



Scientific Society Symposium
Firenze, 8th March 2018



Metformin and Endometrial function

Session organized by the DGGEF - Dr. Amanda Machado Weber

OVERVIEW

- Metformin
- Mechanisms of Metformin
- Effect of Metformin in endometrial cells

METFORMIN

- Derived from isoamylene guanidine – active substance of *Galega officinalis*;



- Widely used in the treatment of T2DM;
- Approval in 1958 UK and 1995 USA;
- First-line therapy for T2DM patients;
- ≈ 120 million prescriptions per year worldwide;
- Favorable benefit-risk profile: ∅ hypoglycaemia or weight gain.

METFORMIN

- Also suggested as:



CARDIOVASCULAR PROTECTIVE

ANTI-INFLAMMATORY

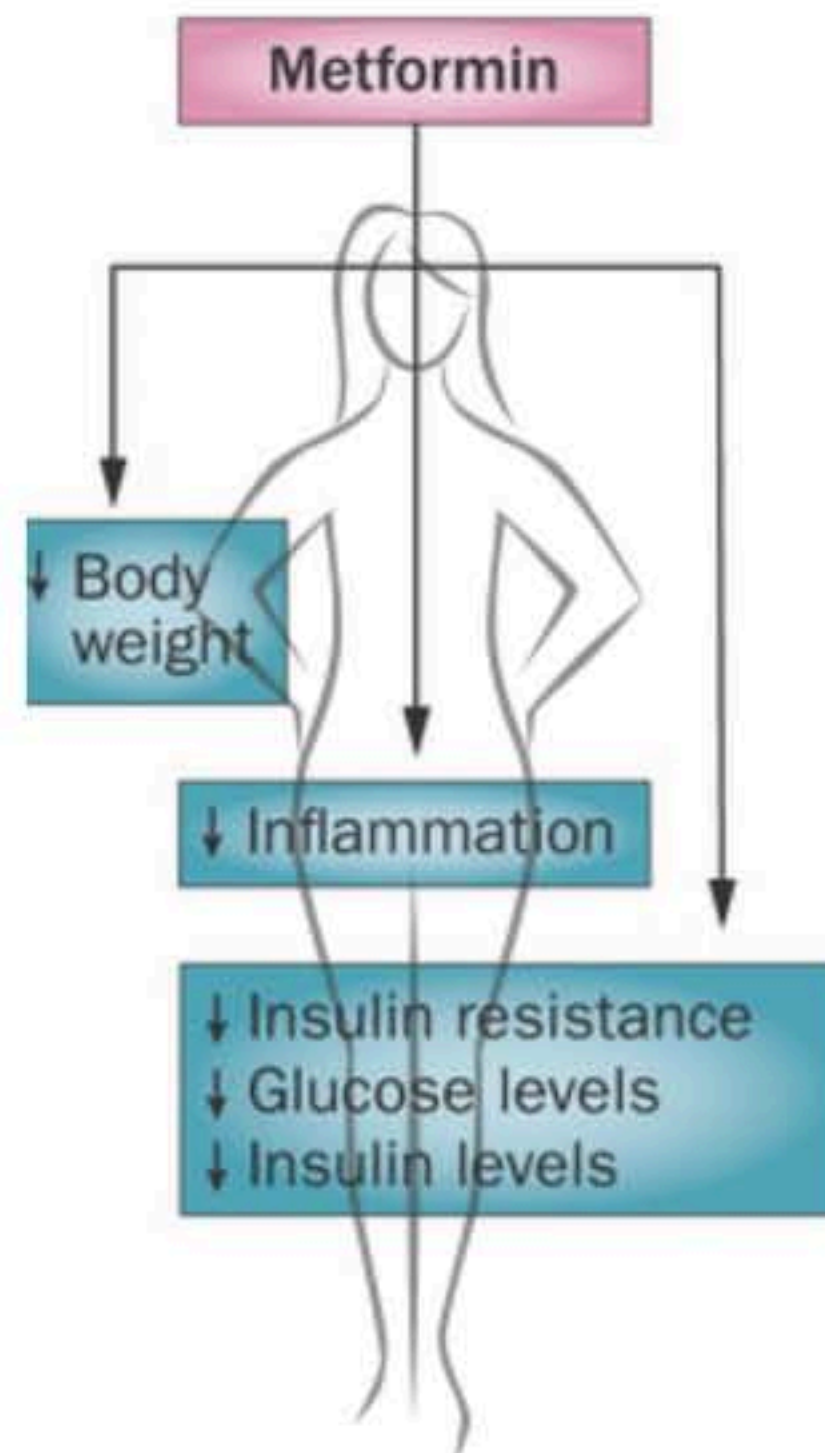
NEUROPROTECTIVE

ANTICANCER

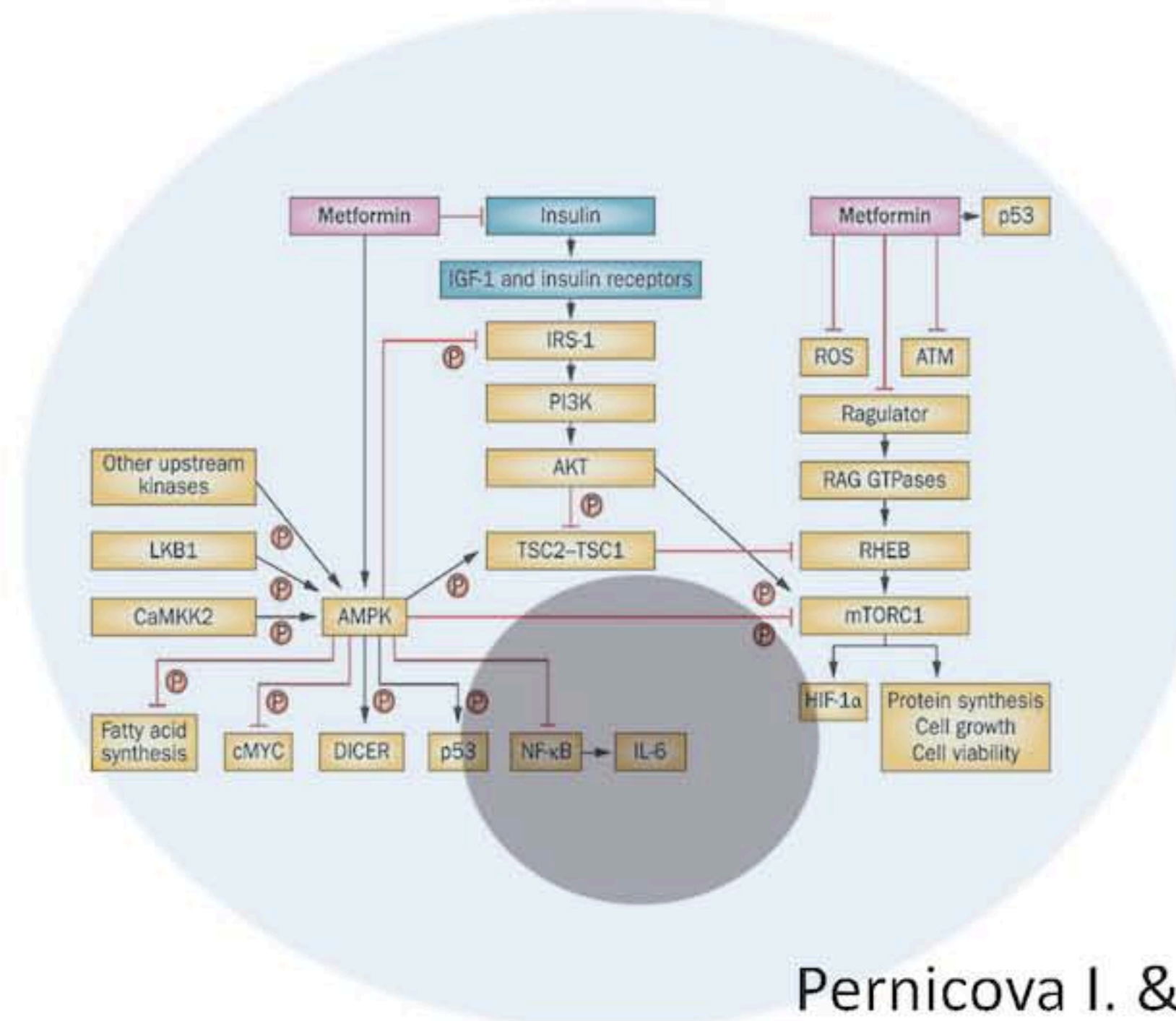
MECHANISMS OF METFORMIN



INDIRECT EFFECT



DIRECT EFFECT



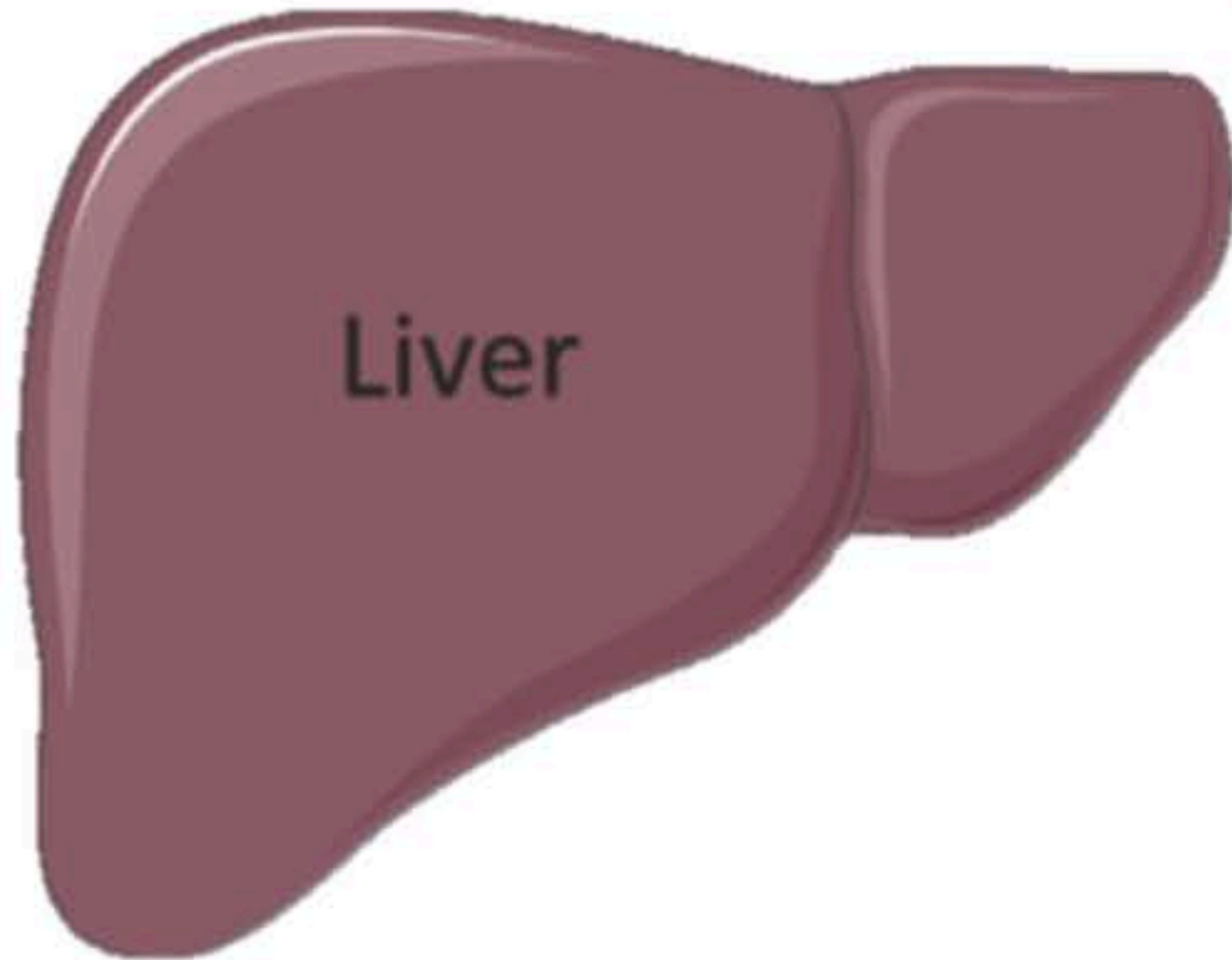
Pernicova I. & Korbonits M., 2014

Metformin and Endometrial function

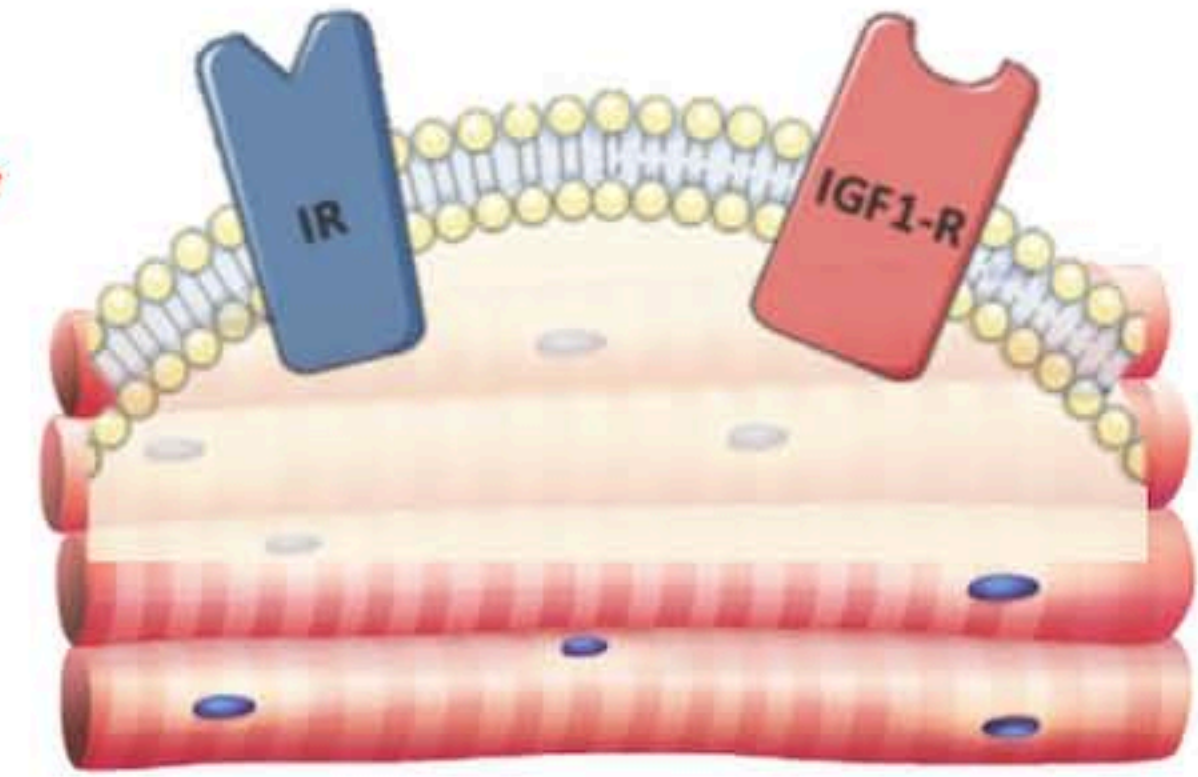
INDIRECT EFFECTS



Glucose-6-phosphatase
Glucokinase



Ø GLUCONEOGENESIS

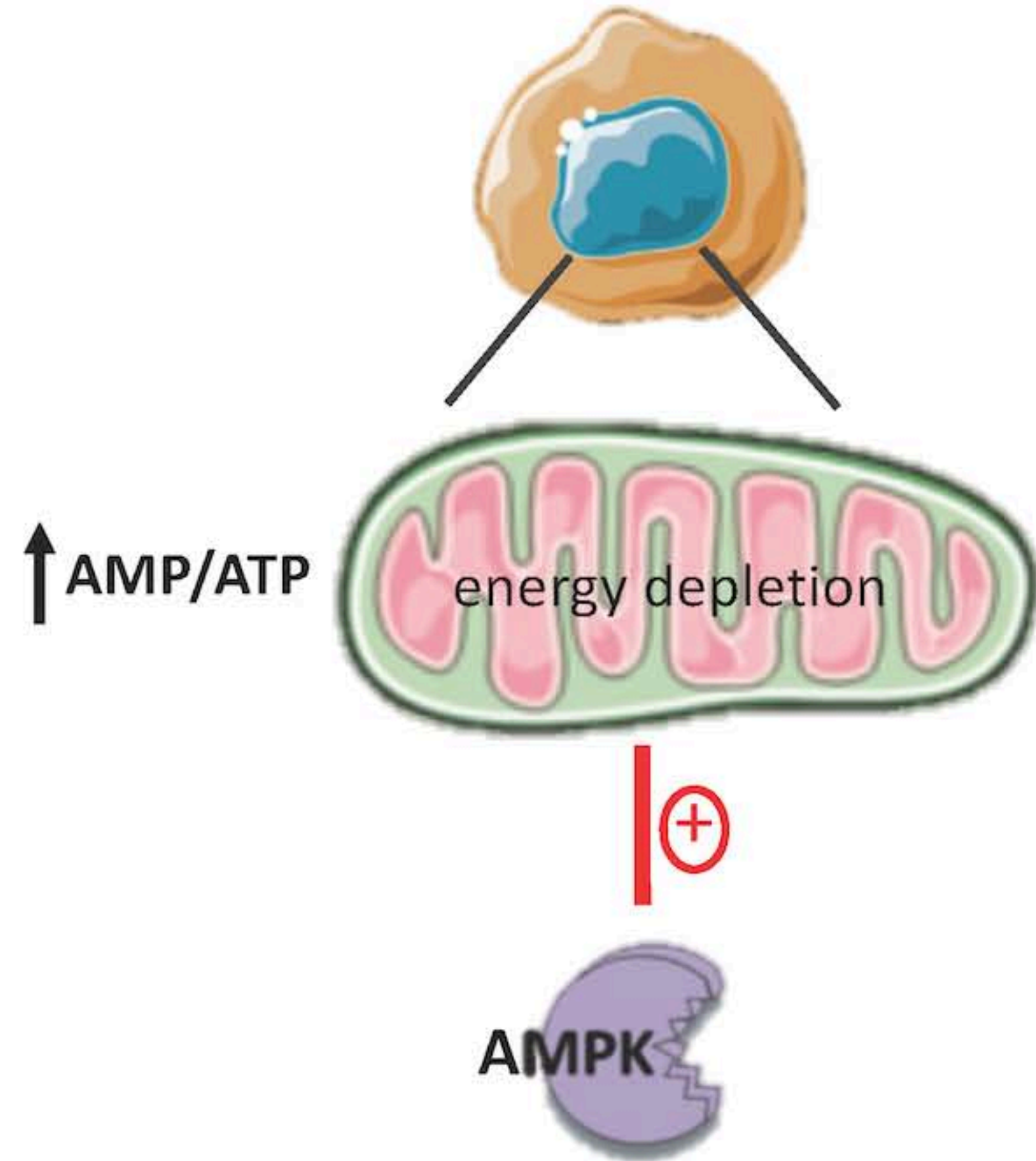


Skeletal muscle



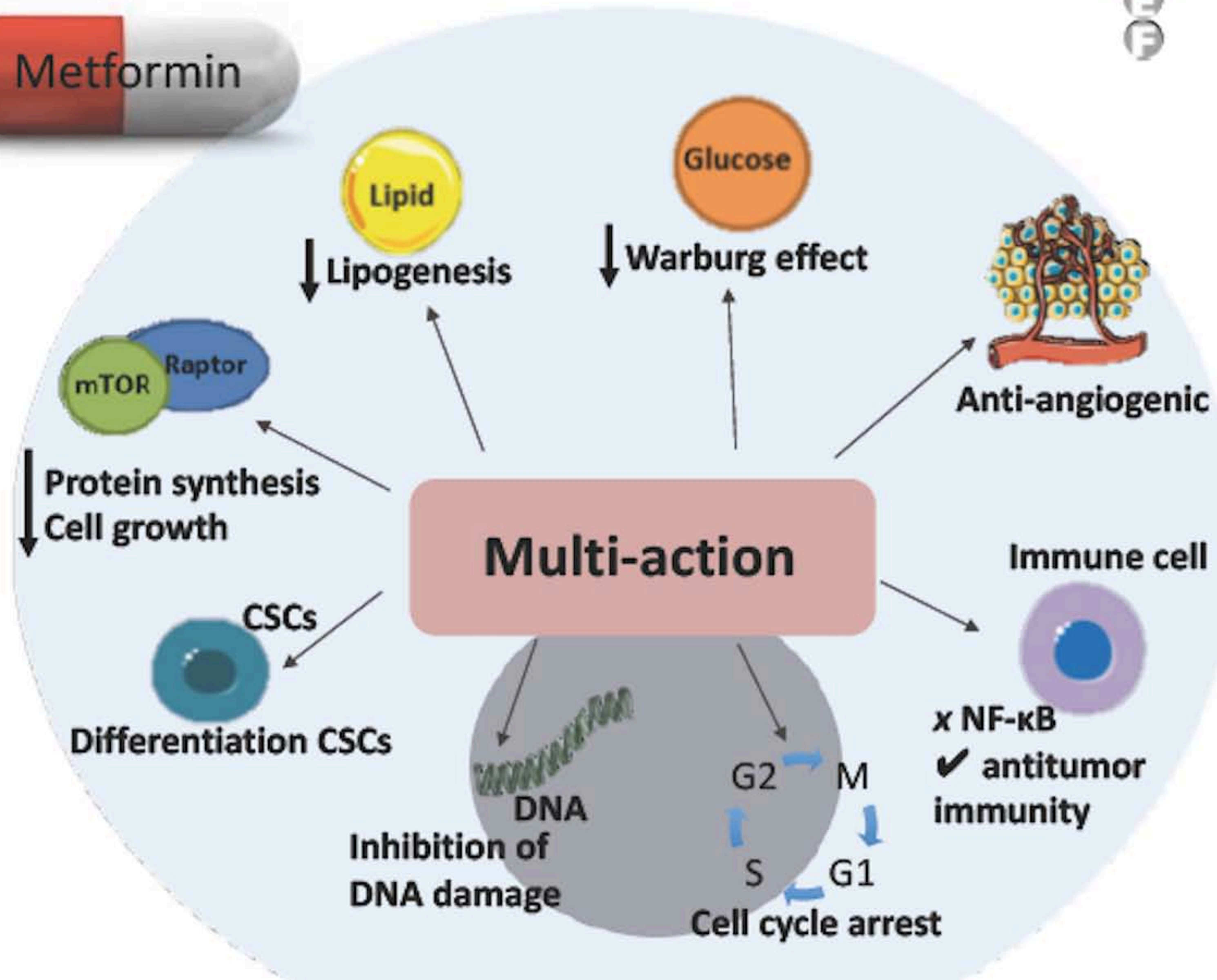
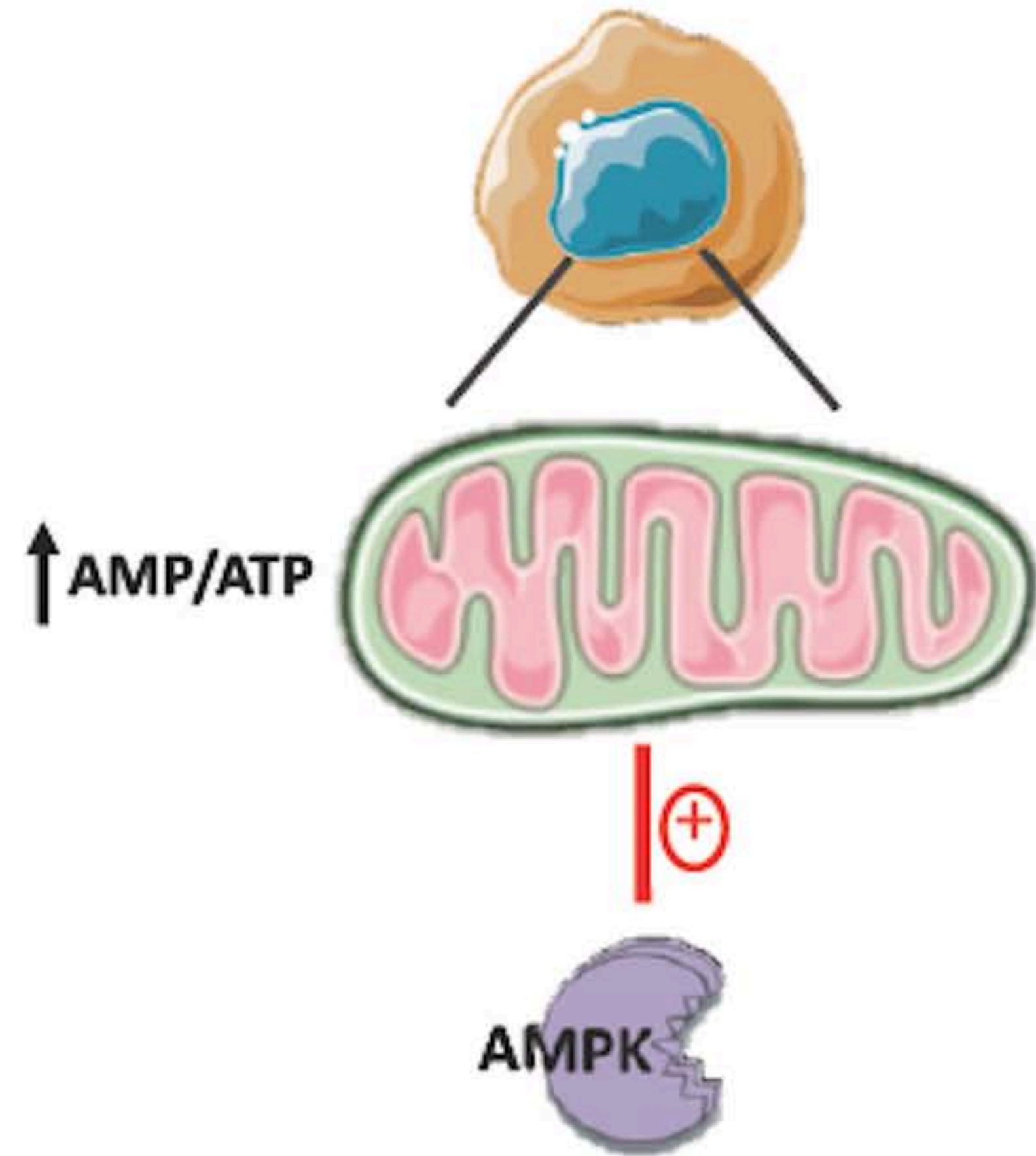
Metformin and Endometrial function

DIRECT EFFECTS



Metformin and Endometrial function

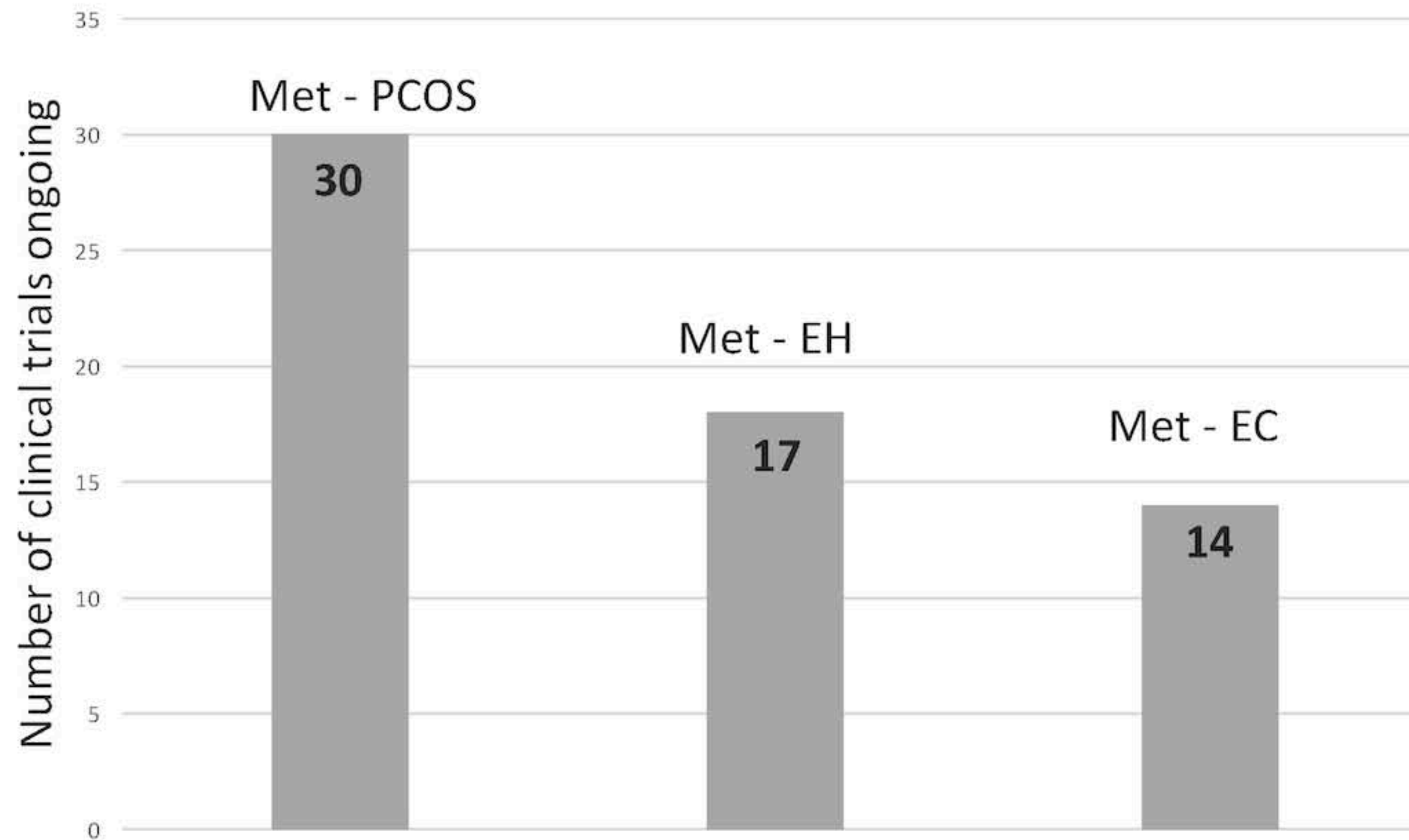
DIRECT EFFECTS



EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

NIH U.S. National Library of Medicine

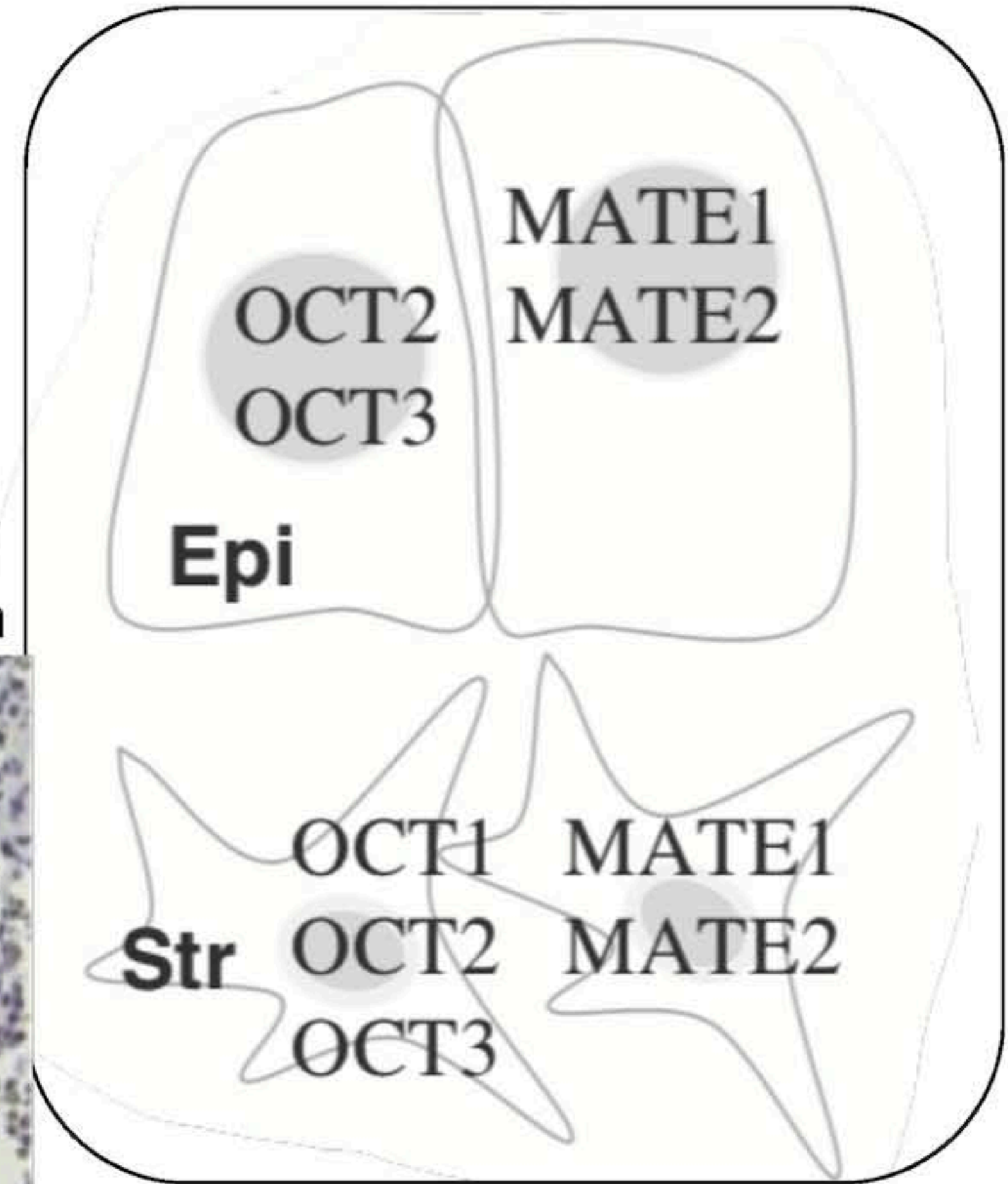
ClinicalTrials.gov



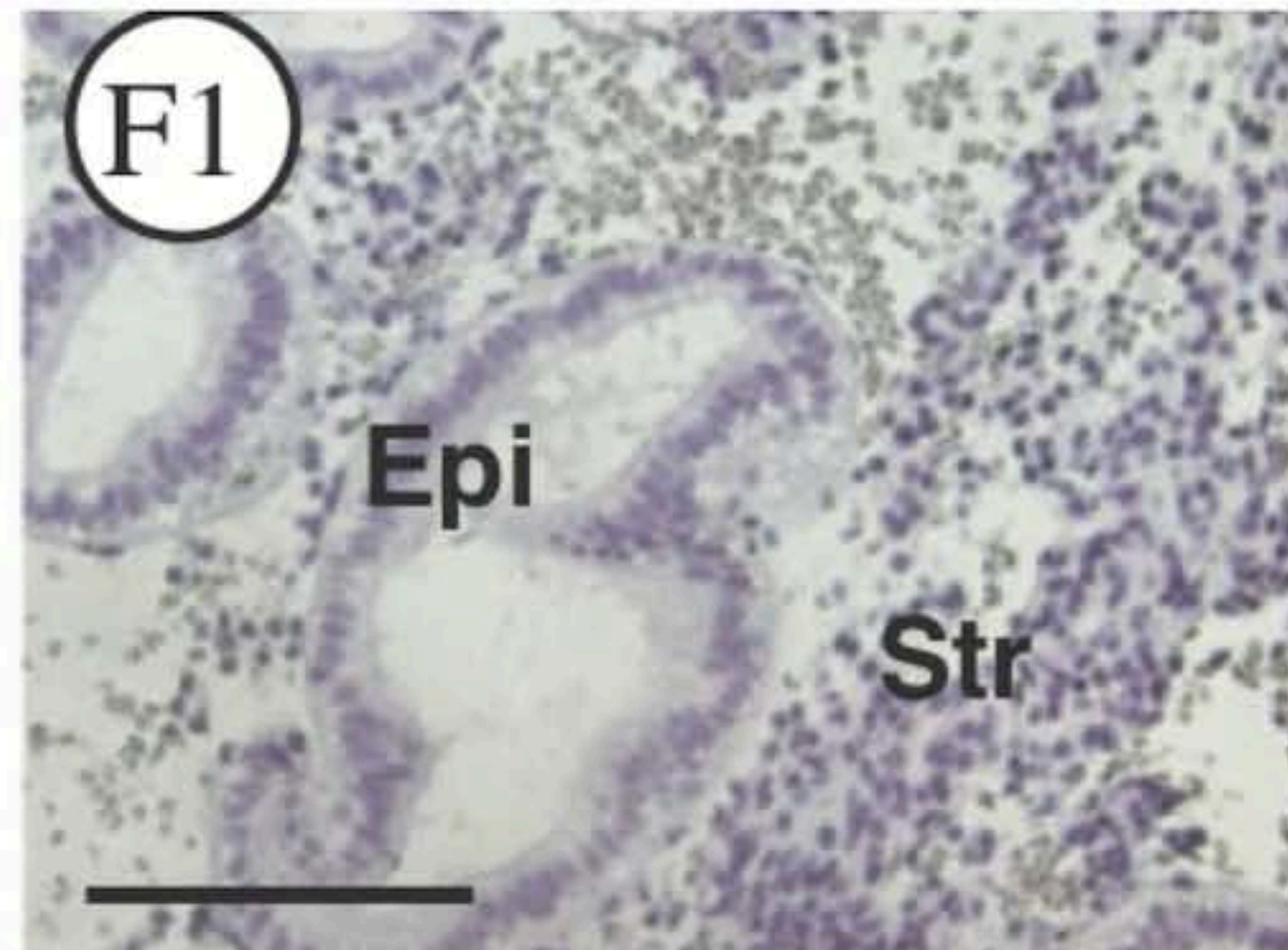
PCOS – Polycystic ovary syndrome; EH – Endometrial hyperplasia; EC- Endometrial cancer

EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

- Metformin is highly hydrophilic;
- OCTs transporter → cellular uptake;
- MATEs transporter → excretion.



Human Endometrium



Specie and tissue specific



Role in therapeutic efficiency

Shao *et al.*, 2014

EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Fertility

- Metformin reestablish ovulatory cycles in PCOS (Lord et al., 2003)



Cochrane Database of Systematic Reviews

2017

Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review)

Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH

→ no conclusive evidences about metformin treatment on implantation and live birth rates.

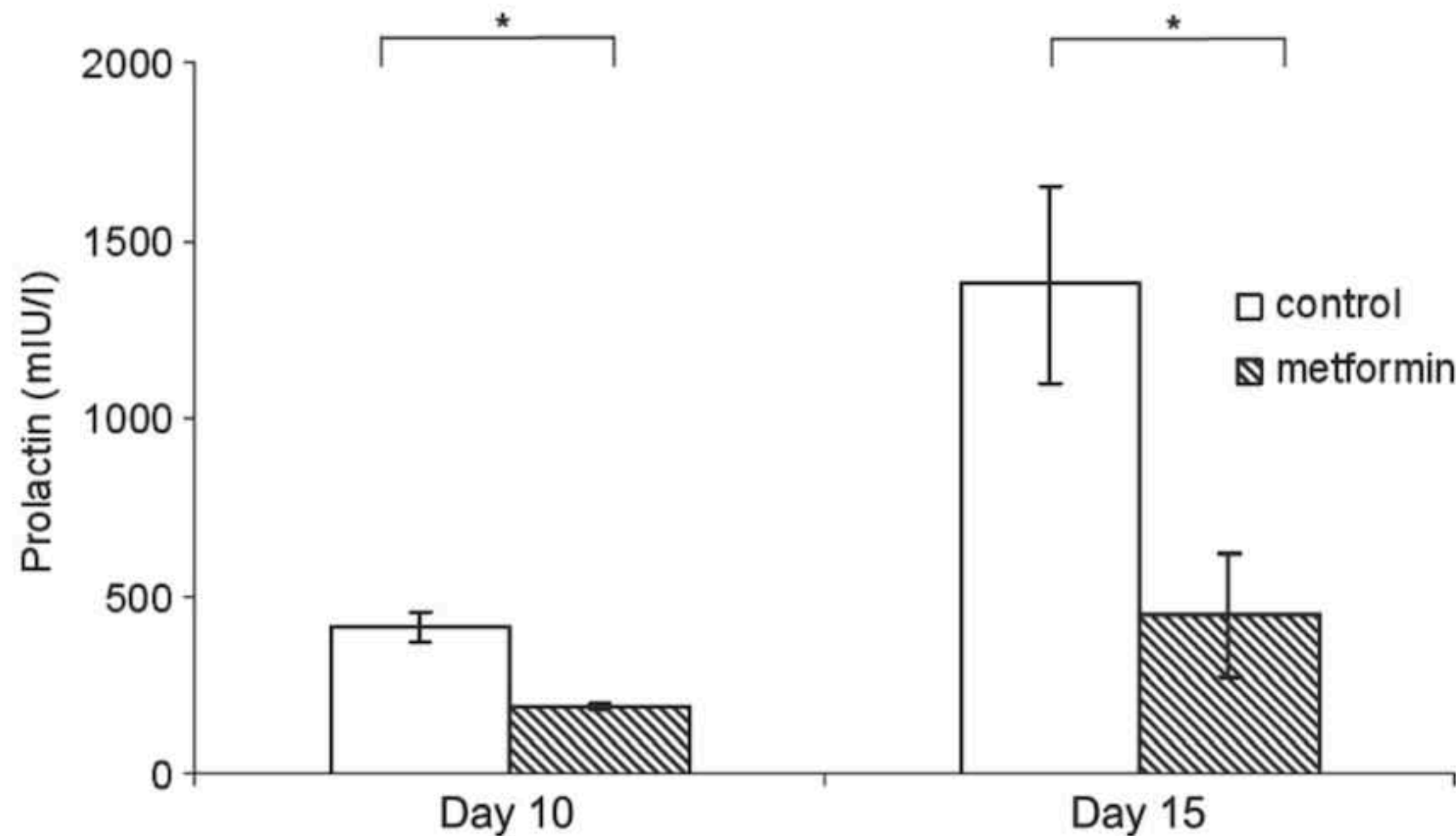
EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Fertility

Germeyer *et al.*, 2011; Freis *et al.*, 2017



UniversitätsKlinikum Heidelberg



↓ ESC decidualization
↑ IL-8 and IL-1 β levels

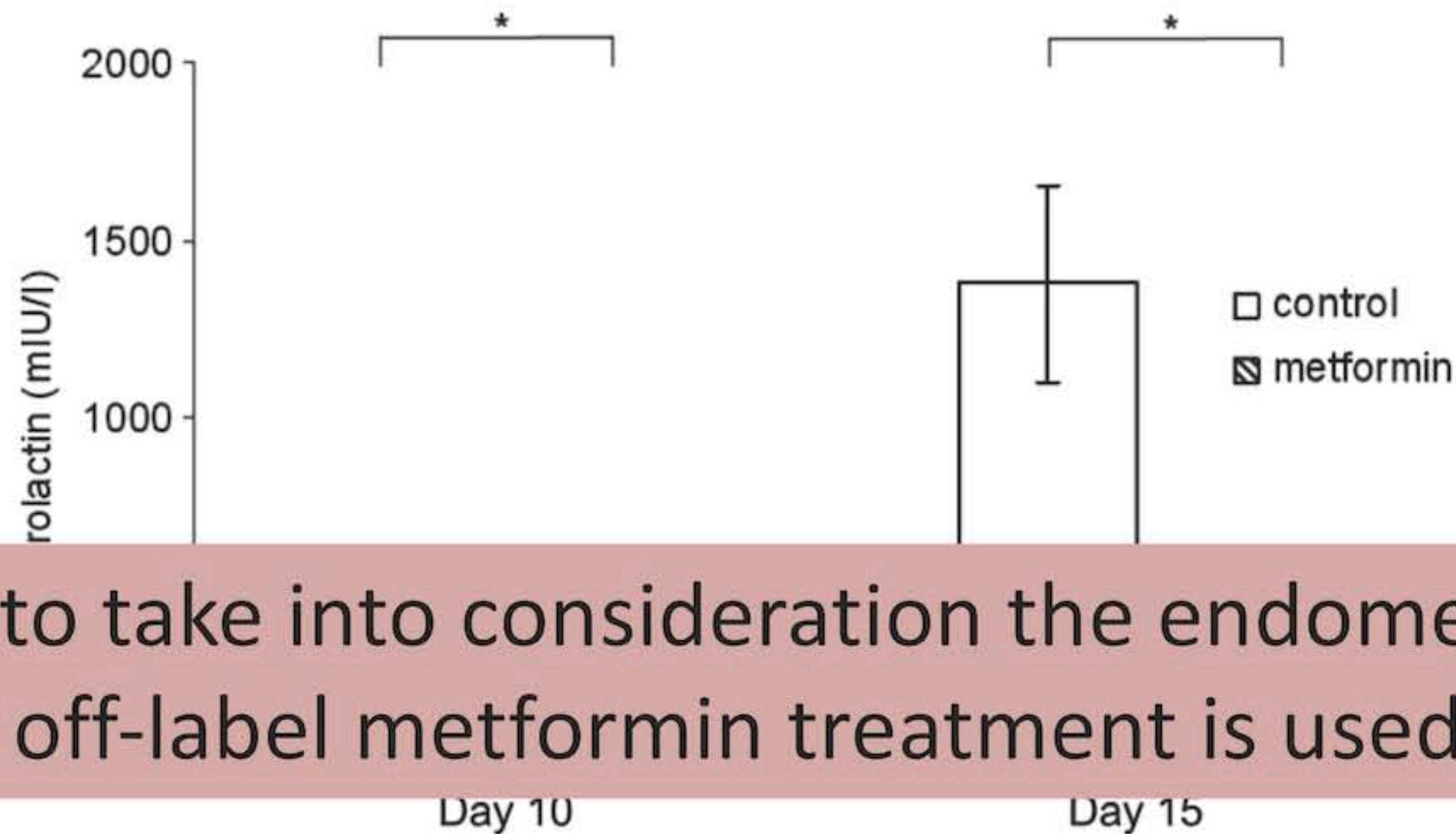
EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Fertility

Germeyer *et al.*, 2011; Freis *et al.*, 2017



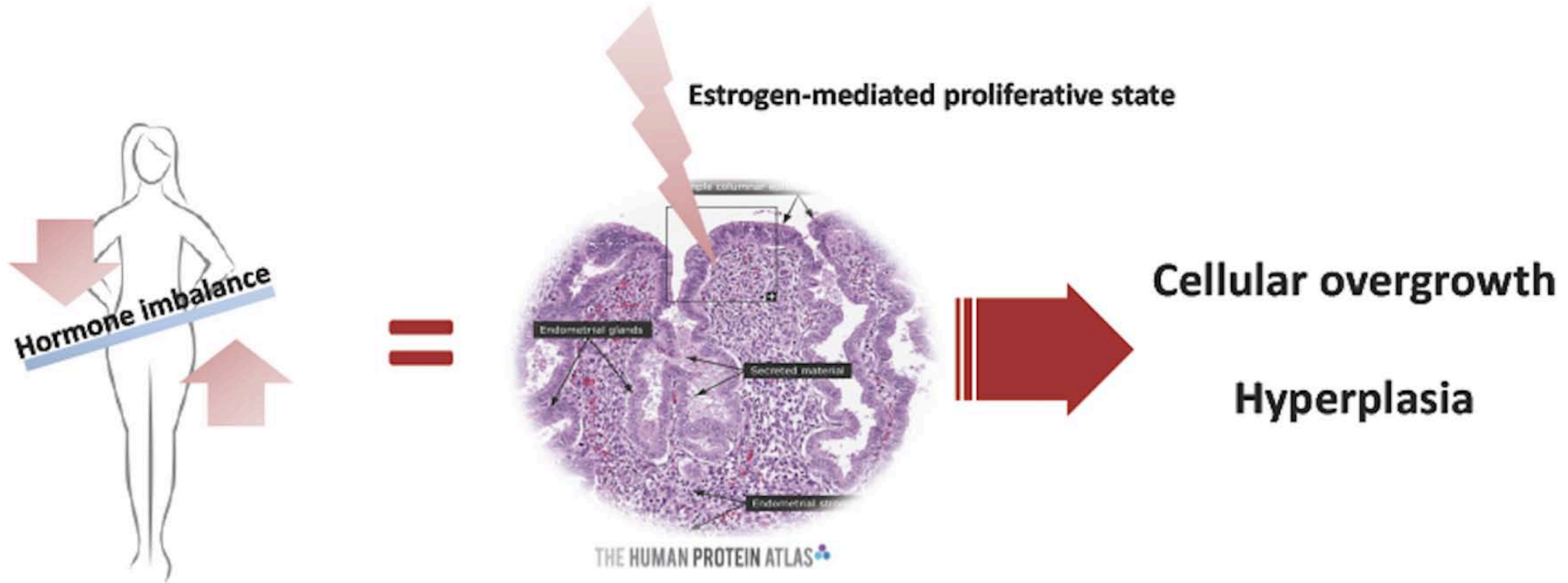
UniversitätsKlinikum Heidelberg



↓ ESC decidualization
↑ IL-8 and IL-1 β levels

Importance to take into consideration the endometrial microenvironment when off-label metformin treatment is used for PCOS patient

EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

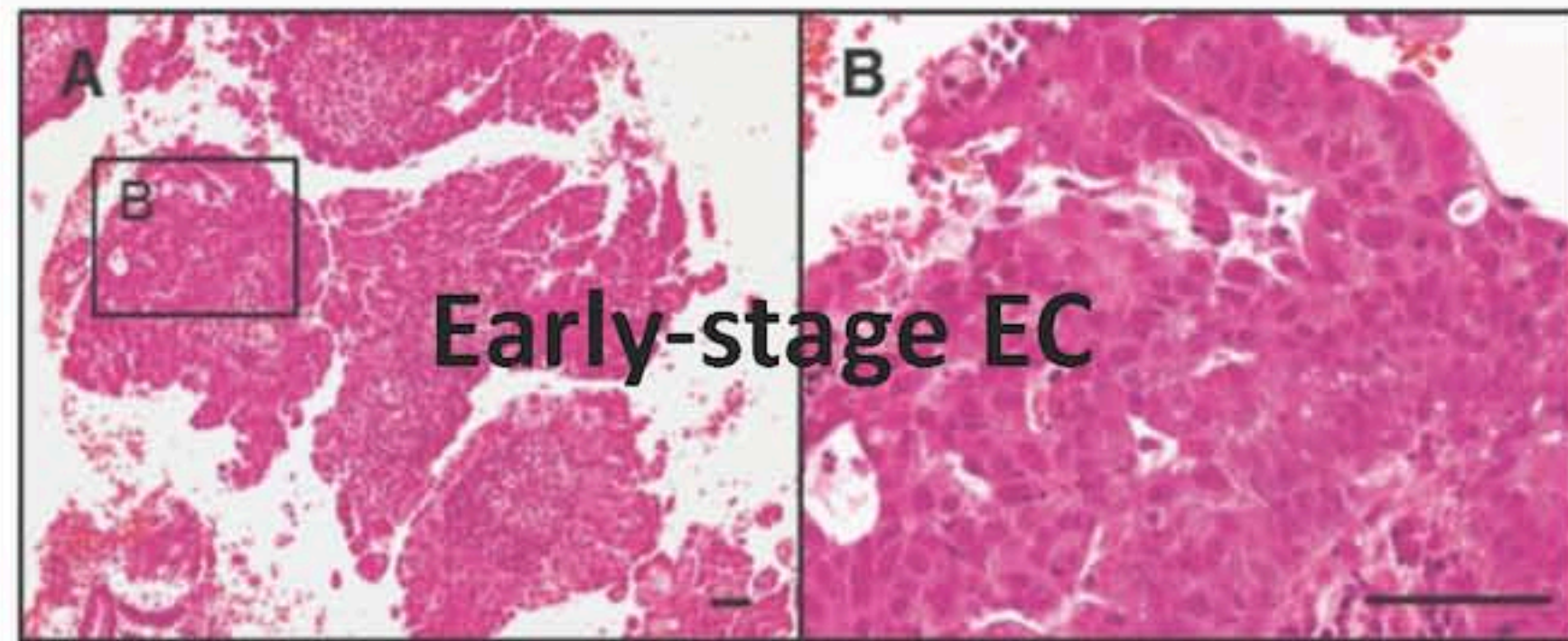


EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

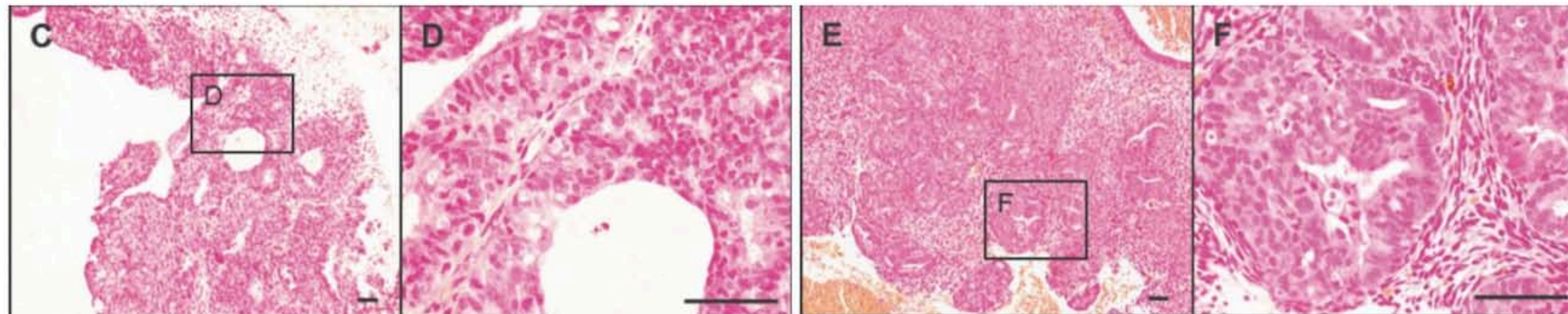
Antiproliferative

Metformin + Oral Contraceptive

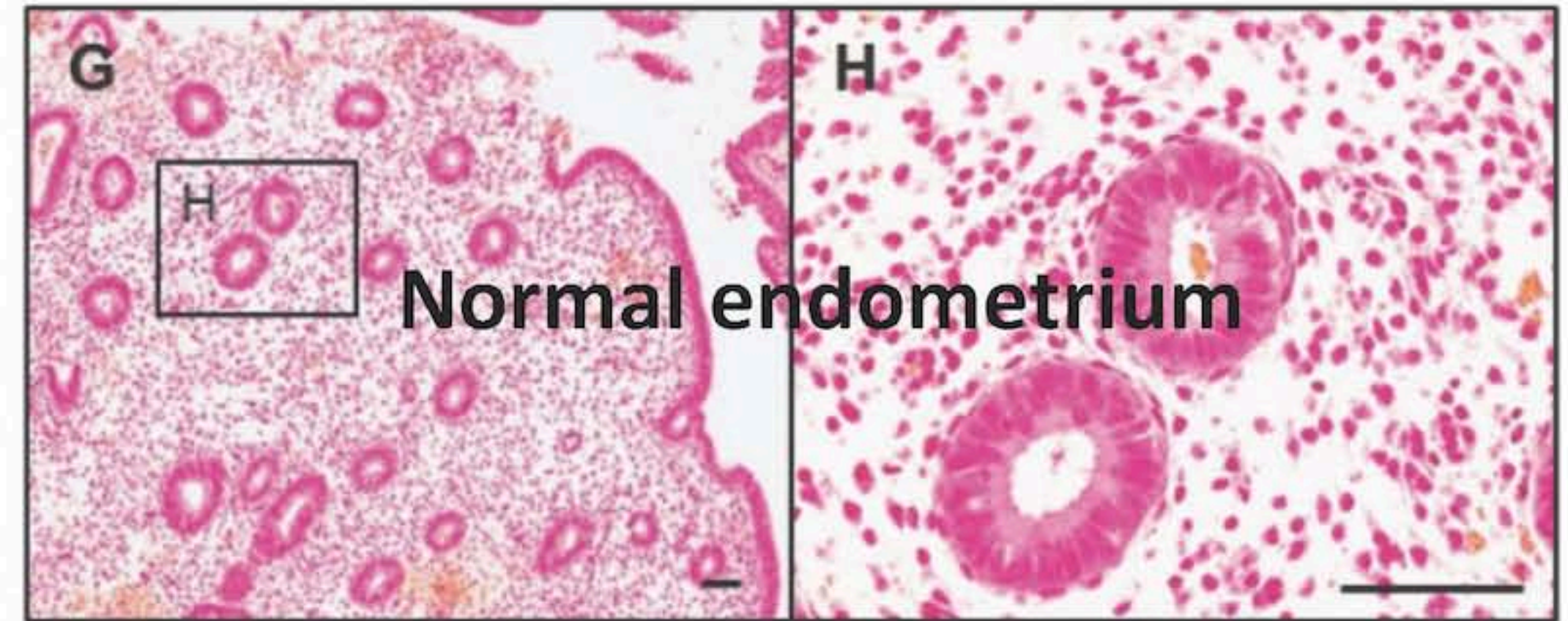
PCOS-IR endometrium before treatment



PCOS-IR endometrium during treatment

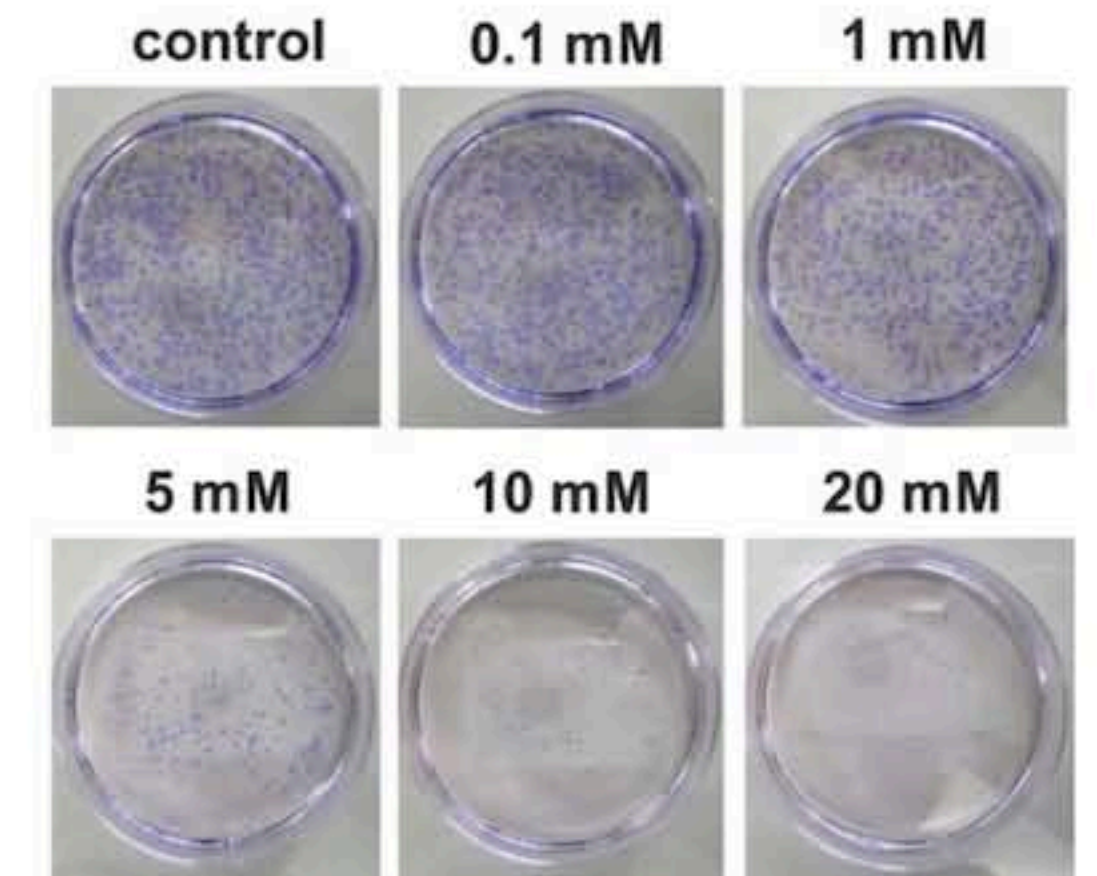
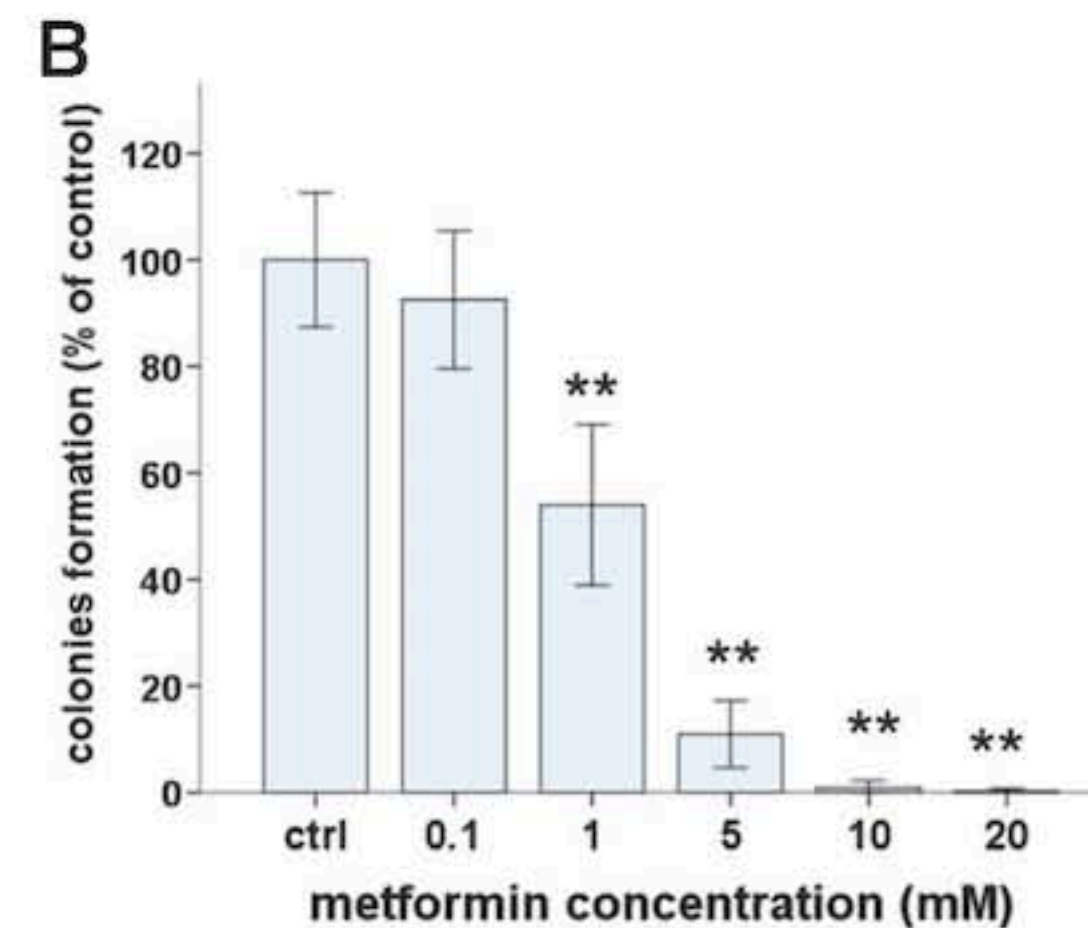
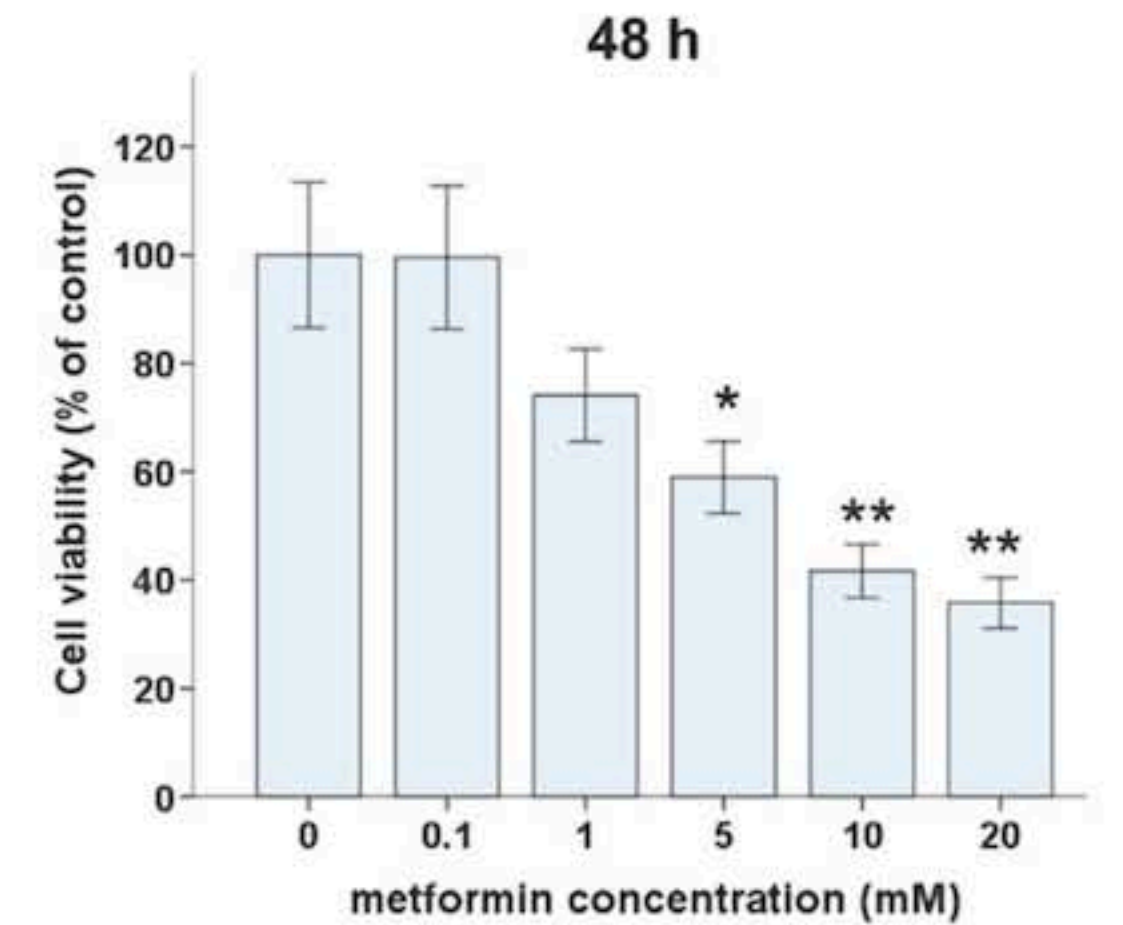
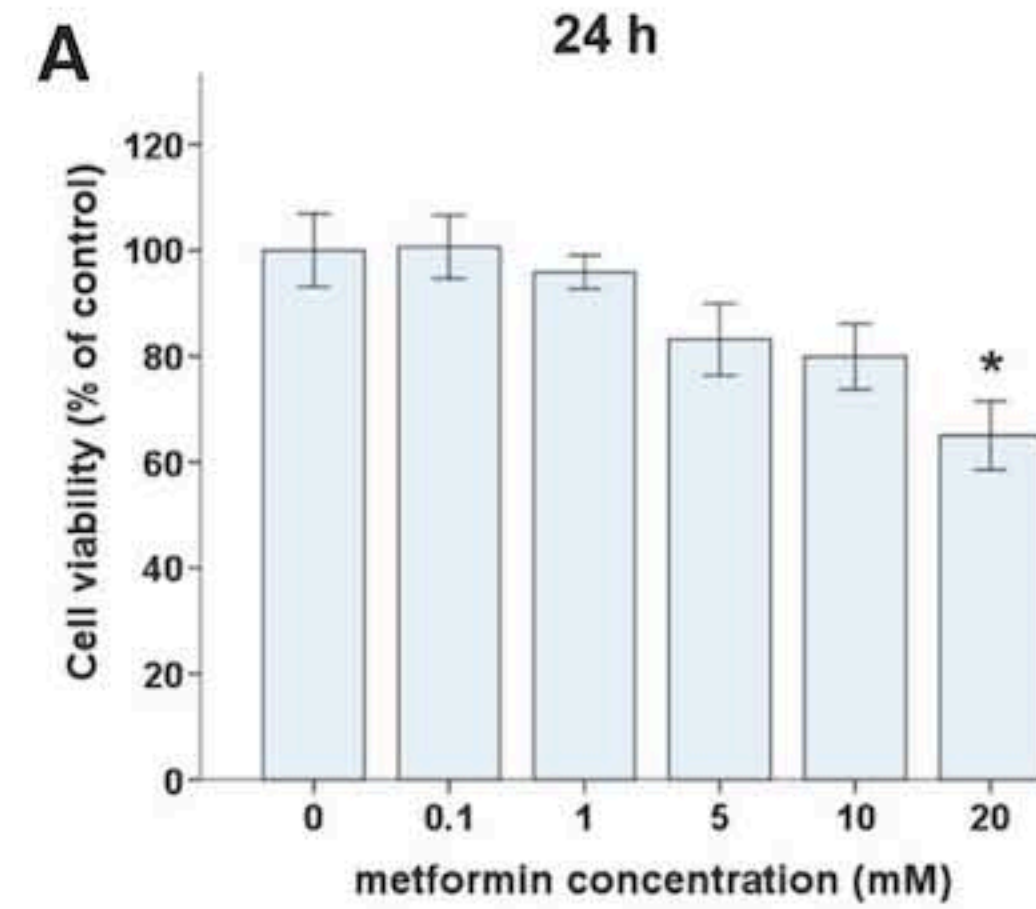
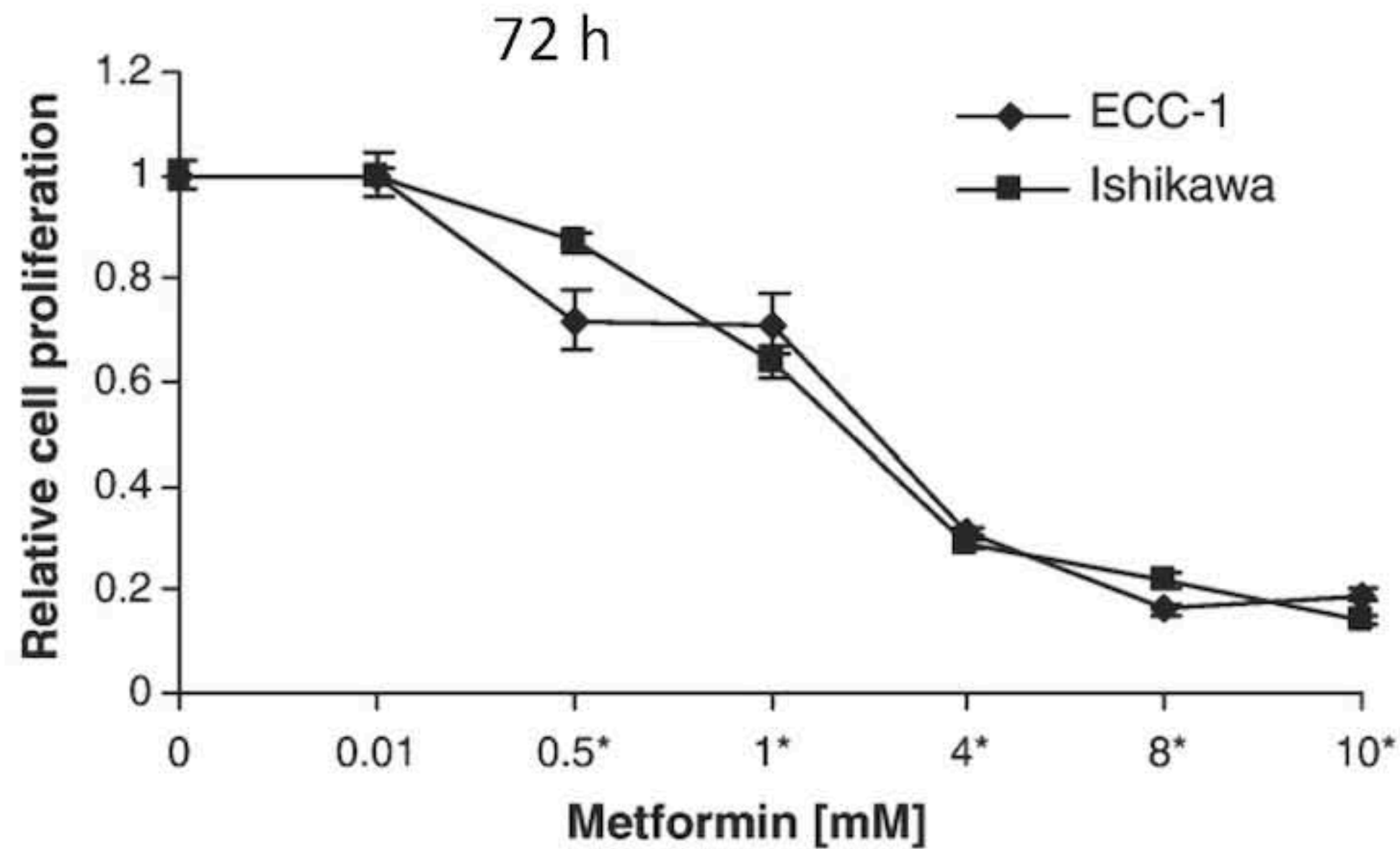


After 6 months treatment



EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Antiproliferative



Cantrel *et al.*, 2010; Takahashi *et al.* 2014

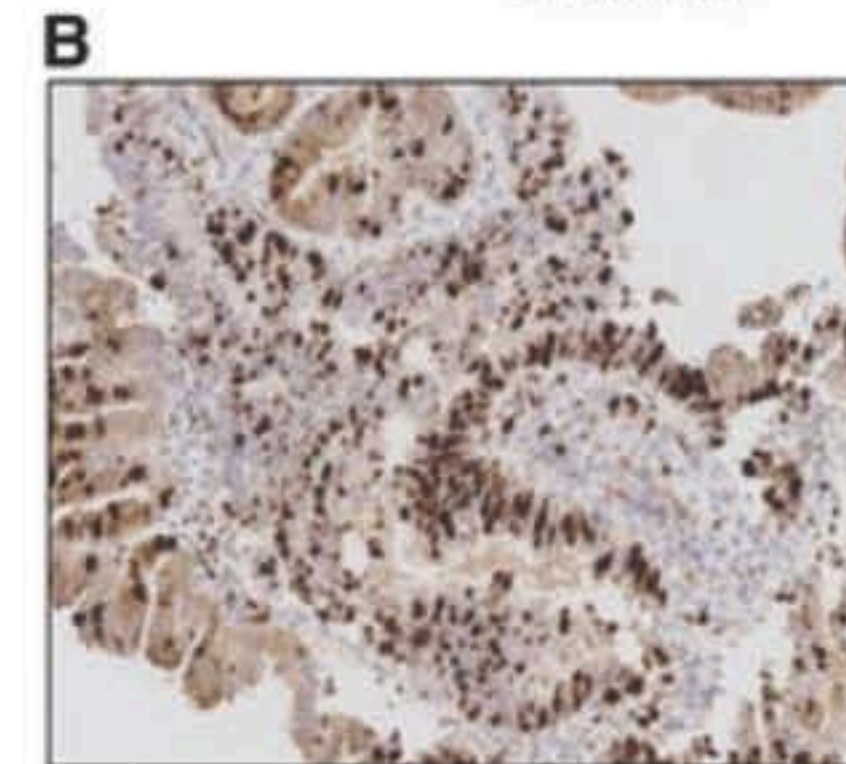
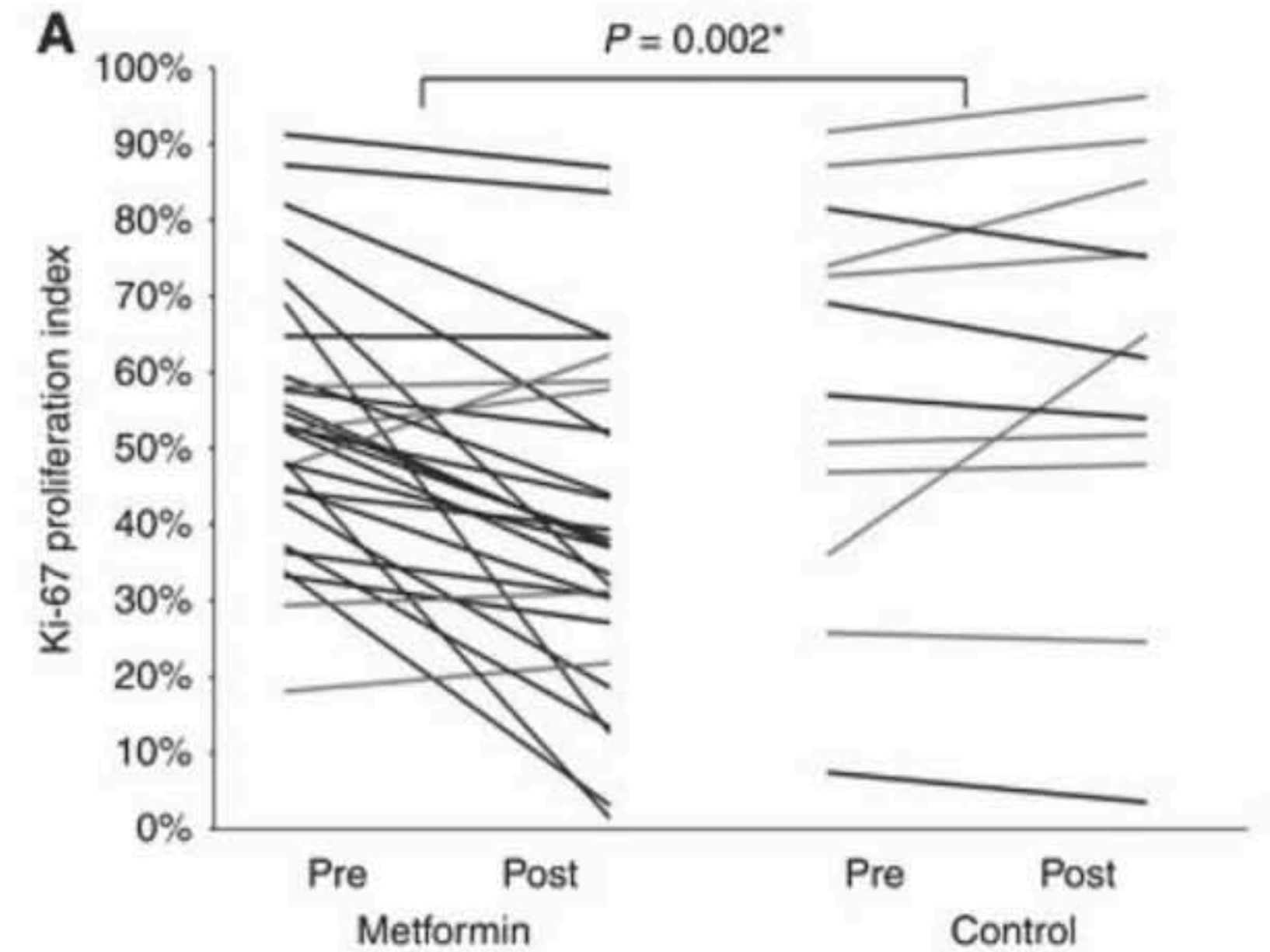
EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Antiproliferative

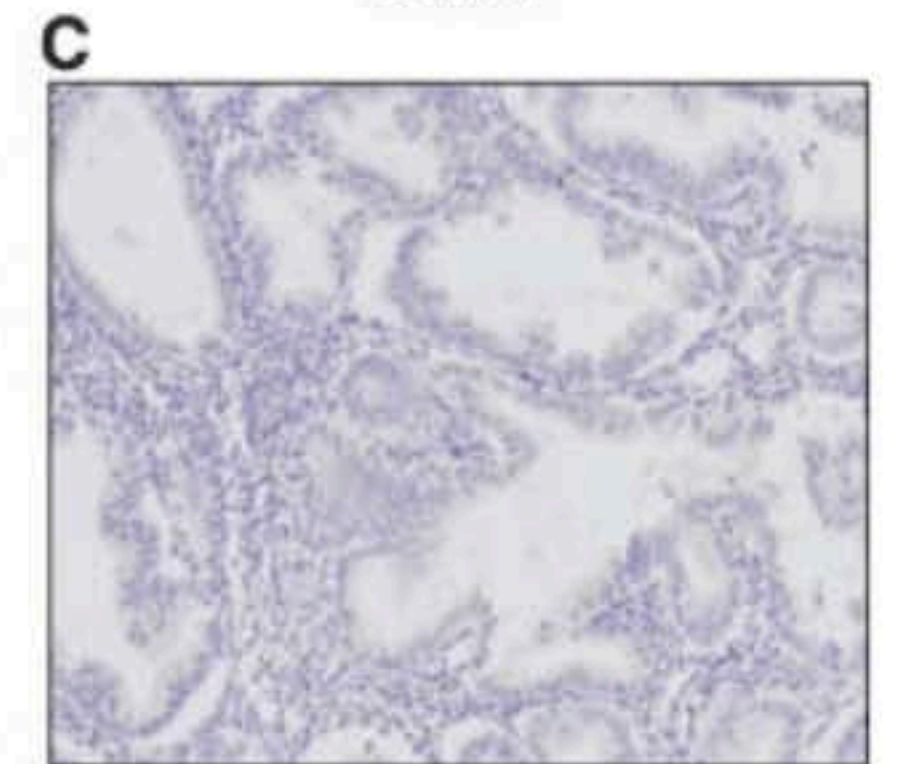
- AEH and EC patients; → presurgical window
- Metformin 850 mg twice daily up to 30 days;
- Non-treated patients;

Short-term presurgical antiproliferative effect of metformin

Sivalingam *et al*, 2016



Premetformin treatment

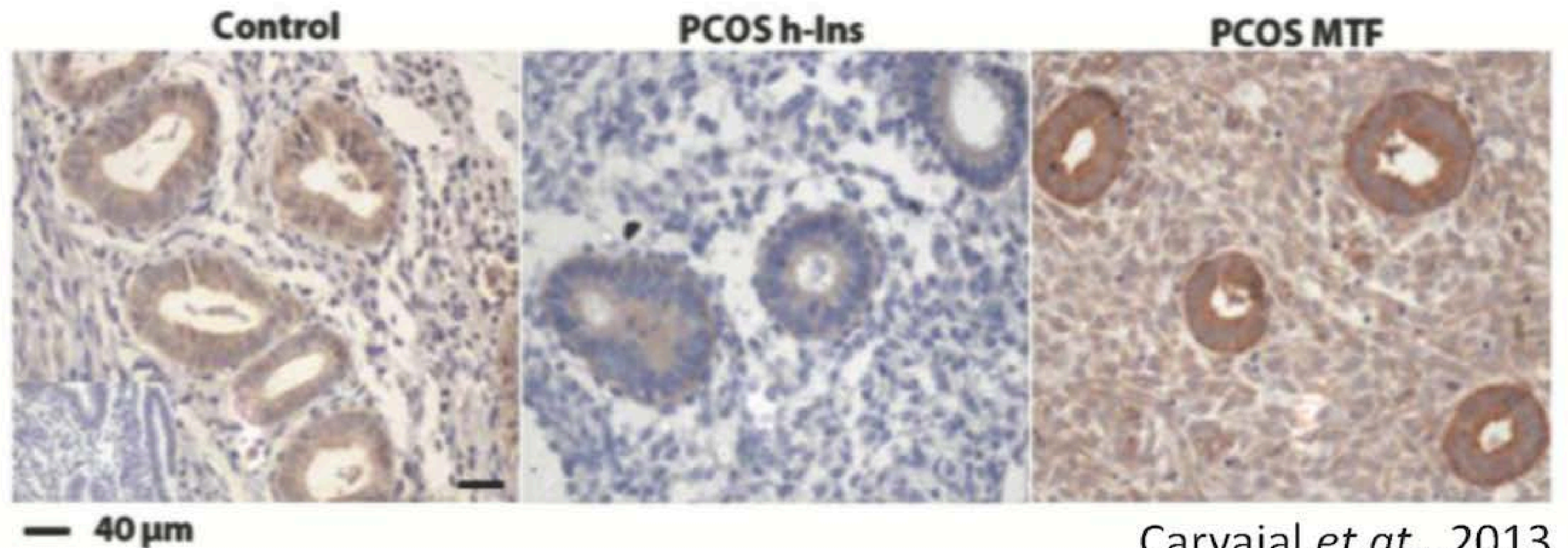
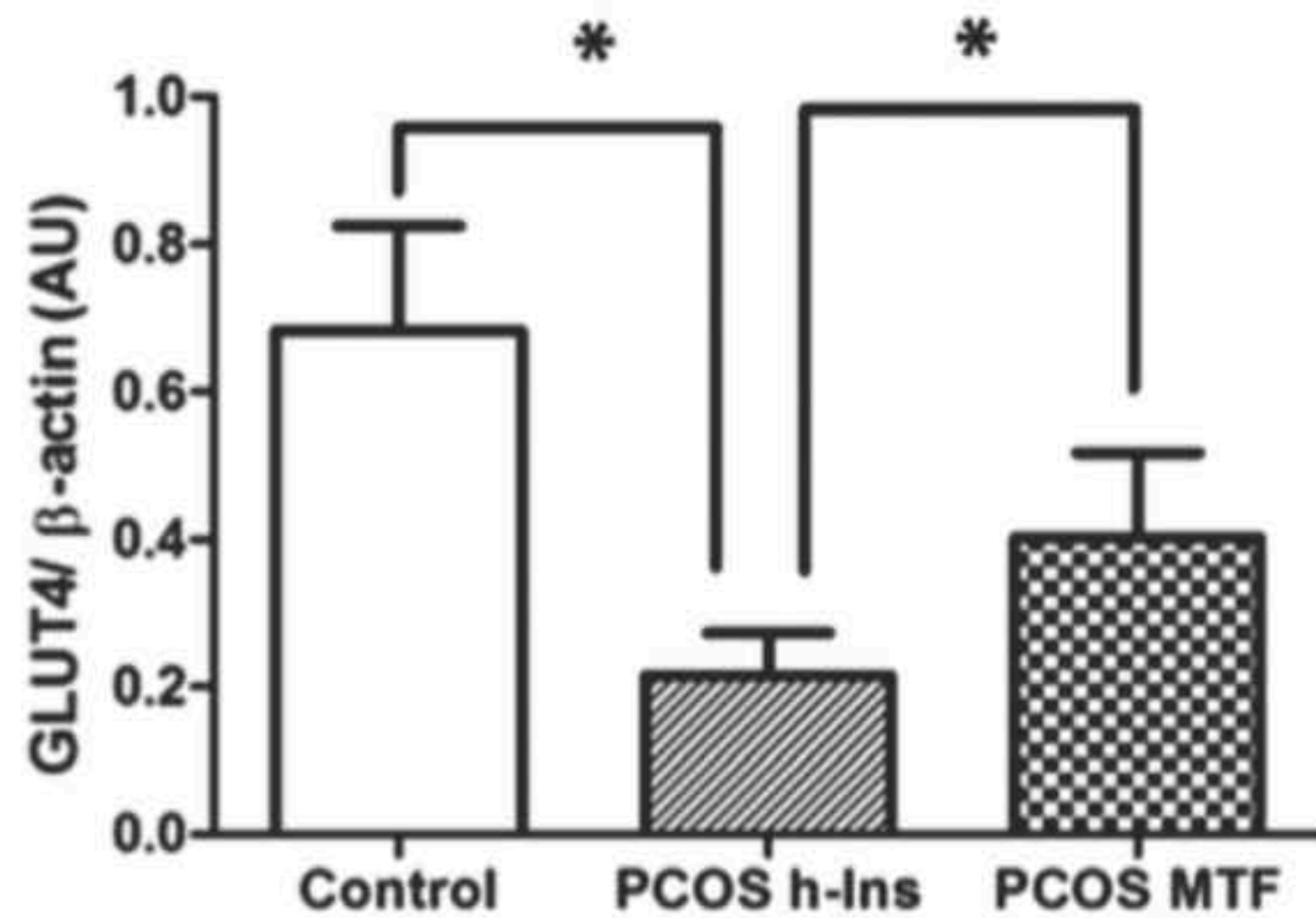


Postmetformin treatment

EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Increases GLUT4 expression

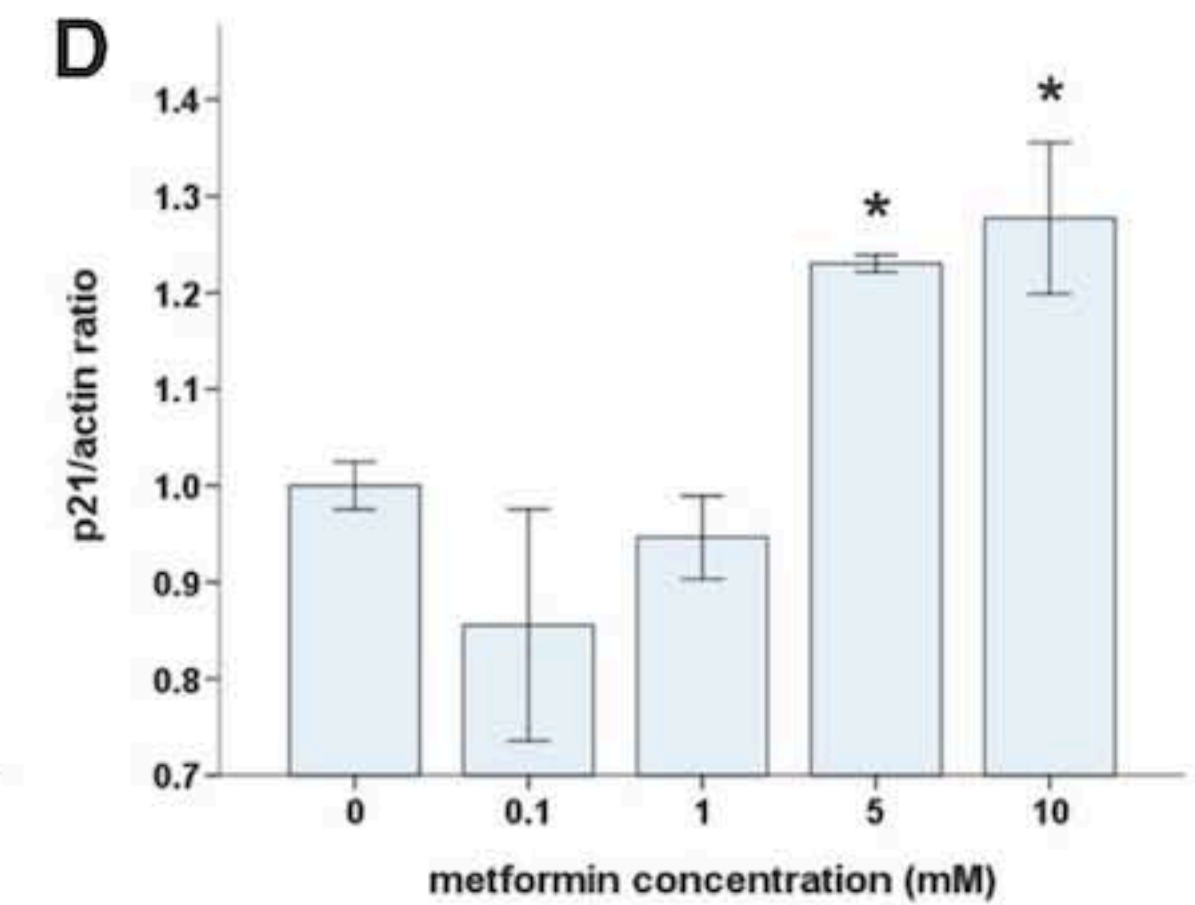
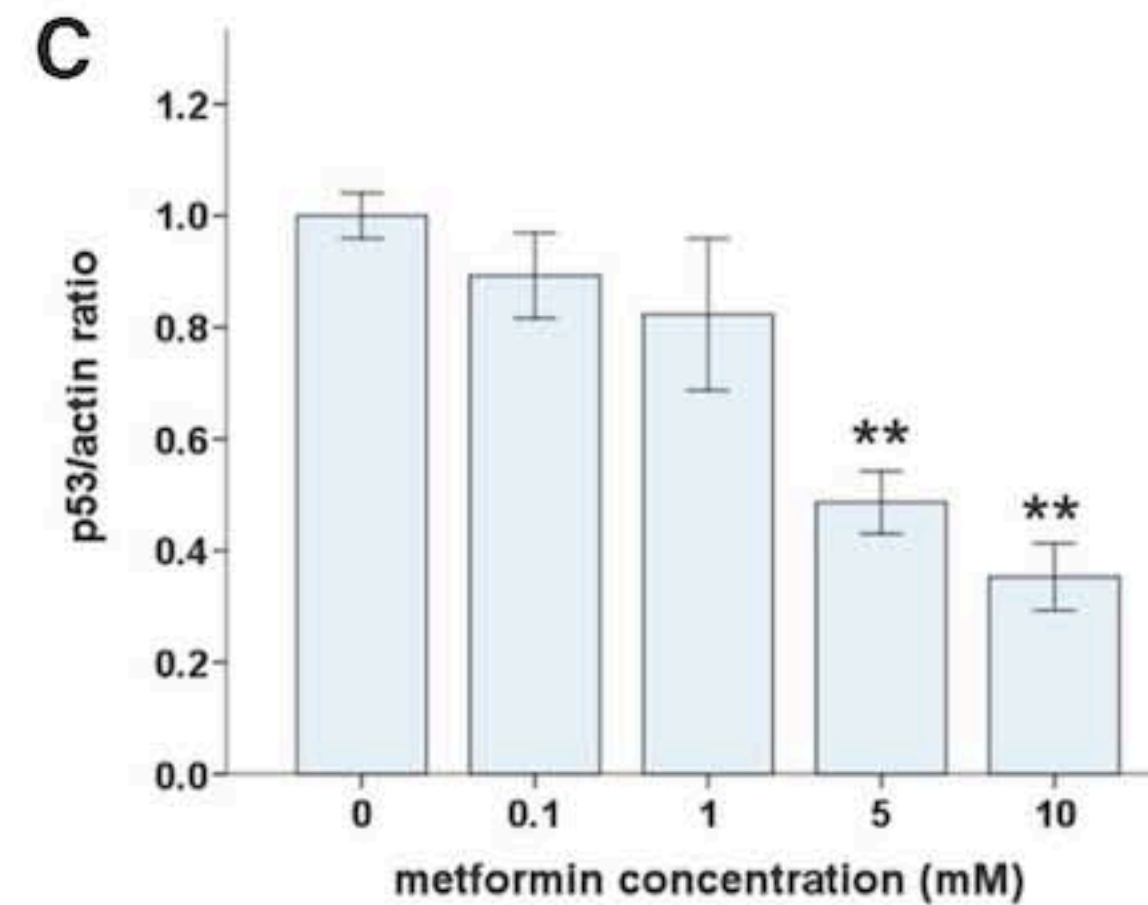
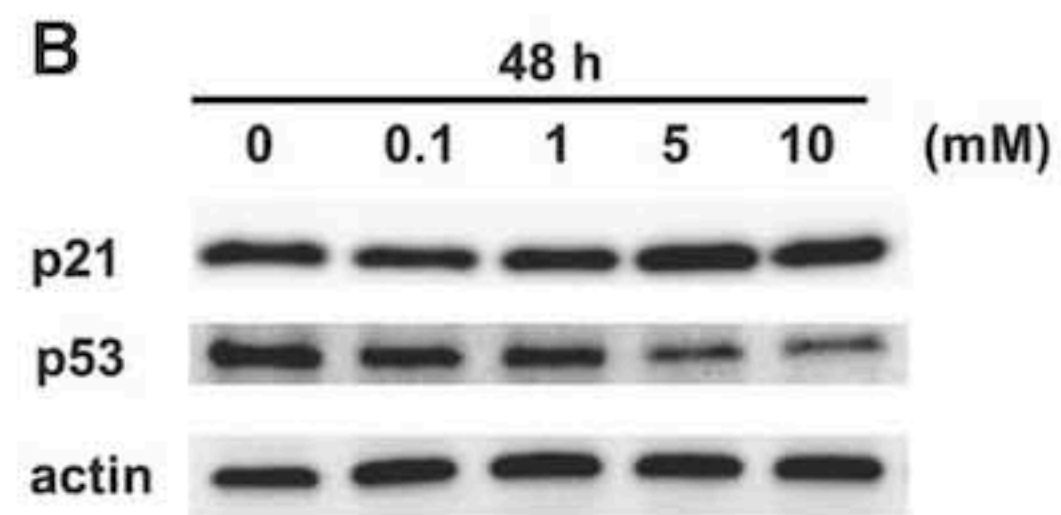
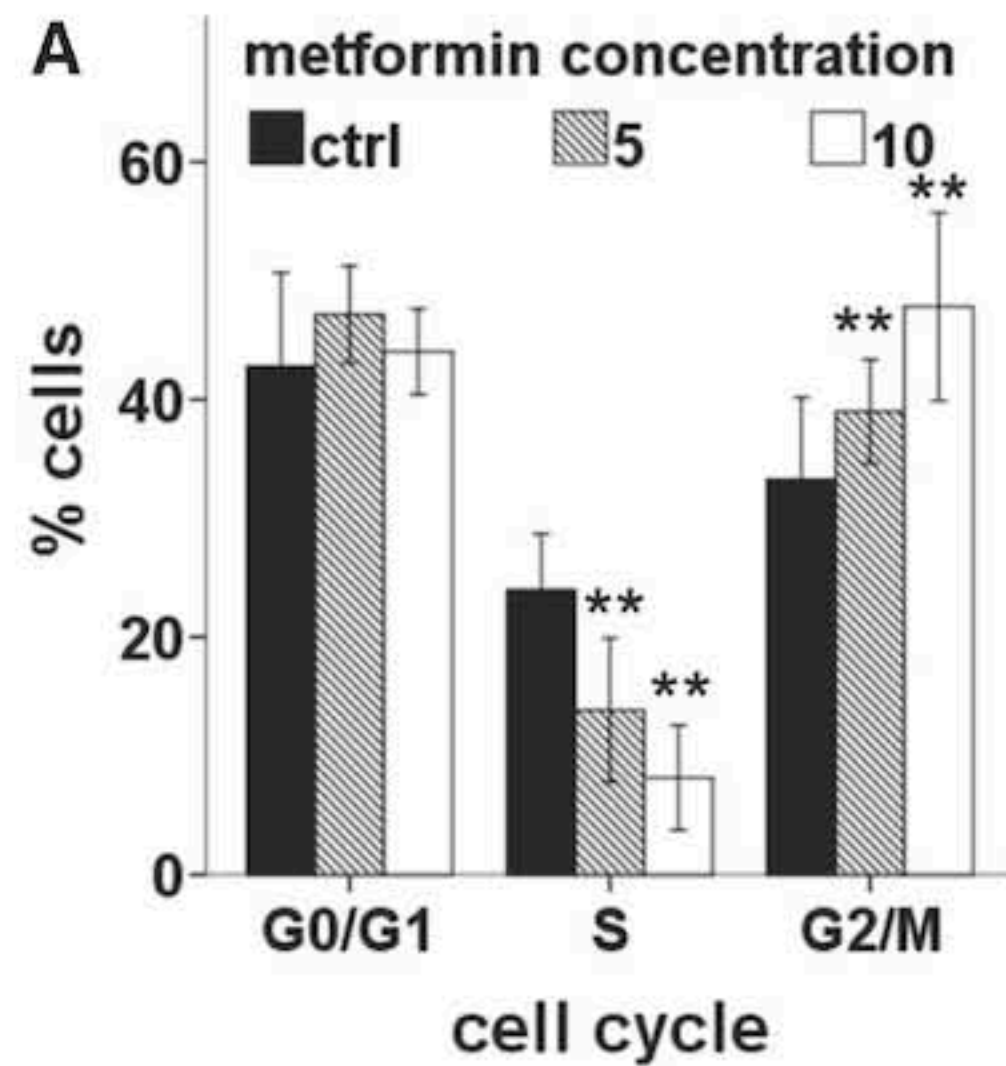
- Hyperinsulinemic patients have low GLUT4 endometrial expression;
- Act directly improving insulin resistance condition.



Carvajal *et al.*, 2013

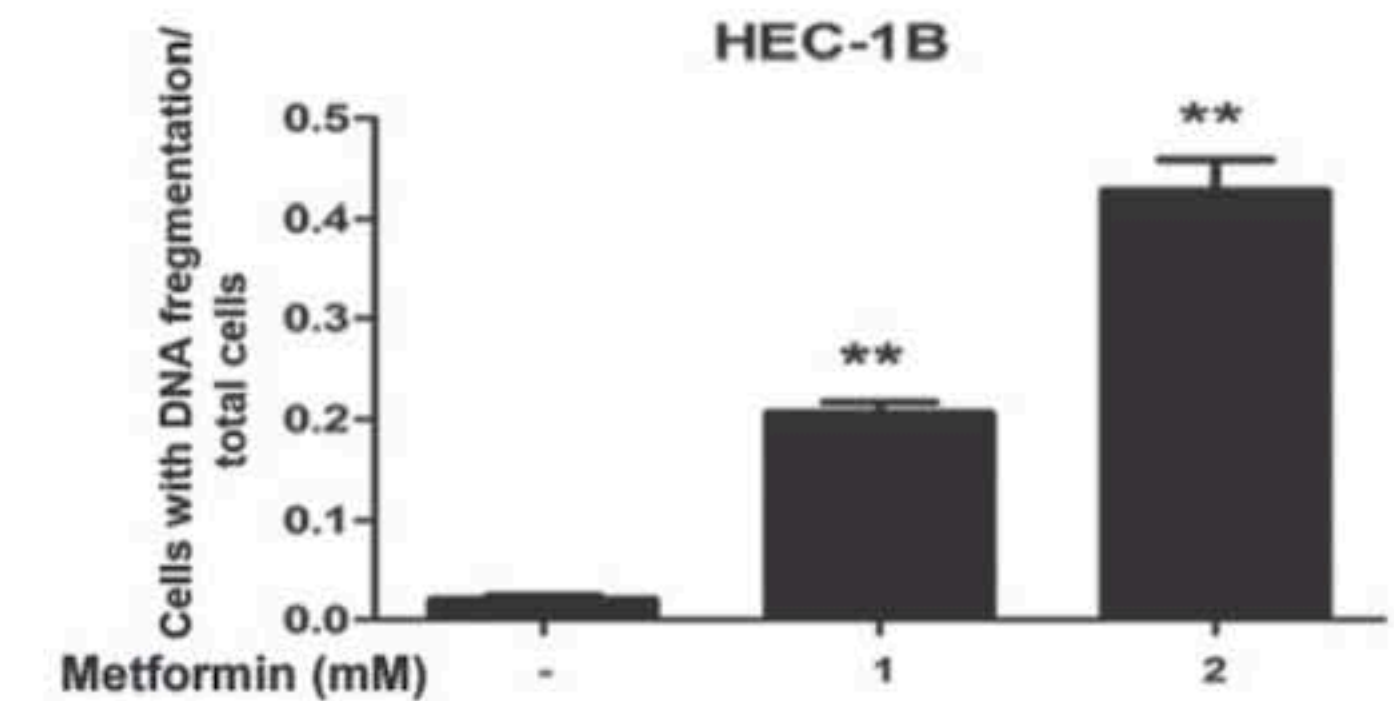
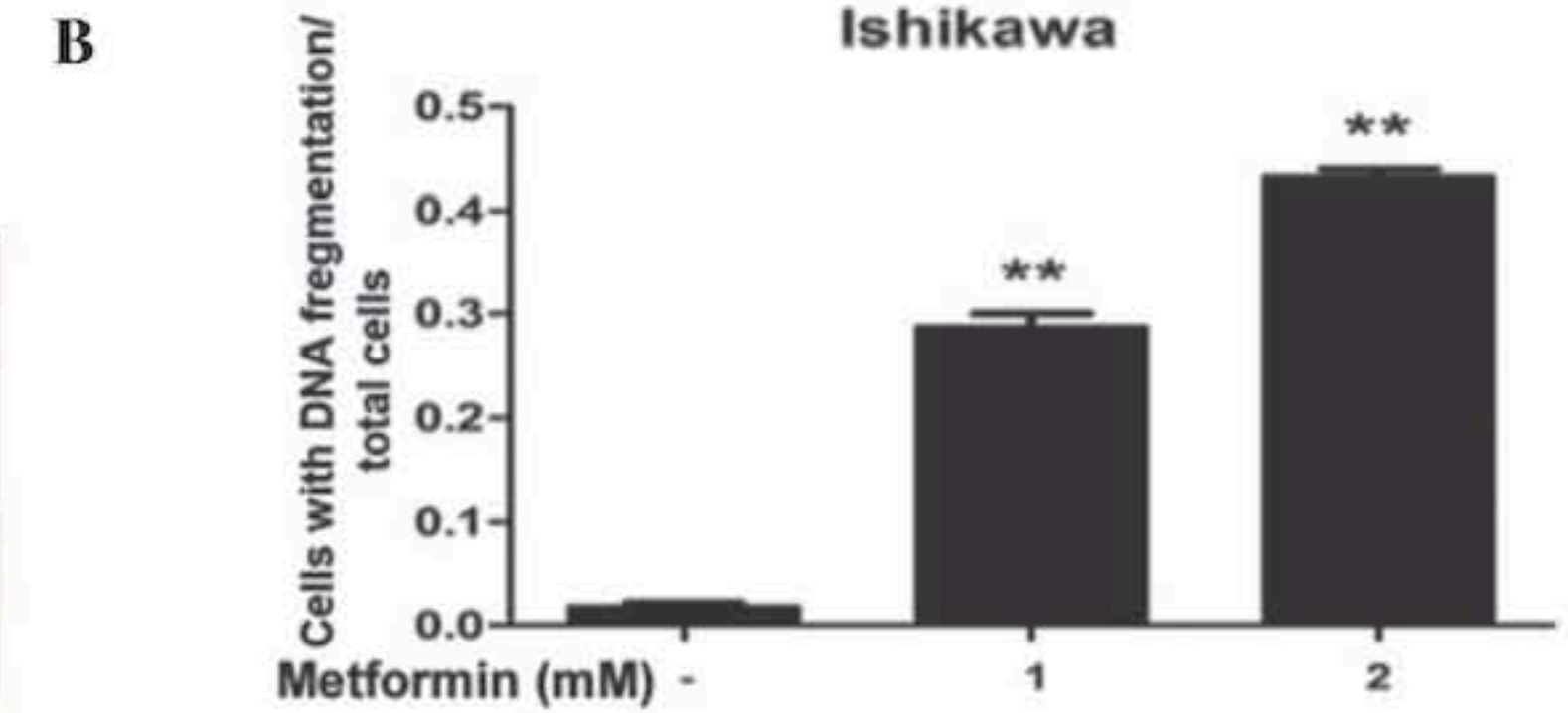
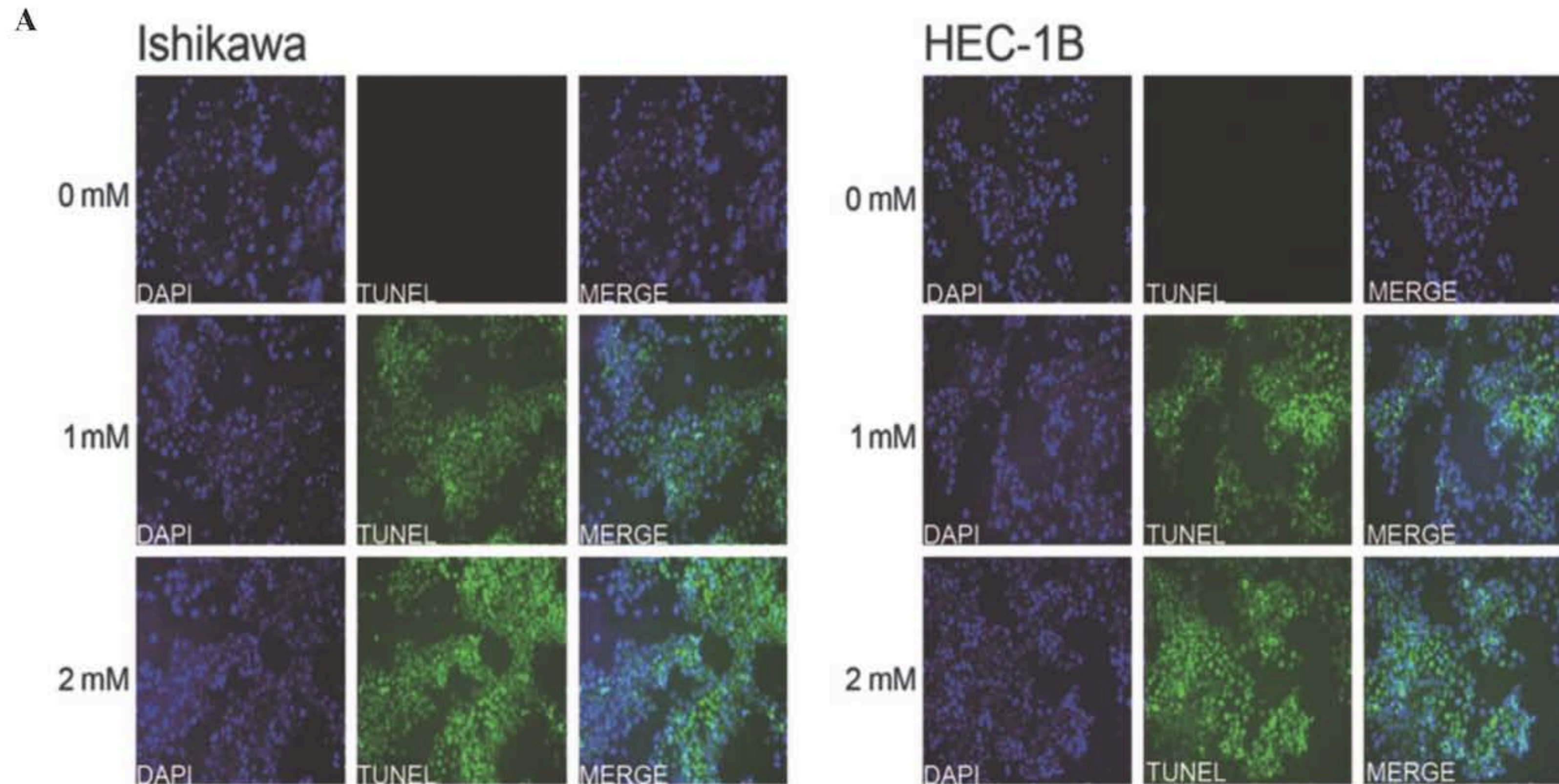
EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Induce cell cycle arrest



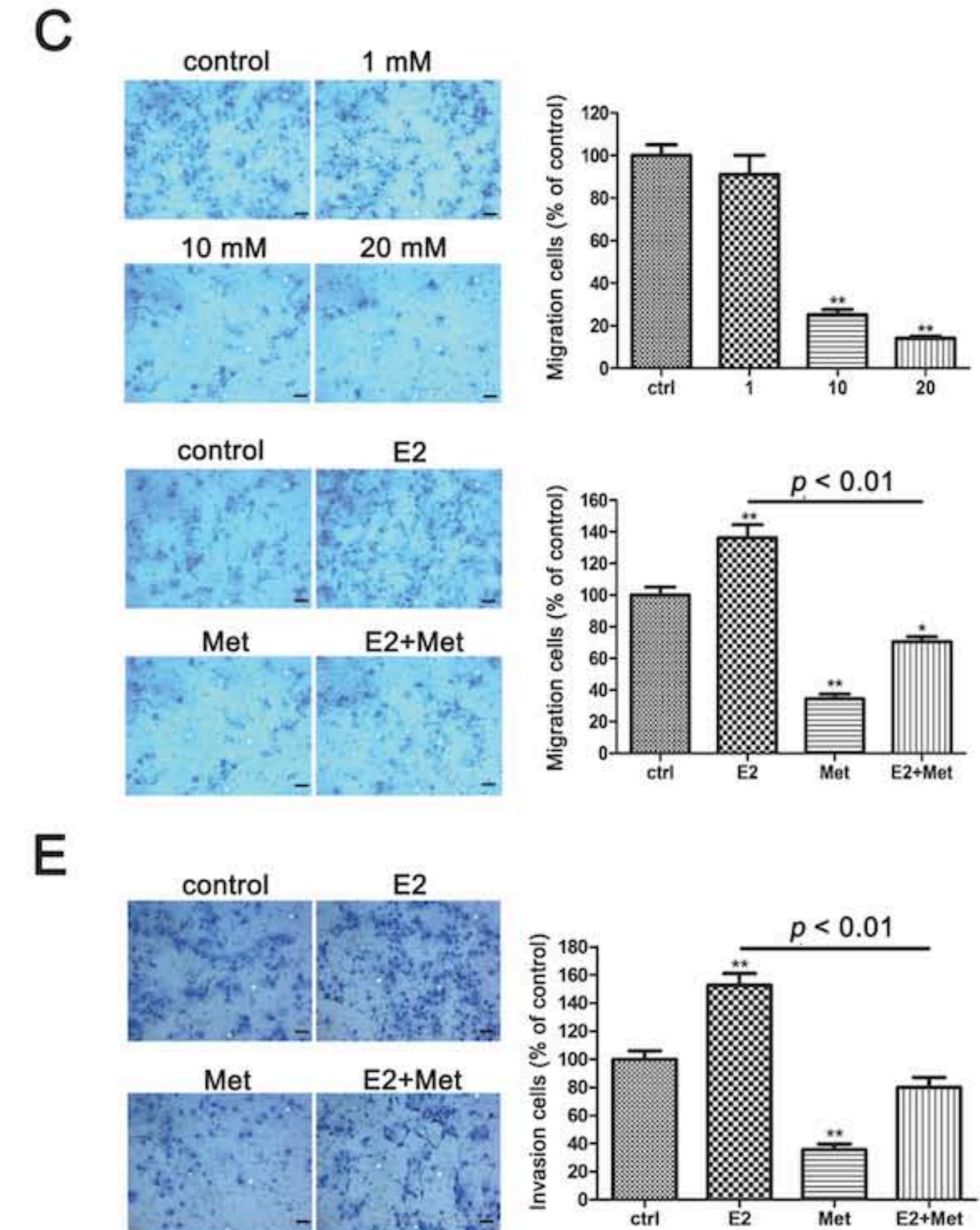
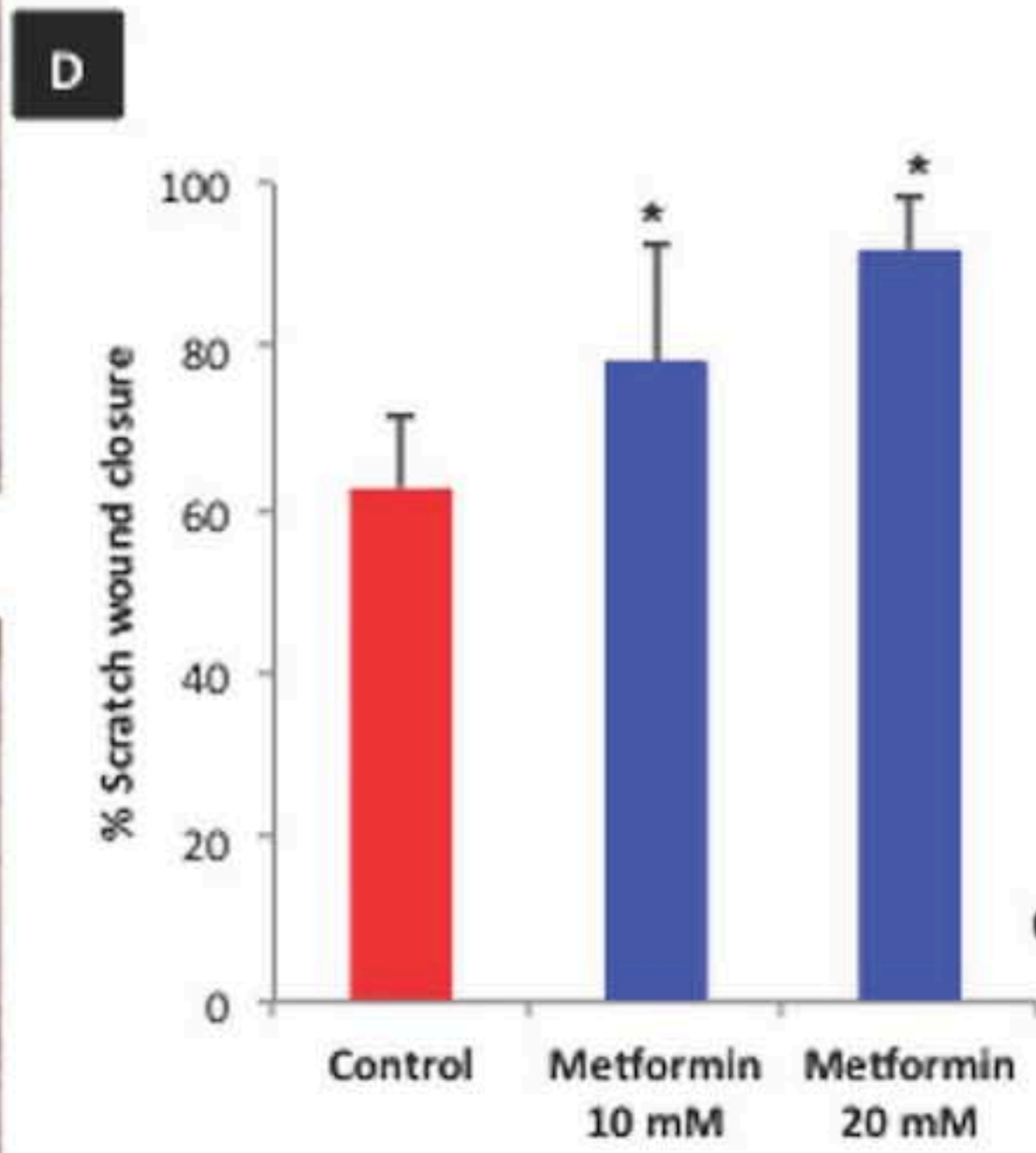
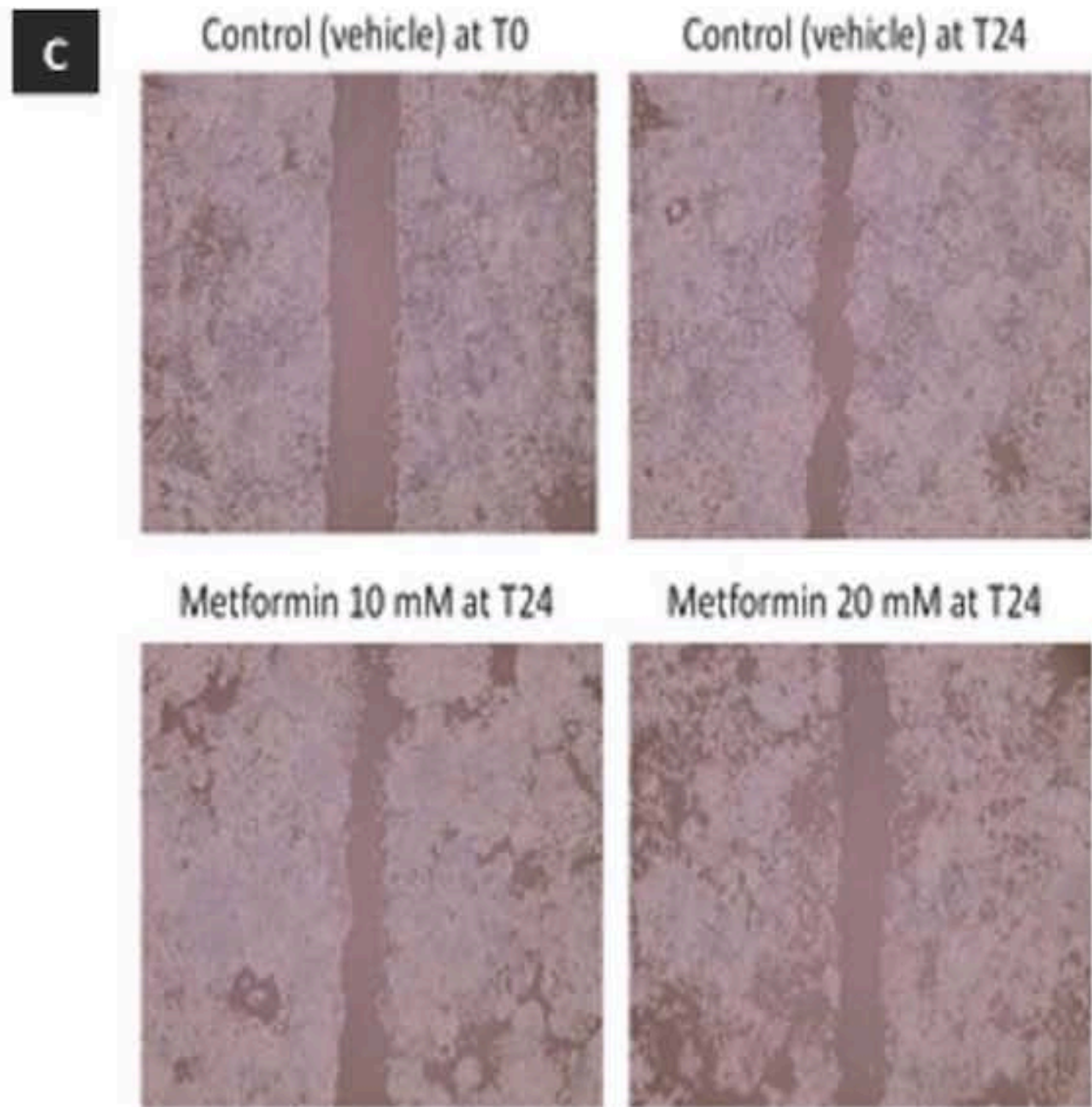
EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Induce apoptosis



EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

Antimetastatic



Liu *et al.*, 2016; Wallbillich *et al.*, 2017

EFFECT OF METFORMIN IN ENDOMETRIAL CELLS

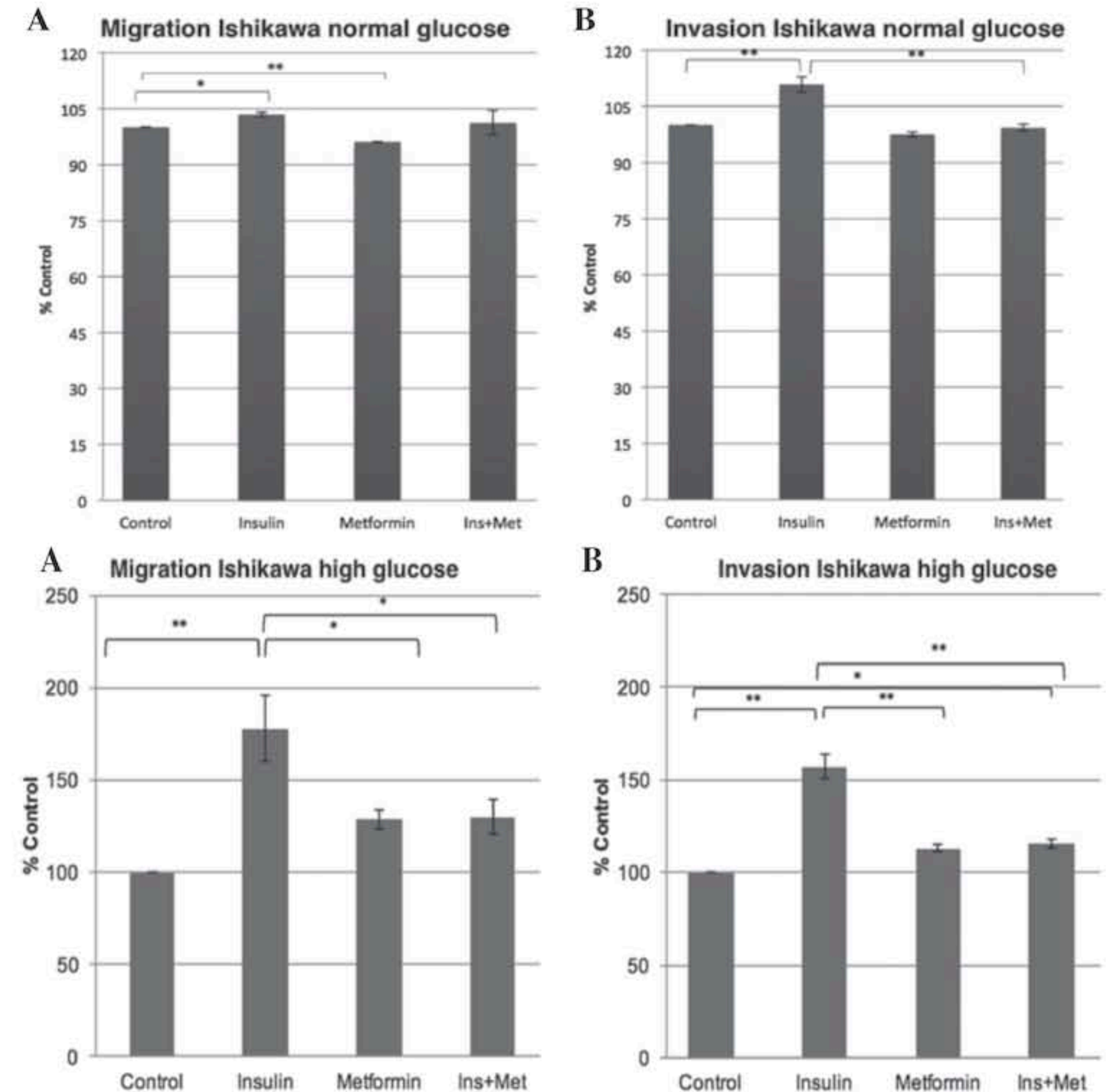
Antimetastatic

de Barros Machado *et al.*, 2016



UniversitätsKlinikum Heidelberg

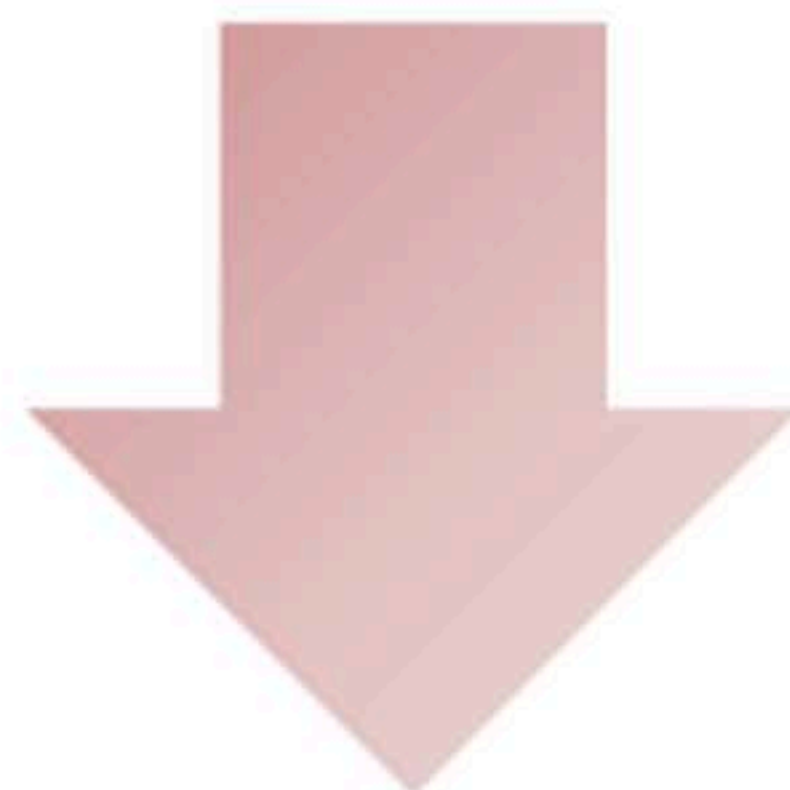
- Inhibit insulin metastatic effect;
- EC cells show resistance to Met effect in high glucose environment.



Metformin and Endometrial function



Fertility



Endometrial cancer



Scientific Society Symposium
Firenze, 8th March 2018



Metformin and Endometrial function

Amanda.MachadoWeber@med.uni-heidelberg.de



UniversitätsKlinikum Heidelberg

Department of Gynecological Endocrinology and
Fertility Disorders

Session organized by the DGGEF - Dr. Amanda Machado Weber