

Leptin Regulation of VEGF in Breast Cancer Cells

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Dr. Judah Folkman

1933-2008

**“Father of Tumor
Angiogenesis”**



Folkman J.

Tumor angiogenesis: therapeutic implications.

New England Journal of Medicine
1971; 285: 1182-1186.



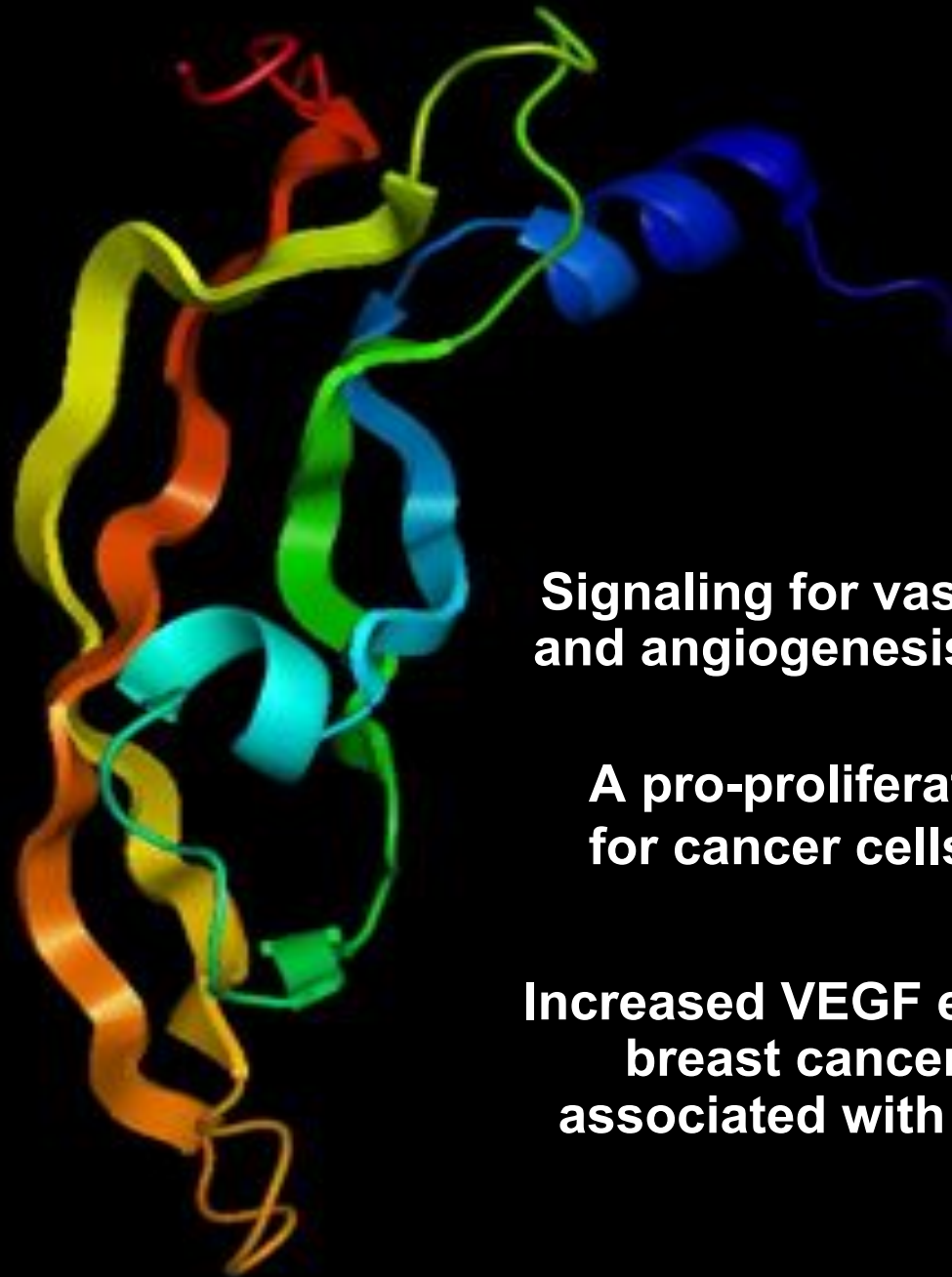
“Avascular solid tumors must
produce a secretable circulating
factor called: TAF (tumor -
angiogenesis factor).

It should be possible to develop
'antiangiogenesis' drugs to induce
a state of tumor dormancy and
hence prolong survival of cancer
patients.” - Judah Folkman, MD

VEGF

Vascular
Endothelial
Growth Factor

34-46 kD



**Signaling for vasculogenesis
and angiogenesis.**

**A pro-proliferative factor
for cancer cells**

**Increased VEGF expression in
breast cancer is strongly
associated with poor outcome**

Leptin



Small protein (16 kD)

Helical cytokine

Product of the obese gene
(*ob*)

Secreted mainly by
adipocytes

Pleiotropic & ubiquitous molecule

Leptin (1994 Zhang et al)

Angiogenesis
Mitosis
inflammation

Functions:
Regulator of energy
balance/appetite

Pathological processes

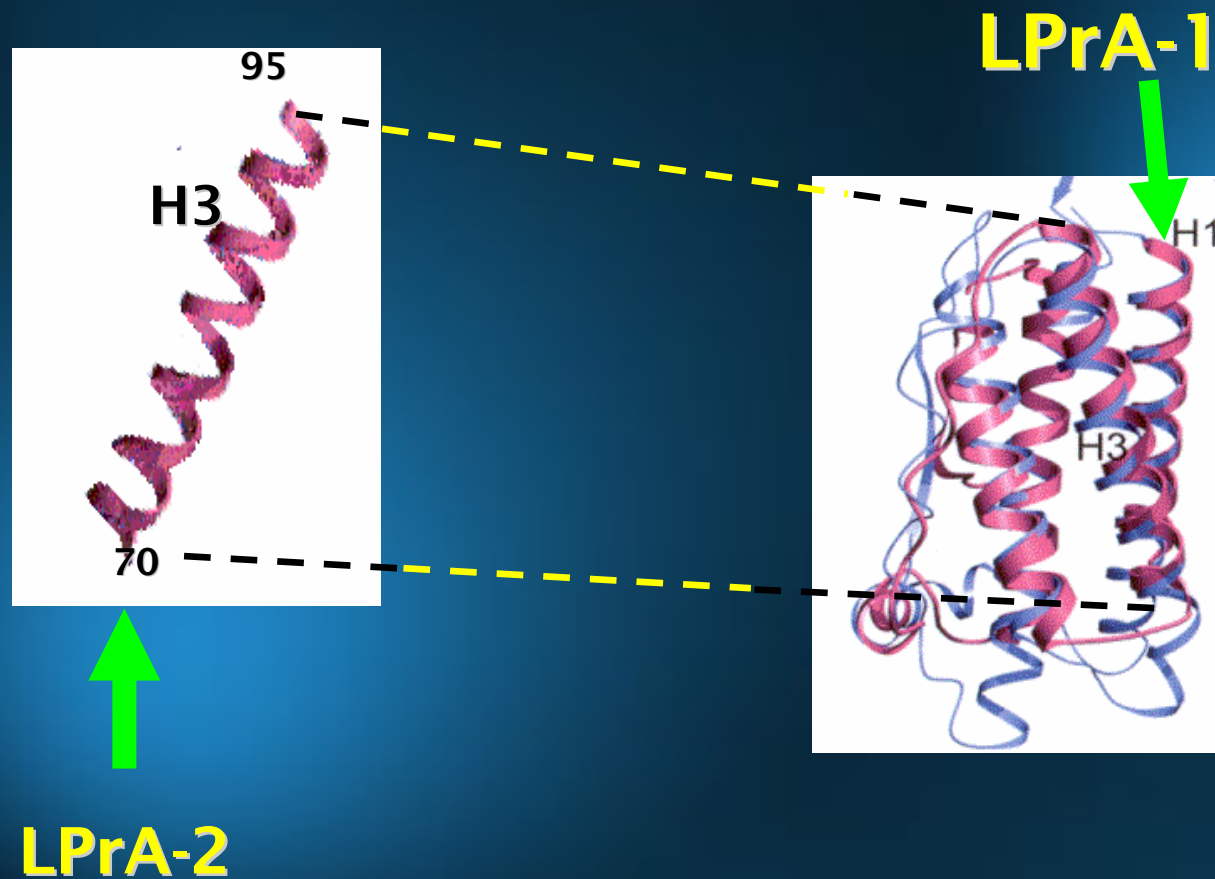
Cancer
endometriosis
diabetes
arthritis, etc.

2009

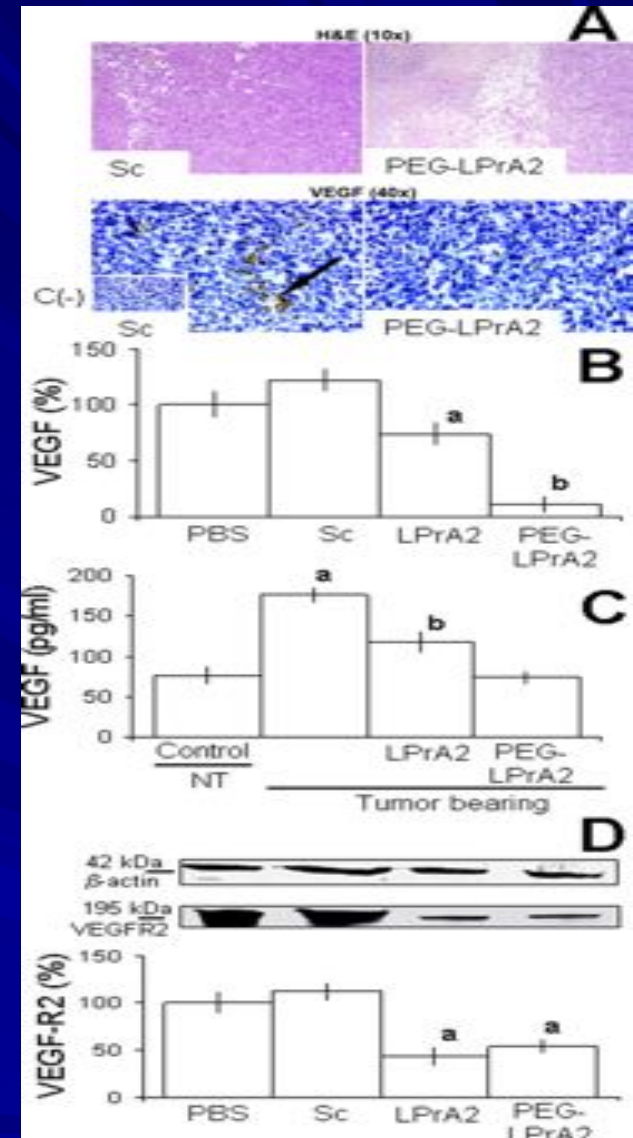
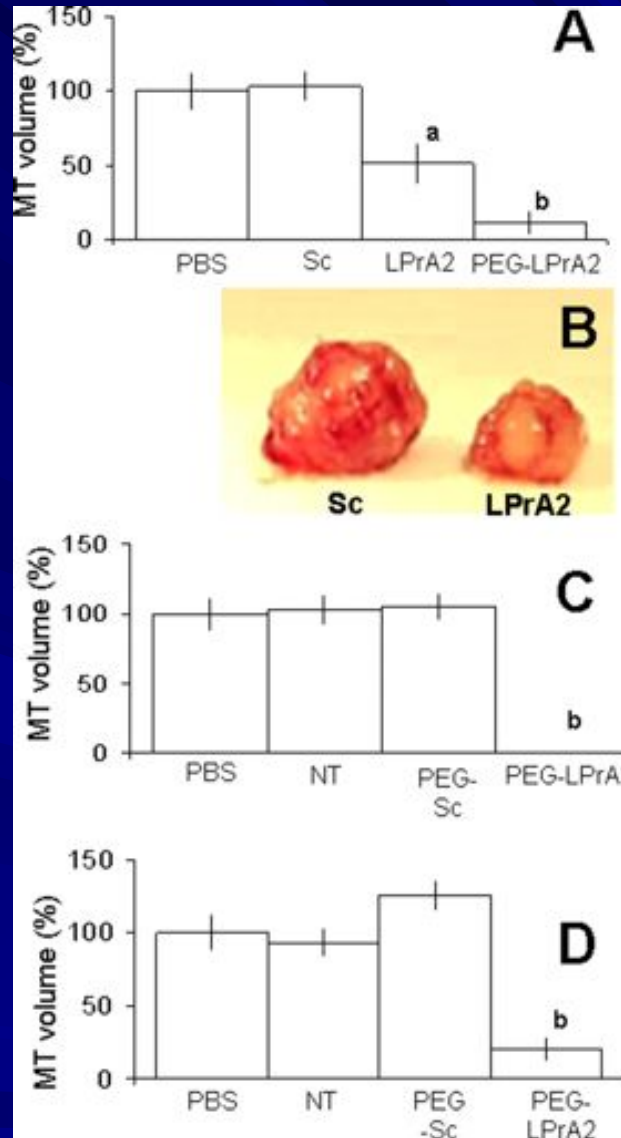
reproductive process

Ovulation
Endometrial receptivity
Embryo implantation

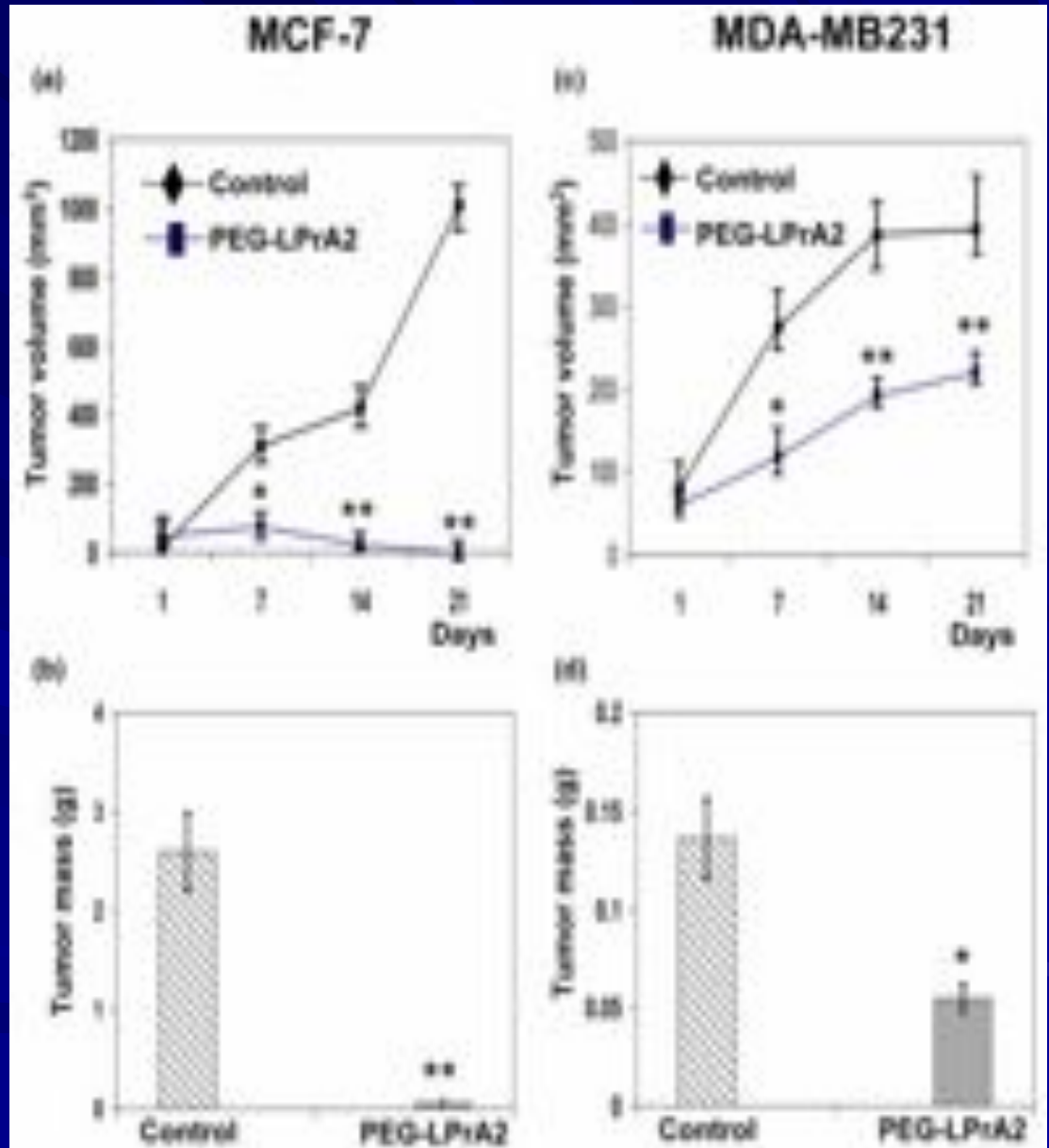
Designing Leptin Peptide Receptor Antagonists



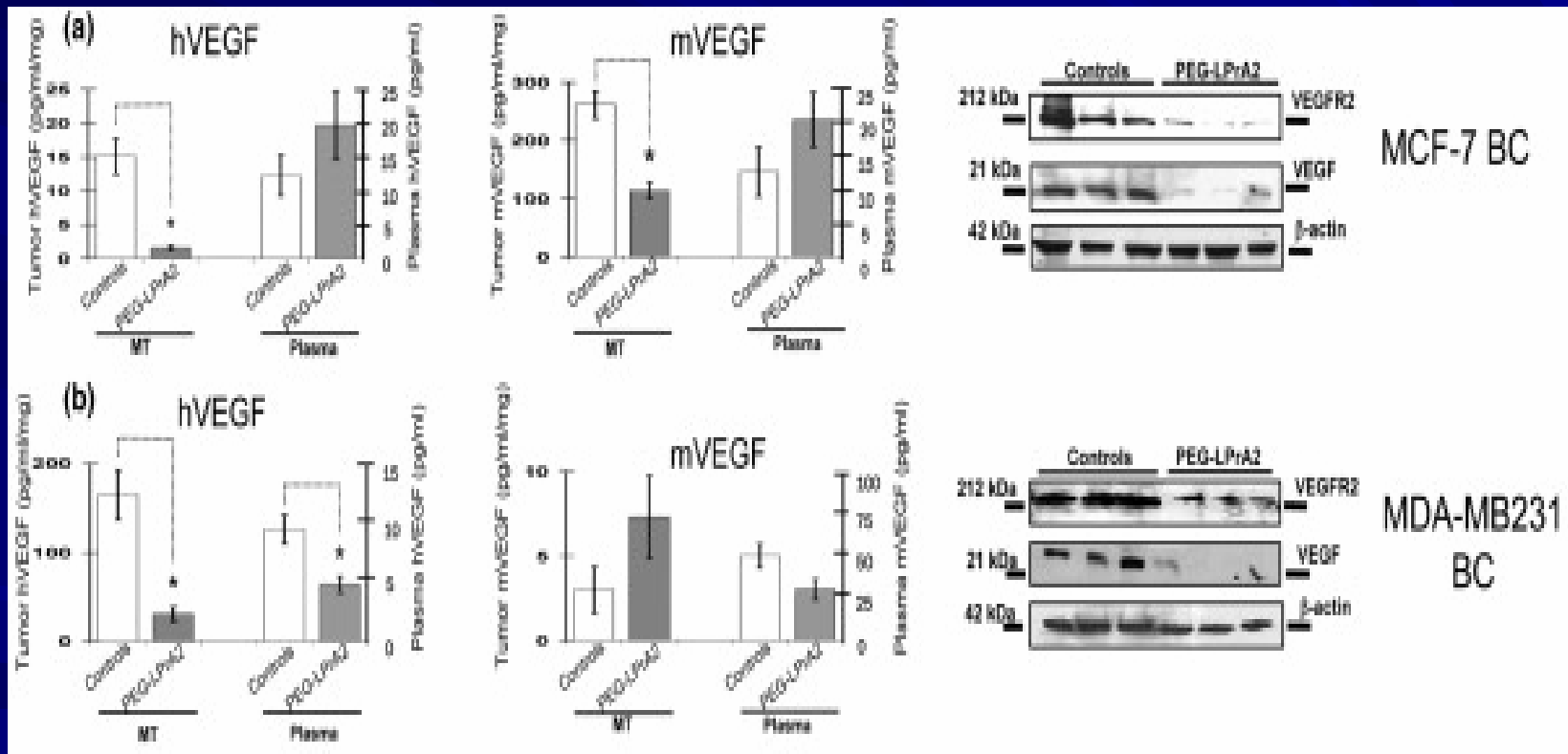
Inhibition of leptin signaling reduces the growth of 4T1 mammary tumors and expression of VEGF/VEGF-R2 levels

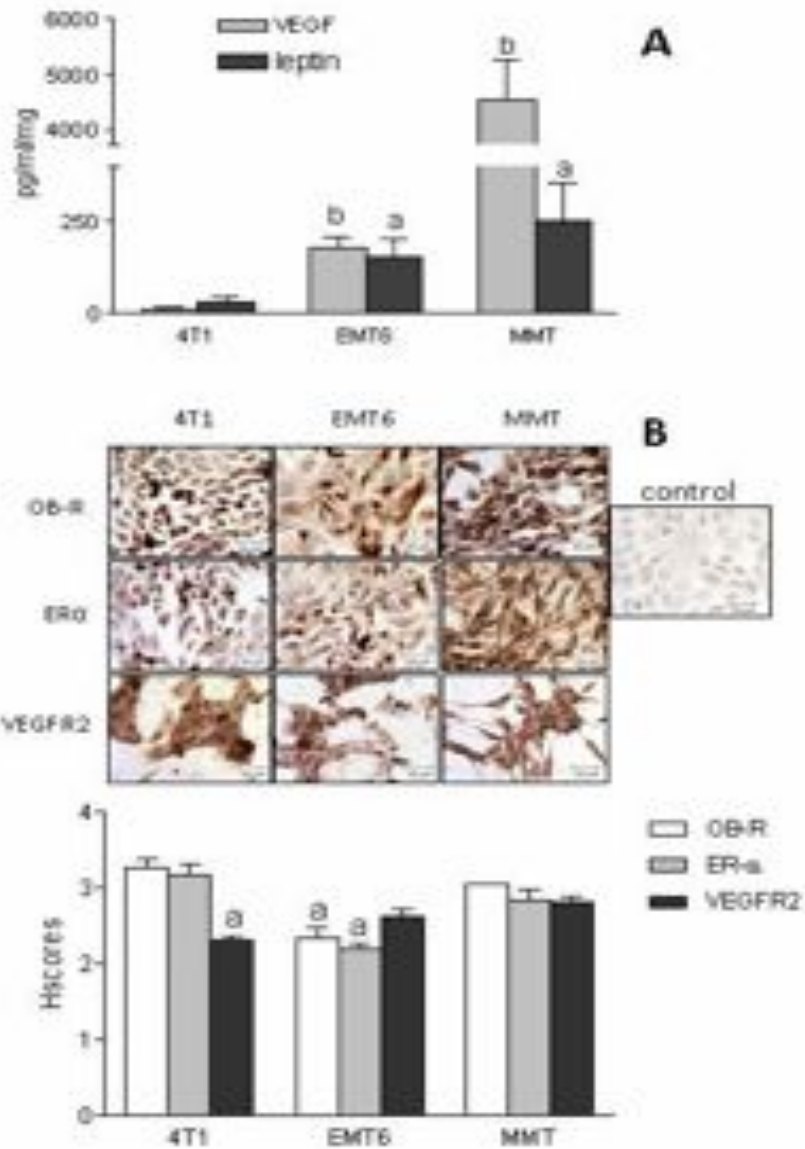


Inhibition of leptin signaling decreases the growth of established MCF-7 and MDA-MB231 BC xenografts.

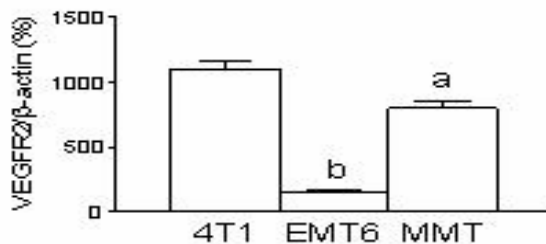
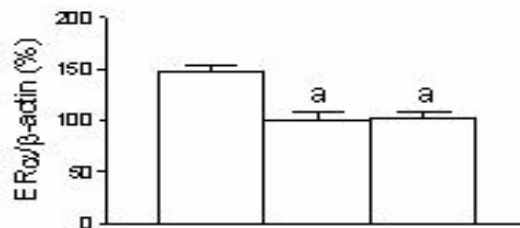
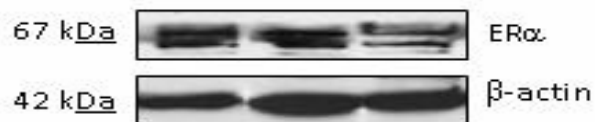
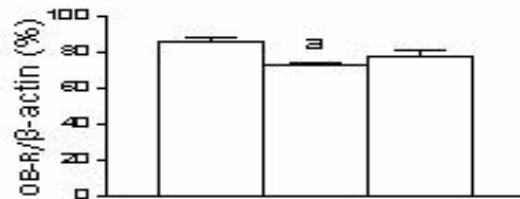
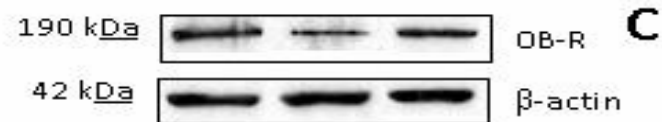


Inhibition of leptin signaling decreases the levels of VEGF in MCF-7 and MDA-MB231 BC xenografts.





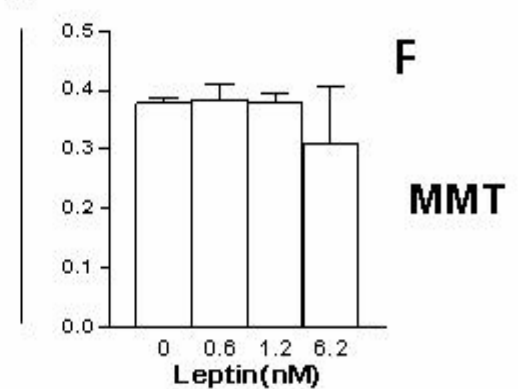
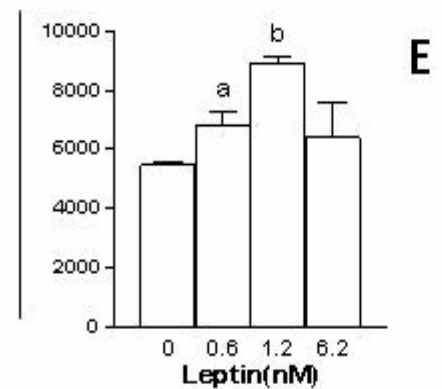
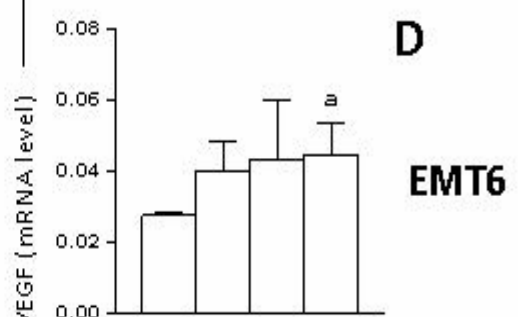
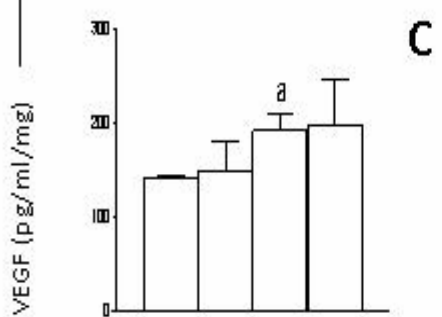
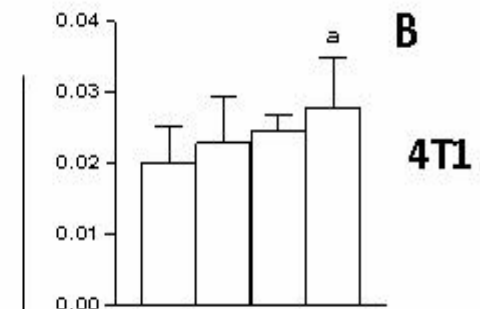
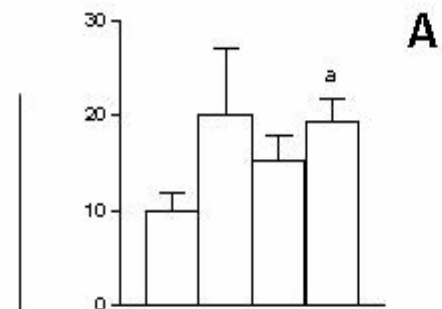
Basal expression of VEGF/VEGFR2, Leptin /OB-R and ER α in Mouse mammary cancer cells (4T1, EMT6 and MMT) [ELISA & ICC]



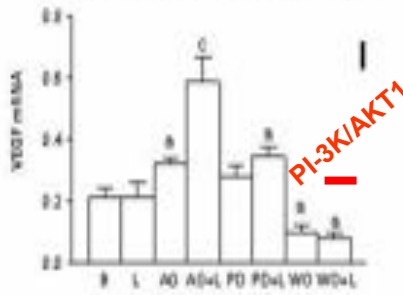
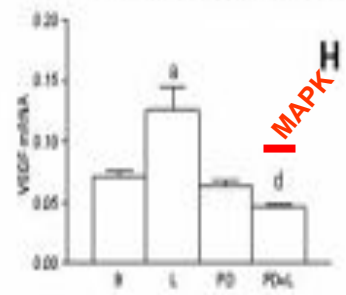
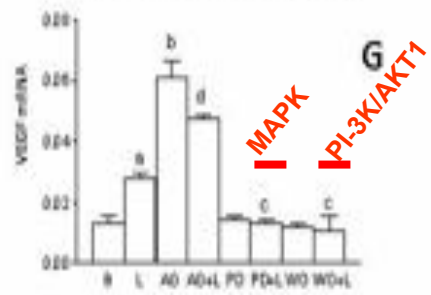
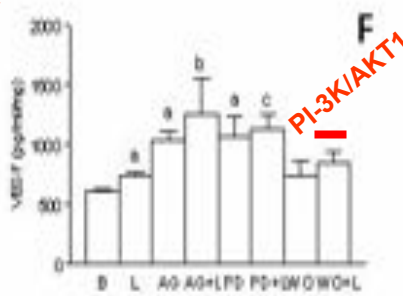
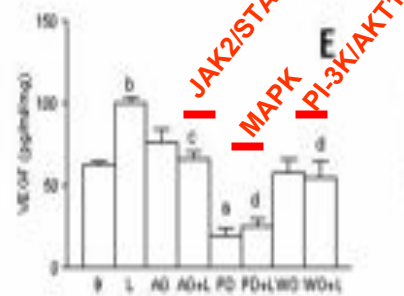
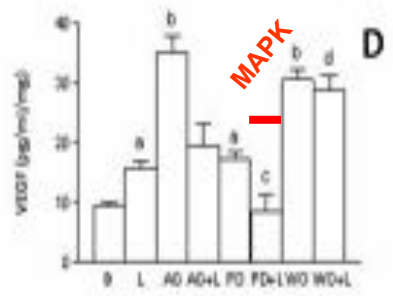
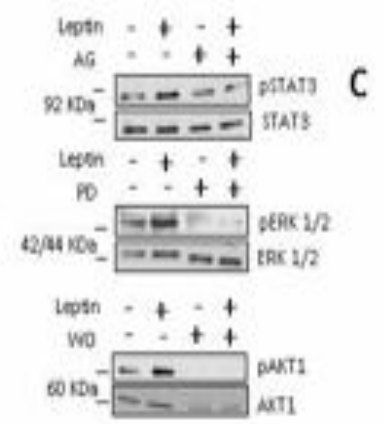
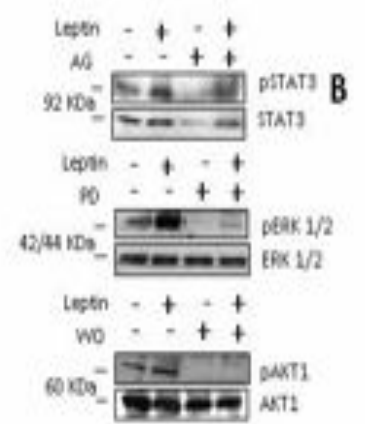
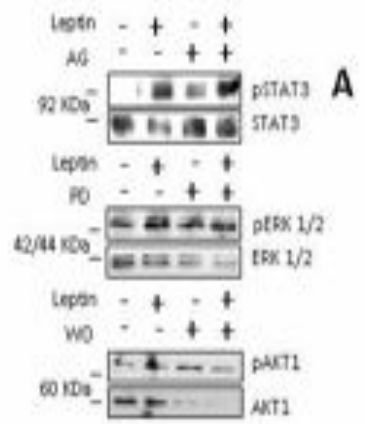
Basal expression of VEGFR2, OB-R and ER α by Mouse mammary cancer cells (4T1, EMT6 and MMT) [Western blot analysis]

VEGF protein

VEGF mRNA



Leptin
upregulates
VEGF
expression in
MT cells



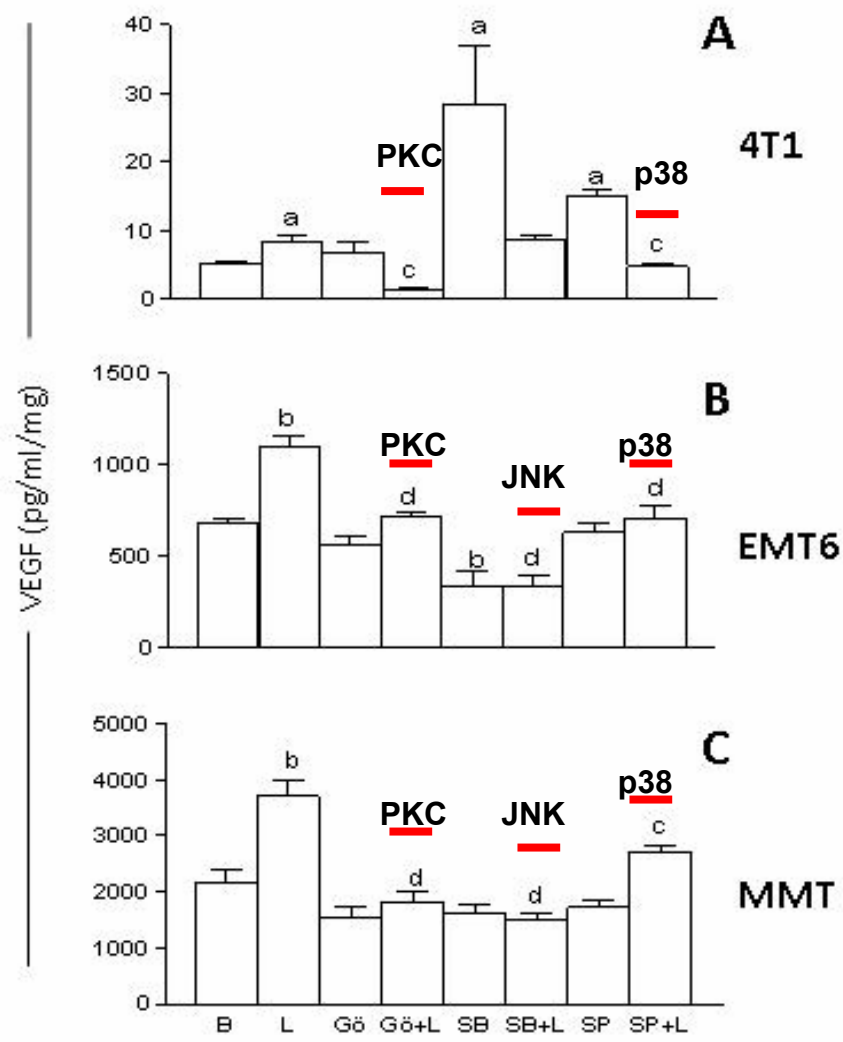
4T1

EMT6

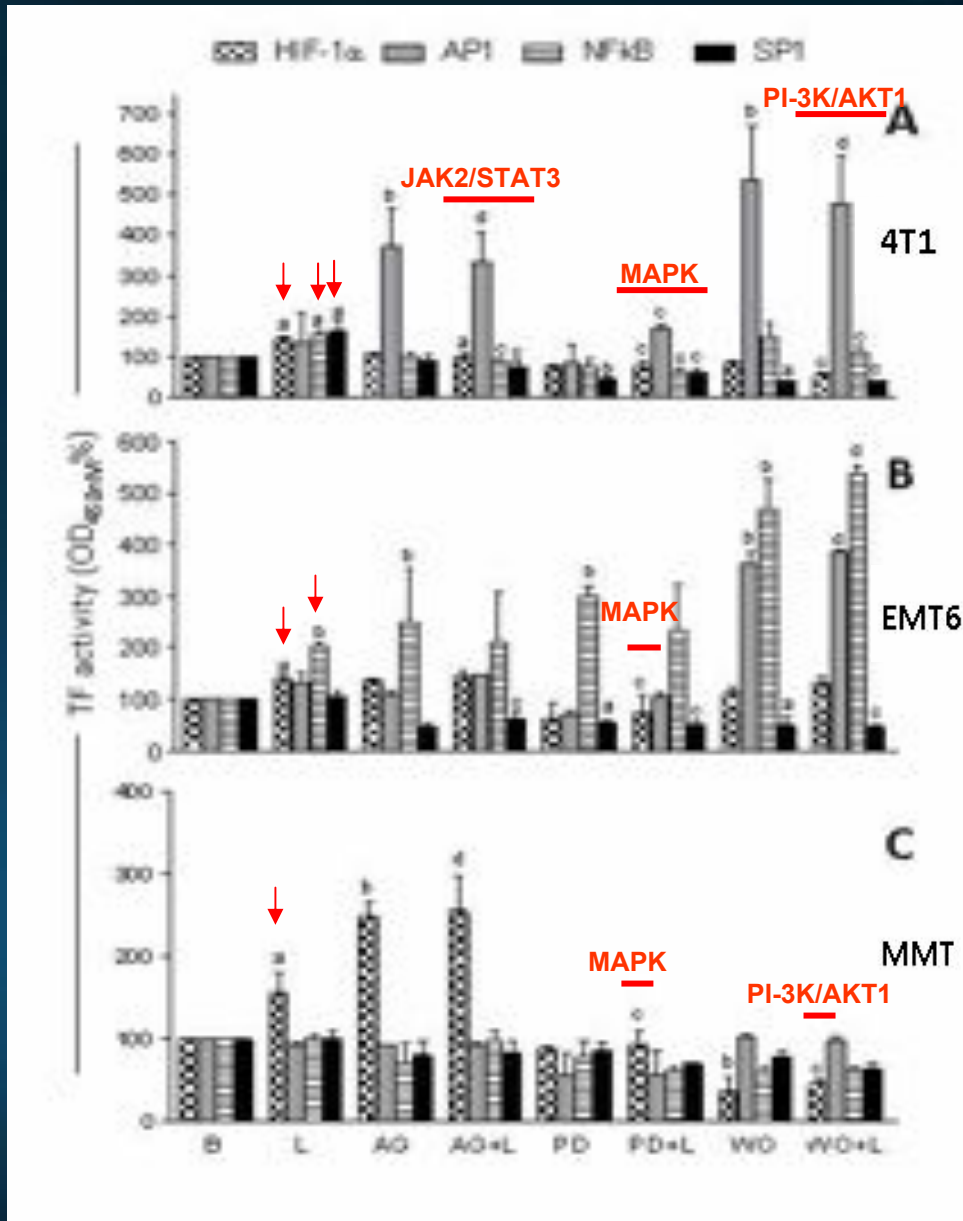
MMT

Leptin-induced
canonic
signaling
pathways
involved in
VEGF
regulation

AG: AG490 (JAK2-STAT3) ; PD:PD98059 (MAPK/ERK 1/2); W: wortmannin (PI-3K/AKT1)

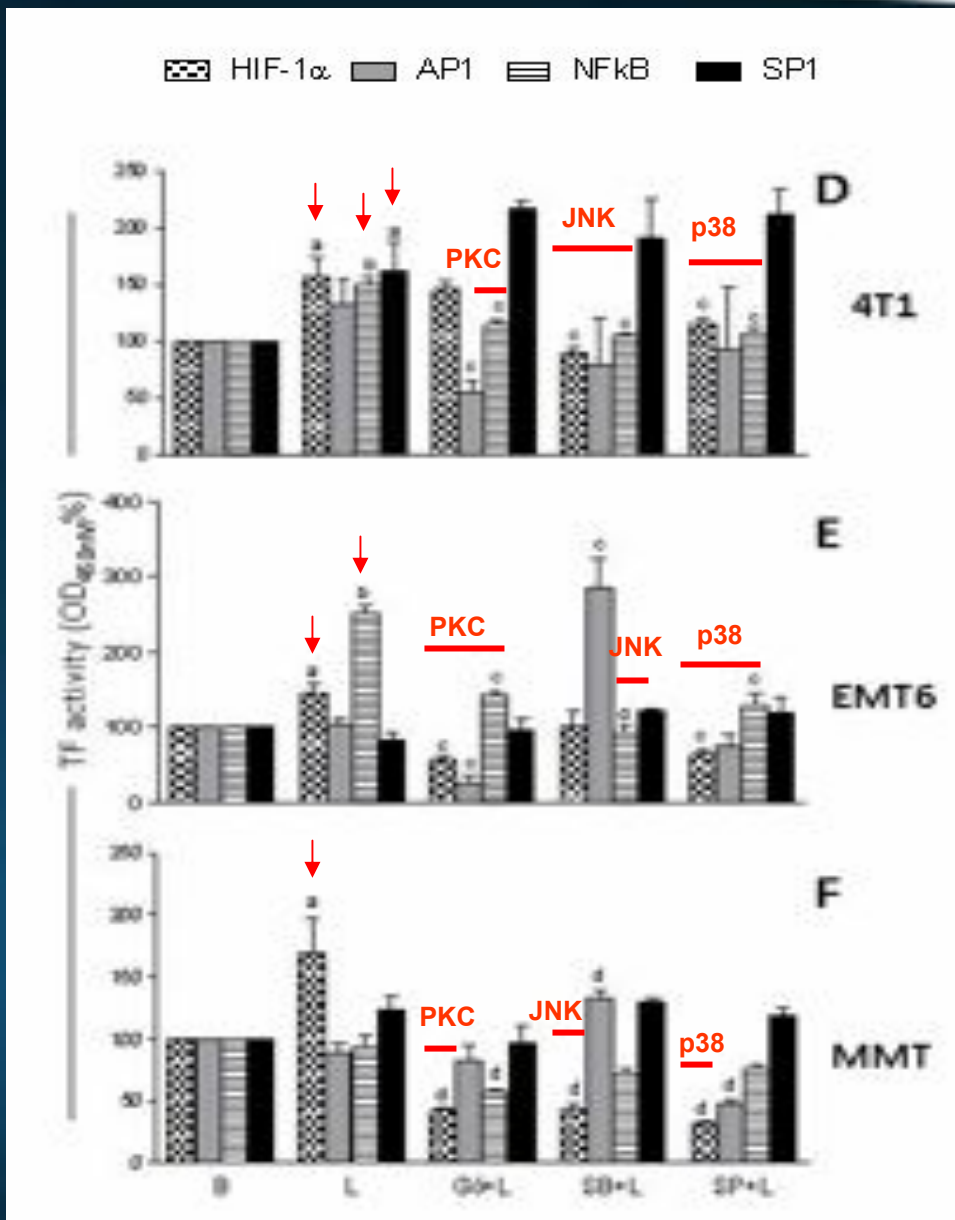


Leptin-induced non-canonical signaling pathways involved in VEGF regulation



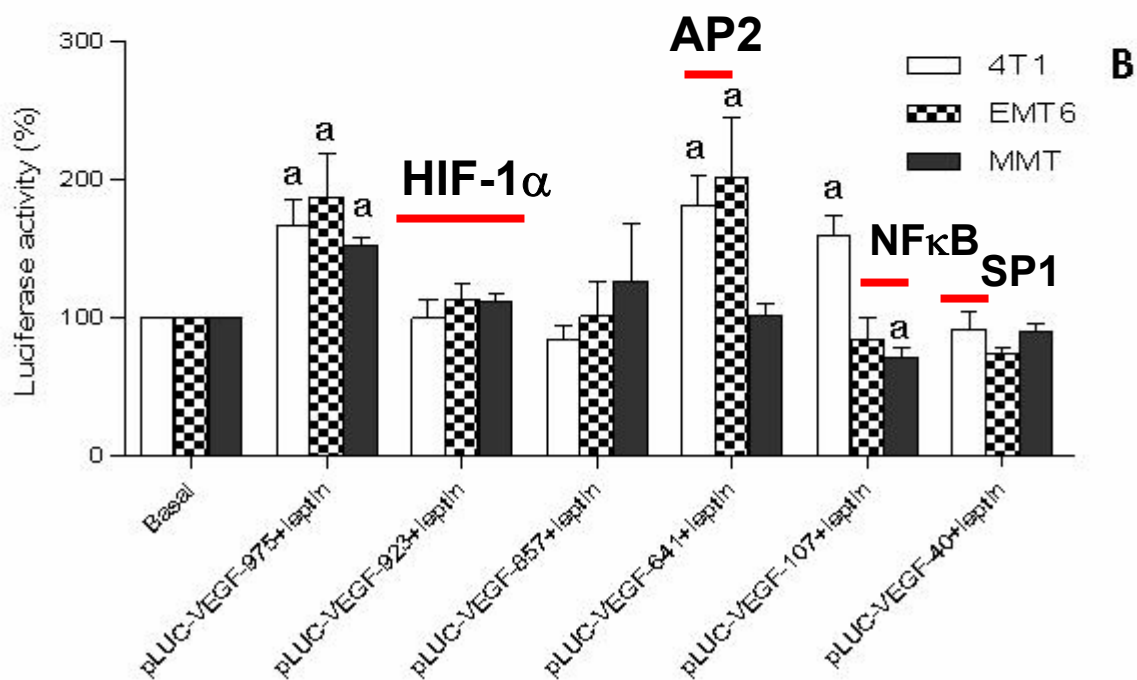
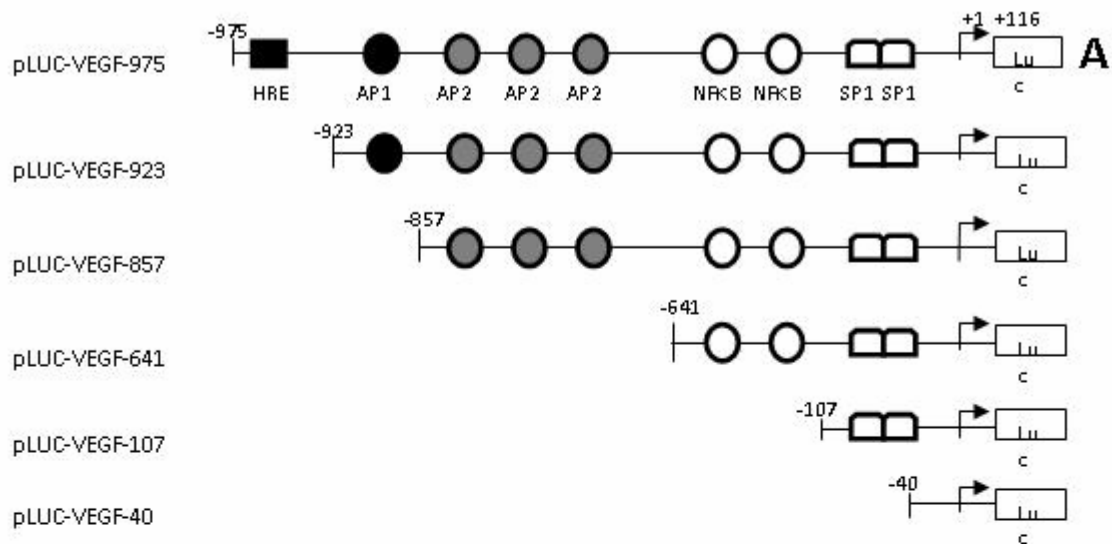
Leptin-induced
 Transcription
 Factors &
 canonic signaling
 pathways
 involved in
 VEGF regulation

AG: AG490 (JAK2-STAT3) ; PD:PD98059 (MAPK/ERK 1/2); W: wortmannin (PI-3K/AKT1);

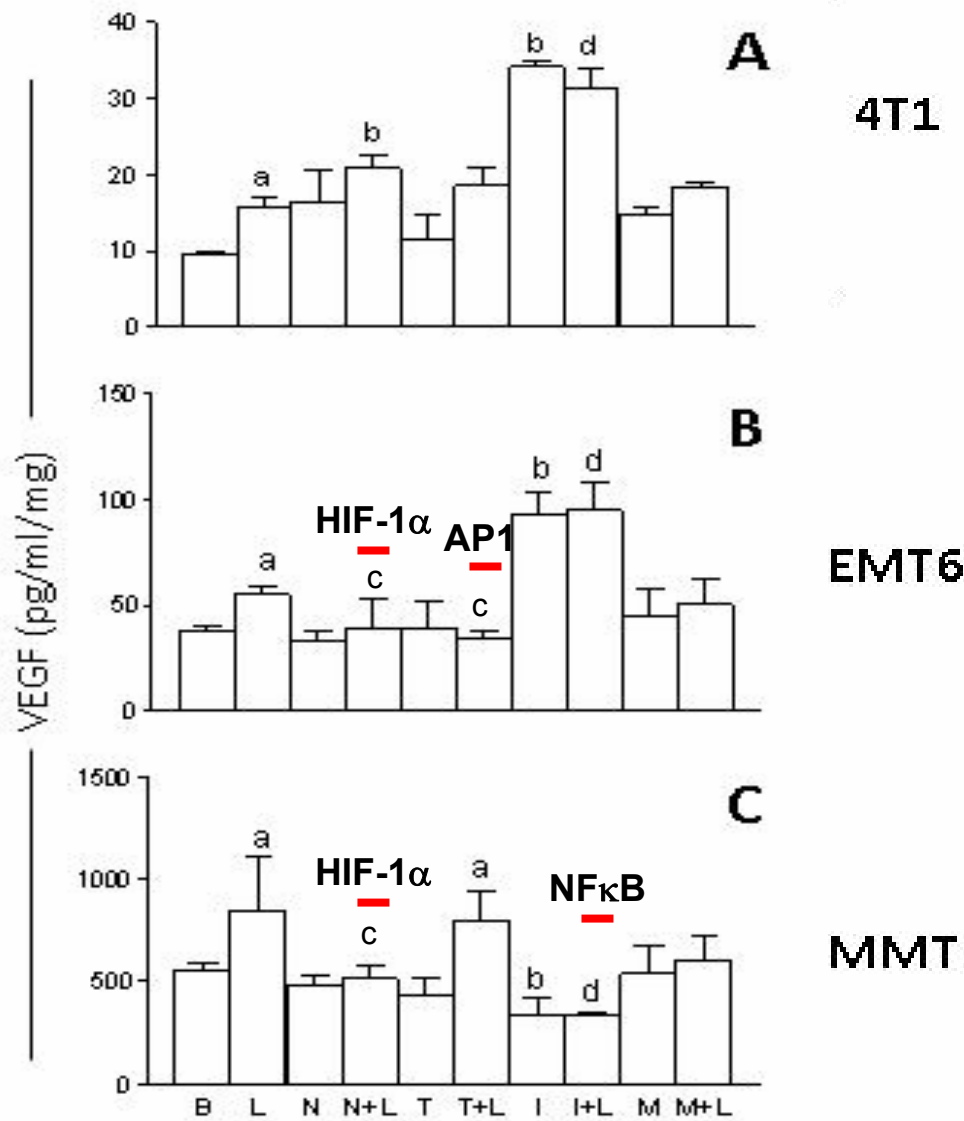


Leptin-induced
Transcription
Factors & non-
canonical signaling
pathways involved
in VEGF regulation

Go:Go6976 (PKC); SB: SB203580 (JNK); SP: SP600125 (P38 kinase)



**Leptin
regulation of
VEGF
promoter in
MT cells.**



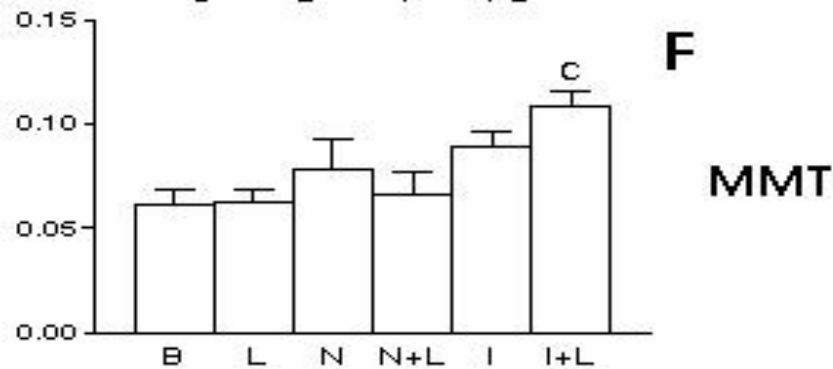
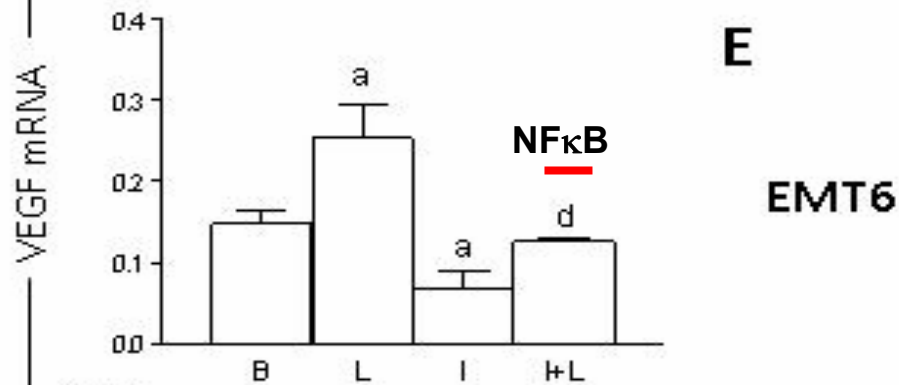
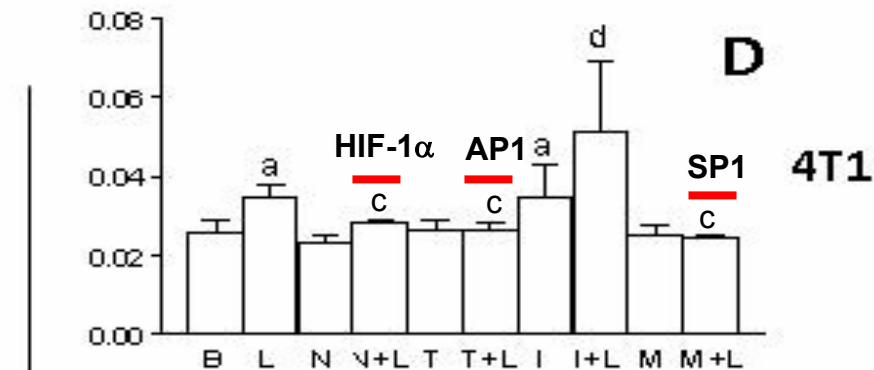
Effects of transcription factor inhibitors on leptin regulation of VEGF protein

NS98 (for HIF-1 α)

Tanshione IIA (for AP1)

IKK antagonist (for NF κ B)

Mythramycin A (for SP1)



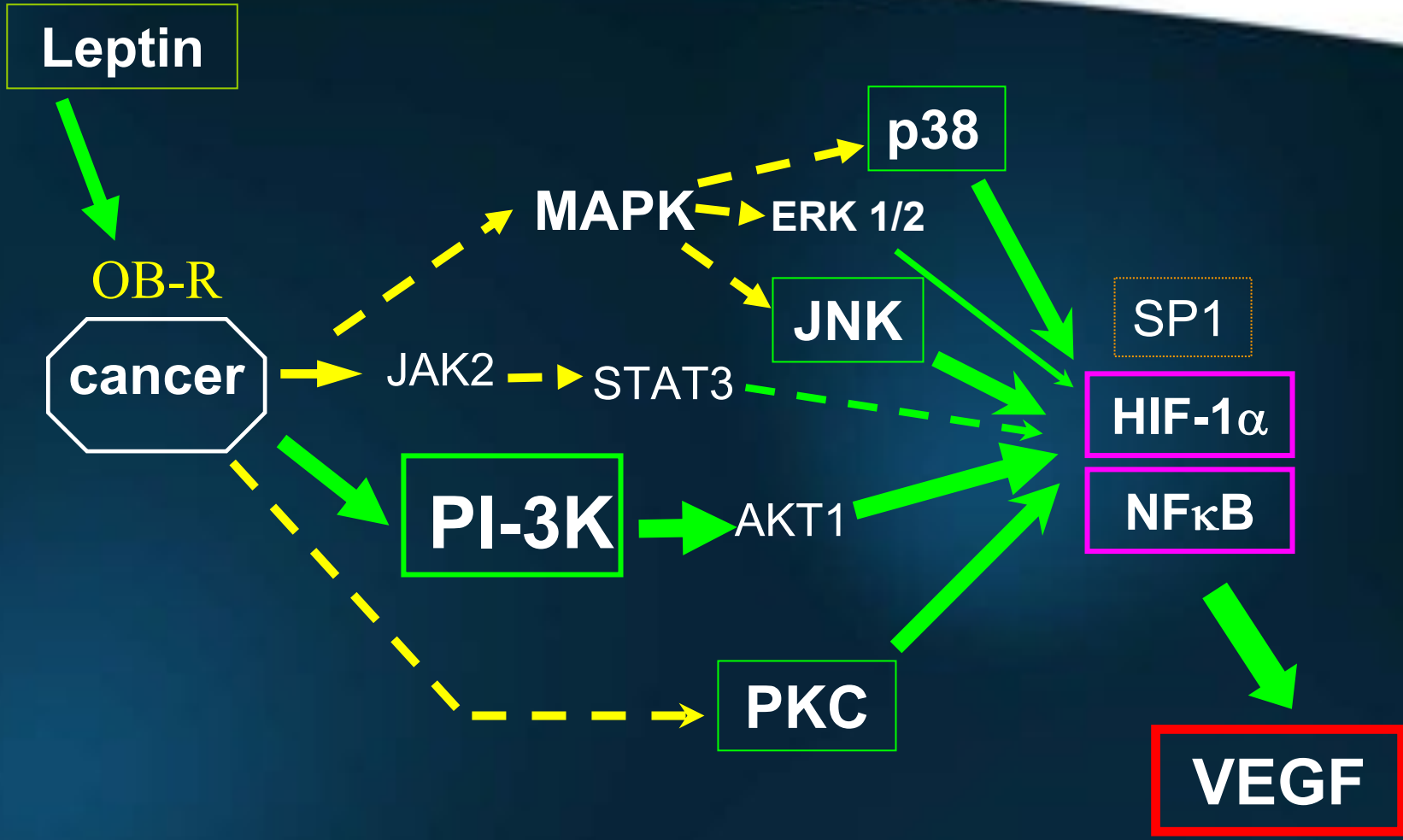
Effects of transcription factor inhibitors on leptin regulation of VEGF mRNA

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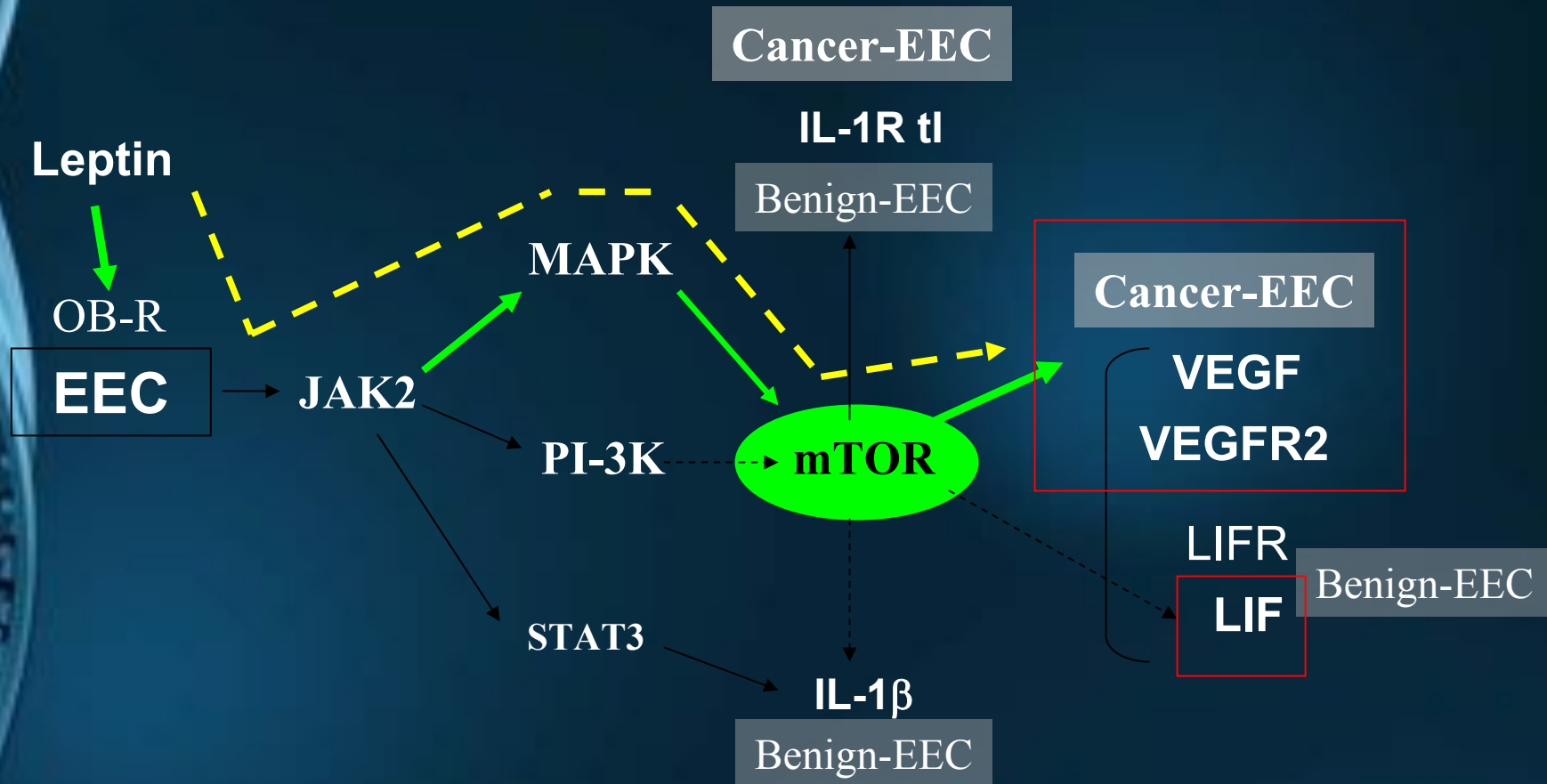
Tanshione IIA (for AP1)

IKK antagonist (for NF κ B)

Mythramicin A (for SP1)



Leptin-induced upregulation of VEGF expression in MT cells mainly involves the activation of HIF-1 α and NF κ B through PI-3K/AKT1 and, PKC, JNK and p38 . However, leptin can also induces MAPK/ERK 1/2 signaling pathway to activate HIF-1 α .



Molecular mechanisms of leptin induction of pro-angiogenic/pro-inflammatory factors in endometrial cancer cells

Carino et al., Int. J. Cancer 2008, 123: 2782-2790



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