PHYSIOLOGICAL ROLE OF PROGESTERONE IN THE LUTEAL PHASE AND THE ENDOMETRIUM

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DISCLOSURE

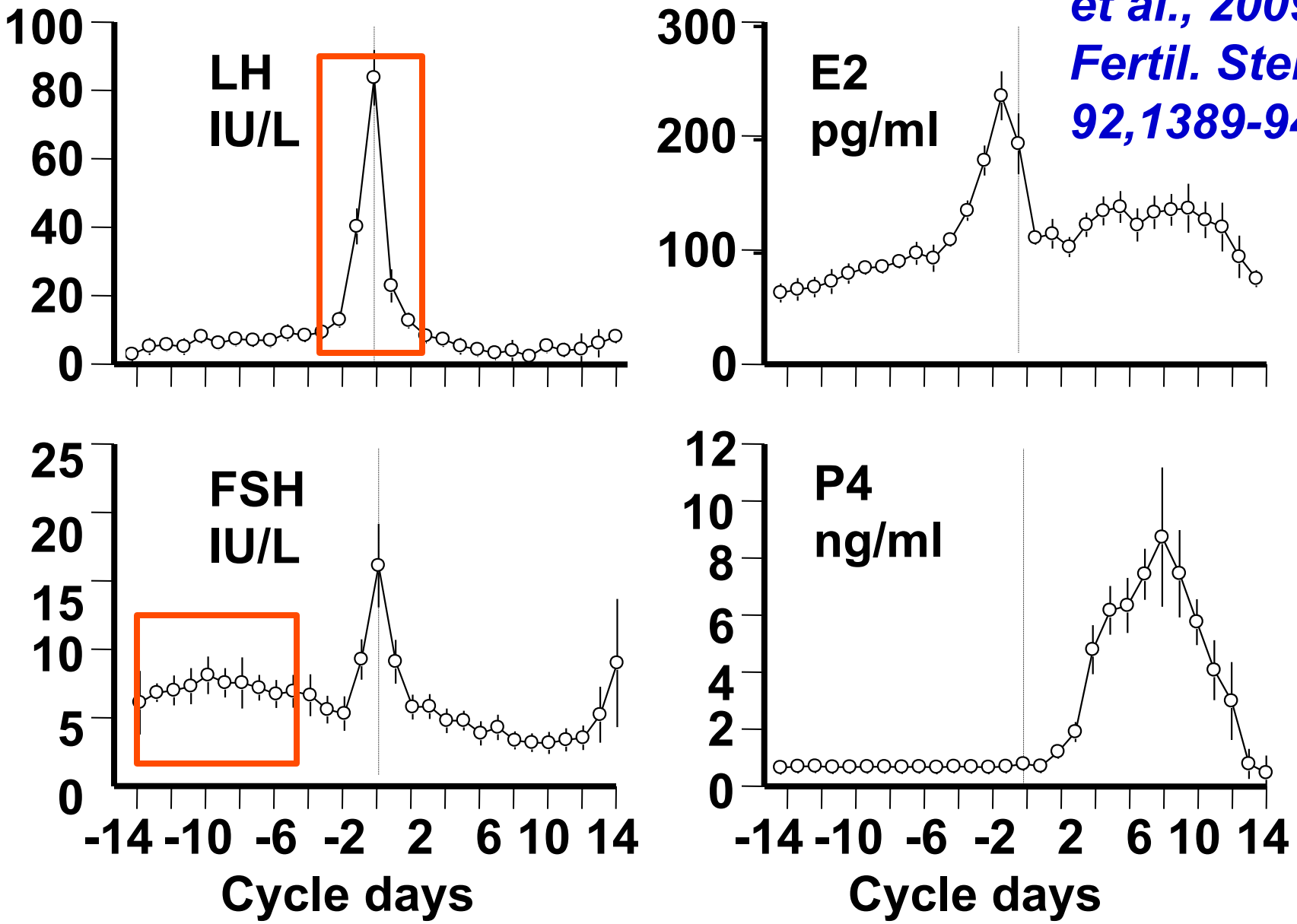
Nothing to disclose

Learning Objectives

At the conclusion of this presentation, the participant should be able to:

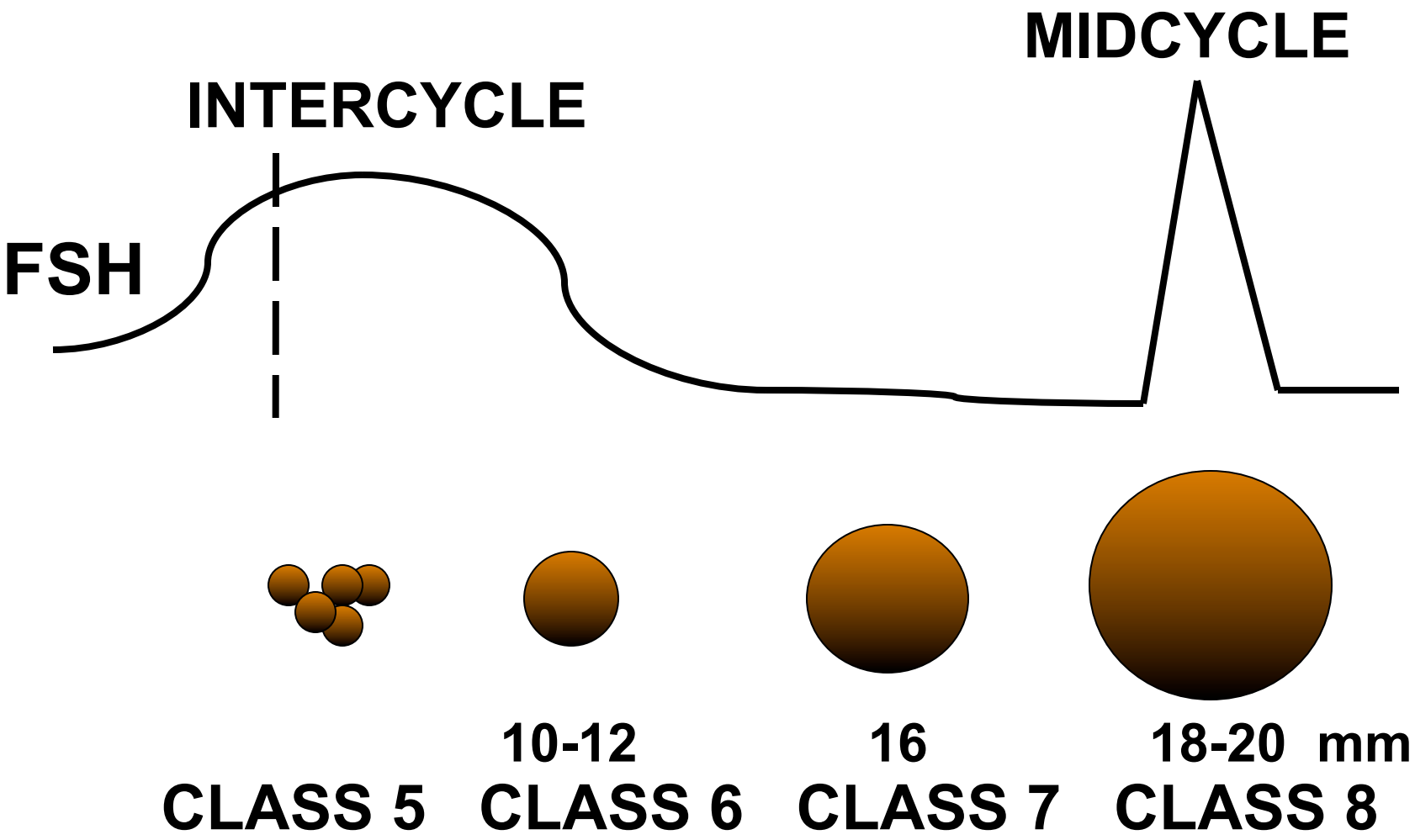
- **Discuss the role of LH in corpus luteum formation**
- **Describe the endocrine role (feedback) of progesterone in the luteal phase**
- **Summarize the paracrine actions of progesterone within the corpus luteum**
- **Describe the progesterone actions in the endometrium preparing for receptivity**

NORMAL CYCLE



Dafopoulos et al., 2009 Fertil. Steril. 92,1389-94

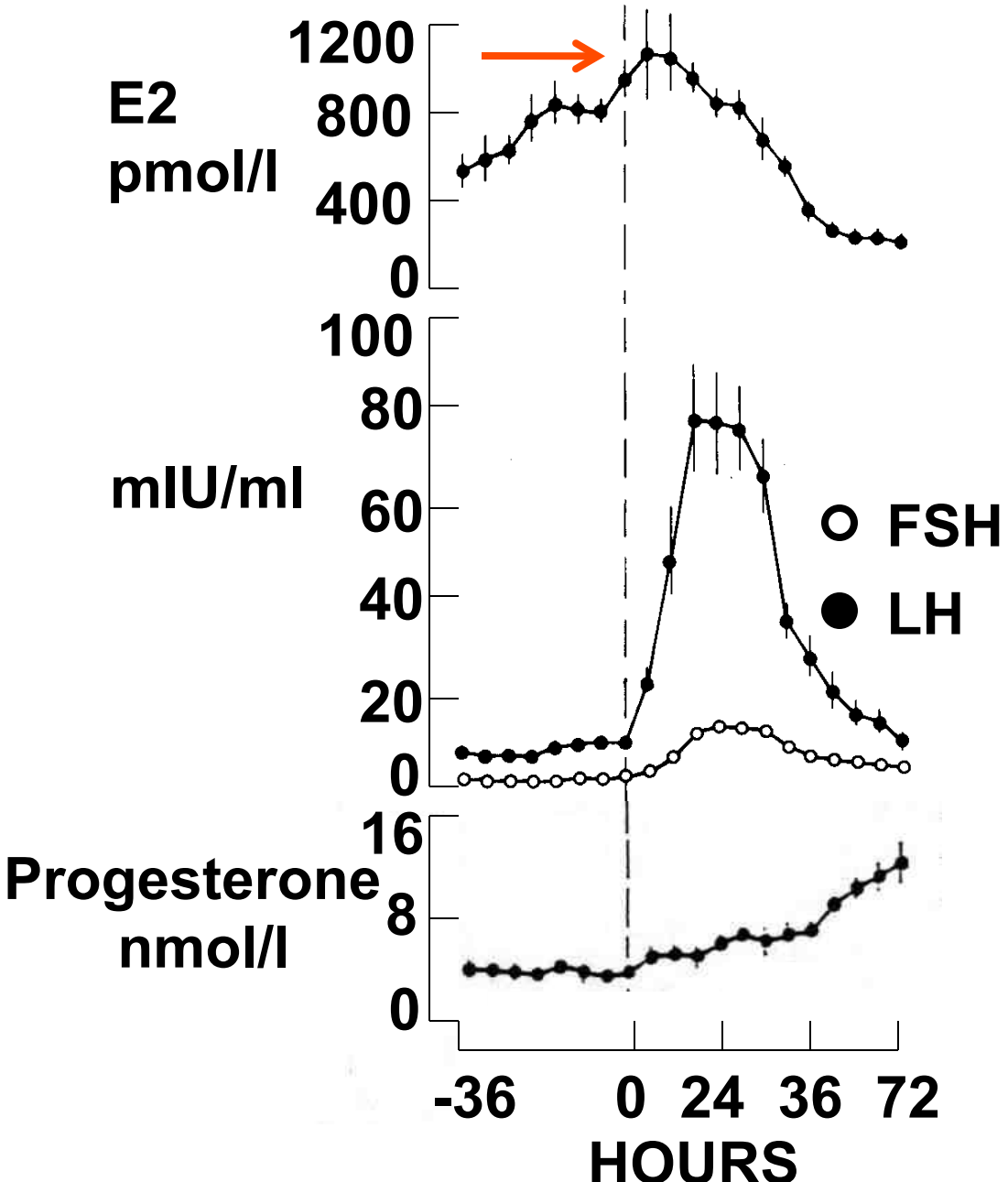
GROWTH OF THE DOMINANT FOLLICLE



Messinis, 2008

In: *Infertility and Assisted Reproduction, Cambridge UP, pp. 10-24*

NORMAL LH SURGE

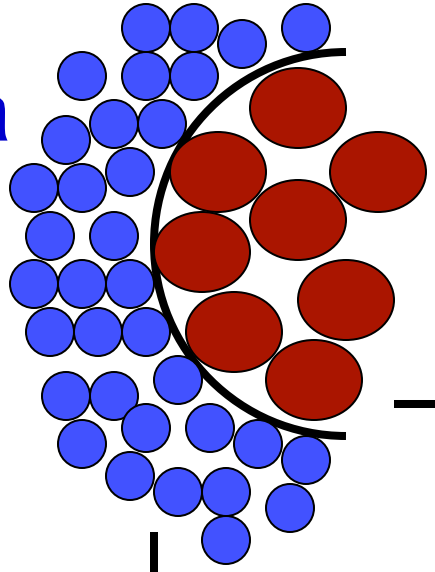


Messinis, 1989
PhD thesis (UK)

LH SURGE INDUCES:

- **Luteinization**
- **Resumption of oocyte meiosis**
- **Follicle rupture**
- **Corpus luteum formation**

FORMATION OF CORPUS LUTEUM FOLLOWING THE LH SURGE



Theca cells

Granulosa cells

Small luteal cells

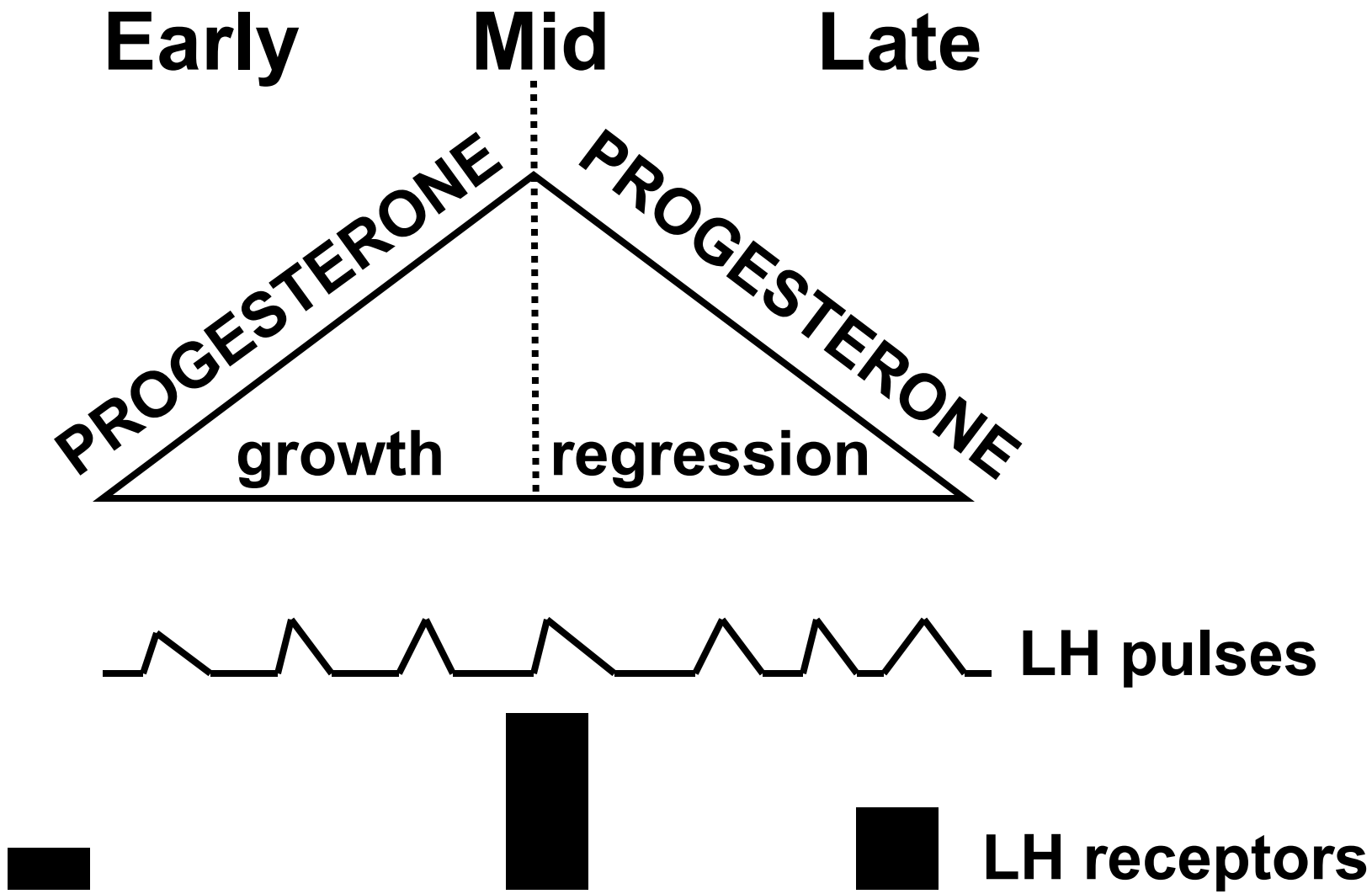
Large luteal cells

Progesterone

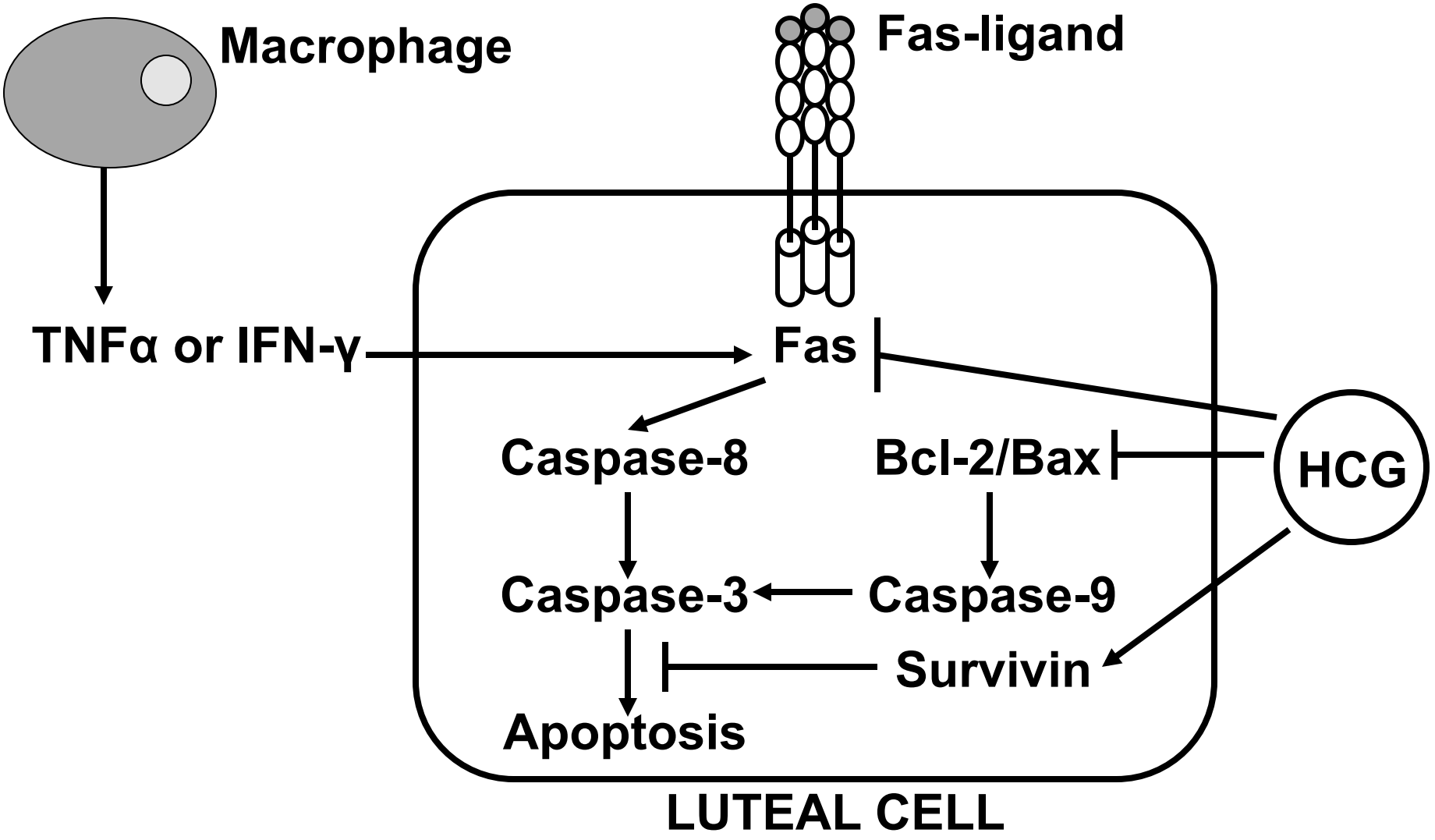
(Human)

Retamales et al., 1994
Hum. Reprod. 9, 591-96

CORPUS LUTEUM FUNCTION



HCG RESCUES CORPUS LUTEUM



Sugino & Okuda, 2007, J. Reprod. Dev. 53, 977-986

PROGESTERONE ROLE IN THE LUTEAL PHASE

- **Endocrine (feedback mechanisms)**
- **Local in corpus luteum (luteotrophic)**
- **Endometrium**

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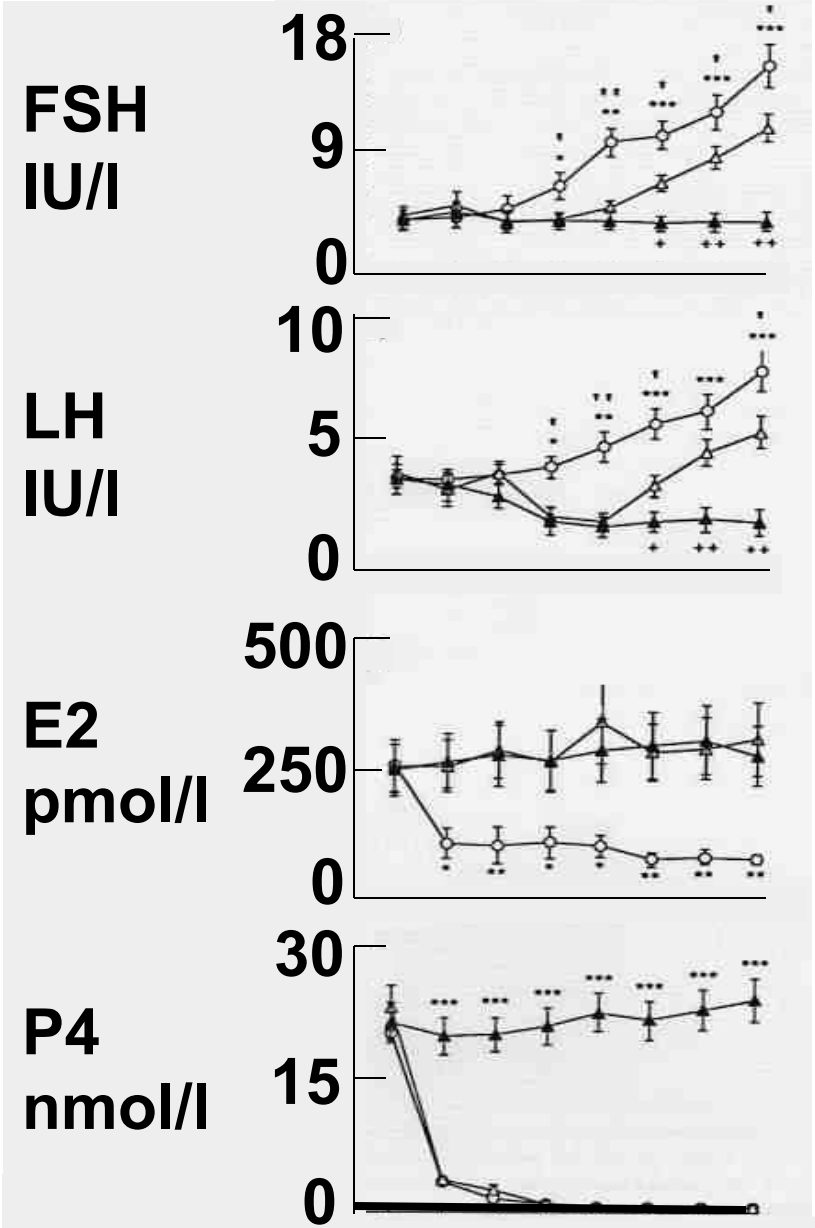
NEGATIVE FEEDBACK

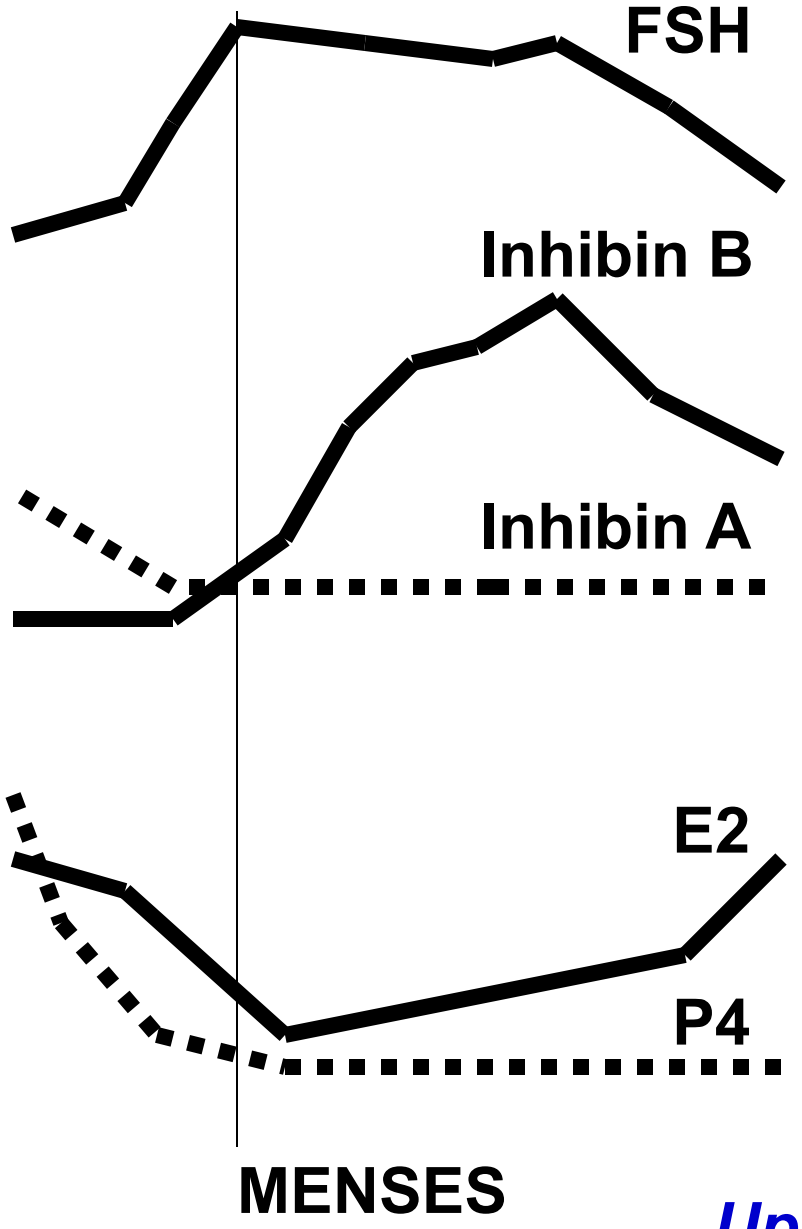


O CONTROL
Δ E2
▲ E2+P4

Messinis et al., 2002
Hum. Reprod.
17, 299-303

(Luteal phase)

INTERCYCLE RISE OF FSH

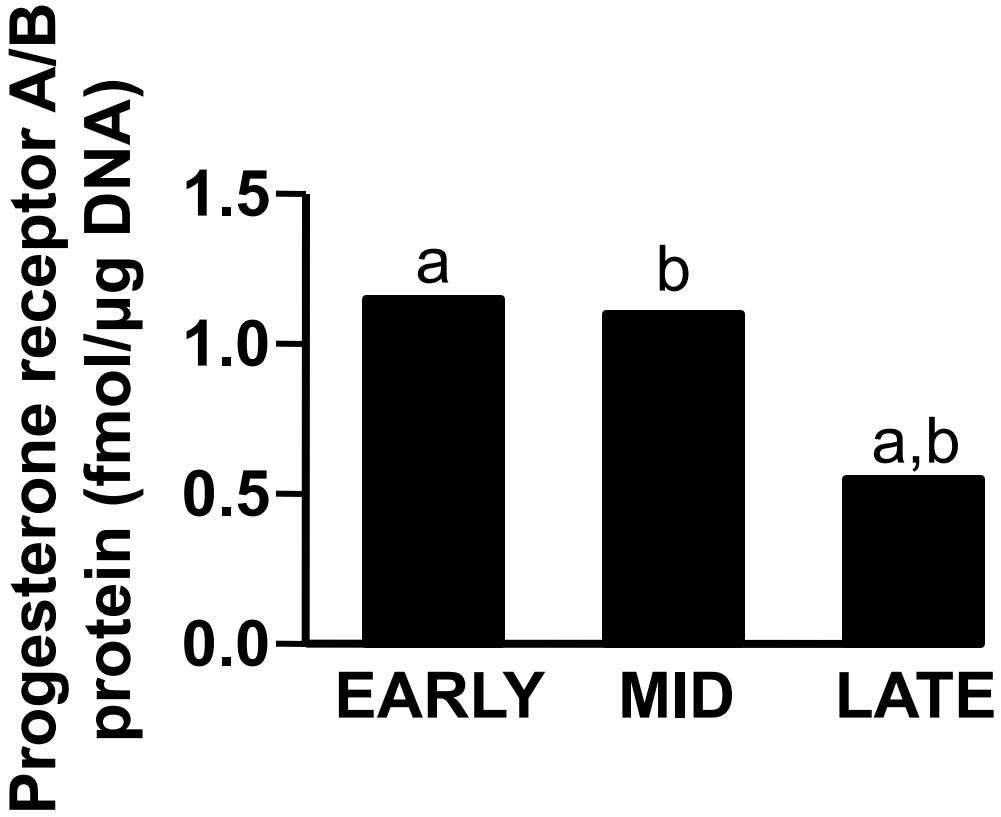


Messinis 2006
Hum. Reprod.
Update 12, 557-571

PROGESTERONE ROLE IN THE LUTEAL PHASE

- Endocrine (feedback mechanisms)
- **Local in corpus luteum (luteotropic)**
- Endometrium

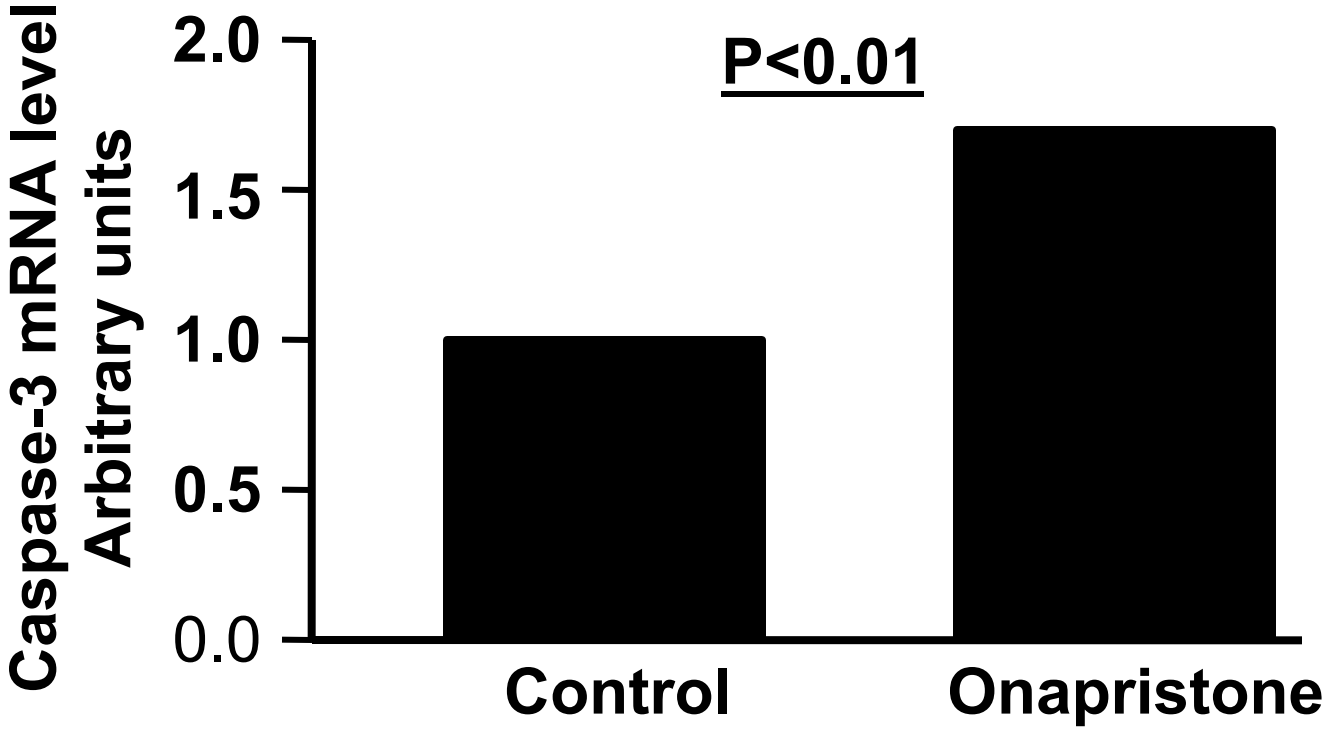
PROGESTERONE RECEPTOR A/B (human corpus luteum)



a,b P<0.05

Ottander et al., 2000
Biol. Reprod. 62, 655-63

PROGESTERONE PREVENTS APOPTOSIS (luteotrophic action)



***COWS** (corpus luteum)*
Cultured mid-luteal cells
(Similar data with Fas mRNA)

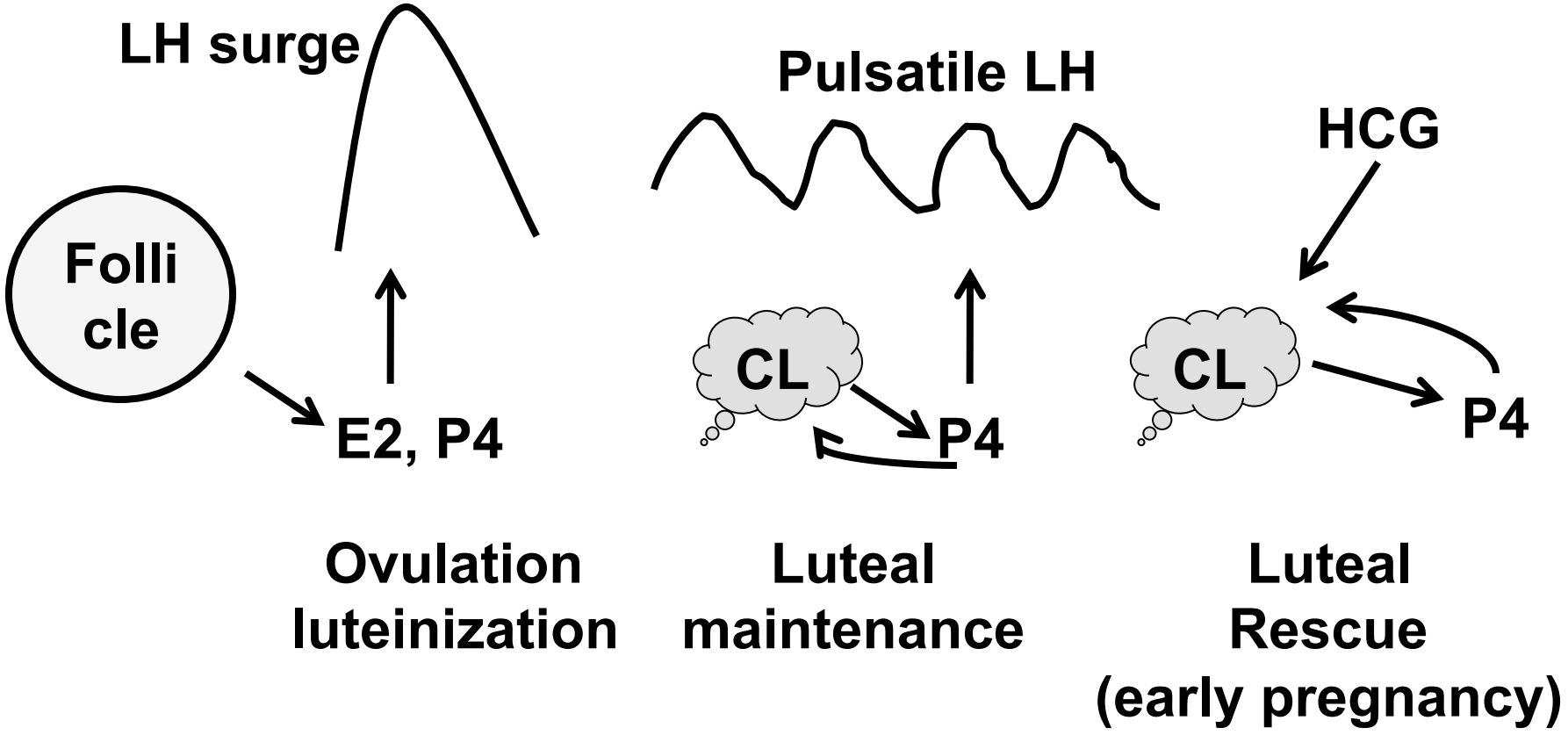
Based on:
Okuda et al., 2004
Biol. Reprod. 71, 2065-71

LH AND PROGESTERONE PREVENT CORPUS LUTEUM DEGRADATION

- **LH suppresses MMP-1 in the primate corpus luteum via progesterone**
- **LH suppresses gelatinases, either at the mRNA (MMP-2) or protein (MMP-2 and -9) levels, perhaps in part via steroids, including progesterone**
- **LH promotes TIMP expression, perhaps via steroids, including progesterone.**

Young & Stouffer, 2004
Biol. Reprod. 70, 244-50

ENDOCRINE AND PARACRINE REGULATION OF THE CORPUS LUTEUM



PROGESTERONE ROLE IN THE LUTEAL PHASE

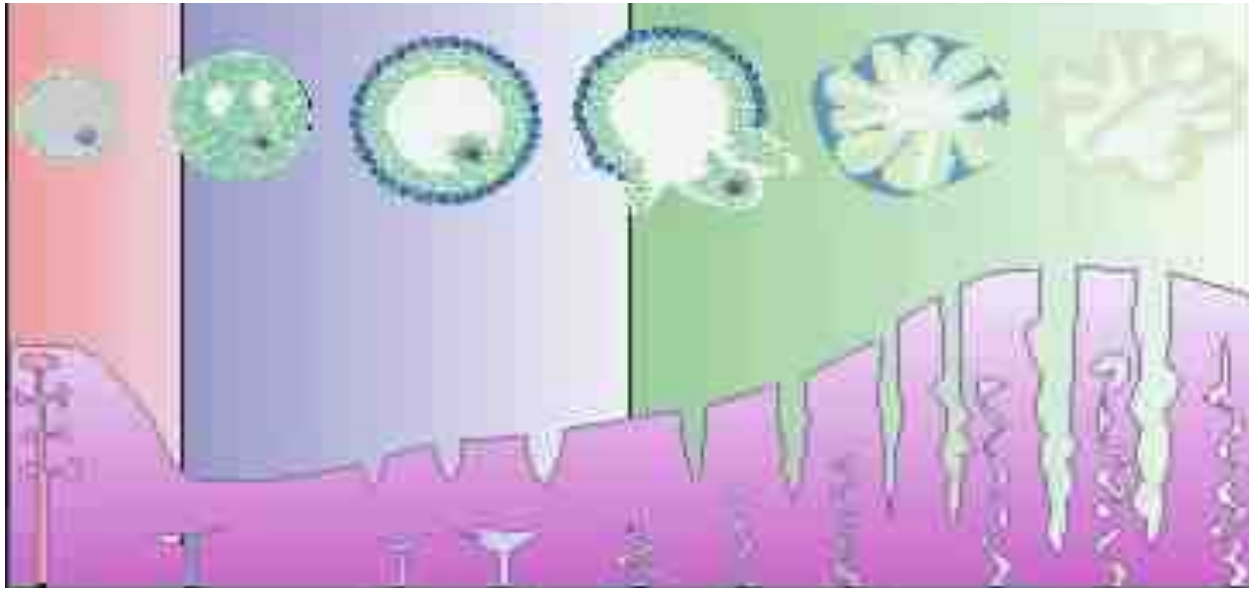
- Endocrine (feedback mechanisms)
- Local in corpus luteum (luteotropic)
- **Endometrium**

MENSTRUAL CYCLE

FOLLICULAR PHASE **LUTEAL PHASE**

Follilce

Endome-trium



Shedding (Menstruation Regeneration) **Proliferative (Proliferation)** **Secretory (Differentiation)**

ENDOMETRIAL CHANGES

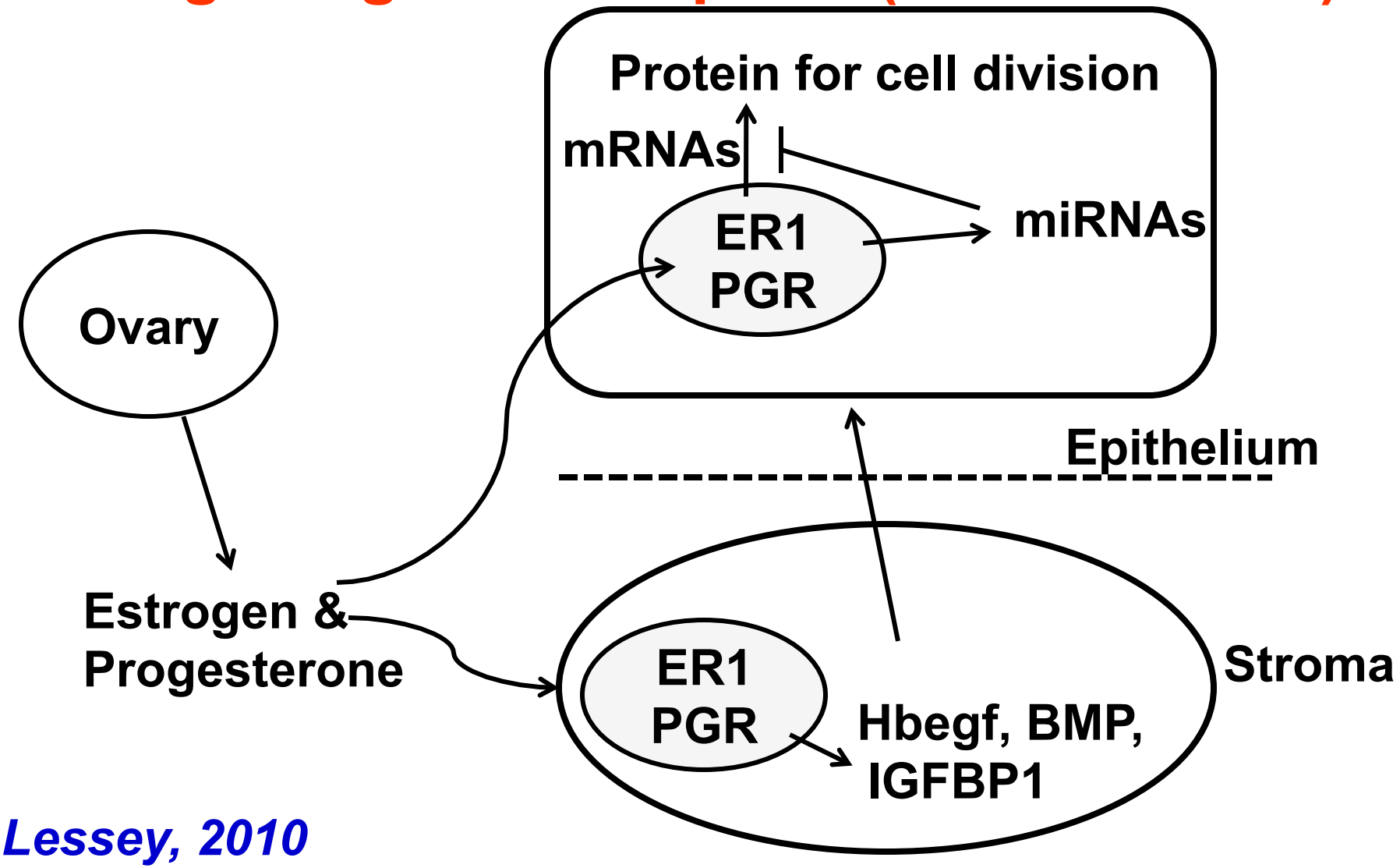
FOLLICULAR PHASE (Estrogen dominated)

- Cellular proliferation in both the glandular epithelium and stromal cells

LUTEAL PHASE (Progesterone dominated)

- First half
  - Decline in proliferation
  - Secretory differentiation
- Second half
  - Proliferation in epithelial cells is low
  - Decidual changes (high proliferation) in stroma

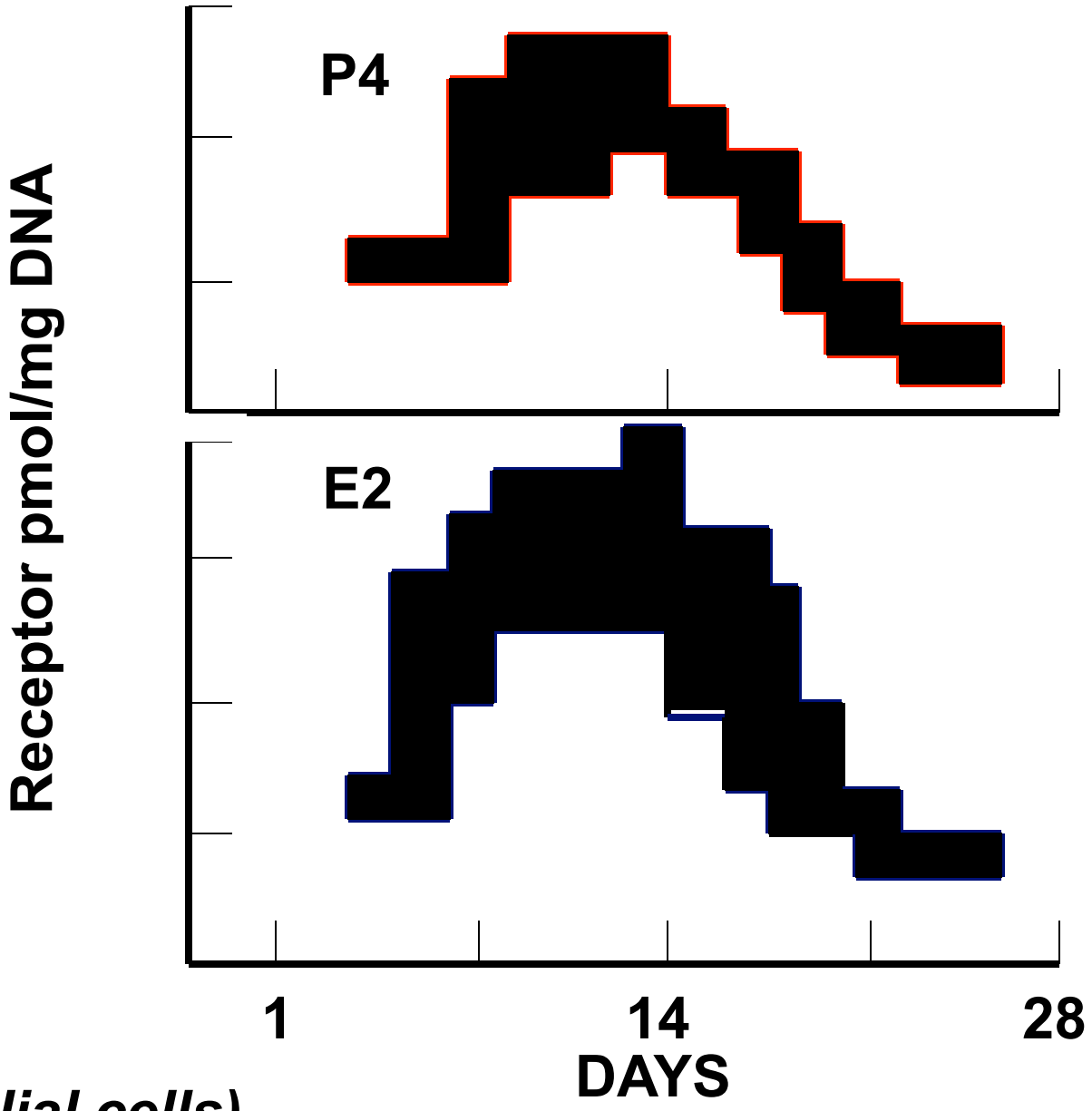
Ovarian steroids regulate the endometrium through cognate receptors (ESR1 or PGR)



Lessey, 2010
Biol. Reprod. 82, 653-655

SC

RECEPTORS IN ENDOMETRIUM



(Epithelial cells)

PROGESTERONE ACTS ON

- The endometrial epithelial cells
- The stroma
  - Cells
  - Matrix
  - Blood vessels

ROLE OF PROGESTERONE IN ENDOMETRIUM

- **Prepares the uterine epithelium for receptivity**
- **Antagonizes estrogen-induced proliferation in uterine epithelium**
- **Differentiates endometrial stromal cells to a decidual phenotype**

DECIDUALIZATION

- **Morphological and biochemical differentiation of endometrial stromal cells into decidual cells (from small stromal fibroblast into large epithelioid decidual cells)**
- **Influx of specialized uterine NK cells**
- **Profound angiogenesis**
- **(Critical role of PRA)**

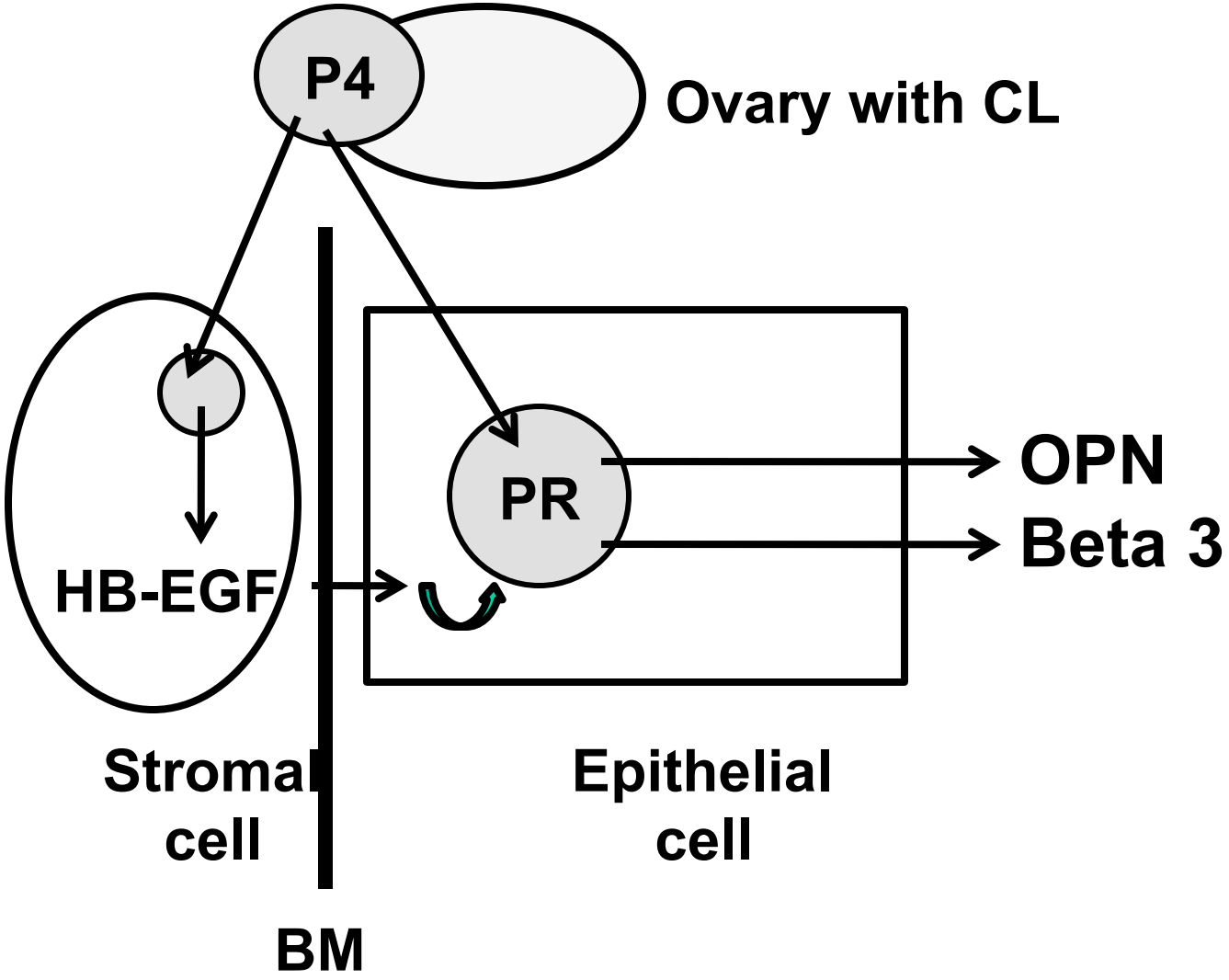
PROGESTERONE-INDUCED ENDOMETRIAL PROTEINS

- **IGFBP-1 (Placental protein 12)**
- **Glycodelin (Progesterone-associated endometrial protein or placental protein 14)**

ENDOMETRIAL BIOMARKERS

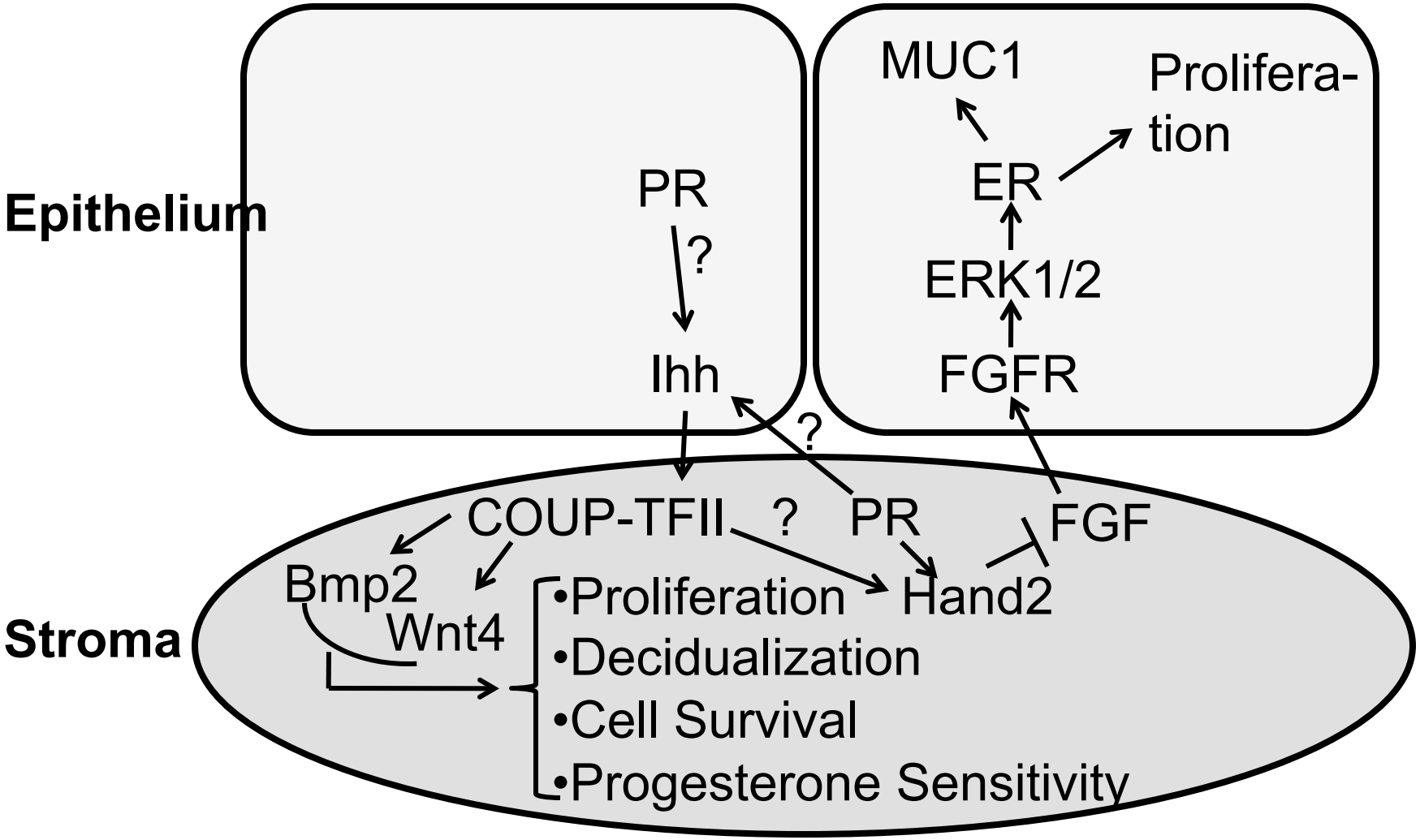
- LIF
- Cytokines (IL-6, IL-11)
- Growth factors (TGF-β, EGF, HB-EGF, IGF)
- Integrins (α4β1, αvβ3)
- Osteopontin

PROGESTERONE EFFECTS ON THE ENDOMETRIUM (Paracrine mediators)



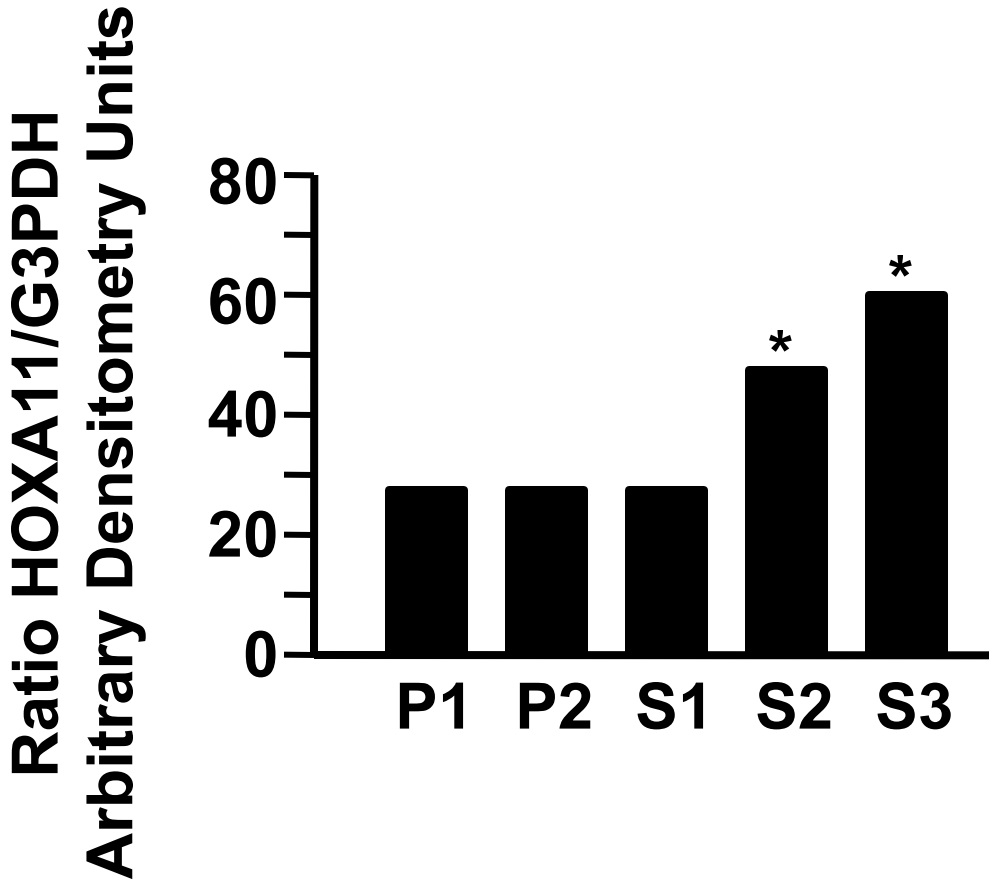
Lessey, 2003; Steroids, 68, 809-15

Progesterone regulated paracrine signaling model in endometrium at implantation



Wetendorf & DeMayo, 2012; Mol. Cell. Endocrinol. 357, 108-118

HOXA 11 EXPRESSION IN HUMAN ENDOMETRIUM



P: Proliferative
S: Secretory

HOXA 10 expression shows a similar pattern

Taylor et al., 1999
JCEM 84, 1129-35

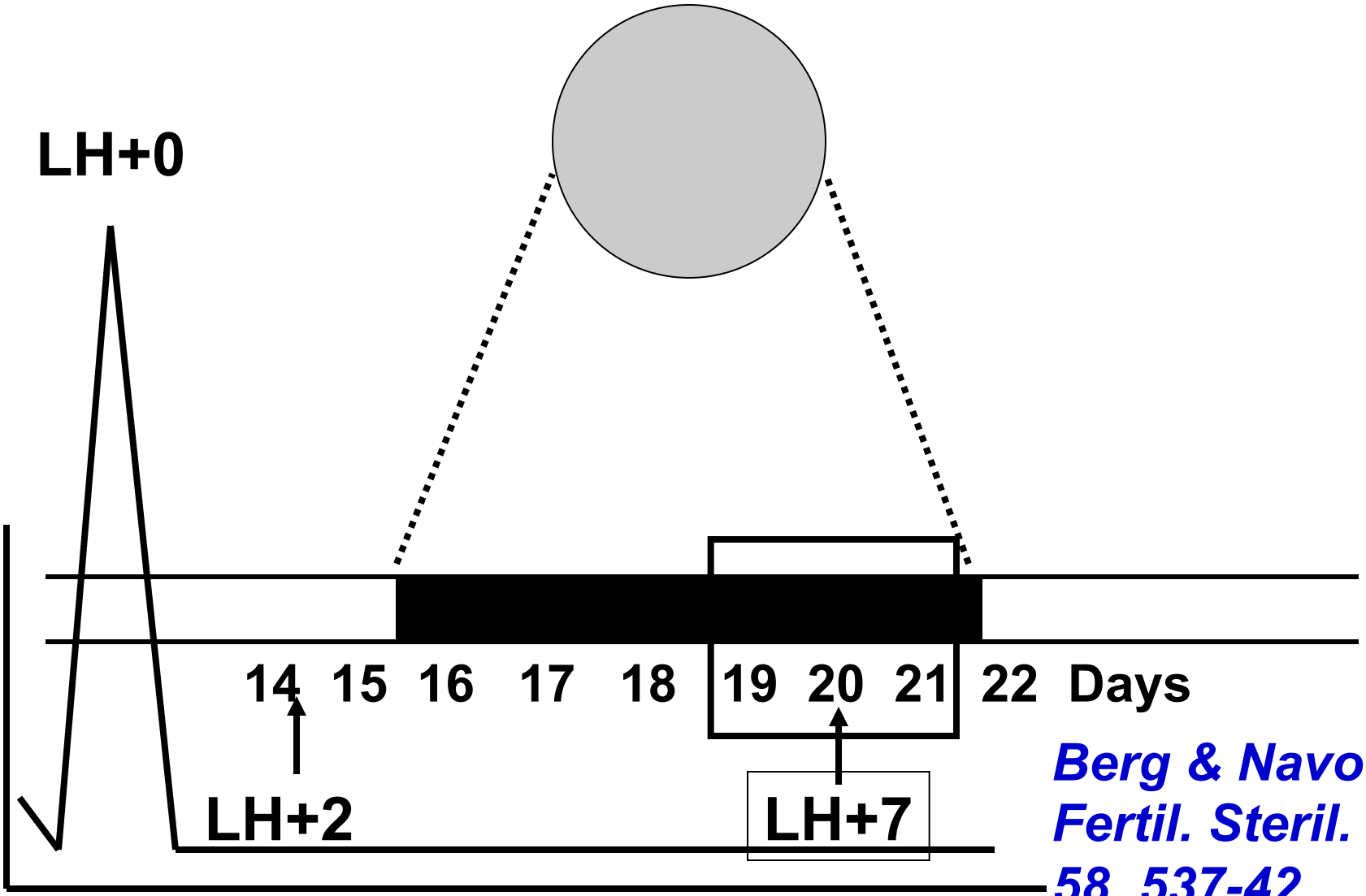
NH

MARKERS ASSOCIATED WITH UTERINE RECEPTIVITY

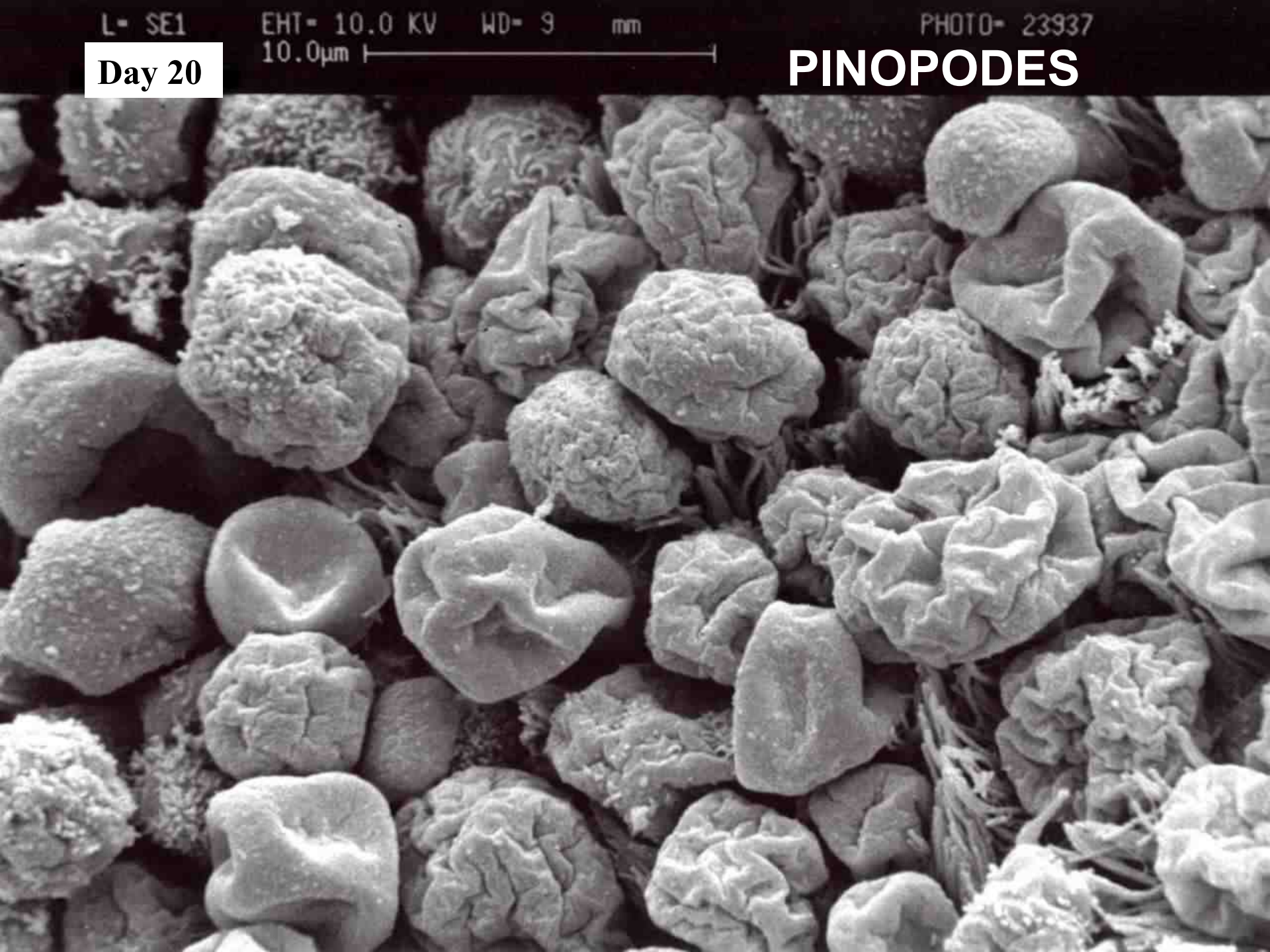
- **Morphological features (*histology, pinopodes*)**
- **Cellular adhesion molecules family (*integrins, selectins, cadherins, immunoglobulins, mucins*)**
- **Cytokines (*LIF, IL-6, IL*-1)**
- **Prostaglandins**

Achache & Revel, 2006
Hum. Reprod. Update, 12, 731-746

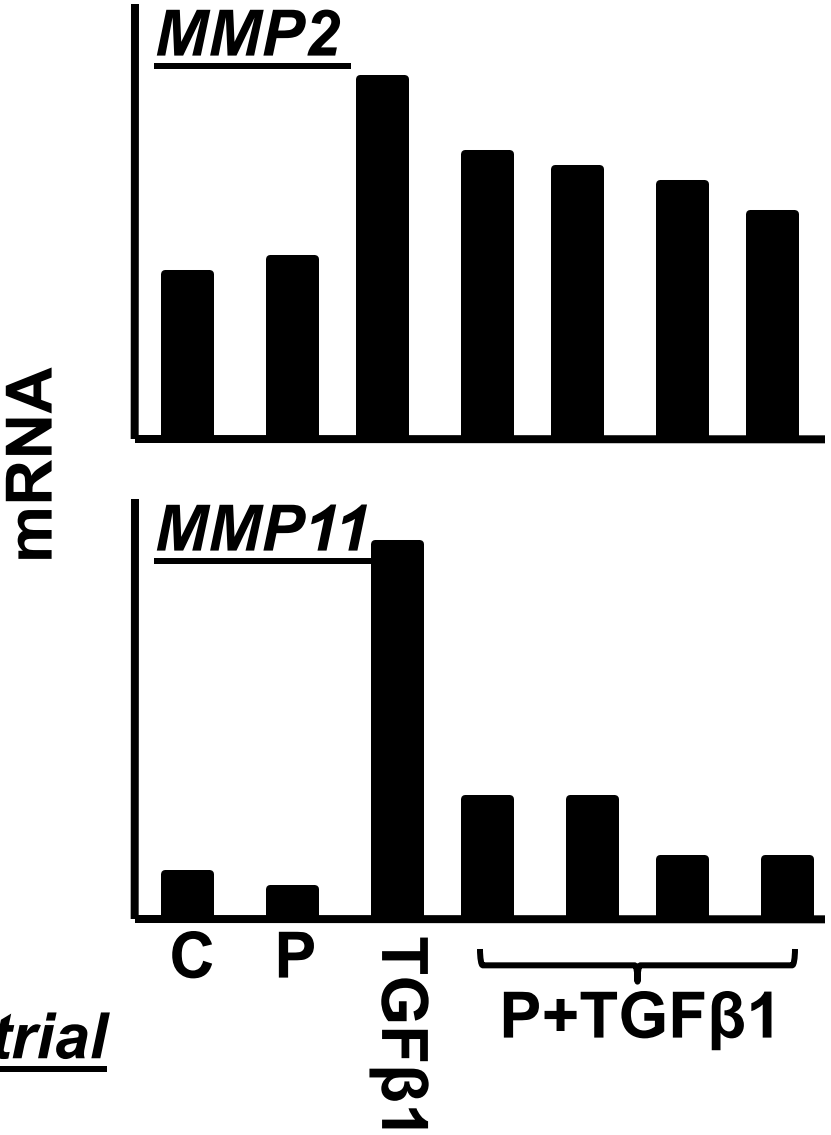
WINDOW OF IMPLANTATION



Berg & Navot, 1992
Fertil. Steril.
58, 537-42


L= SE1
EHT= 10.0 KV
WD= 9 mm
PHOTO= 23937
10.0µm
Day 20
PINOPODES

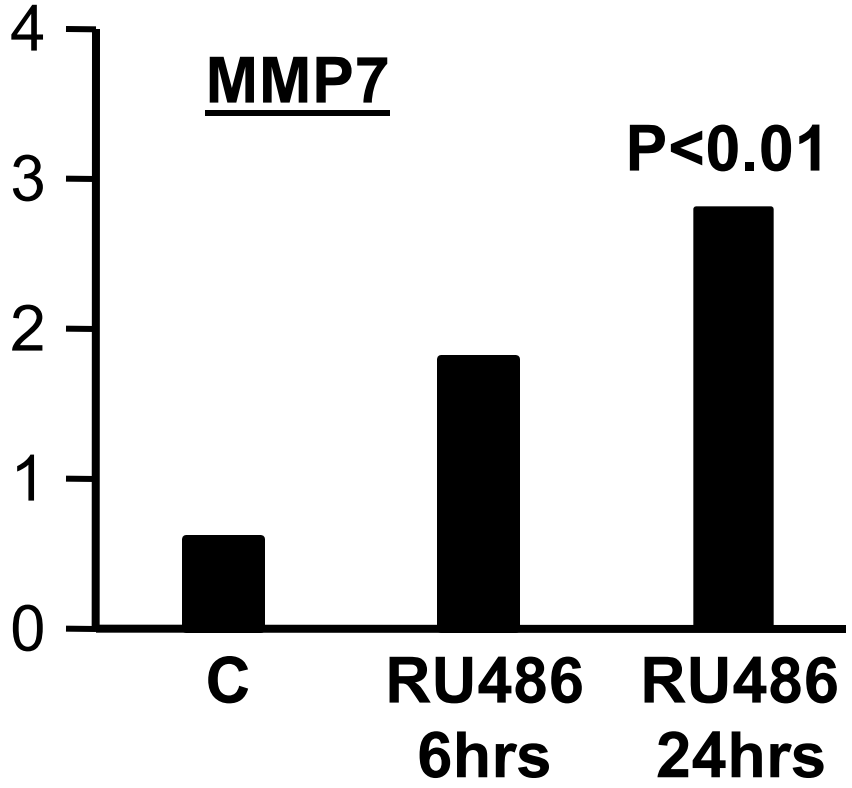
REGULATION OF MMPs BY PROGESTERONE



Human endometrial stromal cells

Based on:
Itoh et al., 2012 JCEM 97, E888-E897

EXPRESSION IN HUMAN ENDOMETRIUM (P4 role)



RU486 was given in-vivo

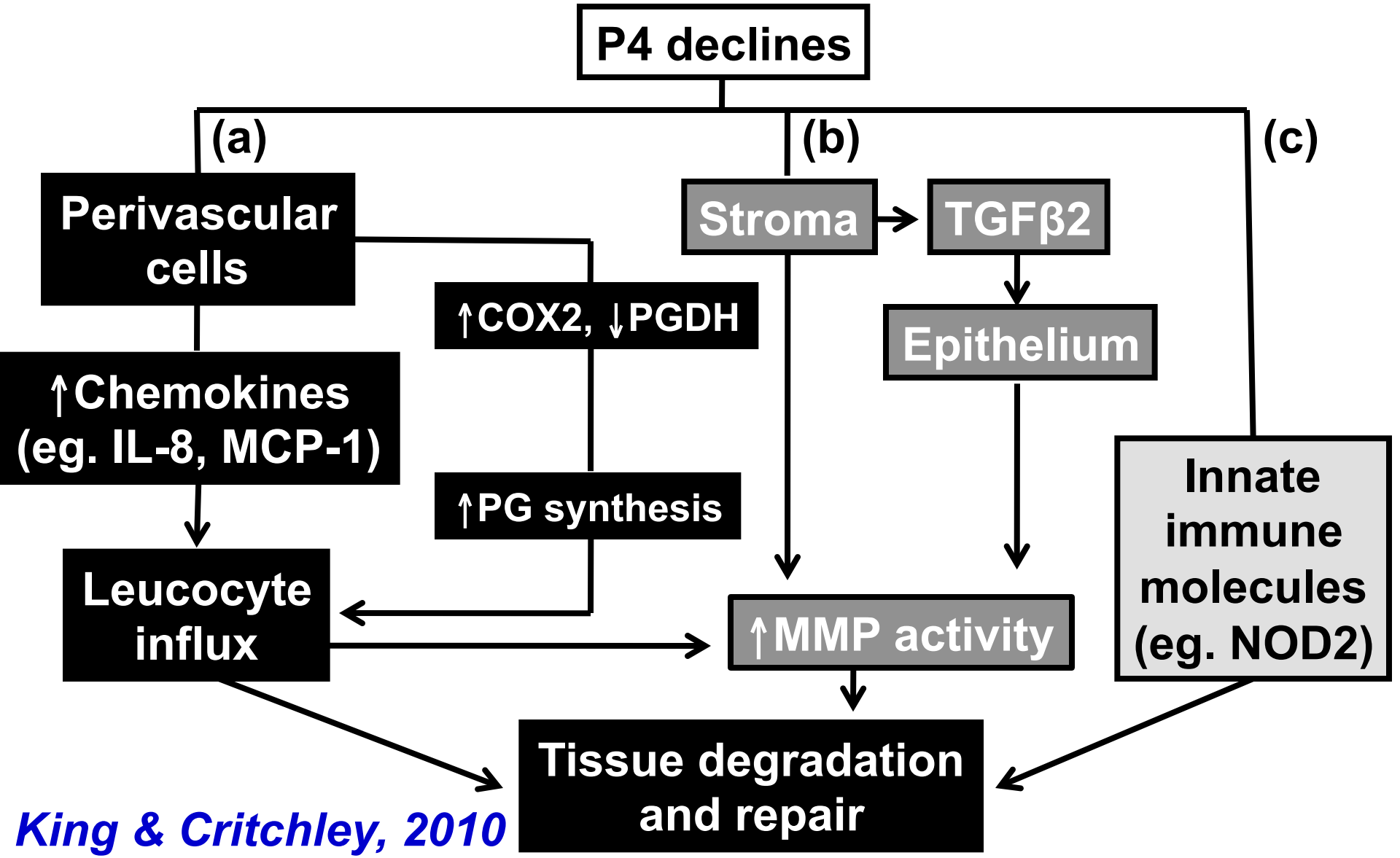
Catalano et al., 2007
Mol. Hum. Reprod. 13, 641-54

AFTER DECIDUALIZATION

- **…the endometrium becomes irreversibly dependent upon progesterone signalling**
- **…falling levels of progesterone trigger a cascade of events that results in proteolytic breakdown of the superficial endometrium, focal bleeding and cell death.**

Brosens & Gellersen, 2006, 36, 389-98

CORPUS LUTEUM REGRESSES



King & Critchley, 2010
J. Steroid Biochem. Mol. Biol. 120, 116-26

TAKE HOME MESSAGES

- **Progesterone is the main steroid that is secreted from the corpus luteum**
- **Progesterone in the luteal phase:**
  - **mediates the negative feedback effect of the ovaries on the hypothalamus and pituitary**
  - **exerts luteotrophic actions via various paracrine mechanisms**
  - **induces decidualization preparing the endometrium for receptivity**

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