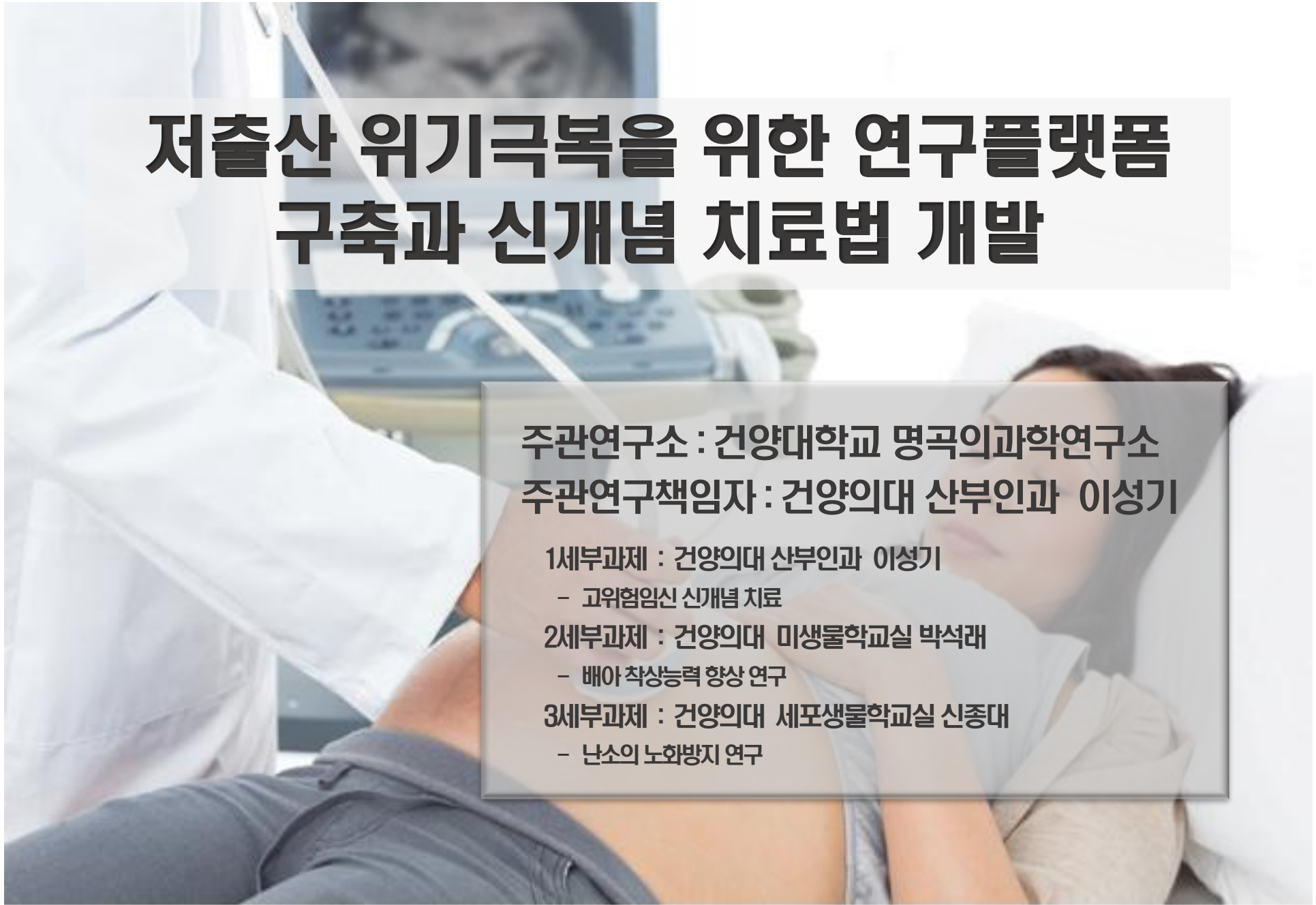
Modulation of the endometrium to overcome implantation failure

2025년 10월 19일

강 재 구

건양대학교 의과대학

약리학교실



저출산 위기극복을 위한 연구플랫폼 구축과 신개념 치료법 개발

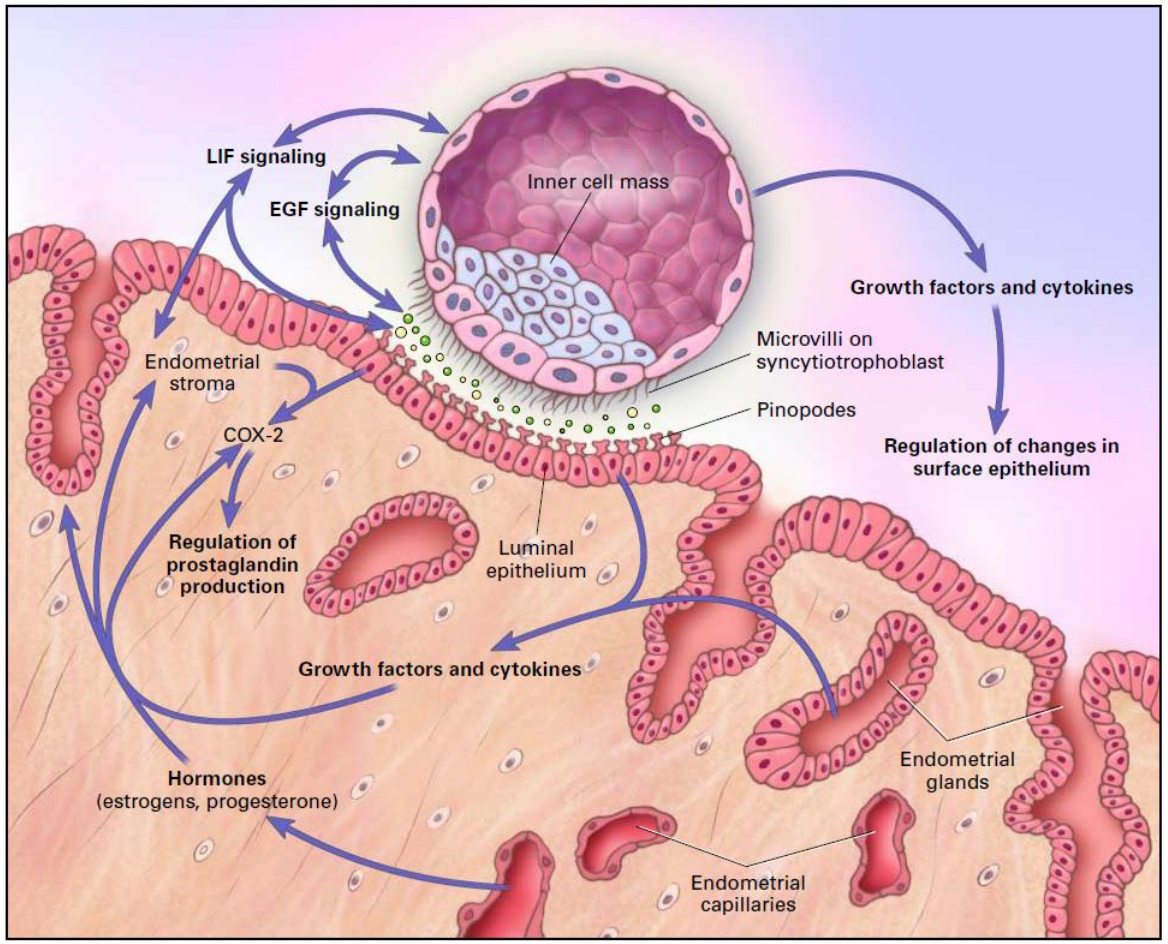
주관연구소 : 건양대학교 명곡의과학연구소
주관연구책임자 : 건양의대 산부인과 이성기

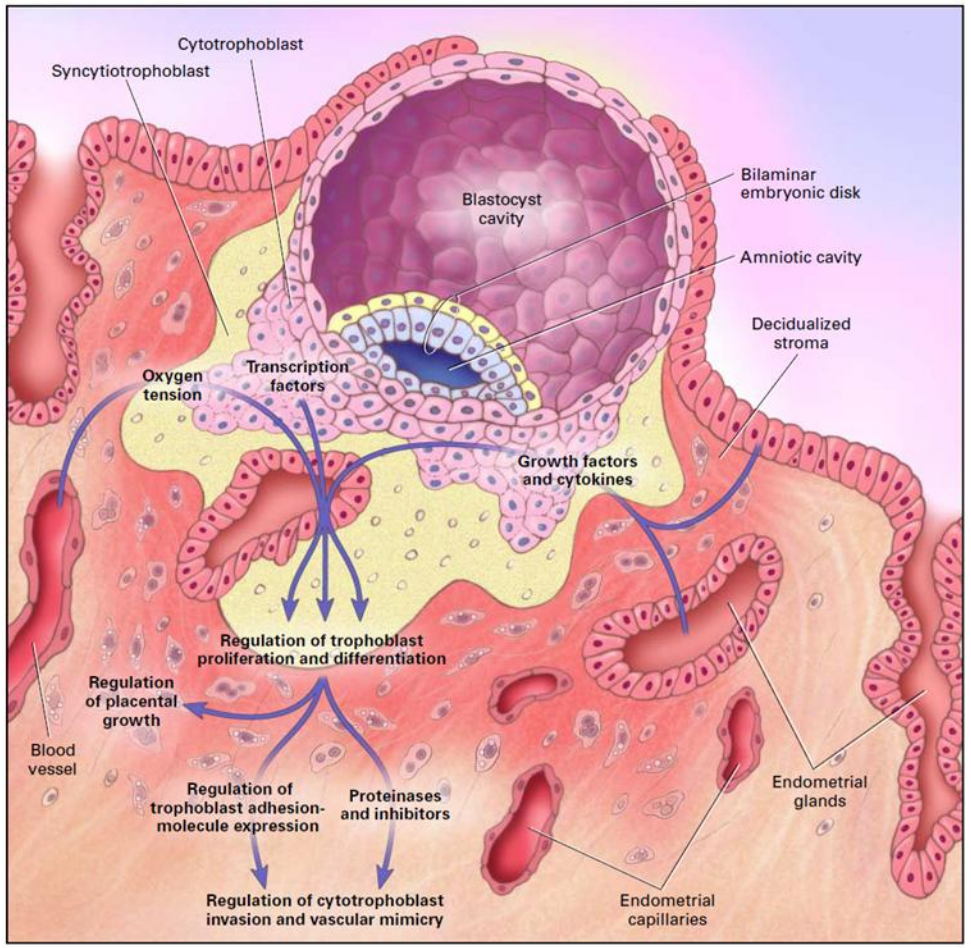
1세부과제 : 건양의대 산부인과 이성기
- 고위험임신 신개념 치료

2세부과제 : 건양의대 미생물학교실 박석래
- 배아 착상능력 향상 연구

3세부과제 : 건양의대 세포생물학교실 신종대
- 난소의 노화방지 연구

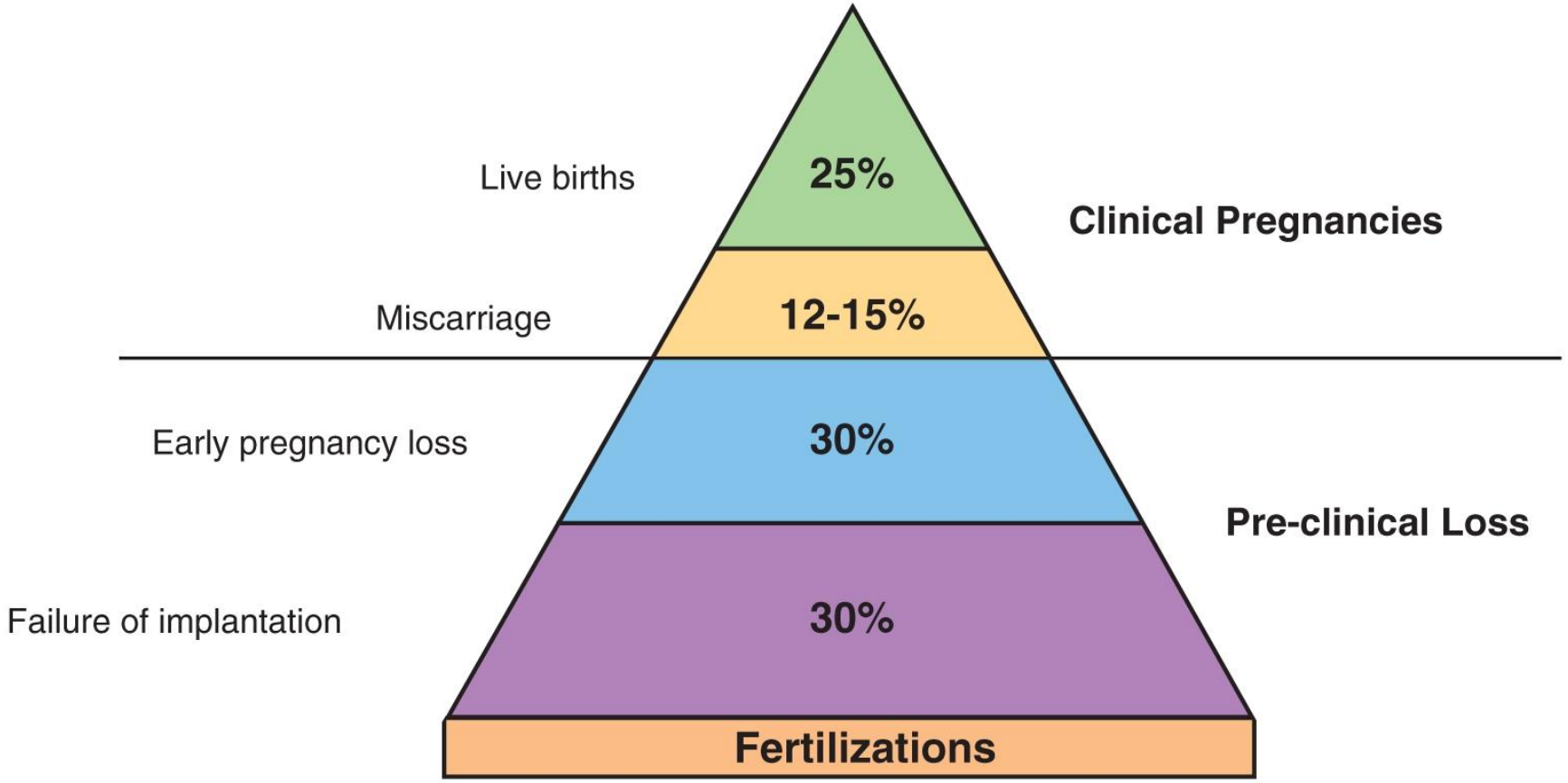
Blastocyst Apposition and Adhesion & Implantation

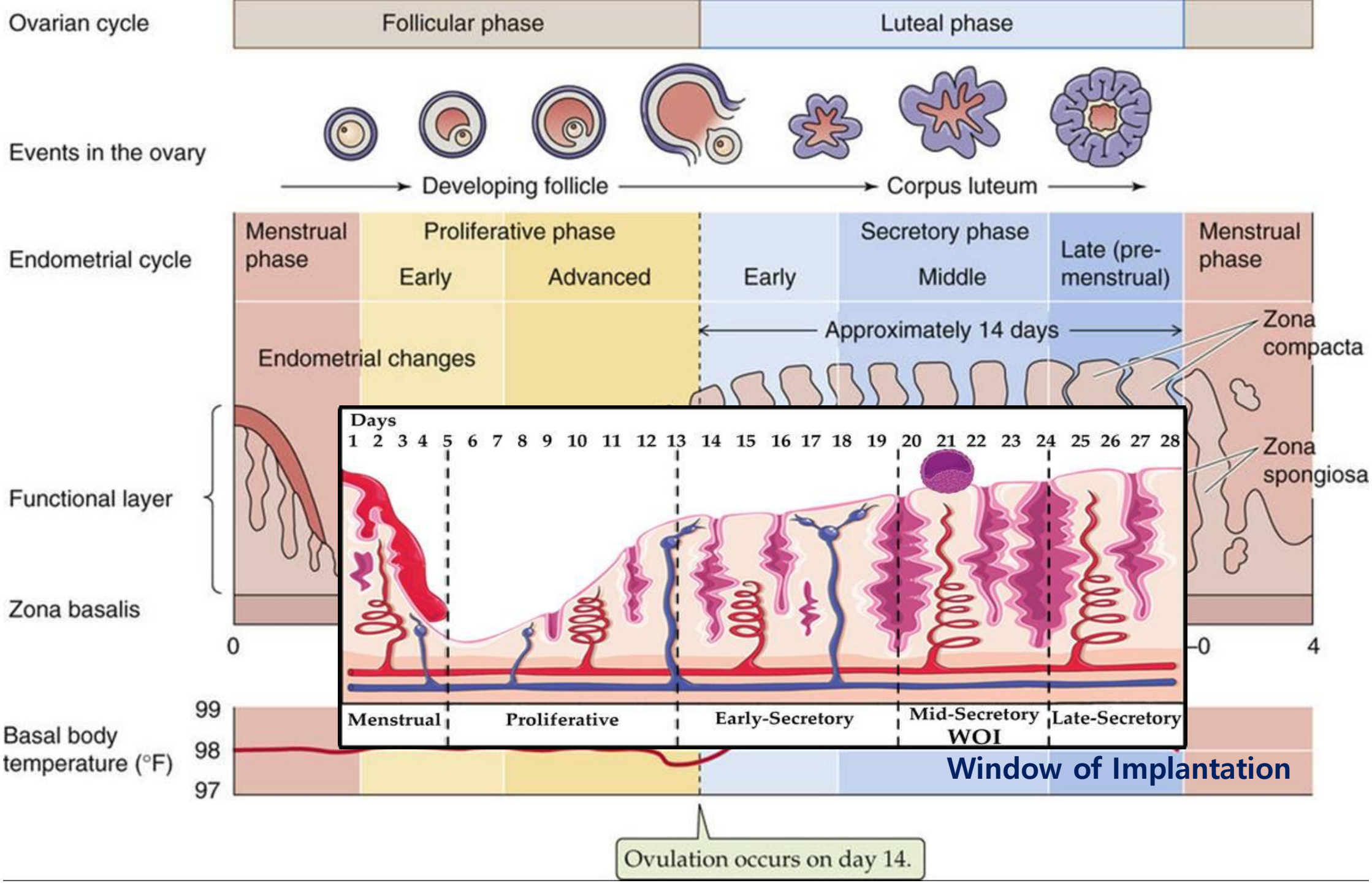




Norwitz et al. NEJM, 2001

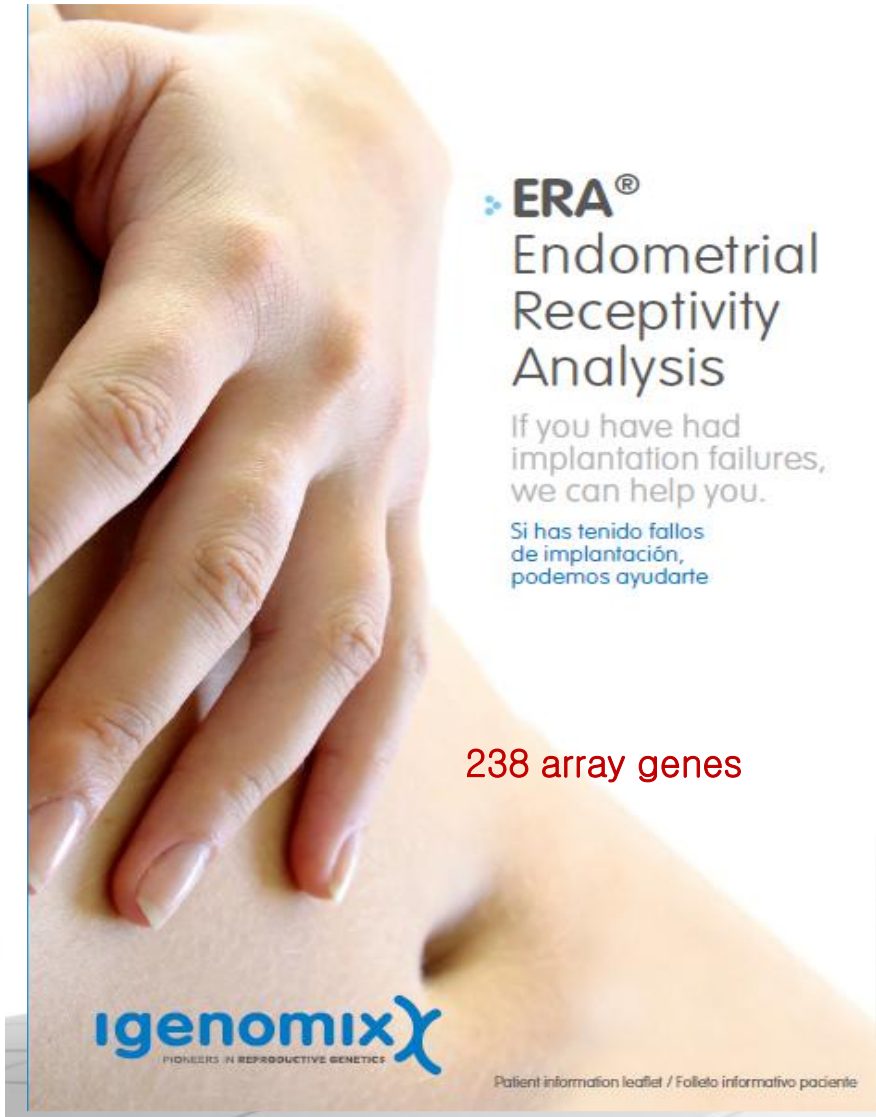
Outcome of Fertilization: Continuity of implantation & pregnancy




Ovarian cycle
Follicular phase
Luteal phase
Events in the ovary
Developing follicle
Corpus luteum
Endometrial cycle
Menstrual phase
Proliferative phase
Early
Advanced
Secretory phase
Early
Middle
Late (pre-menstrual)
Menstrual phase
Endometrial changes
Approximately 14 days
Zona compacta
Zona spongiosa
Functional layer
Zona basalis
Days
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Menstrual
Proliferative
Early-Secretory
Mid-Secretory
WOI
Late-Secretory
Window of Implantation
0
0
4
Basal body temperature (°F)
99
98
97
Ovulation occurs on day 14.

ERA : IVF 과정에서 배아 착상 최적 시기 (이식일) 결정

- **2014**년 첫 학회 발표 이후 지금까지 약 **3**만 **5**천여명의 반복적 착상 실패 환자들에서 시행
- 국내는 **2018**년에 도입 시행



EMMA & ALICE : 자궁내막 미생물 분석 및 독소 세균 확인 검사

A complete view of endometrial health

Recent studies led by Igenomix indicate that the endometrium is a key factor for reproductive success.

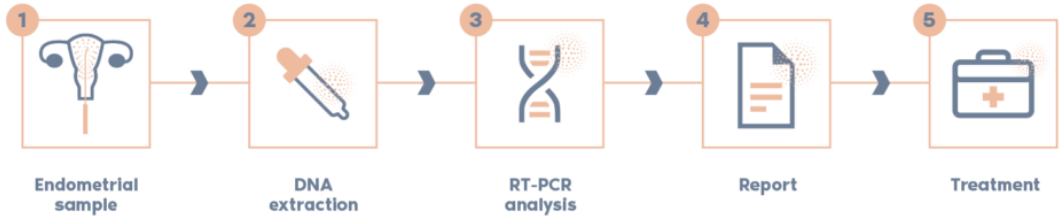
Embryo

Three tests using only one endometrial sample

	ALICE	EMMA	ERA
	Analysis of Infectious Chronic Endometritis	Endometrial Microbiome Metagenomic Analysis	Endometrial Receptivity Analysis
	Detects pathogenic bacteria	Indicates the endometrial microbiome balance	Determines the window of implantation
	ALICE detects chronic endometritis, a condition affecting 30% of infertile patients that is linked to implantation failure and recurrent miscarriage	EMMA provides information on the proportions of all endometrial bacteria, including those linked to higher pregnancy rates. Includes ALICE	ERA establishes the time when the endometrium is receptive, and reports the optimal time for personalized embryo transfer
Analyzes:			
Endometrial receptivity			✓
Chronic endometritis	✓	✓	
Endometrial flora		✓	

Methodology

EMMA TEST REQUIRES ONLY A SMALL ENDOMETRIAL SAMPLE



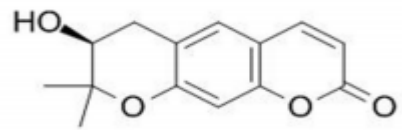
자궁내막 착상 증강물질 탐색 1 : 한의학 유효물질 시험

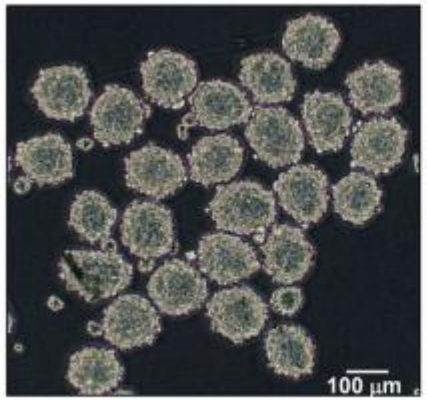
Kim *et al. BMC Complementary Medicine and Therapies* (2020) 20:36
https://doi.org/10.1186/s12906-020-2822-z

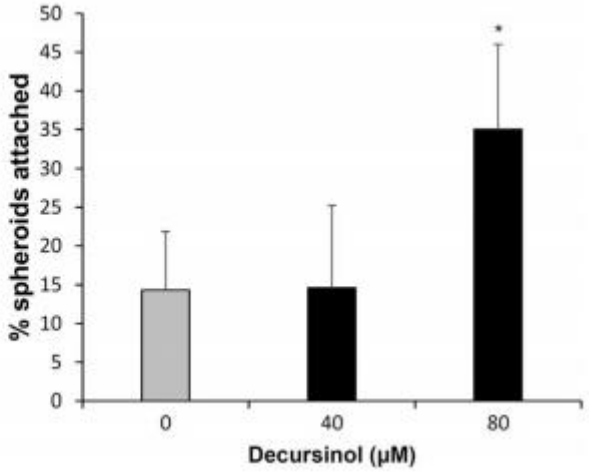
BMC Complementary Medicine and Therapies

RESEARCH ARTICLE Open Access

Decursinol from *Angelica gigas* Nakai enhances endometrial receptivity during implantation







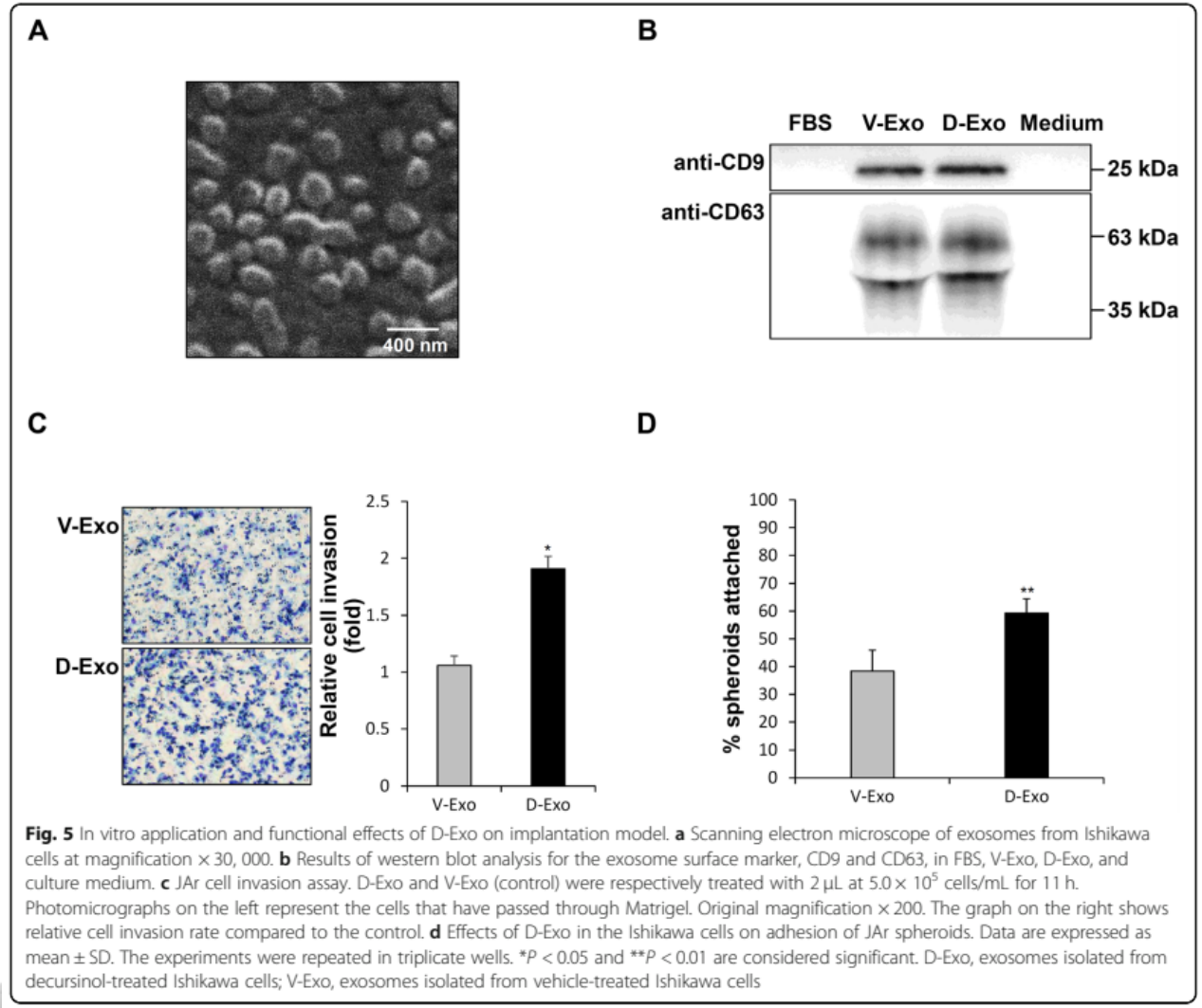
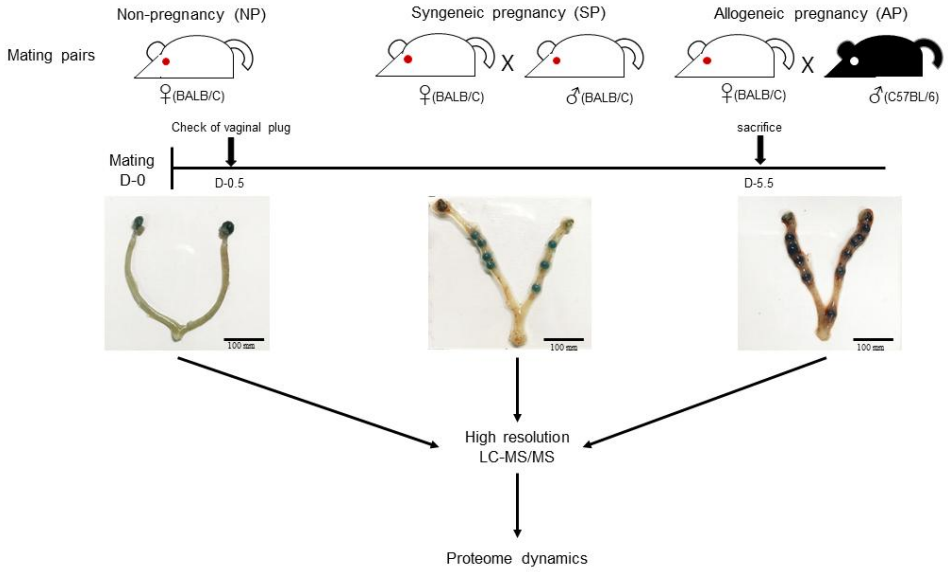
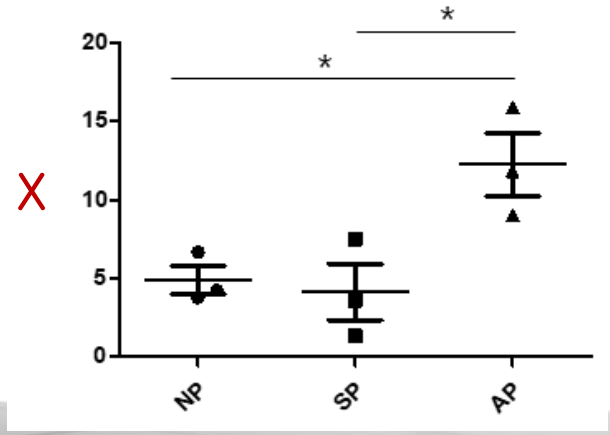
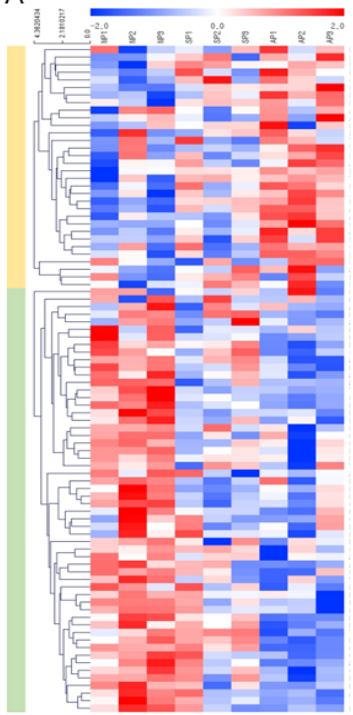


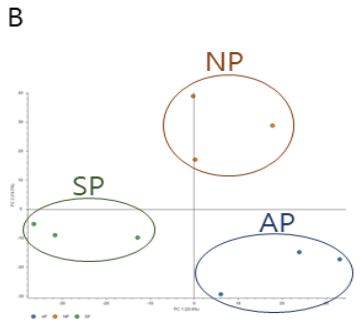
Fig. 5 In vitro application and functional effects of D-Exo on implantation model. **a** Scanning electron microscope of exosomes from Ishikawa cells at magnification × 30, 000. **b** Results of western blot analysis for the exosome surface marker, CD9 and CD63, in FBS, V-Exo, D-Exo, and culture medium. **c** JAr cell invasion assay. D-Exo and V-Exo (control) were respectively treated with 2 μL at 5.0×10^5 cells/mL for 11 h. Photomicrographs on the left represent the cells that have passed through Matrigel. Original magnification × 200. The graph on the right shows relative cell invasion rate compared to the control. **d** Effects of D-Exo in the Ishikawa cells on adhesion of JAr spheroids. Data are expressed as mean ± SD. The experiments were repeated in triplicate wells. $^*P < 0.05$ and $^{**}P < 0.01$ are considered significant. D-Exo, exosomes isolated from decursinol-treated Ishikawa cells; V-Exo, exosomes isolated from vehicle-treated Ishikawa cells

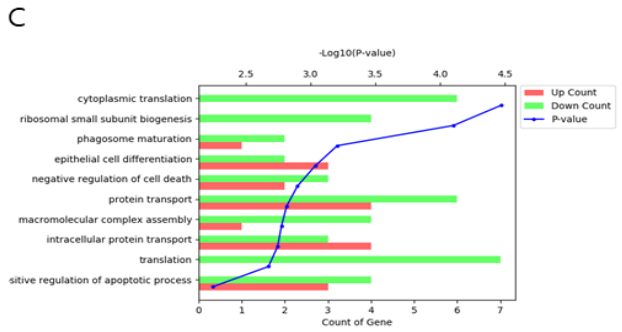
자궁내막 착상 증강물질 탐색 2 : 면역관용 관련 내인성 단백질 탐색

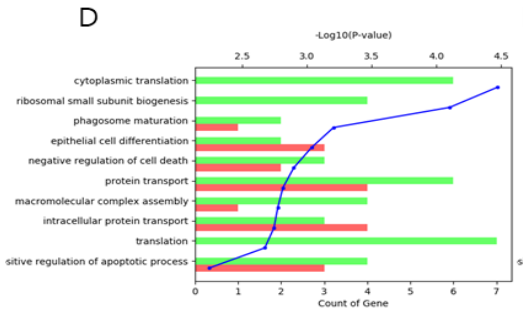


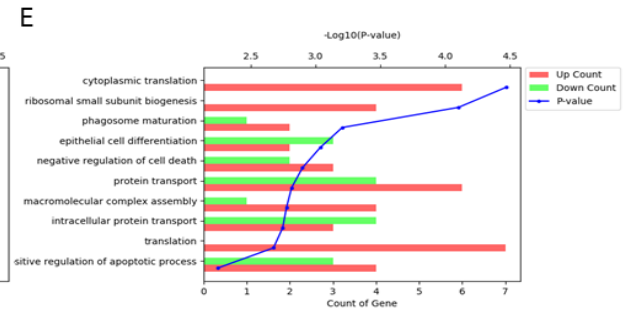












- 비임신 및 동계 자궁과 비교해 동종이계 자궁에서 88개 단백질 발현의 유효한 변화 발견 → 기능 분석 중
- 자궁착상 증강 관련성 높은 **후보 X 선정** (분비 증가)
- **Unpublished Data**

자궁내막 착상 증강물질 탐색 3 : Exosome로 전달되는 유효인자 시험

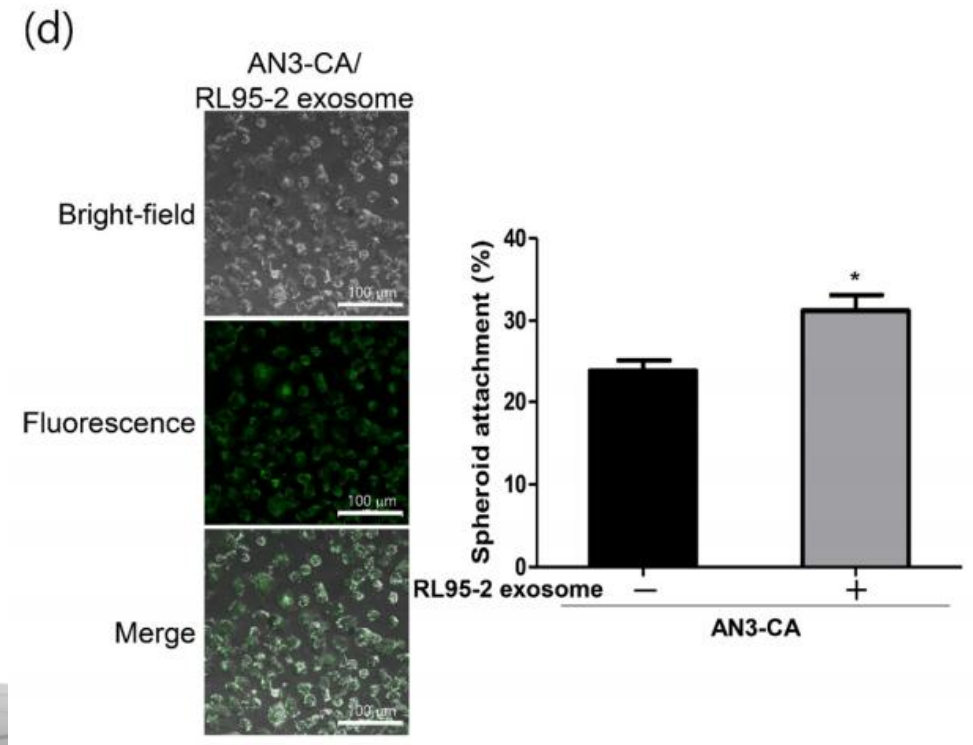
International Journal of *Molecular Sciences*

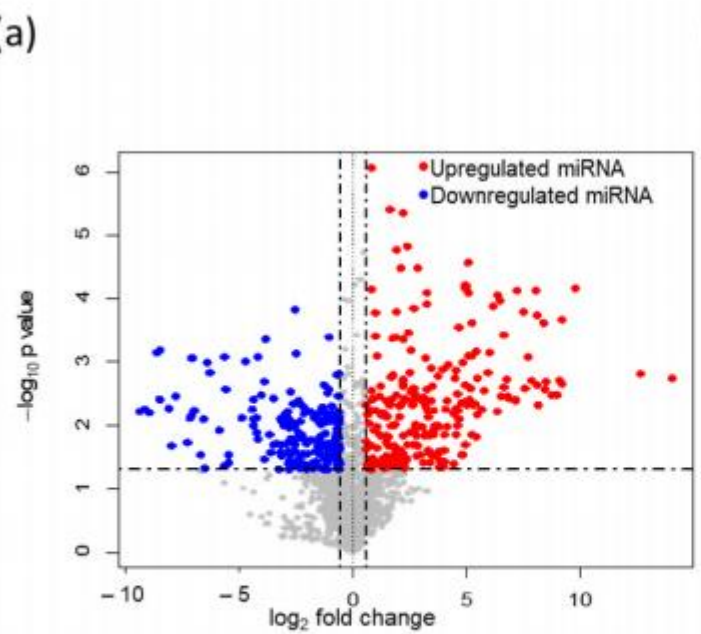
Int. J. Mol. Sci. **2023**, *24*, 15149. https://doi.org/10.3390/ijms242015149

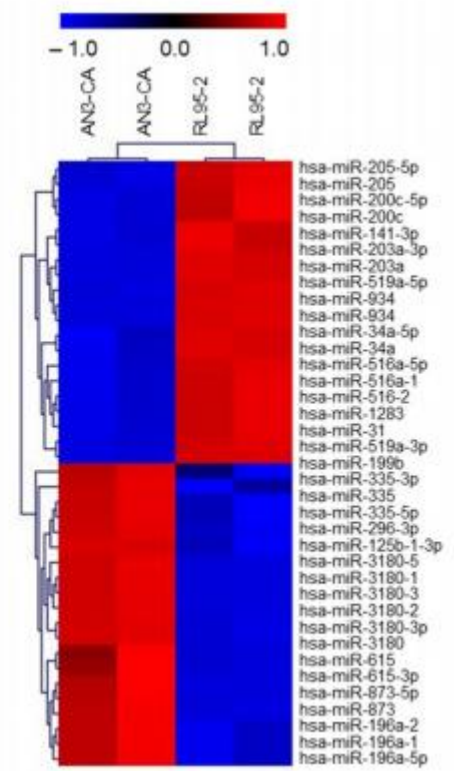
MDPI

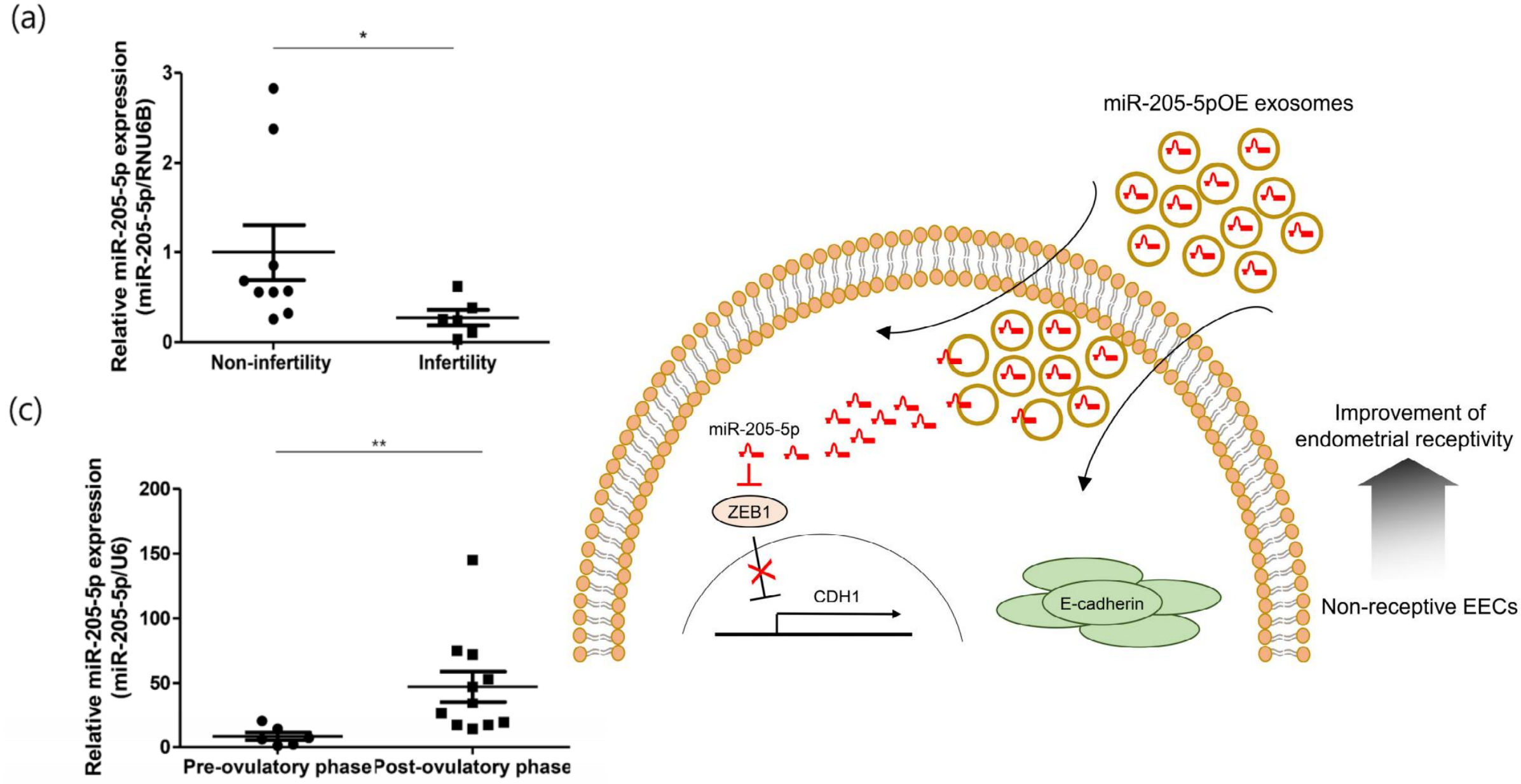
Article

Exosomal miR-205-5p Improves Endometrial Receptivity by Upregulating E-Cadherin Expression through ZEB1 Inhibition





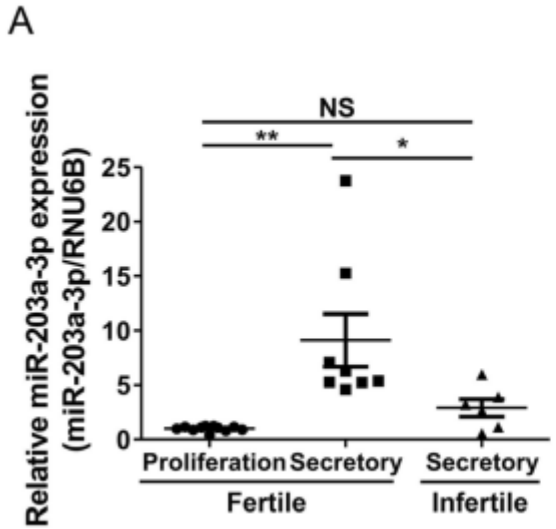


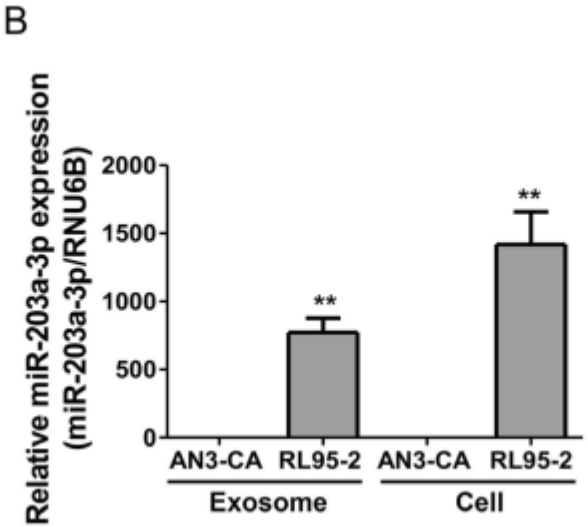

(a)
*
Relative miR-205-5p expression
(miR-205-5p/RNU6B)
3
2
1
0
Non-infertility
Infertility
(c)
**
Relative miR-205-5p expression
(miR-205-5p/U6)
200
150
100
50
0
Pre-ovulatory phase
Post-ovulatory phase
miR-205-5pOE exosomes
miR-205-5p
ZEB1
CDH1
E-cadherin
Improvement of
endometrial receptivity
Non-receptive EECs

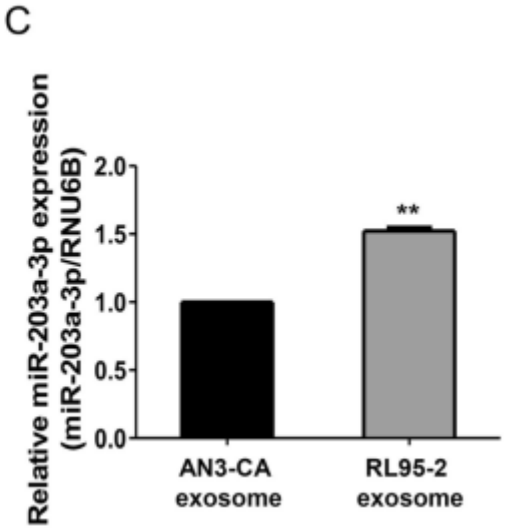
자궁내막 착상 증강물질 탐색 4 : Exosomal miR-203a-3p

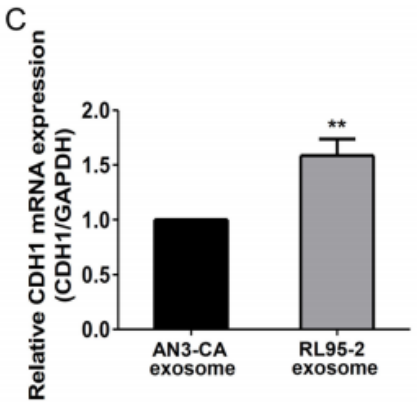
Reproductive Medicine and Biology, 2025; 24:e12689
https://doi.org/10.1002/rmb2.12689

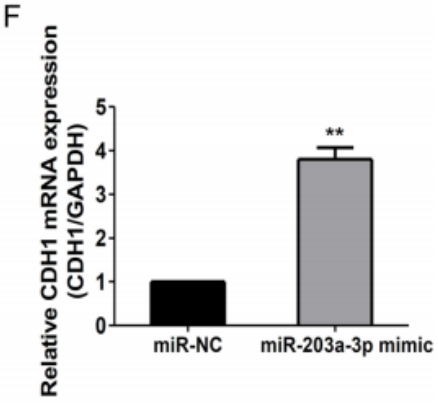
Exosomal miR-203a-3p Enhances Endometrial Receptivity by Upregulating E-Cadherin Expression Through the Direct Targeting of SNAI1 in Endometrial Epithelial Cells

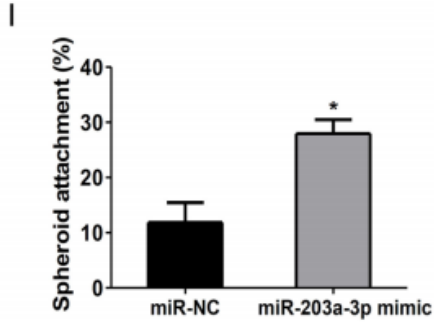


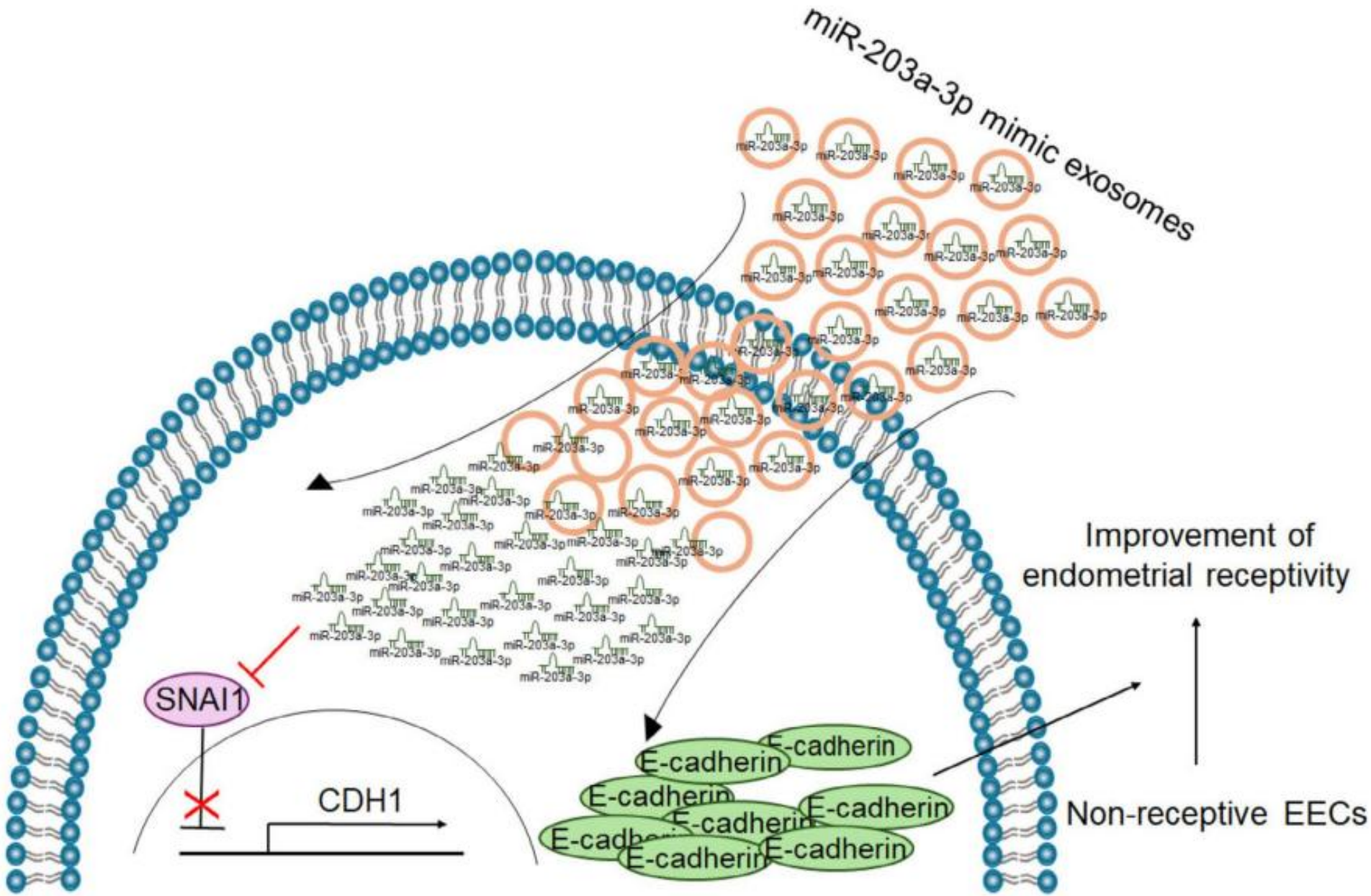




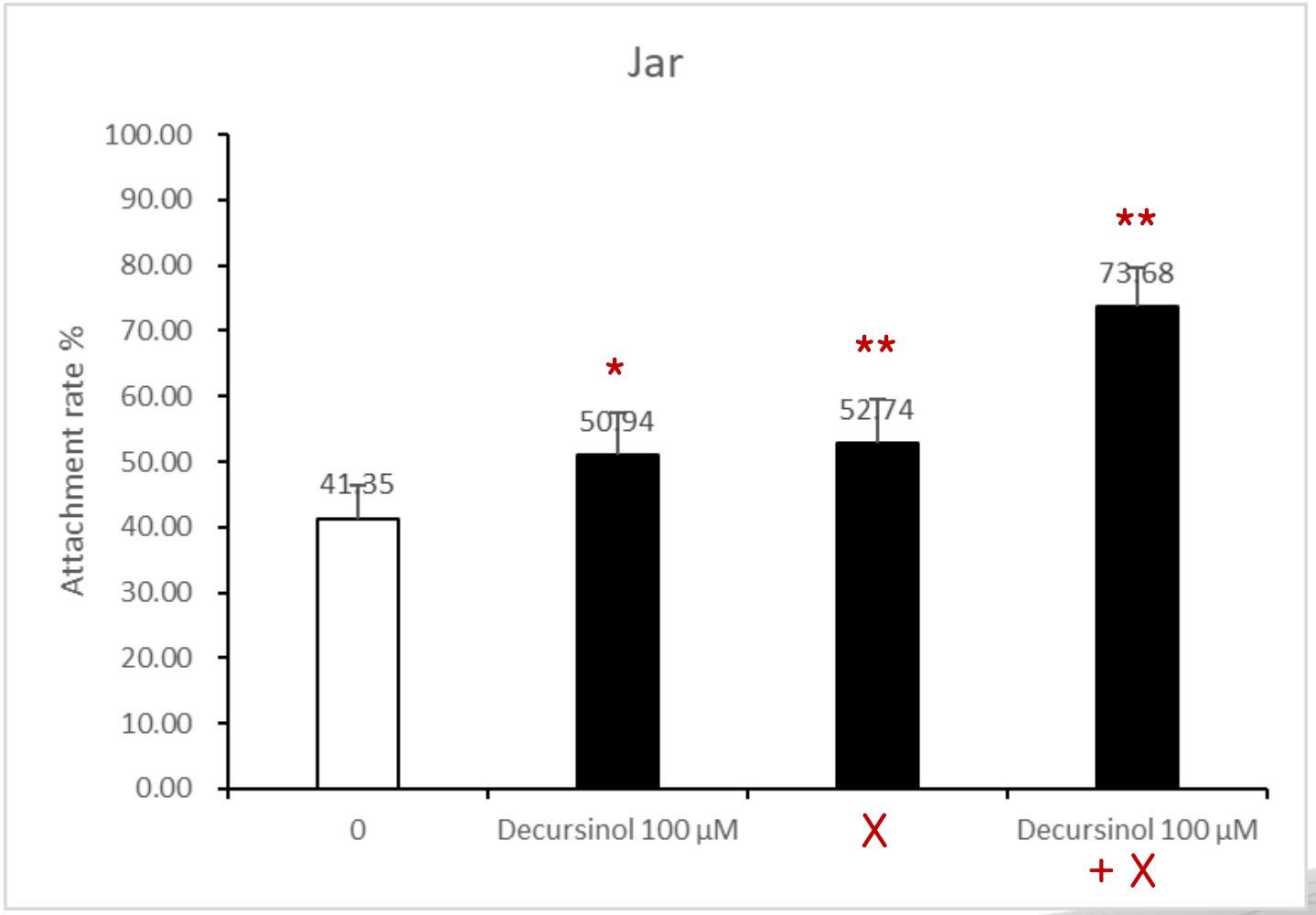


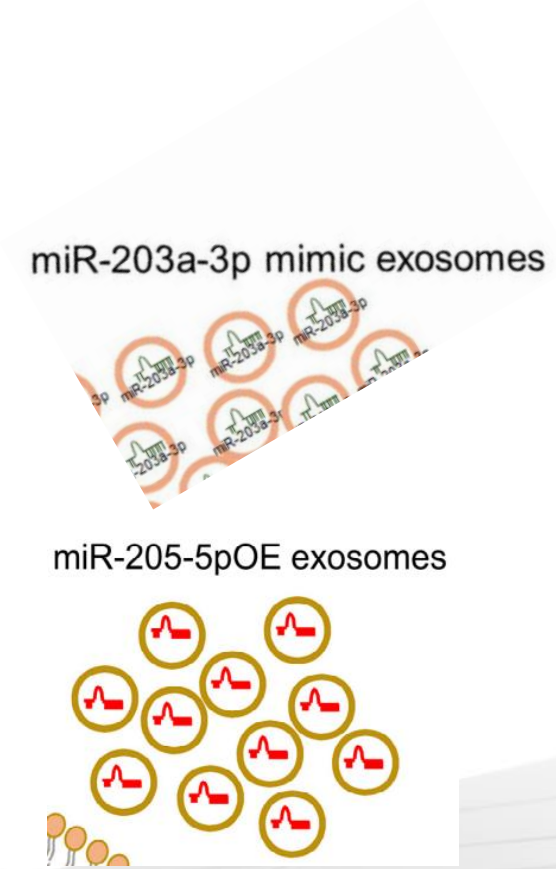





miR-203a-3p mimic exosomes
miR-203a-3p
SNAI1
CDH1
E-cadherin
Improvement of
endometrial receptivity
Non-receptive EECs

EndPower (안) : 최적의 자궁내막 착상 증강제 개발





EndPower (안) : HUcMSCs Exosomes 활용 계획

Assessment of stemness markers in CI-MSC using qPCR

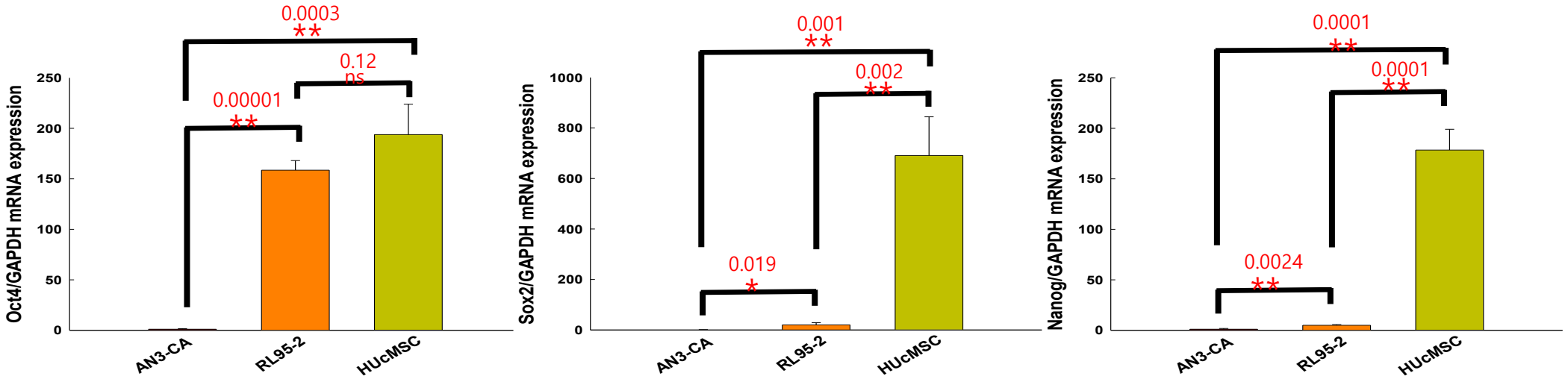


Figure 1. Expression of Oct4, Sox2, and Nanog in conditionally immortalized human umbilical cord mesenchymal stem cells (CI-HUCMSCs). CI-HUCMSCs at passage 11 were cultured, and the expression of Oct4, Sox2, and Nanog were assessed by real-time PCR. GAPDH was used as a internal reference gene for normalization of gene expression. NS: No significance. Error bars represent the means ± SD(n=3). **P<0.005. *P<0.05.

Cell-type specific expression analysis of miR-205 and miR-203

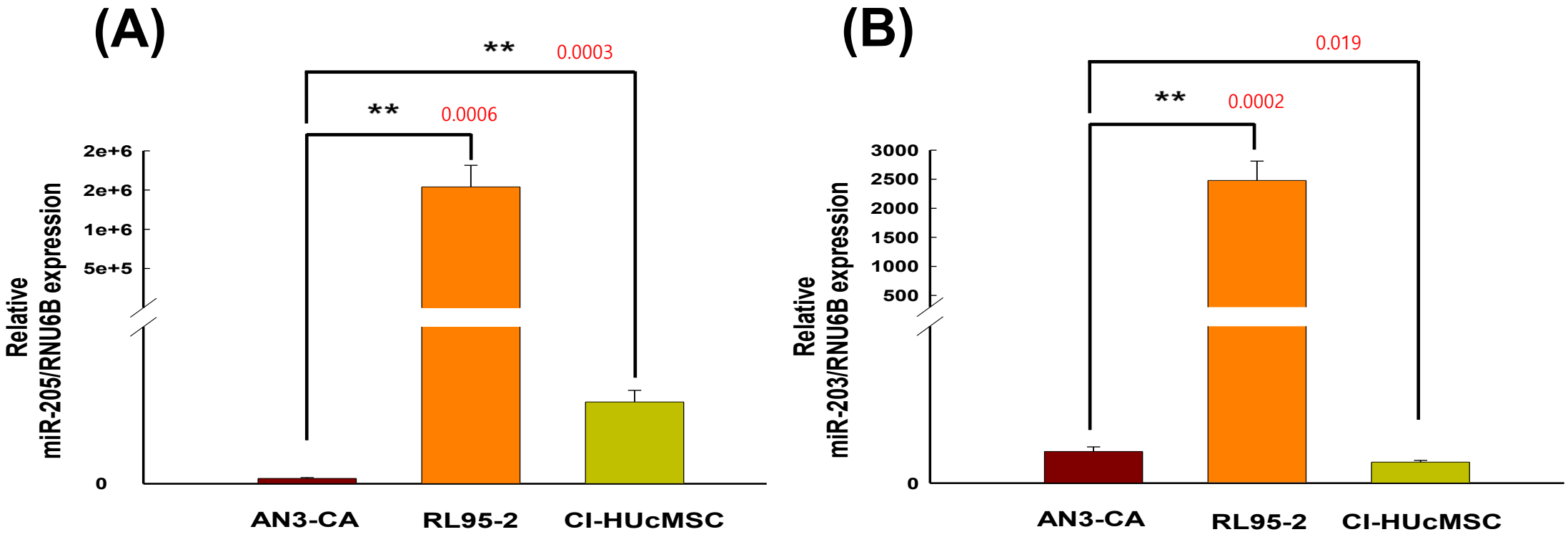


Figure 2. Quantitative analysis of miR-205 and miR-203 expression in endometrial and mesenchymal stem cells.

(A) Expression levels of miR-205 in AN3-CA, RL95-2, and CI-HUCMSCs.

(B) Expression levels of miR-203 in AN3-CA, RL95-2, and CI-HUCMSCs.

Expression of miR-205, and miR-203 was assessed by real-time PCR. RNU6B was used as an internal reference gene for normalization. Error bars indicate means ± SD. (n=3). **P<0.005.

EnCUTE (안) : 자궁내막 착상 관련 진단 마커 개발

EXPERIMENTAL AND THERAPEUTIC MEDICINE
SPANDIDOS PUBLICATIONS

Exp Ther Med. 2021 Jun; 21(6): 660.
Published online 2021 Apr 20. doi: 10.3892/etm.2021.10092

PMCID: PMC8097233
PMID: 33968190

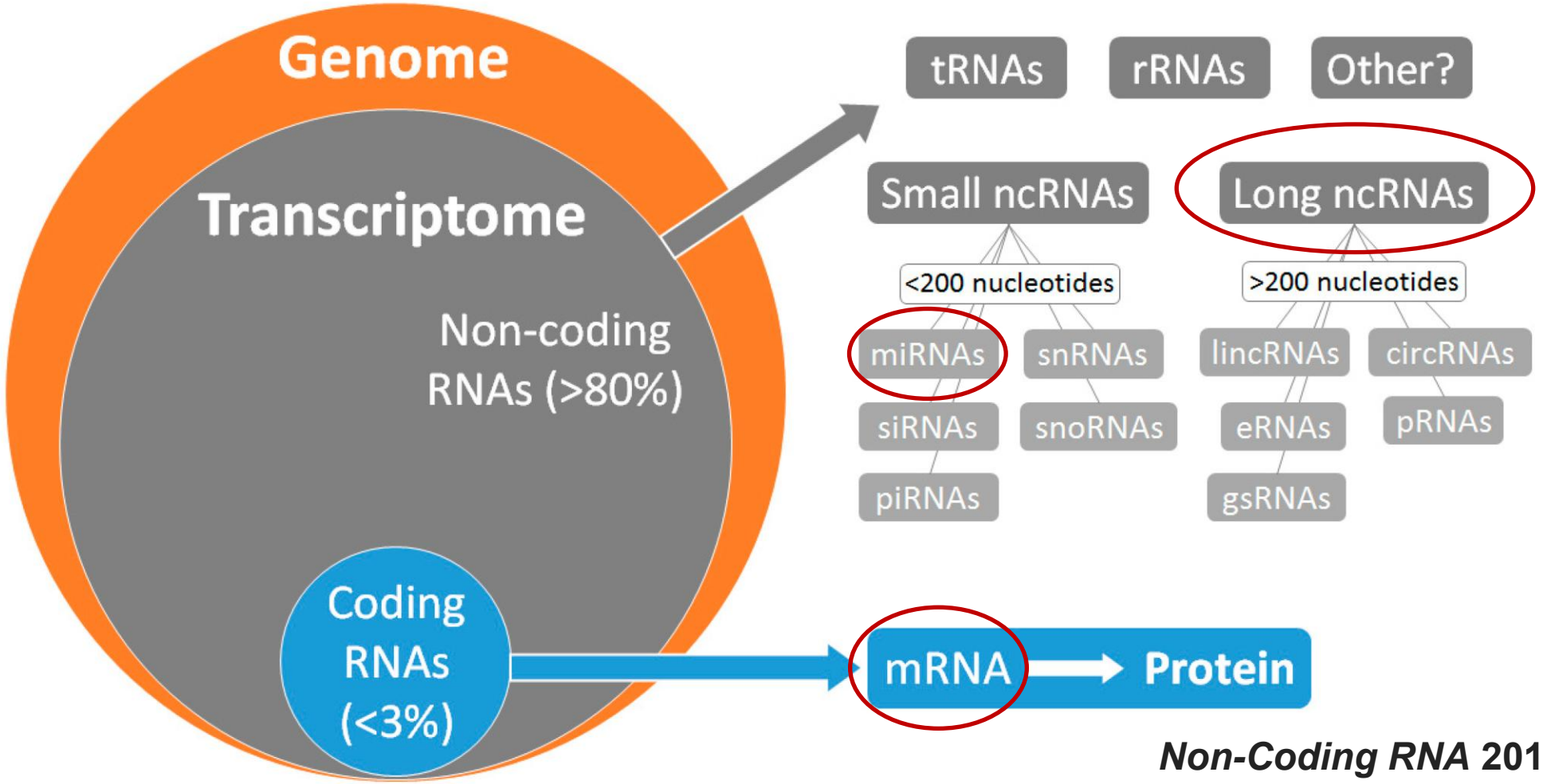
Transcriptomic analysis and competing endogenous RNA network in the human endometrium between proliferative and mid-secretory phases

Variables/Group	Proliferative phase (n=15)	Secretory phase (n=15)	P-value
Age (years)	37.5±2.7	36.9±2.4	0.53[a]
BMI (kg/m^2)	22.6±3.3	22.2±3.4	0.77[a]
Number of live births, n (%)			0.09[b]
1	4 (26.6)	7 (46.6)	
2	7 (46.6)	8 (53.3)	
3	4 (26.6)	0 (0.0)	
Number of abortions, n (%)			0.13[b]
0	13 (86.6%)	10 (66.6%)	
1	1 (6.6%)	5 (33.3%)	
2	1 (6.6%)	0 (0.0%)	

P-values were determined using the [a]Student t-test and [b]Fisher's exact test. Age and BMI data are presented as the mean ± SD.

This study was approved by the Bioethics Committee of Konyang University Hospital (IRB File No. 2018-11-007-005).

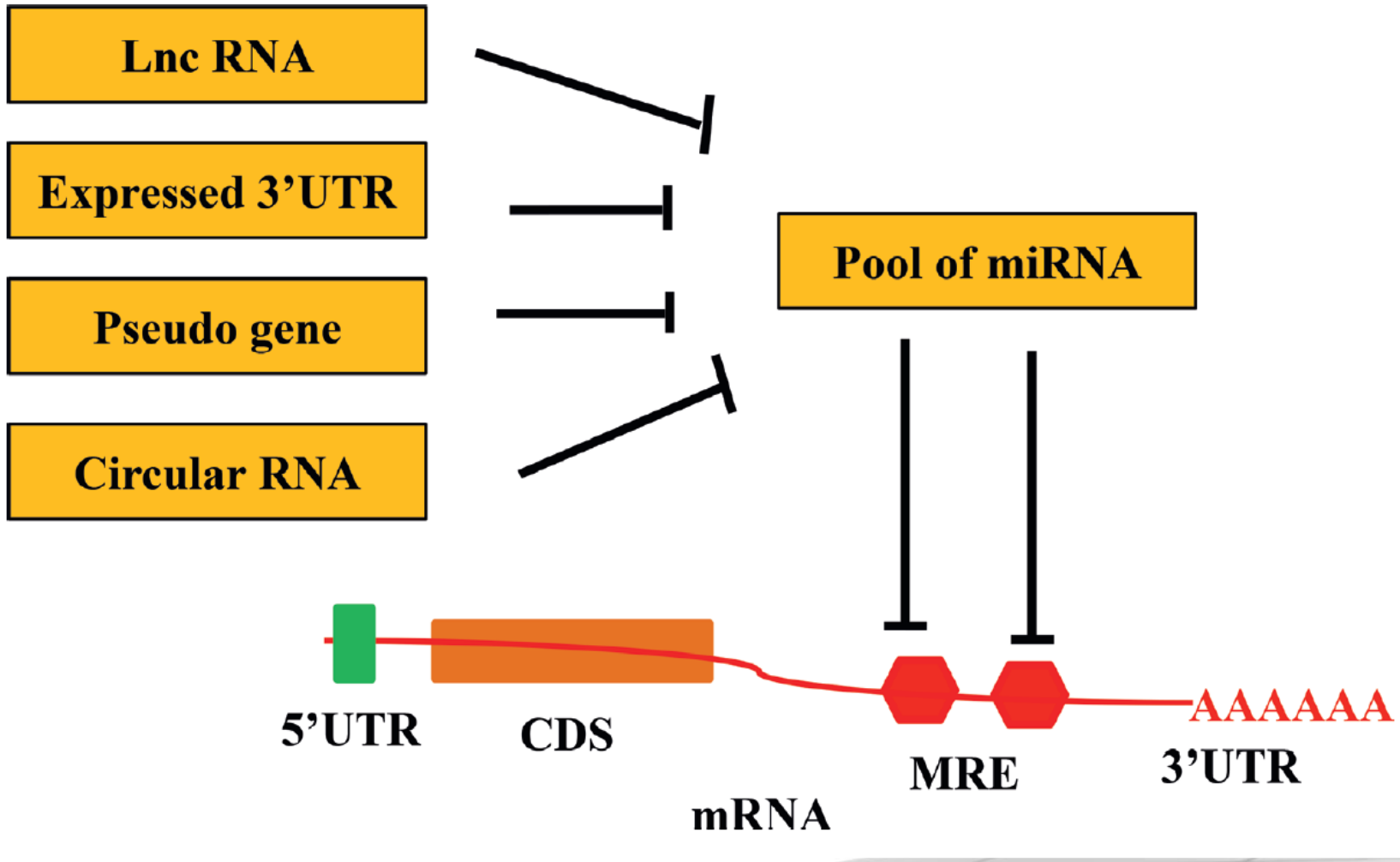
Coding and non-coding RNAs in the human genome



***Non-Coding RNA* 2019, *5*(2), 31**

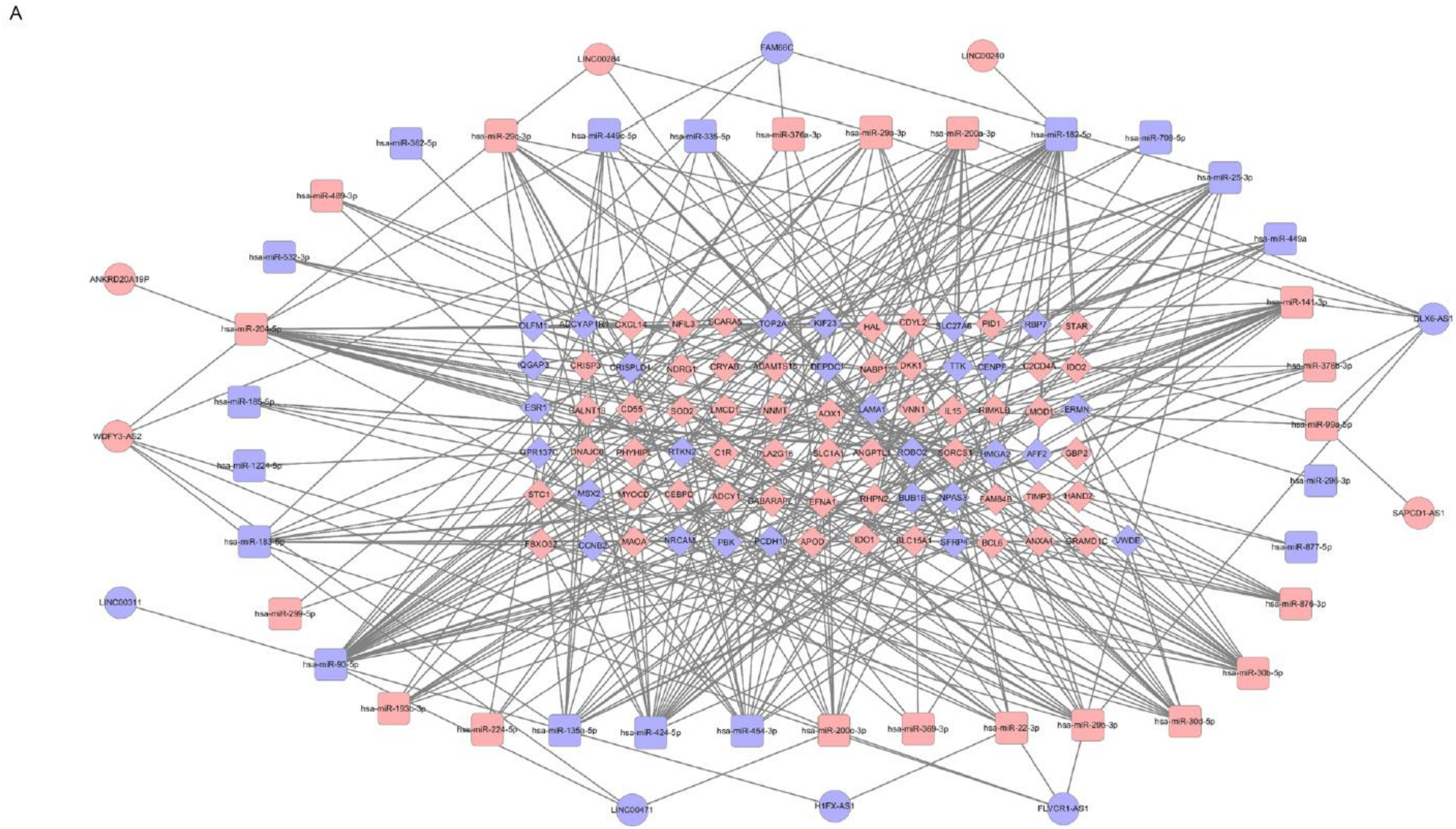
tRNAs, transfert RNAs; rRNAs, ribosomal RNAs; ncRNAs, noncoding RNAs; miRNAs, microRNAs; siRNAs, small-interfering RNAs; snRNAs, small nuclear RNAs; snoRNAs, small nucleolar RNAs; piRNAs, piwi-interacting RNAs; linRNAs, long intergenic RNAs; eRNAs, extracellular RNAs; gsRNAs, germline small RNAs; circRNAs, circular RNAs; pRNAs, promoter-associated RNAs; mRNA, messenger RNA.

The competitive endogenous RNAs (ceRNAs) hypothesis

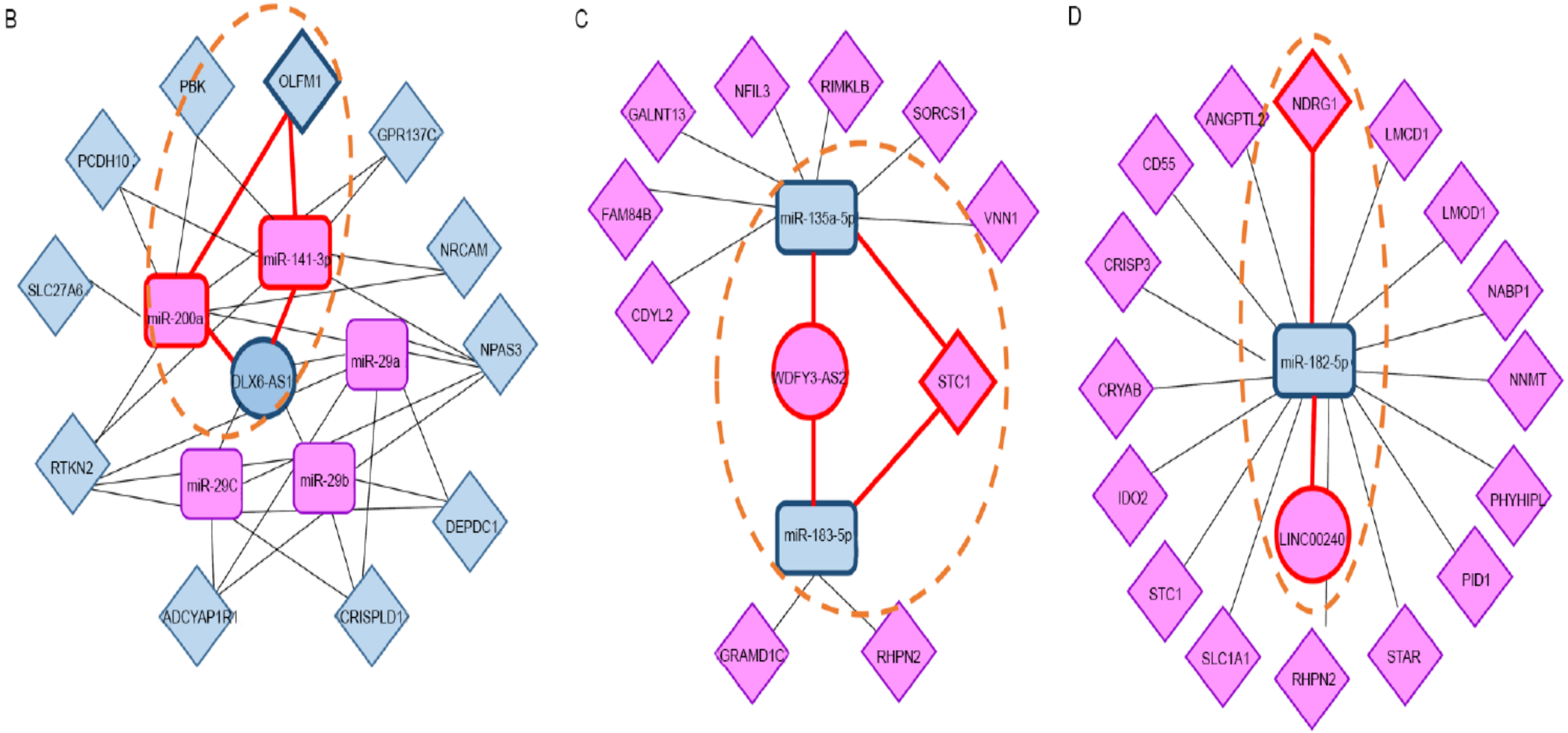


http://dx.doi.org/10.5772/intechopen.76125

lncRNA/miRNA/mRNA ceRNAs network related to endometrial receptivity



Three ceRNAs subnetwork for endometrial receptivity



EnCUTE (안) 마커 후보 1 : SIRT1

Reproductive Biology 22 (2022) 100672

Contents lists available at ScienceDirect

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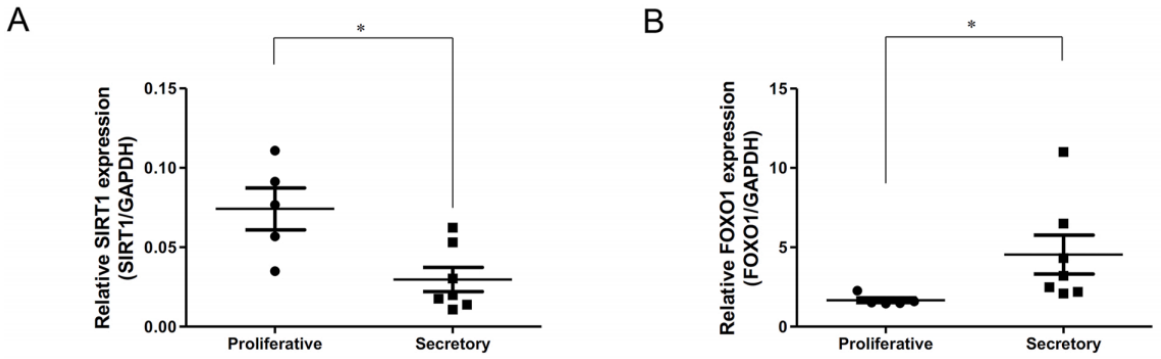
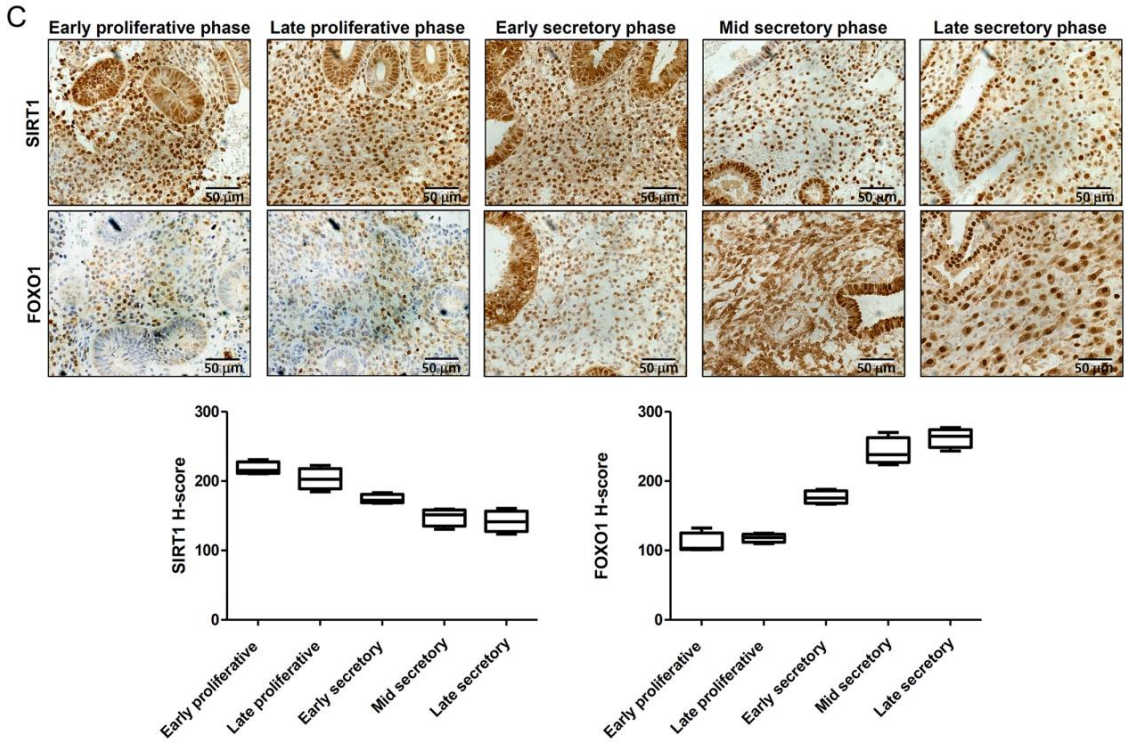
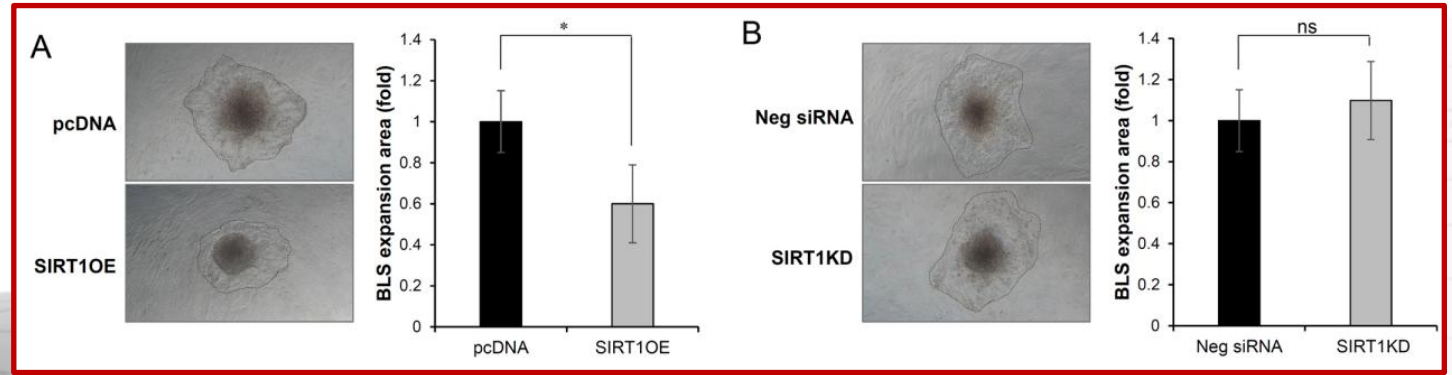
journal homepage: www.journals.elsevier.com/reproductive-biology

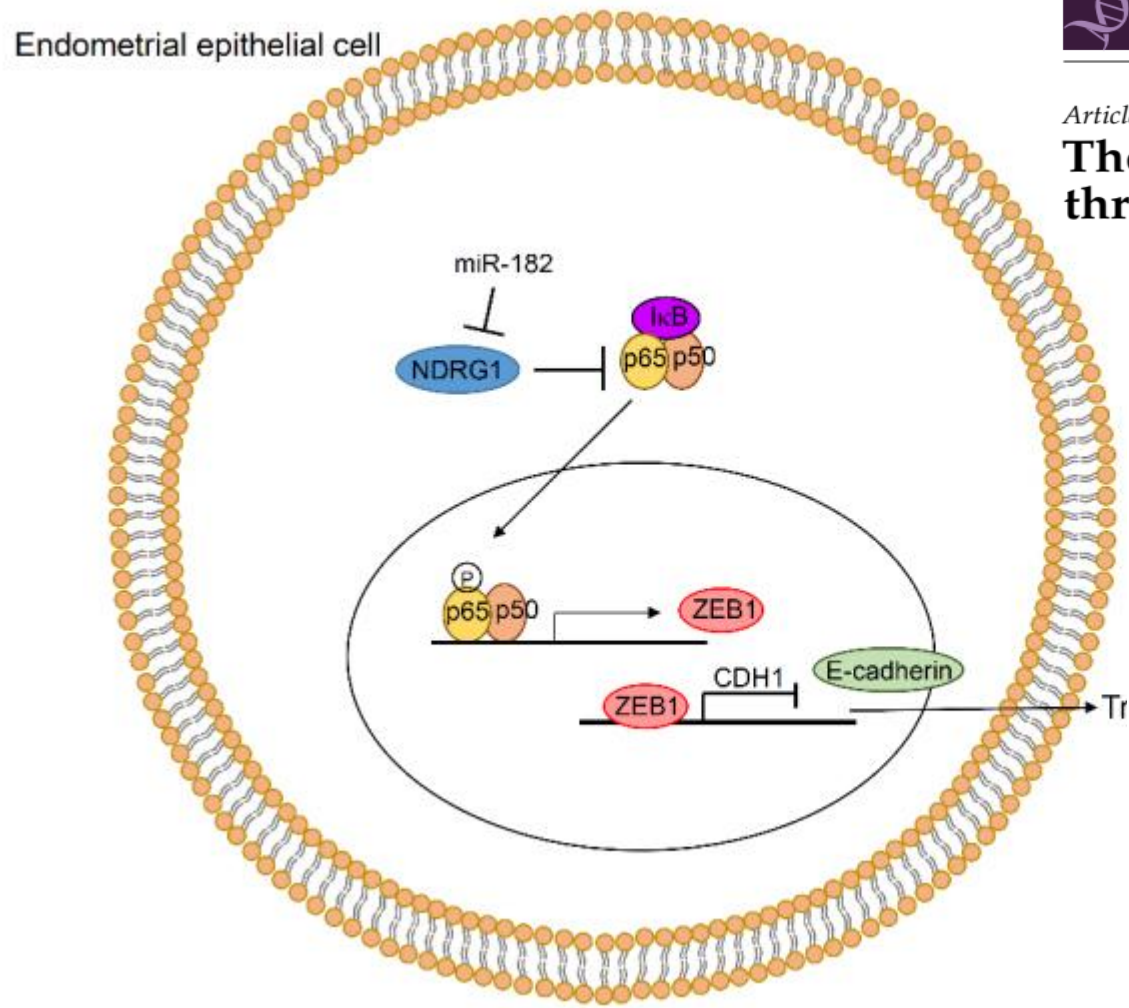
SIRT1 suppresses *in vitro* decidualization of human endometrial stromal cells through the downregulation of forkhead box O1 expression







EnCUTE (안) 마커 후보 2 : miR-182-5p



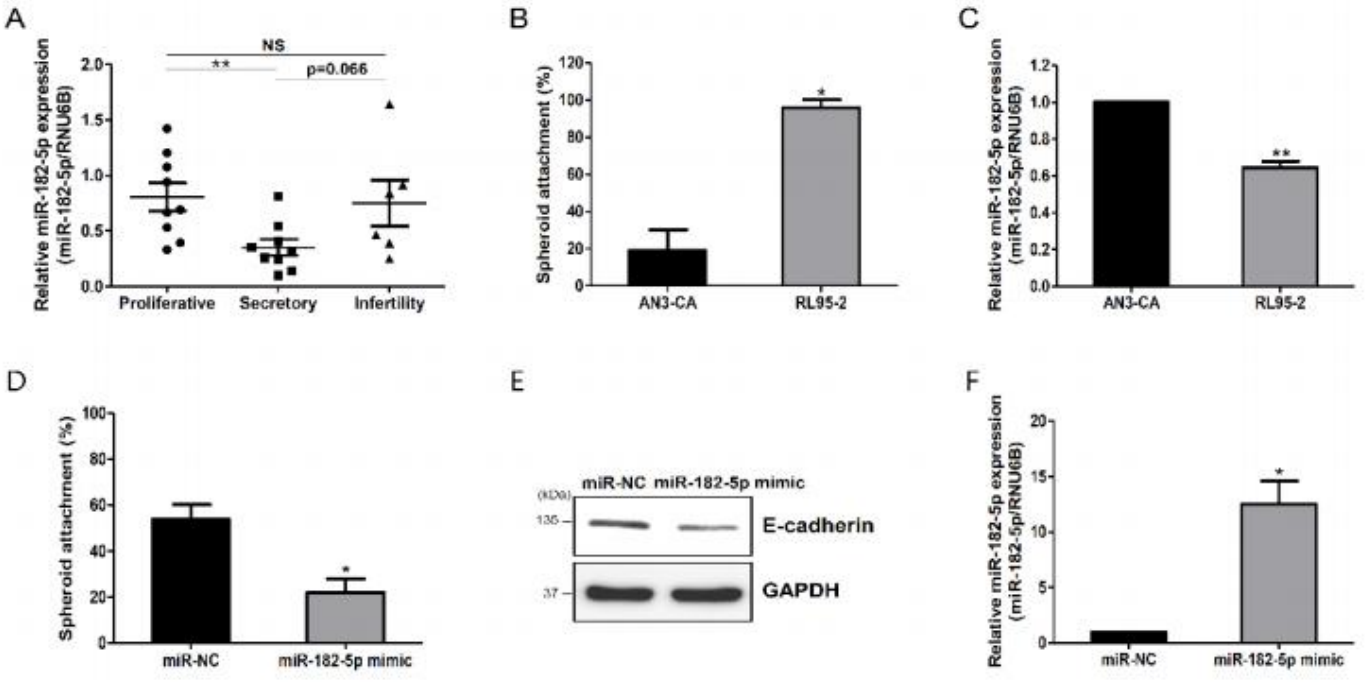
International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2022**, *23*, 12303. https://doi.org/10.3390/ijms232012303

MDPI

Article

The miR-182-5p/NDRG1 Axis Controls Endometrial Receptivity through the NF-κB/ZEB1/E-Cadherin Pathway

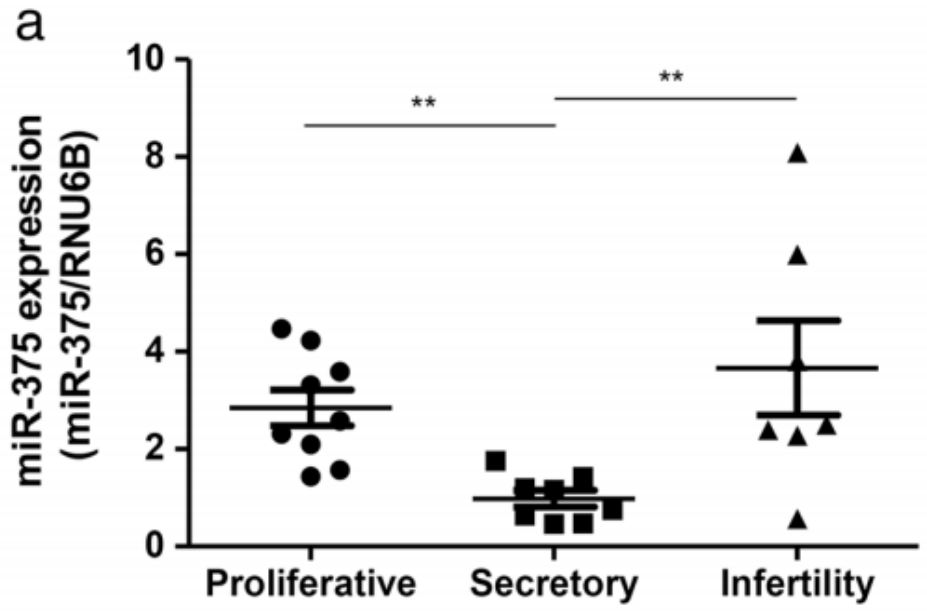


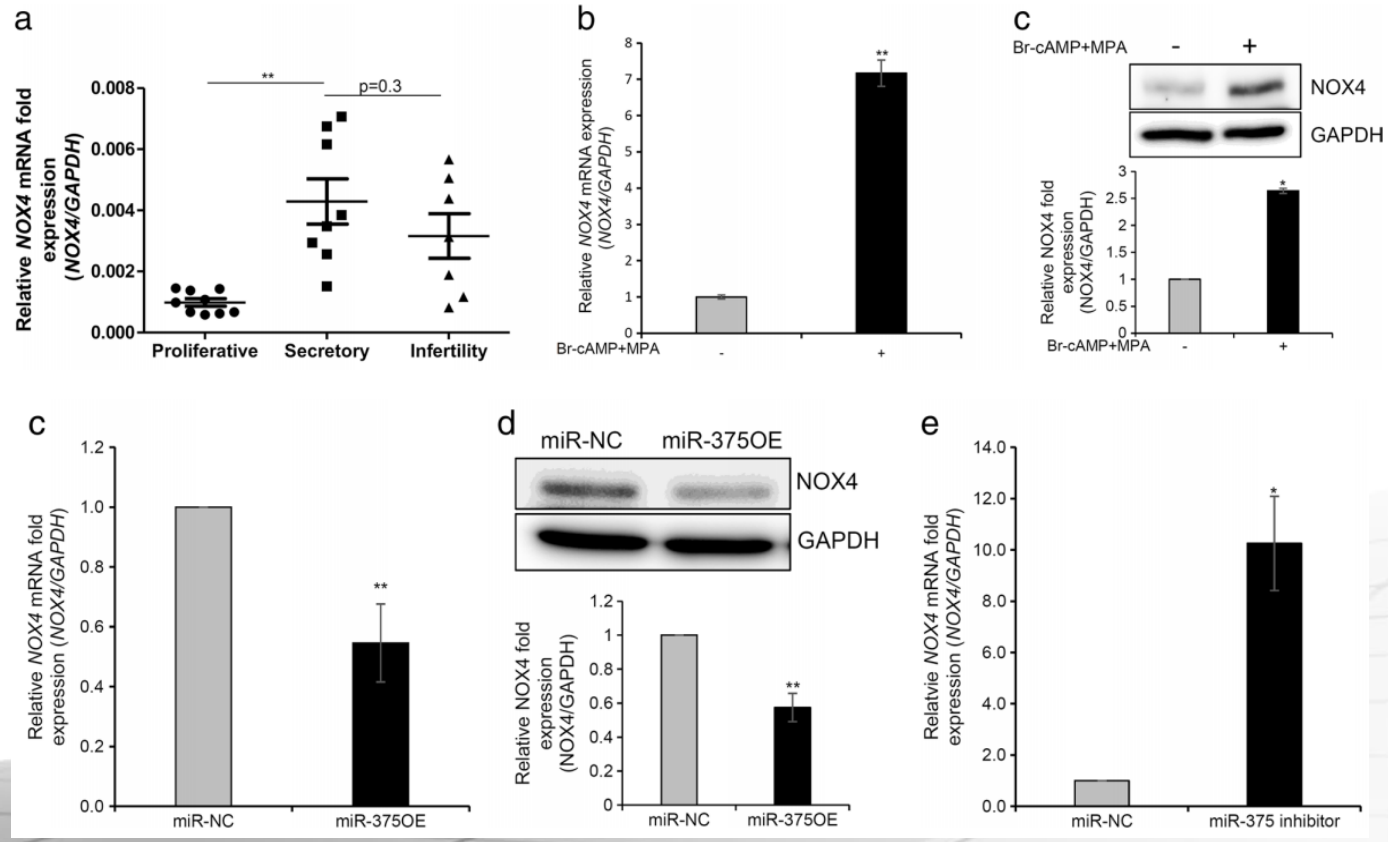
EnCUTE (안) 마커 후보 3 : miR-375

Reproductive Sciences
https://doi.org/10.1007/s43032-022-00854-w
Published online: 24 January 2022

REPRODUCTIVE BIOLOGY: ORIGINAL ARTICLE

Impairment of Decidualization of Endometrial Stromal Cells by hsa-miR-375 Through NOX4 Targeting

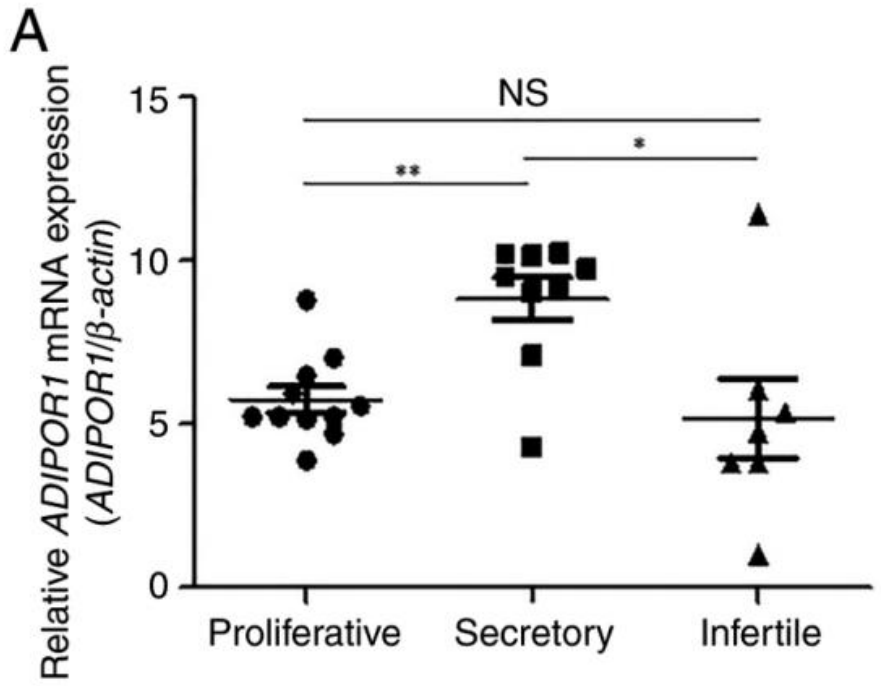




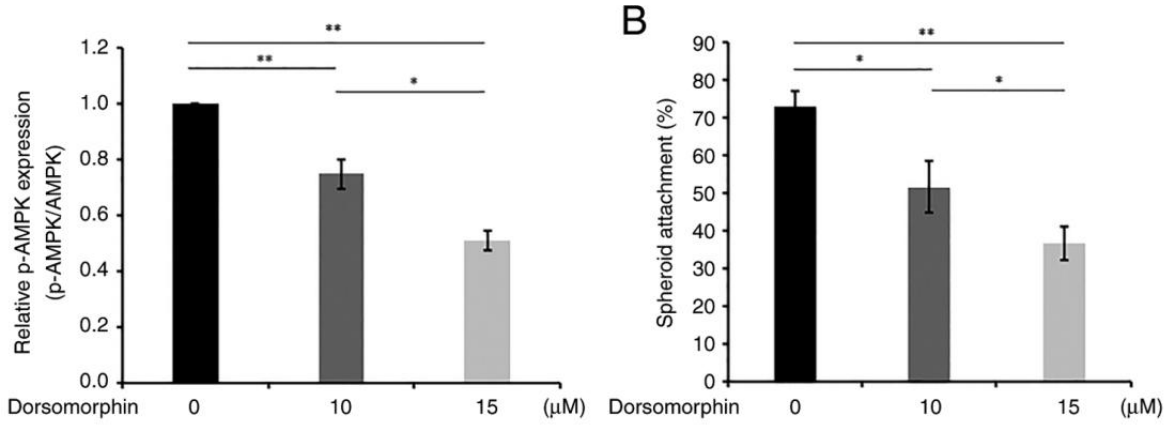
EnCUTE (안) 마커 후보 4 : Adiponectin receptor 1

SPANDIDOS PUBLICATIONS
MOLECULAR MEDICINE REPORTS 30: 184, 2024

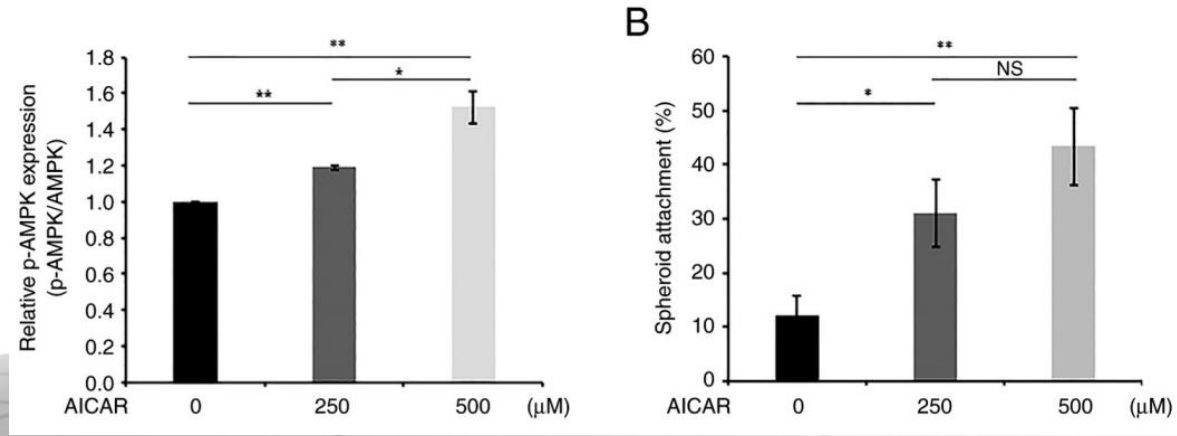
Adiponectin receptor 1 regulates endometrial receptivity via the adenosine monophosphate-activated protein kinase/E-cadherin pathway



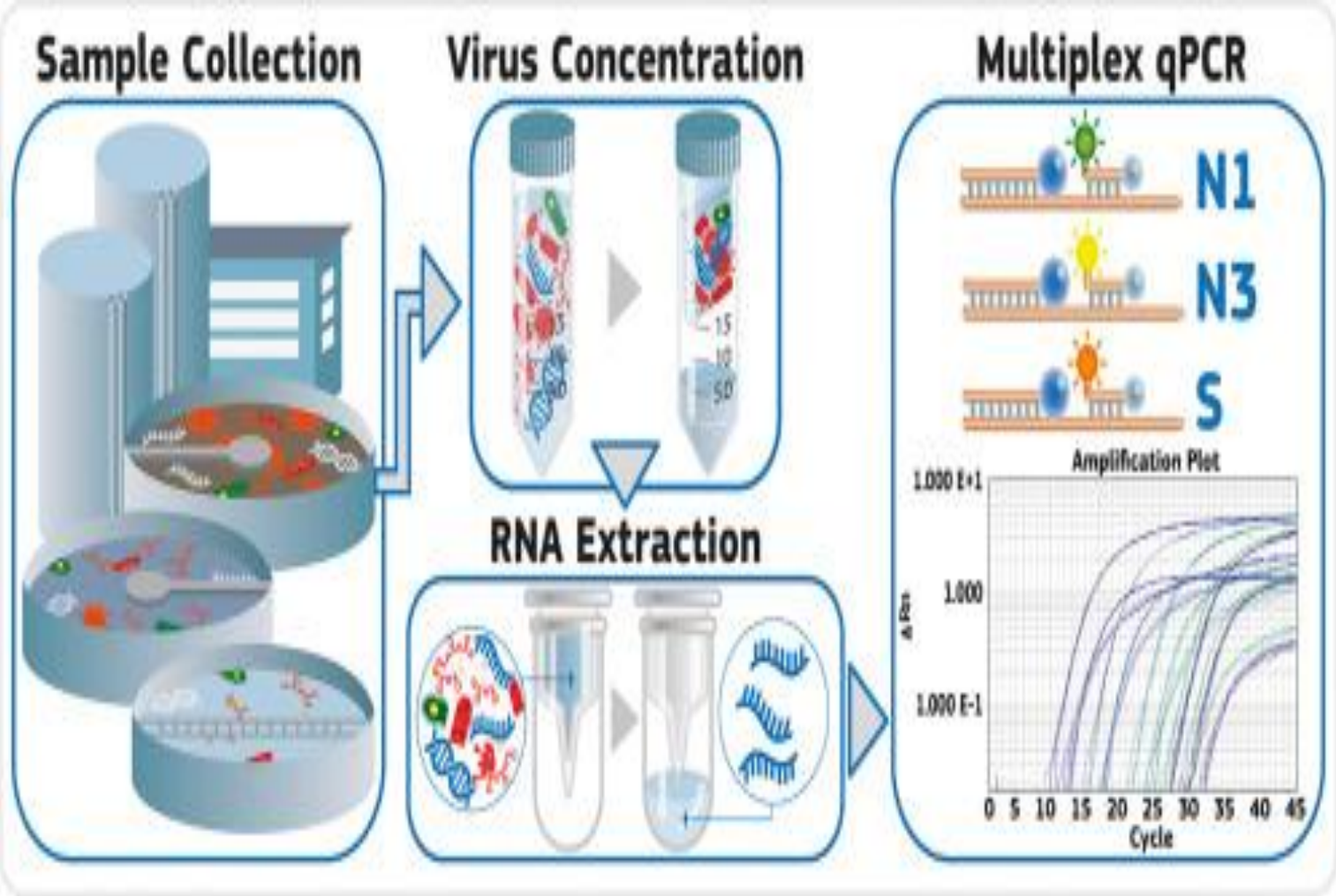
AMPK Signal Inhibitor



AMPK Signal Activator



EnCUTE (안) : Endometrium Cure Test → Multiplex qPCR



- 임상 시료 대상 특이도 및 민감도 검증
- 최적화된 Multiplex RT-qPCR Kit 개발

- 진단 결과에 따른 적절한 치료
- 예; SIRT1 SiRNA / miR-182-5p inhibitor / miR-375 inhibitor / AMPK Signal activator

2세부 : 배아 착상능력 향상 연구팀

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대단히 감사합니다.