
Lombardi
COMPREHENSIVE
CANCER CENTER at GEORGETOWN UNIVERSITY
17th Biennial Meeting of Asian
Breast Cancer Society
Global Breast Cancer Conference
Seoul, South Korea
Symposium 1
October 8, 2009
Understanding the Complexity of Estrogen Action
V. Craig Jordan OBE, PhD, DSc, FMedSci
Scientific Director at the Lombardi Comprehensive Cancer Center
Vice Chairman of the Department of Oncology

EUROPEAN JOURNAL OF CANCER 44 (2008) 30–38

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Tamoxifen: Catalyst for the change to targeted therapy

*V. Craig Jordan**

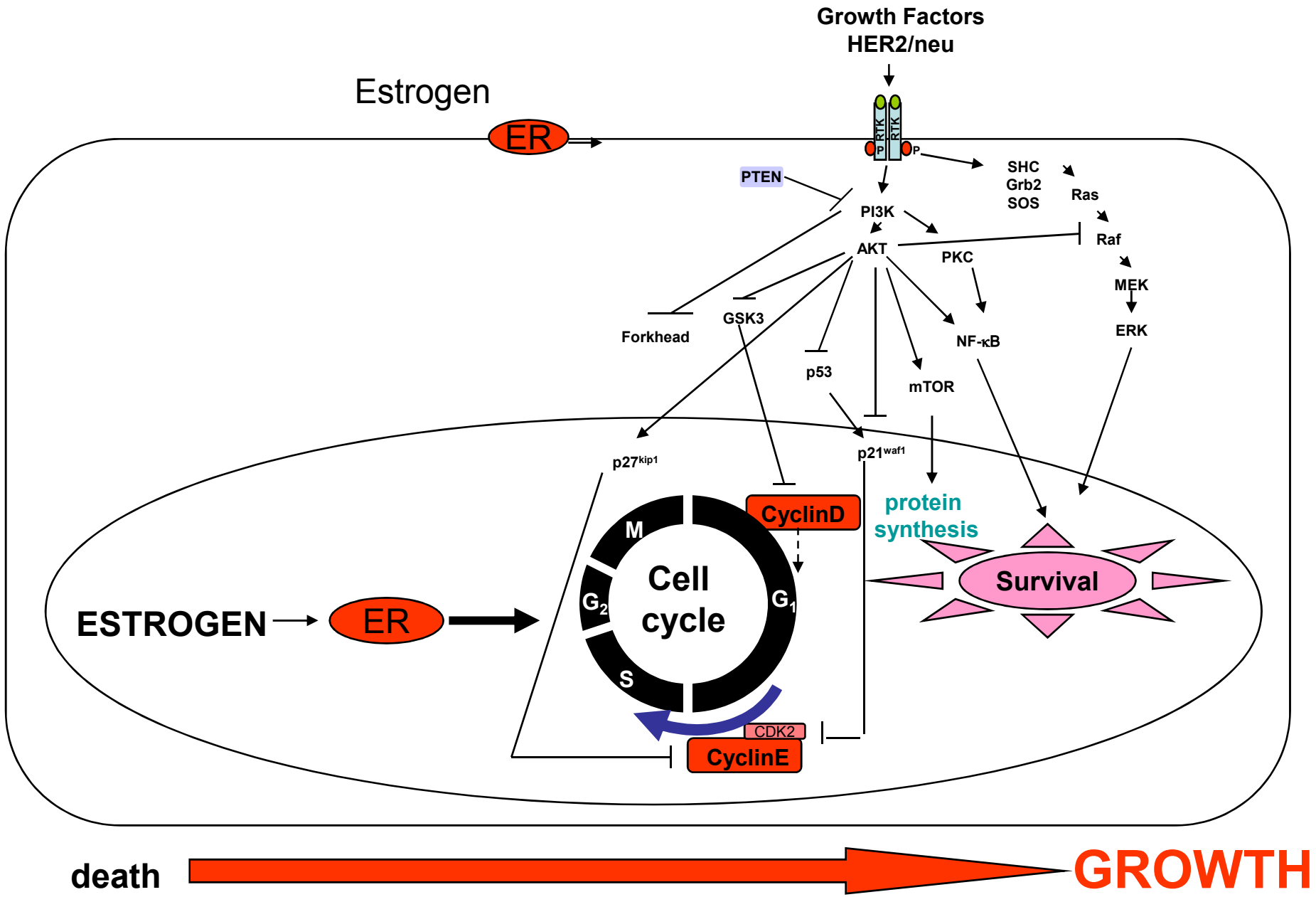
Alfred G. Knudson Chair of Cancer Research, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, United States

Target the Estrogen Receptor (ER)

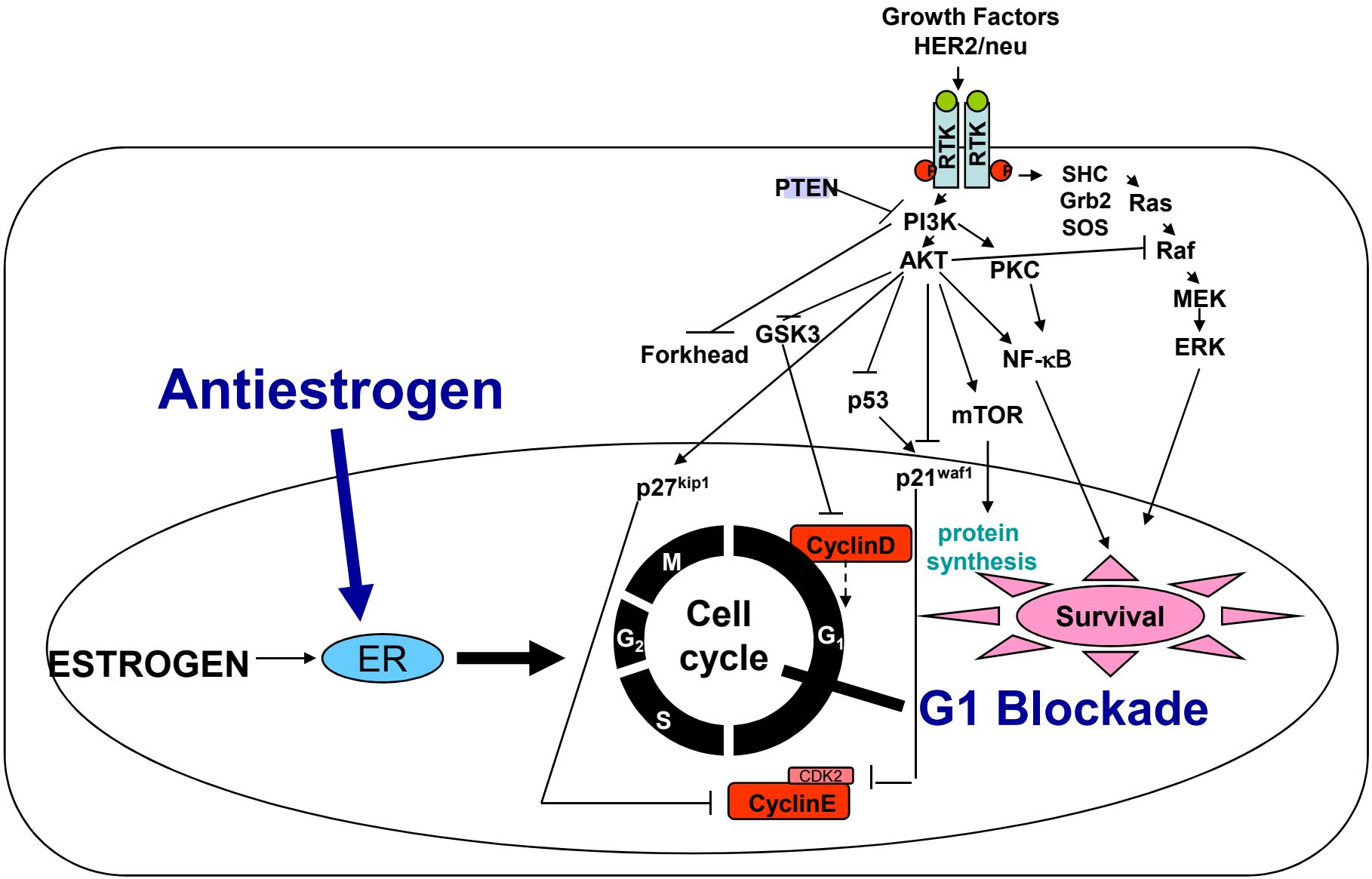
Long term therapy

Jordan & Koerner, *Eur J Cancer*, 11:205-06,1975
Jordan & Allen, *Eur J Cancer,* 16:239-251,1980

Estrogen Receptor as the Target in Breast Cancer

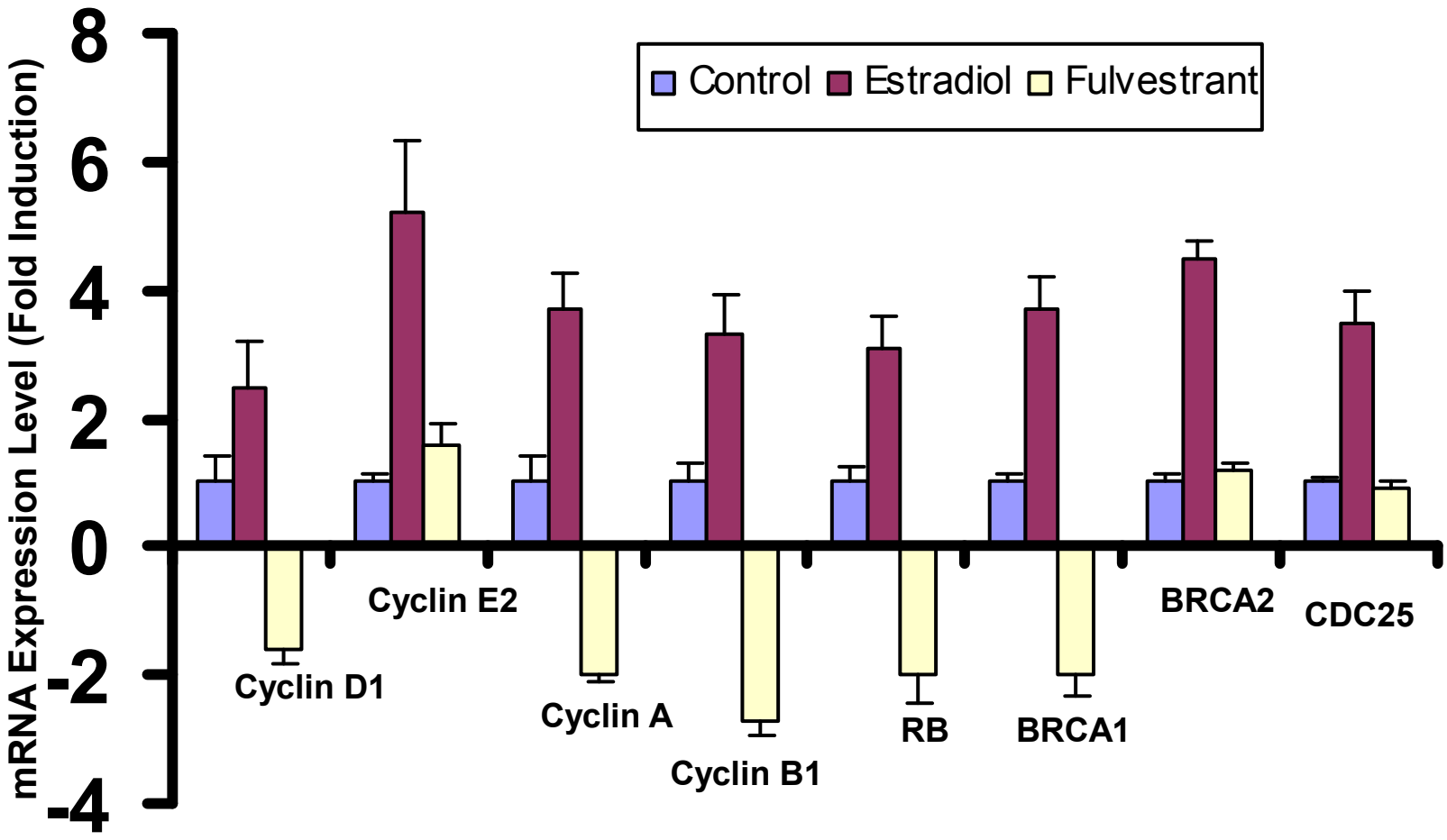


Estrogen Receptor as the Target in Breast Cancer



no growth but cells survive

Effects of Estradiol and Fulvestrant on Positive Regulators of Cell Cycle in MCF-7 Cells



BRCA1- Breast Cancer Susceptibility gene 1
CDC25- Cell Division Cycle 25

Consequences of long term antihormonal therapy is the development of drug resistance

Cancer Research 48, 5183-87, 1988

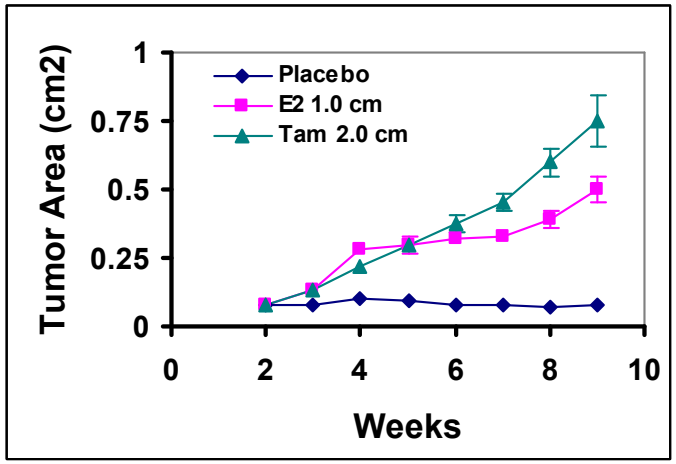
Development of Tamoxifen-stimulated Growth of MCF 7 Tumor in Athymic Mice after Long Term Antiestrogen Administration

Marco M. Gottardis and V. Craig Jordan
Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, WI 53792, USA

Cancer Research 49, 4765-69, 1989

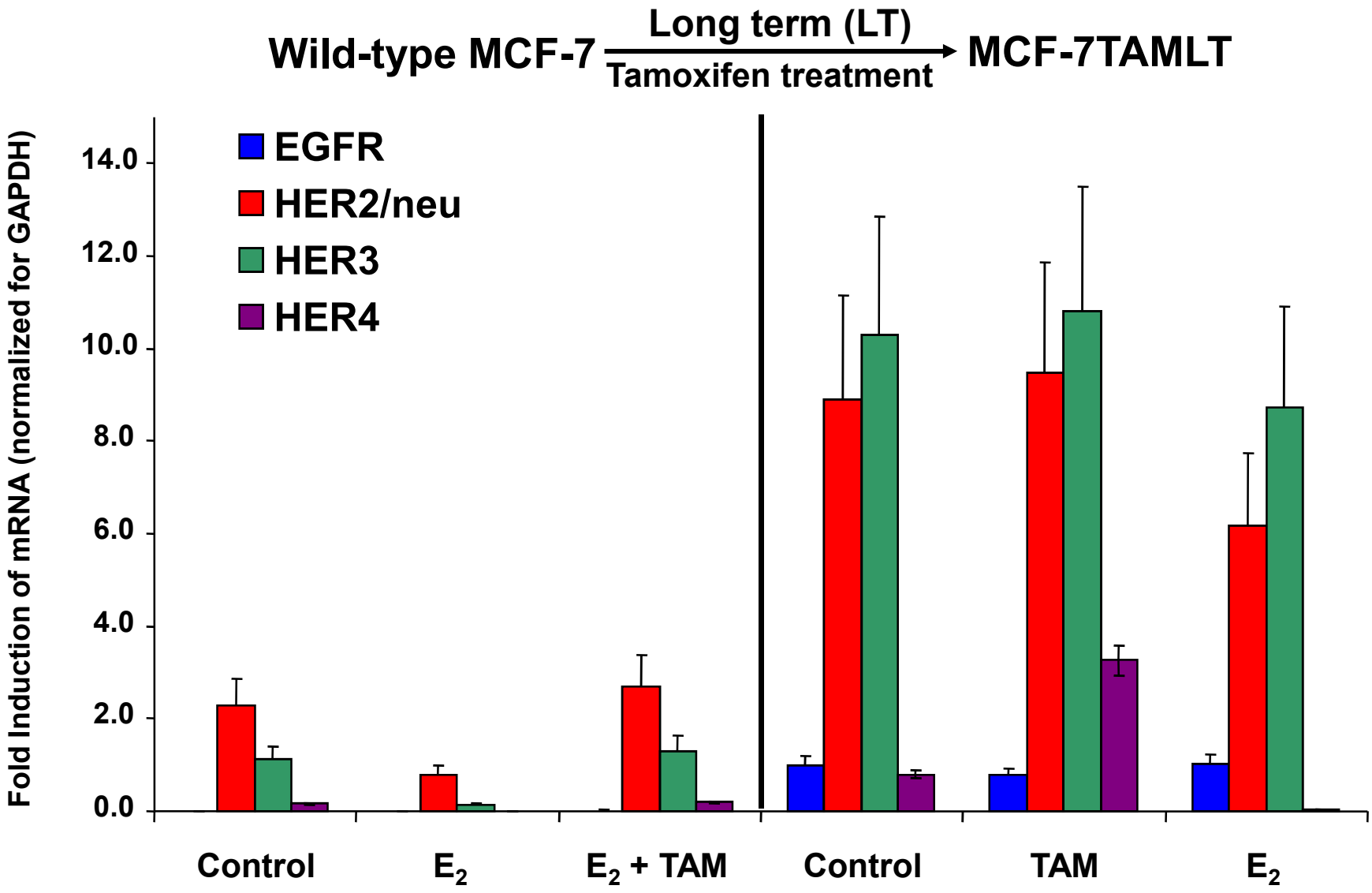
Differential Ability of Antiestrogens to Stimulate Breast Caner Cell (MCF-7) Growth *in vivo* and *in vitro*

Marco M. Gottardis, Randall J. Wagner, Ernest C. Borden, and V. Craig Jordan
Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, WI 53792, USA

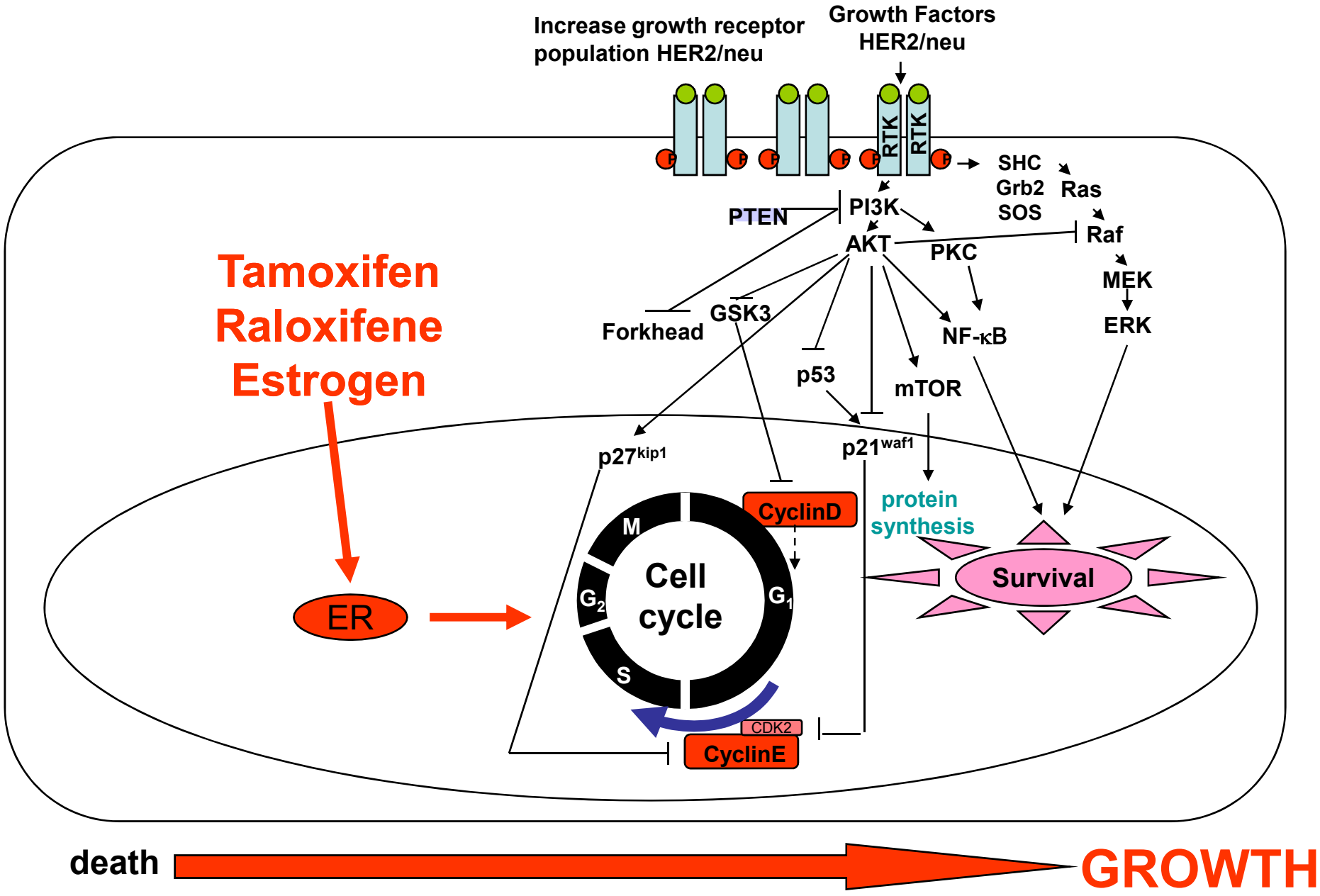


Transplantable laboratory model of tamoxifen stimulated breast cancer growth

Overexpression of Growth Factor Receptors in Tamoxifen-Stimulated Tumors



Drug Resistance to SERMs



CLINICAL CONCEPT

Former laboratory models of SERM resistance replicate failure of tamoxifen after 1 or 2 years of treatment in metastatic breast cancer

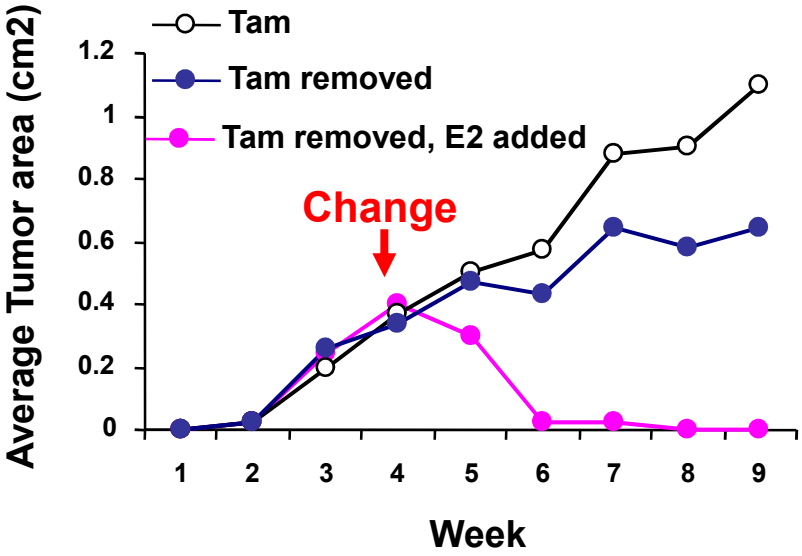
QUESTION

Can laboratory models be developed that can mimic 5 years of adjuvant tamoxifen treatment for micro-metastatic breast cancer?

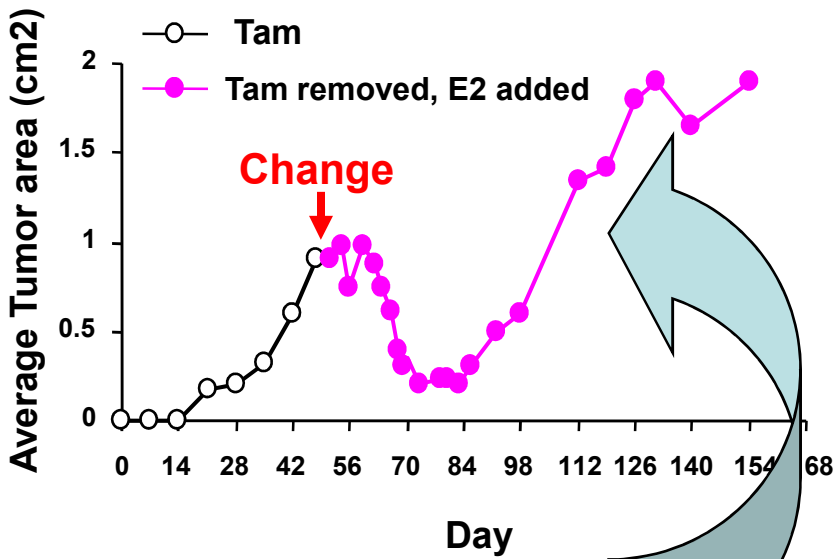
St. Gallen 1992

Wolf & Jordan, *Recent Results in Cancer Research*; 127:23-32, 1993

Regression of MCF-7 Tamoxifen stimulated tumors after administration of estradiol



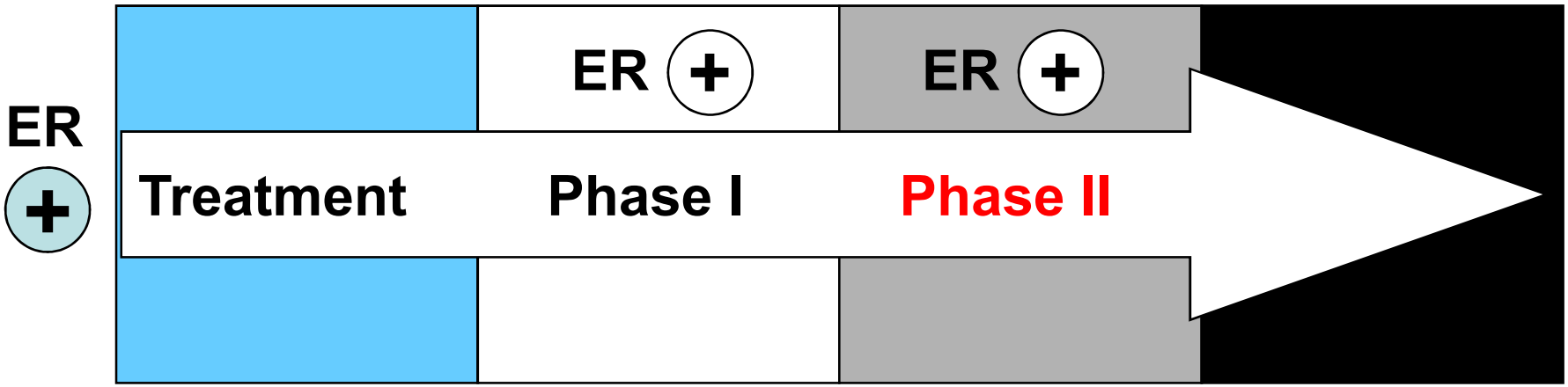
Regression and regrowth of Tamoxifen stimulated tumors during estradiol treatment



Tumor regains antihormonal sensitivity
Loss of drug resistance

Yao et al. *Clinical Cancer Research*; 6:2028-36, 2000

EVOLUTION OF SERM RESISTANCE



This is why aromatase inhibitor or fulvestrant work as 2nd line therapies

1. E_2 or SERM-stimulated
2. FUL inhibited

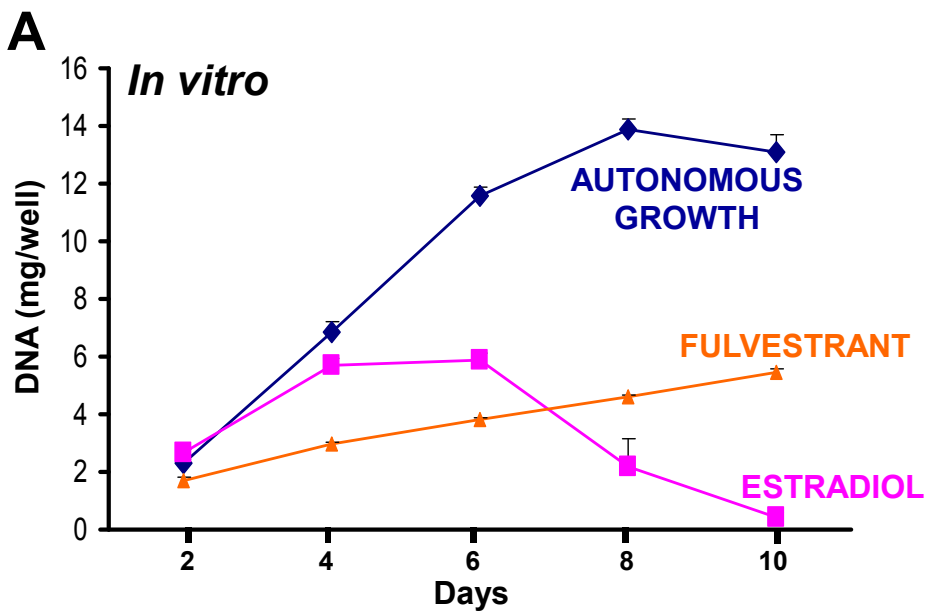
1. E_2 Inhibited
2. SERM stimulated
3. FUL inhibited

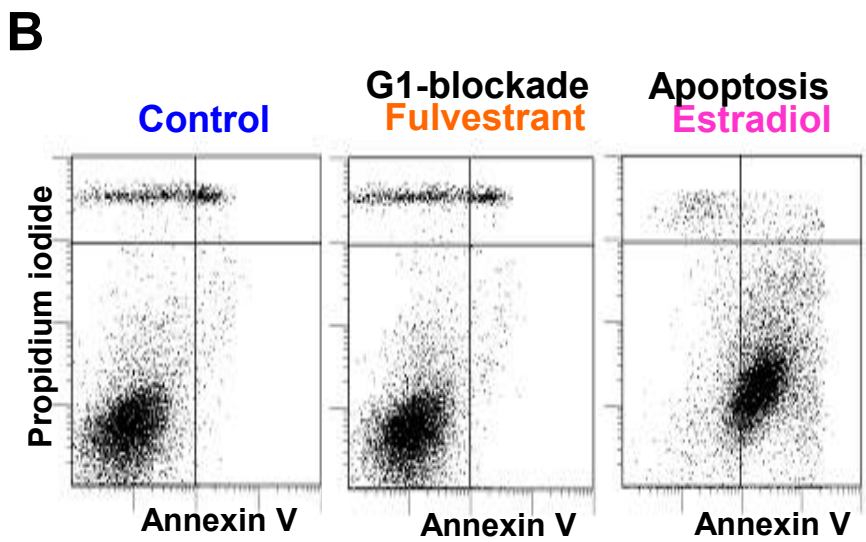
Autonomous growth

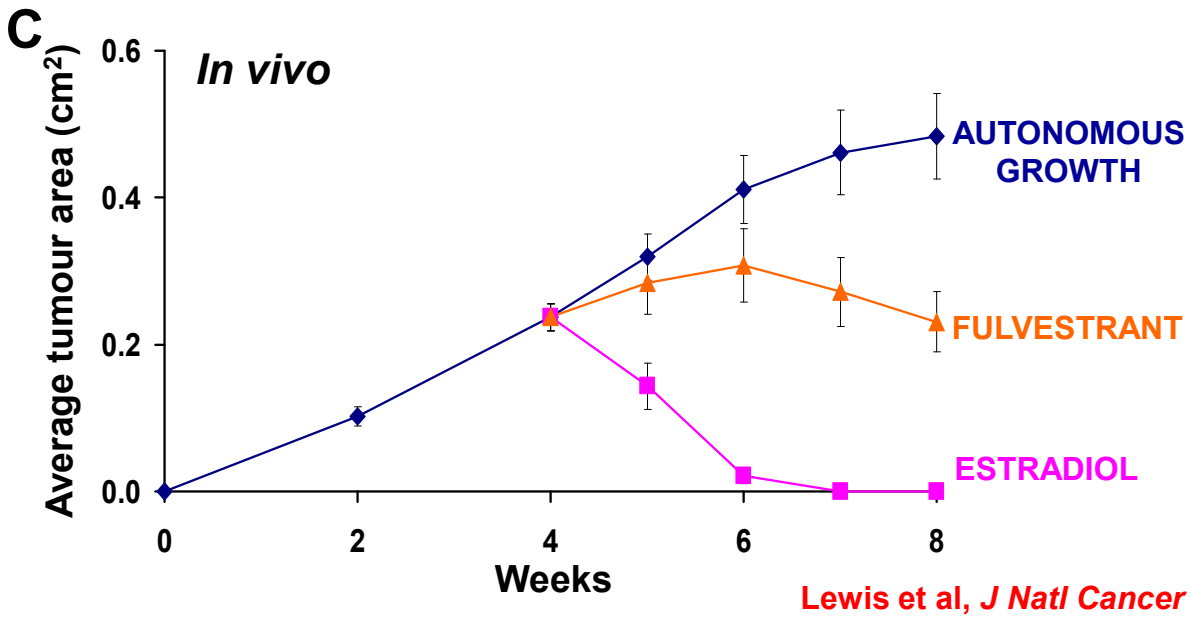
Jordan, VC. *Selective estrogen receptor modulation: Concept and consequences in cancer. Cancer Cell;* 5:207-213, 2004

Does estrogen withdrawal for prolonged periods supersensitize cancer cells to the apoptotic action of estrogen?

Estrogen Induces Apoptosis and Tumor Regression in a Breast Cancer Cell Line Resistant To Estrogen Deprivation

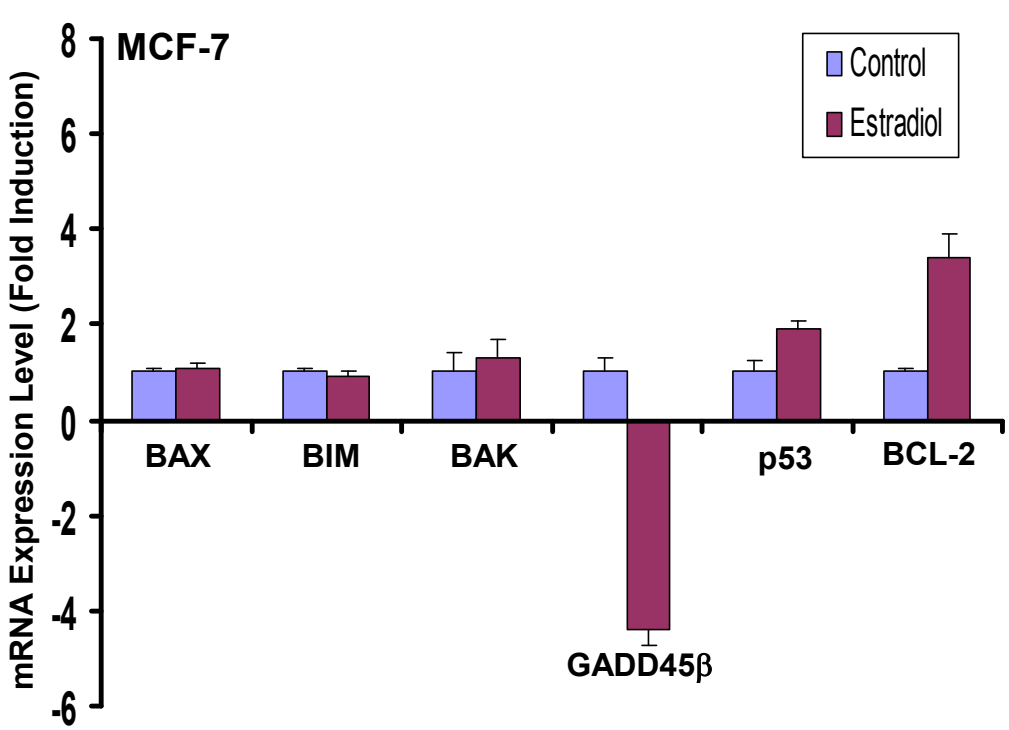


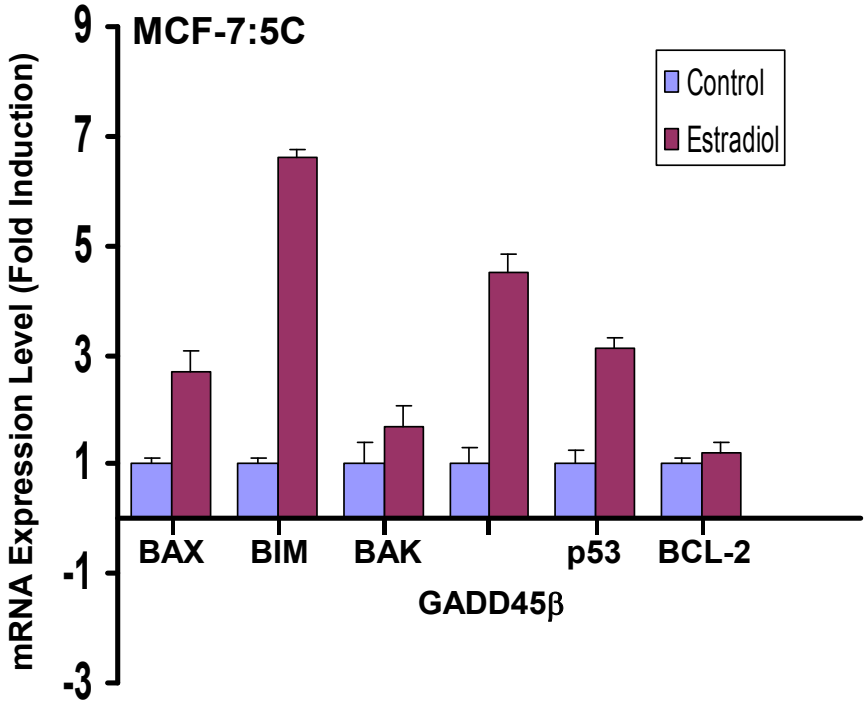




Lewis et al, *J Natl Cancer Inst*; 97:1746-59, 2005

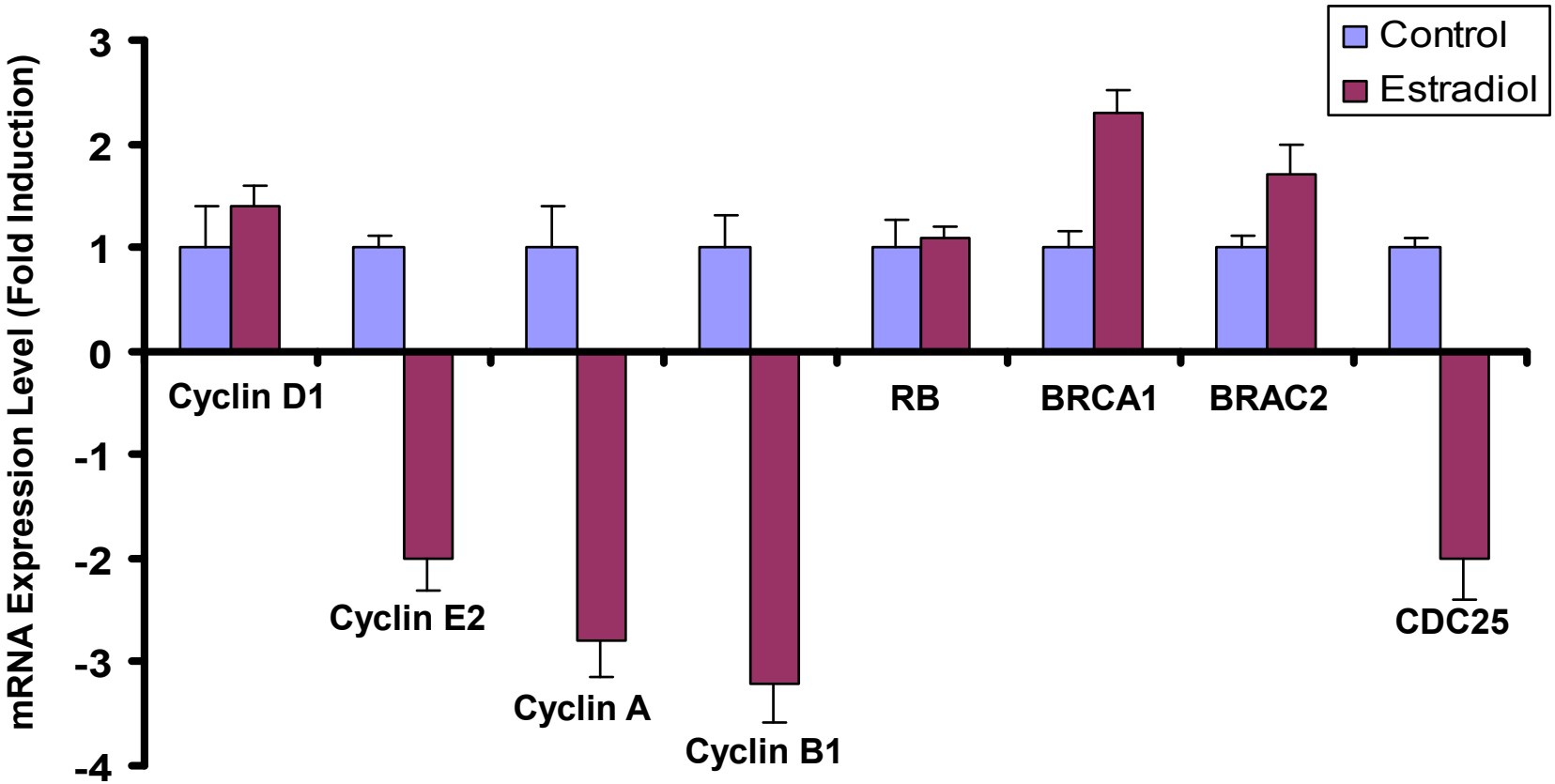
Effect of Estradiol on Apoptosis-Related Genes in MCF-7:5C Cells



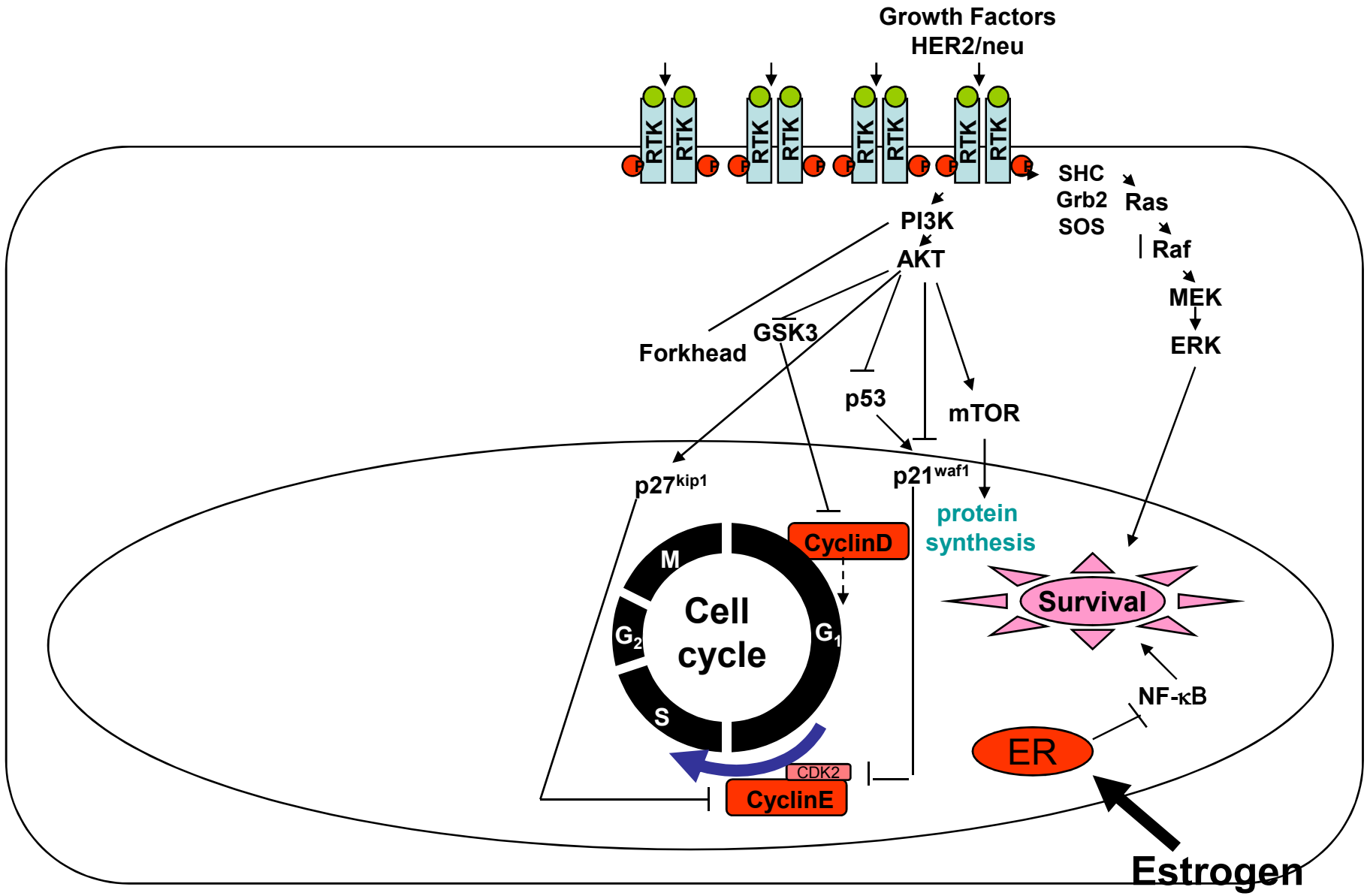


GADD45β– Growth arrested DNA damage induced

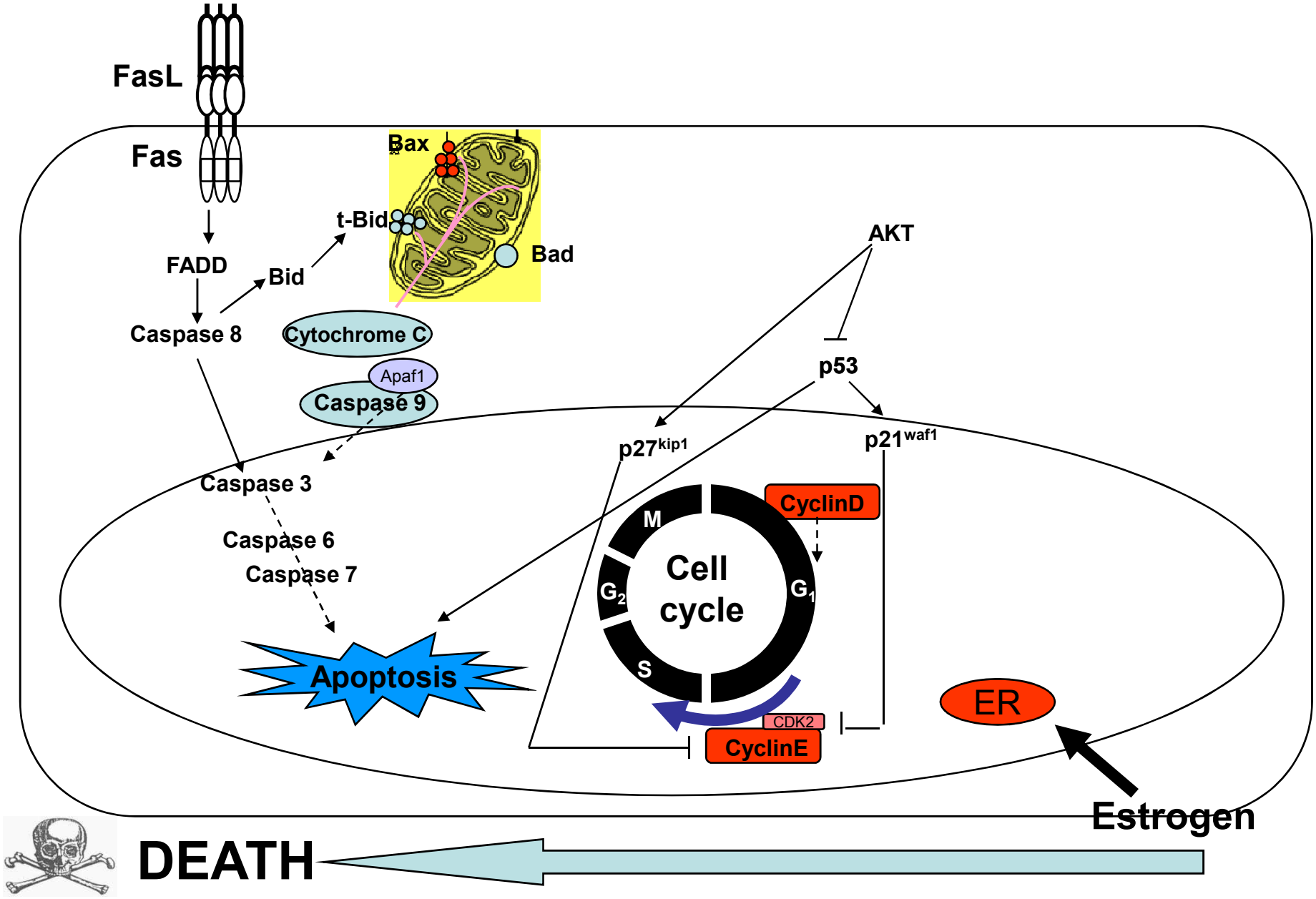
Effect of Estradiol on Positive Regulators of Cell Cycle in MCF-7:5C Cells



Estrogen to Kill Breast Cancer Cells



Estrogen to Kill Breast Cancer Cells



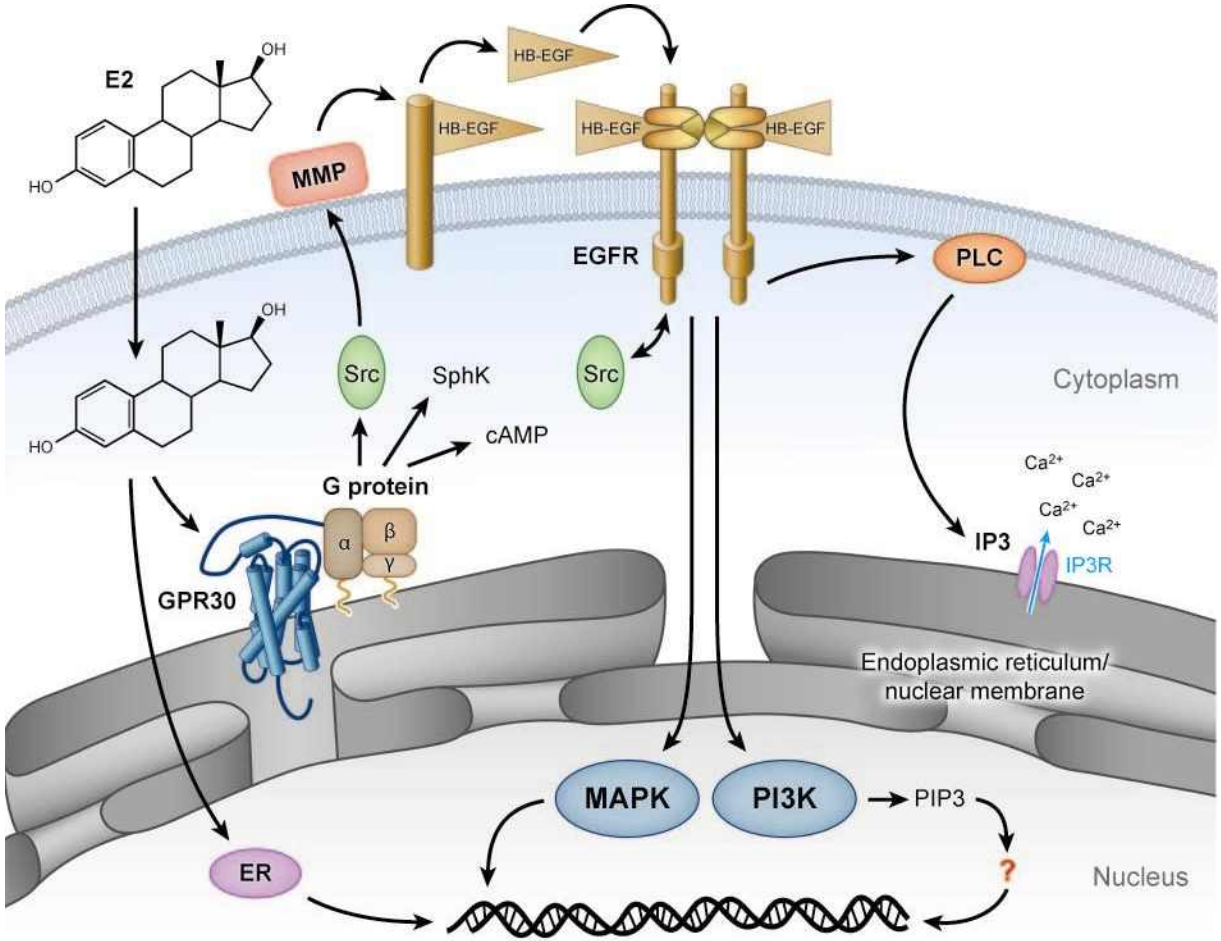
New Ideas in Endocrine Therapy

- Do we know how estrogen works?

  Not really.

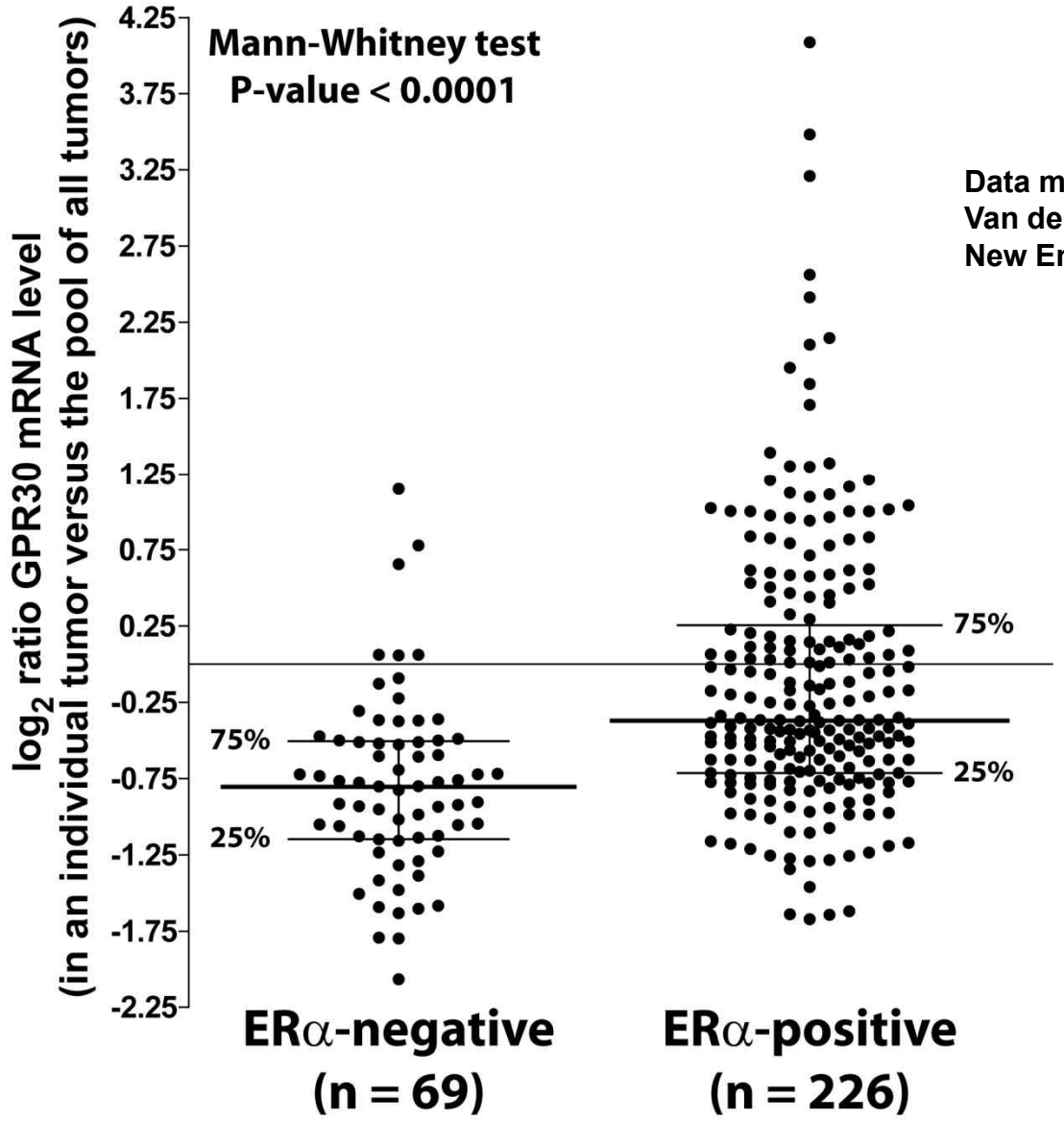
- Can we enhance estrogen induced apoptosis?

GPR30 and ERα Signal Transduction



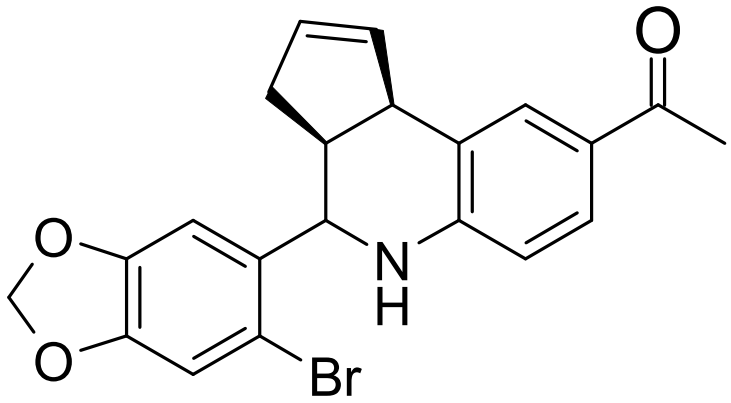
Prossnitz ER, et al. 2008.
Annu. Rev. Physiol. 70:165–90

GPR30 mRNA Levels Associated with ERα-positive Status in Human Breast Cancer



Data mined from microarray study
Van de Vijver et al,
New Engl J Med, 2002

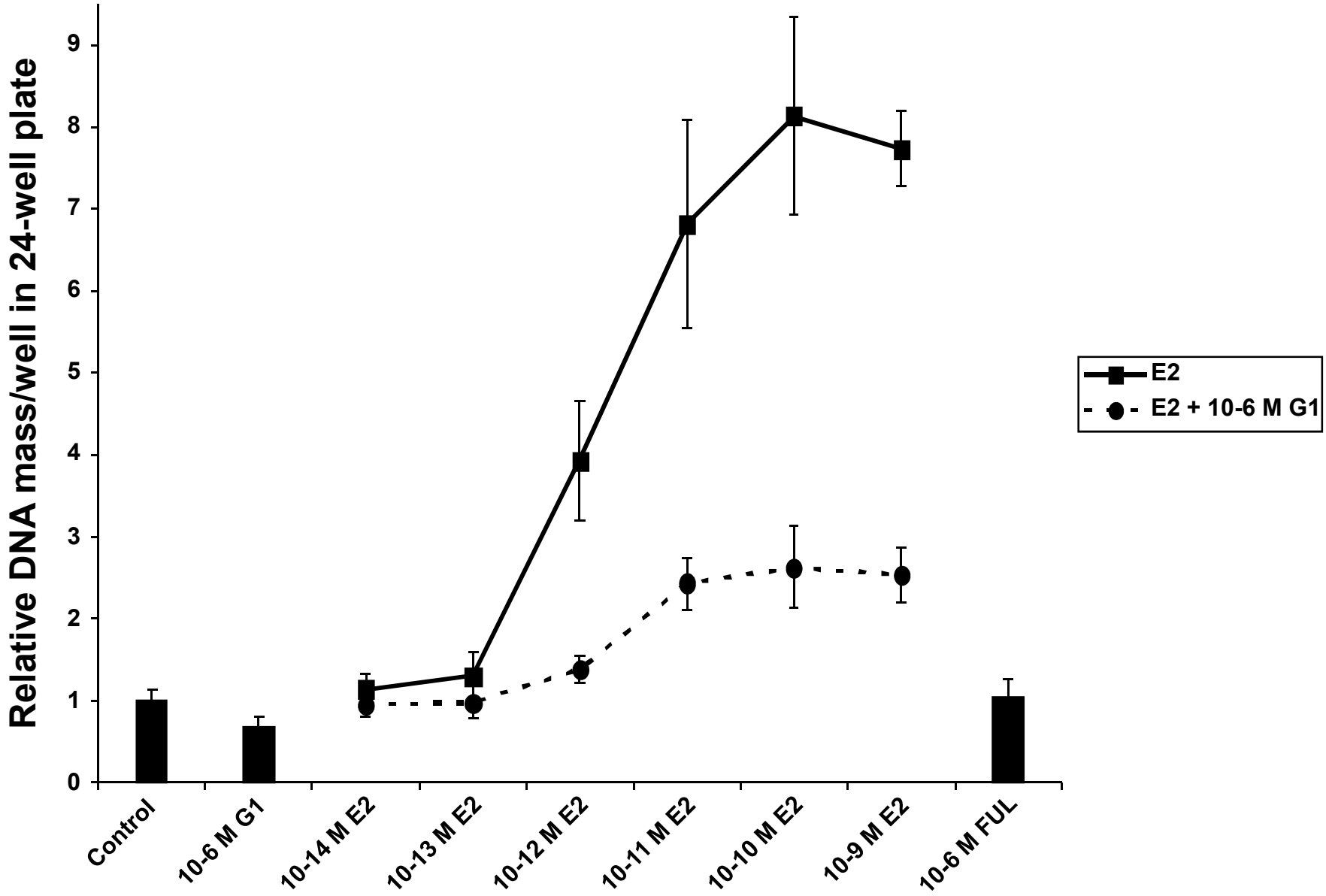
GPR30 Agonist G-1



K_d = 8 nM
No Significant binding to ERs up to 1 μM

Bologa et al., Nat Chem Biol, 2006

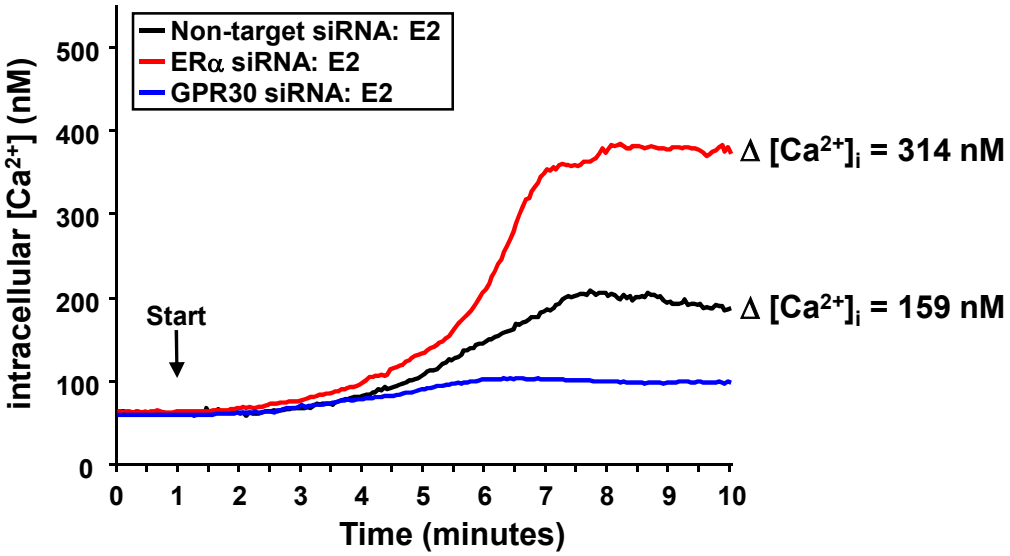
G1 Inhibits E_2-Stimulated Growth of MCF-7 Cells



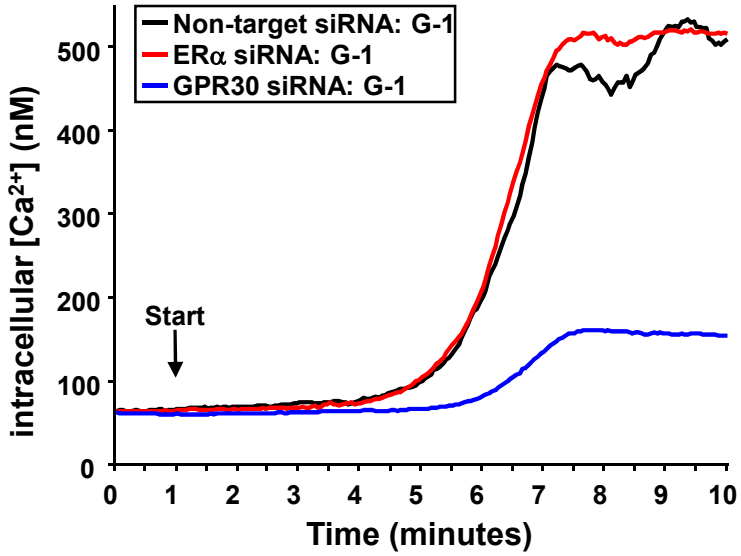
Ariazi, et al. (unpublished)

ERα Suppresses GPR30-Mediated E_2-Induced Ca^{2+} Mobilization

E_2-induced Calcium Mobilization



G-1 -induced Calcium Mobilization

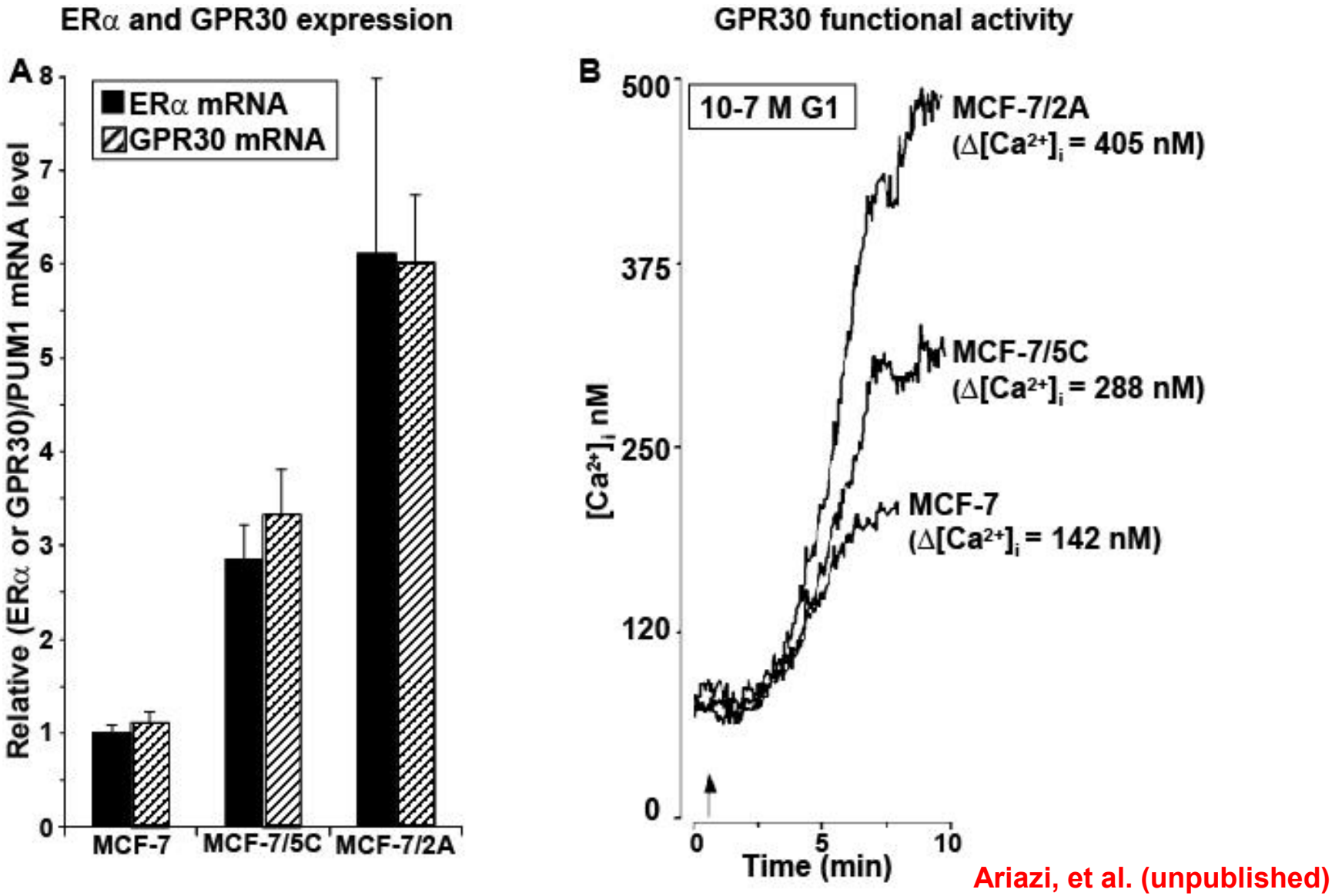


Knockdown of ERα Increases E_2-induced Ca^{2+} Mobilization

- Low levels of intracellular Ca^{2+} mobilization are important for growth
- High levels of Ca^{2+} mobilization inhibit growth and induce apoptosis

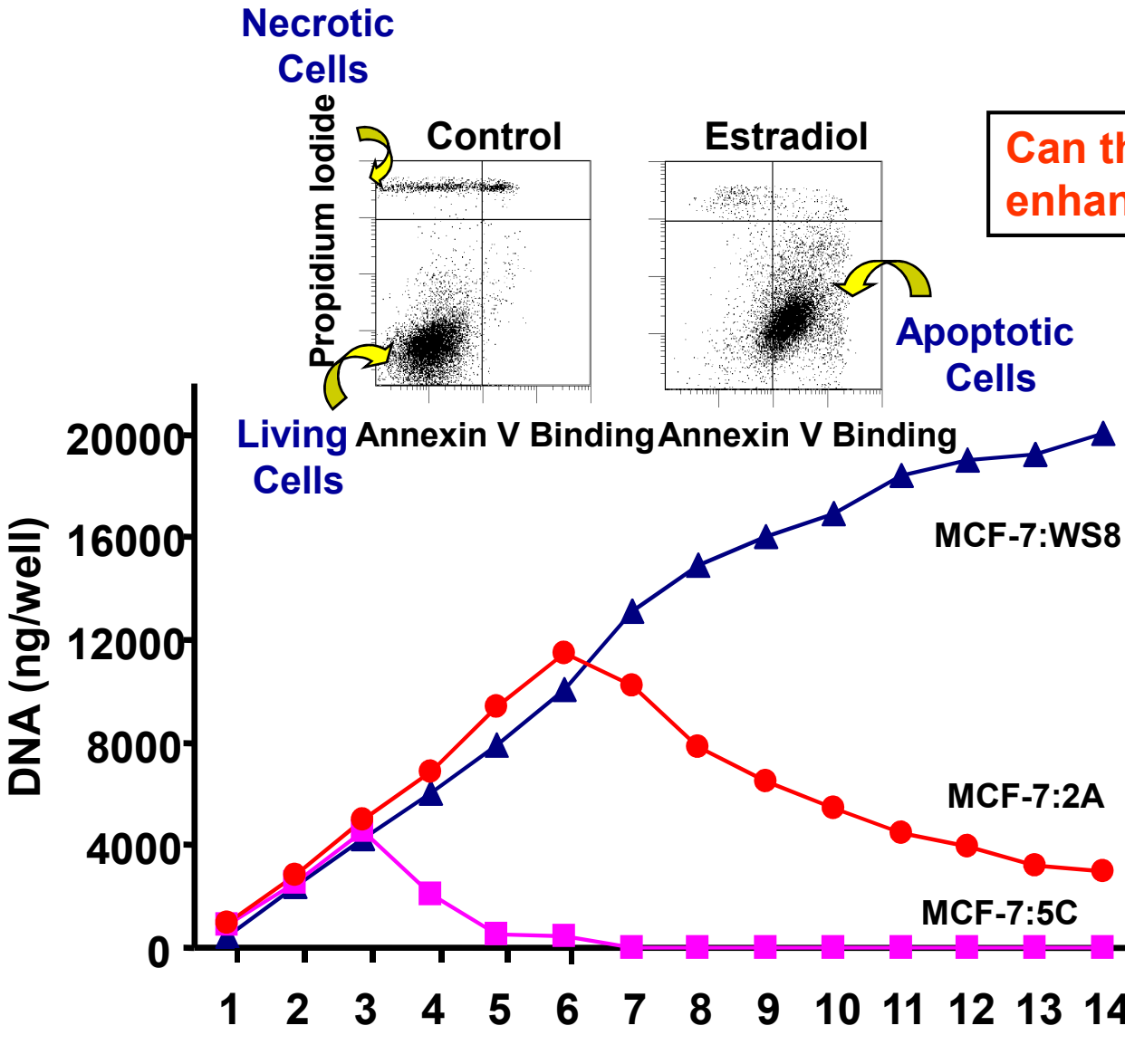
Ariazi, et al. (unpublished)

GPR30 Expression and Functional Activity Increases in Antihormone Resistant MCF-7 Cell Sublines



Ariazi, et al. (unpublished)

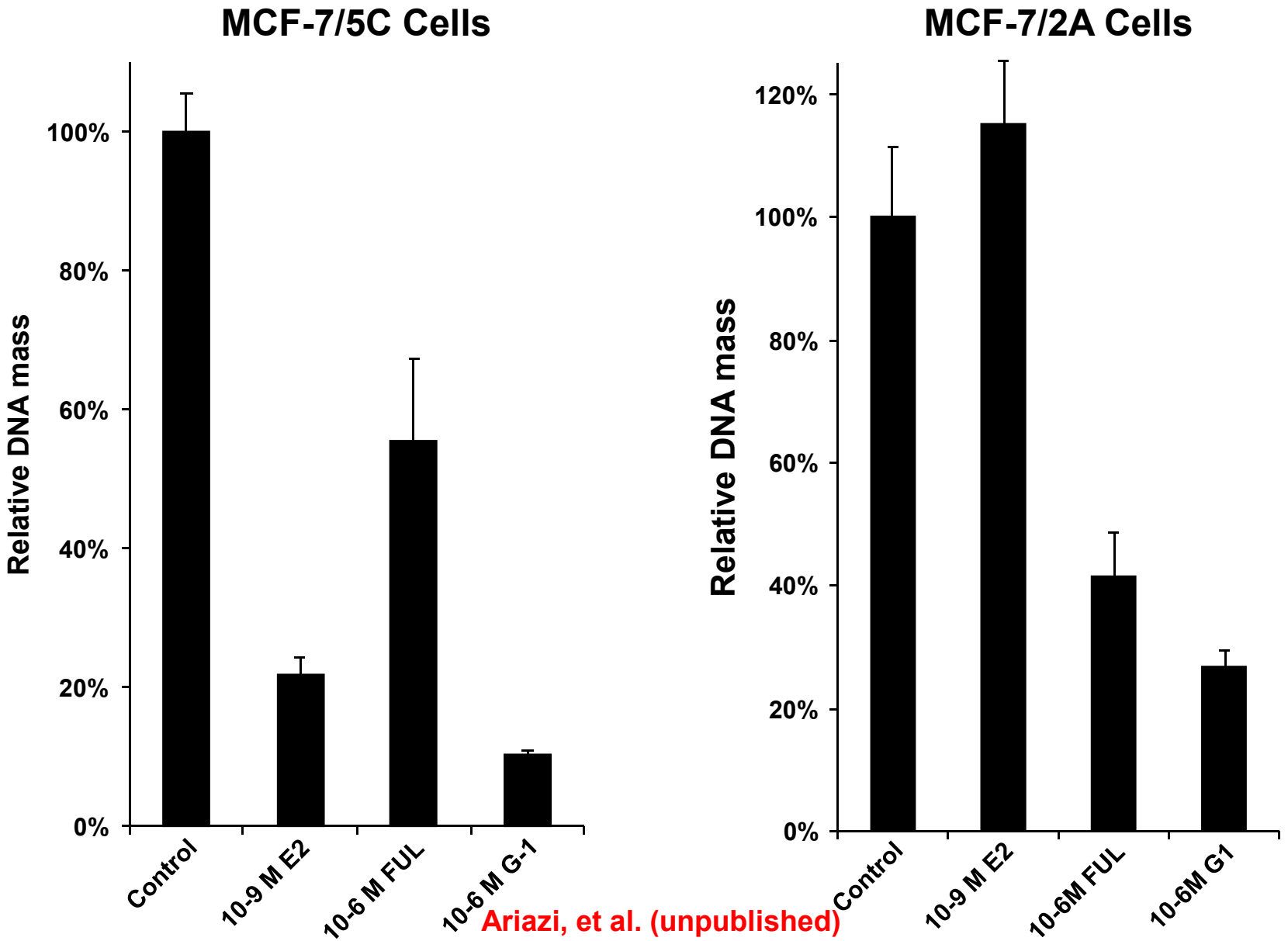
Comparison of the Growth of MCF-7 cells with Antihormone-Resistant Breast Cancer Cells (In Presence of Estrogen)



Can the action of estrogen be enhanced in MCF7-2A cells?

Lewis-Wambi et al, *Breast Cancer Res*;10:R104, 2008

G1 Inhibits Proliferation of Two Independent Antihormone Resistant MCF-7 Cell Sublines



Ariazi, et al. (unpublished)

GPR30 CONCLUSIONS

- Specific activation of GPR30 inhibits estrogen stimulated growth
- Specific activation of GPR30 mobilizes calcium to impair cell growth
- Antihormone resistant cells have elevated levels of GPR30
- Specific activation of GPR30 can accelerate cell death in antihormone resistant cells refractory to estrogen

New Ideas in Endocrine Therapy

- Do we know how estrogen works?

- Can we enhance estrogen induced apoptosis?

  Yes.

Advances in Targeted Therapeutics and Prevention

- **Tamoxifen for the treatment and prevention of breast cancer (reinvented from a failed contraceptive)**
- **Raloxifene for the prevention of osteoporosis and breast cancer (reinvented from a failed breast cancer drug)**
- **Recognition of the selective estrogenic and antiestrogenic actions of "non steroidal antiestrogens" (new drug group called Selective Estrogen Receptor Modulators or SERMs)**
- **Discovery of the new apoptotic actions of estrogen (understanding why high dose estrogen treatment was effective in controlling the growth of some breast cancers)**

Jordan VC, *Nat Rev Drug Discov*; 2:205-13, 2003
Jordan VC, *Eur J Cancer*; 44:30-8, 2008