mTOR e le altre vie di trasduzione del segnale: Implicazioni cliniche

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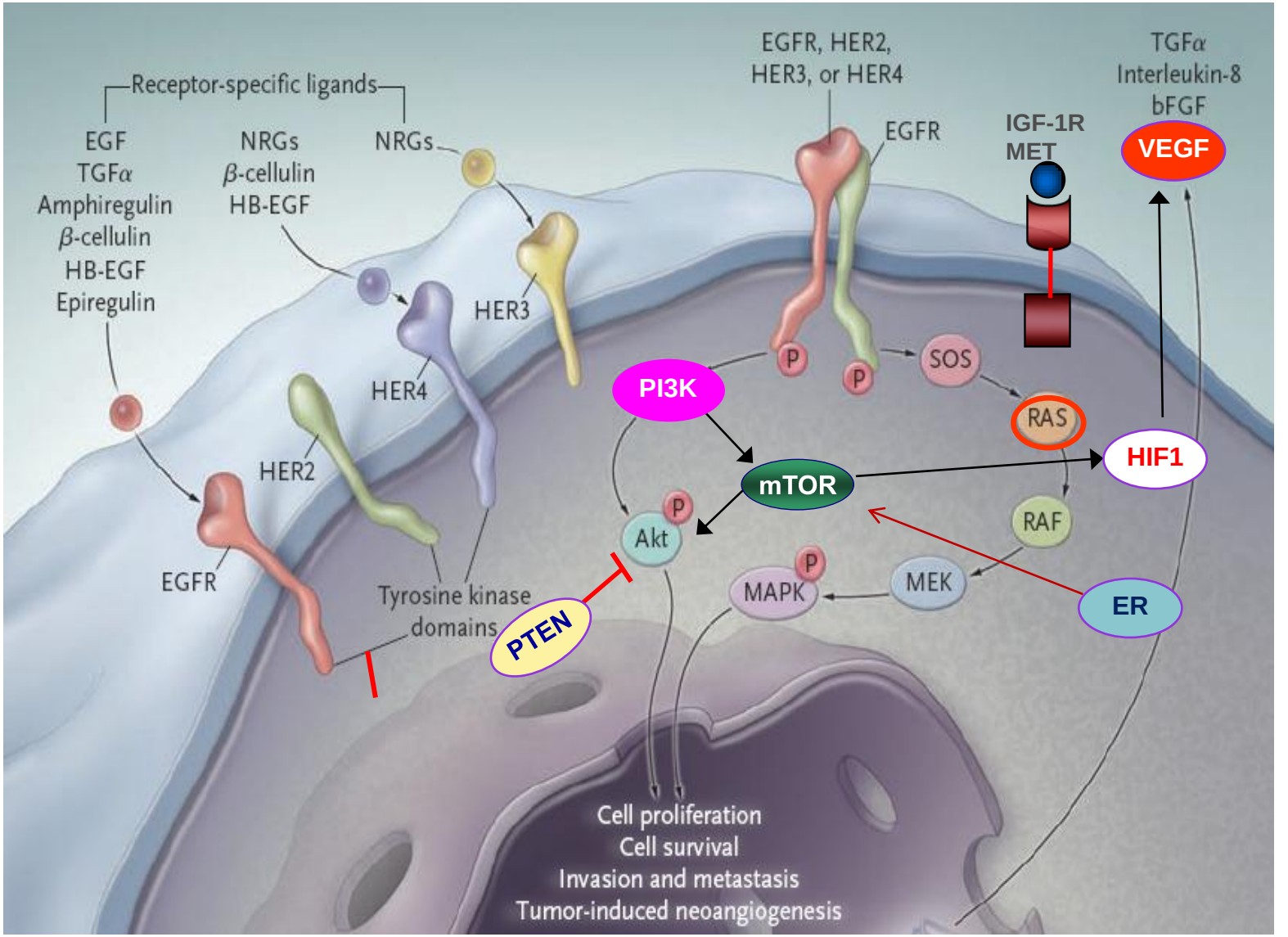
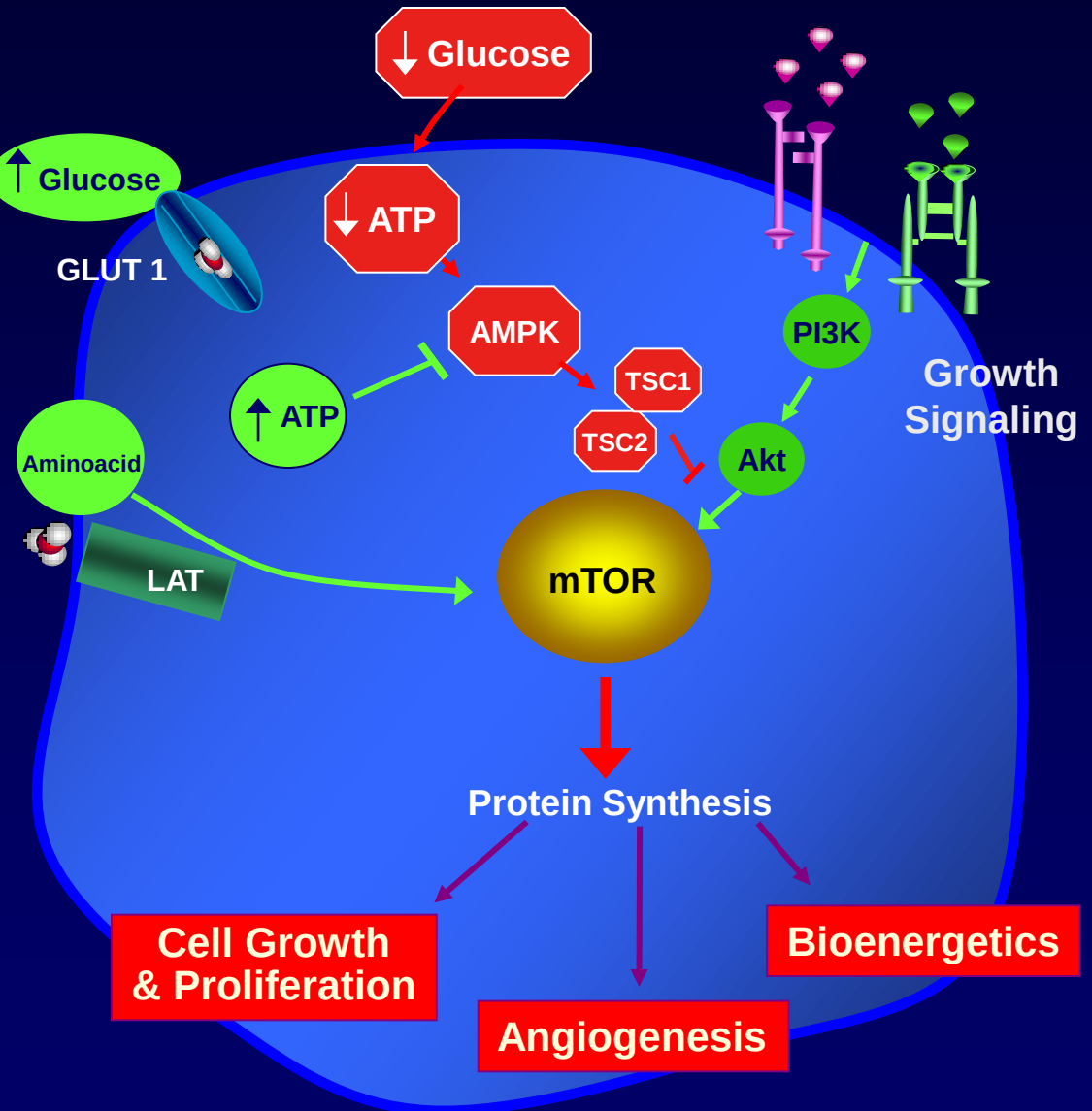
Verona

HER-dependent signalling pathways



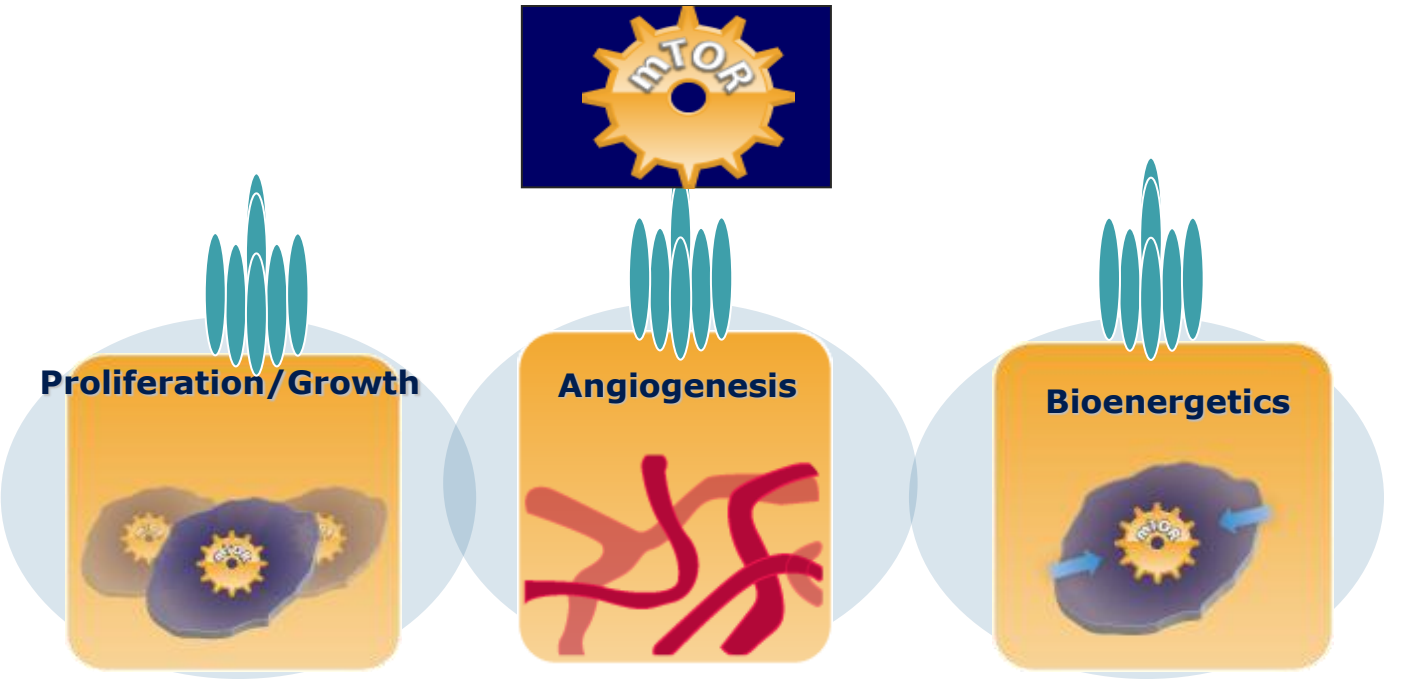
Ciardiello F & Tortora G, *New England J Medi 2008*

mTOR integrates the signals of nutrients and growth factors

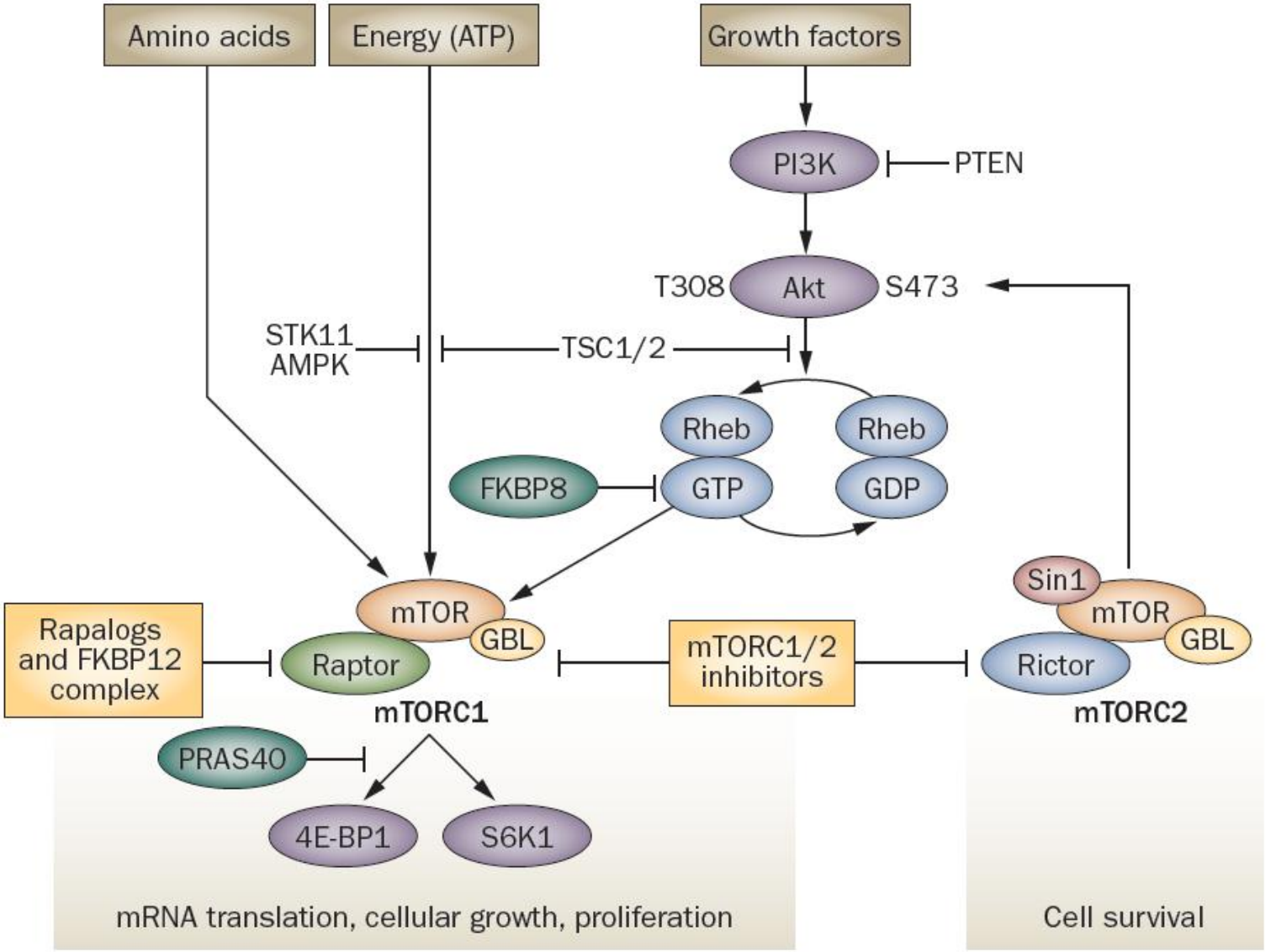


- mTOR senses availability of amino acids, metabolic fuel, and energy
- Nutrients and energy stores are essential for protein synthesis, cell growth, proliferation, and survival
- mTOR activation can increase the expression of nutrient transporters
- mTOR activation supports growth and survival by increasing cell access to nutrients and metabolic fuels

mTOR is a key machinery integrating the 3 pillars of growth: proliferation, angiogenesis and nutrient availability (bioenergetics)



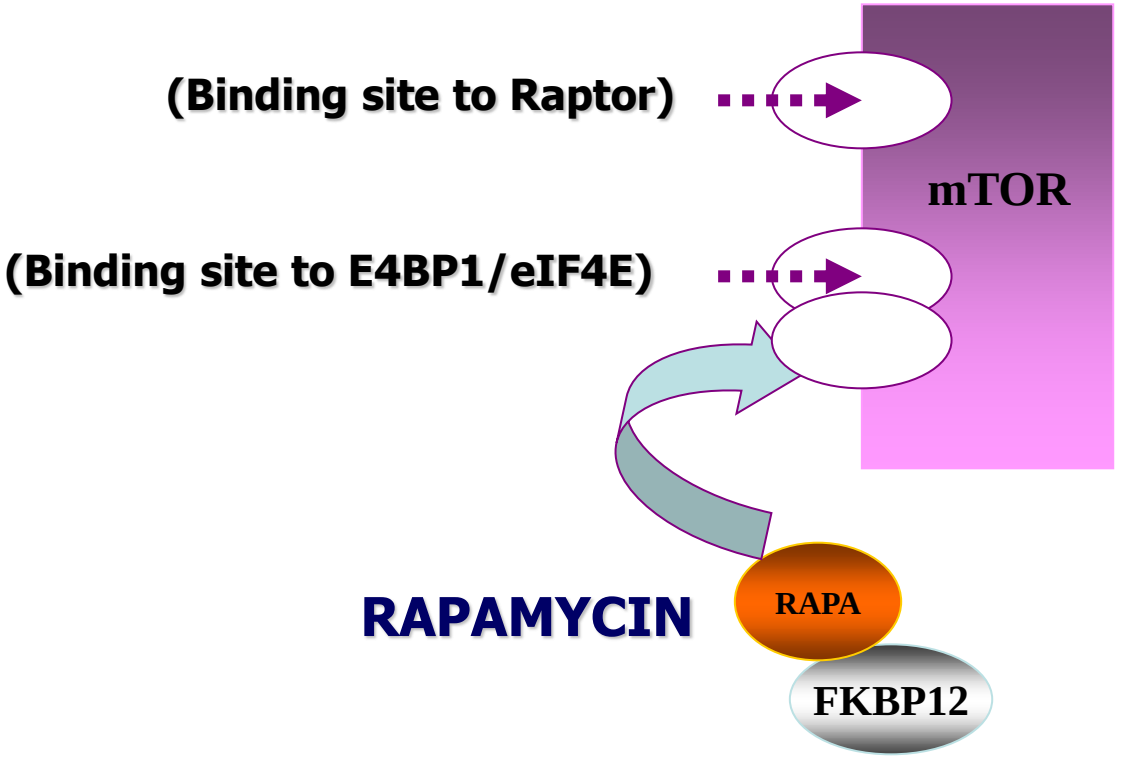
mTOR pathway and inhibitors

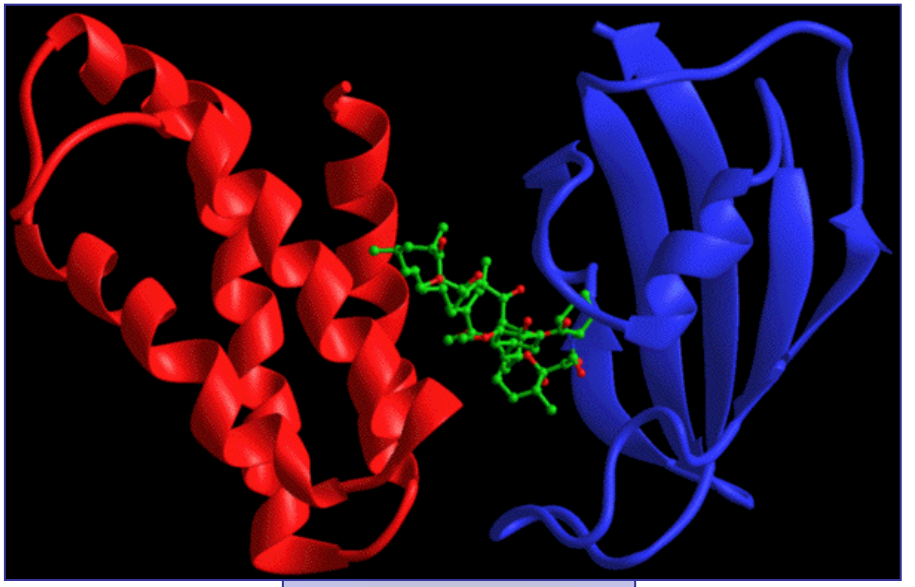


Dancey, J. *Nat. Rev. Clin. Oncol.* 7, 209–219 (2010);

RAPAMYCIN INTERACTIONS WITH mTOR/FKBP12

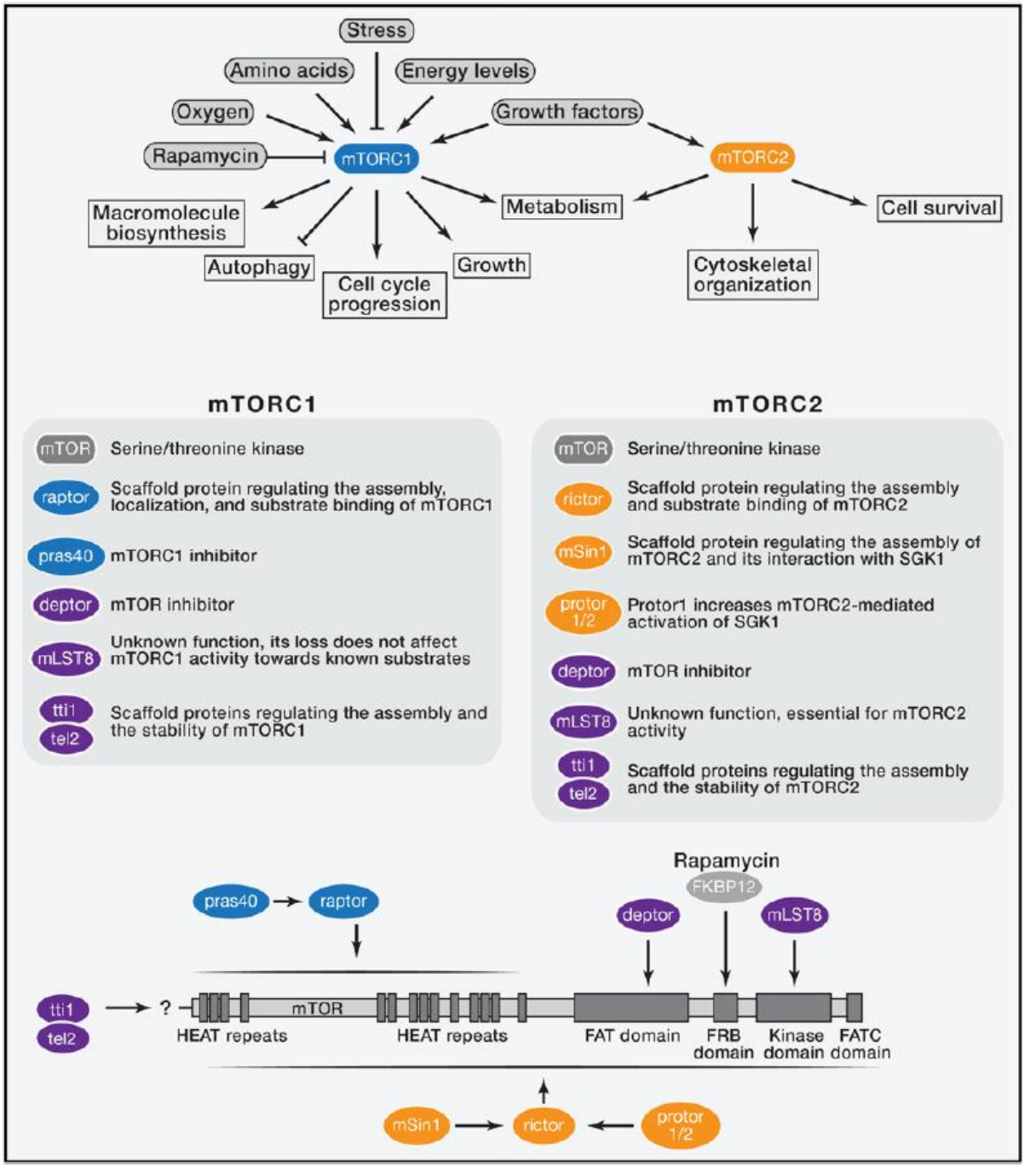
Rapamycin and FKBP12 create a drug-receptor complex that interacts with mTOR





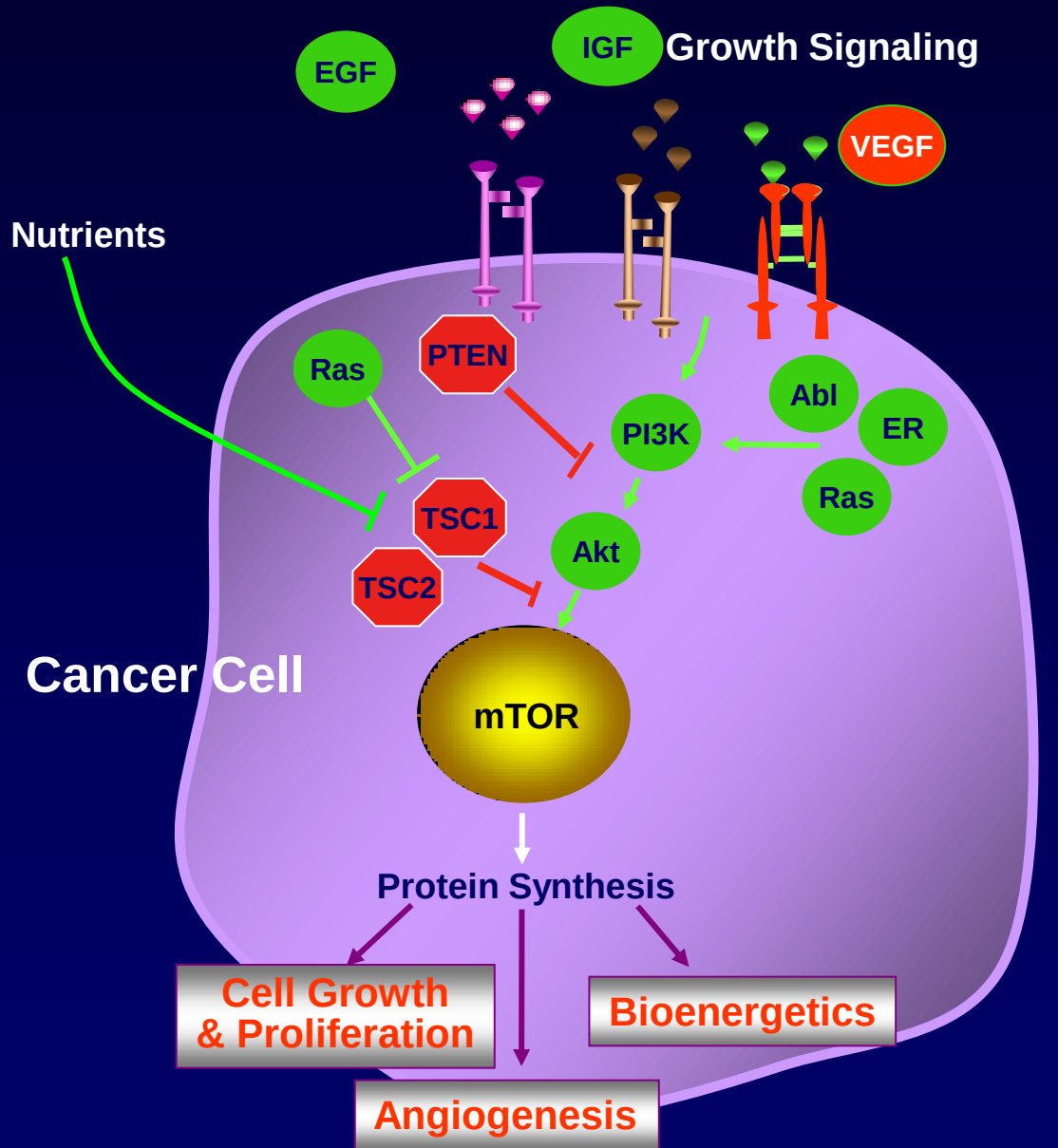
mTOR inhibition by rapamycin lasts for 5 days

mTORC1 and mTORC2



Laplante M and Sabatini DM, ***Cell*** 2012

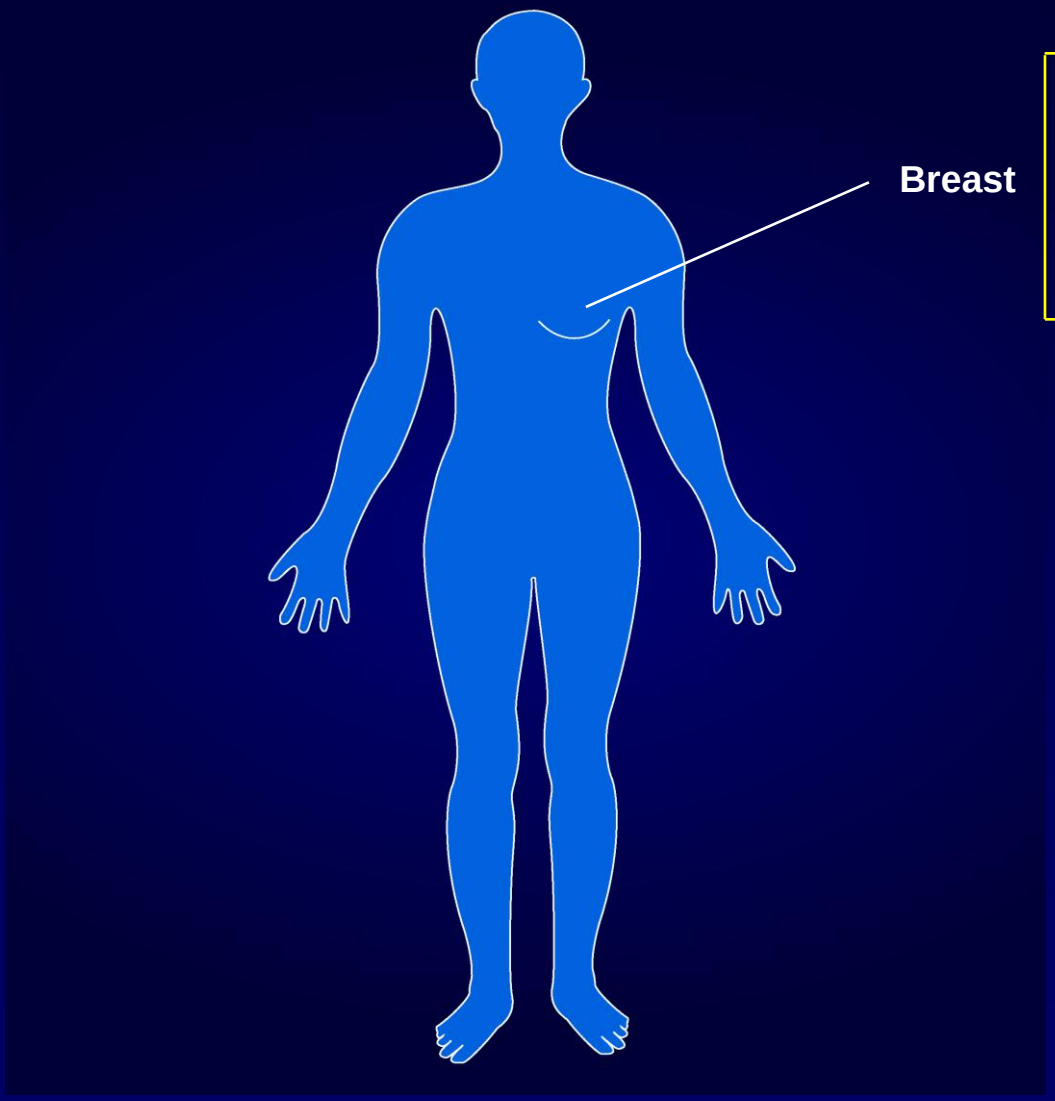
mTOR Pathway is deregulated by mutations in cancer



- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators[1,2]
- Regulators of mTOR activity
  - mTOR activating
  - mTOR deactivating
- Deregulation of mTOR can result in loss of growth control and metabolism[1,3]
- Mutations in the mTOR pathway have been linked to specific cancers[4]

Averous and Proud. *Oncogene*. 2006 ;25(48):6423-6435.
Mamane et al. *Oncogene*. 2006;25(48):6416-6422.
Ellisen. *Cell Cycle*. 2005;4(11):1500-1502.
Kaper et al. *Cancer Res*. 2006;66(3):1561-1569.

mTOR Pathway is Deregulated in Breast Cancer

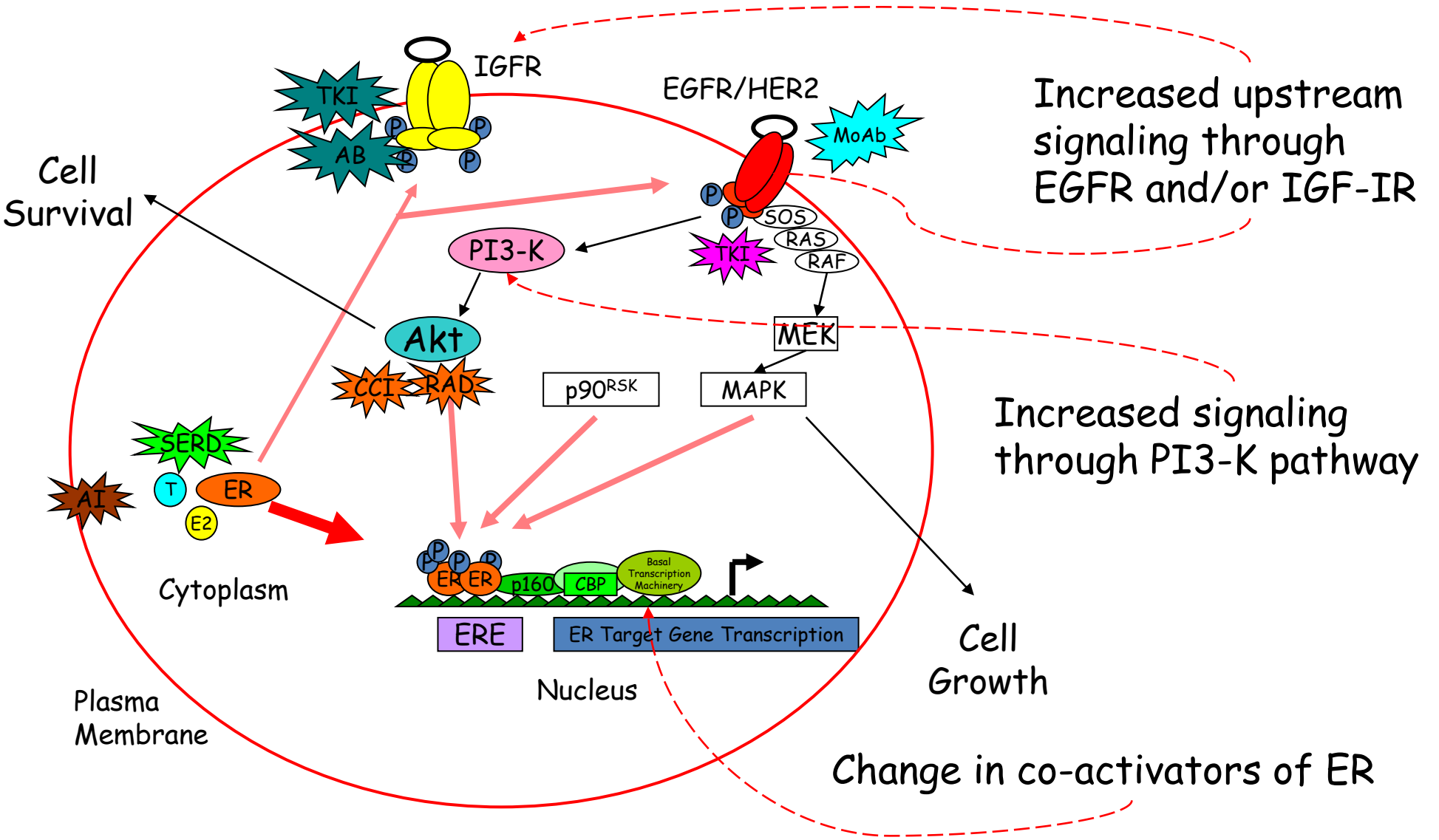


Mechanisms of resistance to anti-HER2 agents in breast cancer

Mechanisms of resistance	Factors involved
Alterations in binding sites or RTK domain	MUC4 $p95^{HER2}$, ECD mutations of TK domain
Overexpression of alternative ErbB ligands/ receptors dimerization	EGFR-HER2; HER2-HER3 etc. ErbB ligands (TGFα, EGF, HB-EGF, Heregulin etc.)
Dimerization/interaction with other structurally unrelated receptors	IGF1-R MET
Loss of downstream controllers	PTEN
Activation of downstream signaling pathways	PI3K-Akt MEK MAPK/Erk mTOR
Other factors	Notch Microenvironment Chemokine receptors and Integrins Metabolism Host-related factors Stem cells

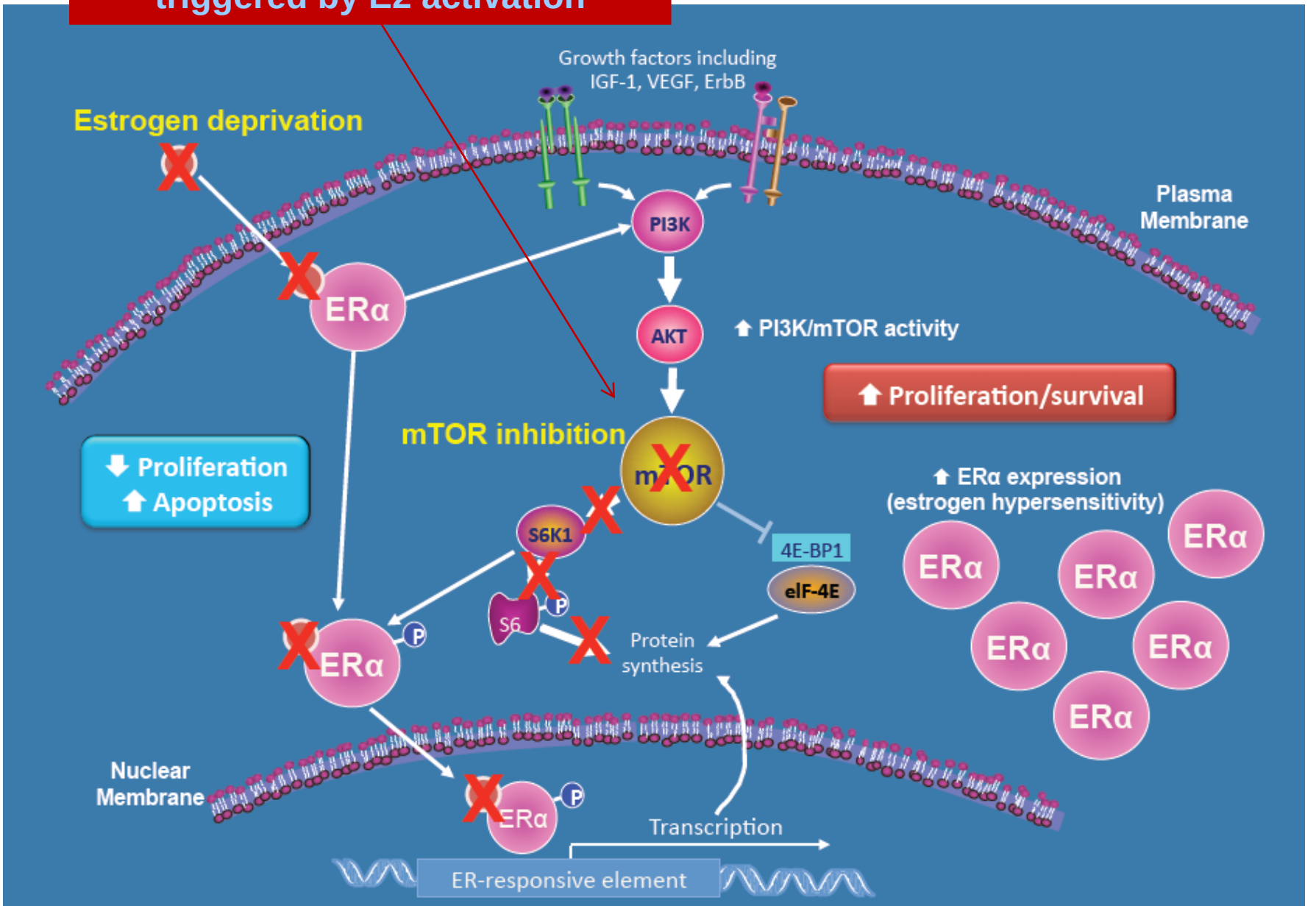
Tortora G, *J Natl Cancer Inst*, 2012

Mechanisms of SERM Resistance



From Johnston *CCR*. 2005.

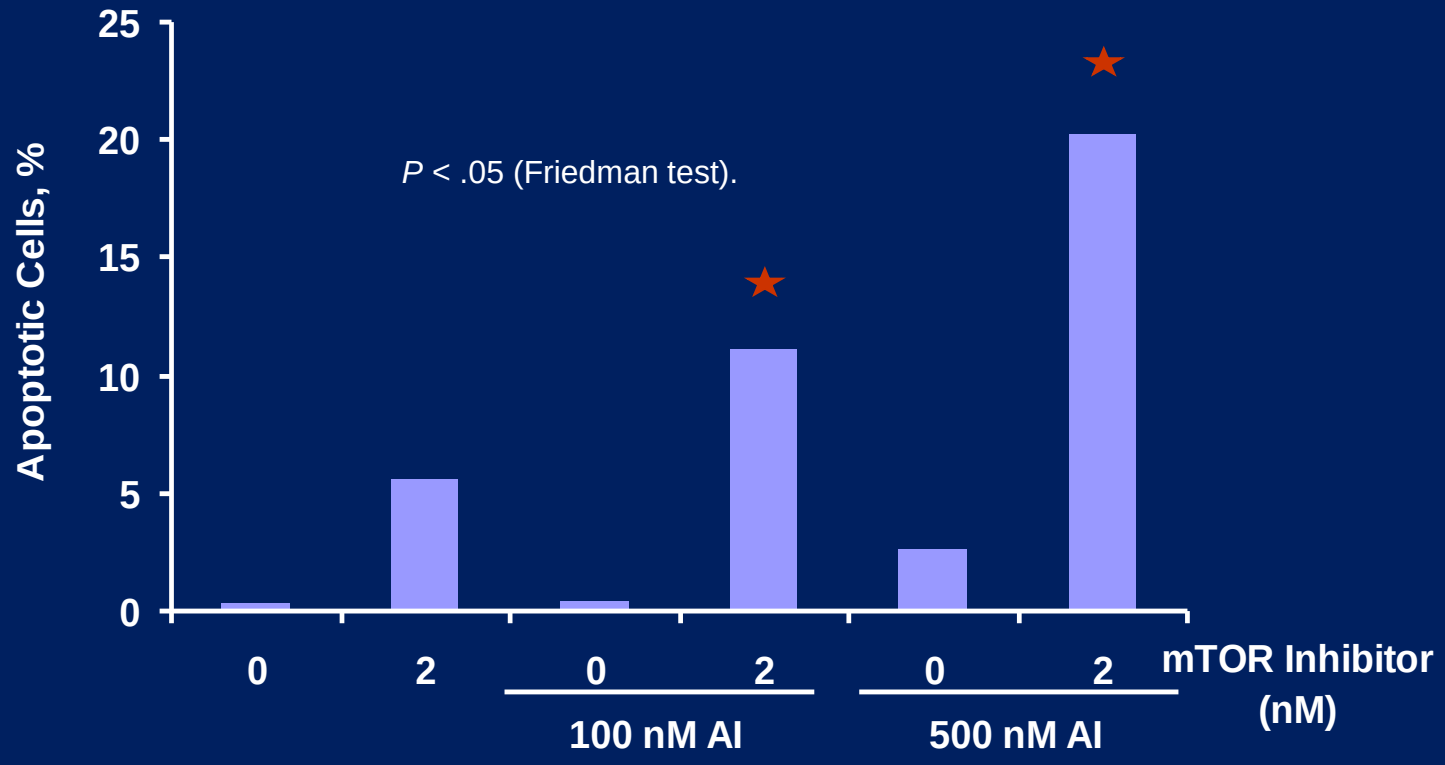
mTOR transduces the signal triggered by E2 activation



1. Bjornsti MA, et al. *Nat Rev Cancer*. 2004;34(5):335-348; 2. Crespo JL, et al. *Microbiol Mol Biol Rev*. 2002;66(4):579-591; 3. Huang S, et al. *Cancer Biol Ther*. 2003;2(3):222-232; 4. Mita MM, et al. *Clin Breast Cancer*. 2003;4(2):126-137; 5. Wullschleger S, et al. *Cell*. 2006;124(3):471-484; 6. Johnston SR. *Clin Cancer Res*. 2005;11(2 pt 2):889s-899s.

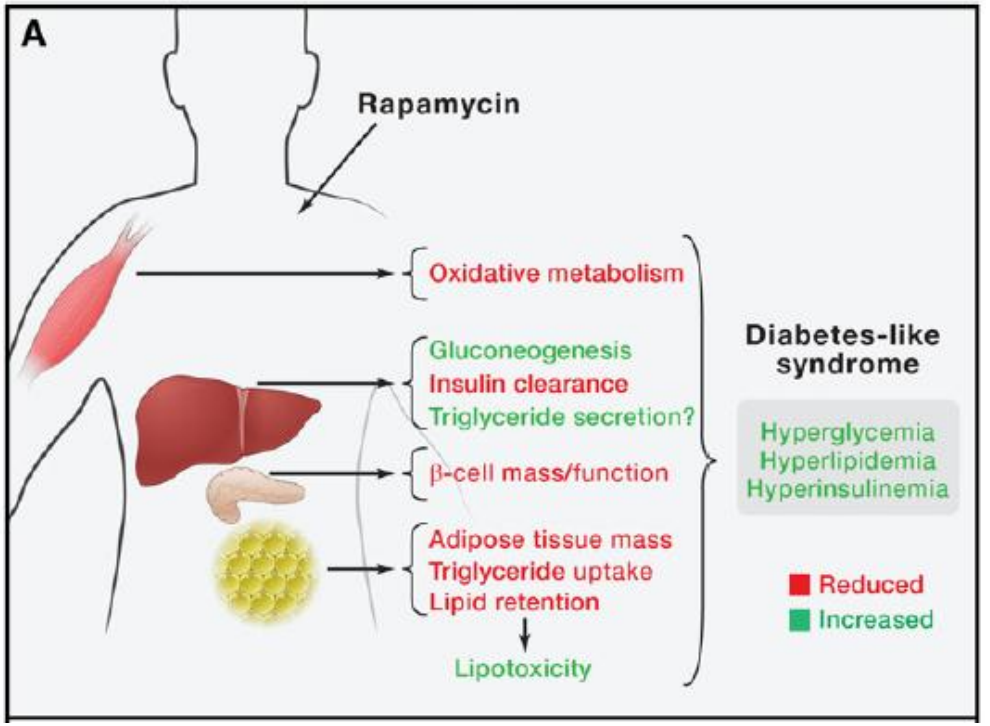
Dual mTOR and Aromatase Inhibition Induces Apoptosis in Breast Cancer Models

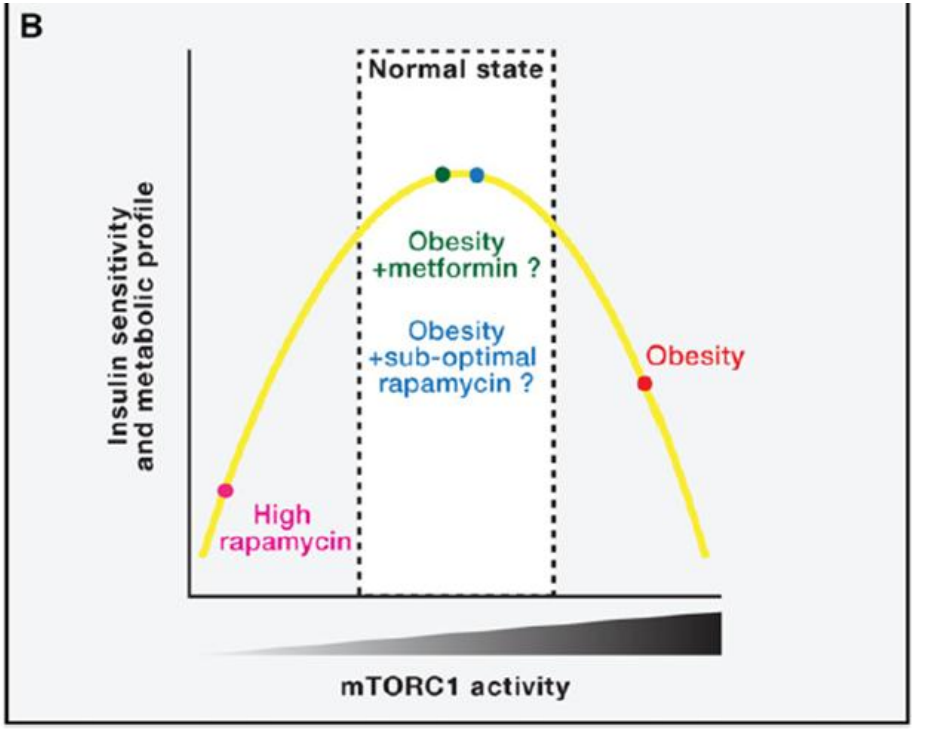
- RAD001 and letrozole combination preclinical studies in MCF7/Aro and T47D/Aro breast cancer cell lines expressing endogenous aromatase – striking combination effects were observed
  - Synergistic effect on inhibition of proliferation, decreased cell cycle progression and cell viability
  - Results show promise in treatment of estrogen-sensitive breast cancers that have not yet developed resistance

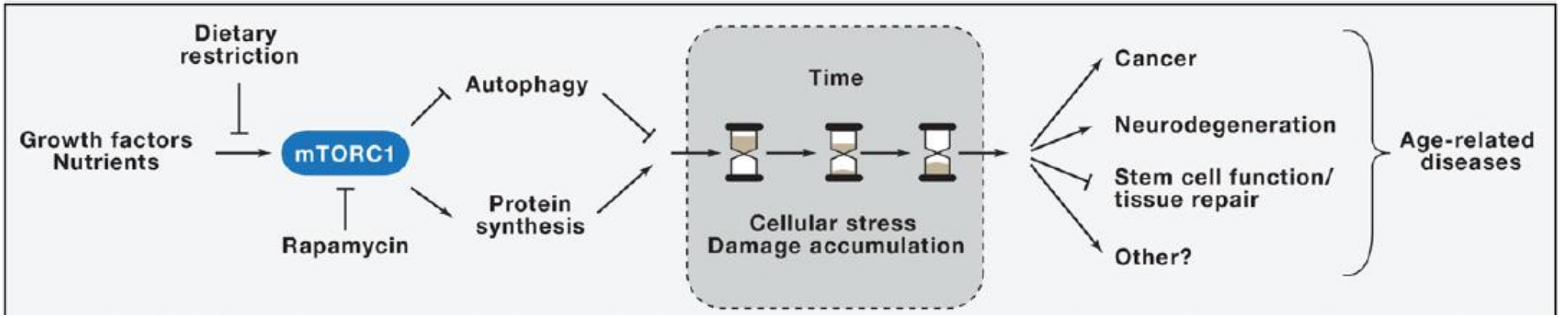


Modified from Boulay et al. *Clin Cancer Res*. 2005;11:5319-5328

mTOR, obesity, insulin and aging

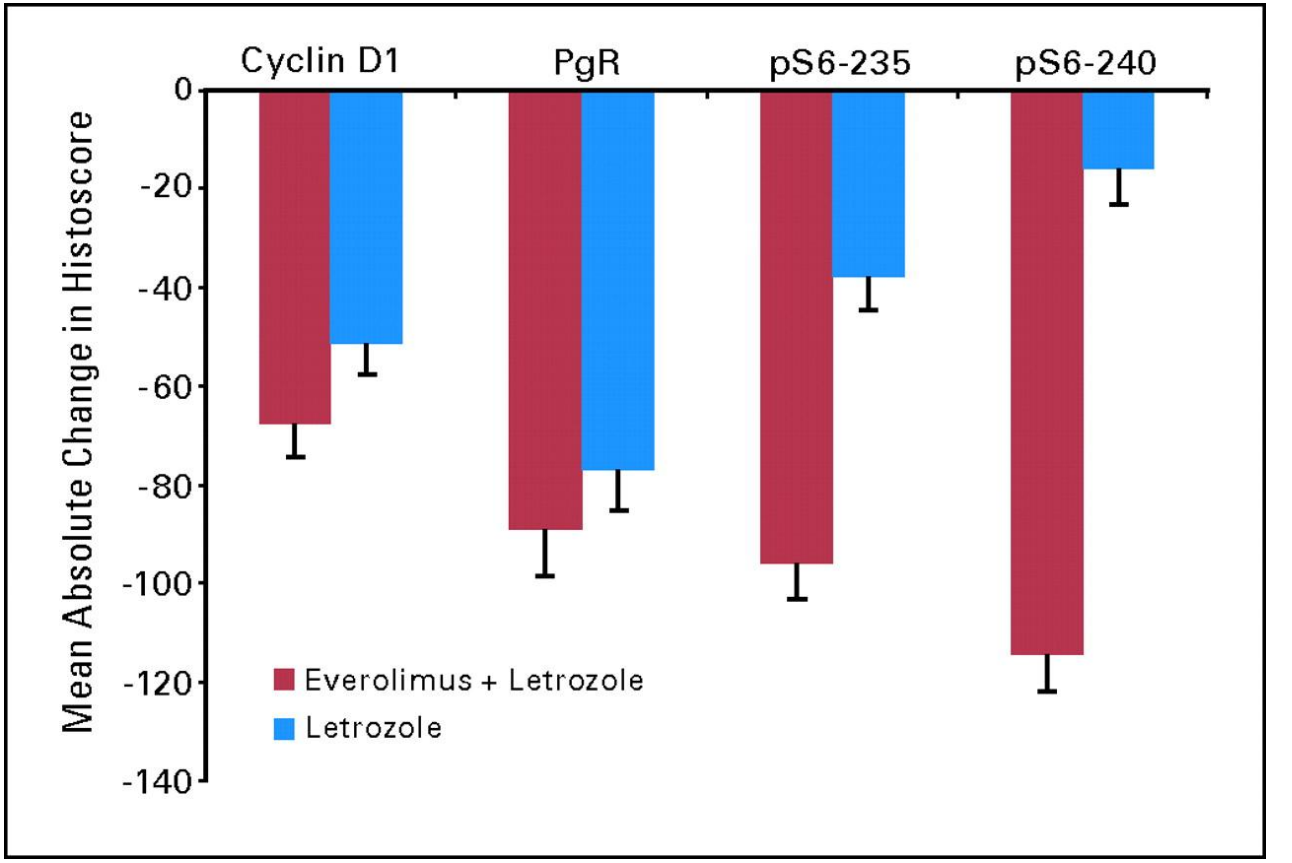






Laplante M and Sabatini DM, ***Cell*** l 2012

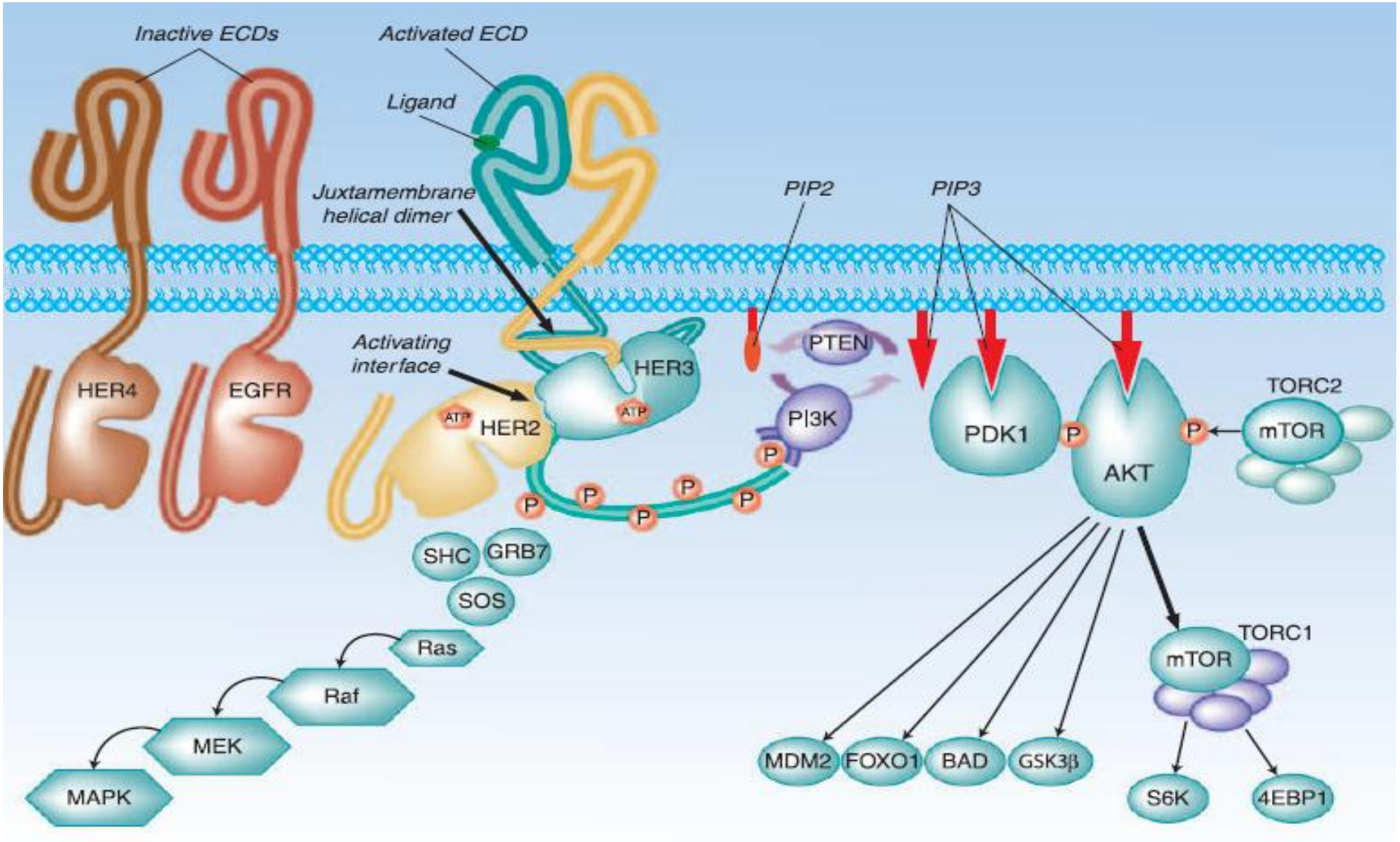
Absolute change in histoscore from baseline to day 15 for cyclin D1, PgR, pS6-235, and pS6-240 in the letrozole and letrozole-plus-everolimus arms.



Subgroup of patients with higher level of mTOR activity (pS6K) at baseline had a higher RR (82% vs 60%).

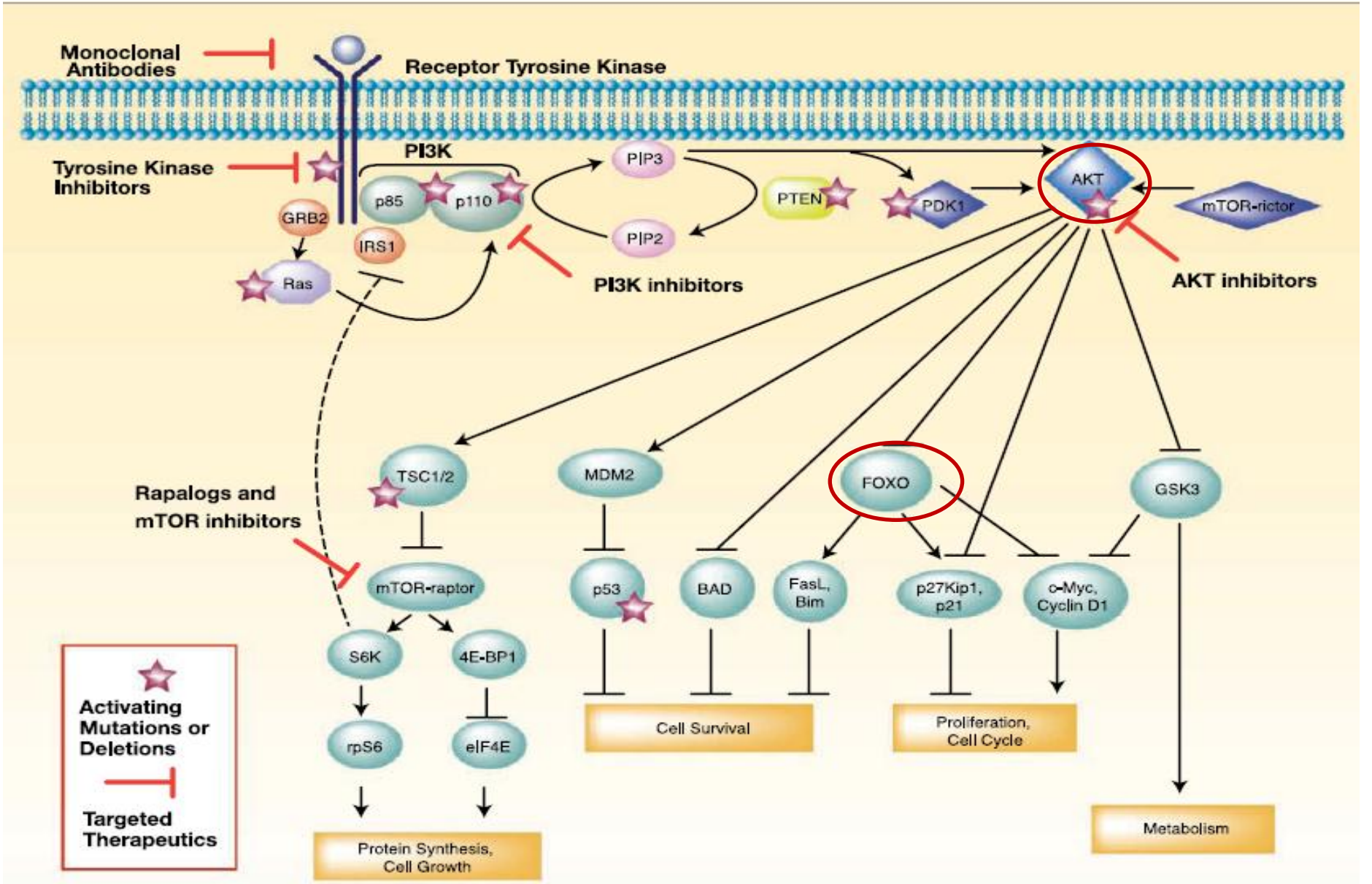
Baselga J et al. JCO 2009;27:2630-2637

HER3 ENGAGED IN SIGNALING



Campbell M.R: et al., Clin Cancer Res; 16: 1373–83., 2010

Signal through class I PI3Ks



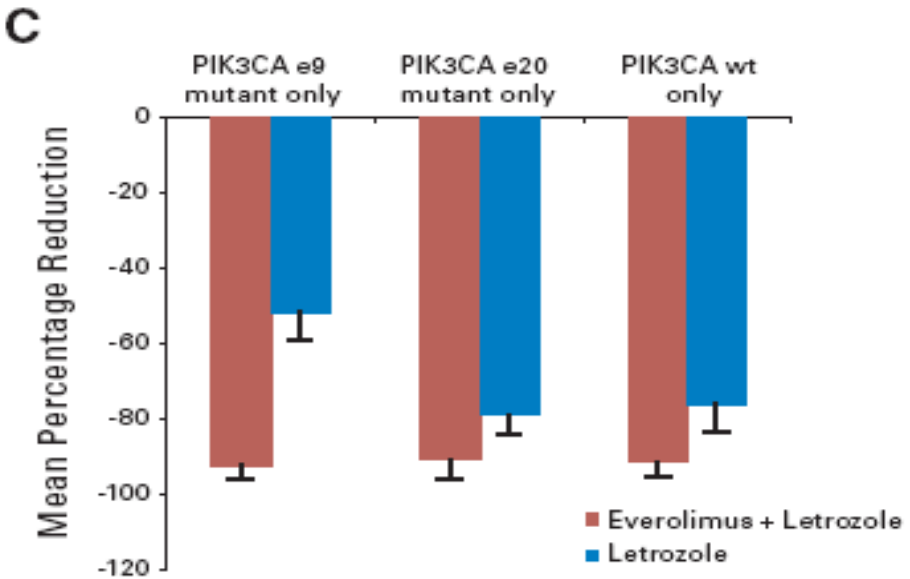
Di Cosimo & Baselga. *Clin Cancer Res* 2009;15:5017–9

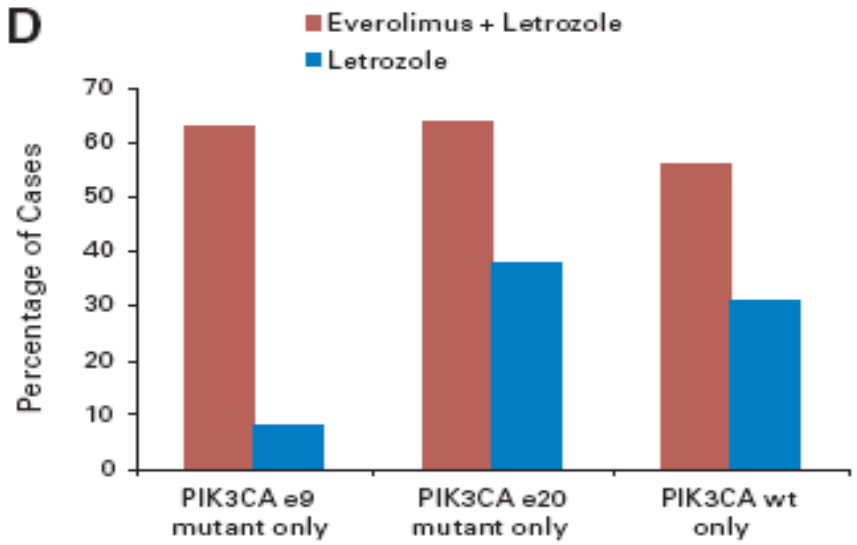
Aberrancies in the PI3K/AKT/mTOR pathway by breast cancer subtype

Subtype	Aberration	Frequency
All breast tumors	*PIK3CA*	10%–40%
	PTEN	~50%
	AKT	5%–24%
HR-positive tumors	*PIK3CA*	35%–40%
	PTEN	2%–4%
	AKT	2%–3%
Triple negative breast cancer	*PIK3CA*	8%–9%
	PTEN	15%–30%
	AKT	0%
HER2 amplified	*PIK3CA*	20%–25%
	PTEN	30%–40%
	AKT	0%

Hernandez-Aya LF and Gonzales Angulo AM The Oncologist, 16: 404-414, 2011

Biomarker analysis: PI3-Kinase

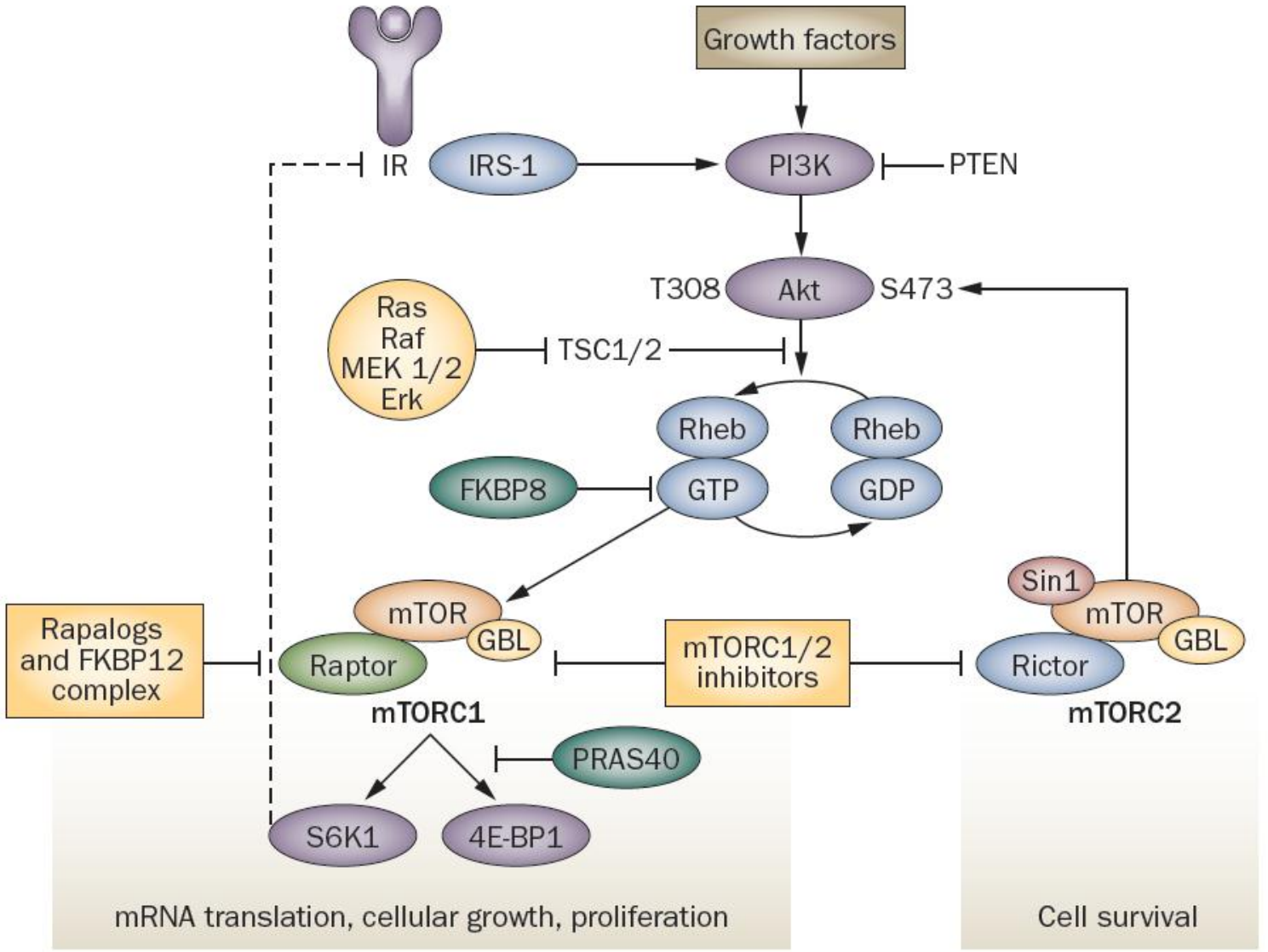




Exploring the relationship between PIK3CA mutation and Ki67, the small number of exon 9 allosteric domain mutants showed a relatively poor antiproliferative response to letrozole alone but a good response to letrozole plus everolimus

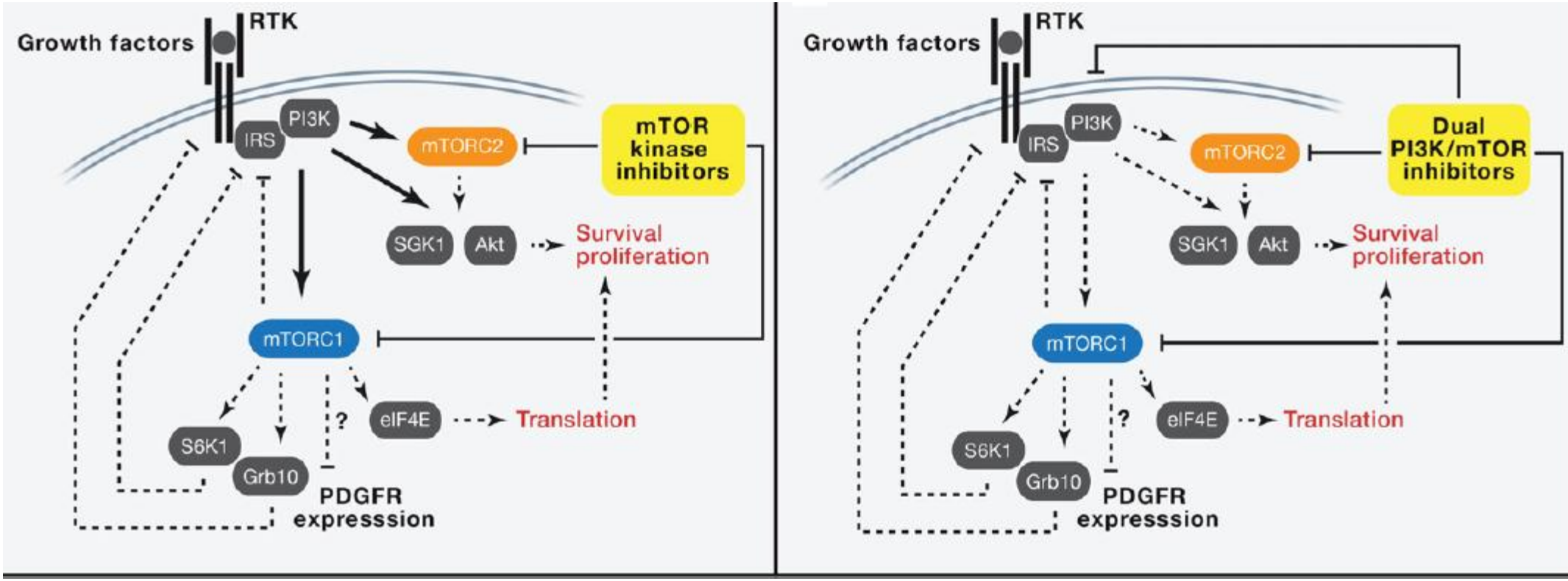
Baselga J et al. JCO 2009;27:2630-2637

Feedback loops in mTOR pathway and inhibitors



Dancey, J. *Nat. Rev. Clin. Oncol.* 7, 209–219 (2010);

Inhibition of mTORC1 and mTORC2



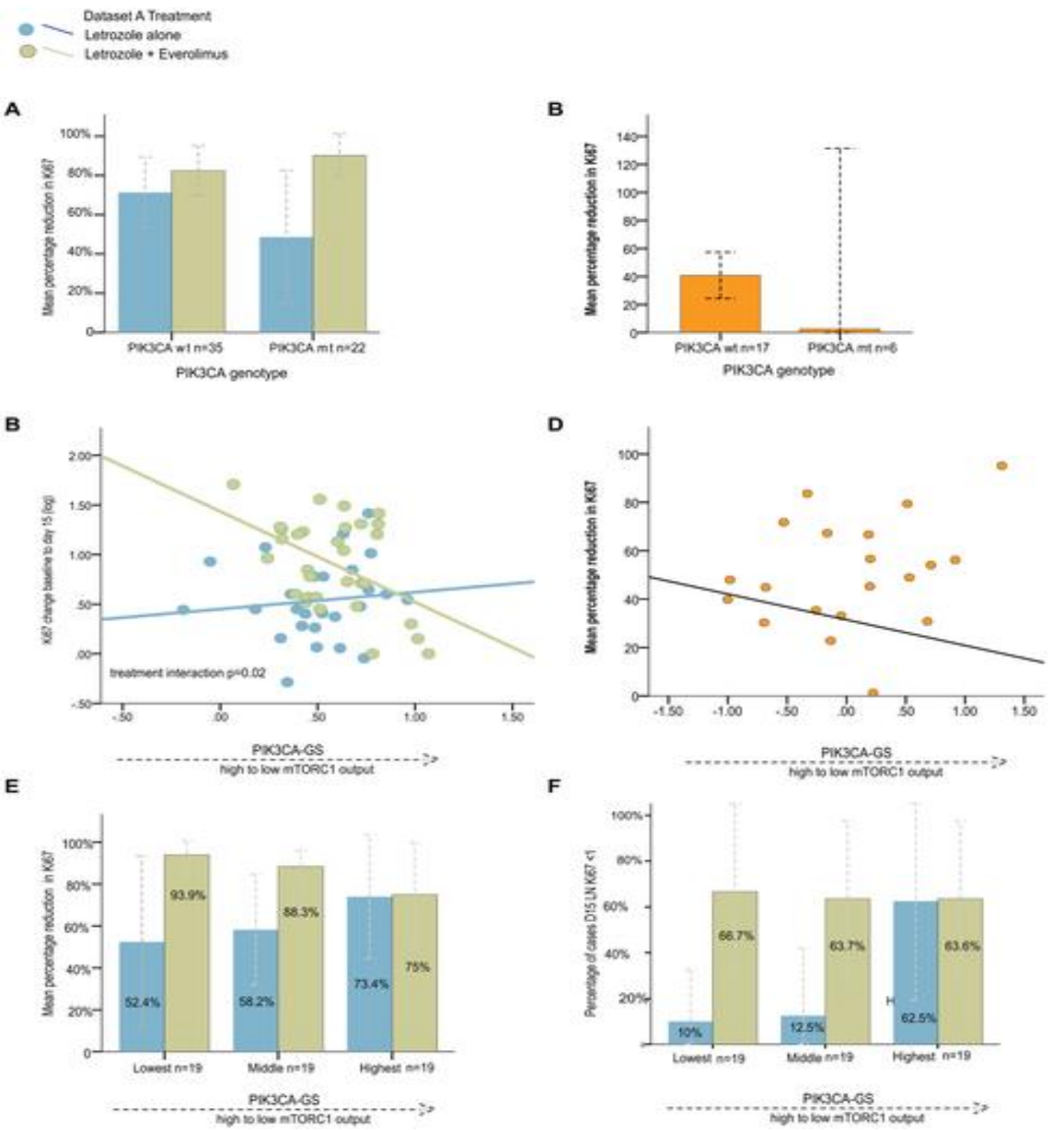
Laplante M and Sabatini DM, ***Cell***l 2012

PI3K/mTOR inhibitors being investigated for treatment of HR-positive advanced breast cancer

Agents	Phase	Patient population	Treatment	Clinicaltrials.gov
mTOR inhibitors				
Ridaforolimus	II	ER+, HER2− advanced BC	Ridaforolimus + dalotuzumab vs exemestane vs ridaforolimus or dalotuzumab monotherapy	NCT01234857
	II	ER+, HER2− advanced BC	Ridaforolimus + dalotuzumab vs exemestane vs ridaforolimus + exemestane	NCT01605396
AZD2014	I	ER+ advanced BC	AZK2014 + fulvestrant	NCT01597388
PI3K inhibitors				
XL147	I/II	ER+, HER2− BC refractory to nonsteroidal AI	XL147 + letrozole	NCT01082068
BKM120	III	ER+, HER2− BC refractory to nonsteroidal AI	BKM120 + fulvestrant vs placebo + fulvestrant	NCT01610284
	I	HR+ advanced BC	BKM120 + letrozole Intermittent BKM120 + letrozole	NCT01248494
	I	ER+ stage IV BC	BKM120 + fulvestrant	NCT01339442
GDC-0941	II	HR+ advanced BC resistant to AI	GDC-0941 + fulvestrant vs placebo + fulvestrant	NCT01437566
Dual PI3K/mTOR inhibitors				
XL765	I/II	ER+, HER2− BC refractory to nonsteroidal AI	XL765 + letrozole	NCT01082068
BEZ235	I	HR+ advanced BC	BEZ235 + letrozole	NCT01248494
PF-04691502	II	ER+, HER2− early BC	PF-04691502 vs PF-04691502 + letrozole vs letrozole	NCT01430585
GDC-0980	II	HR+ advanced BC to AI	GDC-0980 + fulvestrant vs placebo + fulvestrant	NCT01437566

Shtivelband MI, The Breast (2013),

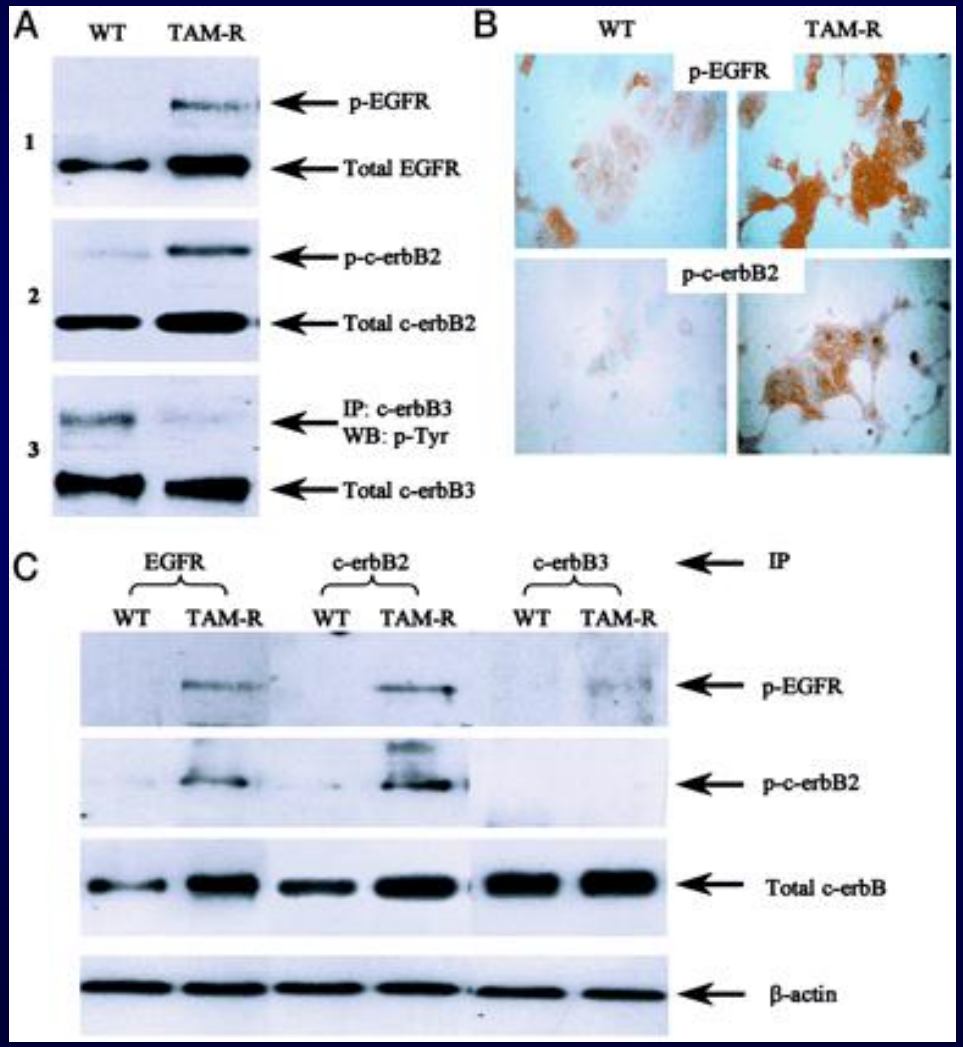
PIK3CA Genotype and a PIK3CA Mutation-Related Gene Signature and Response to Everolimus and Letrozole in ER Positive Breast Cancer

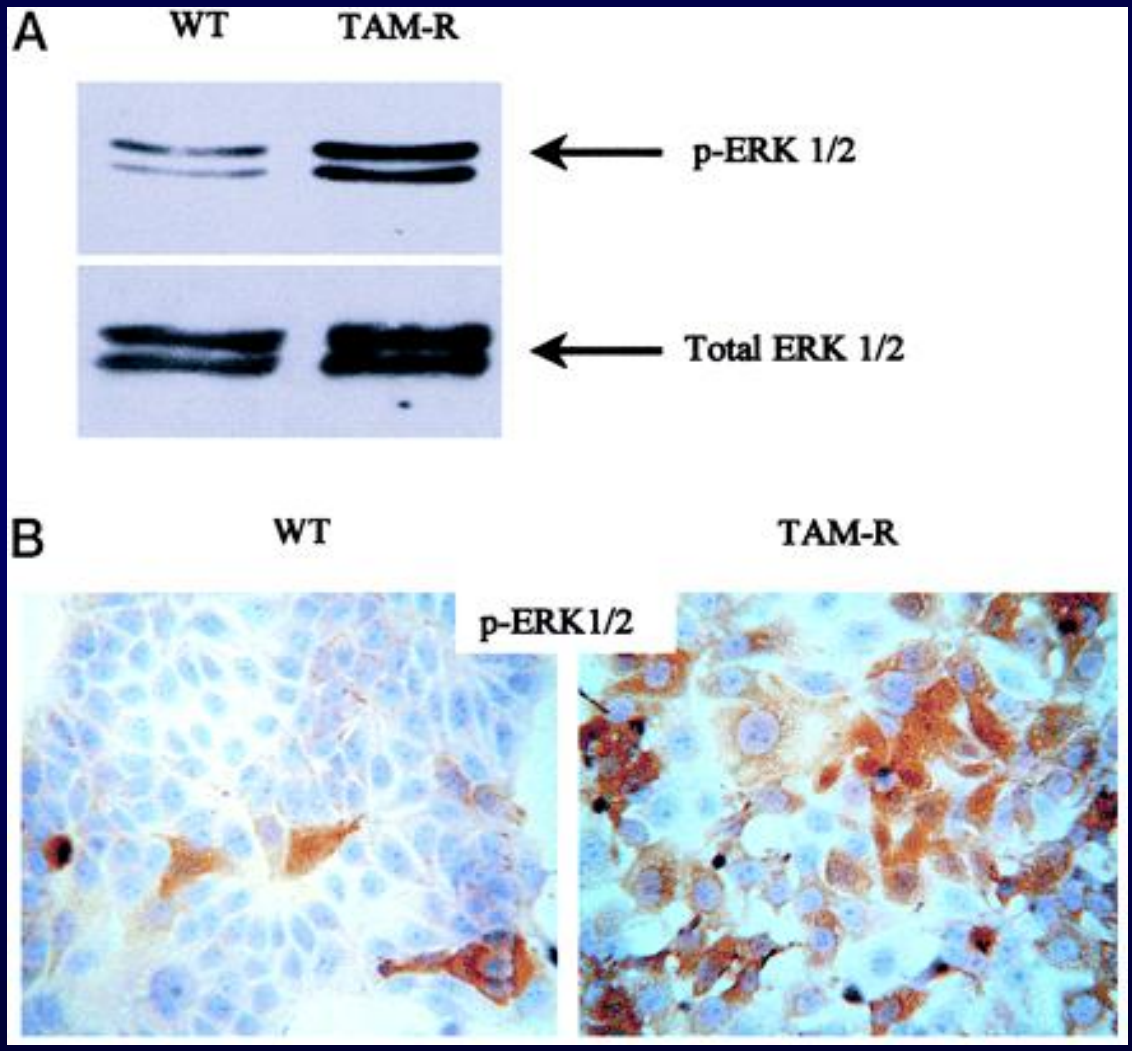


Relative change in % Ki67 from baseline to day 15 by treatment arm.

Loi S et al., *PLoS ONE* 8(1) 2013

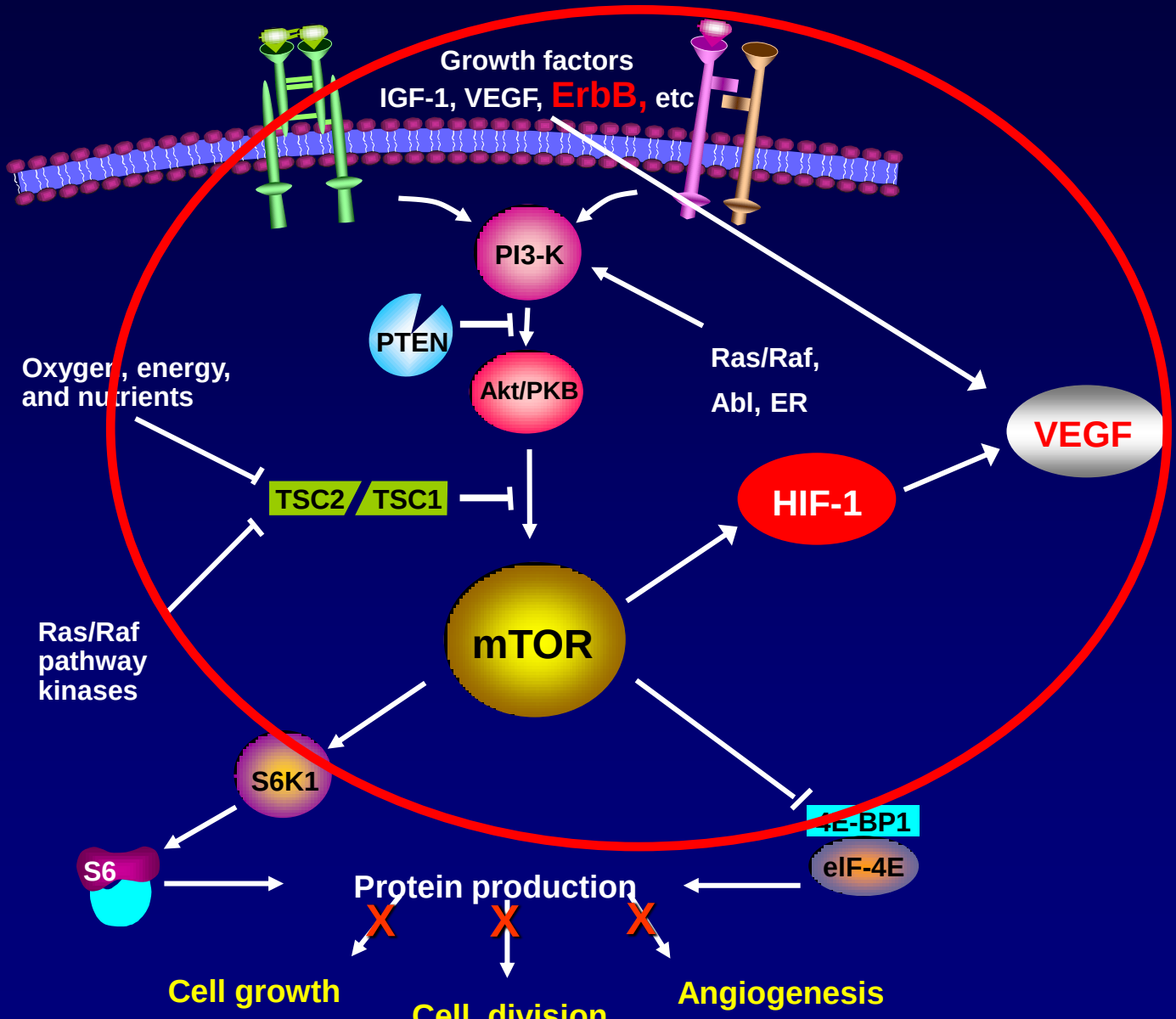
Increase of activated EGFR/HER2 dimers in tamoxifen-resistant breast cancer cells



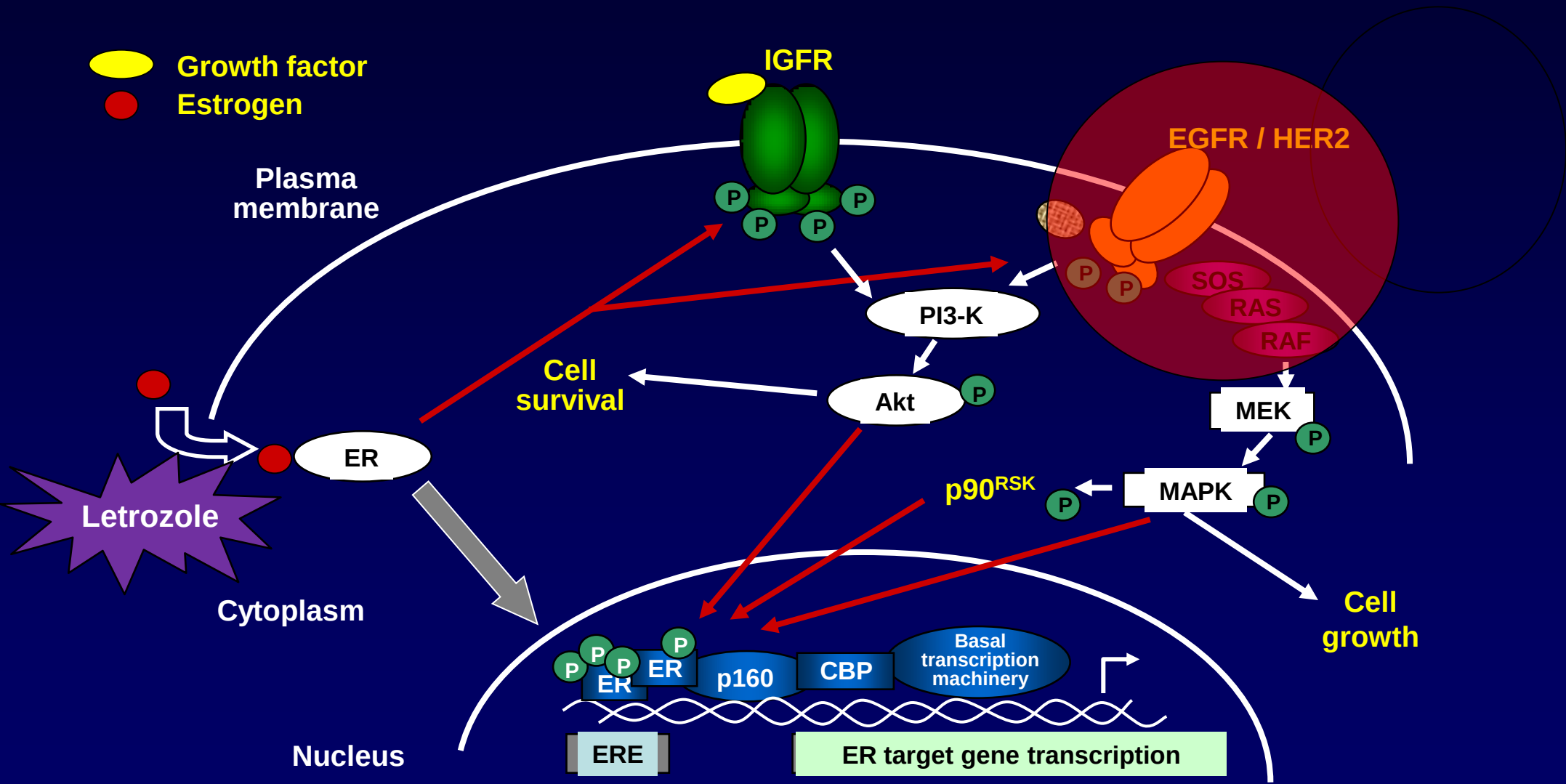


Knowlden et al., Endocrinology 2003

The mTOR pathway is functionally linked to ErbB/HER and VEGF

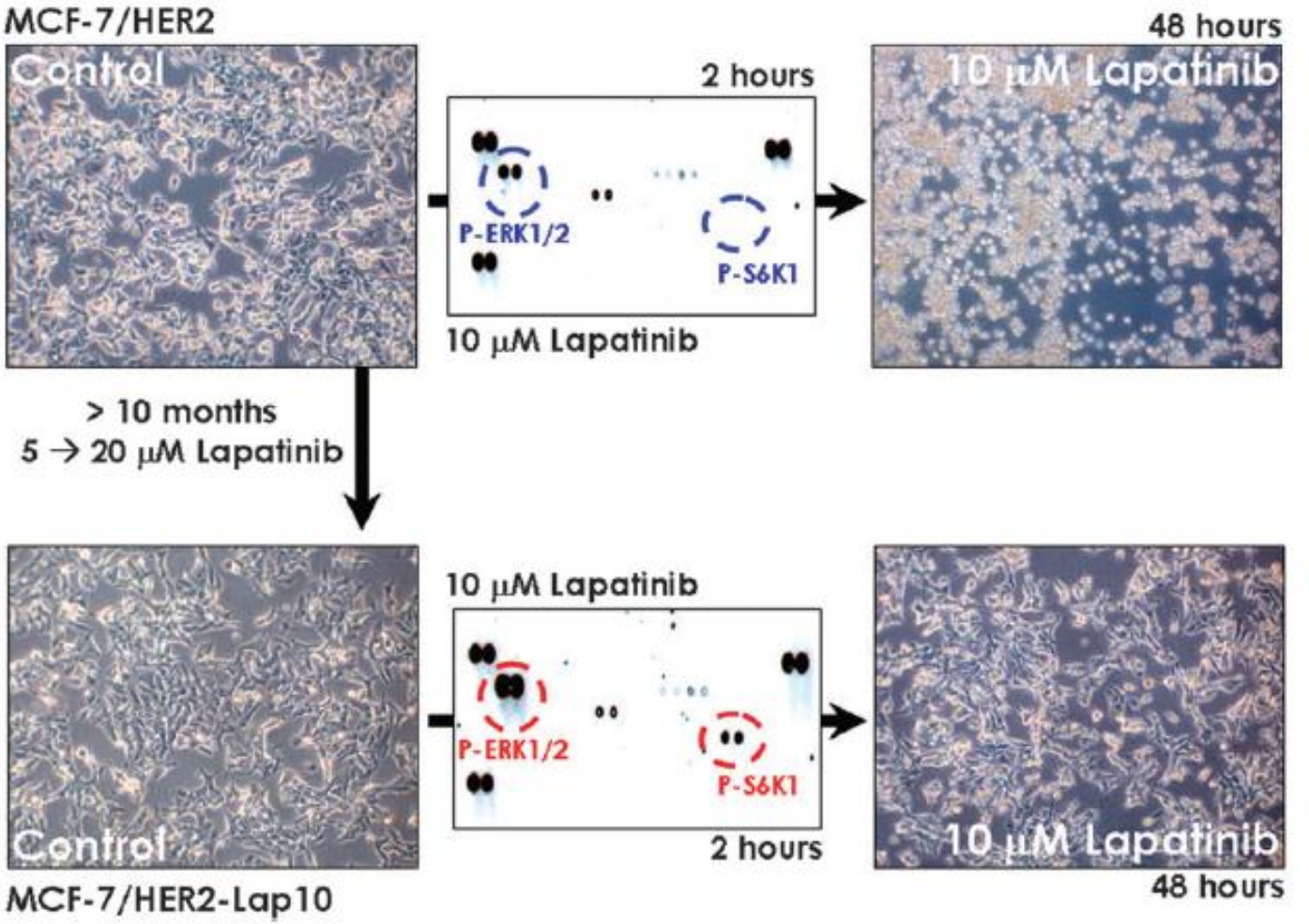


Cross-Talk Between Signal Transduction and Endocrine Pathways



Adapted from Johnston S. *Clin Cancer Res*. 2005;11:889S-899S.

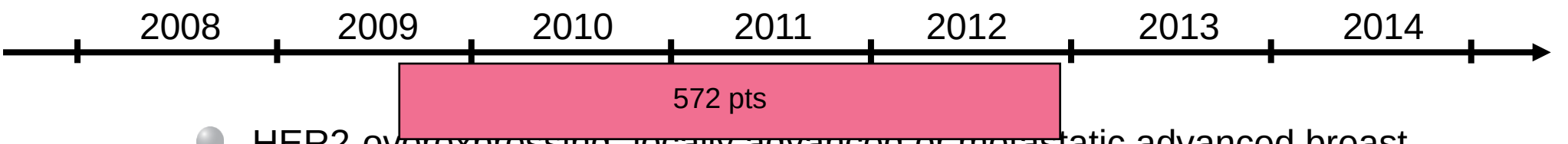
Phosphoproteome analysis identifies the mTOR effector p70S6K1 as a specific biomarker for lapatinib resistance



Vasquez-Martin A., Annals of Oncology 19: 1097–1109, 2008

Phase III Study W2301: vinorelbine + trastuzumab ± everolimus in trastuzumab-resistant and taxane-pretreated HER2+ advanced breast cancer

BOLERO-3
Breast cancer trials of OraL EveROlimus



- HER2-overexpressing, locally advanced or metastatic advanced breast cancer, prior taxane therapy and resistant to trastuzumab*
- Stratification by prior lapatinib (Yes vs No)

SCREEN
<21 days prior to Day 1

Randomize
1:1
N=572

Everolimus 5.0 mg p.o. daily
Vinorelbine 25 mg/m^2 Days 1, 8, 15
Trastuzumab 2 mg/kg† Days 1, 8, 15

Placebo po daily
Vinorelbine 25 mg/m^2 Days 1, 8, 15
Trastuzumab 2 mg/kg† Days 1, 8, 15

1 cycle = 21 days

PFS

Survival
ORR
CBR
Safety

PK
Biomarkers

* Trastuzumab resistance defined as progression on adjuvant trastuzumab ≤ 12 months of last infusion, or progression while on or ≤ 4 weeks of receiving last dose of trastuzumab for metastatic disease

Cancer Therapy: Preclinical

Clinical Cancer Research

Dual mTORC1/2 and HER2 Blockade Results in Antitumor Activity in Preclinical Models of Breast Cancer Resistant to Anti-HER2 Therapy

Celina García-García[1], Yasir H. Ibrahim[1], Violeta Serra[1], Maria Teresa Calvo[1], Marta Guzmán[1], Judit Grueso[1], Claudia Aura[2], José Pérez[1], Katti Jessen[3], Yi Liu[3], Christian Rommel[3], Josep Tabernero[1], José Baselga[4,5], and Maurizio Scaltriti[4,5]

The simultaneous blockade of both PI3K/Akt/mTOR and ERK pathways obtained by combining lapatinib with INK-128 acts synergistically in inducing cell death and tumor regression in breast cancer models refractory to anti-HER2 therapy

Garcia-Garcia et al *Clin Cancer Res;* 18(9); 2603-12.