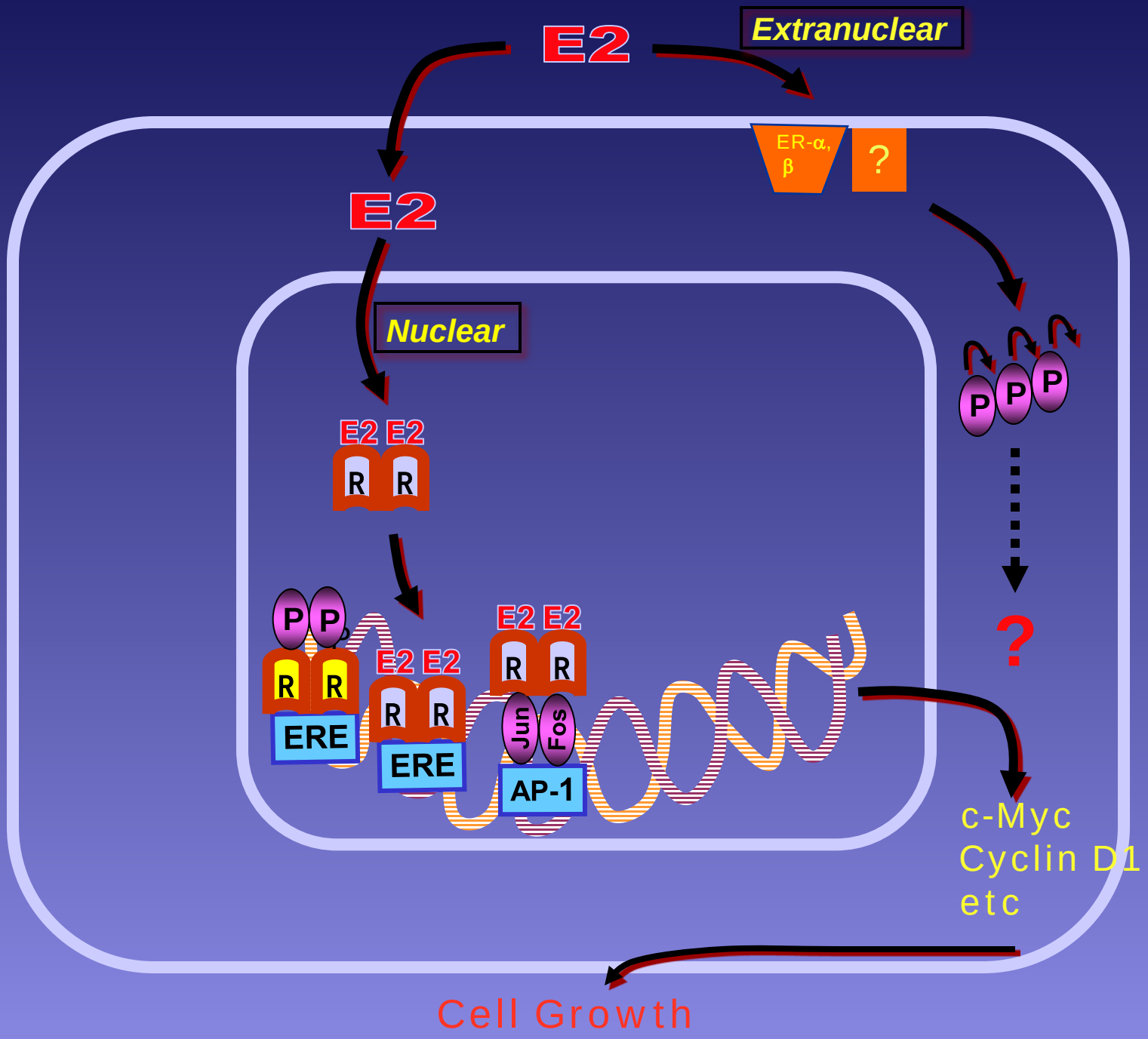
Molecular Events in Biophasic Non-genomic Estrogen and Antiestrogen Signaling

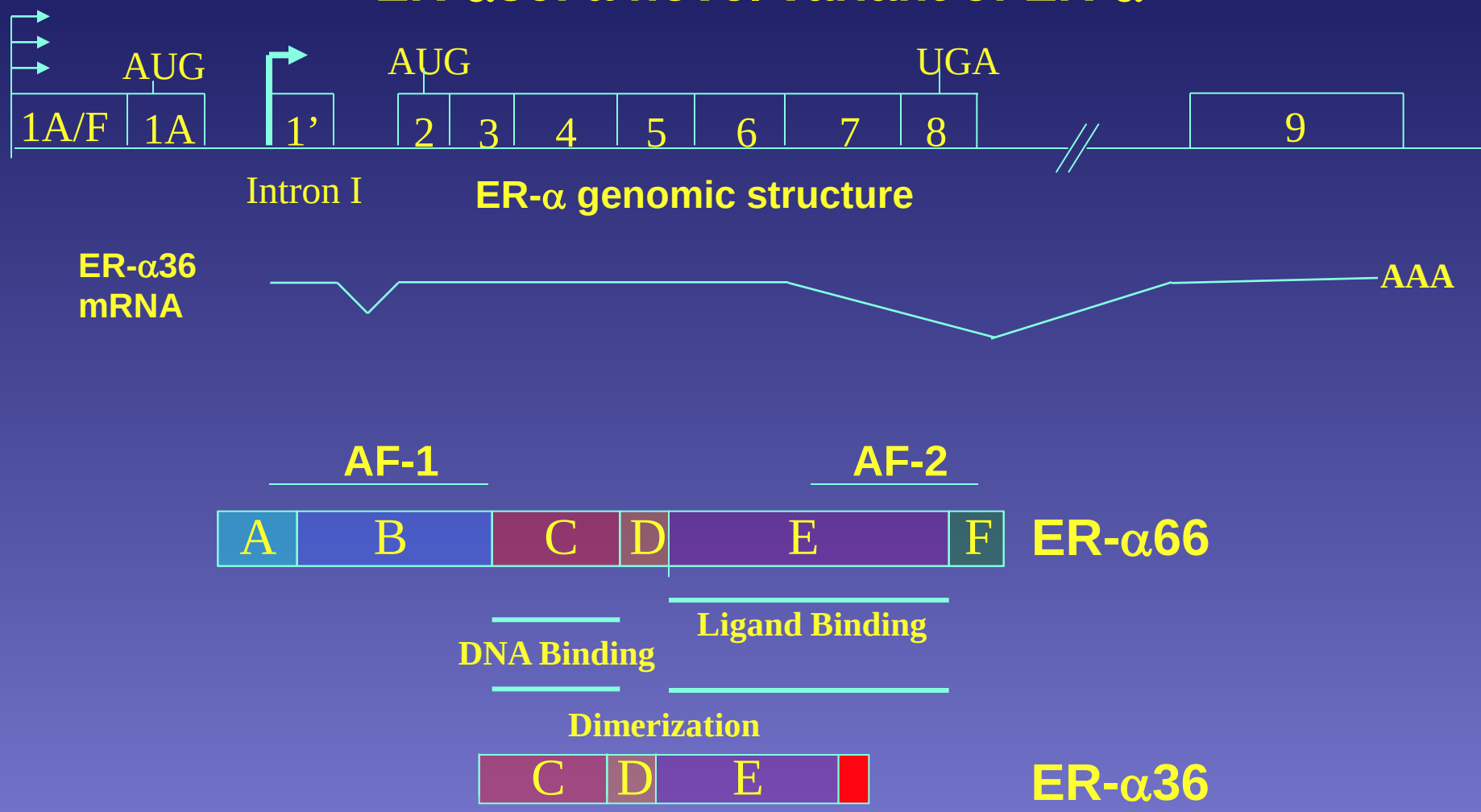
ZhaoYi Wang, Ph.D.

Creighton University Medical School

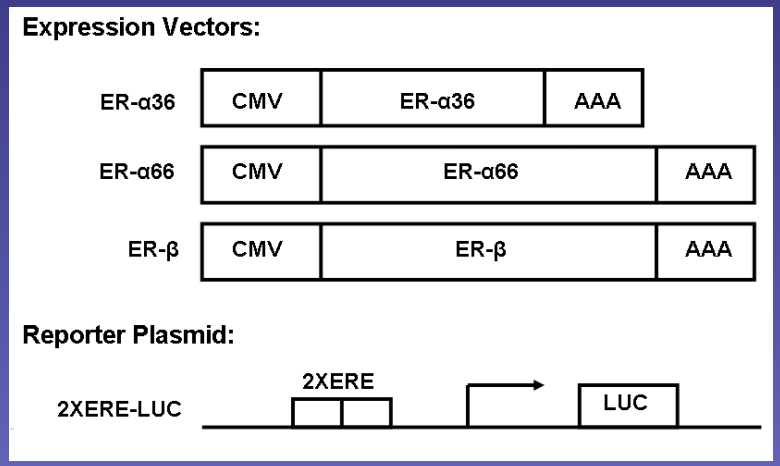
The 12th International Conference,
Dose-Response 2013.

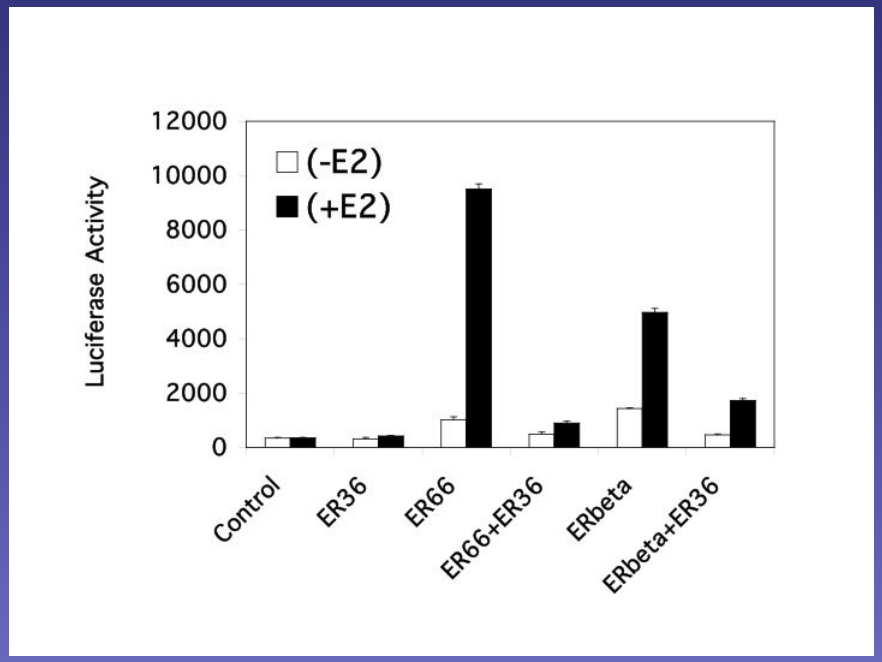

E2
Extranuclear
ER-α, β
?
E2
Nuclear
E2 E2
R R
P P P
?
P P
R R
ERE
E2 E2
R R
ERE
E2 E2
R R
Jun
Fos
AP-1
c-Myc
Cyclin D1
etc
Cell Growth

ER-α36: a novel variant of ER-α



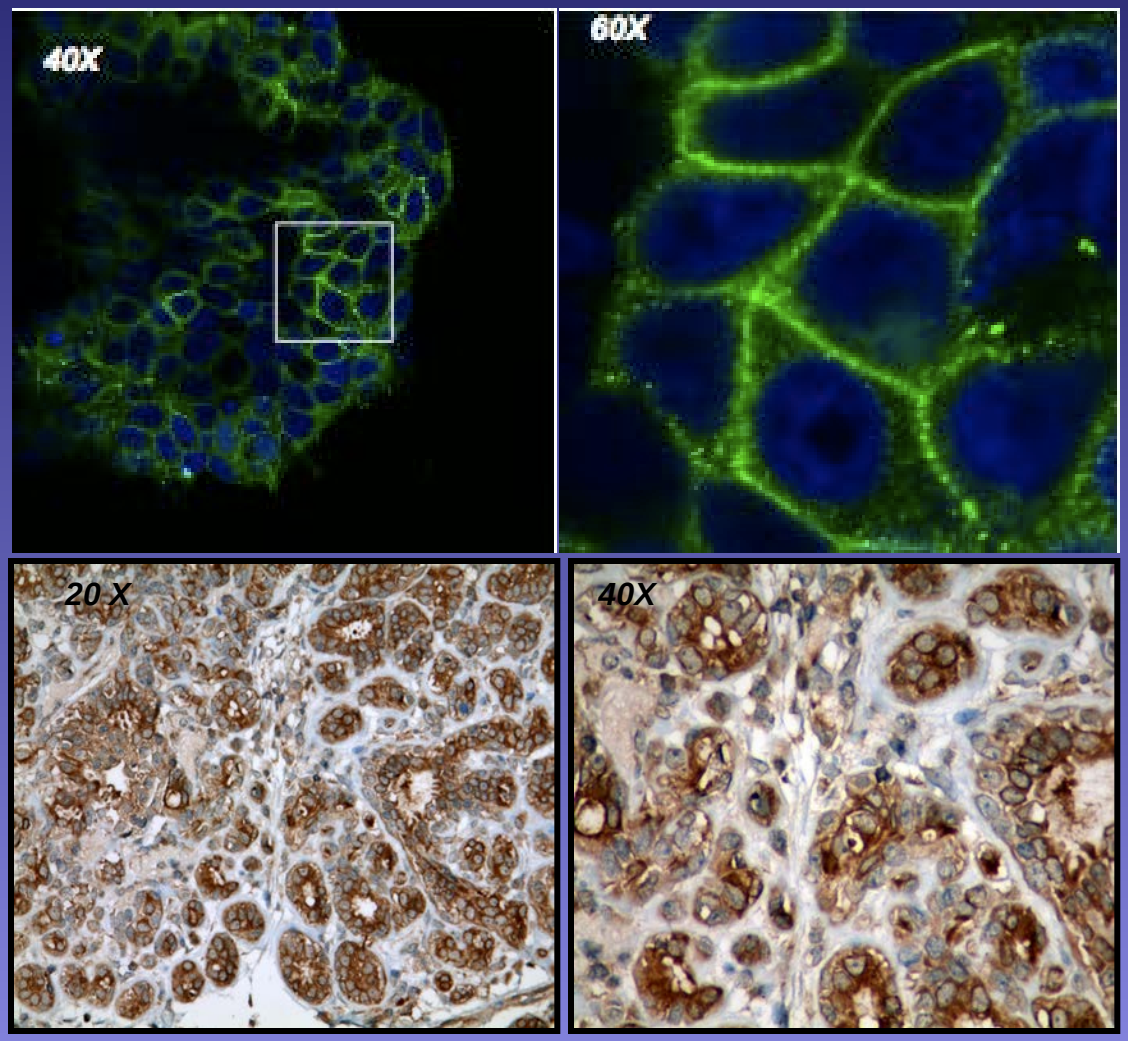
ER-α36 inhibits AF-1 and AF-2 activities of ER-α and –β



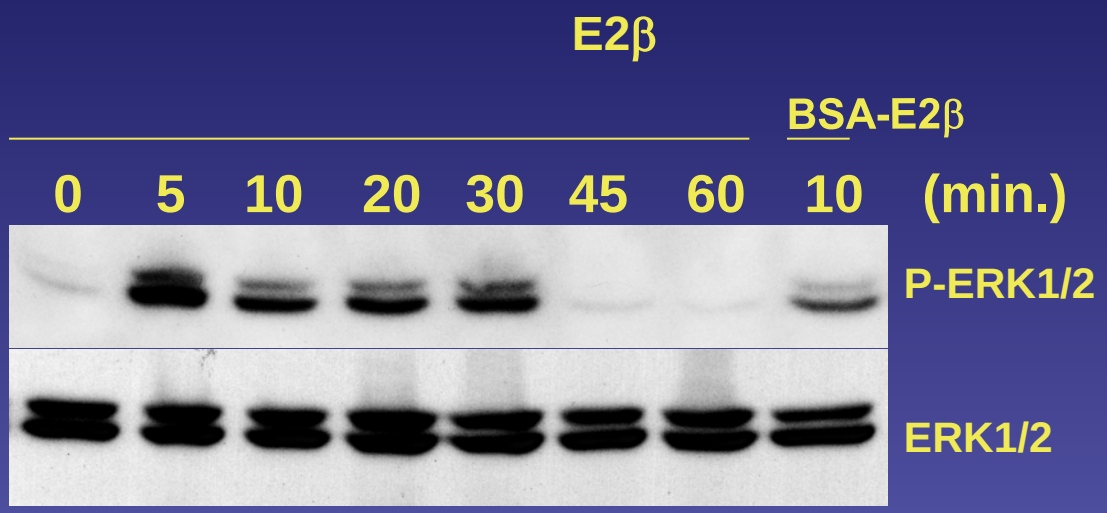


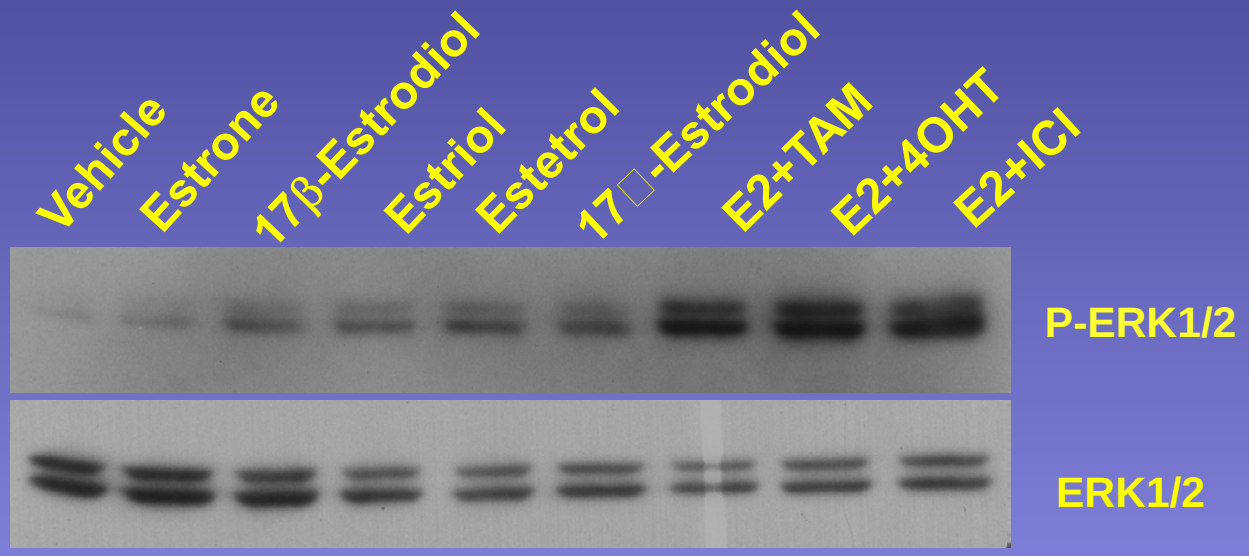
Wang *et. al.*, 2006 *PNAS*, 2006; 103: 9063-9068.

ER-α36 is mainly expressed at the plasma membrane



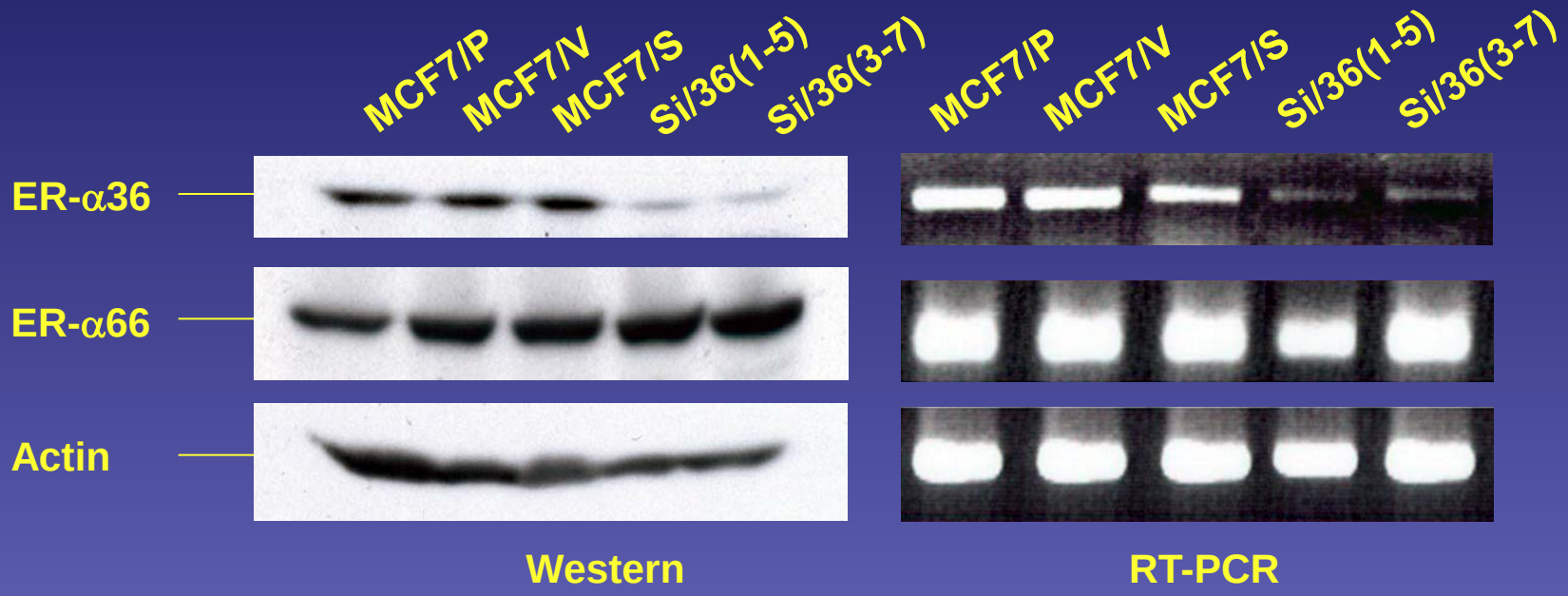
ER-α36 mediates membrane-initiated estrogen signaling

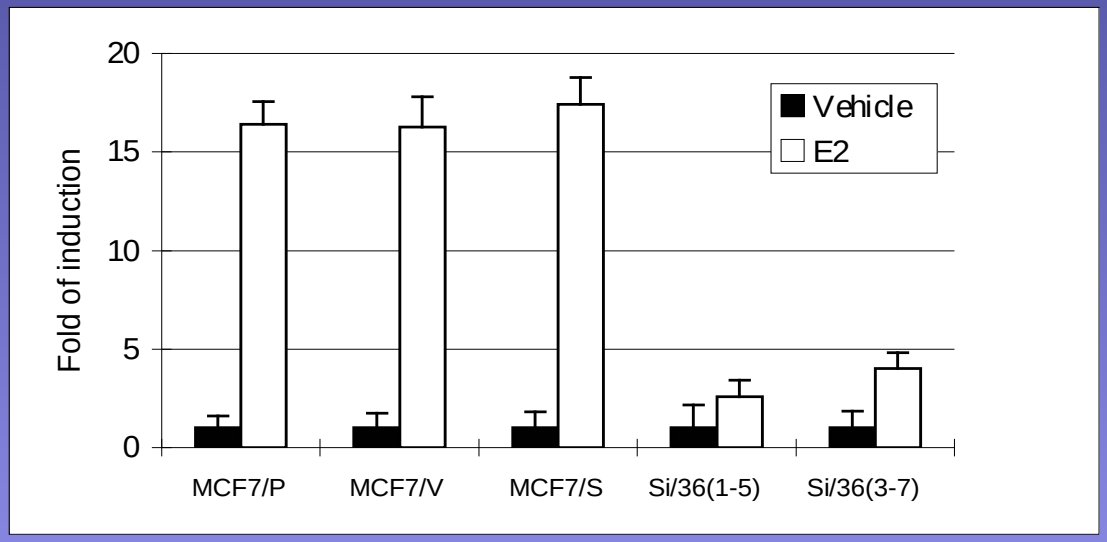




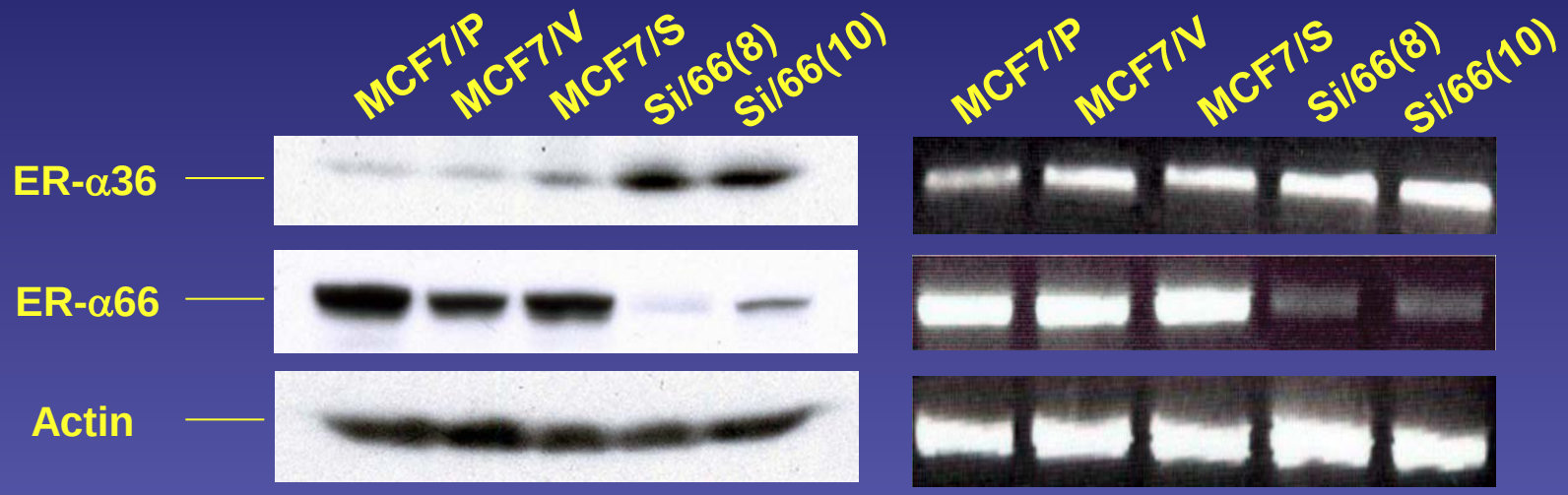
Wang *et. al.*, 2006 *PNAS*, 2006; 103: 9063-9068.

ER-α36 "knockdown" abolishes mitogenic estrogen signaling in ER-positive breast cancer MCF7 cells



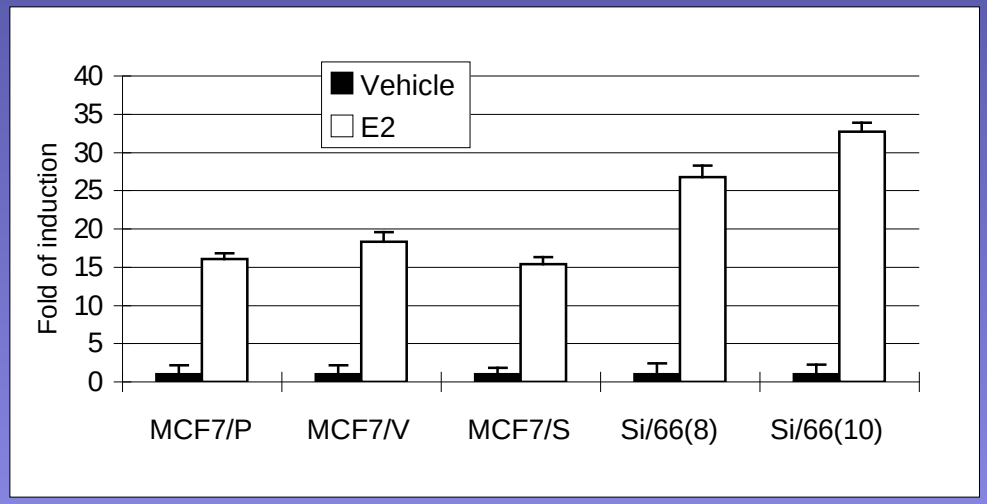


ER-α66 "knockdown" potentiates mitogenic estrogen signaling in ER-positive breast cancer MCF7 cells



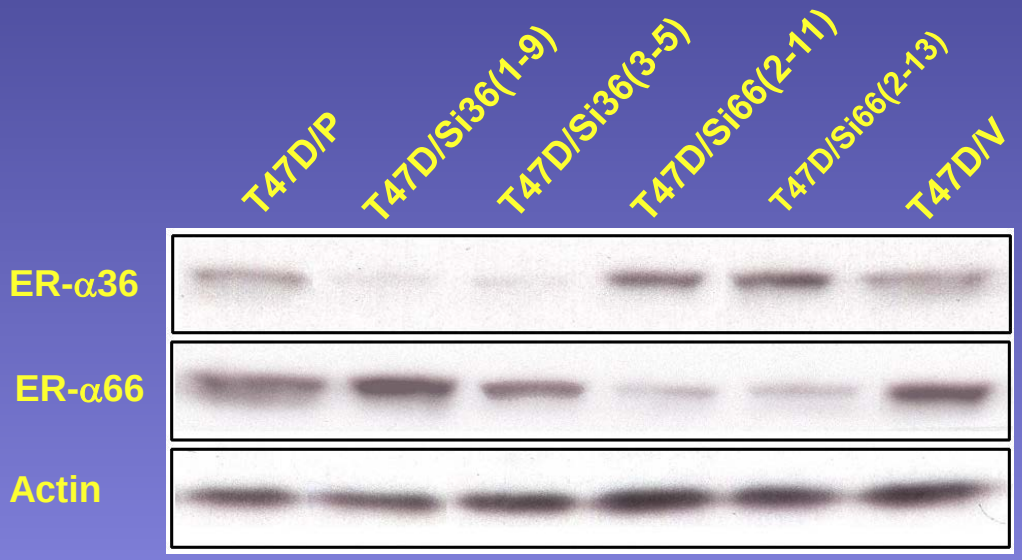
Western

RT-PCR

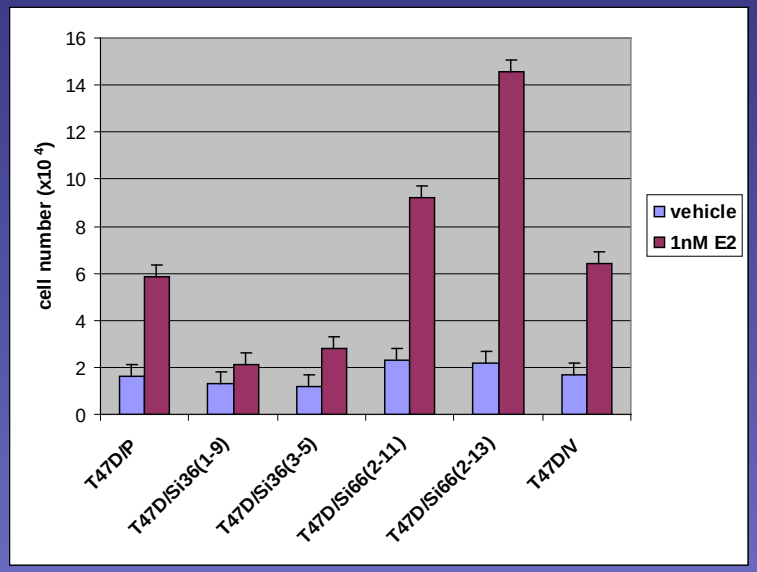


ER-α36 not ER-α66 "knockdown" abolishes mitogenic estrogen signaling in ER-positive breast cancer T47D cells

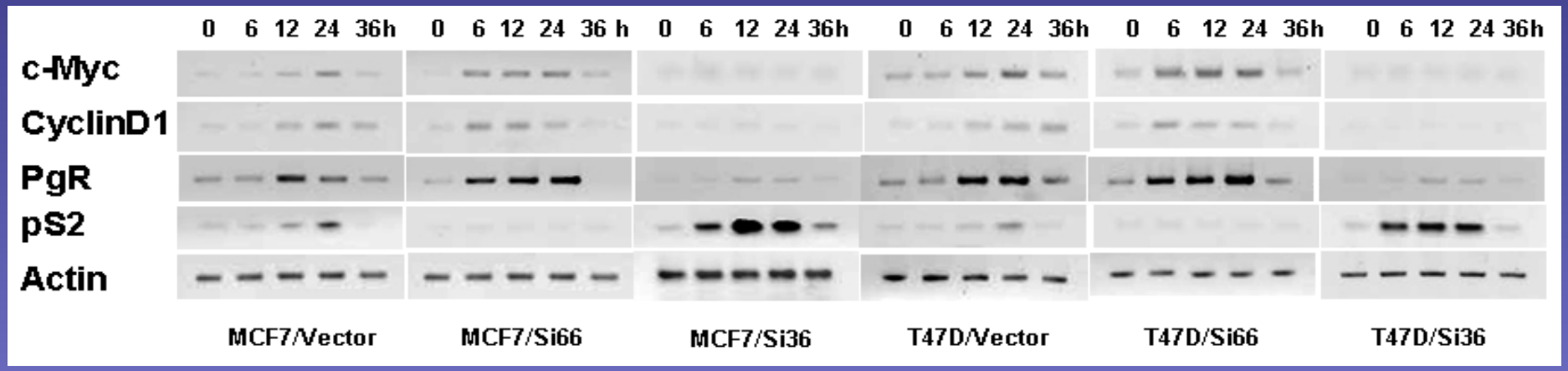
RT-PCR

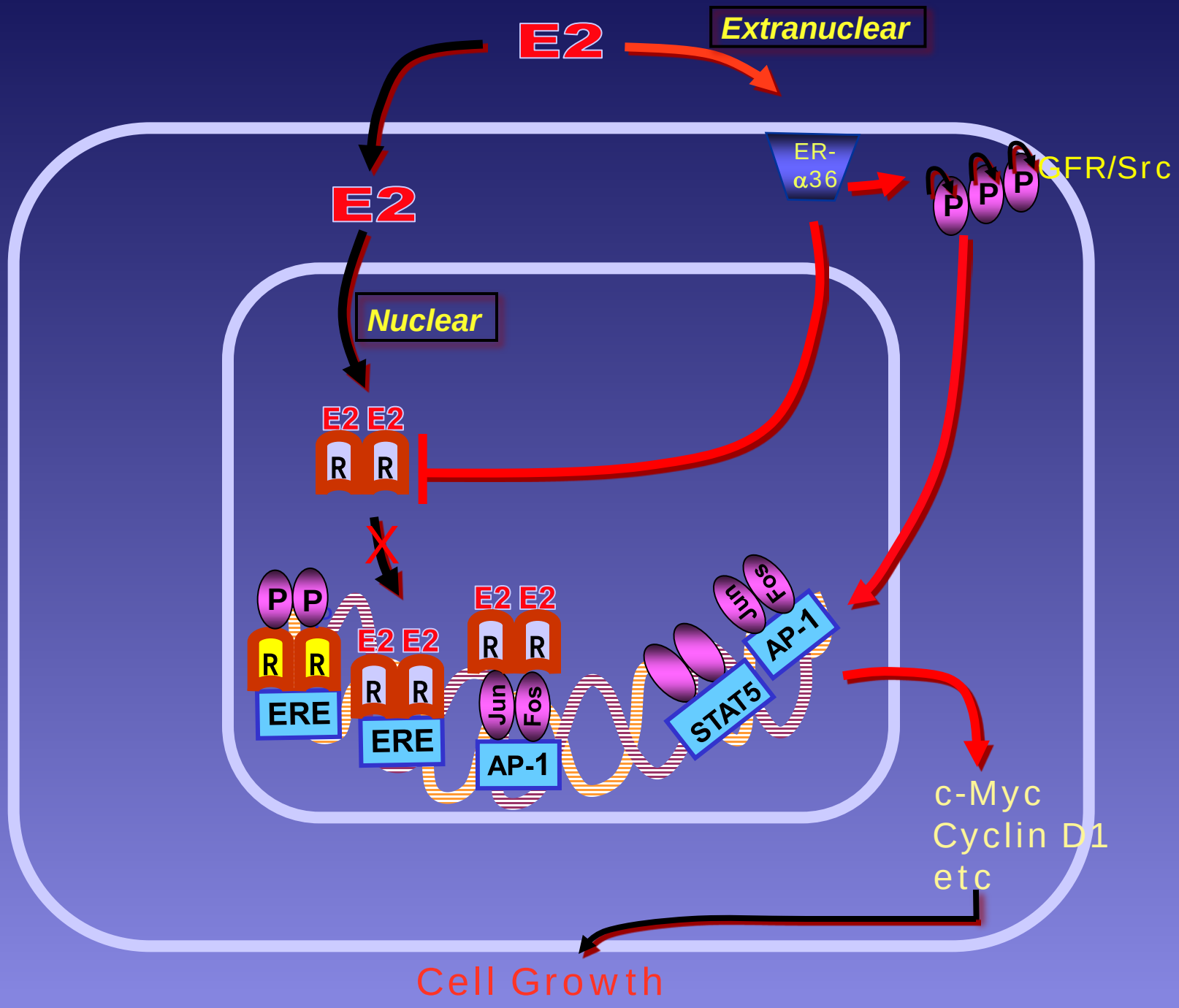


Western

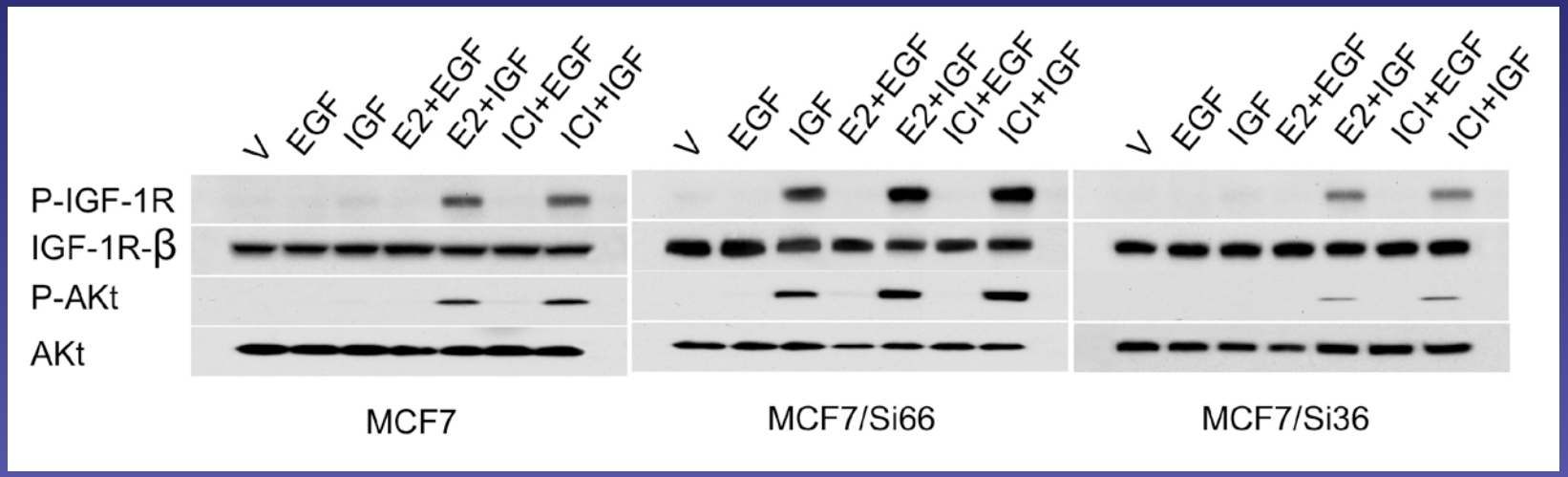


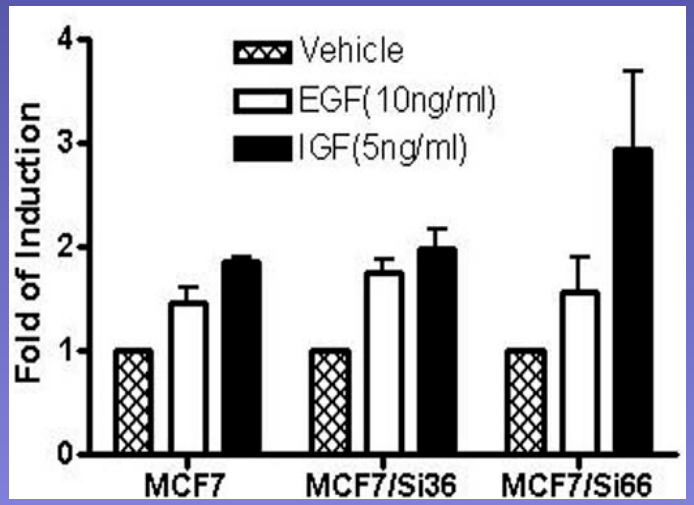
Induction patterns of estrogen responsive genes in variants of MCF7 and T47D cells



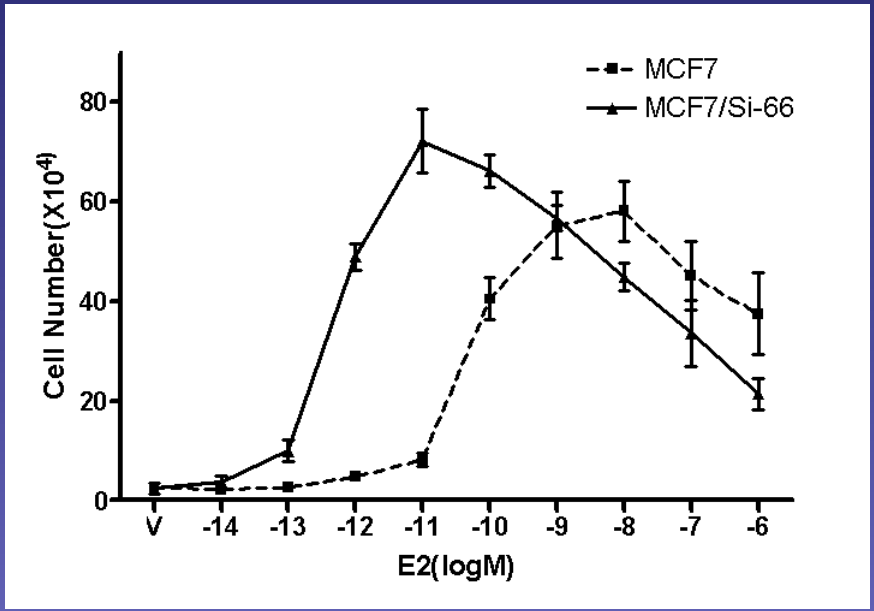

E2
Extranuclear
E2
ER-
α36
P P P
GFR/Src
Nuclear
E2 E2
R R
X
P P
R R
ERE
E2 E2
R R
ERE
E2 E2
R R
Jun
Fos
AP-1
Jun
Fos
AP-1
STAT5
c-Myc
Cyclin D1
etc
Cell Growth

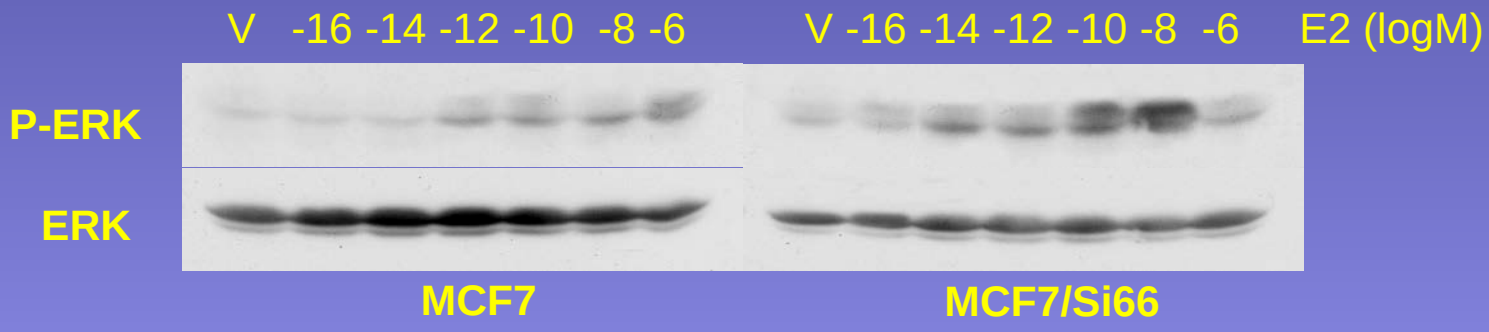
ER-α66 "knockdown" potentiates IGF signaling in MCF7 cells



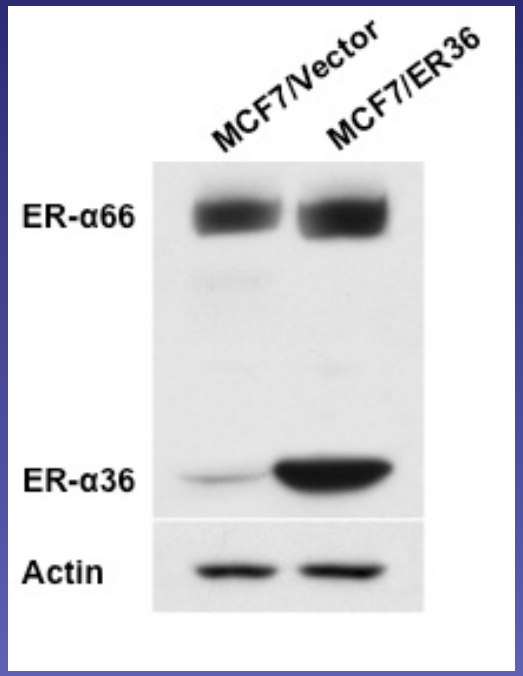


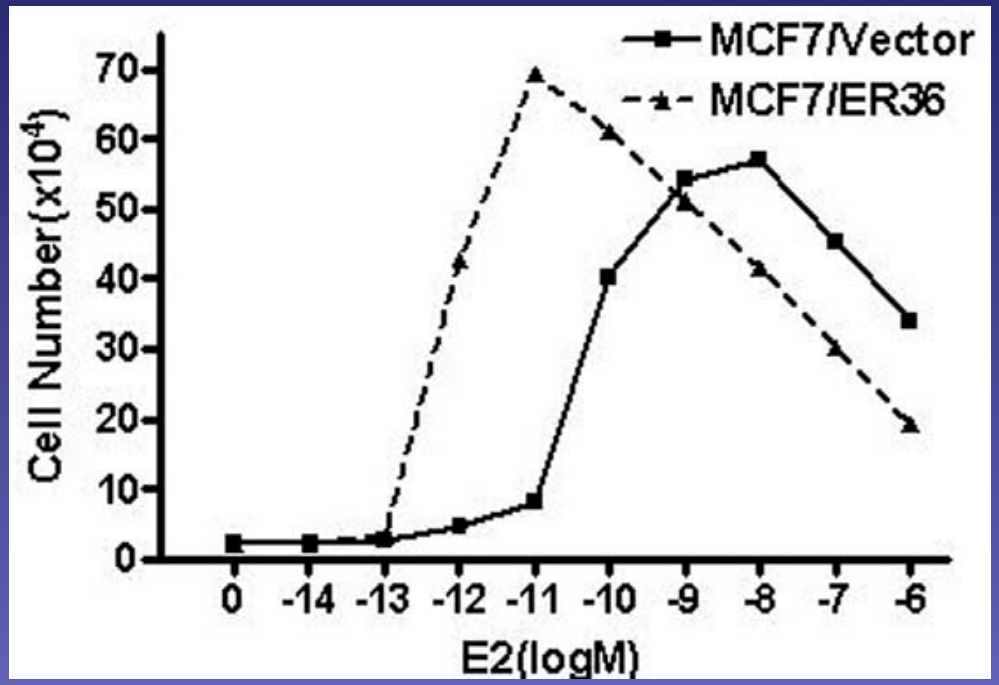
ER-α66 "knockdown" leads to estrogen hypersensitivity

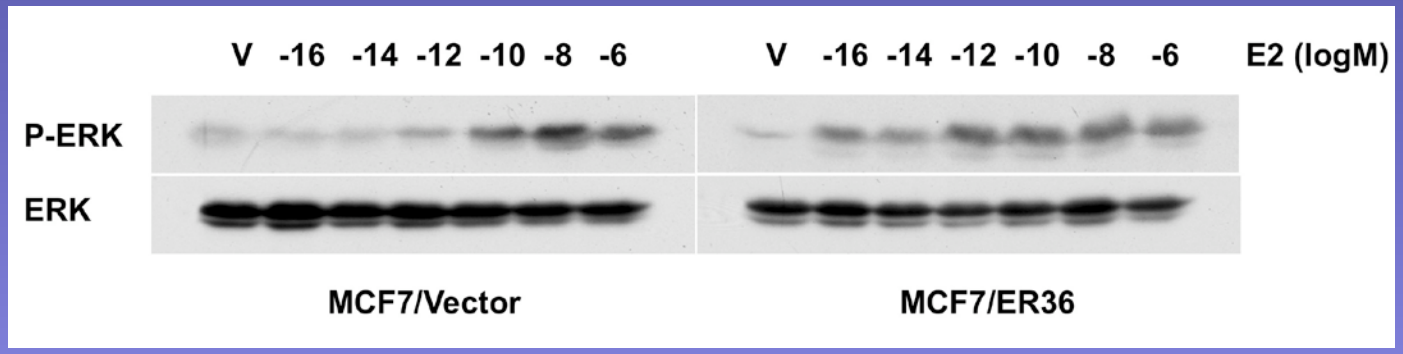




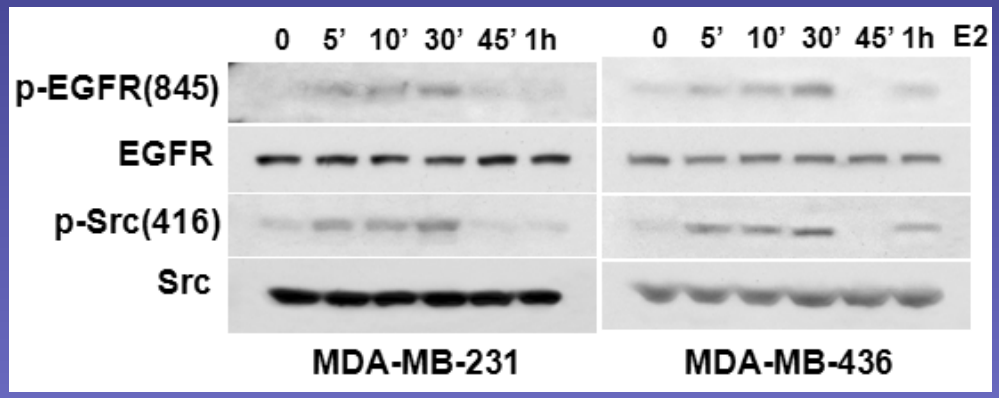
Forced expression of ER-α36 leads to estrogen hypersensitivity

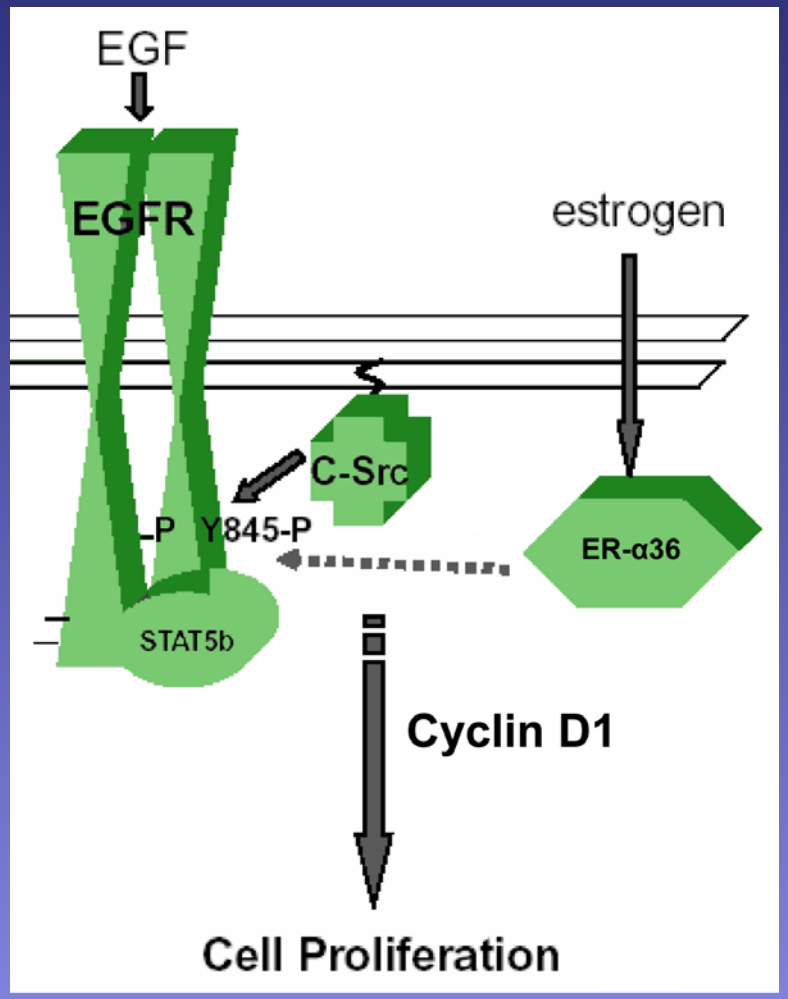




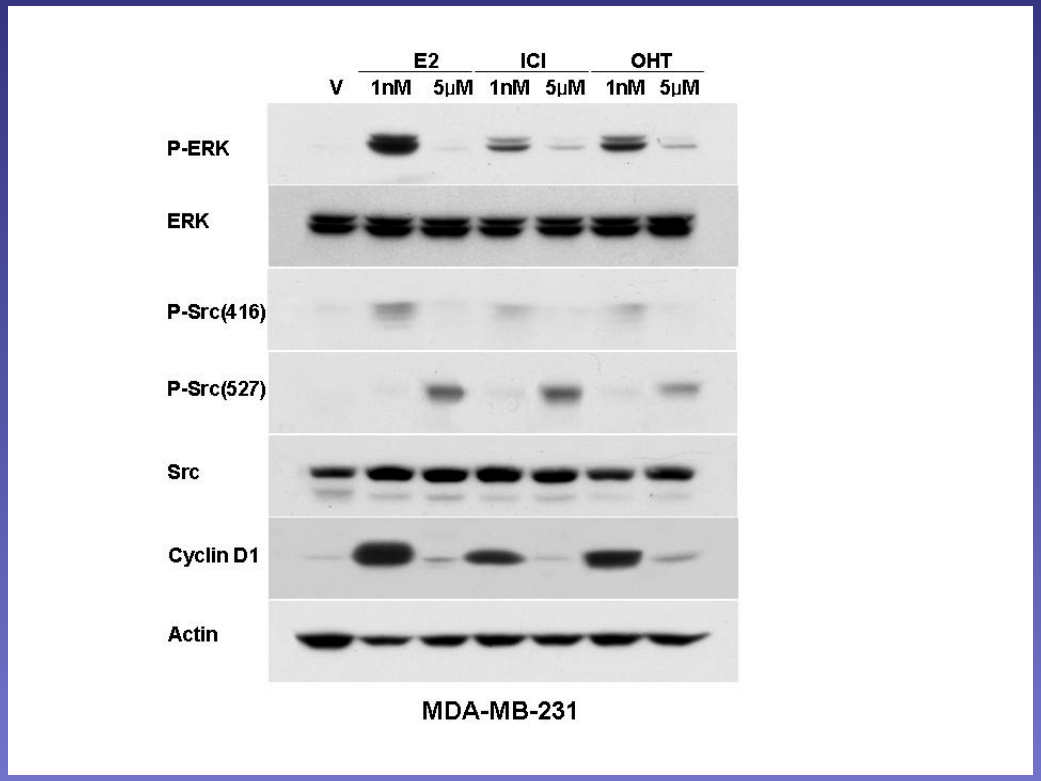


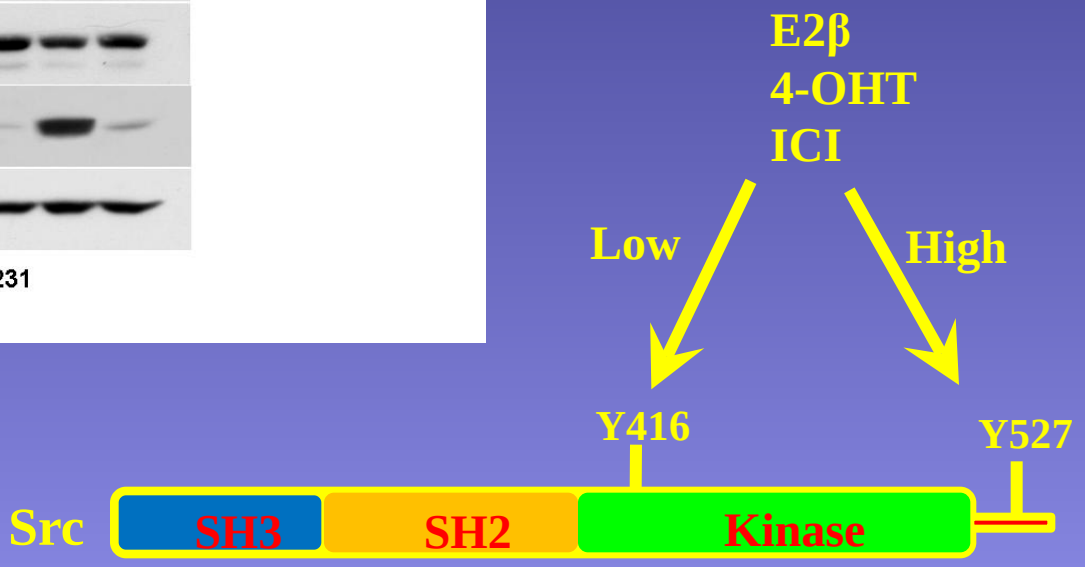
The involvement of the EGFR/Src/STAT5 pathway in ER-α36 mediated rapid estrogen signaling



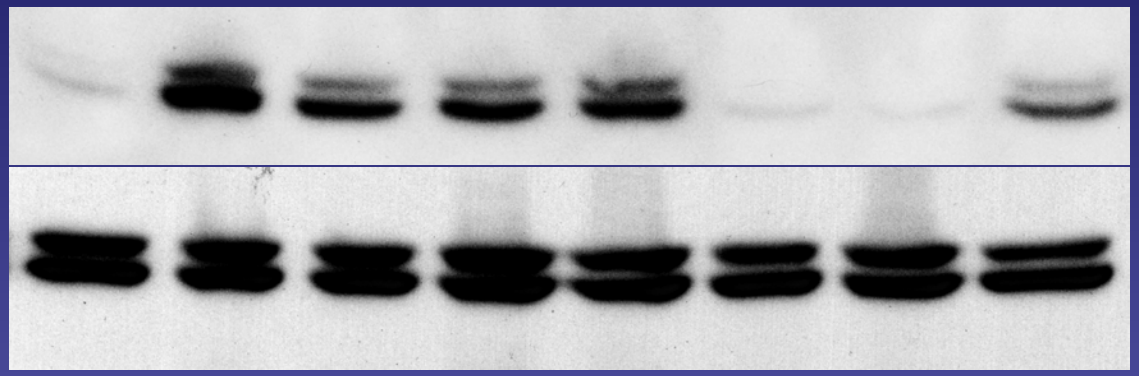


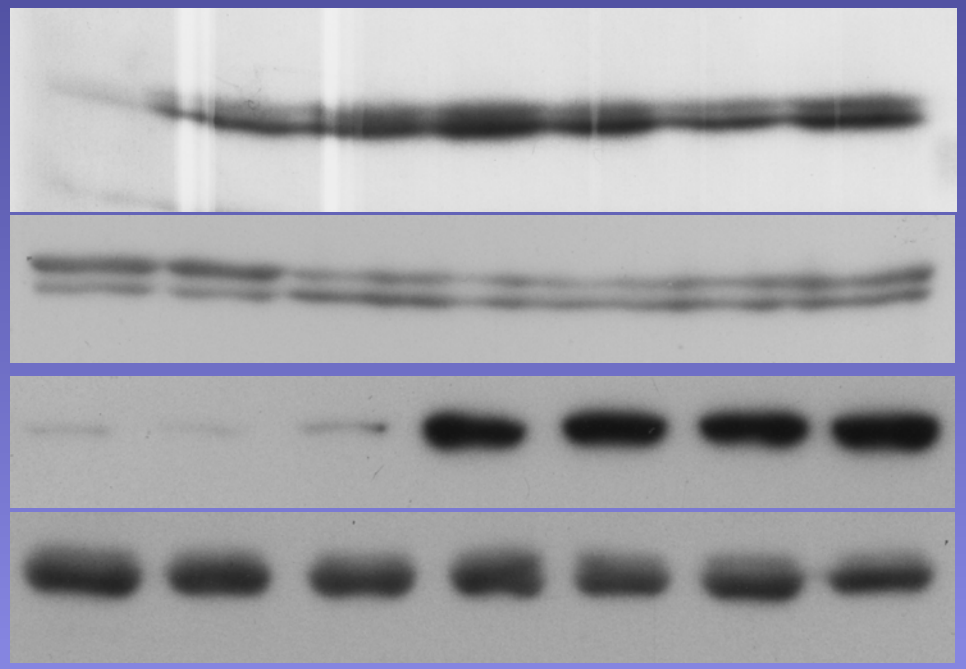
Src acts as a switch of biphasic estrogen and antiesrogen signaling



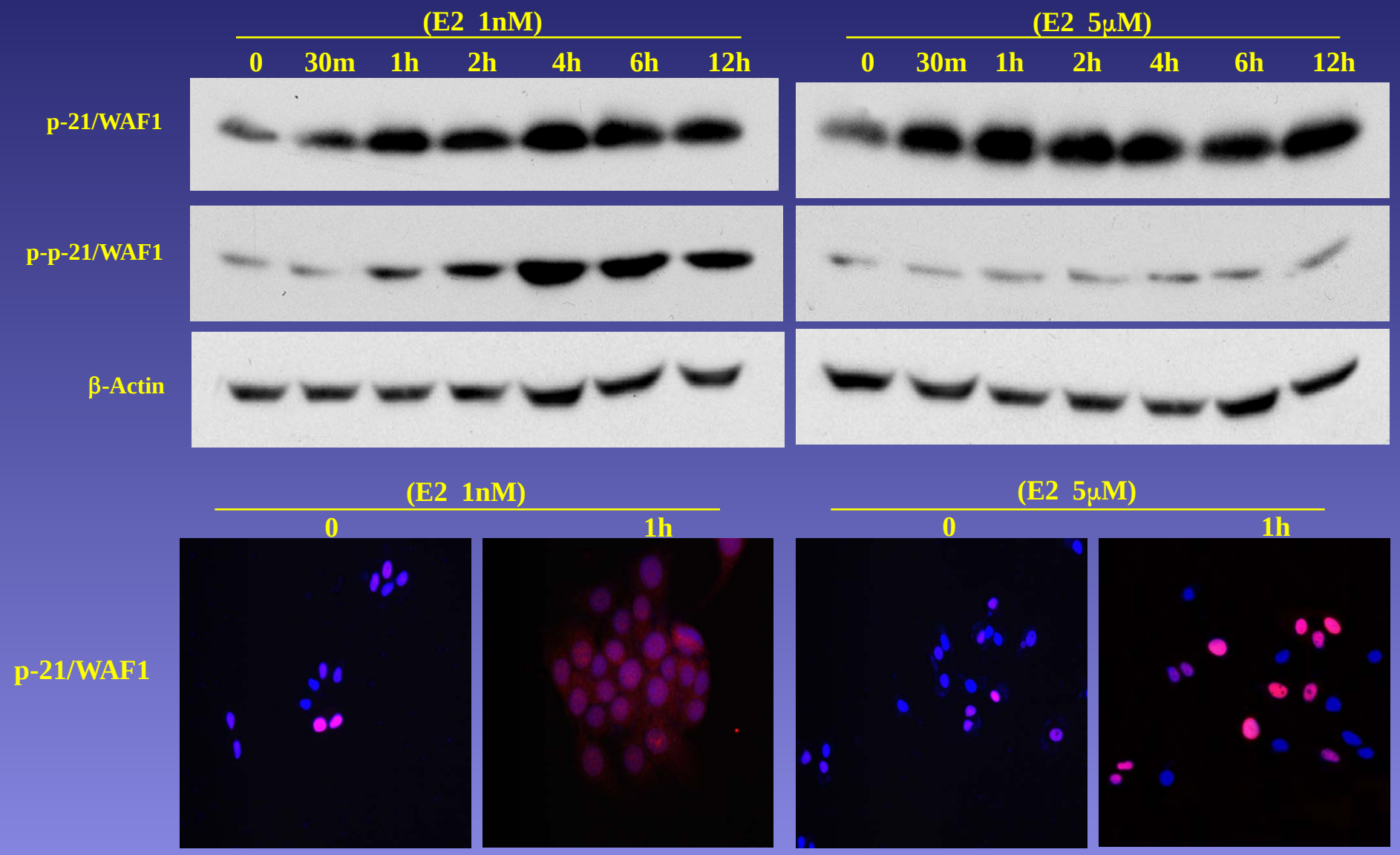


Transient vs sustained ERK activation

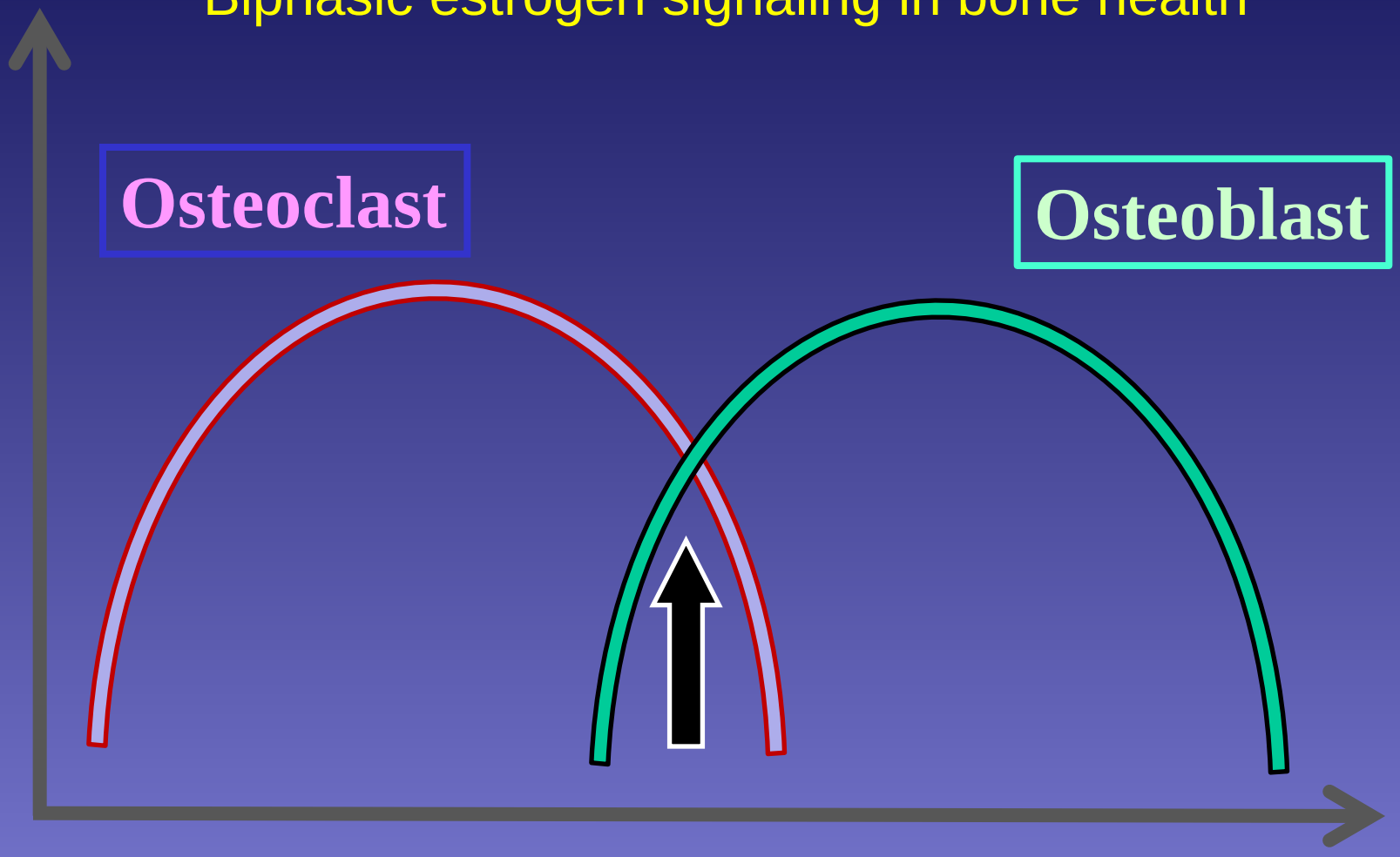




Phosphorylation and distribution of p21 are involved in biphasic estrogen signaling



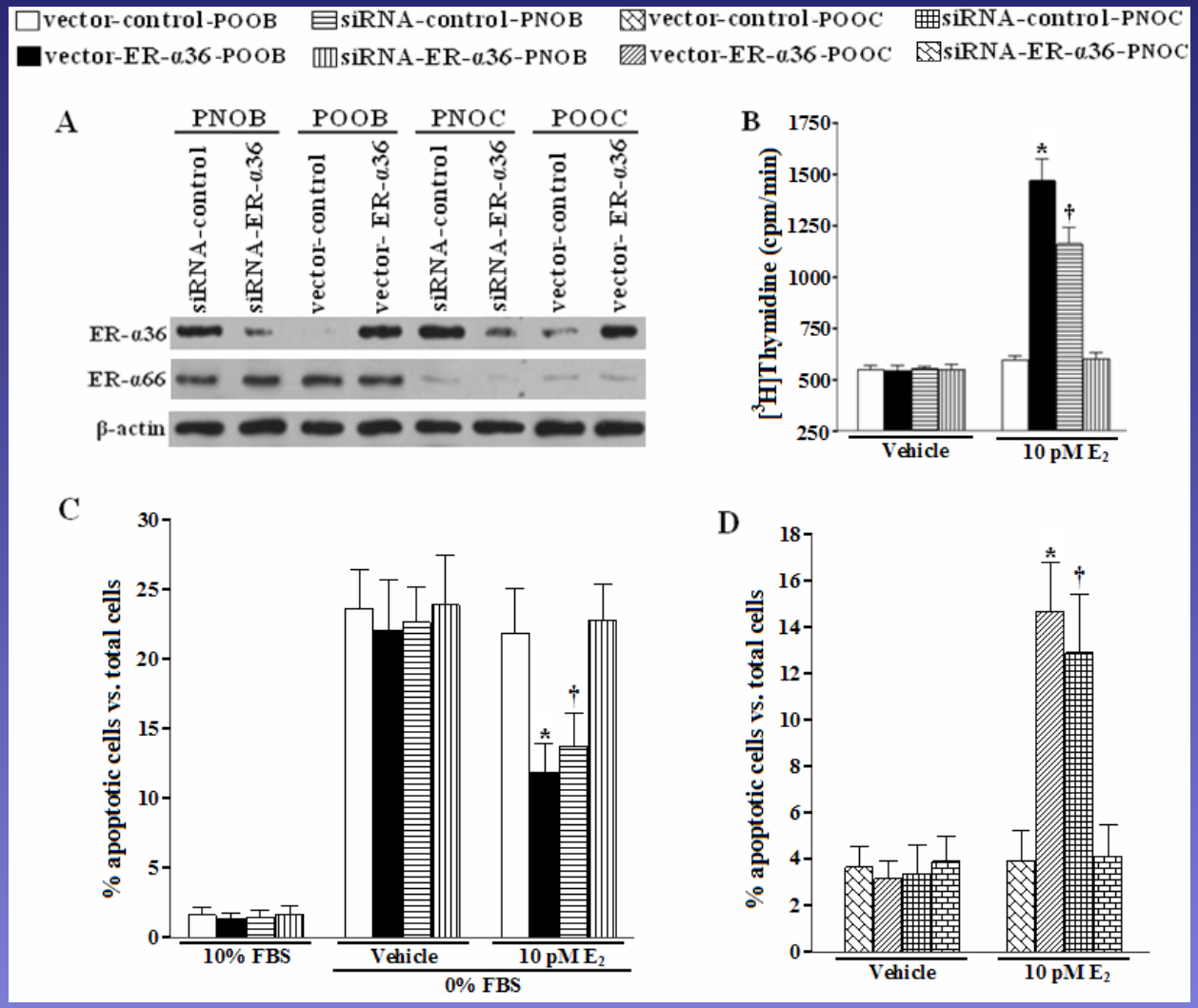
Biphasic estrogen signaling in bone health



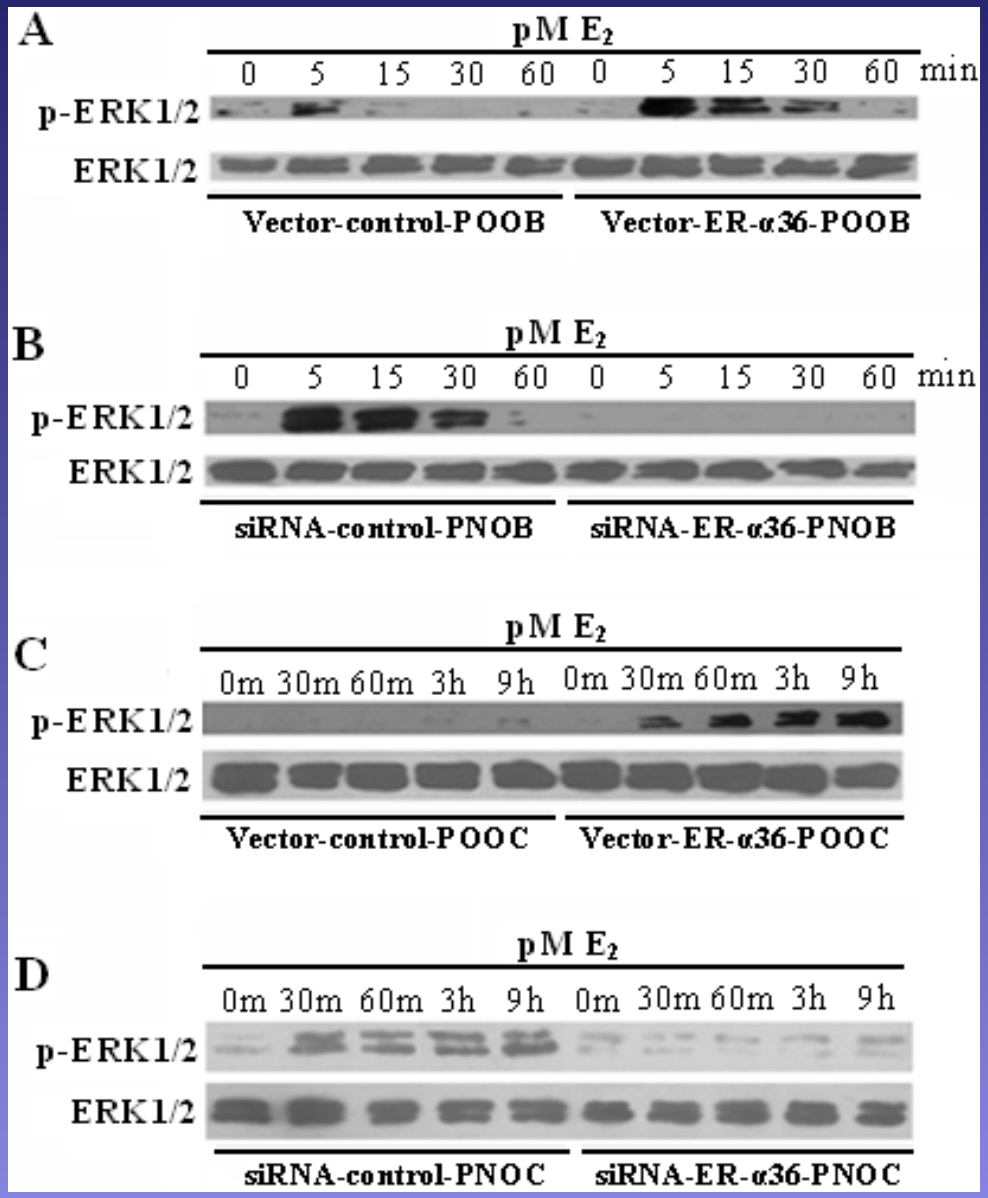
Estrogen Concentration

1. **High ER-α36**
2. **Low ER-α66**

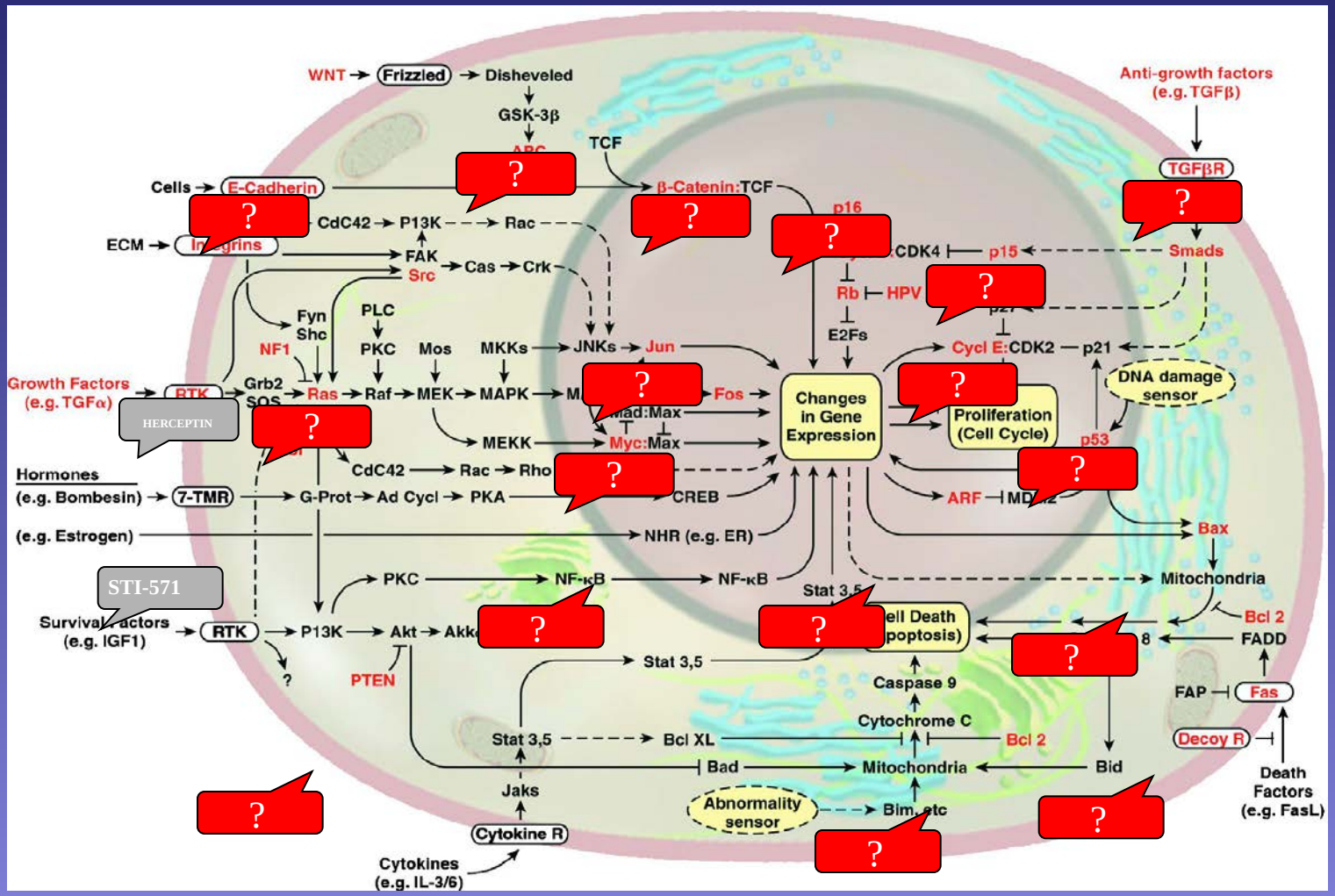
Osteoclasts express low levels of ER-α66



ER-α36 mediates estrogen-induced transient and sustained ERK activation in OB and OC, respectively



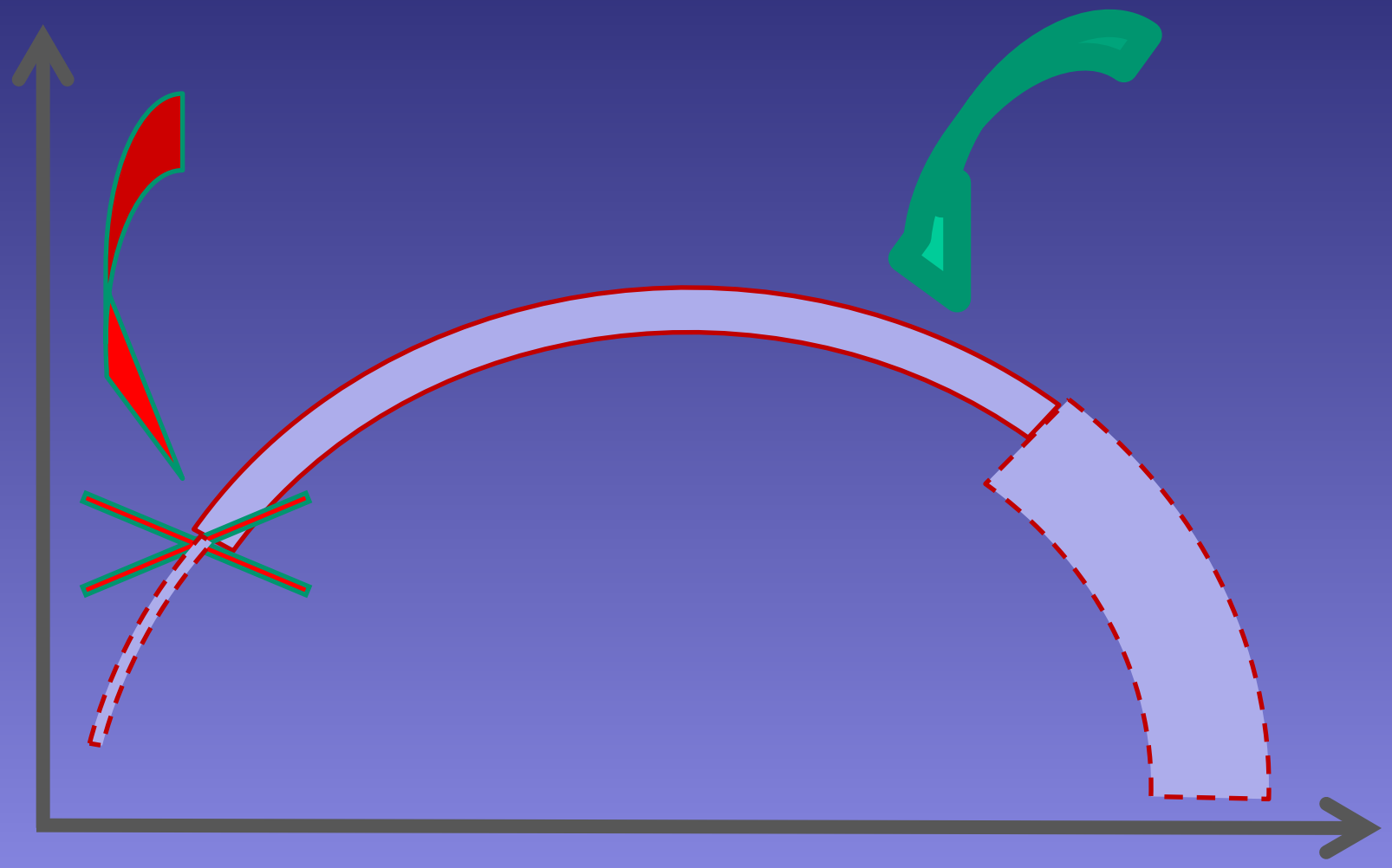
Thousands of Targets for Cancer Treatment



From Hanan and Weinberg

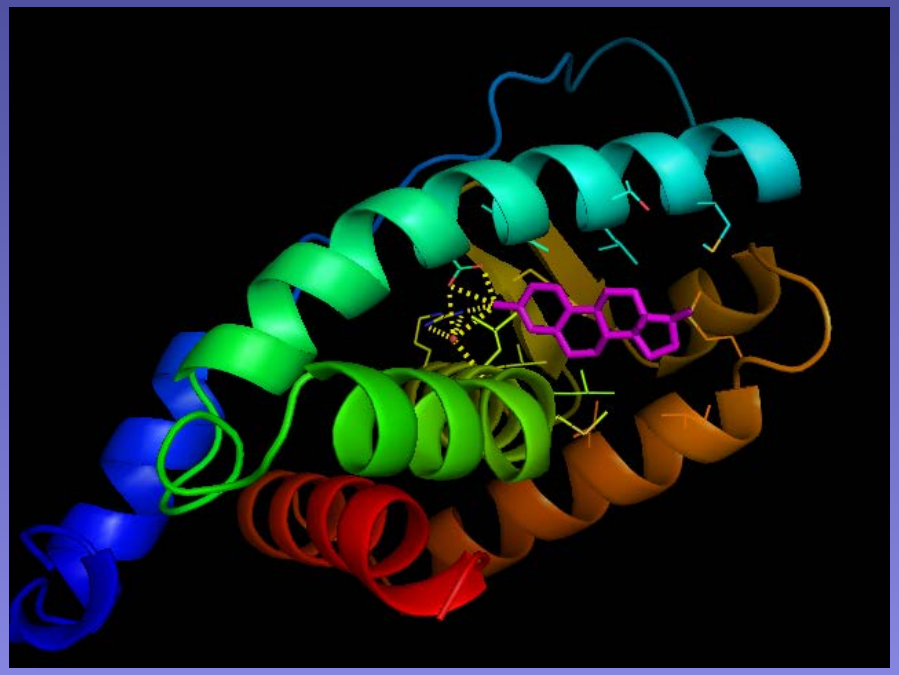
Cancer Treatment

Starved vs Stuffed



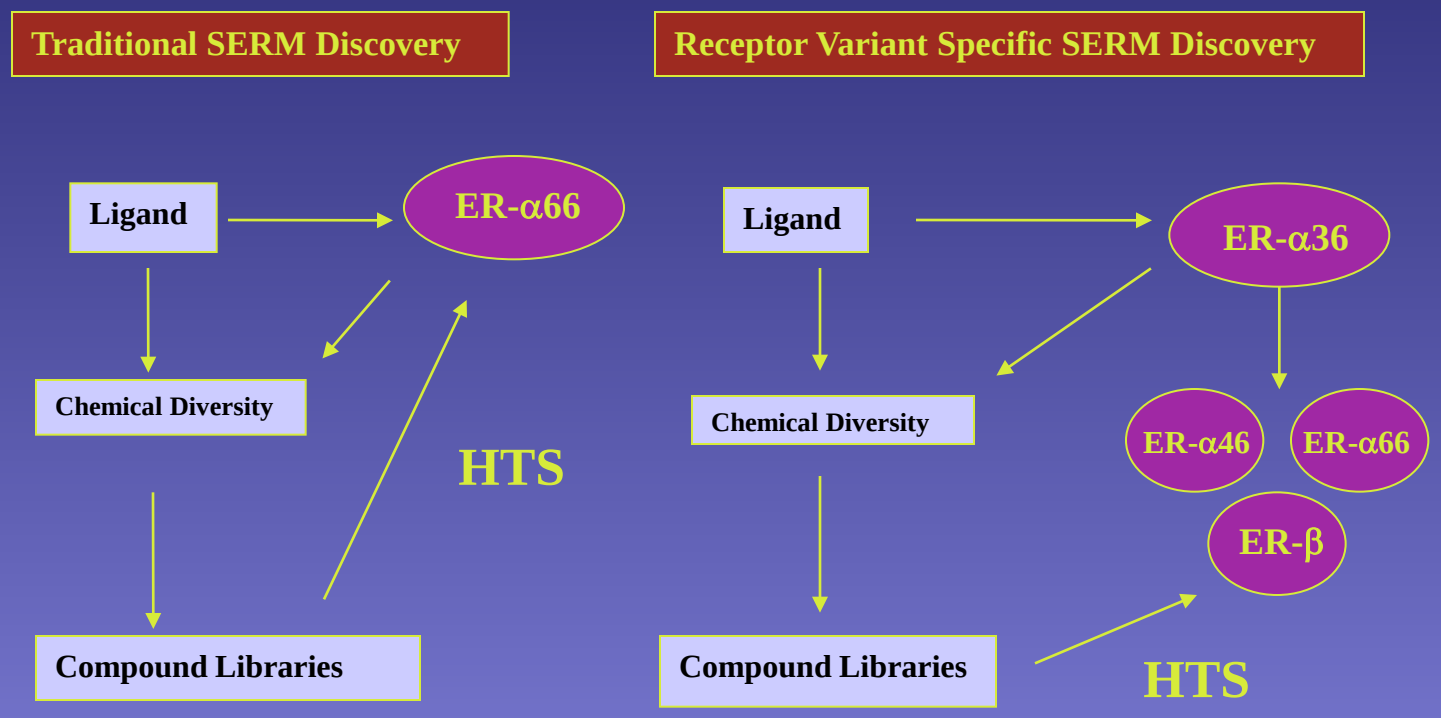
The ligand-binding domains of the ER-α36 and 66

ER-α66

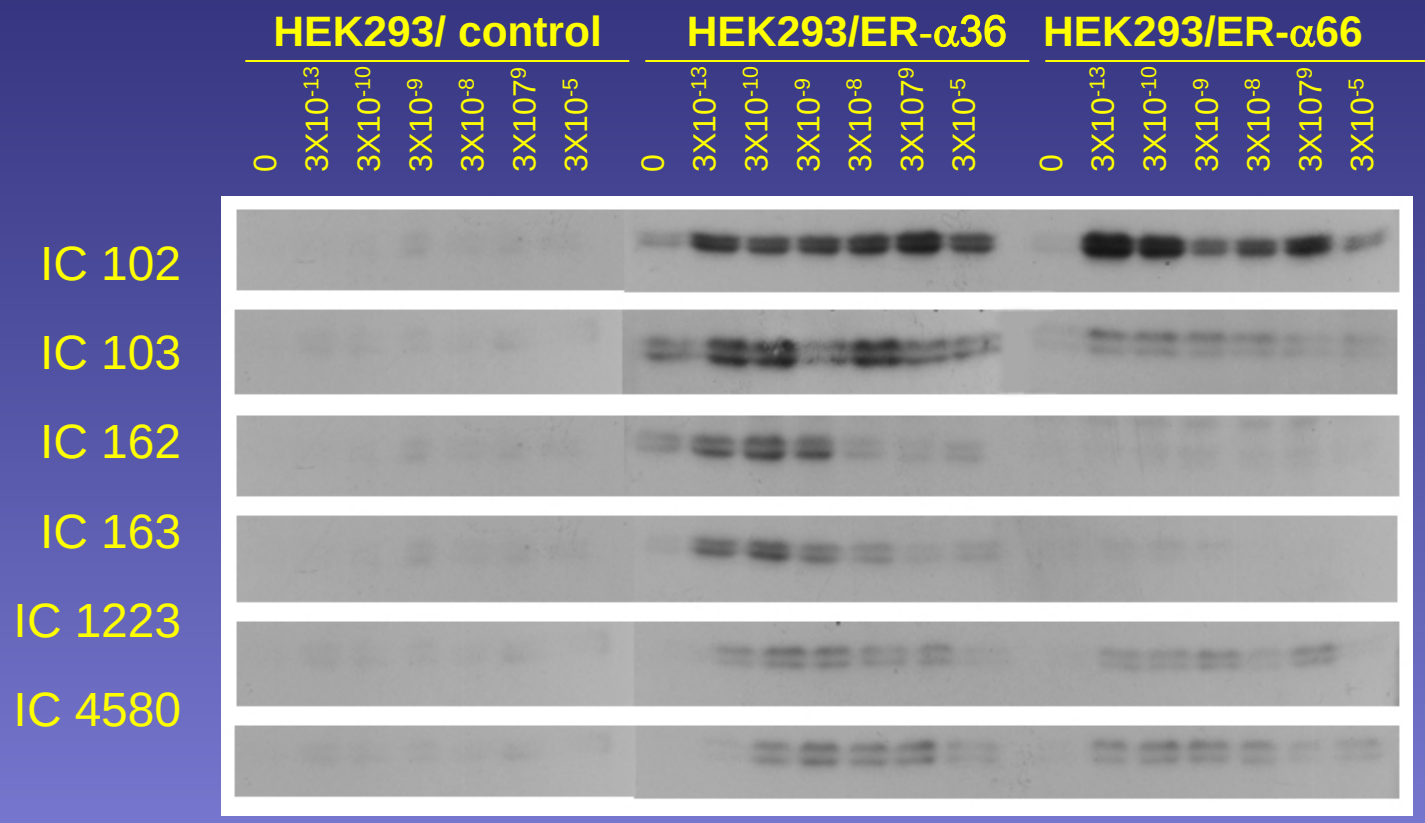


ER-α36

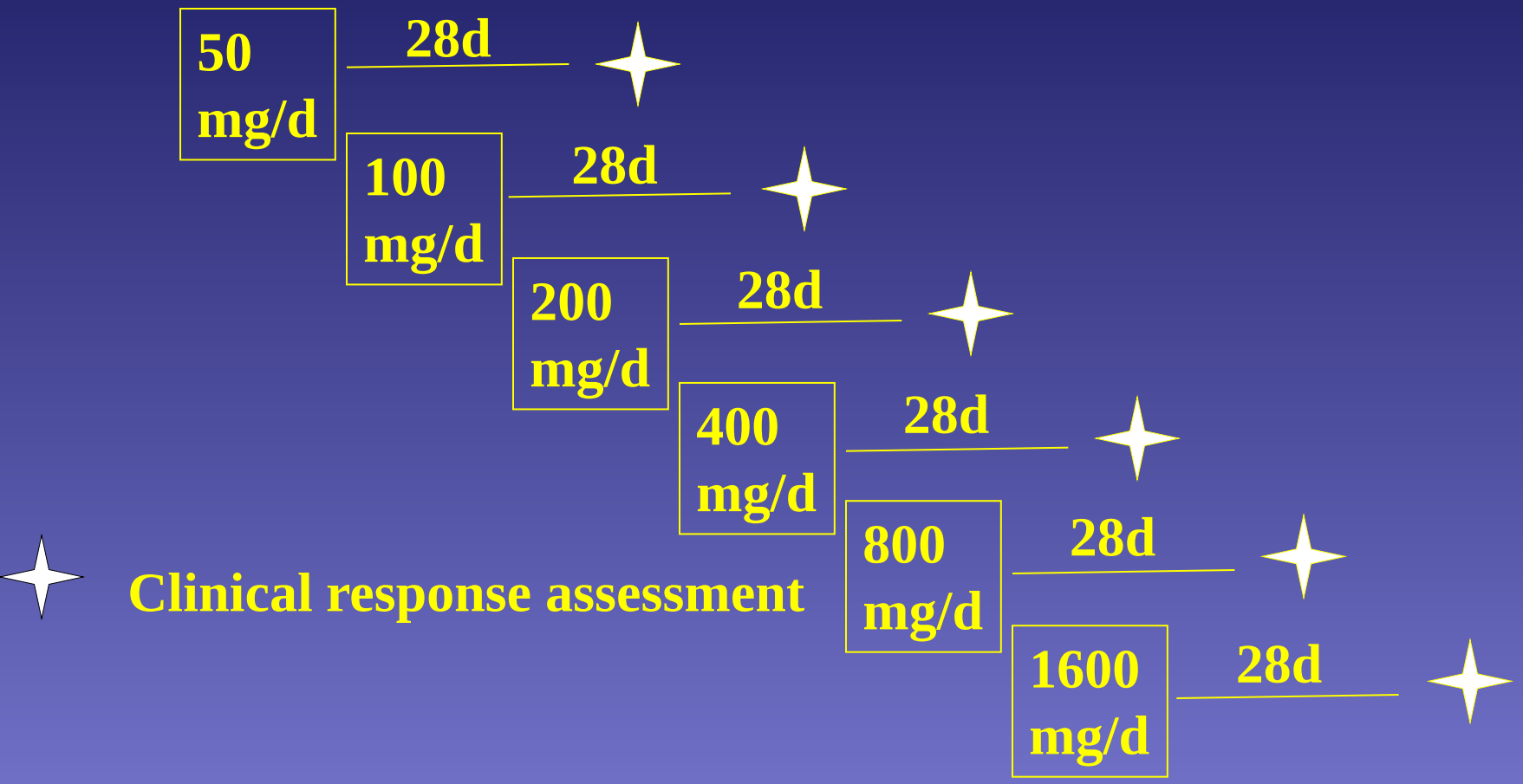
Receptor Variant Specific SERM Discovery

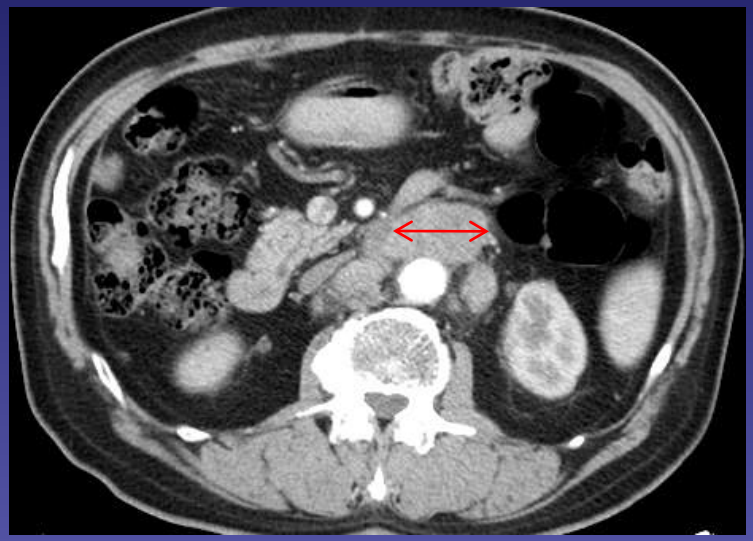


Screening for ER-α36 specific ligands

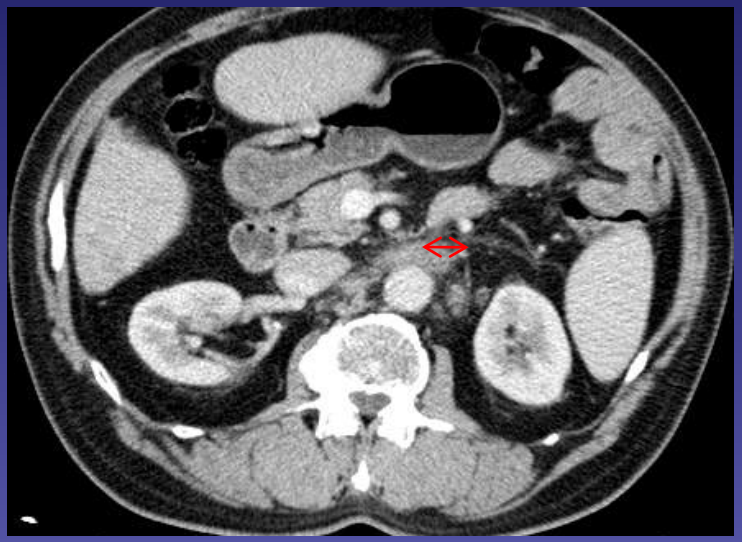


Phase I Dose Escalation Study

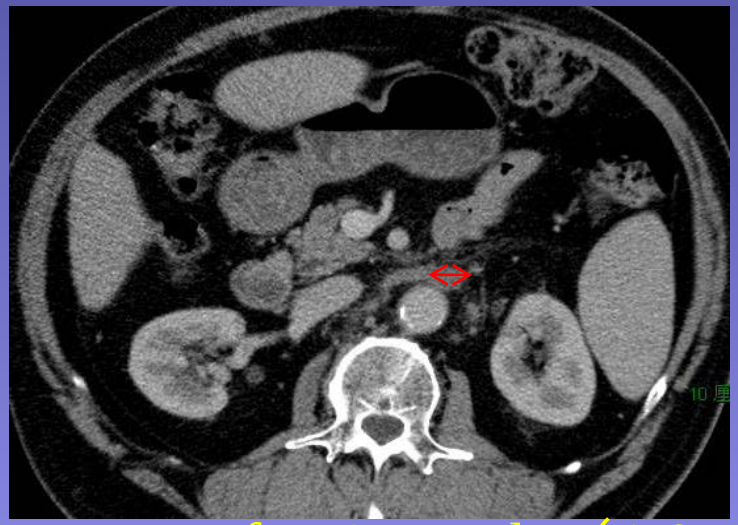




Before treatment （4.6 cm）



Treatment for 2 months（1.0 cm）



Treatment for 4 months（1.0 cm）

Conclusions

1. Biphasic growth signaling is an important regulatory mechanism in biological processes.

2. Src acts as a switch of biphasic growth signaling.

3. Transient or sustained ERK activation plays a role in biphasic growth signaling.

4. Phosphorylation and re-distribution of p21 are involved in biphasic growth signaling.

Acknowledgments

Wang's Lab.

XinTian Zhang

Lin Ding

LianGuo Kang

Collaborators

YueTao Xia (PCI)

Dennis Lubahn (UMC)

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Nebraska Tobacco Settlement Biomedical Research Program Awards.