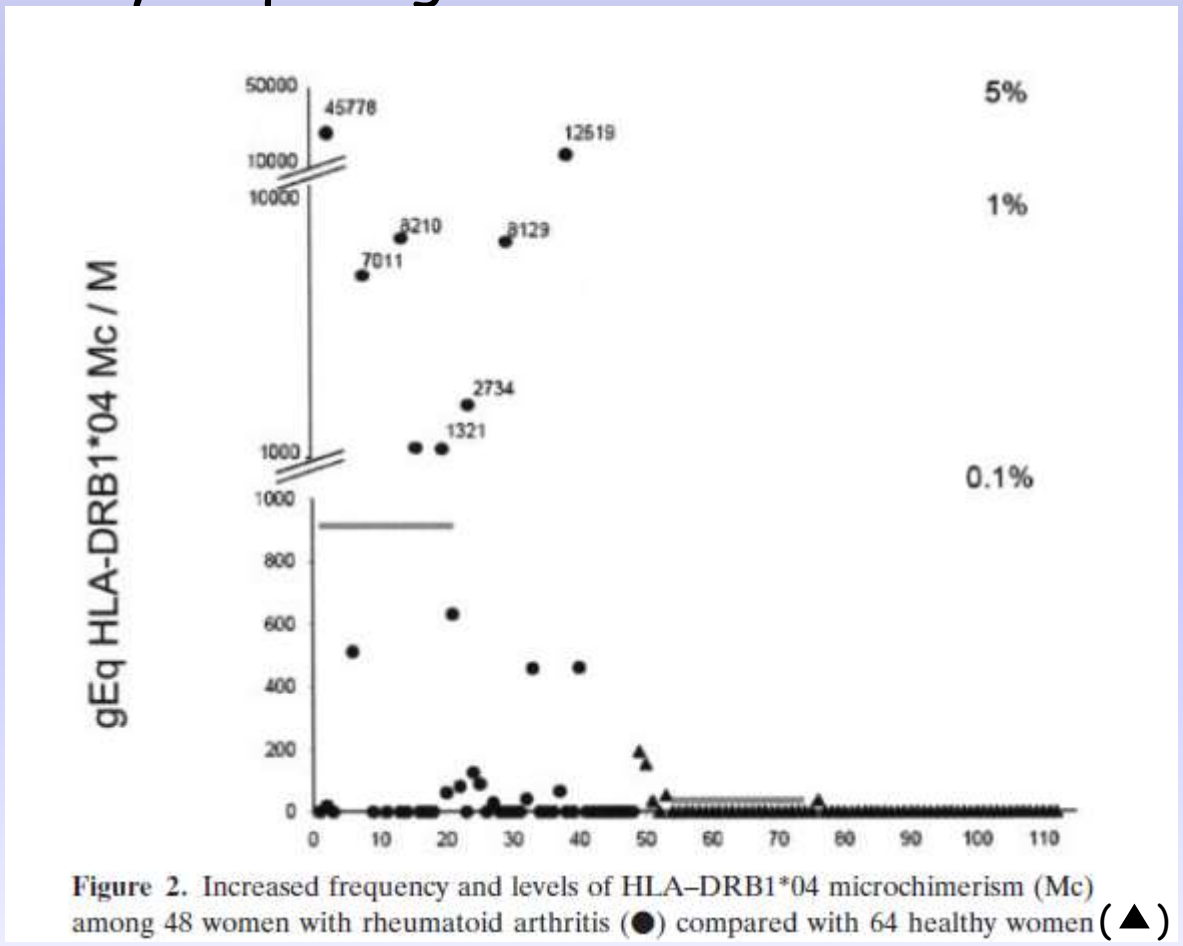
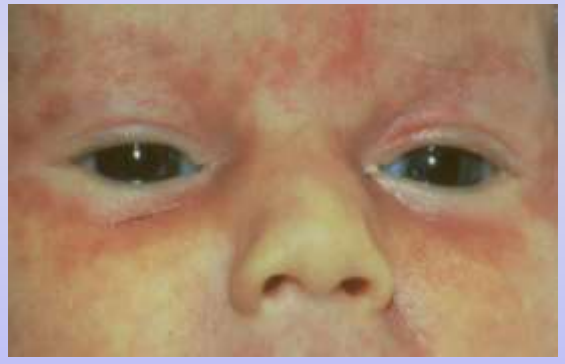
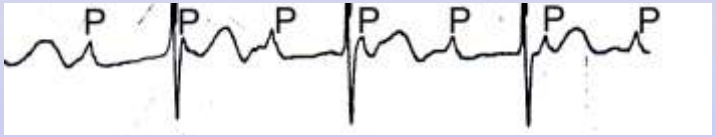



**Figure 2.** Increased frequency and levels of HLA–DRB1*04 microchimerism (Mc) among 48 women with rheumatoid arthritis (●) compared with 64 healthy women (▲)

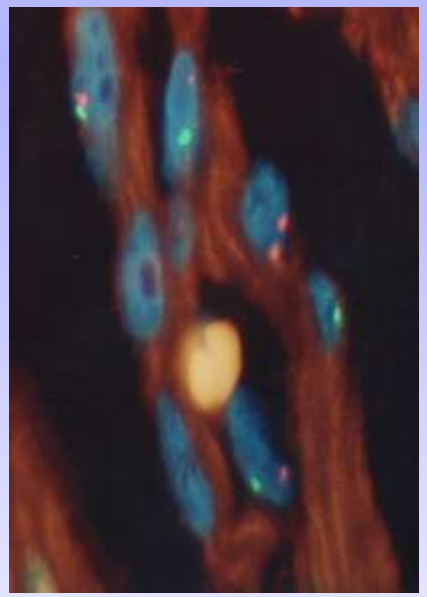
Rak J et al
*Arthritis Rheum* 60:73-80,2009

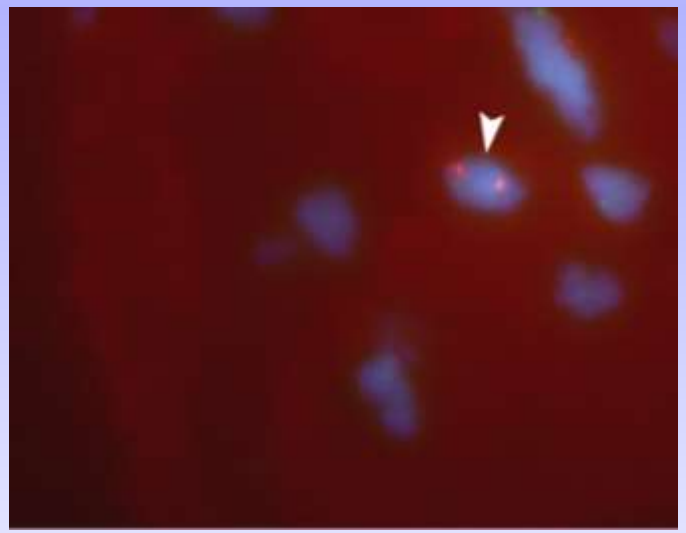
# MC IN NEONATAL LUPUS SYNDROME

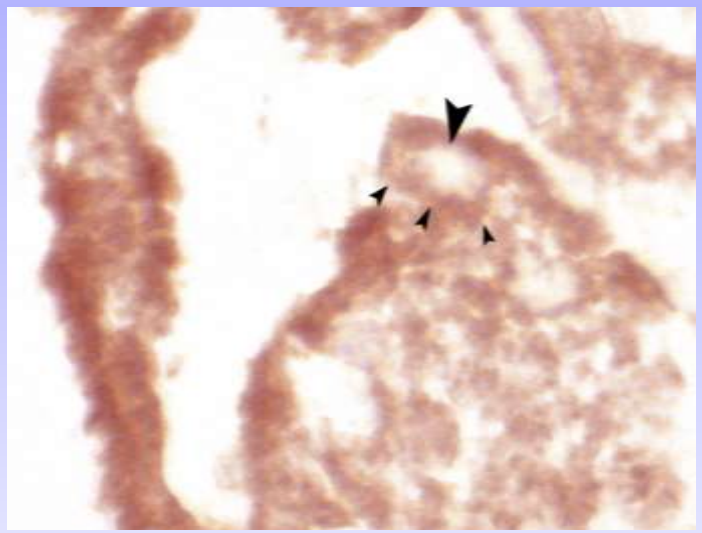





Hallmark features: skin rash, congenital heart block



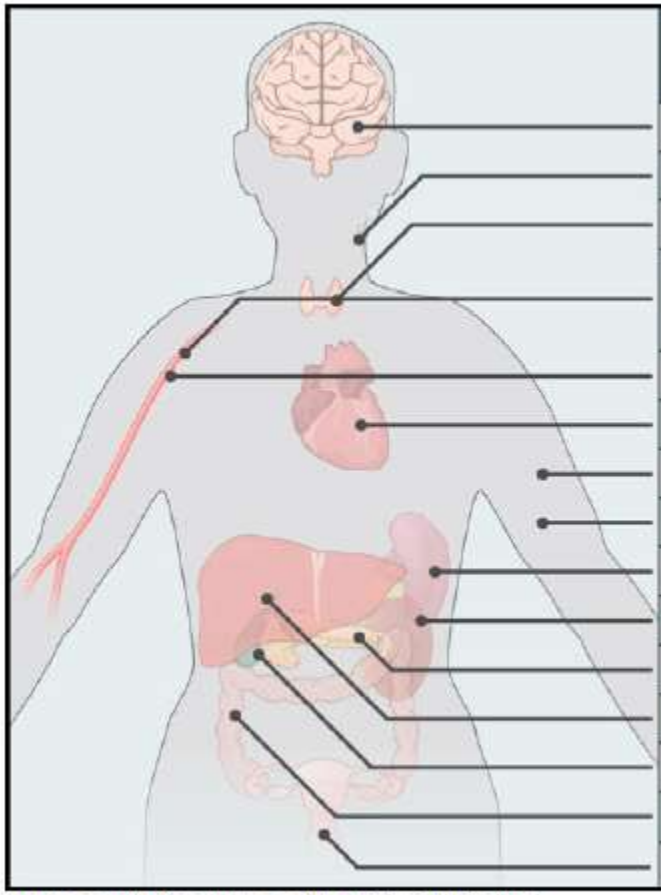




Maternal cells in neonatal lupus heart express sarcomeric a-actin

Stevens AM et al
*Lancet* 362:1617-23,2003

# Cell types of Mc in Humans



| Organ | Presumed cell type | Maternal origin Mc | Fetal origin Mc |
|---|---|---|---|
| Brain | Neurons(murine) | | X |
| Lymph node | Hematopoietic cells | | X |
| Thyroid | Epithelial cells, thyrocytes | | X |
| Blood | T cells, B cells, monocytes/ macrophages, NK cells, granulocytes | X | X |
| Blood | Lymphoid progenitor cells | | X |
| Heart | Cardiac myocytes | X | X |
| Skin | Endothelial cells | | X |
| Skin | Keratinocytes | X | |
| Spleen | Hematopoietic cells | | X |
| Kidney | Renal tubular cells | X | |
| Pancreas | Islet beta cells | X | |
| Liver | Hepatocytes | X | X |
| Gallbladder | Epithelial cells | | X |
| Intestine | Epithelial cells | | X |
| Cervix | Epithelial cells | | X |

*Human studies unless otherwise indicated

TRENDS in Immunology

The Otherness of Self: Microchimerism in Health and Disease

Nelson JL *Trends in Immunol* 33(8):421-8,2012

*Epigenomics*. 2010 December ; 2(6): 797–806. doi:10.2217/epi.10.57.

# Transgenerational genetic effects

**Vicki R Nelson**[1] and **Joseph H Nadeau**[1,†]

[1]Department of Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA

Does transgenerational Mc impact health?

# Is the preexisting Mc "graft" from a woman's mother displaced when she acquires a new "graft" with fetal Mc?

1975

2004

2012

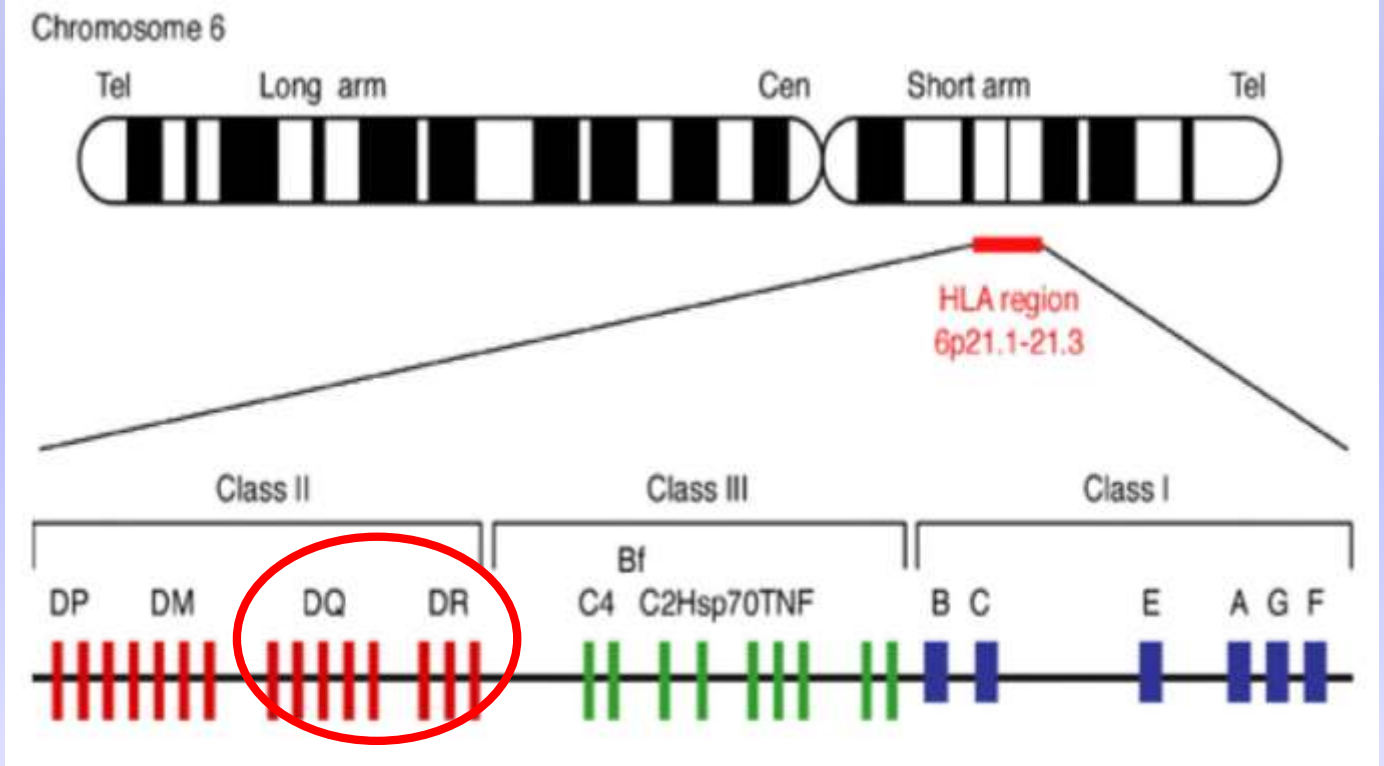
Mc from a woman's own mother decreases with increasing parity

| Parity | # | Mc+ | OR | 95% CI | p value |
|---|---|---|---|---|---|
| 1 | 36 | 12 (33%) | 1.0 | | |
| 2 | 50 | 3 (6%) | 0.11 | (0.03-0.42) | 0.001 |
| 3-4 | 14 | 0 | | | |

Gammill H et al
*Blood* 116:2706-12,2010

# HLA molecules at the Interface of autoimmunity and Alloimmunity

**Major Histocompatibility Complex**




HLA: Human Leukocyte Antigen

# Does the HLA relationship across generations affect risk of autoimmune disease vs healthy allo-immunity?

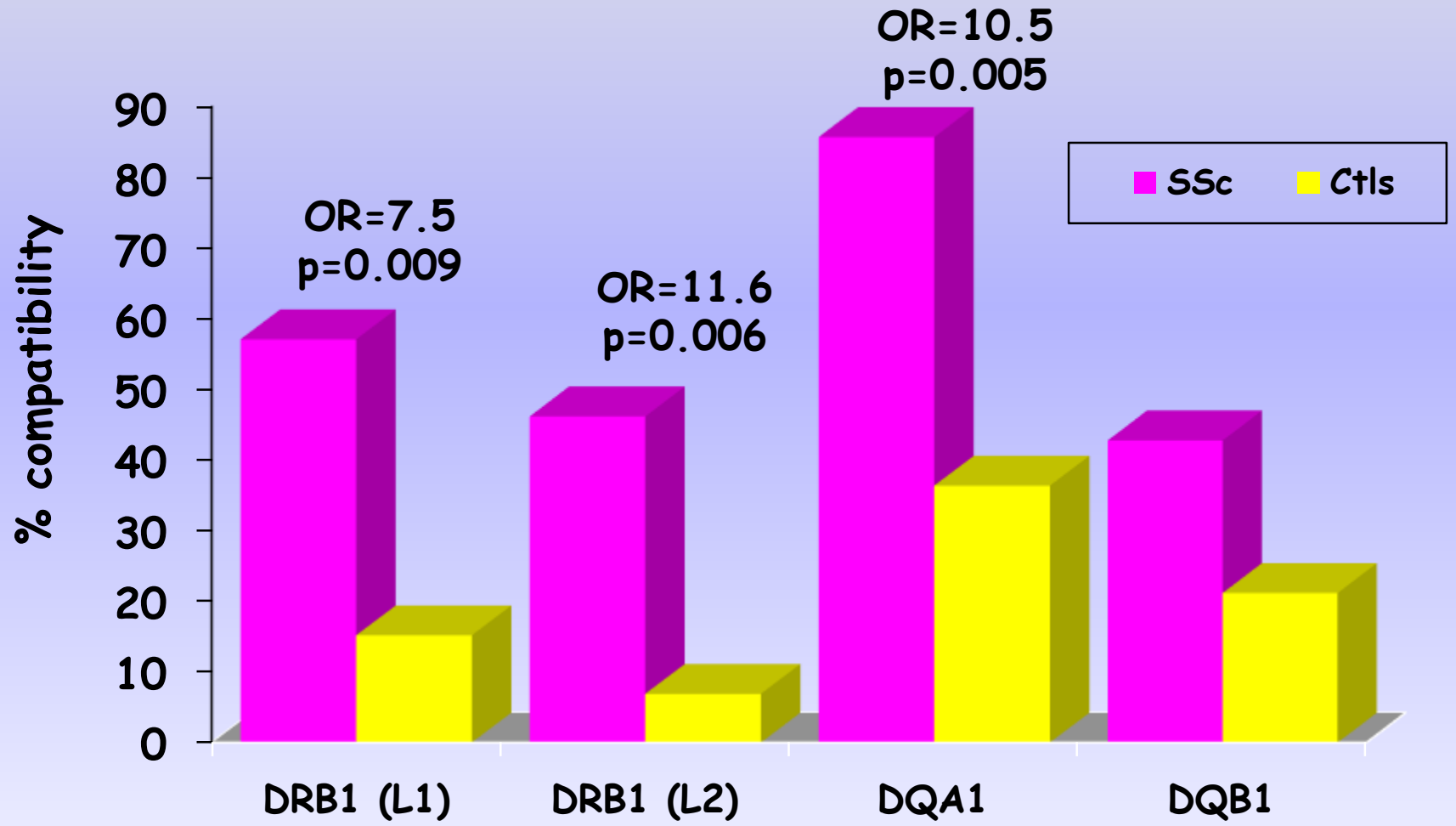
examples shown for HLA-DRB1*

| Bi-directional Incompatibility | Bi-directional Compatibility | One direction compatible from mother's perspective | One direction compatible from child's perspective |
|---|---|---|---|
| Mother 04 15 | Mother 04 11 | Mother 04 11 | Mother 04 04 |
| Child 04 07 | Child 04 11 | Child 04 04 | Child 04 07 |

A few examples of multi-generational HLA-relationships …

| | | |
|---|---|---|
| Grandmother 04 15 | Grandmother 04 15 | Grandmother 04 04 |
| Mother 04 07 | Mother 04 07 | Mother 04 07 |
| Child 04 08 | Child 04 15 | Child 04 08 |

# Increased HLA-Compatibility Across Generations in Systemic Sclerosis Families




* Compatibility of patient's mother from her child's perspective

# Mc in Health vs. Autoimmunity

The normal fetus produces $T_{reg}$ to non-inherited maternal HLA antigens, also found in children [1]

A Foxp3 enhancer that is essential for peripheral $T_{reg}$ but not for thymic $T_{reg}$ only found in placental mammals [2]

"Consider the placenta as a selective immigration policy"

... the legacy of pregnancy as benefits and risks of immigrants

If transdifferentiated Mc is part of normal biology, "self" is redefined & loss of tolerance to immigrants could cause disease

[1] Mold J *Science* 322:1562-5,2008 [2] Samstein RM *Cell* 150:29-38,2012

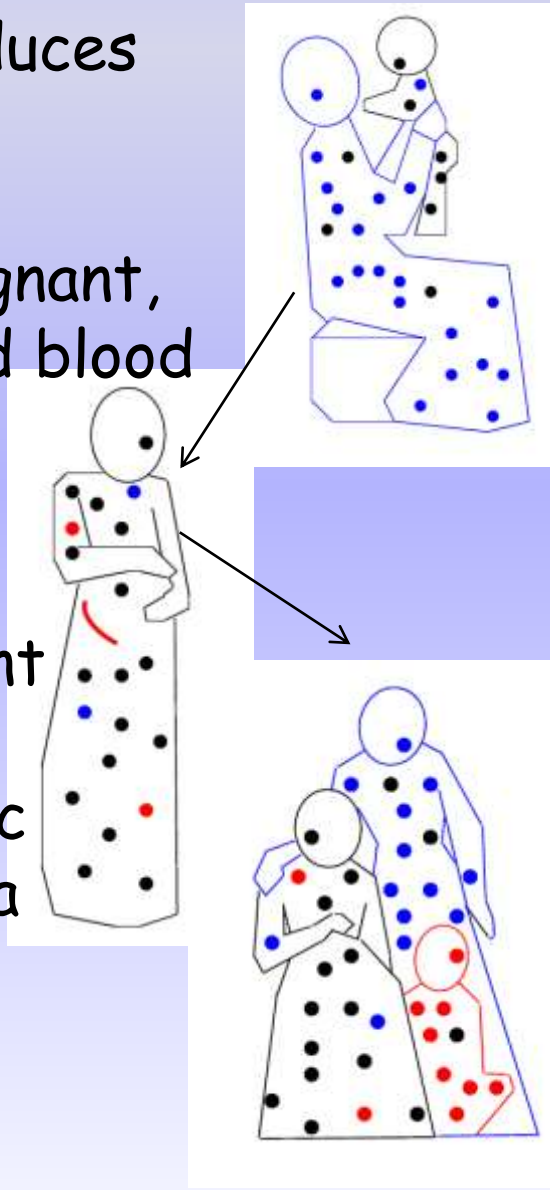
# Transgenerational Mc in Systemic Sclerosis: Hypothesis

- Maternal Mc acquired during fetal life produces differentiated maternal Mc in tissues

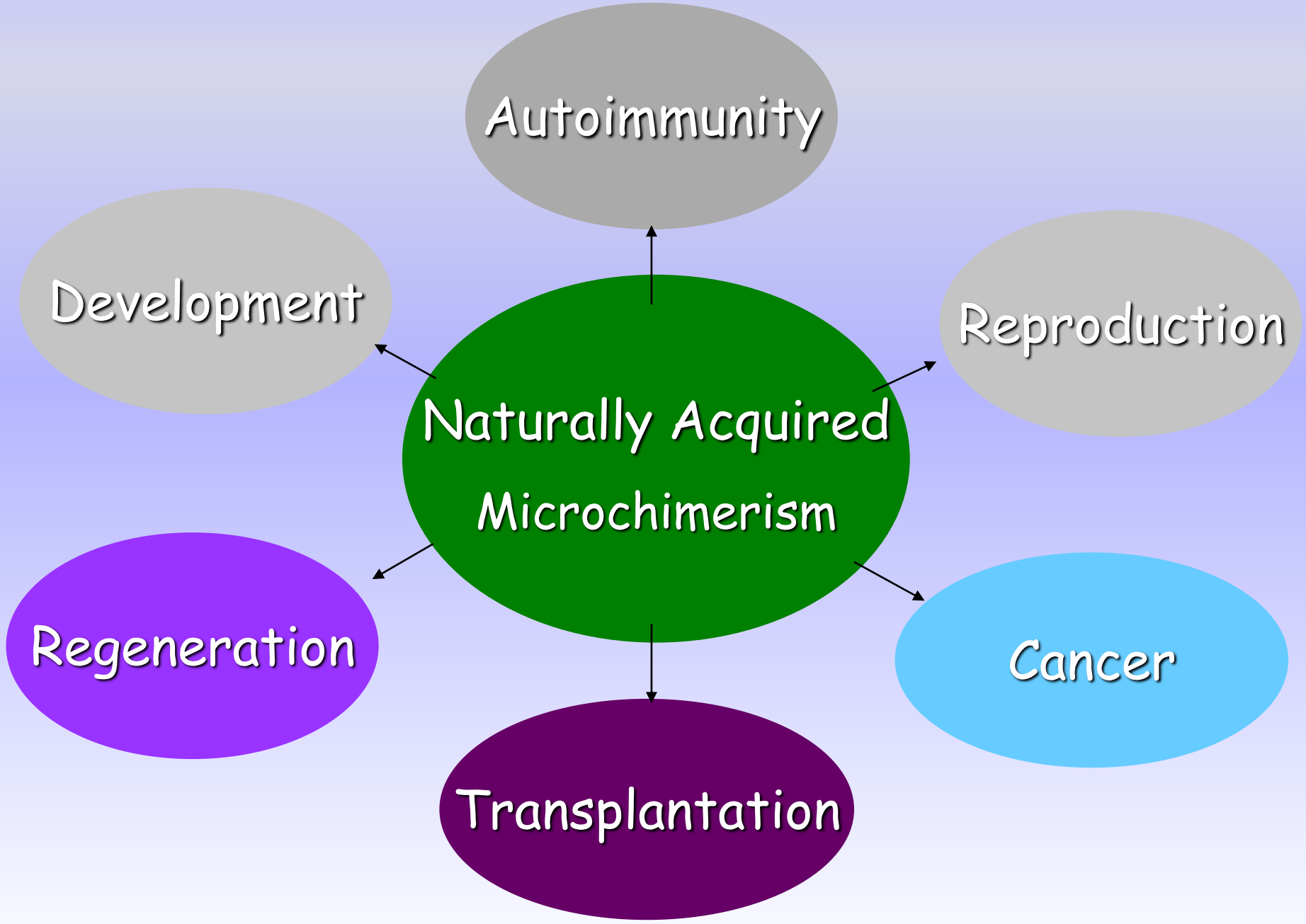
- Normally when an adult woman becomes pregnant, fetal Mc replaces maternal Mc in tissues and blood

- When maternal Mc (harbored by the adult woman) is HLA indistinguishable from the fetal Mc perspective replacement is deficient

- Indolent inflammation occurs as maternal Mc has reactivity to fetal Mc, but not vice versa



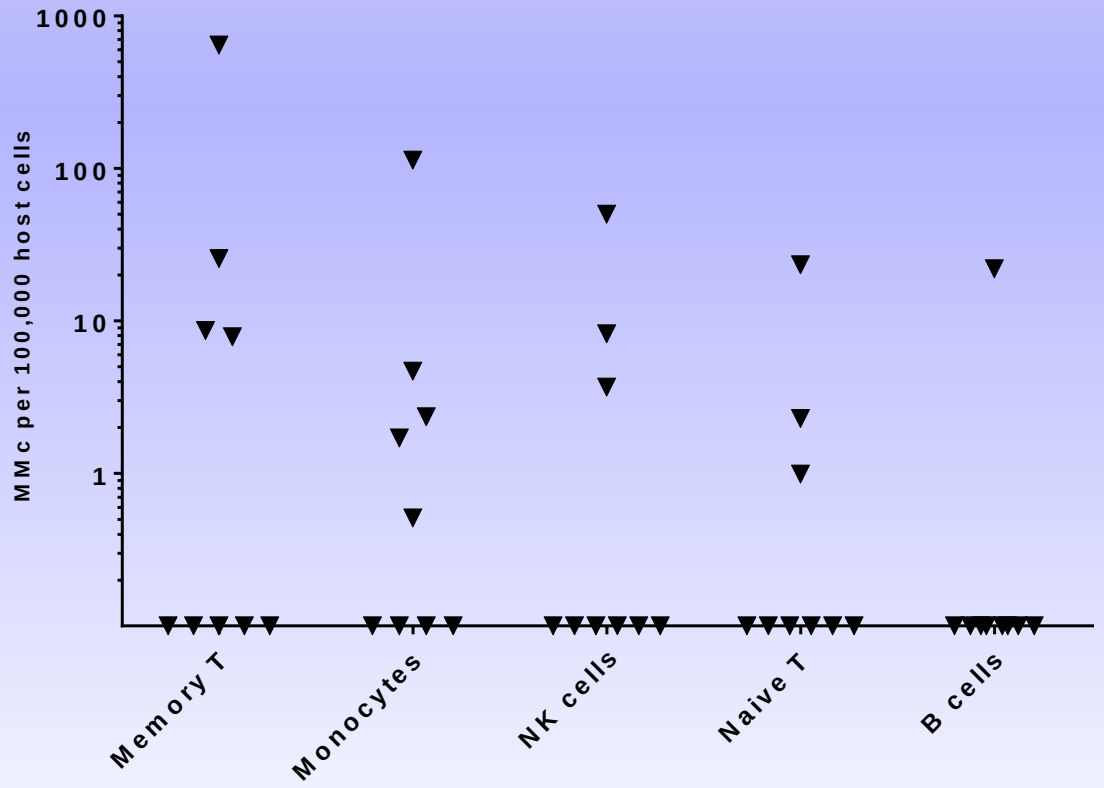
# Potential Effects of Mc from Maternal-Fetal Exchange



# Maternal Mc as Anti-Leukemia in Patients Receiving Cord Blood Transplantation

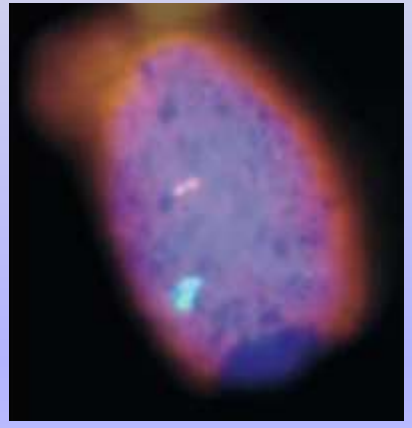
| HLA-B | | |
|---|---|---|
| Mother | 08 | 07 |
| CB unit | 08 | 35 |
| Patient | 08 | 35 |

Studies in progress: 22/34 (65%)
cord bloods positive for maternal Mc
1 to 1348 genome equivalents per $10^5$



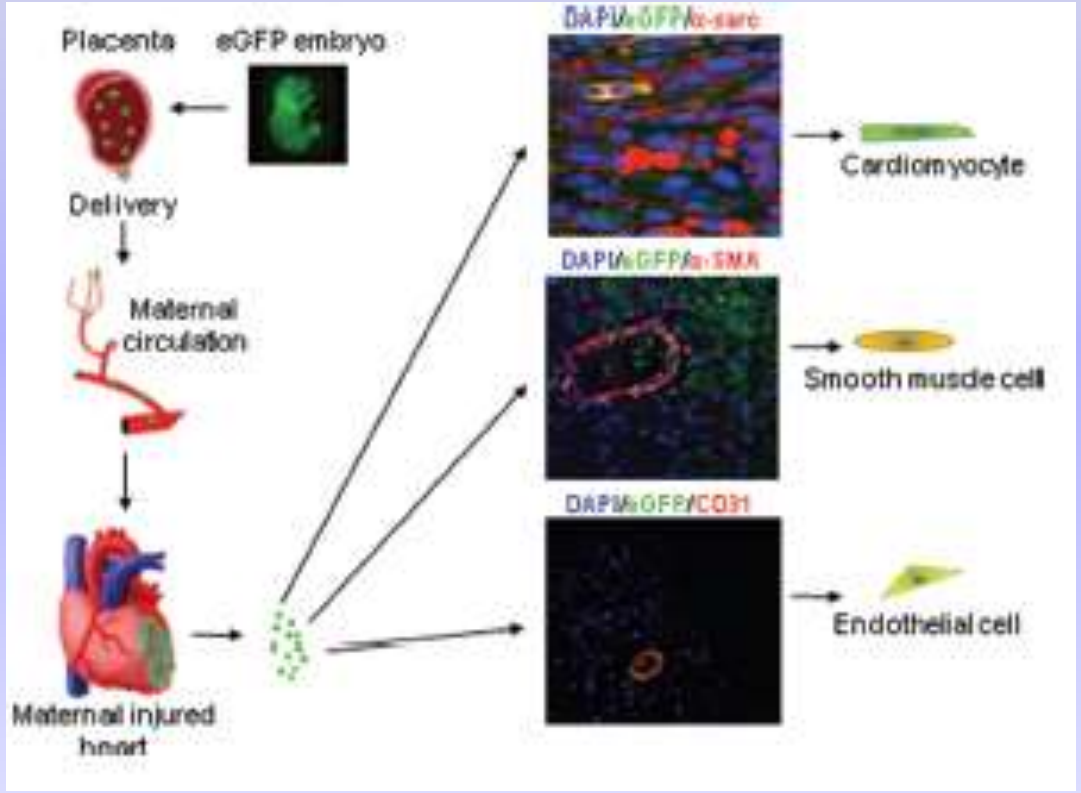

Van Rood J et al
*PNAS* 109:2509, 2012

# REPAIR: FETAL MC WITH MULTILINEAGE POTENTIAL



Male cell in the thyroid tissue, appears to be a thyroid cell not a blood cell

Khosroteharani K et al
*JAMA* 292:75-80, 2004




Kara RJ et al
*Circ Res* 110:82-93, 2012

# Summary: Our Natural Immigrants, for Better or for Worse

- Microchimeric T lymphocytes could be effectors, attacking healthy tissue (allo-autoimmunity)
- Mc as "mini-gene transfer": protection or risk of an autoimmune disease depending on the HLA allele
- Differentiated microchimeric cells in tissues could be targets of immune attack (auto-alloimmunity)
- Mc likely contributes to protection against some malignancies (healthy allo-autoimmunity)
- Mc may travel to injury sites and be reparative
- Multiple Mc "grafts" can be acquired, and interactions among grafts may have a diversity of consequences

# "I contain multitudes"

## Walt Whitman

JL Nelson
*Scientific American* 298:72-9,2008

# Acknowledgements

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