The place of immunology

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IVIRMA Global Innovation

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SOCIETY in 2020

- Increased maternal age in 1st birth

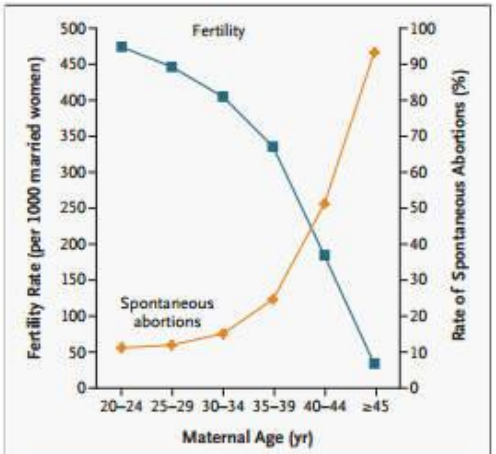
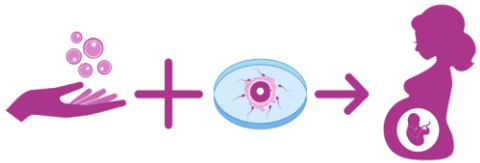


Figure. Fertility and Miscarriage Rates as a Function of Maternal Age.

- Increased demand Egg donation (7,561 cycles)



Implantation Failure

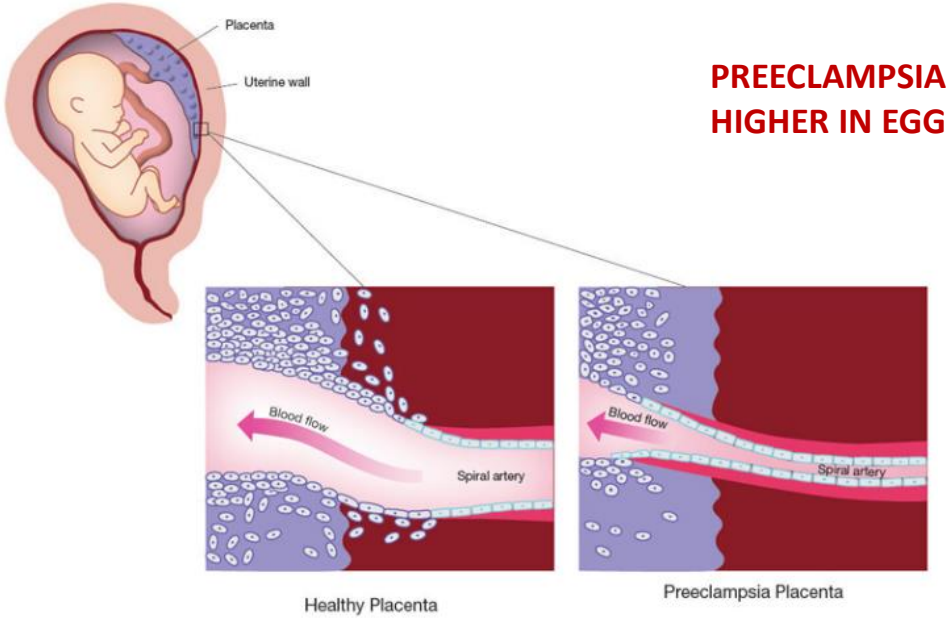
70% chromosome related

and the rest?

- **Reproductive Immunology**
- **Microbiota? Endometrium and WOI?**

How much does the uterus matter?

Oocyte Donation: Obstetric Complications



PREECLAMPSIA RISK
HIGHER IN EGG DONATION

- **Other ART** (**OR, 2.54; P < .0001**)
- **Natural Conception** (**OR, 4.34; P < .0001**).

HTA RISK
HIGHER IN EGG DONATION

- **Other ART** (**OR, 3; P < .0001**)
- **Natural Conception** (**OR, 7.94; P < .008**).

2016 Royal College of Obstetricians and Gynaecologists. Databases 1982-2016
Masoudian P. et al . Am J Obstet Gynecology 2016; Savasi VM. Hum Reprod Update 2016

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2018.1528577

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

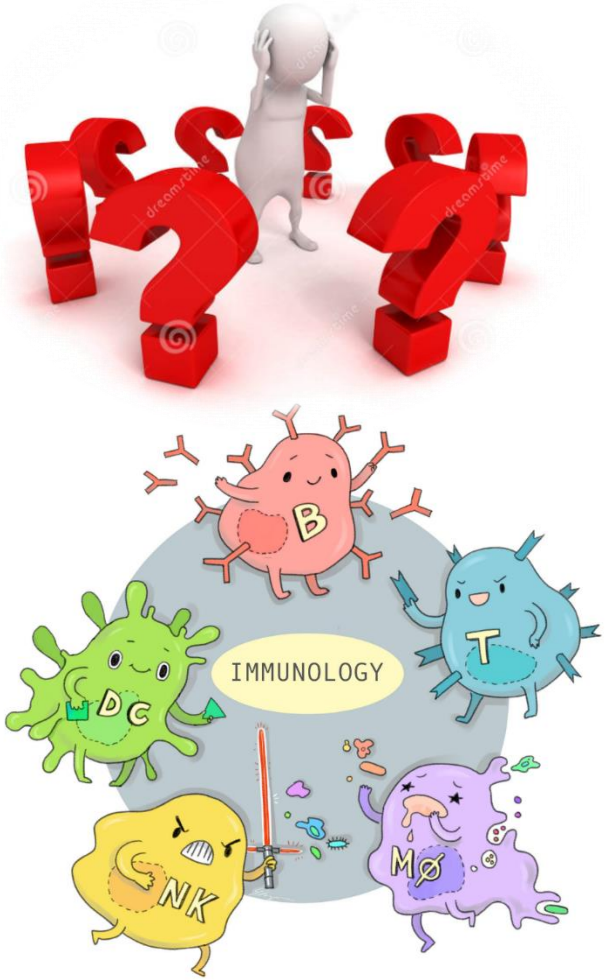
Increased incidence of obstetric and perinatal complications in pregnancies achieved using donor oocytes and single embryo transfer in young and healthy women. A prospective hospital-based matched cohort study

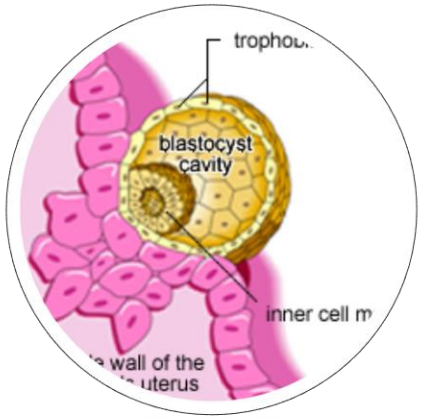
Kenny A. Rodriguez-Wallberg[a,b], Ann-Sofie Berger[a], Antonia Fagerberg[a], Jan I. Olofsson[c], Christina Scherman-Pukk[a], Pelle G. Lindqvist[d,e] and Josefine Nasiell[e,f]

[a]Department of Reproductive Medicine, Division of Gynecology and Reproduction, Karolinska University Hospital, Stockholm, Sweden; [b]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [c]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden; [d]Department of Obstetrics and Gynecology, Södersjukhuset, Stockholm, Sweden; [e]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; [f]Department of Obstetrics and Gynecology, Karolinska University Hospital, Stockholm, Sweden

- Gestational hypertensive (AOR 4.25)
- Pre-eclampsia (AOR 3.99)

IMMUNE Maladaptation?



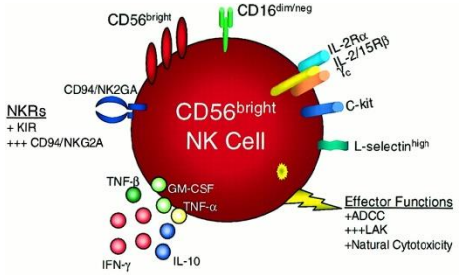


Reproductive Immunology

✓**Wrong assumption:**

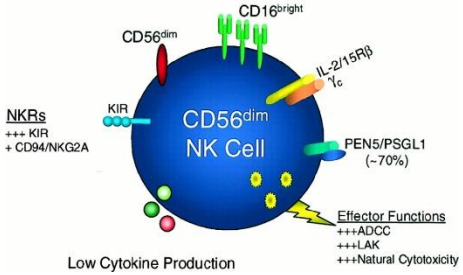
"NK cells are bad – let´s get rid of them!"

uNK cells



✓**A lot of misunderstood immune concepts in the literature**

pbNK cells



- IVIG, Intralipid, antiTNFa
- Corticosteroids
- AAS, LMWH…

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Still an Open Debate

Reply: First do no harm: continuing the uterine NK cell debate

ARTICLE *in* HUMAN REPRODUCTION · JANUARY 2016
Impact Factor: 4.57 · DOI: 10.1093/humrep/dev290

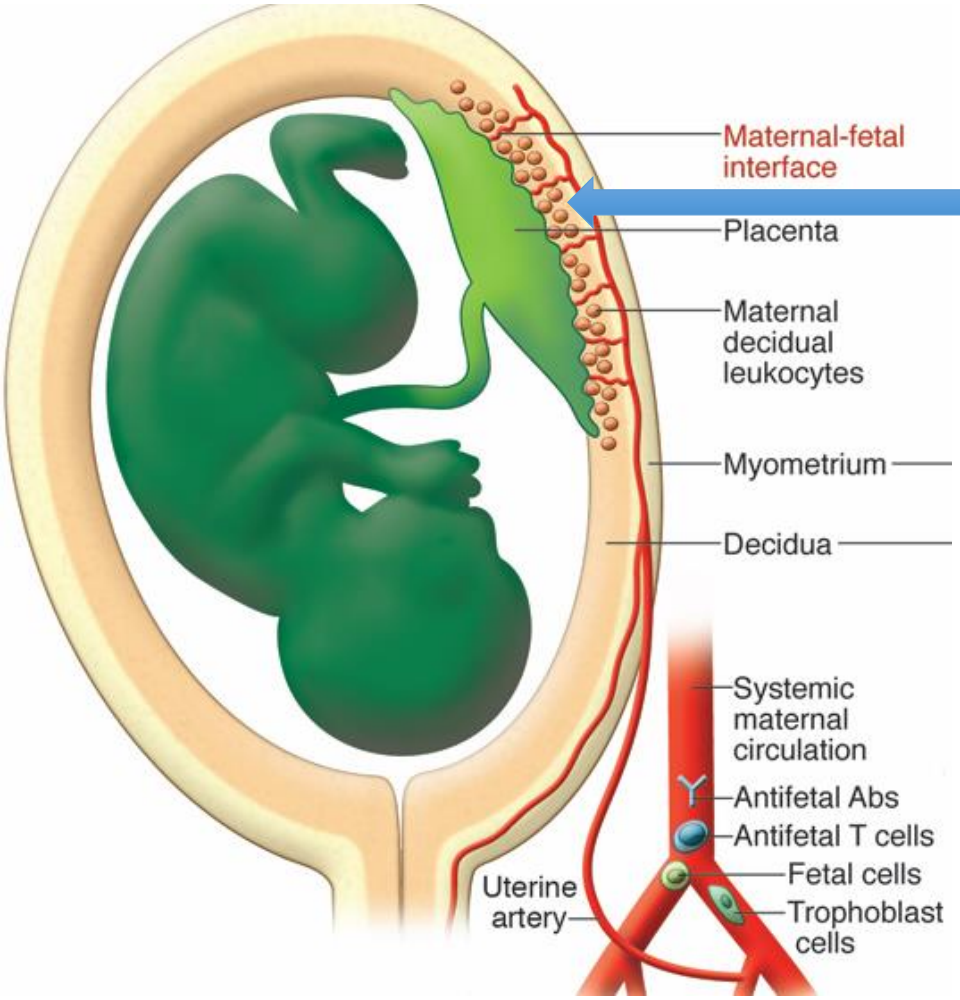
Ashley Moffett[1,2,*] and Norman Shreeve[2,3]

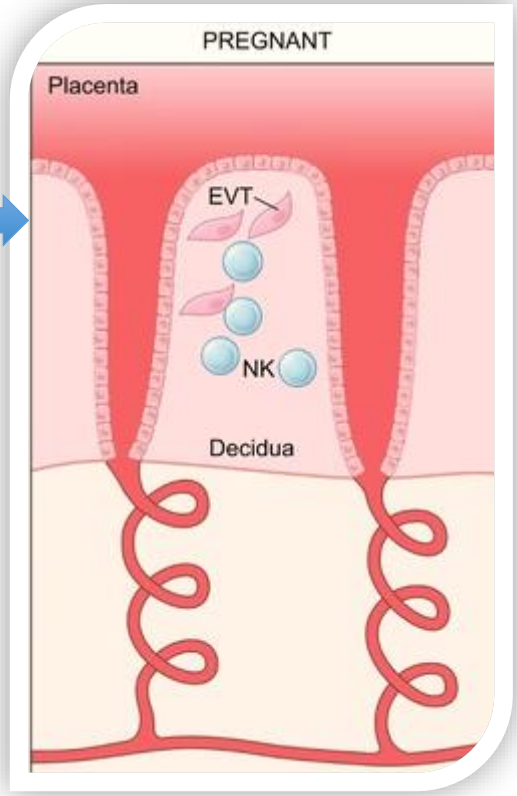
human reproduction

LETTER TO THE EDITOR

Immune testing and treatment: still an open debate

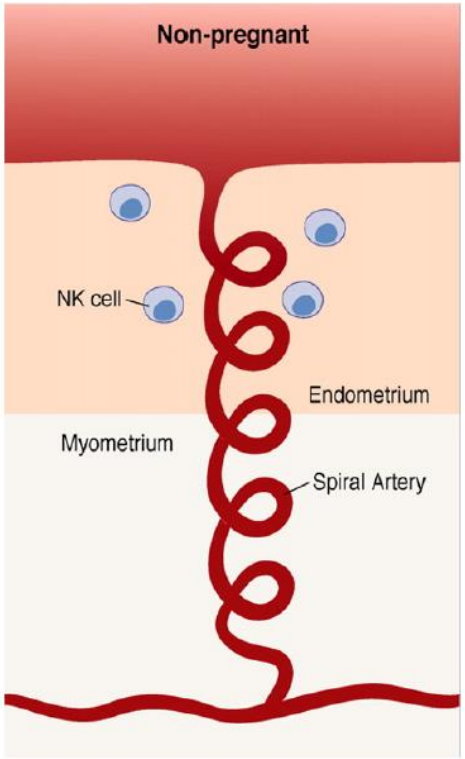
D. Alecsandru* and J.A. García-Velasco **2015**

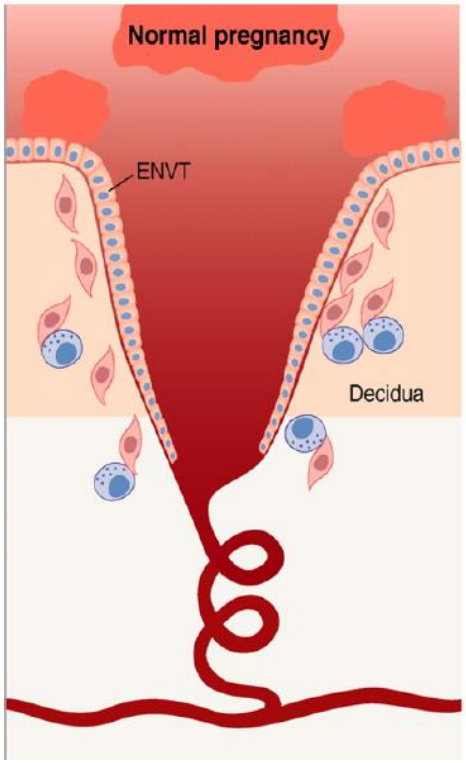




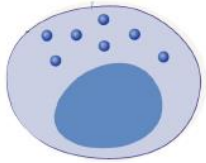
A. Moffett and F. Colucci. JCI **.2014**

EVT invasión and remodeling of spiral arteries: **crucial steps** for correct placentation



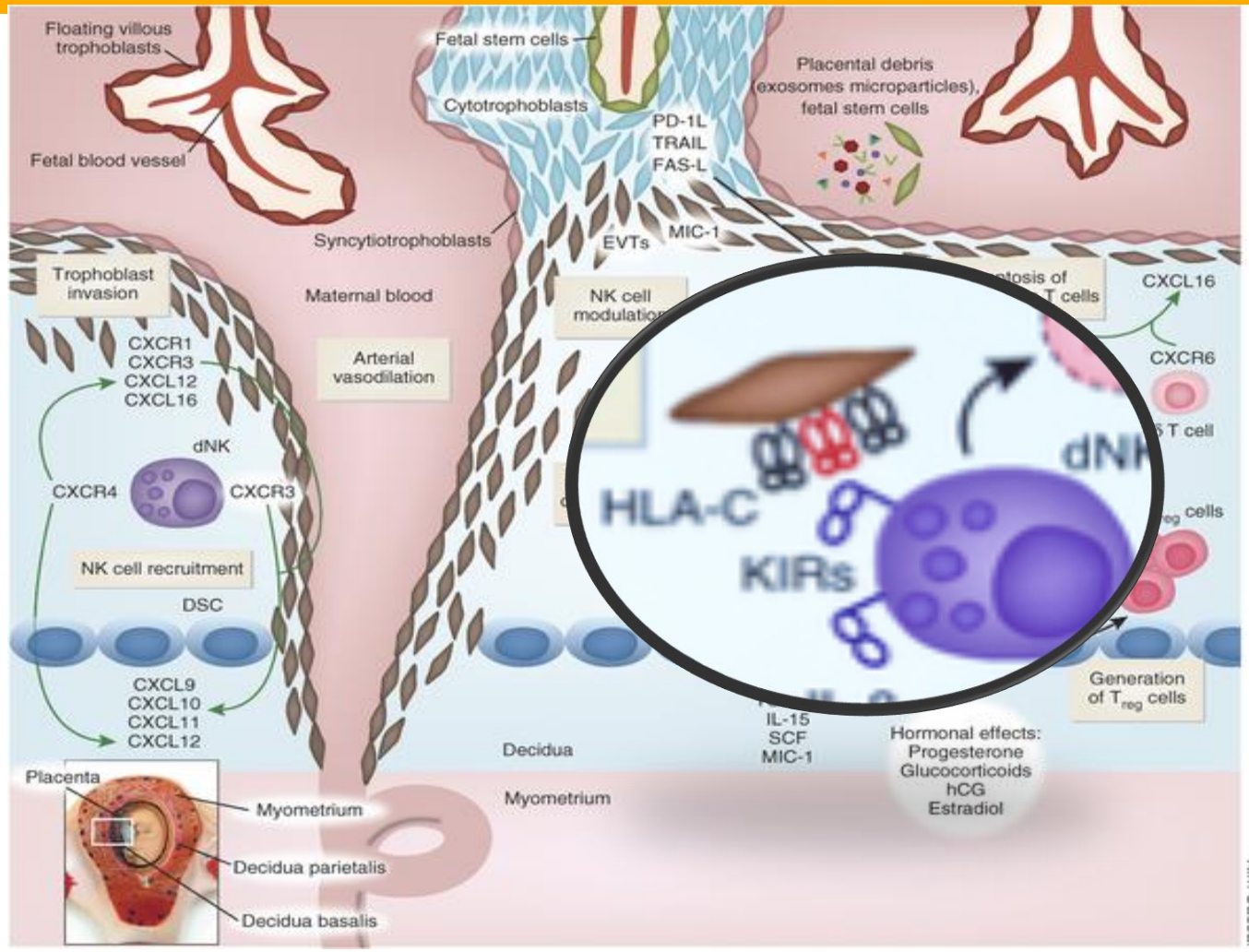


Extravillous Trophoblast Cells (EVT)



Uterine Natural Killer Cells (uNK, dNK)

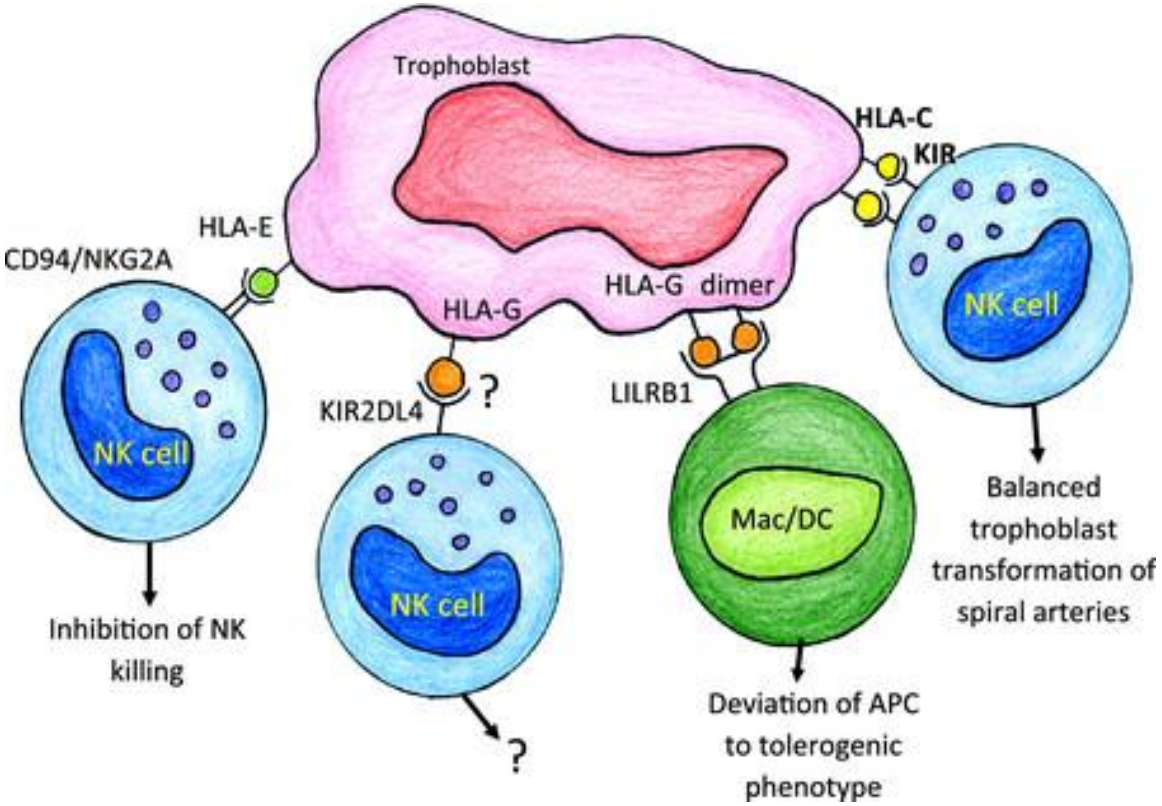
Parham, J Exp Med 2004



Arck and Hecher. Nature Medicine.2013

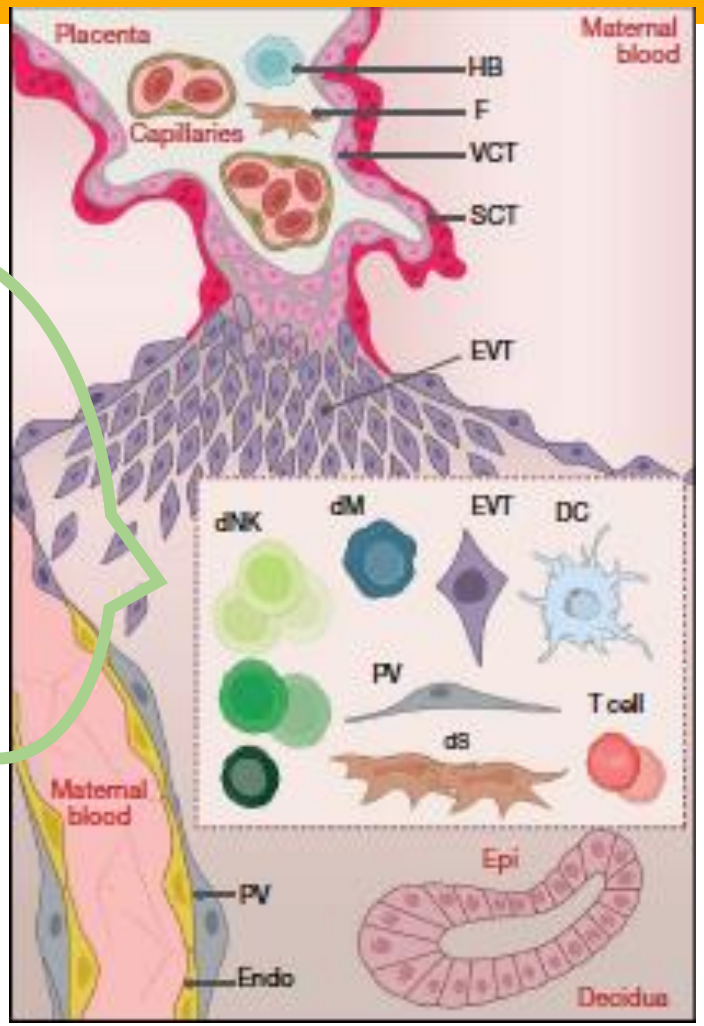
Highly polymorphic
26,512 HLA I+II alleles

Throphoblast:
does not express HLA class II



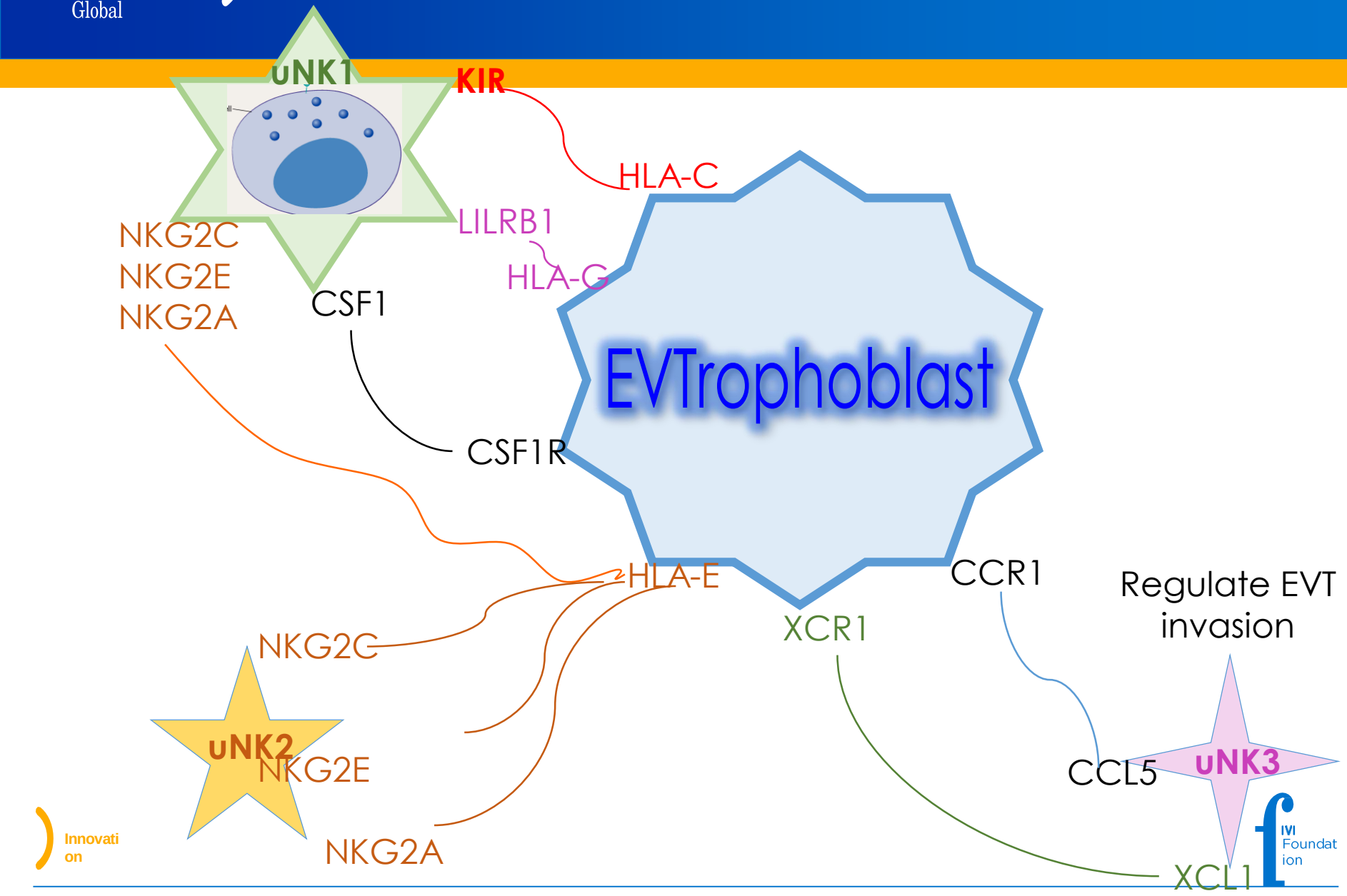
A.Moffett and F. Colucci. Immunological Reviews. 2015

dNK1
dNK2
dNK3



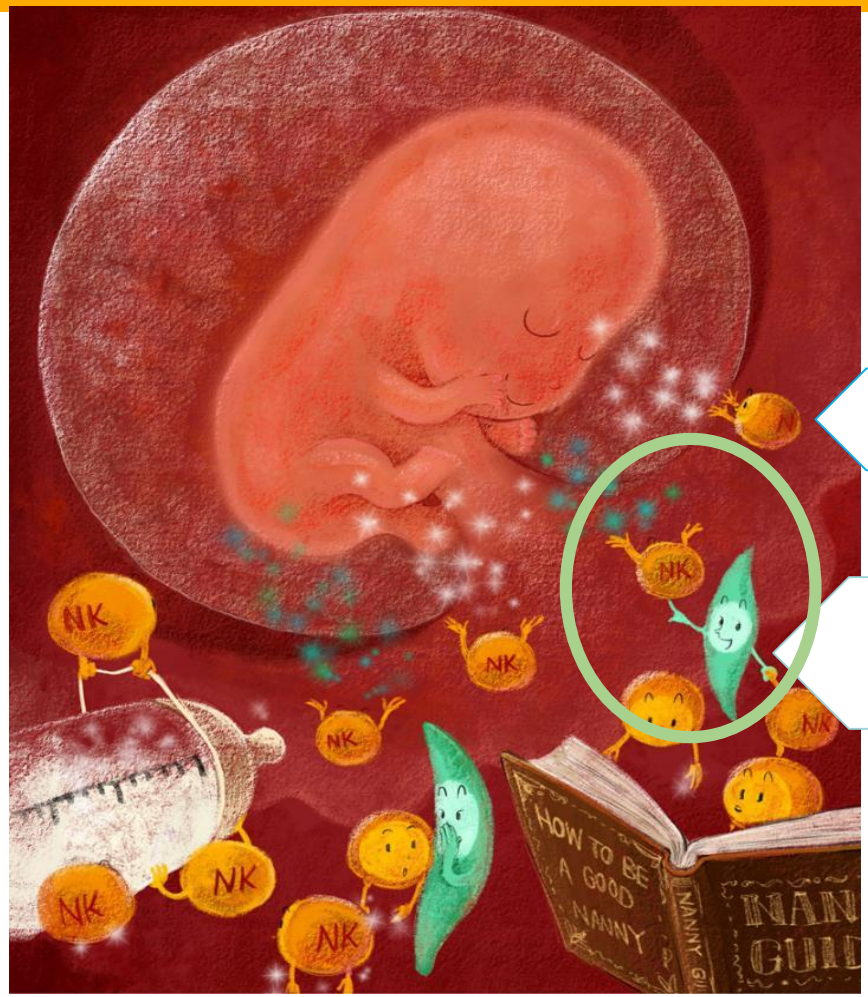
Single-cell reconstruction of the early maternal-fetal interface in humans

Roser Vento-Tormo el all. Nature. Nov 2018.


uNK1
KIR
HLA-C
LILRB1
HLA-G
NKG2C
NKG2E
NKG2A
CSF1
CSF1R
EVTrophoblast
HLA-E
CCR1
Regulate EVT invasion
XCR1
NKG2C
uNK2
NKG2E
NKG2A
CCL5
uNK3
XCL1

KIR alleles 1,100

5.709 HLA-C alleles (December 2019)

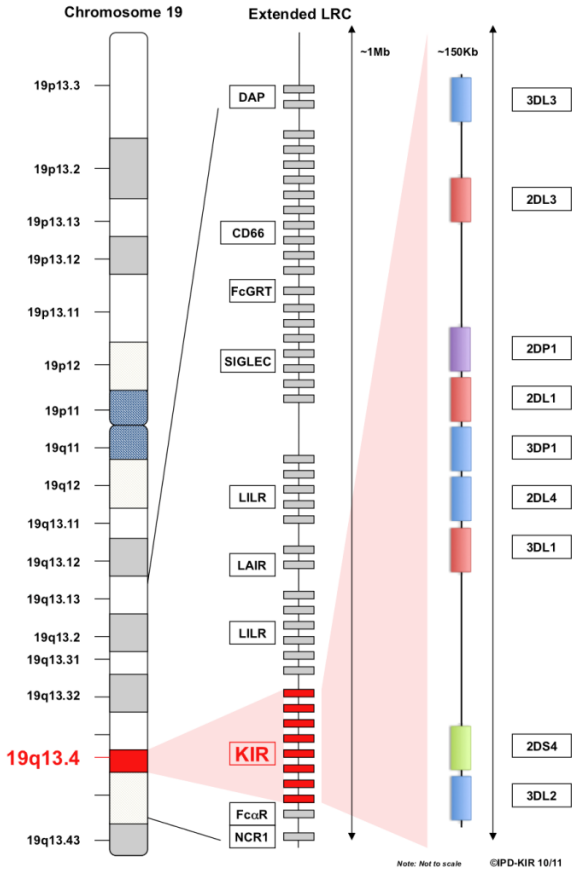


uNK **KIR**

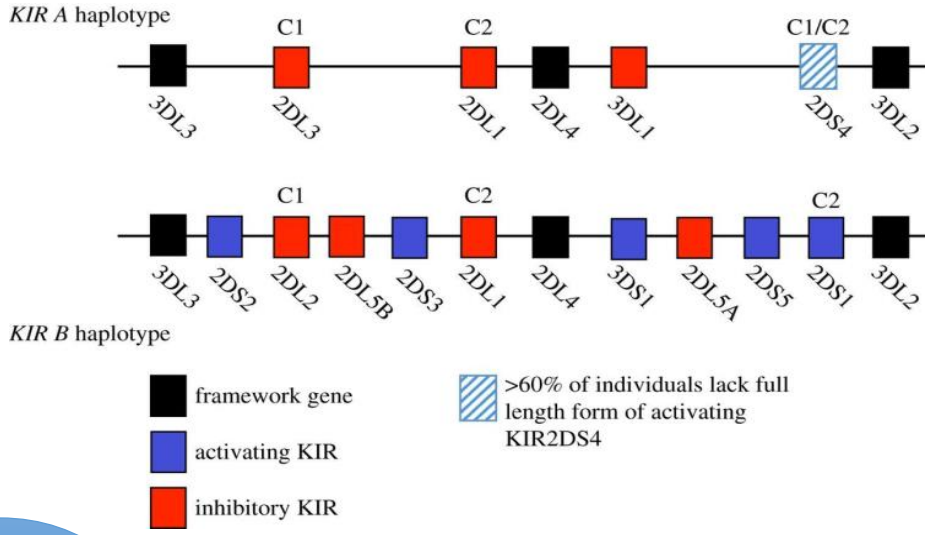
Trophoblast cell
HLA-C

KIR-HLA-C system: highly polymorphic

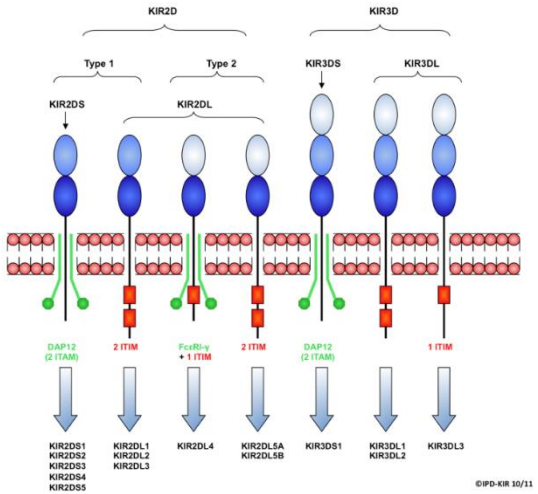
Activating signals (blue) in KIR group B



Position of KIR genes on chromosome 19



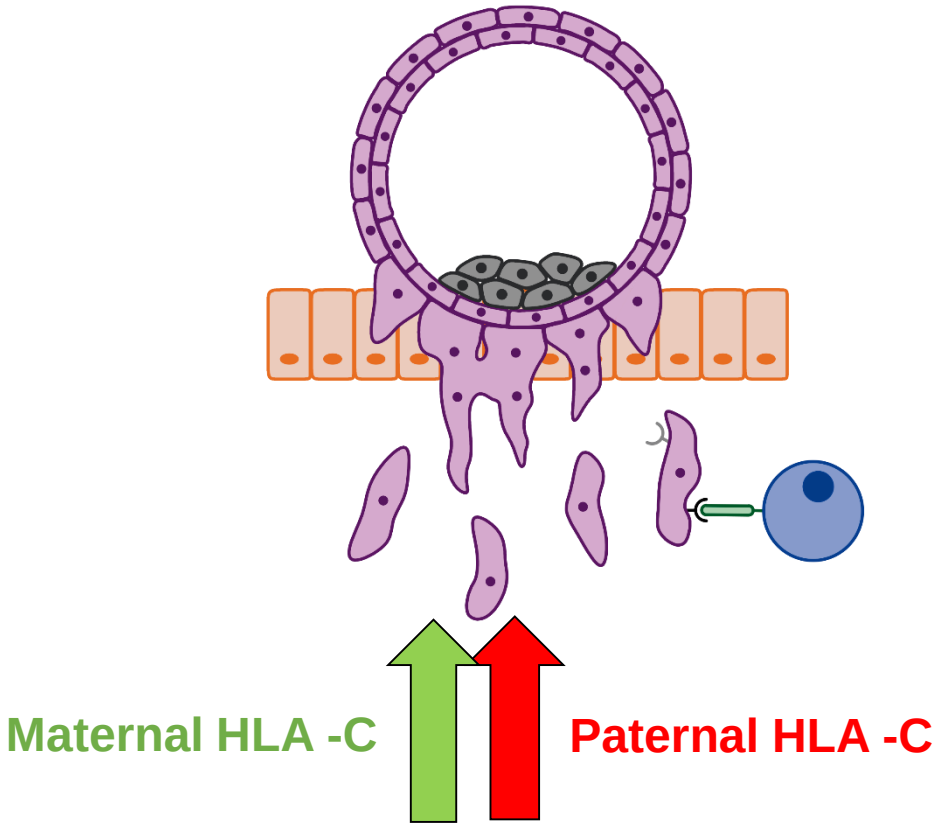
KIR AA
AB
BB



Activating KIR genes (green), inhibiting (red)

HLA-C

- C1C1
- C1C2
- C2C2

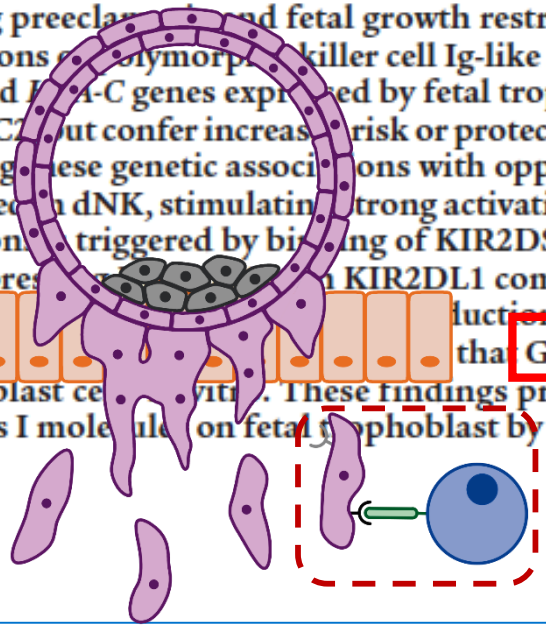


Maternal uterine NK cell–activating receptor KIR2DS1 enhances placentation

Shiqiu Xiong,[1] Andrew M. Sharkey,[1] Philippa R. Kennedy,[1] Lucy Gardner,[1] Lydia E. Farrell,[1] Olympe Chazara,[1] Julien Bauer,[1] Susan E. Hiby,[1] Francesco Colucci,[2] and Ashley Moffett[1]

[1]Department of Pathology and Centre for Trophoblast Research, and
[2]Department of Obstetrics and Gynaecology, University of Cambridge, Cambridge, United Kingdom.

Reduced trophoblast invasion and vascular conversion in decidua are thought to be the primary defect of common pregnancy disorders including preeclampsia and fetal growth restriction. Genetic studies suggest these conditions are linked to combinations of polymorphic killer cell Ig-like receptor (*KIR*) genes expressed by maternal decidual NK cells (dNK) and *HLA-C* genes expressed by fetal trophoblast. Inhibitory KIR2DL1 and activating KIR2DS1 both bind HLA-C2 but confer increased risk or protection from pregnancy disorders, respectively. The mechanisms underlying these genetic associations with opposing outcomes are unknown. We show that KIR2DS1 is highly expressed in dNK, stimulating strong activation of KIR2DS1$^+$ dNK. We used microarrays to identify additional responses triggered by binding of KIR2DS1 or KIR2DL1 to HLA-C2 and found different responses in dNK coexpressing KIR2DS1 and KIR2DL1 compared with dNK only expressing KIR2DL1. Activation of KIR2DS1 dNK induced production of soluble products including GM-CSF, detected by intracellular FACS and ELISA. We found that GM-CSF enhanced migration of primary trophoblast and JEG-3 trophoblast cell lines in vitro. These findings provide a molecular mechanism explaining how recognition of HLA class I molecules on fetal trophoblast by an activating KIR on maternal dNK may be beneficial for placentation.



JCI 2013

What is known already?

The *Tel-B* region of the *KIR B* haplotype protects against disorders of pregnancy, particularly when the fetus has a *C2* gene

Maternal *KIR B* regions present[A]	*KIR* genotype frequencies (%) in all controls and affected cases		Maternal *KIR* frequencies (%) in pregnancies with fetal *C2*		Maternal *KIR* frequencies (%) only in pregnancies with fetal *C1*	
	Controls ($n = 592$)	Affected ($n = 975$)	Controls ($n = 235$)	Affected ($n = 513$)	Controls ($n = 188$)	Affected ($n = 338$)
None (*KIR AA*)	27.5	36.9[C]	17.0	23.4[G]	11.8	13.0
Cen-B alone	27.4	30.1	14.2	17.7	12.5	12.1
Tel-B alone	19.3	14.6[D]	11.1	9.4	8.7	6.4
Cen-B plus *Tel-B*	25.8	18.5[E]	13.2	9.8	11.3	9.2
All with *Tel-B*[B]	45.1	33.0[F]	24.3	19.2[H]	20.0	15.6
Trend test	$P < 0.001$		$P = 0.002$		NS	

Hiby et al. J Clin Investigation. 2010

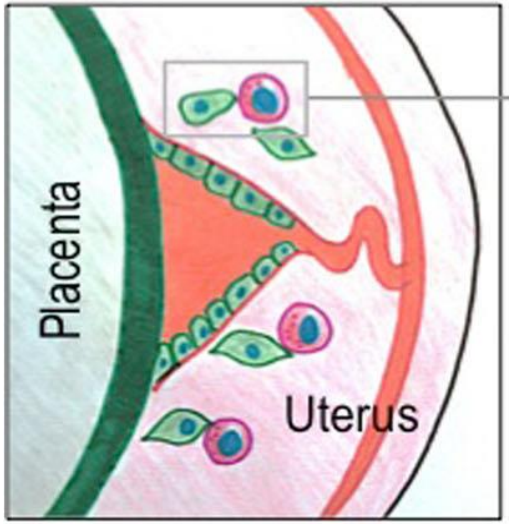
What is known already?

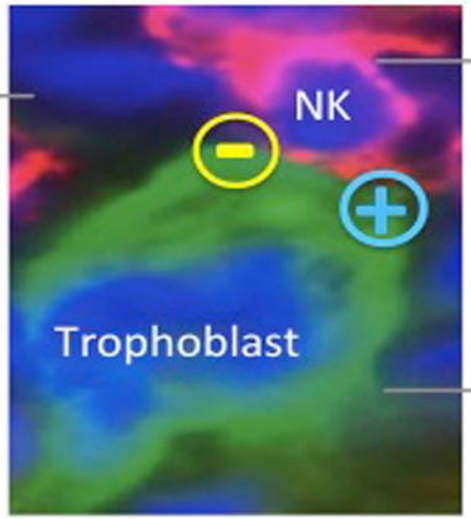
Maternal *KIR AA* frequency is increased in affected compared with control pregnancies when the fetus has more *C2* genes than the mother or when fetal *C2* is inherited paternally

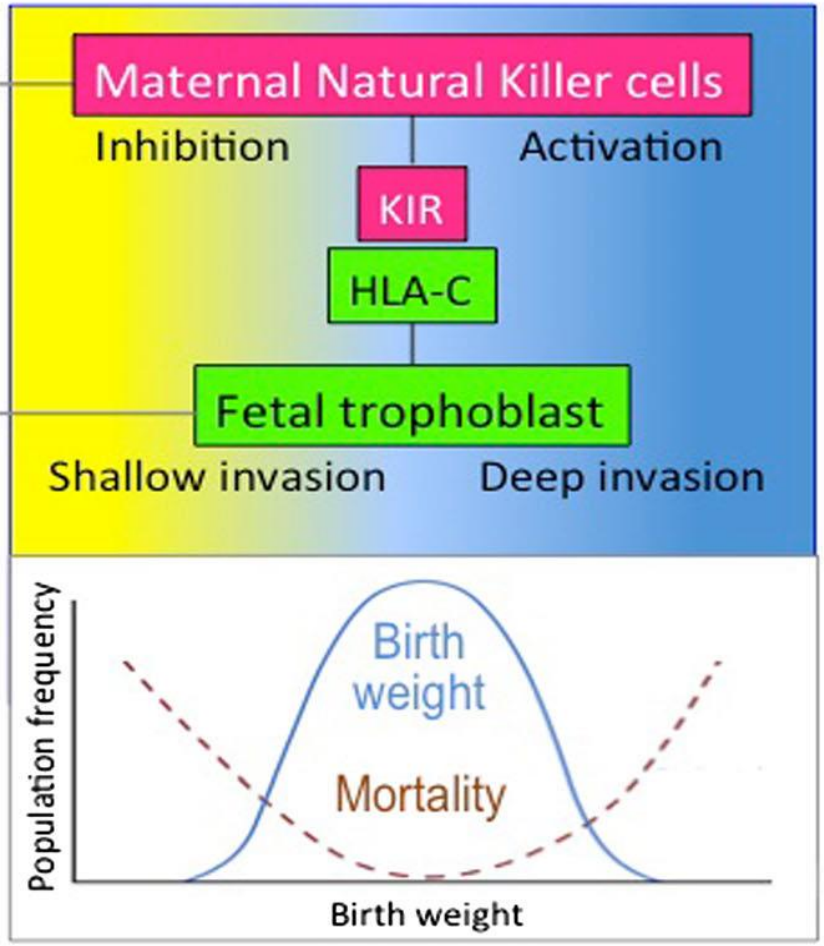
Parameter	OR[A]	*P*	*n* (affected/controls)
Effect of relative dose of maternal and fetal *C2* genes[B]			
Fetus had fewer *C2* genes than the mother	0.97	1.00	177/85
Fetus had the same number of *C2* genes	1.43	0.06	364/233
Fetus had more *C2* genes than the mother	2.09 (1.24–3.51)	0.007	188/105
Effect of origin of fetal *C2* genes[C]			
Paternal origin	2.02 (1.14–3.58)	0.022	135/90
Maternal origin	1.11	0.90	91/61

Hiby et al. J Clin Investigation. 2010

Maternal-Fetal Interface





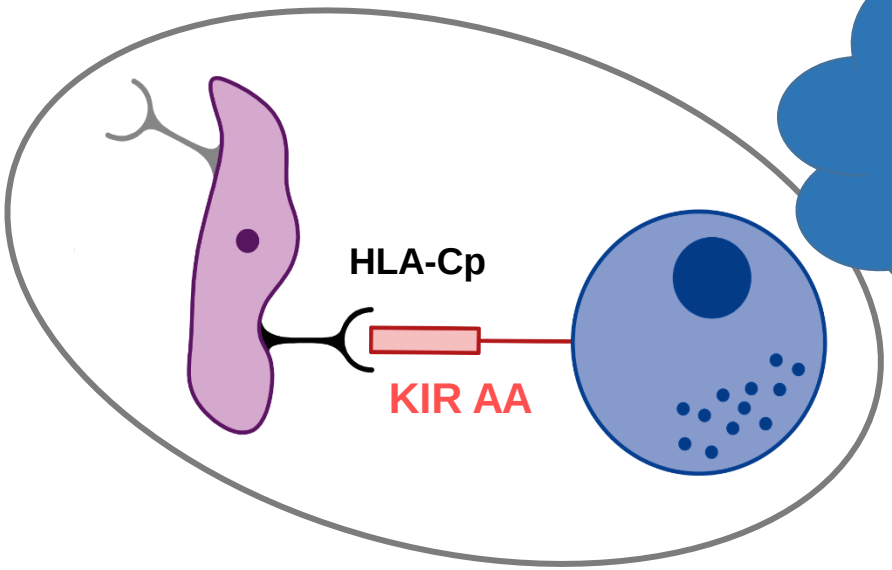


Francesco Colucci. Inmunogenetics.2017

Mortality of mother and child (brown curve) occurs at the two extremes of birth weight (blue curve). Adapted from Hiby et al (2014), J Immunol, *192*, 5069-5073.

What is known already?

PATERNAL HLA-C2



MATERNAL KIR AA

Recurrent Miscarriage
Preeclampsia
Fetal Growth Restriction
Low Birth Weight

Hiby et al 2004, 2008, 2010, 2014. Faridi et al 2011, Moffett A. et al 2017, Alecsandru et al 2014, 2017

IVIRMA Global

What is known already?

Combinations of Maternal KIR and Fetal HLA-C Genes Influence the Risk of Preeclampsia and Reproductive Success

Susan E. Hiby,[1] James J. Walker,[2] Kevin M. O'Shaughnessy,[3] Christopher W.G. Redman,[4] Mary Carrington,[5] John Trowsdale,[1] and Ashley Moffett[1]

J Exp Med 2004

Research article

Maternal uterine NK cell–activating receptor KIR2DS1 enhances placentation

Shiqiu Xiong,[1] Andrew M. Sharkey,[1] Philippa R. Kennedy,[1] Lucy Gardner,[1] Lydia E. Farrell,[1] Olympe Chazara,[1] Julien Bauer,[1] Susan E. Hiby,[1] Francesco Colucci,[2] and Ashley Moffett[1]

JCI 2013

Human Reproduction Vol.23, No.4 pp. 972–976, 2008
Advance Access publication on February 8, 2008
doi:10.1093/humrep/

Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage

S.E. Hiby[1], L. Regan[2], W. Lo[2], L. Farrell[1], M. Carrington[3] and A. Moffett[1,4]

Research article Related Commentary, page 3801

JCI 2010

Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2

N=742

Susan E. Hiby,[1,2] Richard Apps,[1,2,3,4] Andrew M. Sharkey,[1,2] Lydia E. Farrell,[1,2] Lucy Gardner,[1,2] Arend Mulder,[5] Frans H. Claas,[5] James J. Walker,[6,7] Christopher C. Redman,[7,8] Linda Morgan,[7,9] Clare Tower,[10] Lesley Regan,[11] Gudrun E. Moore,[12] Mary Carrington,[3,4] and Ashley Moffett[1,2]

[1]Department of Pathology, University of Cambridge, Cambridge, United Kingdom. [2]Centre for Trophoblast Research, Cambridge, United Kingdom.

Maternal *KIR* in Combination with Paternal *HLA-C2* Regulate Human Birth Weight

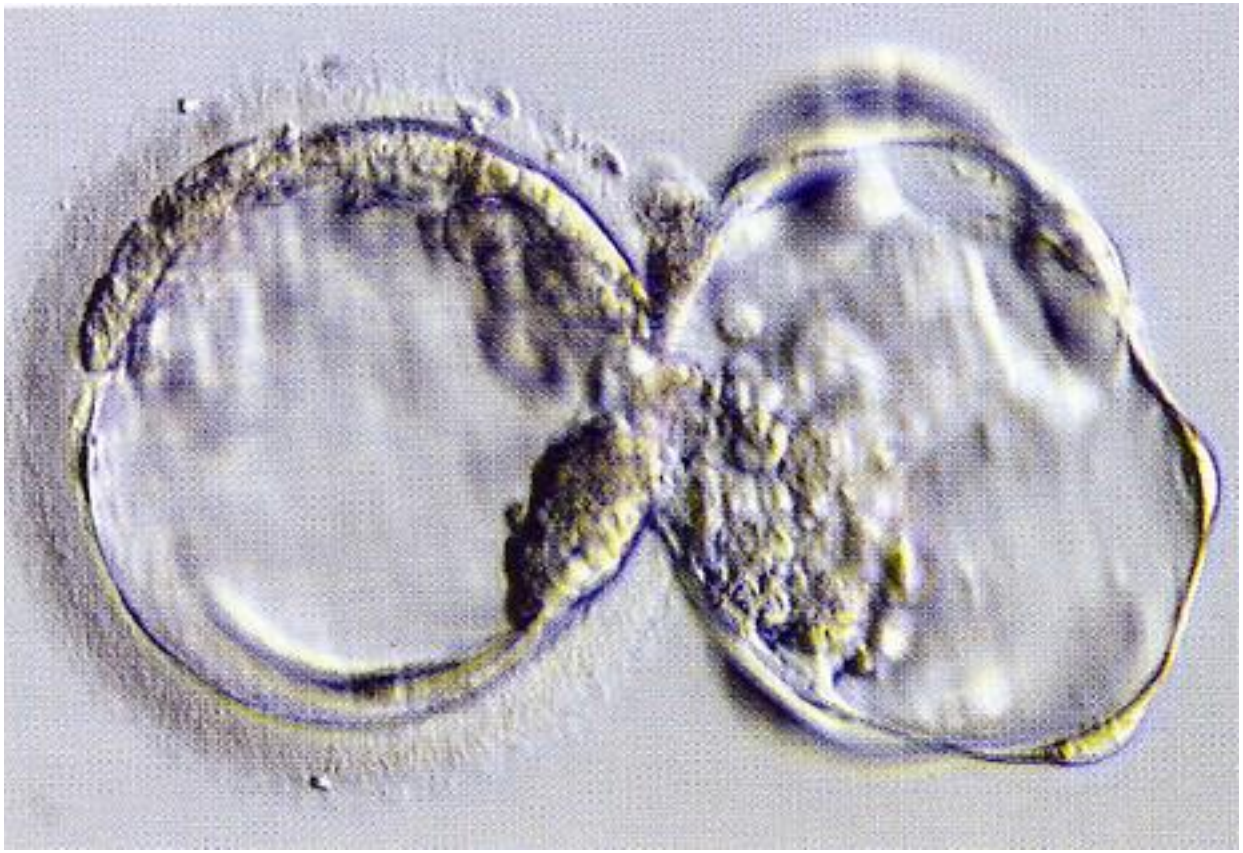
Susan E. Hiby, Richard Apps, Olympe Chazara, Lydia E. Farrell, Per Magnus, Lill Trogstad, Håkon K. Gjessing, Mary Carrington and Ashley Moffett

N=1316

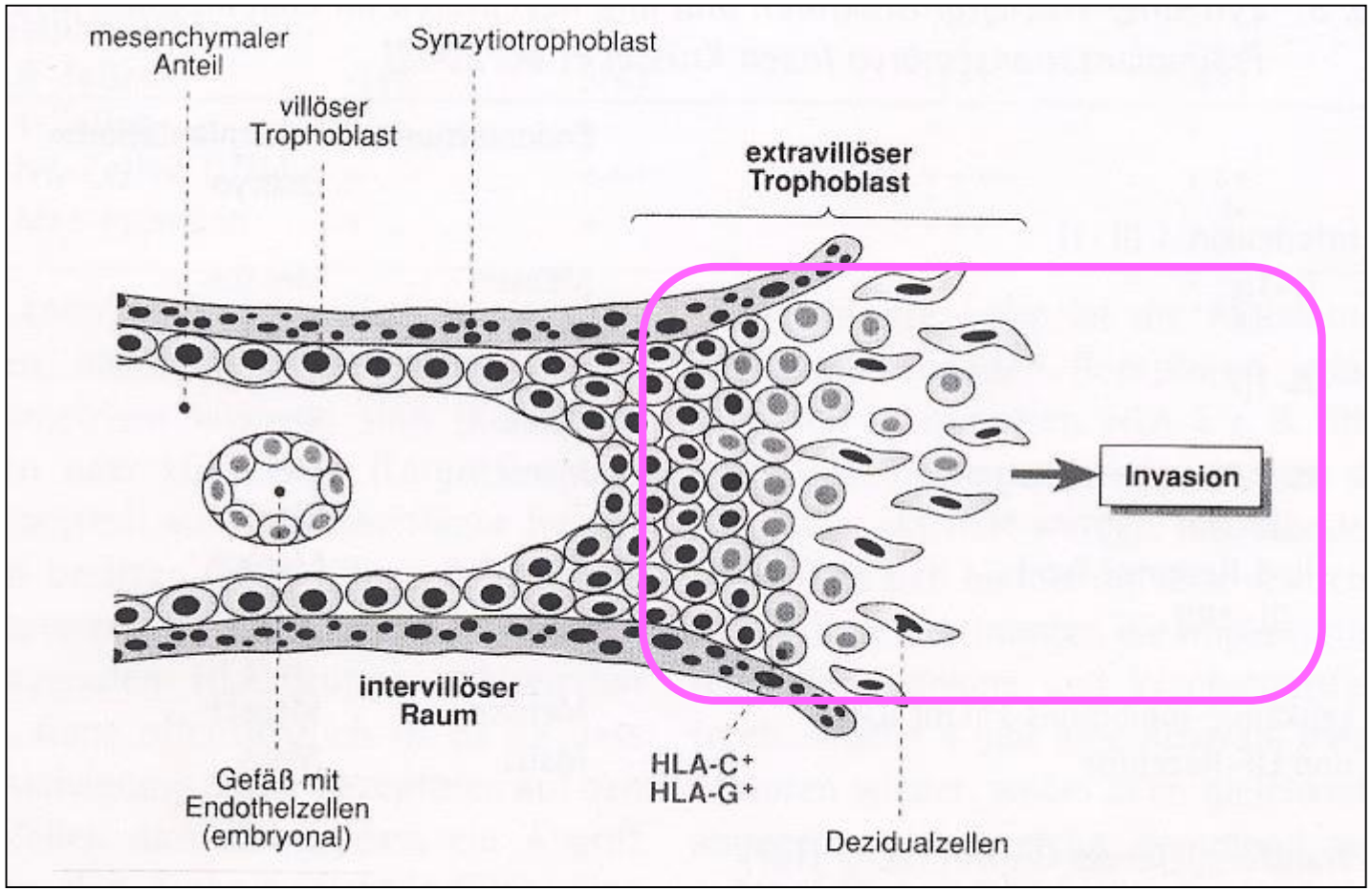
Innovation

IVI Foundation

What about ART?

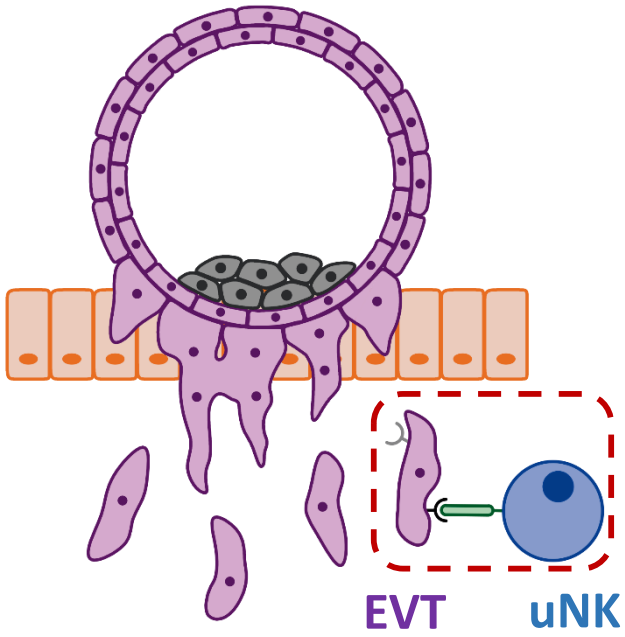


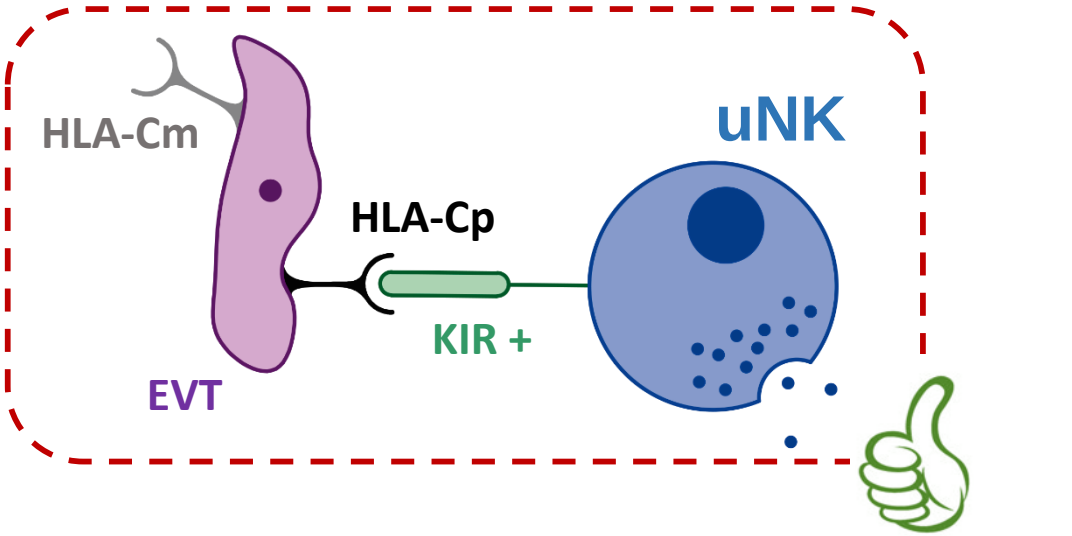
Embryo invasion



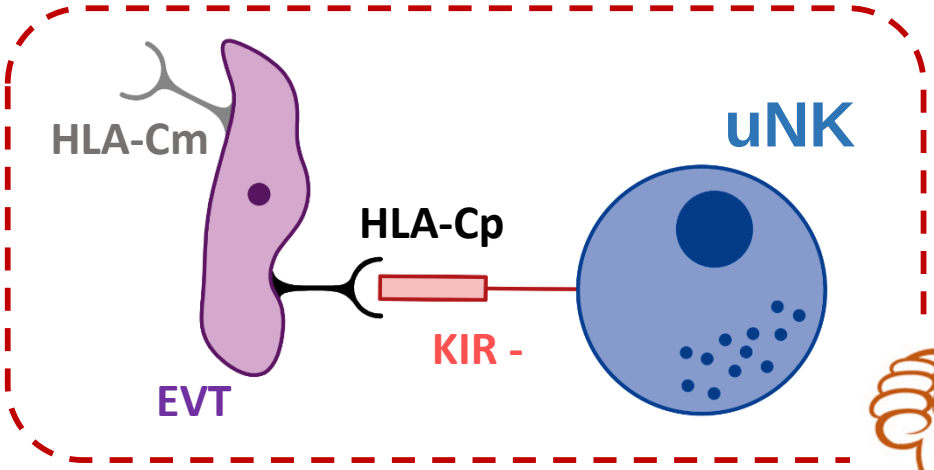
ART-Own Oocytes

Embryo implantation





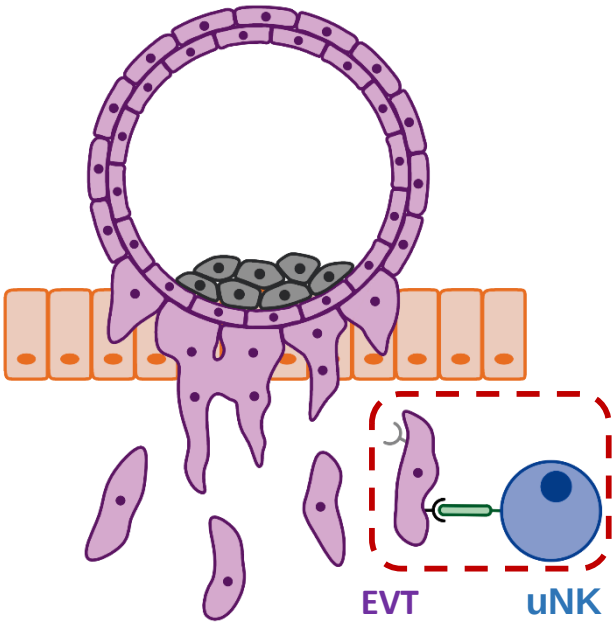
Correct placentation

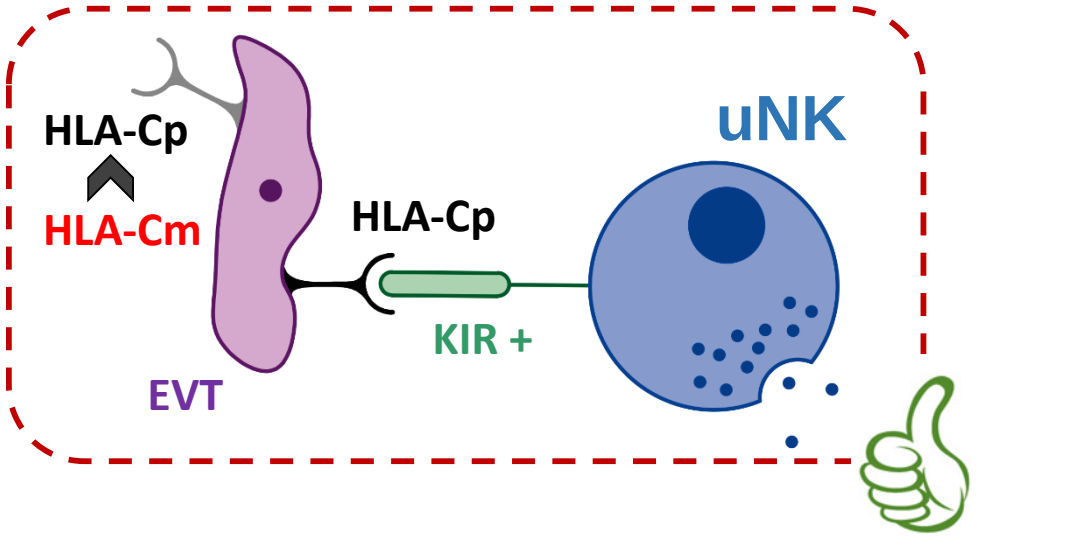


Compromised placentation

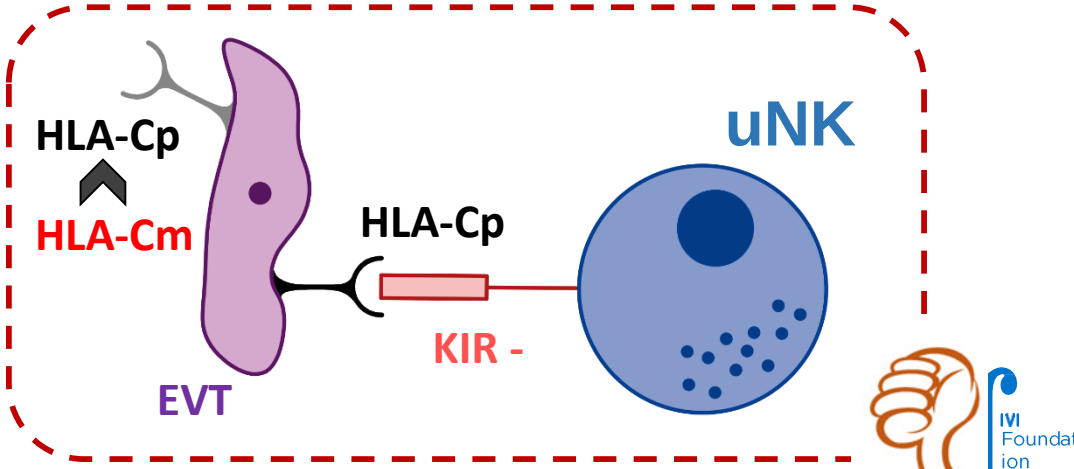
ART-Oocytes DONATION

Embryo implantation





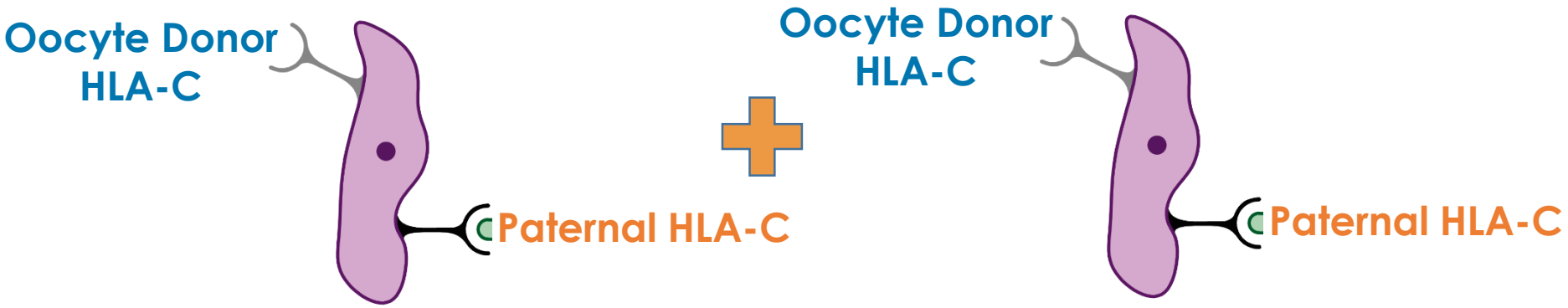
Correct placentation



Compromised placentation

DET

>64% risk of exposure to foreign HLA-C2



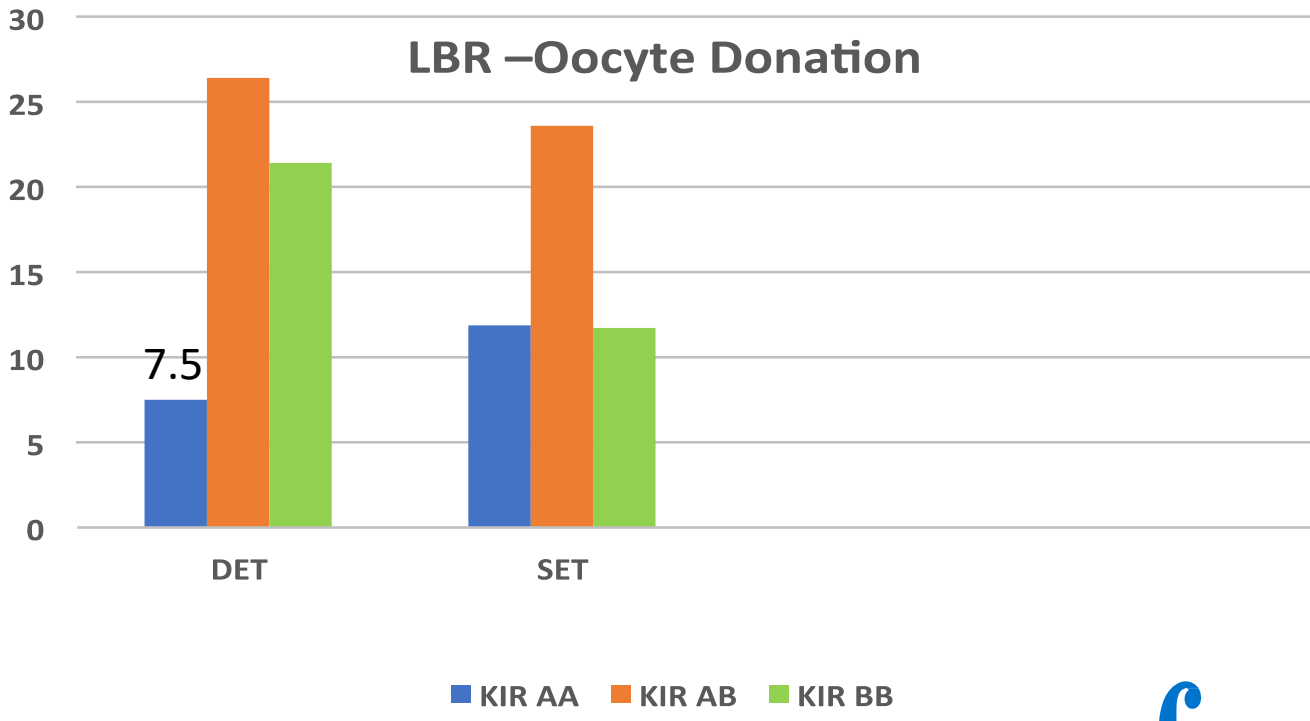
A. Moffett et all. RMBO 2016. D. Alecsandru and J.A. Garcia Velasco. Fertil Steril 2017

human reproduction ORIGINAL ARTICLE *Early pregnancy*

Maternal KIR haplotype influences live birth rate after double embryo transfer in IVF cycles in patients with recurrent miscarriages and implantation failure

D. Alecsandru[1,*], N. Garrido[2], J.L. Vicario[3], A. Barrio[1], P. Aparicio[1], A. Requena[1], and J.A. García-Velasco[1]

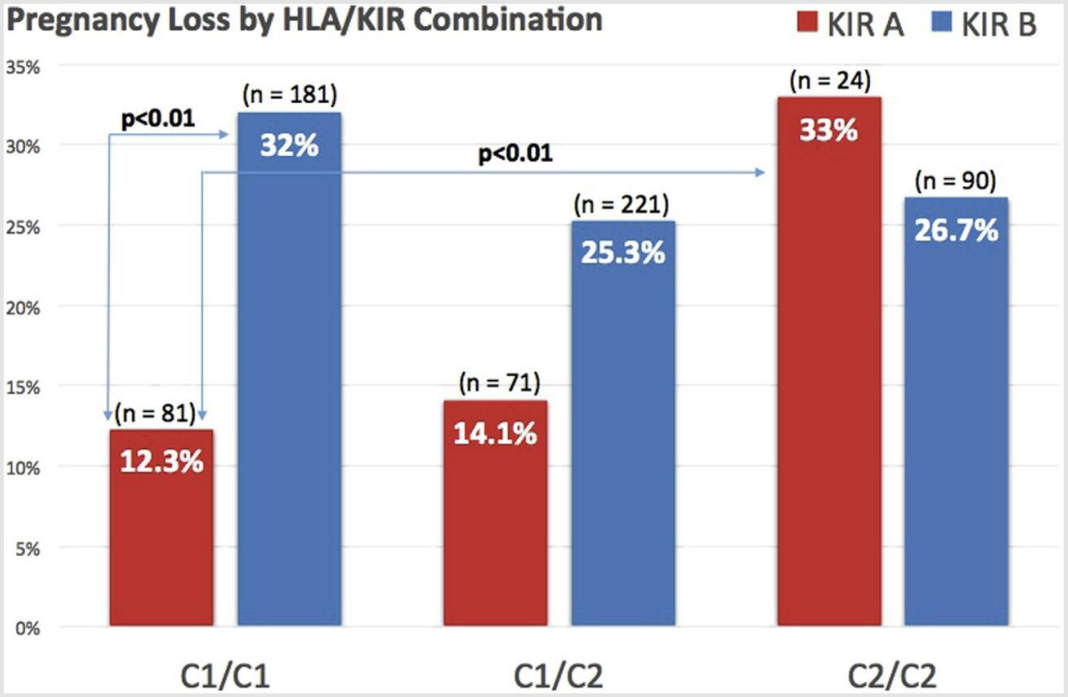
291 RM patients
1.304 cycles



Alecsandru et al. Hum Reprod. Dic. 2014.

Pregnancy loss by maternal KIR - Fetal HLA C Euploid Embryo Transfers

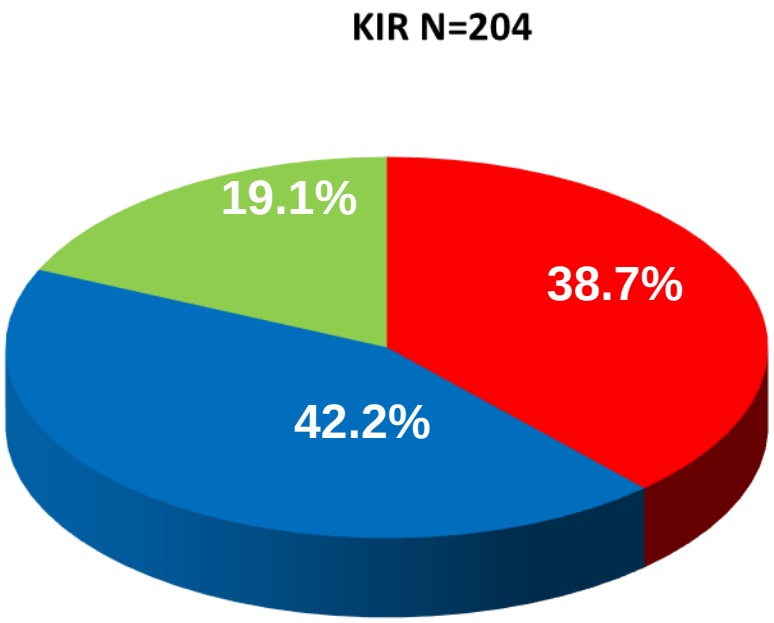
FIGURE 3



Pregnancy loss according to HLA-KIR combination. Among KIR A haplotype carriers, the risk of pregnancy loss was significantly higher if the embryo transferred was C2/C2 (*P*<.01). Among C1/C1 embryos, the chance or pregnancy loss was significantly higher if the recipient was a KIR B haplotype carrier (*P*<.01). KIR = uterine natural killer cell immunoglobulin receptor.

Morin. KIR haplotype, HLA ligands, and loss risk. Fertil Steril 2016.

An Excessive Immune Inhibition and not "Rejection" May Explains Embryo Implantation Failure in ART



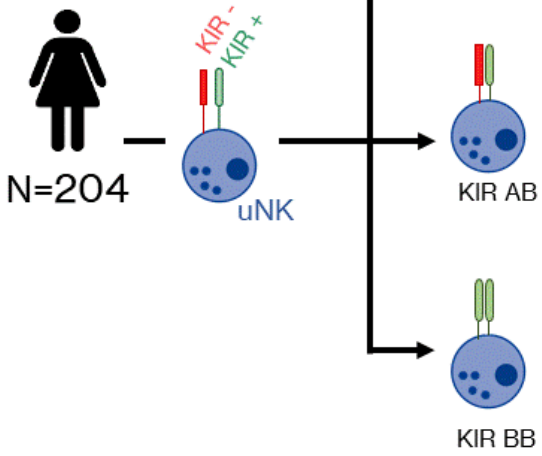
Higher %

KIR AA Spain:

- Basque 16.9%
- Cantabria 31.3%
- Granada 26%

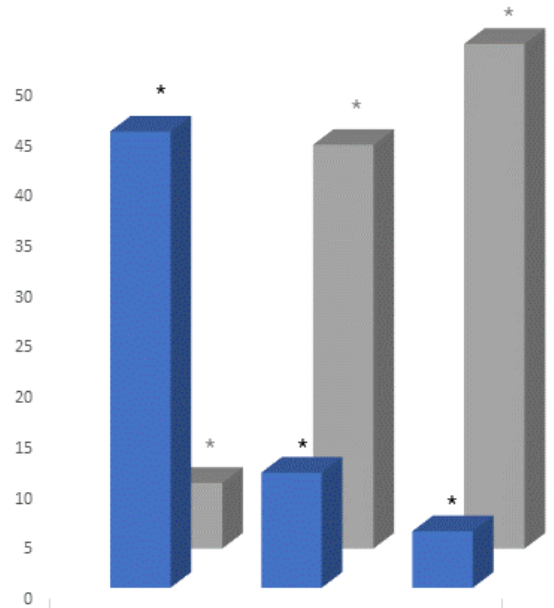
Alecsandru et al. Fertil Steril 2020

Observational Study - 2020



	Miscarriage rate (%)	Live birth rate (%)
KIR AA	26.6	34.2
KIR AB	11.6	47.7
KIR BB	7.7	56.4

Miscarriage and LBR (%) in DET by KIR haplotype

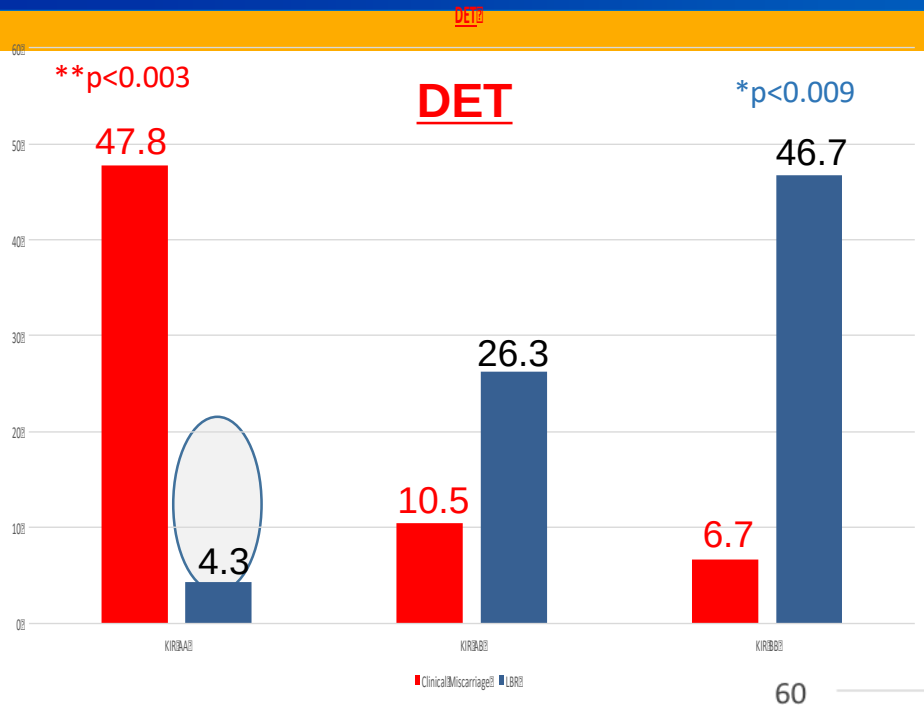


* $p < 0.001$

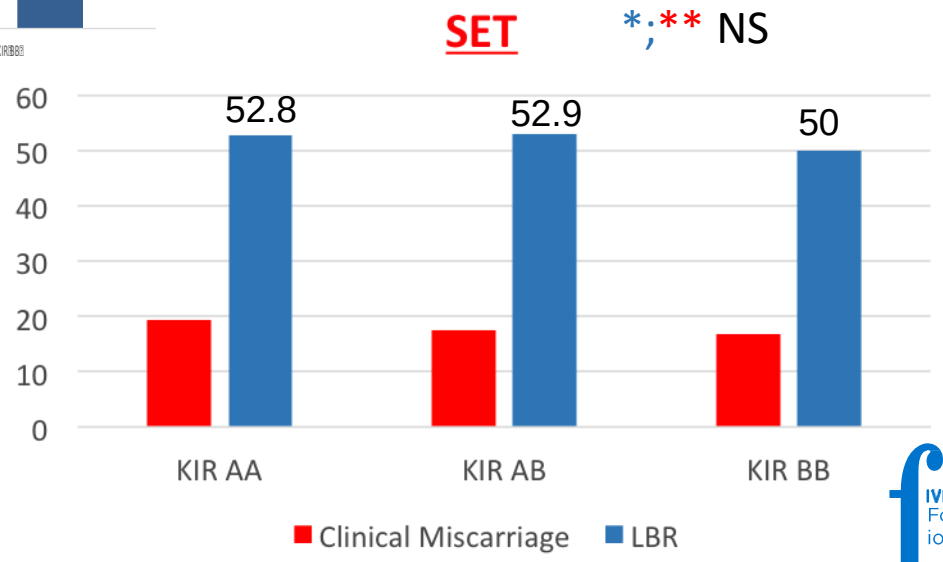
$N_{DET} = 84$

Alecsandru et al. Fertil Steril 2020

An Excessive Immune Inhibition and not "Rejection" May Explains Embryo Implantation Failure in ART



EGG DONOR EMBRYO TRANSFERS

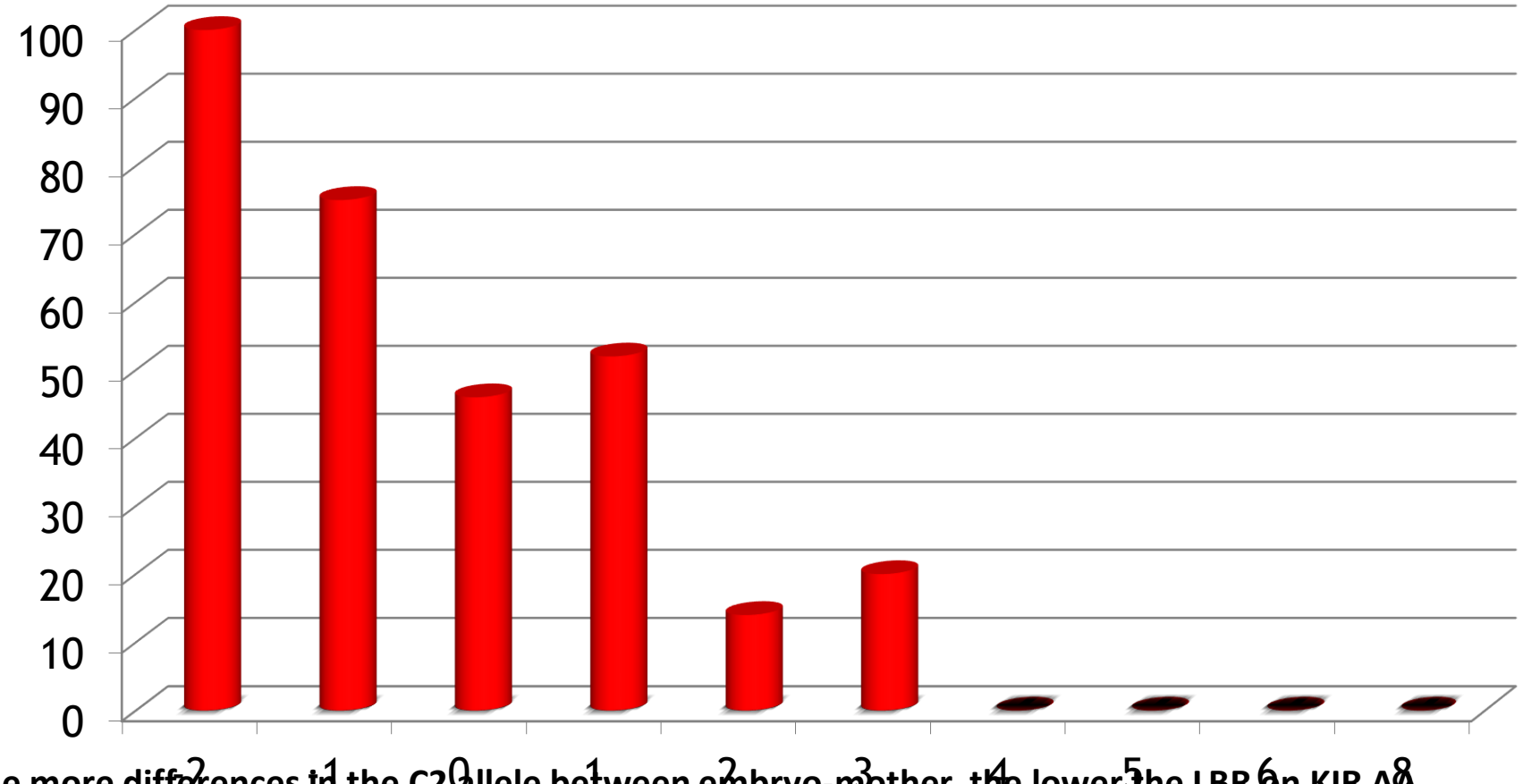


Alecsandru et al. Fertil Steril 2020

IVIRMA Madrid Global

Non-self HLA-C2 load is associated with LBR

LBR by Embryo HLA-C2 on KIR AA



The more differences in the C2 allele between embryo-mother, the lower the LBR on KIR AA

Chi-square p=0.02; Linear-by-Linear Asociation p=0.00

NS on KIR AB, BB

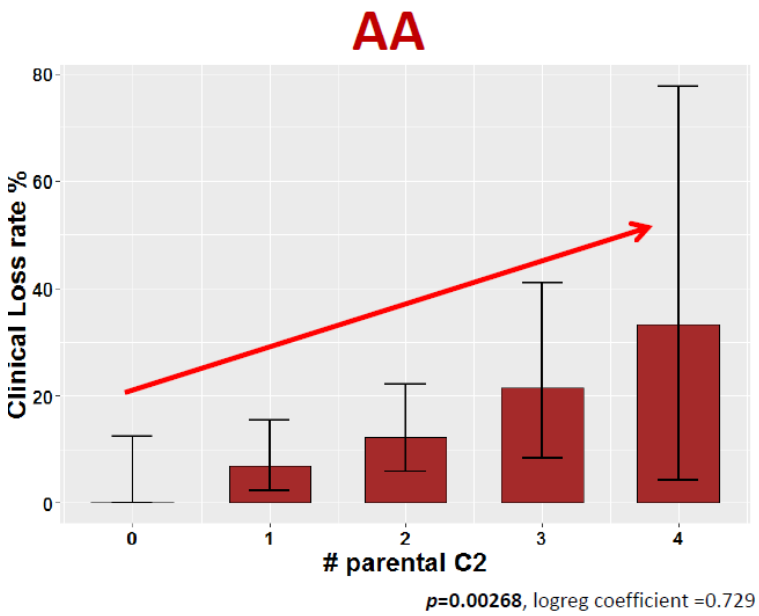
Innovation

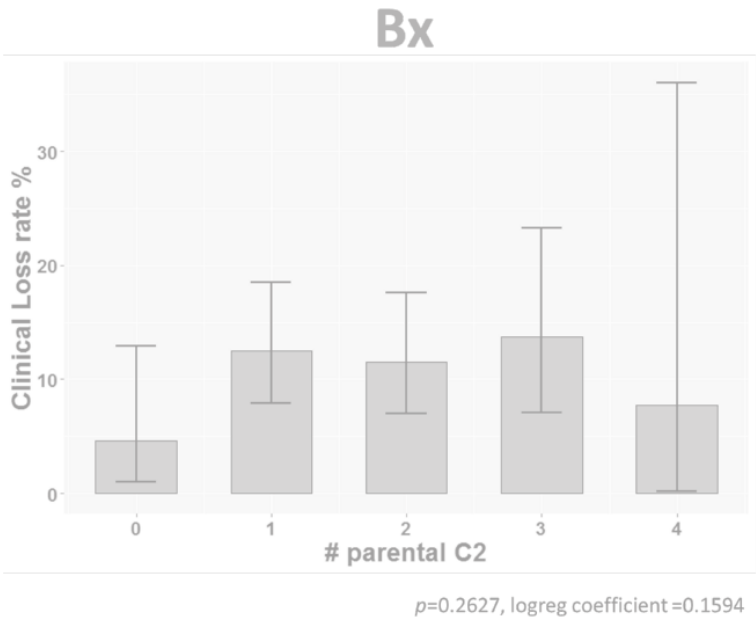
IVI Foundation

Alecsandru et al. Fertil Steril 2020

Parental HLA-C2 load is associated with clinical loss in KIR AA

N= 790 Euploid Embryo Transfers SET

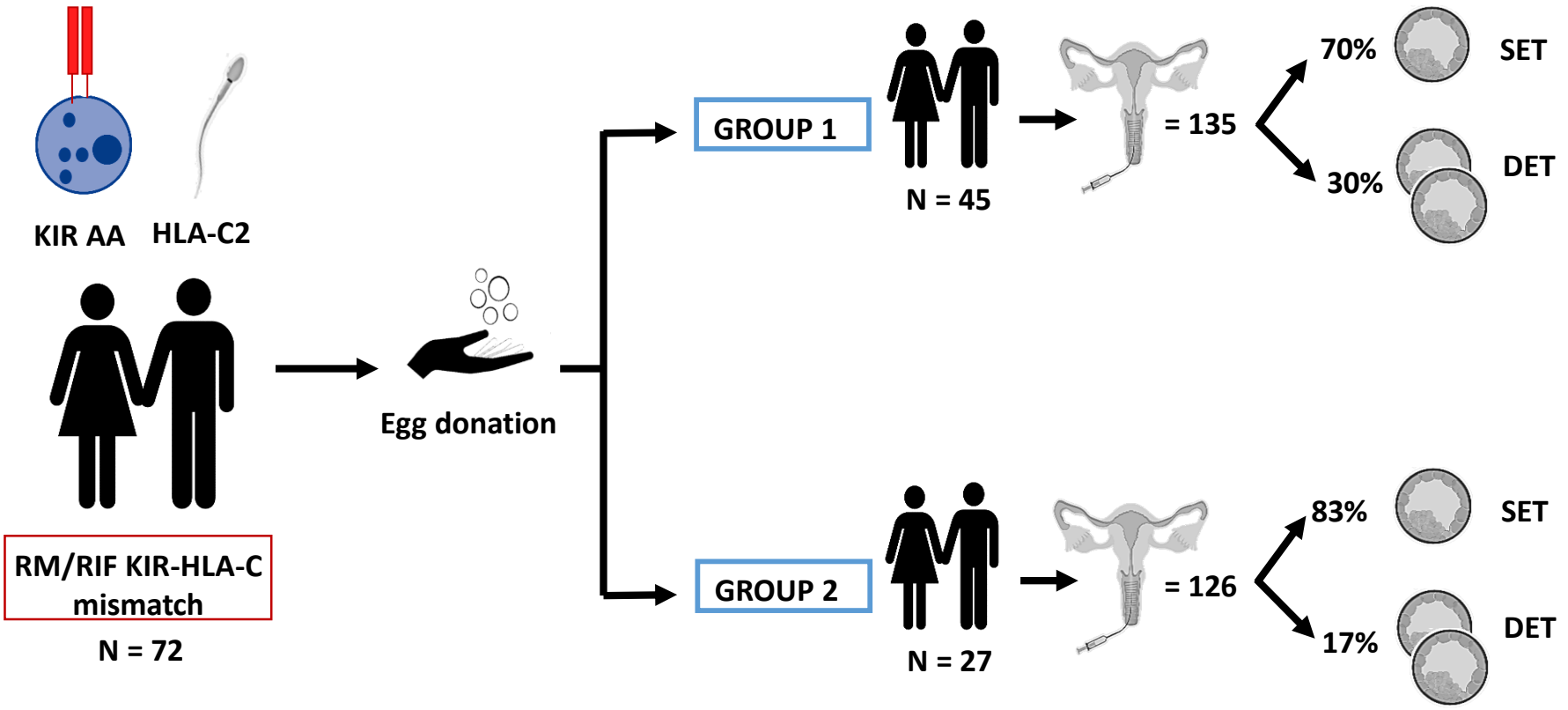




D. Marin et al. ASRM 2019

What can we do for these couples?

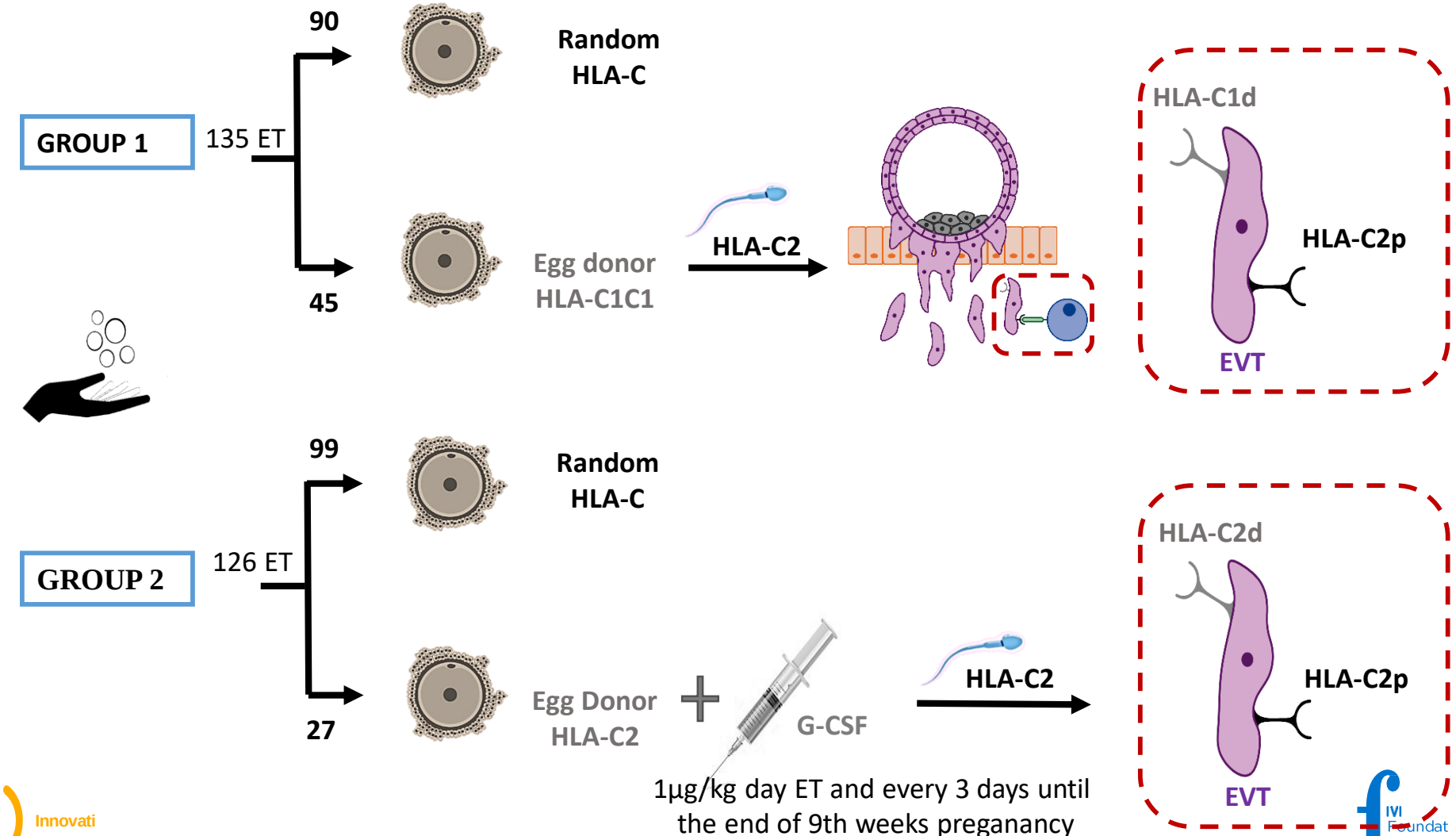
Study Design



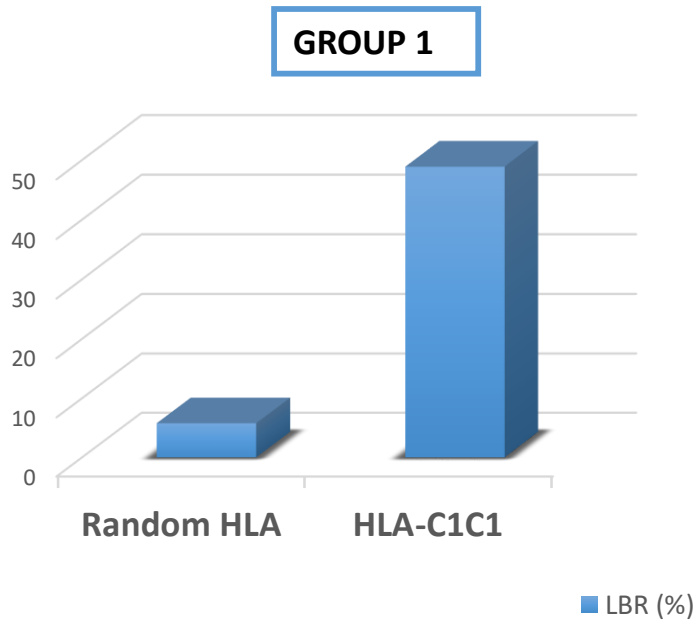
Retrospective study: January 2017 and December 2018

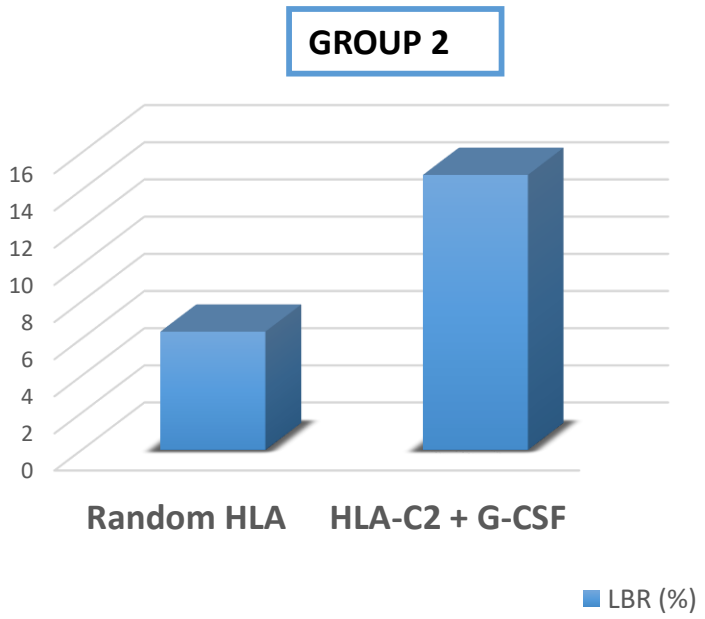
Alecsandru et al. Oral Com ESHRE 2019

Participants, setting, methods



Alecsandru et al. Oral Com ESHRE 2019





GROUP 1	LBR (%)
Random HLA-C	5.7
HLA-C1C1	48.9

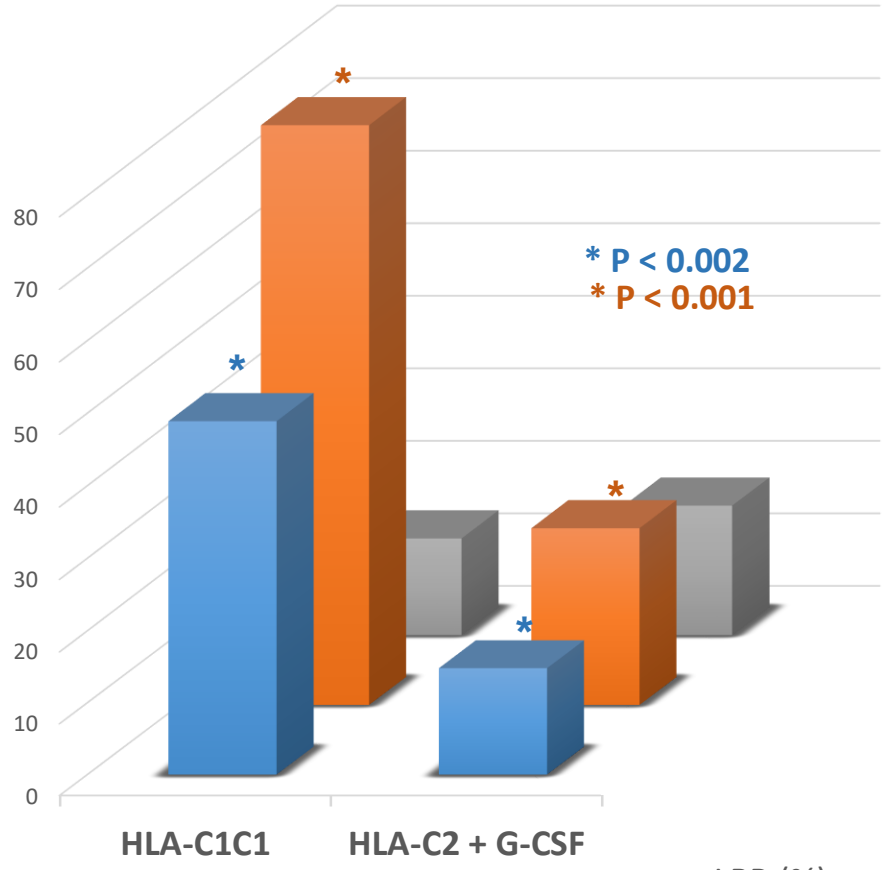
GROUP 2	LBR (%)
Random HLA-C	6.3
HLA-C2 + G-CSF	14.8

Alecsandru et al. Oral Com ESHRE 2019

GROUP 1 vs GROUP 2

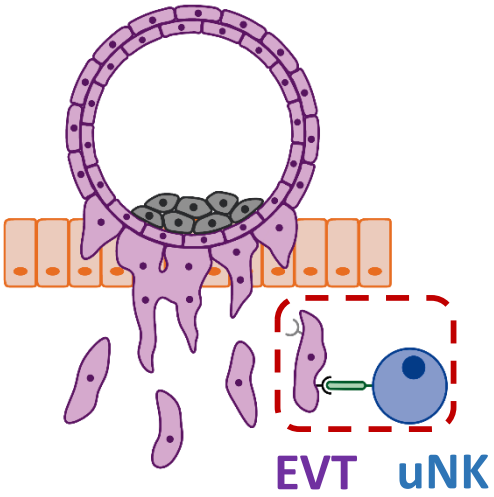
OD 6.82

GROUP 1 vs 2	LBR (%)	PREG (%)	MS (%)
HLA-C1C1	48.9	80	13.3
HLA-C2 + G-CSF	14.8	24.4	17.8



Take Home Messages

Embryo implantation



1 The Maternal Immune System **MATTERS**

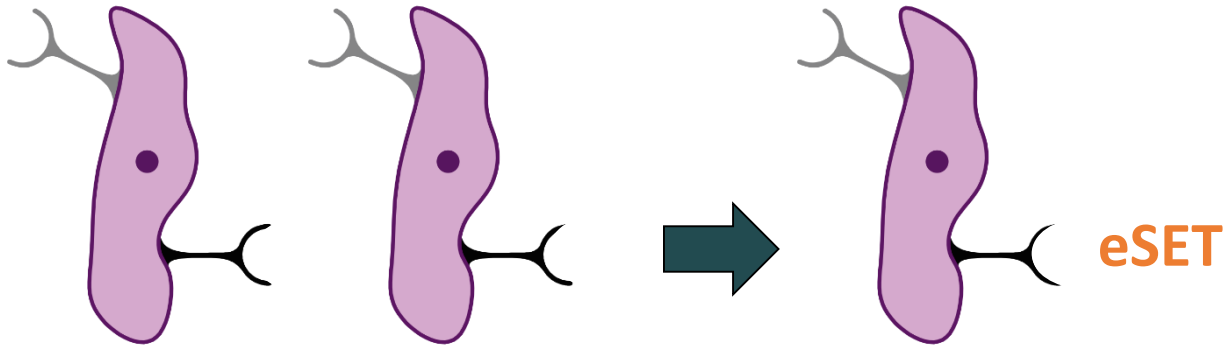
2 DETs **decrease** the LBR in KIRAA patients (30-40% women)

3 **HIGHER** embryo HLA-C2 means **LOWER** LBR in KIRAA

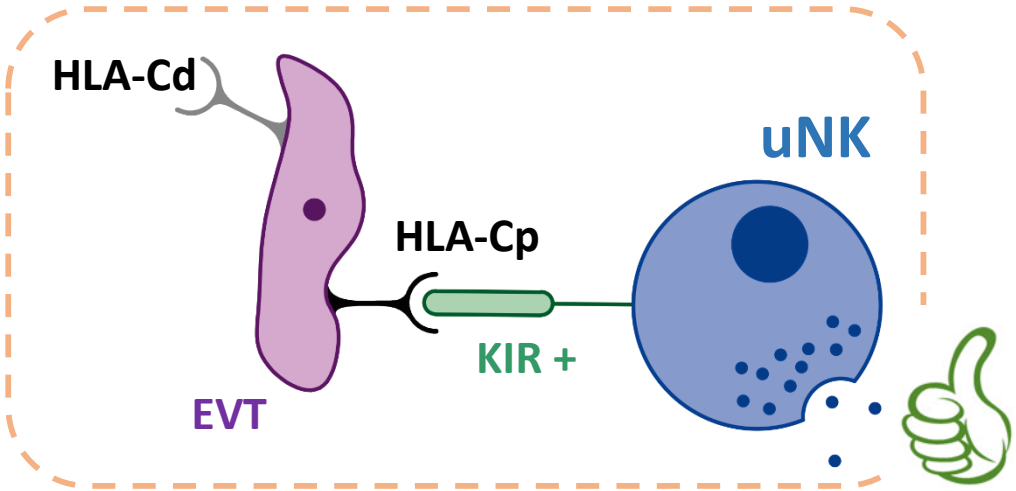
4 This is more evident in **EGG DONATION**

Take Home Messages

1.



2.



KIR-HLA-C Matching

Correct placentation

RCT

SET

- KIR-HLA-C MATCHED EGG DONOR
- RANDOM HLA-C EGG DONORS

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Global

Thank you

- Medical Staff of IVI RMA CLINICS
- Immunology Unit Nurses IVI RMA Madrid
- Andrology Department IVI RMA Madrid