-Omics of Endometrial Receptivity

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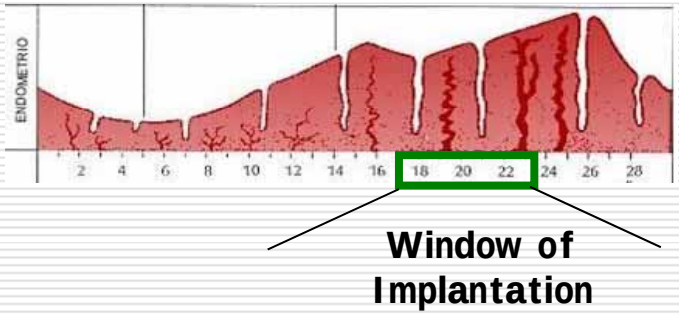
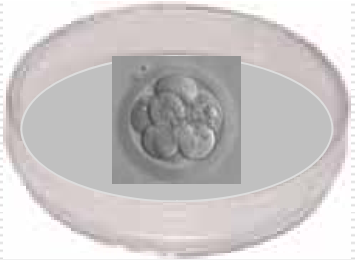
Key Factors Determining Clinical Outcomes

Identification/Modification of receptive endometrium



Embryo Viability Identification

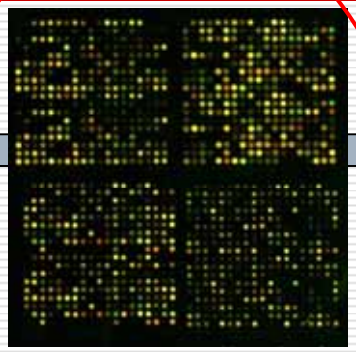


✓ 15% of cycles end in implantation failure of endometrial origin.

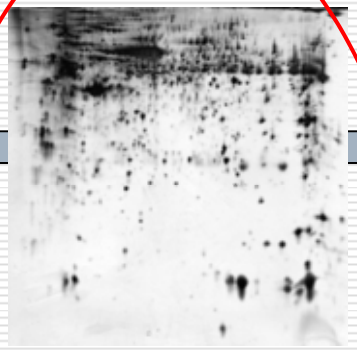
✓ 60%-90% of transferred embryos do not implant or die.

"We cannot improve our future outcomes using the same concepts and techniques employed in the past"

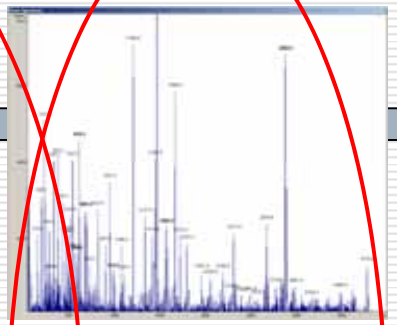
The age of -OMICS



Transcriptome



Proteome



Metabolome

TRANSCRIPTION

TRANSDUCTION

DNA → RNA → mRNA → Protein → METABOLITES

Transcription regulation

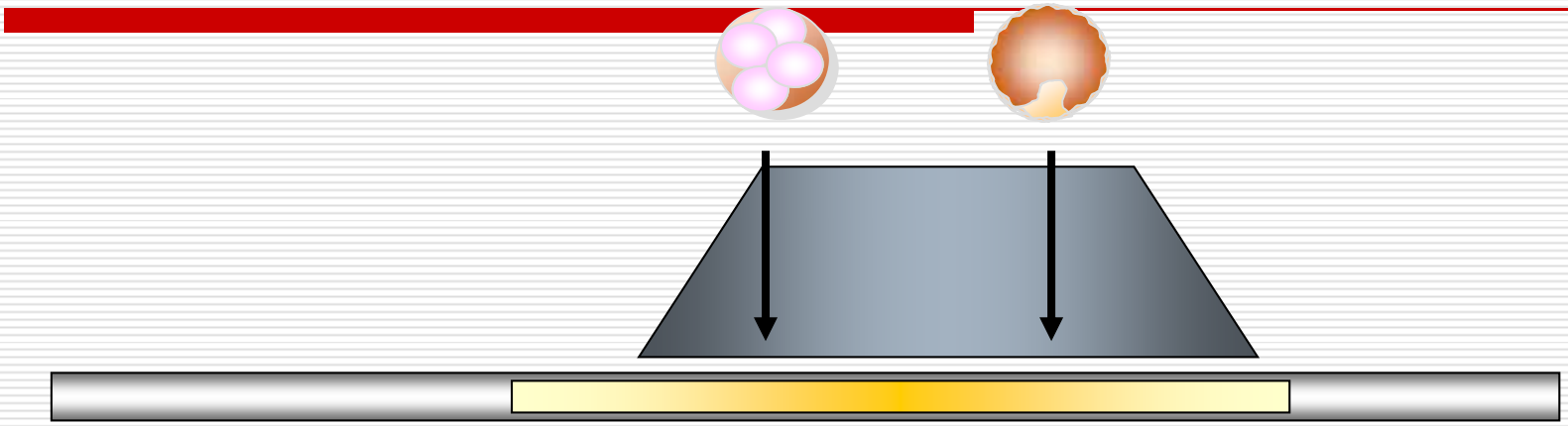
Alternative splicing

Transduction regulation

Outline

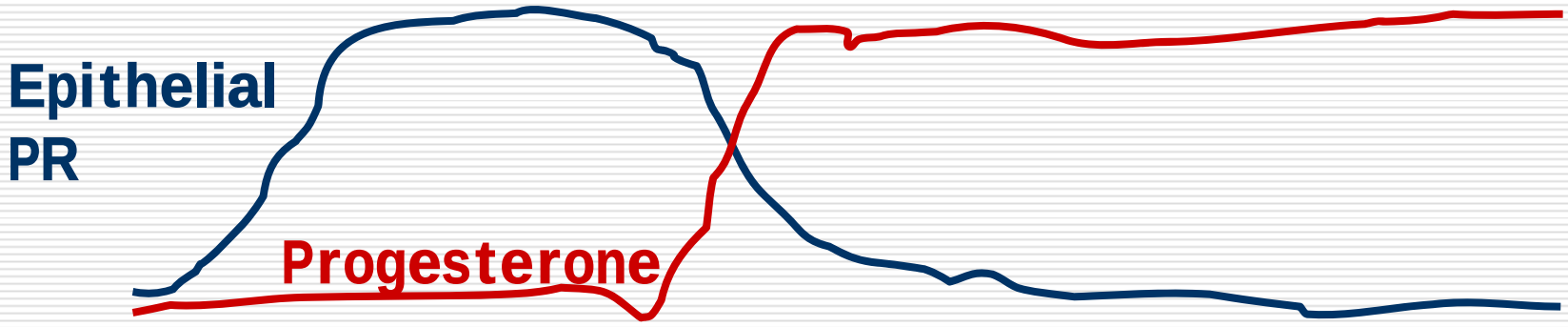
- Description of endometrial receptivity
- Epigenomics
- Genomics in natural and COS cycles.
- Proteomics of Endometrial Receptivity
- Secretomics of Endometrial Receptivity
- Translational markers of endometrial receptivity

Human endometrial receptivity



E_2 14 15 16 17 18 19 20

P P_{+1} P_{+2} P_{+3} P_{+4} P_{+5} P_{+6} P_{+7}



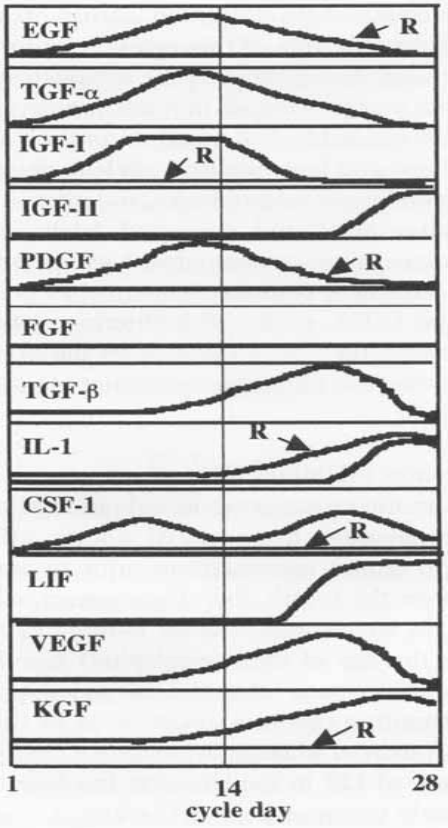
Dating the endometrial biopsy[1]

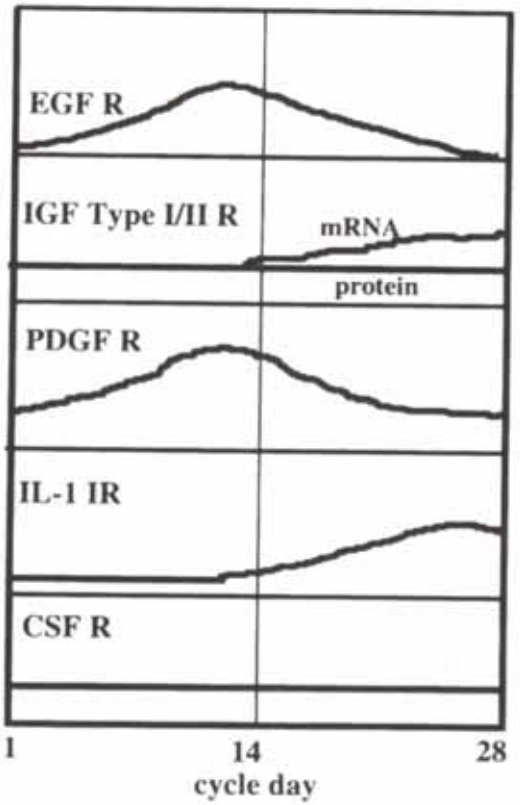
- **Randomized studies**
  - **Interobserver and cycle-to-cycle (60%) variations[2]**
  - **Endometrial dating is not related to fertility status[3]**

Histological dating is not a valid method for the diagnosis of luteal phase deficiency neither guidance throughout clinical management in infertility

1. Noyes, et al. Fertil Steril 1950
2. Murray, et al. Fertil Steril 2004
3. Coutifaris, et al. Fertil Steril 2004

Single-molecule approach does not work

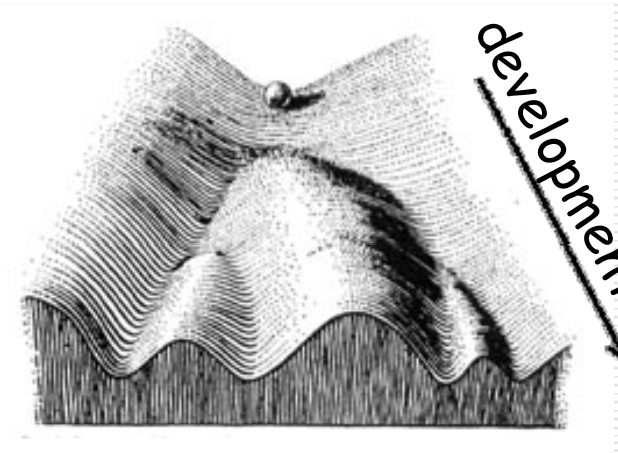




Giudice, et al. Trends Endocrinol Metab 1995

Epigenetics " *…the branch of biology wich studies the casual interactions between genes and their products wich bring the phenotype into being*"

Conrad Waddington, 1940

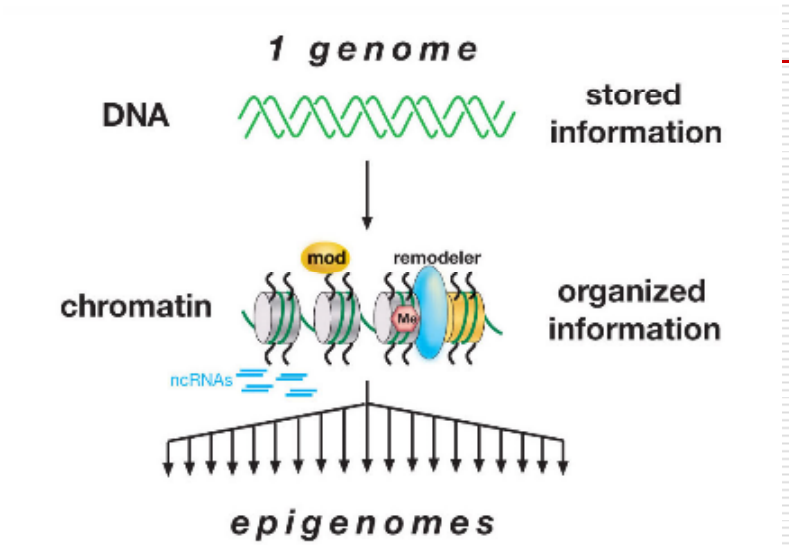


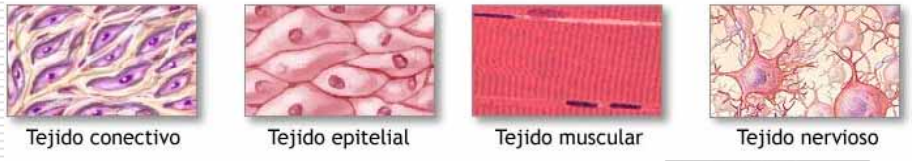
Epigenetic landscape

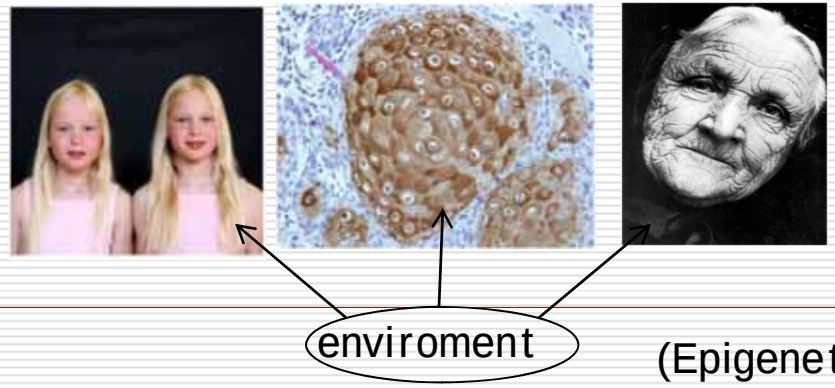
Epigenetics "*…the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence*"

Riggs et al, 1996

The same genetic information leads to different phenotypes

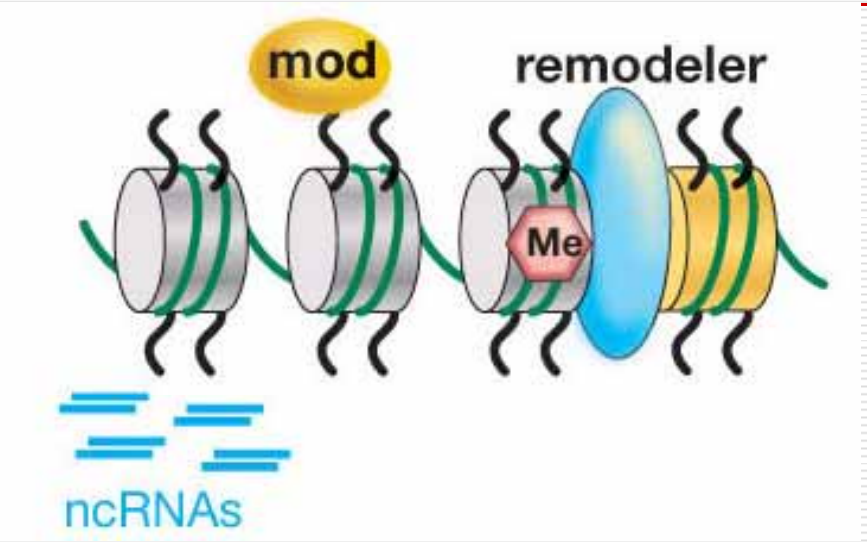






(Epigenetics,David Allis et al, 2004)

Epigenetic mechanisms that control gene expresion

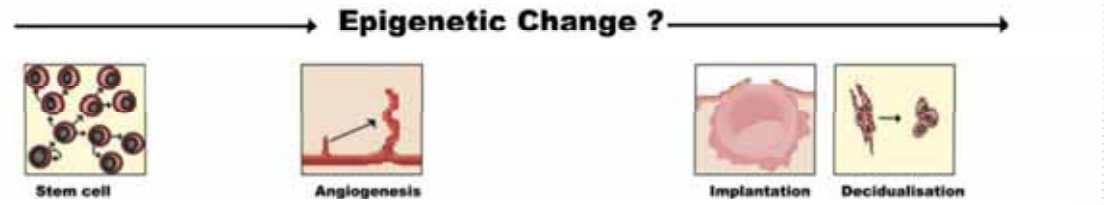


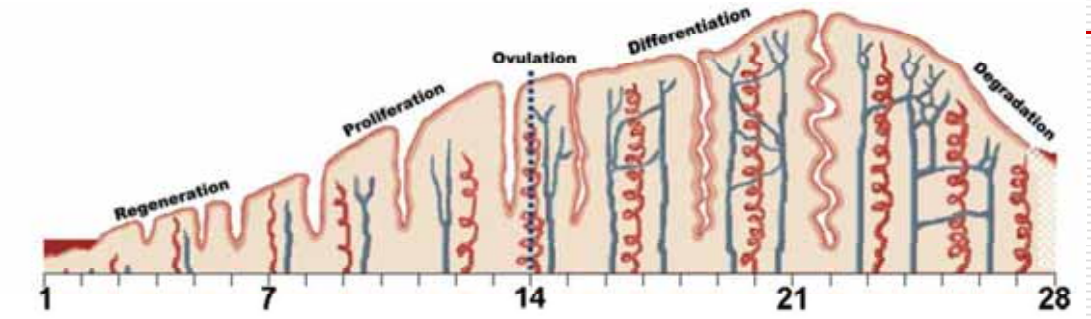
(Epigenetics,David Allis et al, 2004)

- **DNA methylation:** DNA methylation at promoter associated CpG islands is linked to repression of transcription

- **Chromatin modifications:** Histone modifications include acetylation, methylation, phosphorilation, ubiquitylation…

- **Non coding RNA:** Small RNAs that are associated with trasncriptional or translational repression



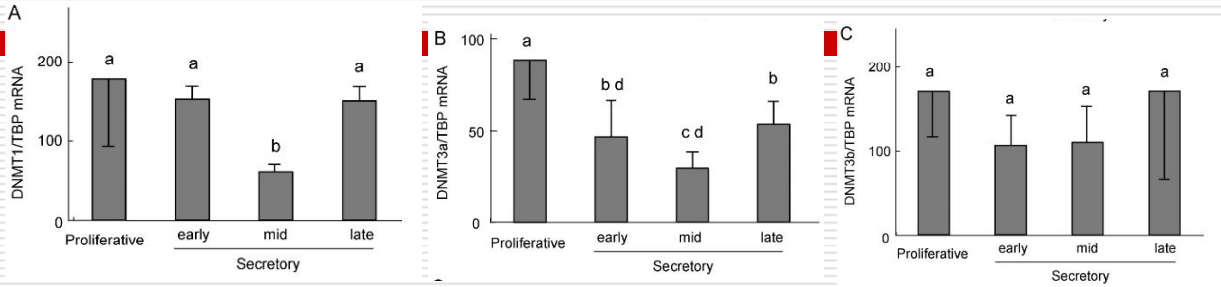


Decidualization:
TSA (histone deacetylase inhibitor) potentiates the decidualization process after E+P treatment (Sakai et al, 2003)

Implantation:
TSA enhances implantation steps by upregulation of glycodelin (Uchida et al, 2007).
AZA (methylation inhibitor) increases implantation rates in epithelial cell lines (Rahnama et al, 2009)

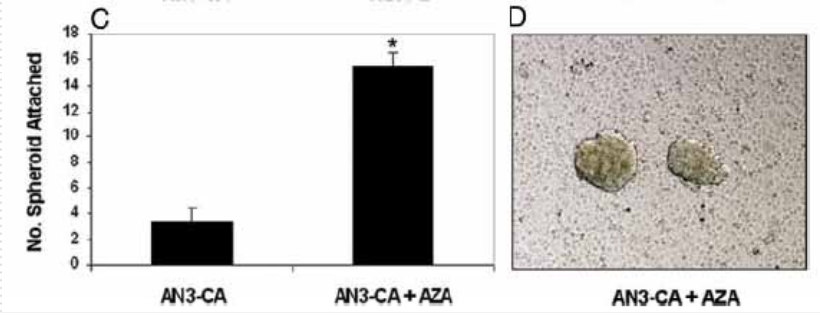
Endometriosis:
Steroidogenic factor-1 (SF-1) is hipomethylated as the estrogen receptor (SR2) in endometriosis while the progesterone receptor is hypermethylated (Xue et al, 2007, Wu et al, 2006).

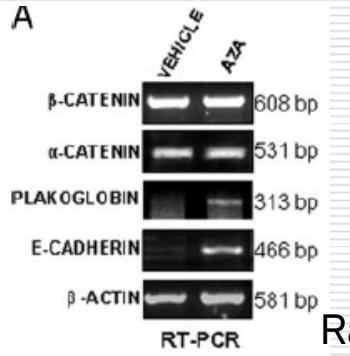
DNMTs expression during the menstrual cycle.



Yamagata et al, 2009

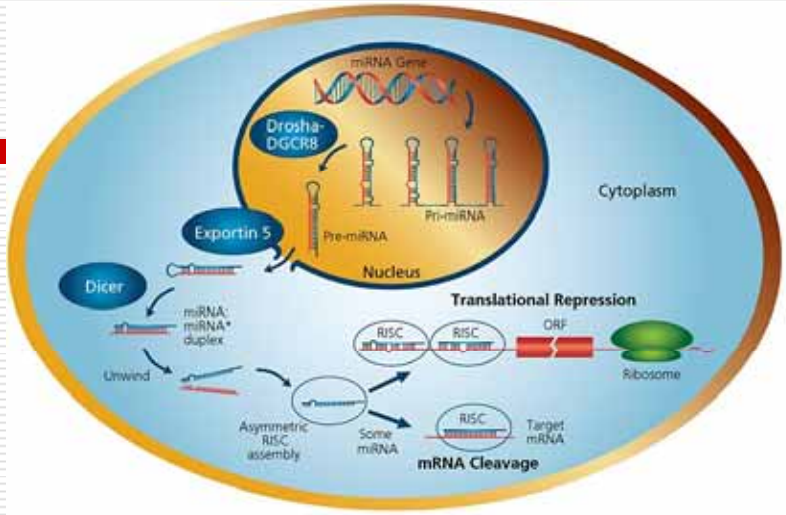
Inhibition of methylation increases endometrial receptivity. Endometrial epithelial cell line AN3-CA treated with AZA increases E-cadh expression.

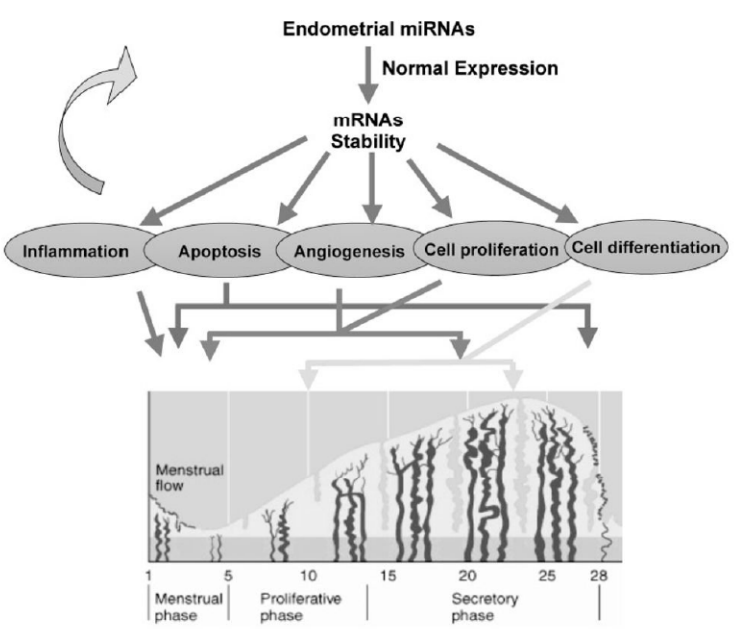


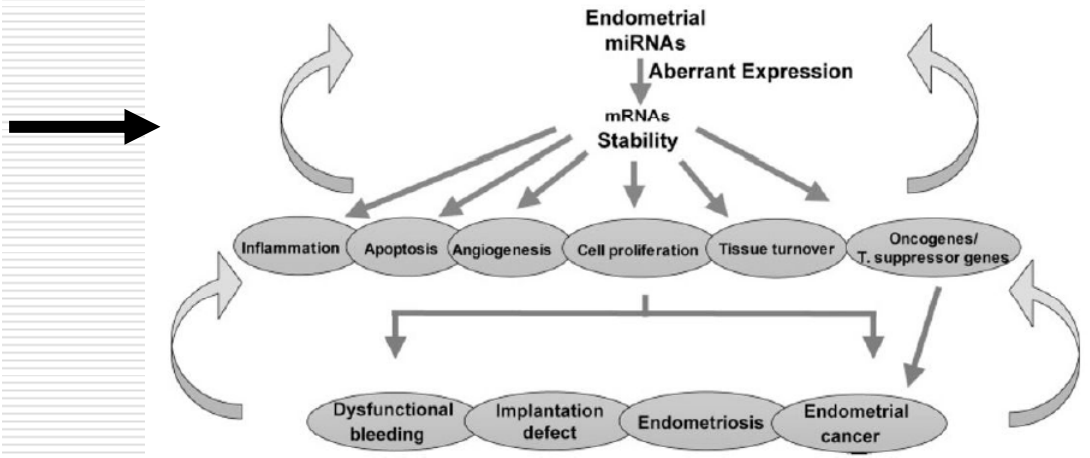


Rahnama et al, 2009

miRNAs potential regulatory function on endometrial gene expresion







Pan and Chegini, 2008

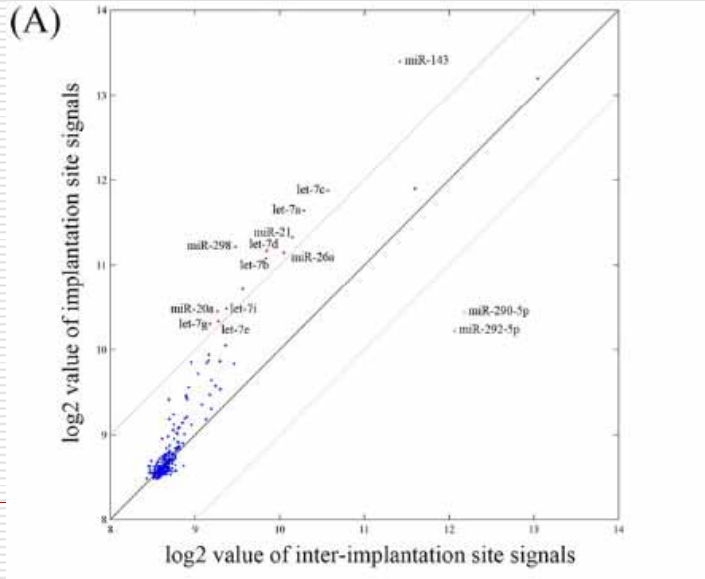
miRNAs profile in midsecretory epithelium endometrium *vs* late proliferative

TABLE 1. MicroRNAs differentially expressed in the late proliferative phase compared to the midsecretory phase endometrial epithelium.

Down-regulated in late proliferative endometrium				Up-regulated in midsecretory endometrium			
miRNA gene	Accession no.[a]	Fold change[b]	*P* value	miRNA gene	Accession no.[a]	Fold change[b]	*P* value
MIR210	MIMAT0000267	7.1	0.0003	*MIR214*	MIMAT0000271	4	0.02
MIR193A-3P	MIMAT0000459	5.2	0.0002	*MIR503*	MIMAT0002874	3.6	0.007
MIR345	MIMAT0000772	3.3	0.002	*MIR134*	MIMAT0000447	3.1	0.03
MIR29B	MIMAT0000100	2.8	0.0007	*MIR450*	MIMAT0001545	3	0.003
MIR29C	MIMAT0000681	2.6	0.005	*MIR382*	MIMAT0000737	2.6	0.03
MIR30B	MIMAT0000420	2.6	0.01	*MIR376A*	MIMAT0003386	2.6	0.04
MIR204	MIMAT0000265	2.6	0.04	*MIR369-5P*	MIMAT0001621	2.4	0.006
MIR203	MIMAT0000264	2.5	0.000086	*MIR222*	MIMAT0000279	2.4	0.04
MIR582-5P	MIMAT0003247	2.3	0.01	*MIR370*	MIMAT0000722	2.3	0.01
MIR30D	MIMAT0000245	2.2	0.005	*MIR542-3P*	MIMAT0003389	2.2	0.04
MIR200C	MIMAT0000617	2.1	0.004	*MIR105*	MIMAT0000102	2.1	0.01
MIR31	MIMAT0000089	2.1	0.02	*MIR127*	MIMAT0000446	2.1	0.01

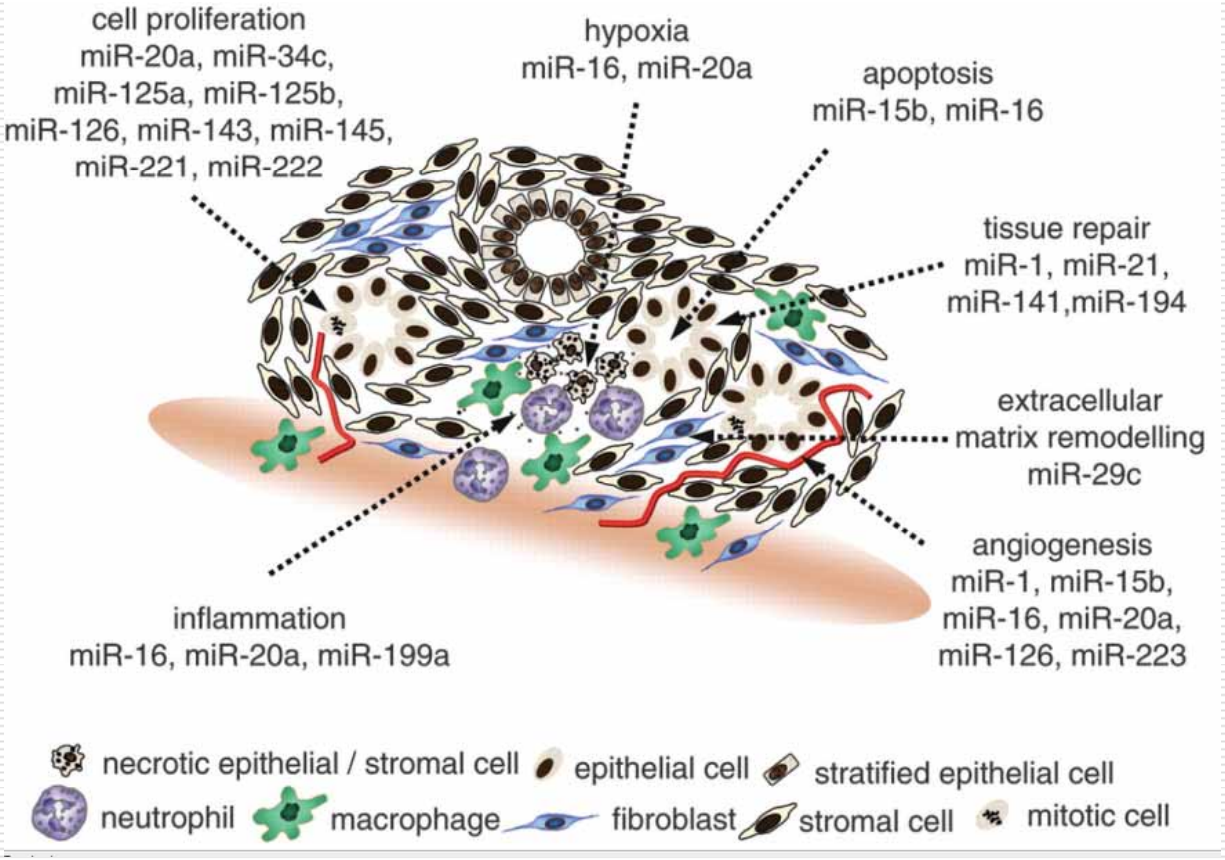
Kuokkanen et al, 2010

miRNAs profile changed in day 5 mouse pregnant uterus



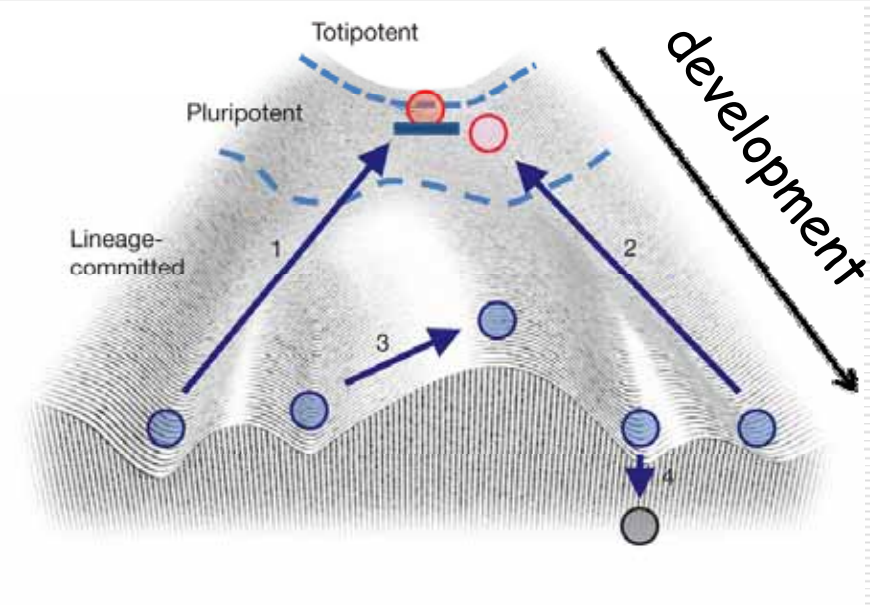
Hu et al, 2008

miRNA regulatory functions during endometriosis lesion development



Ohlsson Teague et al, 2010

This unidirectional and rigid point of view has been challenged by the induction of pluripotent stem cells (IPS)



Yamanaka, 2009

The maintenance of the pluripotent state requires a specific epigenetic status

Genomics

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

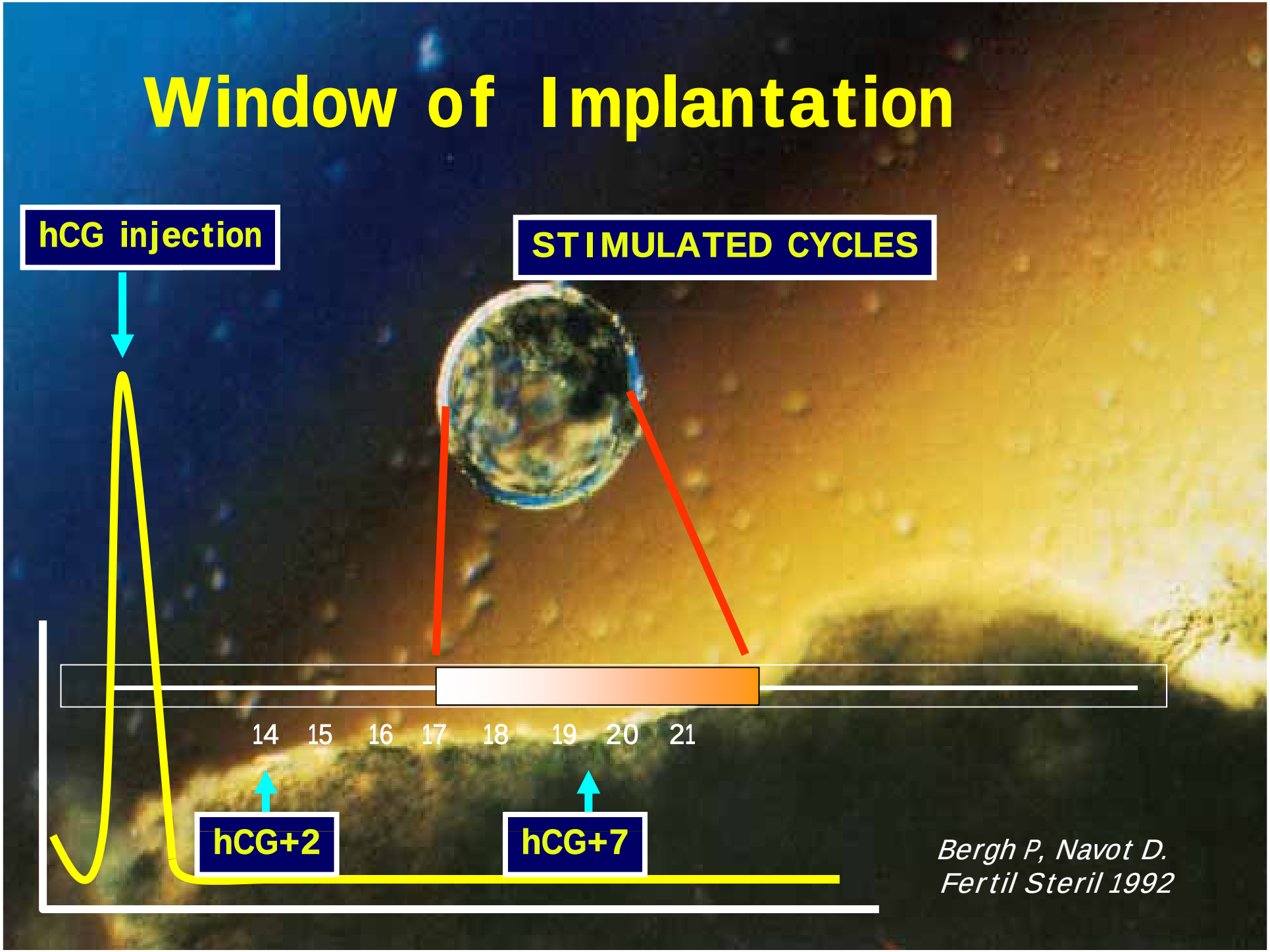
Microarray Analysis and Tumor Classification

John Quackenbush, Ph.D.

DNA MICROARRAY ANALYSIS WAS FIRST DESCRIBED IN THE MID-1990s AS a means to probe the expression of thousands of genes simultaneously[1,2] and was quickly adopted by the research community for the study of a wide range of biologic processes. Most of the early studies had a simple and powerful design: to compare two biologic classes in order to identify the differential expression of the genes in them — genes with potential relevance to a wide range of biologic processes, such as the progression of cancer,[3-6] the causes of asthma,[7-9] heart disease,[10-12] and neuropsychiatric disorders,[13-17] and the analysis of factors associated with infertility.[18-21]

Soon after microarrays were introduced, many researchers realized that the technique could be used to find new subclasses in disease states[22,23] and identify biologic markers (biomarkers) associated with disease[24] and that even the expression

Window of Implantation



Bergh P, Navot D.
Fertil Steril 1992

J.A.Horcajadas, A.Pellicer and **C.Simón**

Table I. Summary of studies performed in human endometrium using microarray analysis

Process studied	Microarray	Company	Number of gene targets	Study
Decidualization	Clontech Atlas array	Stanford University	588	Popovici *et al.* (2000)
Decidualization	Incyte human GEM-V	Incyte Genomics	6918	Brar *et al.* (2001)
Endometrial cancer	Hu6800	Affymetrix	6000	Mutter *et al.* (2001)
WOI	HG-U95A	Affymetrix	12 686	Kao *et al.* (2002)
WOI	HG-U95A	Affymetrix	12 686	Carson *et al.* (2002)
Endometriosis	Human gene genefilter GF211	Research Genetics	4133	Eyster *et al.* (2002)
Endometriosis	Atlas human cDNA expression Array	Clontech	597	Lebovic *et al.* (2002)
Endometrial cancer	Oncochip	Centro Nacional de Investigaciones Oncológicas	6386	Moreno-Bueno *et al.* (2003a)
WOI	Human cytokine expression array	R&D Systems	375	Domínguez *et al.* (2003)
Decidualization	HU-95A	Affymetrix	12 686	Tierney *et al.* (2003)
Endometriosis	Home-made	University of Tokio	23 040	Arimoto *et al.* (2003)
WOI	HG-U95A-E	Affymetrix	>60 000	Borthwick *et al.* (2003)
WOI	HG-U95A	Affymetrix	12 686	Riesewijk *et al.* (2003)
RU486	Home-made	**University of Cambridge**	**~1000**	**Catalano *et al.* (2003)**
Endometriosis	HG-U95A	Affymetrix	12 686	Kao *et al.* (2003)
Endometrial cancer	Home-made	National Cancer Institute	9984	Risinger *et al.* (2003)
Progesterone effect	Human Chip 1K set 1	Takara Shuzo	1000	Okada *et al.* (2003)
Endometriosis	Atlas human 1.2 cDNA expression array	Clontech	1172	Matsuzaki *et al.* (2004)
Endometrial cancer	GEMarray clones	Incyte Genomics	18 098	Cao *et al.* (2004)
Endometrial cancer	Home-made	University of Cambridge	1056	Saidi *et al.* (2004)
Endometrial cancer	U133A	Affymetrix	>22 000	Ferguson *et al.* (2004)
Stimulated cycles	HG_U95Av2	Affymetrix	12 686	Mirkin *et al.* (2004)
Menstrual cycle	Home-made	Peter MacCallum Cancer Institute	10 500	Ponnampalam *et al.* (2004)
Endometrial cancer	U133A	Affymetrix	>22 000	Ferguson *et al.* (2005)
WOI	HG-U95Av2	Affymetrix	12 686	Mirkin *et al.* (2005)
Proliferative phase	BD Atlas nylon cDNA expression array	BD Biosciences Clontech	1200	Yanahiara *et al.* (2005)
Stimulated cycles	HG_U133A	Affymetrix	>22 000	Horcajadas *et al.* (2005)
Stimulated cycles	HG_U133A	Affymetrix	>22 000	Simón *et al.* (2005)
Menstrual cycle	HGU133 Plus 2.0	Affymetrix	54 600	Talbi *et al.* (2005)
Menstrual cycle	**HU-133A**	**Affymetrix**	>22 000	**Punyadeera *et al.* (2005)**
RU486	Home-made	University of Cambridge	>15 000	Sharkey *et al.* (2005)
Endometriosis	Atlas human 1.2 cDNA expression array	Clontech	1172	Matsuzaki *et al.* (2005)
IUD	Home-made	University of Cambridge	>16 000	Horcajadas *et al.* (2006)

JCEM

MHR

Consensus genes: >3.0-fold change

Accession number (Function)	Gene name	Riesewijk	Kao	Carson	Borthwick
UP-REGULATED GENES PRESENT IN THE FOUR WORKS					
AF052124 (Structural protein)	Osteopontin	✓	✓	✓	✓
J02611 (Transporter)	Apolipoprotein D	✓	✓	✓	✓
AB020315 (Signalling)	Dickkopf/DKK1 (hdkk-1)	✓	✓	✓	✓
UP-REGULATED GENES PRESENT IN THREE OUT OF FOUR WORKS					
J04129 (Secretory protein)	Placental protein-14/Glycodelin	✓	✓		✓
M31516 (Immunomodulator)	Decay-accelerating factor for complement (CD55, Cromer blood group system)	✓	✓		✓
M84526 (Complement protein)	Adipsin/complement factor D	✓	✓		✓
M55543 (GTP-binding protein)	Guanylate-binding protein 2, interferon-inducible	✓		✓	✓
AB000712 (Receptor)	Claudin 4/CEP-R	✓	✓	✓	
AA420624 (Signalling)	Monoamine oxidase A (MAOA)	✓	✓		✓
M60974 (Regulatory protein)	Growth arrest and DNA-damage-inducible protein (gadd45)	✓	✓		✓
AB002365 (Cell death factor)	Nip2	✓		✓	✓
TOTAL GENES ANALYSED		153	60	120	85
DOWN-REGULATED GENES PRESENT IN THE FOUR WORKS					
U79299 (Secretory protein)	Olfactomedin-related ER localized protein	✓	✓	✓	✓
TOTAL GENES ANALYSED		58	87	153	40

Horcajadas/ Simón, J Reprod Immunol 2004

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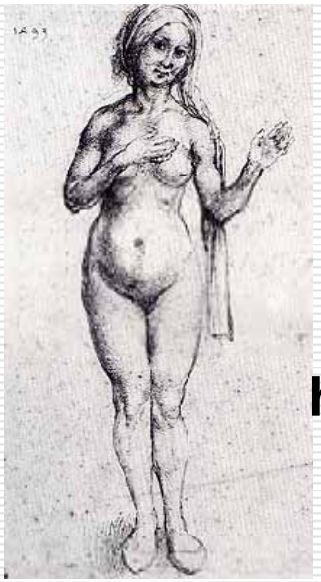
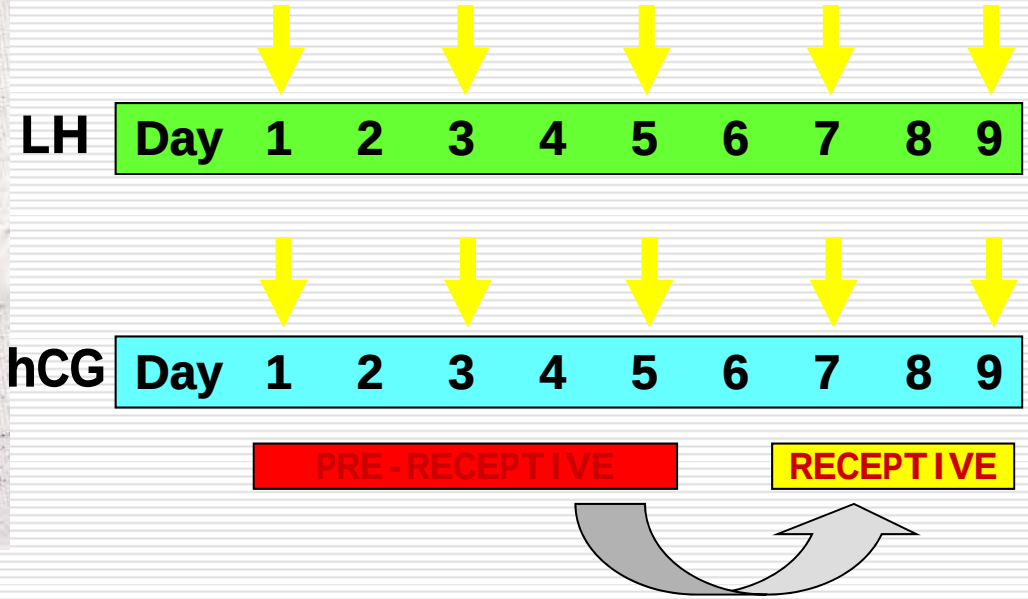
GENE EXPRESSION PROFILING DURING THE WINDOW OF IMPLANTATION IN NATURAL versus STIMULATED CYCLES

EXPERIMENTAL DESIGN

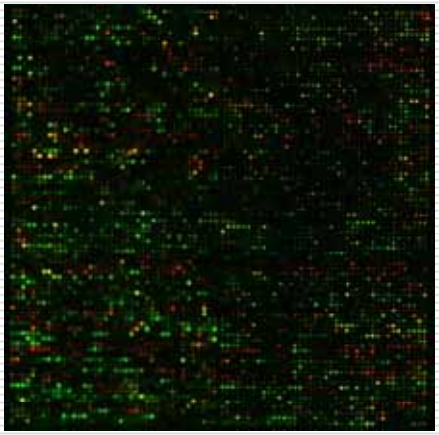
50 WOMEN



FIVE ENDOMETRIAL BYOPSIES AT EACH TIME POINT



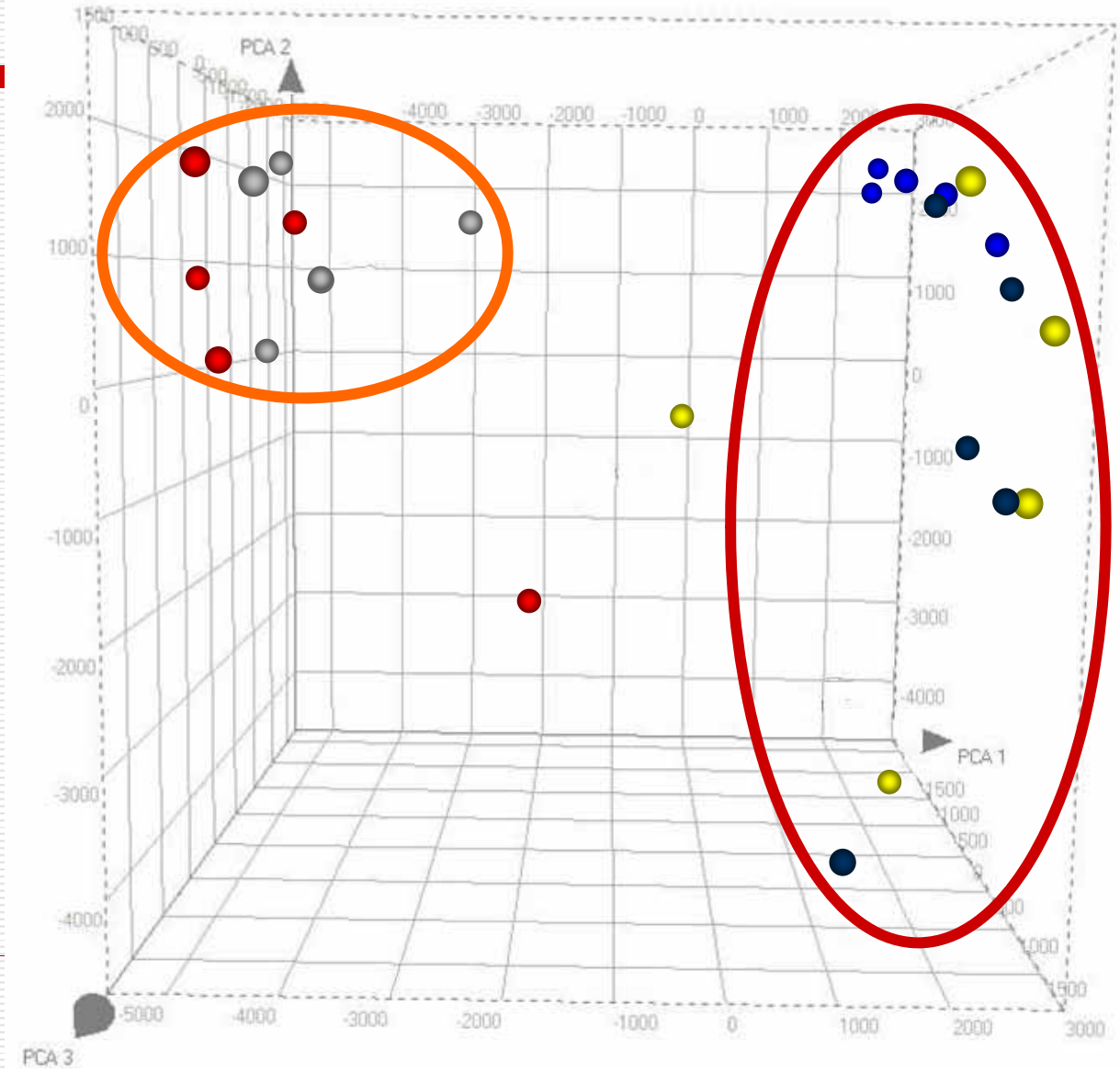
AFFIMETRIX HG-133A >22,000 genes



Caucasian
Fertile women with normal cycles
23–39 years
body mass index:19-25 kg/m2

Horcajadas JA/ Simon C. JCEM 2008

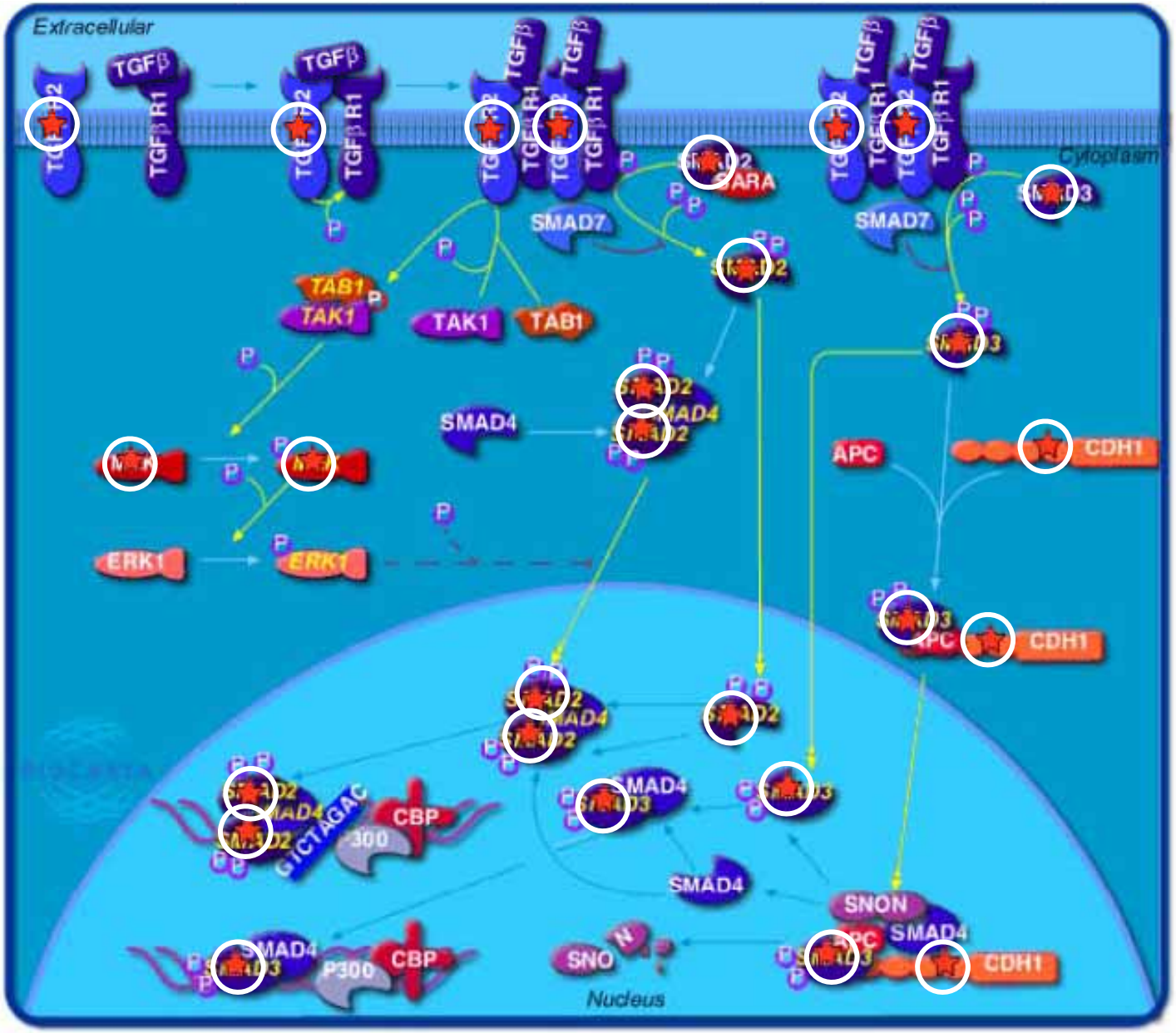
PCA OF THE ENDOMETRIAL SAMPLES FROM LH+1 TO LH+9



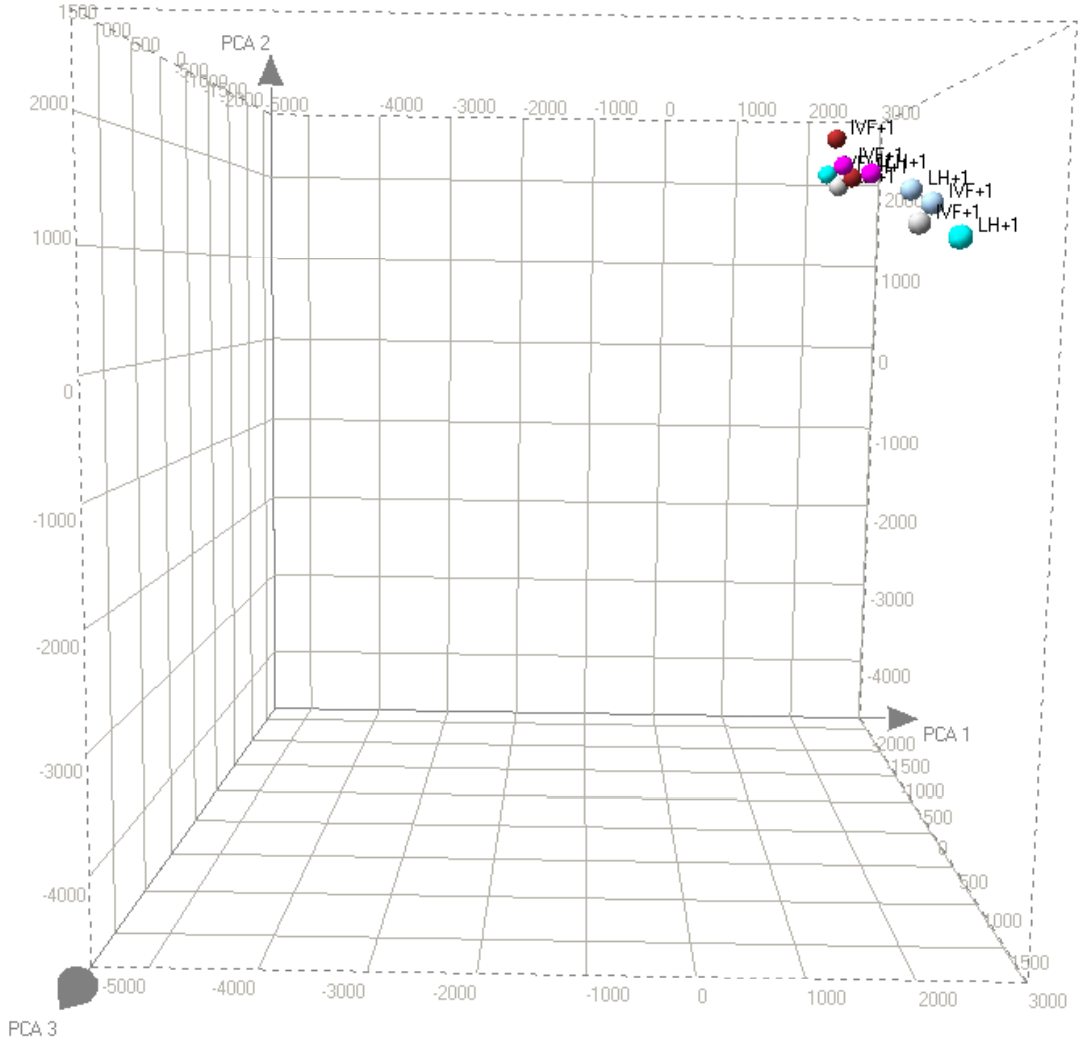
PATHWAYS STATISTICALLY OVER-EXPRESSED IN THE SHIFT FROM PRE- TO RECEPTIVE ENDOMETRIUM

Category	Term	RT	Genes	Count	%	P-Value
KEGG_PATHWAY	COMPLEMENT AND COAGULATION CASCADES	RT		10	2.1%	2,1E-3
KEGG_PATHWAY	FOCAL ADHESION	RT		19	4.0%	3,8E-3
KEGG_PATHWAY	ANTIGEN PROCESSING AND PRESENTATION	RT		10	2.1%	5,3E-3
KEGG_PATHWAY	ADHERENS JUNCTION	RT		10	2.1%	5,7E-3
KEGG_PATHWAY	GAP JUNCTION	RT		11	2.3%	6,8E-3
KEGG_PATHWAY	HISTIDINE METABOLISM	RT		7	1.5%	2,0E-2
KEGG_PATHWAY	NATURAL KILLER CELL MEDIATED CYTOTOXICITY	RT		12	2.5%	2,1E-2
KEGG_PATHWAY	TGF-BETA SIGNALING PATHWAY	RT		9	1.9%	2,6E-2
KEGG_PATHWAY	ARGININE AND PROLINE METABOLISM	RT		7	1.5%	3,1E-2
KEGG_PATHWAY	CYTOKINE-CYTOKINE RECEPTOR INTERACTION	RT		17	3.5%	6,7E-2
KEGG_PATHWAY	CELL ADHESION MOLECULES (CAMS)	RT		10	2.1%	9,3E-2

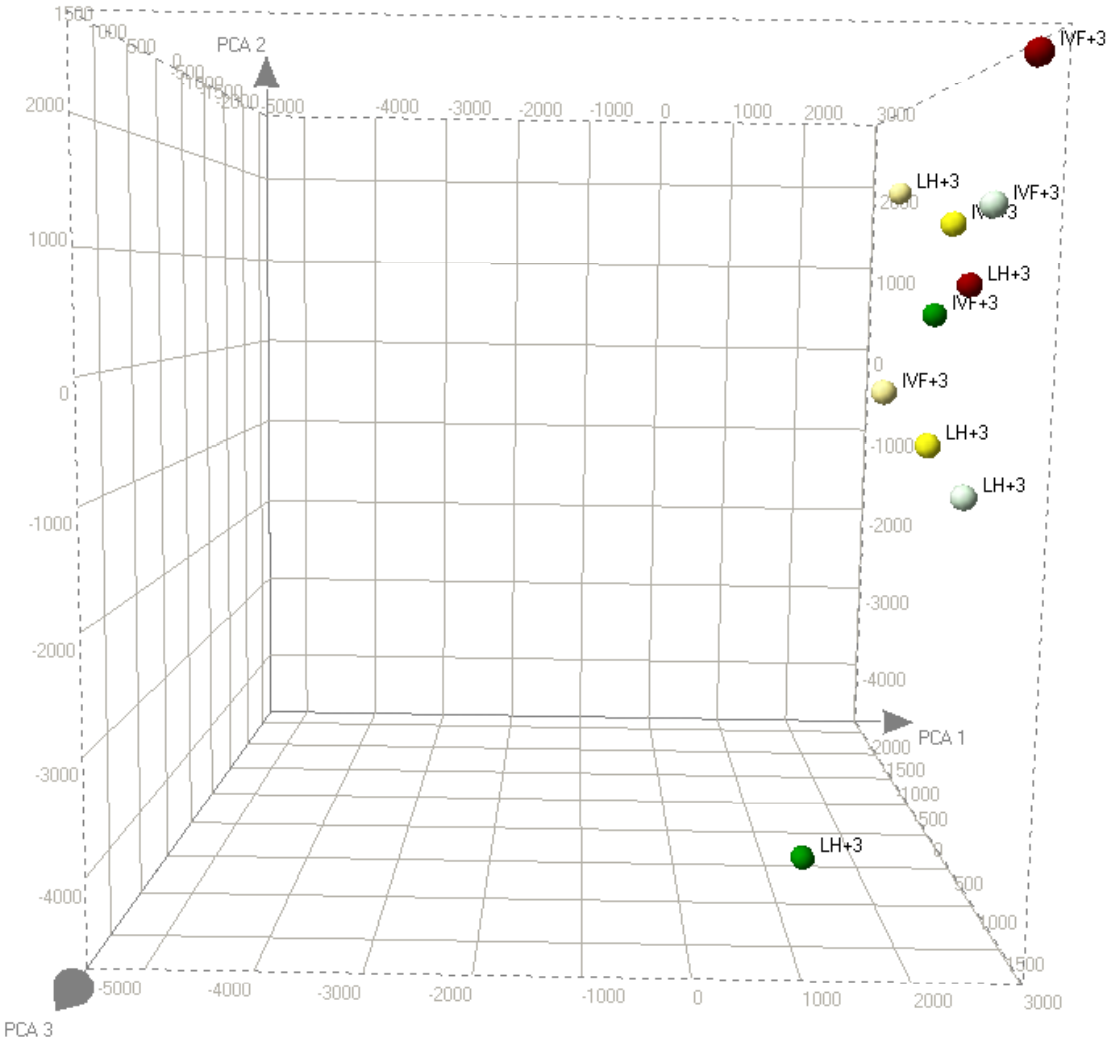
TGF-BETA PATHWAY: MOLECULES OVER-EXPRESSED INTHE RECEPTIVE HUMAN ENDOMETRIUM



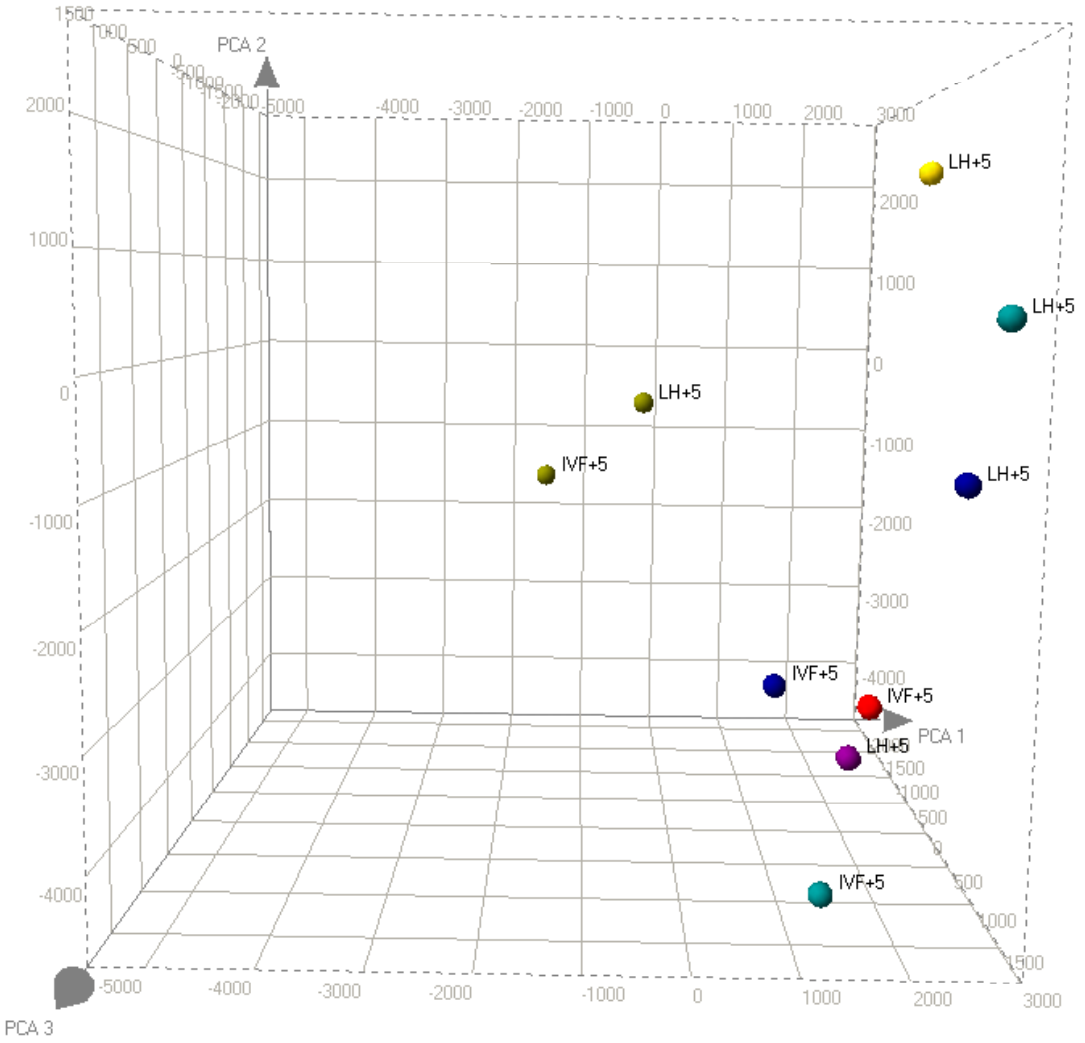
Day LH/hCG+1



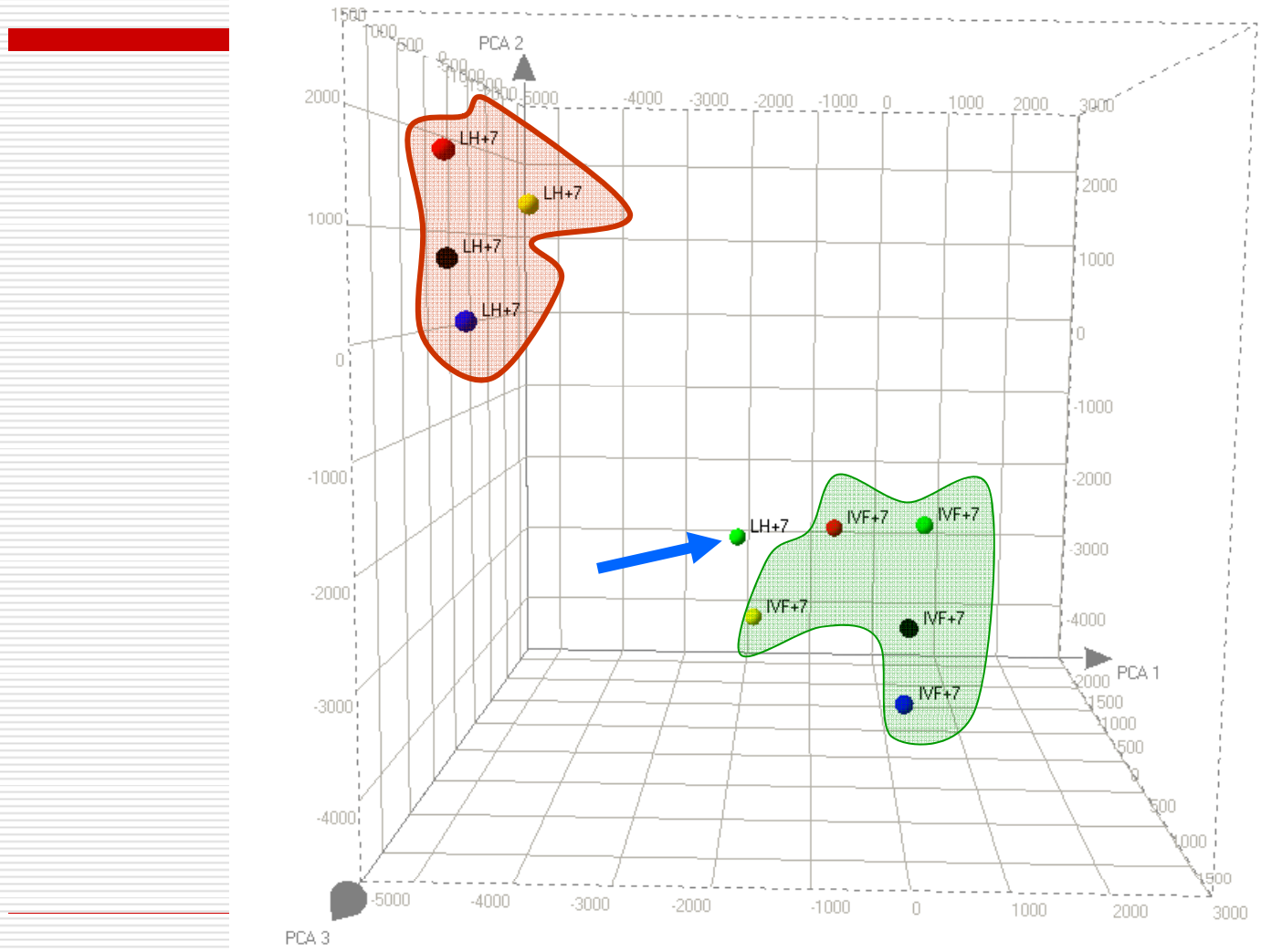
Day LH/hCG+3



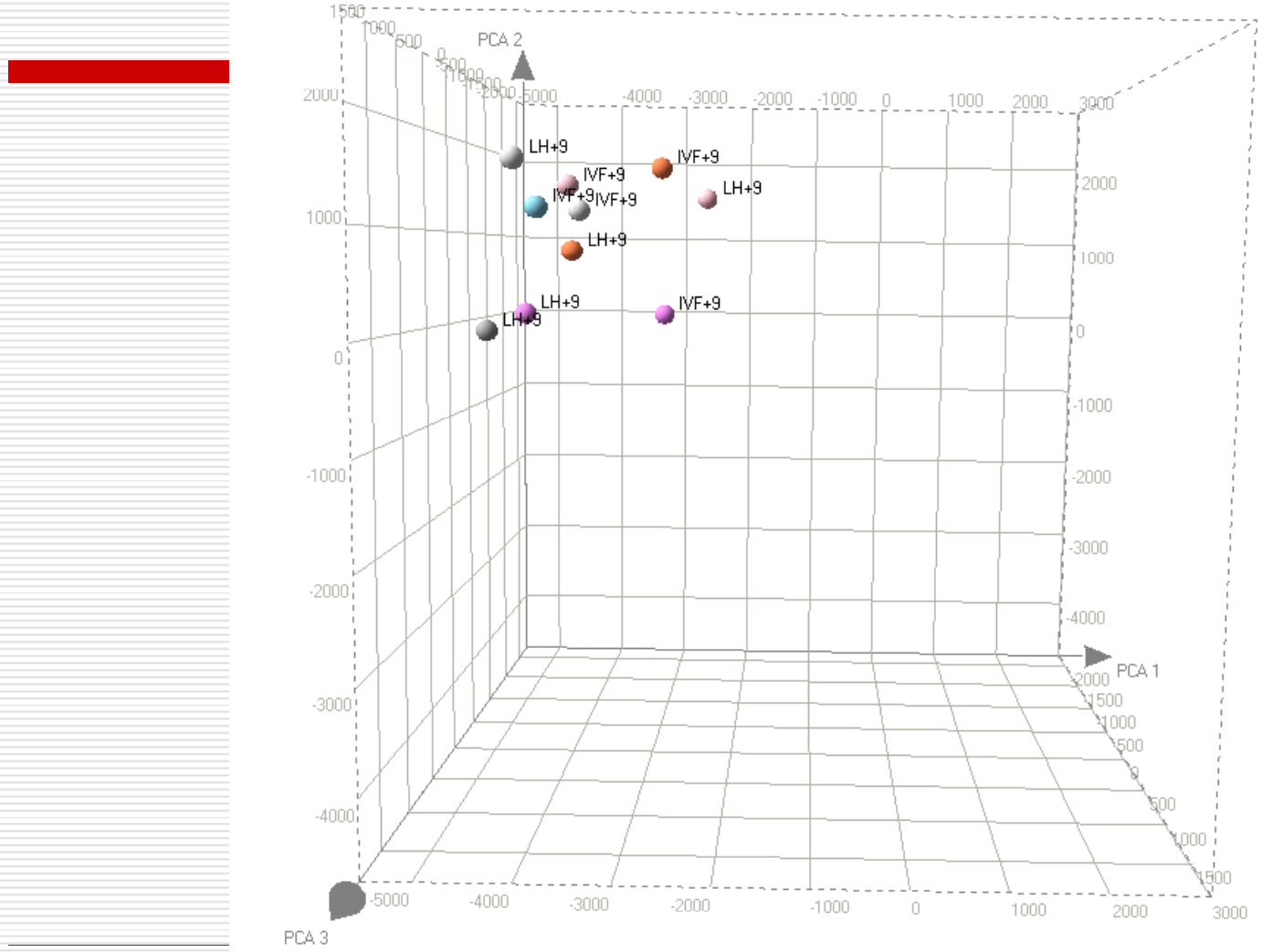
Day LH/hCG+5



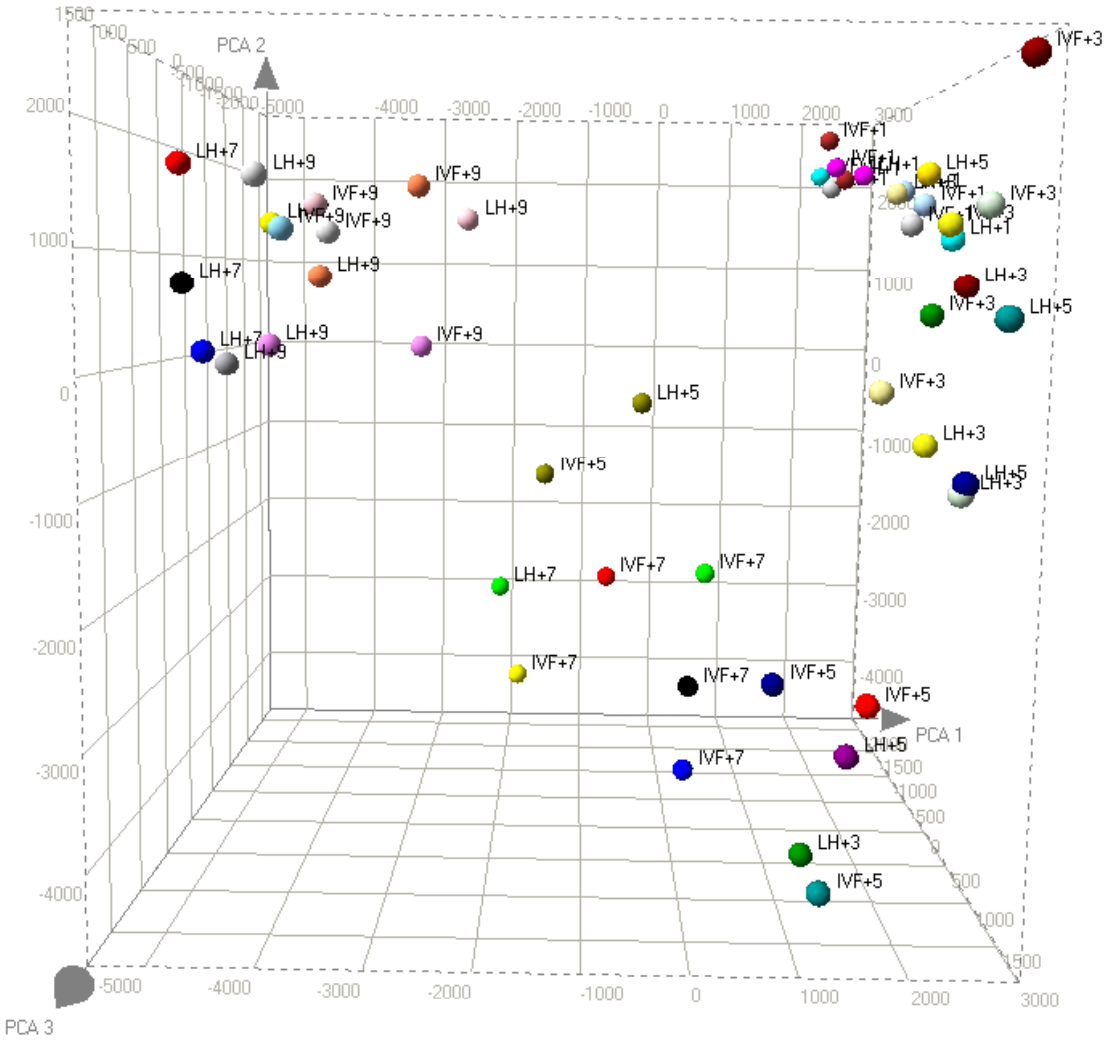
Day LH/hCG+7



Day LH/hCG+9



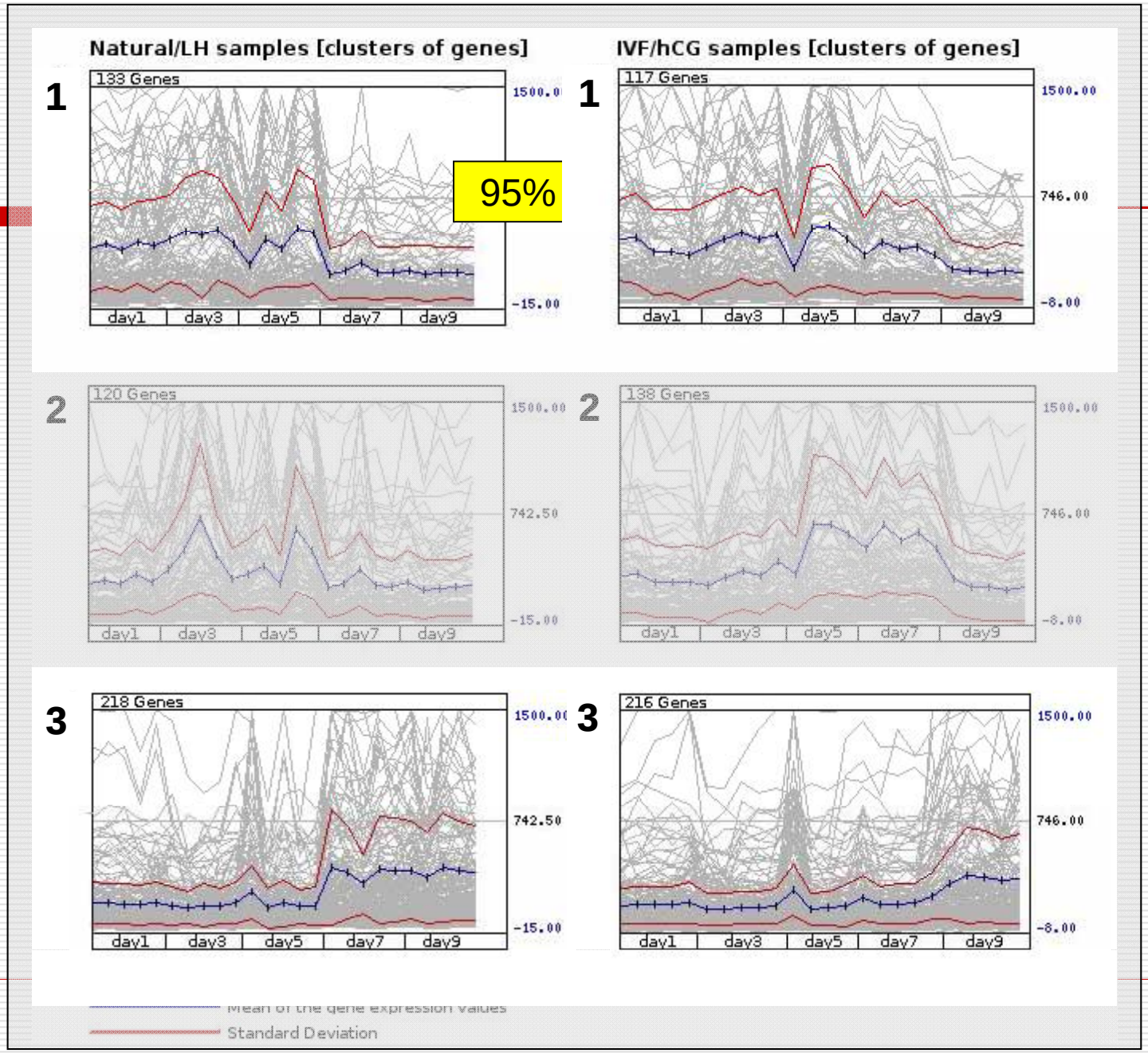
Natural/LH vs IVF across the WOI



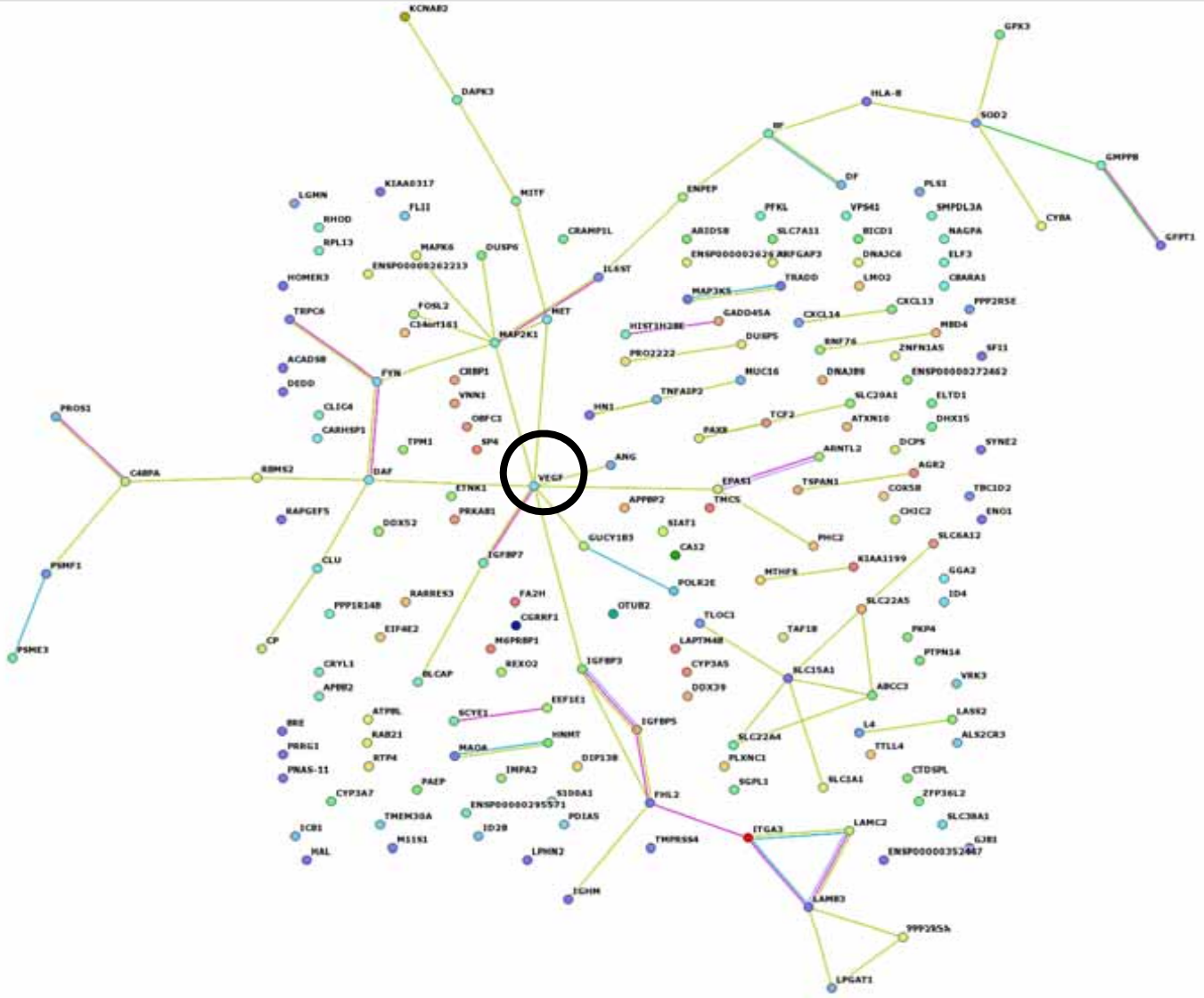
MOST DIFFERENTIATED FUNCTIONALITIES IN RECEPTIVE ENDOMETRIUM IN NATURAL versus STIMULATED CYCLES

NATURAL CYCLE	STIMULATED CYCLE
GO biological process	**GO biological process**
GO terms over-expressed: 1. antigen processing, endogenous antigen via MHC class I 2. antigen presentation, endogenous antigen 3. complement activation, classical pathway 4. response to drug 5. regulation of DNA metabolism 6. mitosis 7. DNA replication 8. small GTPase mediated signal transduction 9. cell division 10. negative regulation of progression through cell cycle 11. skeletal development 12. DNA repair 13. amino acid metabolism 14. cytoskeleton	GO terms over-expressed: 1. **mitotic checkpoint** 2. antigen processing, endogenous antigen via MHC class I 3. **spindle organization and biogenesis** 4. antigen presentation, endogenous antigen 5. **mitotic sister chromatid segregation** 6. regulation of DNA metabolism 7. **microtubule-based movement** 8. cell division 9. **phosphoinositide-mediated signaling** 10. **DNA-dependent DNA replication** 11. **regulation of development** 12. **nucleotide metabolism** 13. DNA repair 14. **cell proliferation** 15. **regulation of signal transduction** 16. **carboxylic acid metabolism** 17. **positive regulation of cellular process** 18. **negative regulation of cellular physiological process**

GENE CLUSTERING IN NATURAL versus STIMULATED CYCLES



Horcajadas JA/ Simon C. JCEM 2008



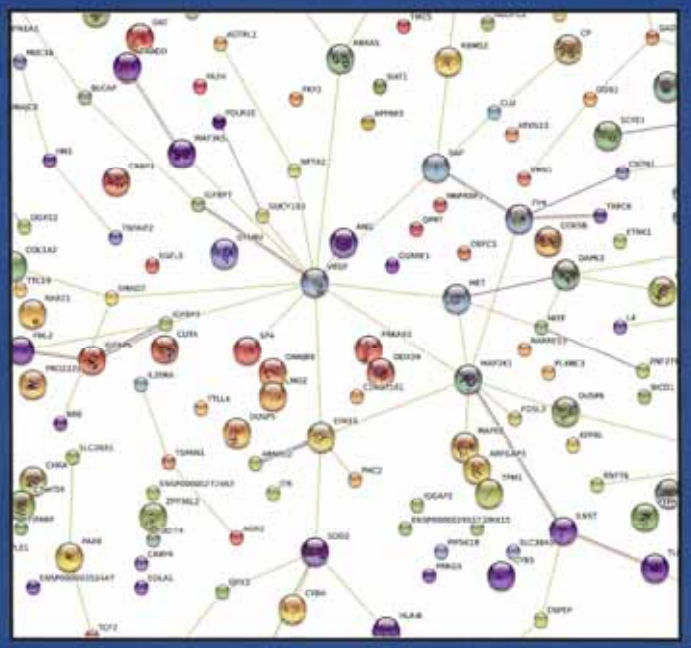
Horcajadas JA/ Simon C. JCEM 2008

EQUIPO IVI

JCEM™

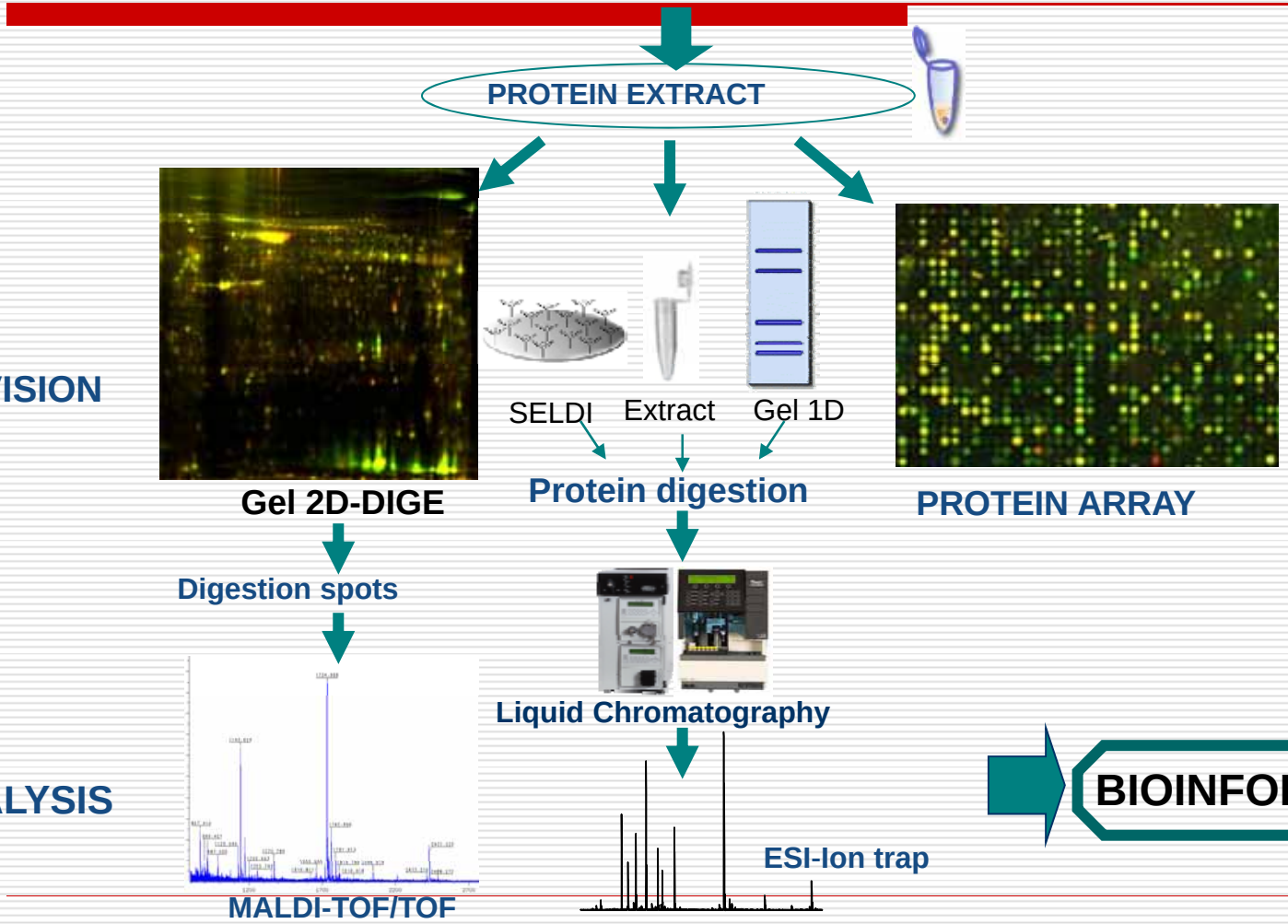
THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Volume 93 • Number 11 • November 2008 • jcem.endojournals.org



THE ENDOCRINE SOCIETY®

Proteomic of Endometrial receptivity



Proteomic of Endometrial receptivity

Human Reproduction, Vol.24, No.10 pp. 2607–2617, 2009
Advanced Access publication on June 25, 2009 doi:10.1093/humrep/dep230

270 281

REC

human reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

Journal of proteome research

Article

Proteomic Characterization of Midproliferative and Midsecretory Human Endometrium

Jenny I-C. Chen, Natalie J. Hannan, Yunxian Mak, Peter K. Nicholls, Jin Zhang, Adam Rainczuk, Peter G. Stanton, David M. Robertson, Lois A. Salamonsen, and Andrew N. Stephens

J. Proteome Res., **Article ASAP** • DOI: 10.1021/pr801024g • Publication Date (Web): 17 February 2009

Conclusions

We identified 32 proteins with different expression between pre-receptive endometrium and refractory.

- Stathmin 1 and annexin A2 have opposite regulation in receptive endometrium compared with the pre-receptive endometrium.
- These proteins appear to be disregulated in refractory endometrium induced by the IUD insertion.

The application of proteomics technology can potentially be used for:

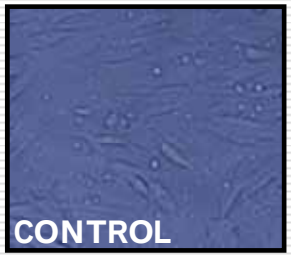
- Search for new biomarkers to determine the endometrial receptivity.
- Identify key molecules to improve implantation in infertile patients.
- Investigate interceptive molecules to prevent implantation of the embryo.

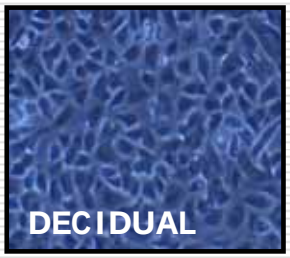
DECIDUALIZATION

Endometrial biopsy

Isolated stromal cells

In vitro decidualizated with P + E_2



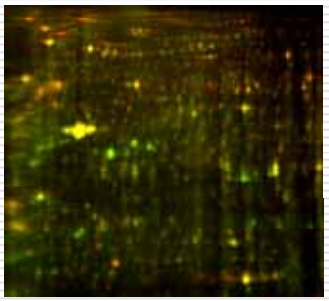


Cells

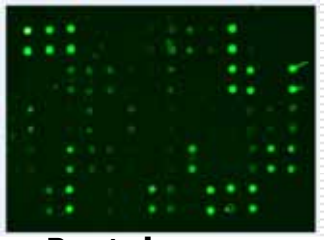
Conditioned media

PROTEOMIC ANALYSIS

N= 11



2D-DIGE



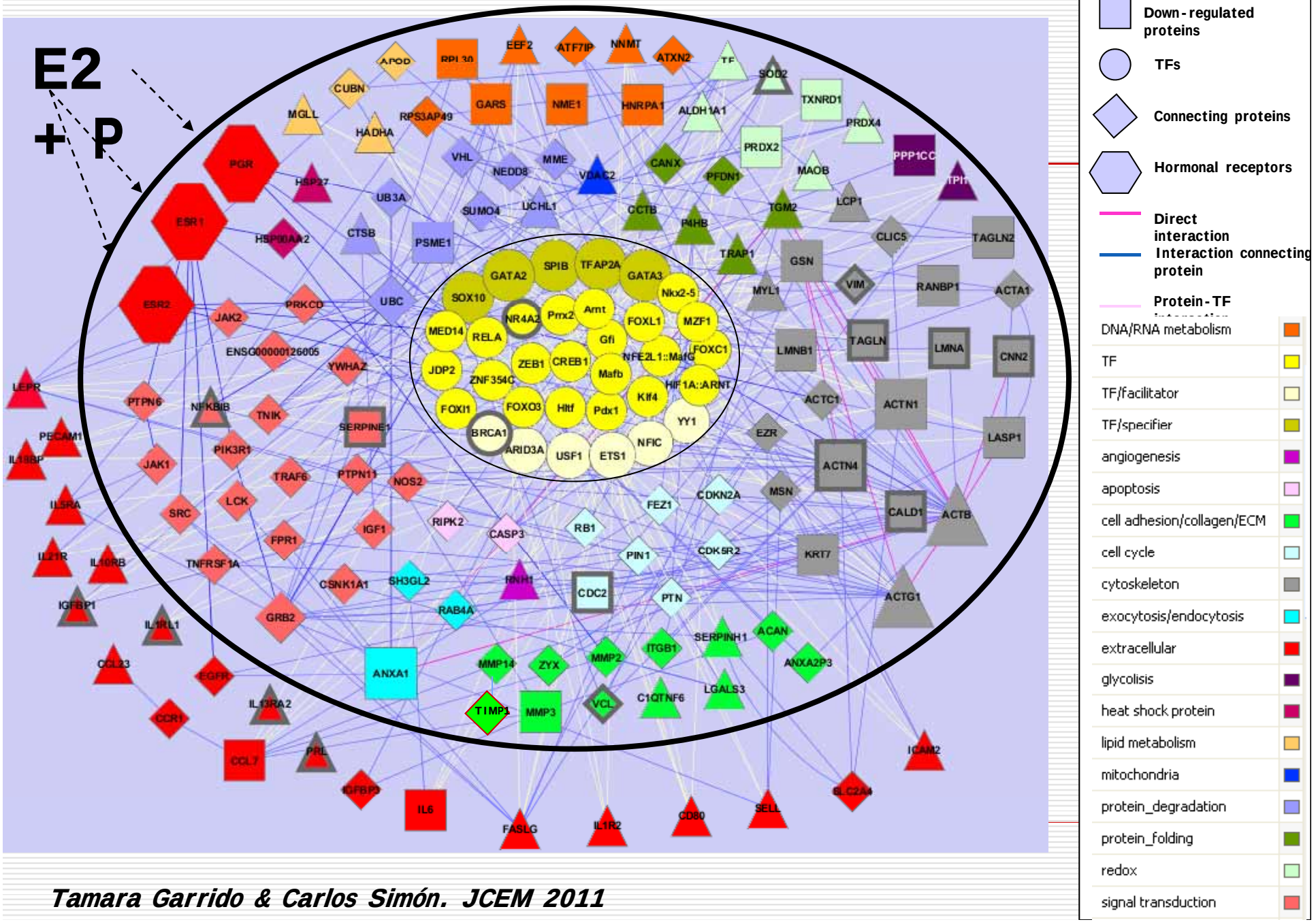
Protein array

SECRETOMIC ANALYSIS

N =7

Tamara Garrido & Carlos Simón. JCEM March 2011

"DECIDUALIZATION INTERACTOME"

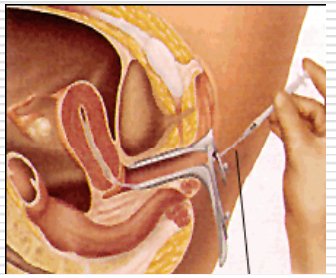


Tamara Garrido & Carlos Simón. JCEM 2011

Secretomics of endometrial receptivity
Non-invasive diagnosis

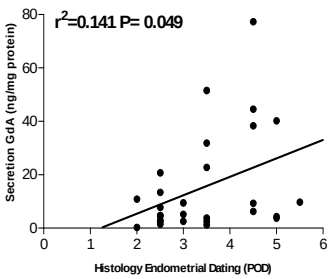
- **Aspiration of endometrial secretion does not affect pregnancy rates**

  Van der Gaast et al. RBmOnline 2002



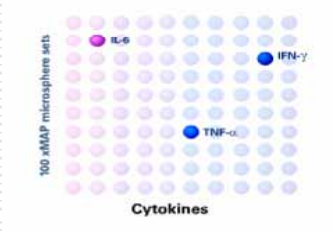
- **Glycodelin levels correlate with menstrual cycle phase on endometrial aspirations**

  Van der Gaast MH, et al. BJOG 2009



- **The profile of cytokines can be determined in endometrial secretions**

  Simón C, et al. J Reprod Immunol 1996
  Boomsma CM et al. RBmOnline 2009

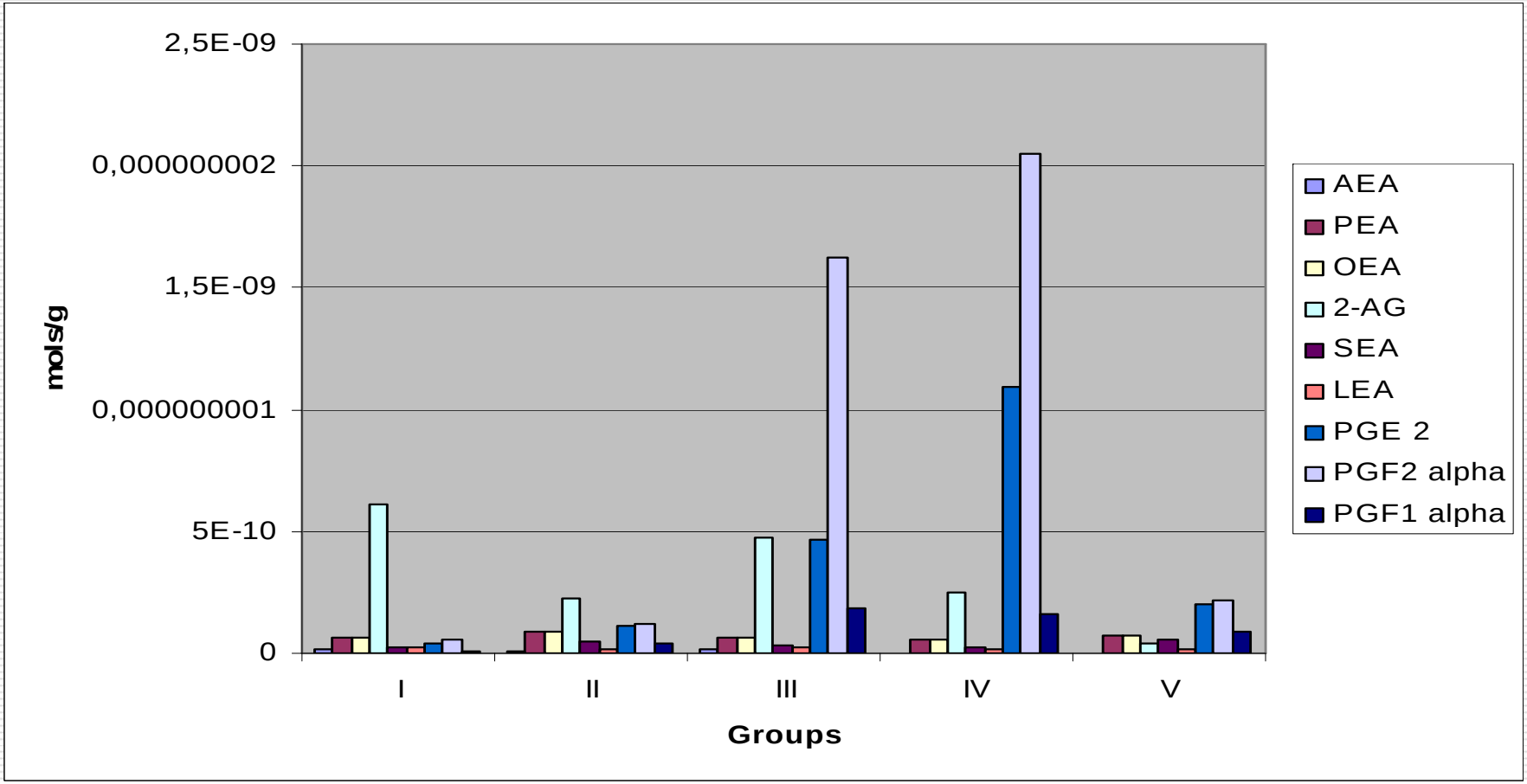


Proteomics

Comprehensive Proteomic Analysis of Human Endometrial Fluid Aspirate

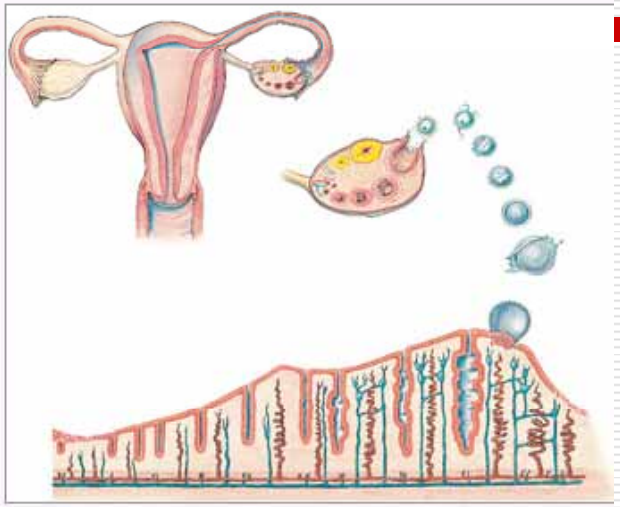
Juan Casado-Vela,[†,#] Eva Rodriguez-Suarez,[†,#] Ibon Iloro,[†,#] Amagoia Ametzazurra,[‡] Nere Alkorta,[†] Juan Antonio García-Velasco,[§] Roberto Matorras,[∥,⊥] Begoña Prieto,[∥,⊥] Sandra González,[⊥] Daniel Nagore,[‡] Laureano Simón,[‡] and Felix Elortza*[,†]

Lipidomics


2,5E-09
0,000000002
1,5E-09
0,000000001
5E-10
0
mols/g
I
II
III
IV
V
Groups
AEA
PEA
OEA
2-AG
SEA
LEA
PGE 2
PGF2 alpha
PGF1 alpha

http://www.etegritytest.com.

Sample Collection



Endometrial quality is identified during the window of implantation. It is crucial that the patient have a carefully timed endometrial biopsy. The specimen must be collected on cycle days 20–24 (7–11 days post LH surge).

Patterns of Integrin Expression

There are three typical patterns:

1. Beta-3 integrin POSITIVE with an "in-phase" endometrium from cycle days 20–24 (7–11 days post LH surge) is a normal pattern of expression.

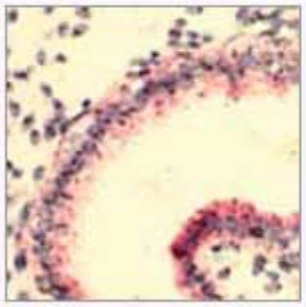
2. Beta-3 integrin NEGATIVE with an "out-of-phase" endometrium occurs in a patient with Luteal Phase Defect; following treatment the patient is advised to undergo a repeat biopsy to confirm diagnosis.[1]

3. Beta-3 integrin NEGATIVE in a patient with a normal "in phase" endometrium is associated with unexplained infertility,[1] minimal or mild endometriosis,[2] or hydrosalpinx. [3]

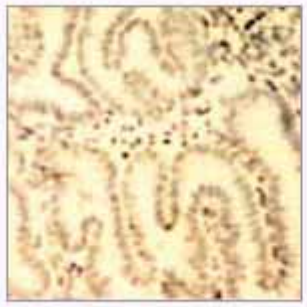
The E-tegrity test:

- Identifies endometrial quality
- Determines Beta-3 integrin presence
- Provides a histologic evaluation of the endometrium

Endometrial Cycle



Positive



Negative

Endometrial Function Test® (EFT®)
endometrialfunctiontest.com

The Endometrial Function Test® (EFT®)

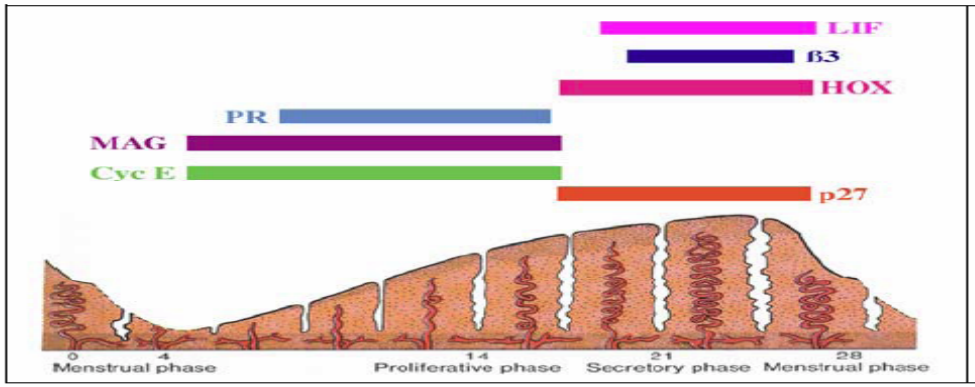


Figure 3. Panel of markers of endometrial development. Researchers have discovered many products that are made by the endometrium. The most important of these products are only made at particular times of the menstrual cycle. For example, progesterone receptor (PR), mouse ascites Golgi mucin (MAG) and cyclin E are normally only made during the proliferative and early secretory phases (cycle days 5 to ~19), while leukemia inhibitory factor (LIF), αvß3 integrin (ß3), HOXA-10 (HOX) and p27 are normally only expressed in the secretory phase (cycle days ~17 to ~28). Modified from *Langman's Medical Embryology*.

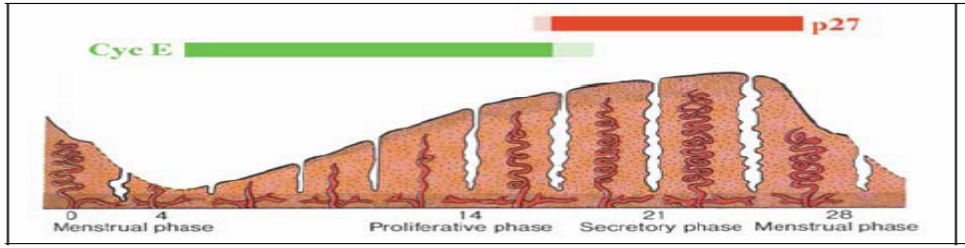


Figure 4. Cyclin E and p27 expression in fertile women. Cyclin E first appears at around cycle day 5 and continues to be expressed up until cycle day 19. After day 19, cyclin E normally is absent. p27, on the other hand, is absent until approximately cycle day 17, where it is seen for the remainder of the cycle. Modified from *Langman's Medical Embryology*.

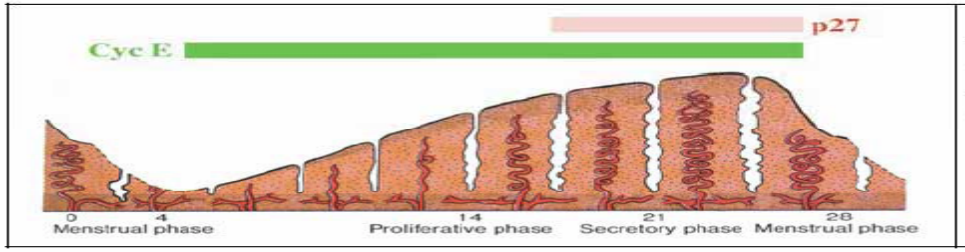


Figure 5. Cyclin E and p27 expression in women with unexplained infertility. The most striking difference between the cyclin expression of fertile women and infertile women is the persistence of cyclin E and decreased presence of p27 into the secretory phase. This finding represents a developmental arrest of the glands in the endometria of these women. Modified from *Langman's Medical Embryology*.

Endometrial Receptivity Array (ERA)

A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature

Patricia Díaz-Gimeno,[a,b] *José A. Horcajadas, Ph.D.,*[c] *José A. Martínez-Conejero, Ph.D.,*[c] *Francisco J. Esteban, Ph.D.,*[d] *Pilar Alamá, M.D.,*[a,b] *Antonio Pellicer, M.D.,*[a,b] *and Carlos Simón, M.D.*[a,b,e]

[a] Fundación IVI-Instituto Universitario IVI, University of Valencia, Valencia; [b] Instituto de Investigación, Sanitaria del Hospital Clinico de Valencia, Valencia University, Valencia; [c] iGenomix, Valencia; [d] Department of Experimental Biology, University of Jaén, Jaén; and [e] Centro de Investigación Principe Felipe, Valencia, Spain

Objective: To create a genomic tool composed of a customized microarray and a bioinformatic predictor for endometrial dating and to detect pathologies of an endometrial origin. To define the transcriptomic signature of human endometrial receptivity.
Design: Two cohorts of endometrial samples along the menstrual cycle were used: one to select the genes to be included in the customized microarray (endometrial receptivity array [ERA]), the other to be analyzed by ERA to train the predictor for endometrial dating and to define the transcriptomic signature. A third cohort including pathological endometrial samples was used to train the predictor for pathological classification.
Setting: Healthy oocyte donors and patients.
Patient(s): Healthy fertile women (88) and women with implantation failure (5) or hydrosalpinx (2).
Intervention(s): Human endometrial biopsies.
Main Outcome Measure(s): The gene expression of endometrial biopsies.
Result(s): The ERA included 238 selected genes. The transcriptomic signature was defined by 134 genes. The predictor showed a specificity of 0.8857 and sensitivity of 0.99758 for endometrial dating, and a specificity of 0.1571 and a sensitivity of 0.995 for the pathological classification.
Conclusion(s): This diagnostic tool can be used clinically in reproductive medicine and gynecology. The transcriptomic signature is a potential endometrial receptivity biomarkers cluster. (Fertil Steril® 2010;■: ■–■. ©2010 by American Society for Reproductive Medicine.)

Key Words: Endometrial receptivity, endometrial dating, microarray, transcriptomic signature, predictor, diagnostic tool

Endometrial Receptivity Array (ERA)

Agilent e-array: https://earray.chem.agilent.com/earray/

-238 Genes
-Probe selection: “Cross-linking”
-569 probes
-8 copies per probe
-Controls

Endometrial Receptivity Array (ERA) Predictor

Customized microarray

Bioinformatic analysis of data obtained by the customized microarray

Classification and prediction from gene expression.

Predictors: Characterization of transcriptome phenotype of normality

Diagnosis Report

iGenomix

Valencia, 27th May, 2010.

Diagnostic Report of Endometrial Receptivity based on Gene Expression

Report N#:
Patient Name: Clinical History N#:
Doctor Name:

Dear Dr.

The endometrial biopsy sample you have sent meets all the minimum quality standards for ERA processing and evaluation. Below, you will find the results and interpretation of endometrial receptivity based on the expression of 238 genes.

Diagnosis Results:

a) ERA analysis has determined that the endometrium has aa genetic receptivity profile of: Implantation Failure (IF)
b) Diagnosis Probability: 0.78

Interpretation of Results:

Receptive (RE): The endometrium's genetic receptivity profile is compatible to a normal receptive endometrium. The diagnostic probability can be found in Part B of the results. This implies a high possibility of avoiding embrionary implantation failure due to endometrial causes. This diagnosis does not take into account failures attributed to other causes such as embryo quality or previous pathologies.

Unreceptive (UR): The endometirum's genetic receptivity profile is compatible to an endometrium out of the receptive phase. The diagnostic probability can be found in Part B of the results. It could be a normal profile compatible to others phases of the cycle or a distinct profile than those defined in this diagnostic method. There exists a higher possibility for embrionary implantation failure.

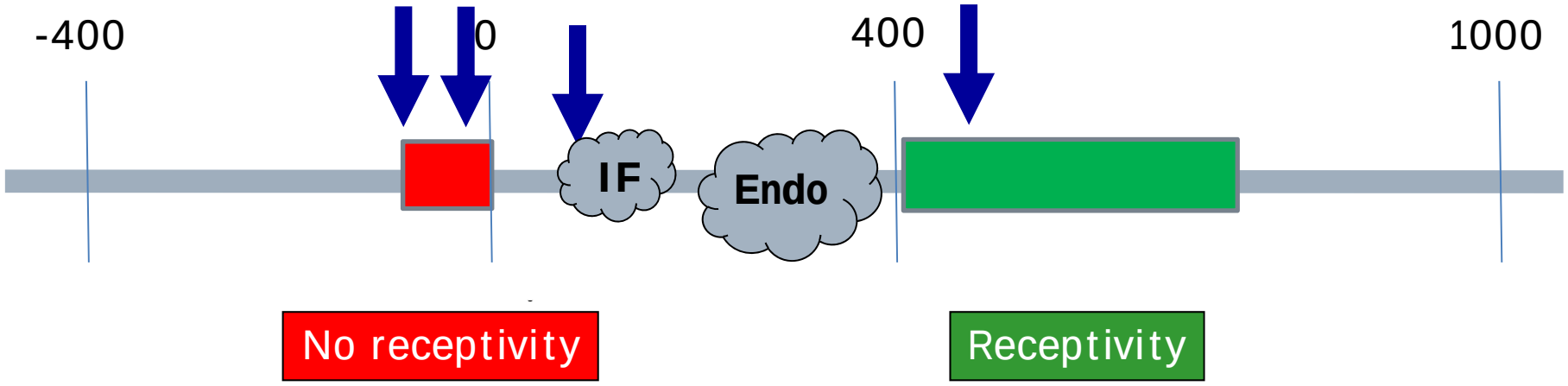
Implantation Failure (IF): The endometirum's genetic receptivity profile demonstrates implantation failure. The diagnostic probability can be found in Part B of the report. It indicates a high possibility of embrionary implantation failure.

Sincerely,

Dr. Jose A. Horcajadas
Scientific Director
iGenomix SL

Genomic Analysis of Endometrial Receptivity (ERA)

To score the Receptive status



Diaz P/ Simon C. Fertil Steril 2010

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Endometrial Data Base

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Monday, 22 September 2008

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- J Mol Diagn 7: 8-16
- Clin Cancer Res 12:1402-1411

Popular

- Mol Hum Reprod 9:253-264
- Molecular Human Reproduction 11:195-205
- Human Reprod 20:2104-2117
- J Clin Endocrinol Metabolism 88:1849-1857
- Cell Mol Life Sci 62:239-250

WELCOME TO ENDOMETRIAL DATA BASE!

Written by EDB´s management

VNIVERSITAT DE VALÈNCIA

EDB is a service of **Fundacion IVI, sponsored by** ***University of Valencia (SPAIN)***, that includes over thousands of data from hundreds of publications.

It contains links to MEDLINE and other life science journals for biomedical articles back to the 1950s.

PubMed also includes links to full text articles and other related resources.

COMING EVENTS

Written by EDB´s management

ASRM 2008 Annual Meeting

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(Quedan 1 elemento) Descargando imagen http://www.endometrialdatabase.com/edb/images/M_images/opml.png...

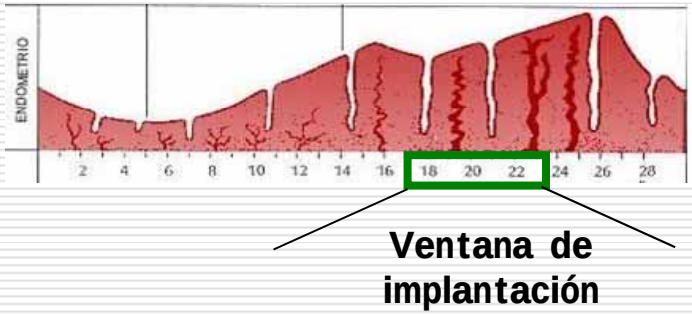
Internet

Conclusions

- Endometrial histology as a diagnostic tool is not useful. Single molecule approach is limited.
- The wide-genomic approach is increasing our knowledge on the genes governing endometrial receptivity being used as a new diagnostic technique.
- Secretomics of endometrial fluid is a potential non disruptive diagnostic tool for human endometrial receptivity.

Possible Clinical Improvements

Identification/Modification of receptive endometrium



✓ 10% Pregnancy rate

Embryo Identification Viable/Normal

✓30% increase pregnancy rate

- **1. Key points of established knowledge**
  - Genomics of endometrial receptivity
- **2. Unresolved areas**
  - Epigenomic
  - Secretomic
- **3. Further Research questions**
  - Non-invasive diagnosis of human endometrial receptivity

C. Simón

A. Pellicer