Modeling Anti-Cancer Therapies: Targeting Simple Mechanisms in Complex Networks

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Overview

- State of the 'War on Cancer'
  - Challenges
  - Signs of promise
- Introducing a new conceptual framework for cellular networks: focusing on mechanisms
- Mathematical models of targeted therapies:-
  - mTOR pathway
  - Combination therapies

Cancer Statistics: Progress on the 'War on Cancer'

- ½-million people will die of cancer in the United States in 2008 (ACS)
- Cancer currently accounts for nearly ¼ of deaths in the U.S., exceeded only by heart disease
- 1.4 million new cases of cancer will be diagnosed in 2008 (ACS)
- 1971: President Richard Nixon declared the 'War on Cancer'; cancer death rates have remained approximately the same since that time while death rates for other major chronic diseases have diminished significantly.

Cancer R&D Spending

- US$200 billion of public and private investment in basic and clinical cancer research in the U.S. since 1971
- Oncology is one of the most active sectors of therapeutic development
  - R&D spending by pharmaceutical industry > US$50 billion annually, ↑ 147% since 1993
  - Drug approval applications ↑ 38%
  - Approval rates for drugs against NEW targets: only 2-3 from entire industry each year

Technological Advances

- 'Omics technologies (genomics, proteomics)
  - Gene arrays, protein arrays
- High-performance computing/data-mining/digital storage technologies
- Technologies to create, screen, test & evaluate targeted chemical compounds

Successes in Molecularly Targeted Therapeutics

- Imatinib mesylate (Gleevec; Novartis)
  - Chronic myelogenous leukaemia (CML)
  - BCR/ABL oncogene

- Gefitinib (Iressa; AstraZeneca)
  - Non-small-cell lung cancer (NSCLC)
  - Somatic mutations in EGFR: L858R, ΔE749-A750

*** Tumor recurrence

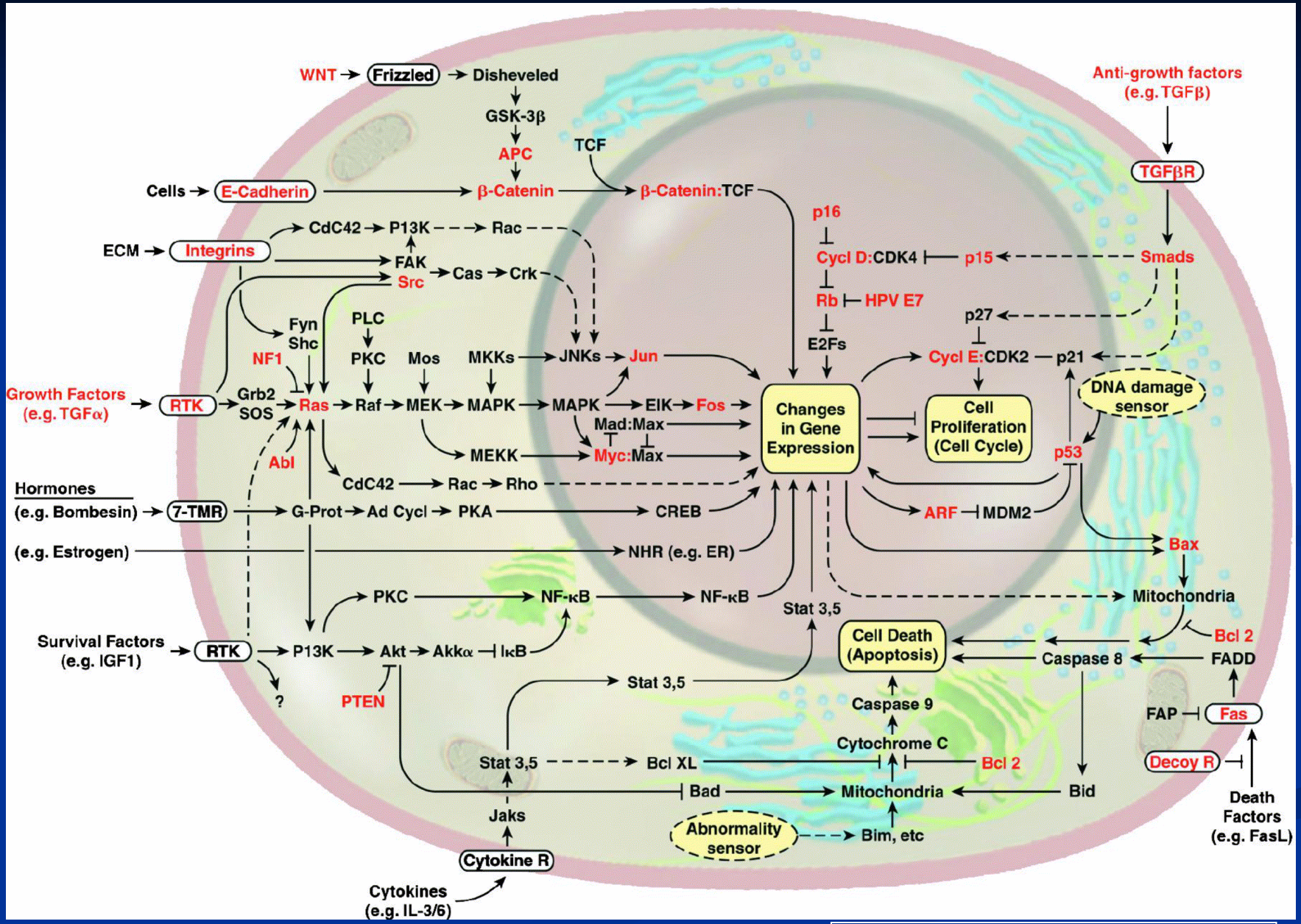
The 'Simple Complexity' Theory of Cell Signaling

ELSEVIER

A control theoretic paradigm for cell signaling networks: a simple complexity for a sensitive robustness

Robyn P Araujo and Lance A Liotta

R.P. Araujo and L.A. Liotta, 2006. A control theoretic paradigm for cell signaling networks: a simple complexity for a sensitive robustness. *Curr. Opin.Chem. Biol.* **10:** 81-87



Hanahan and Weinberg, 2000.

- ‘Simplicity within Complexity’:
  - Versatility & sophistication wide variety of responses to wide variety of possible stimuli
  - Overarching simplicity: able to orchestrate well-defined and mathematically-tractable mechanisms. Eg. Switch, oscillations, etc.
- ‘Sensitivity within Robustness’:
  - Robustness to unwanted perturbations, while responding specifically and sensitively to relevant inputs

Mathematical Models of 'Network-Targeted' Therapies

Nature Reviews Drug Discovery | AOP, published online 12 October 2007; doi:10.1038/nrd2381

PERSPECTIVES

OPINION

Proteins, drug targets and the mechanisms they control: the simple truth about complex networks

Robyn P. Araujo, Lance A. Liotta and Emanuel F. Petricoin

Abstract | Realizing the promise of molecularly targeted inhibitors for cancer therapy will require a new level of knowledge about how a drug target is wired into the control circuitry of a complex cellular network. Here we review general homeostatic principles of cellular networks that enable the cell to be resilient in the face of molecular perturbations, while at the same time being sensitive to subtle input signals. Insights into such mechanisms may facilitate the development of combination therapies that take advantage of the cellular control circuitry, with

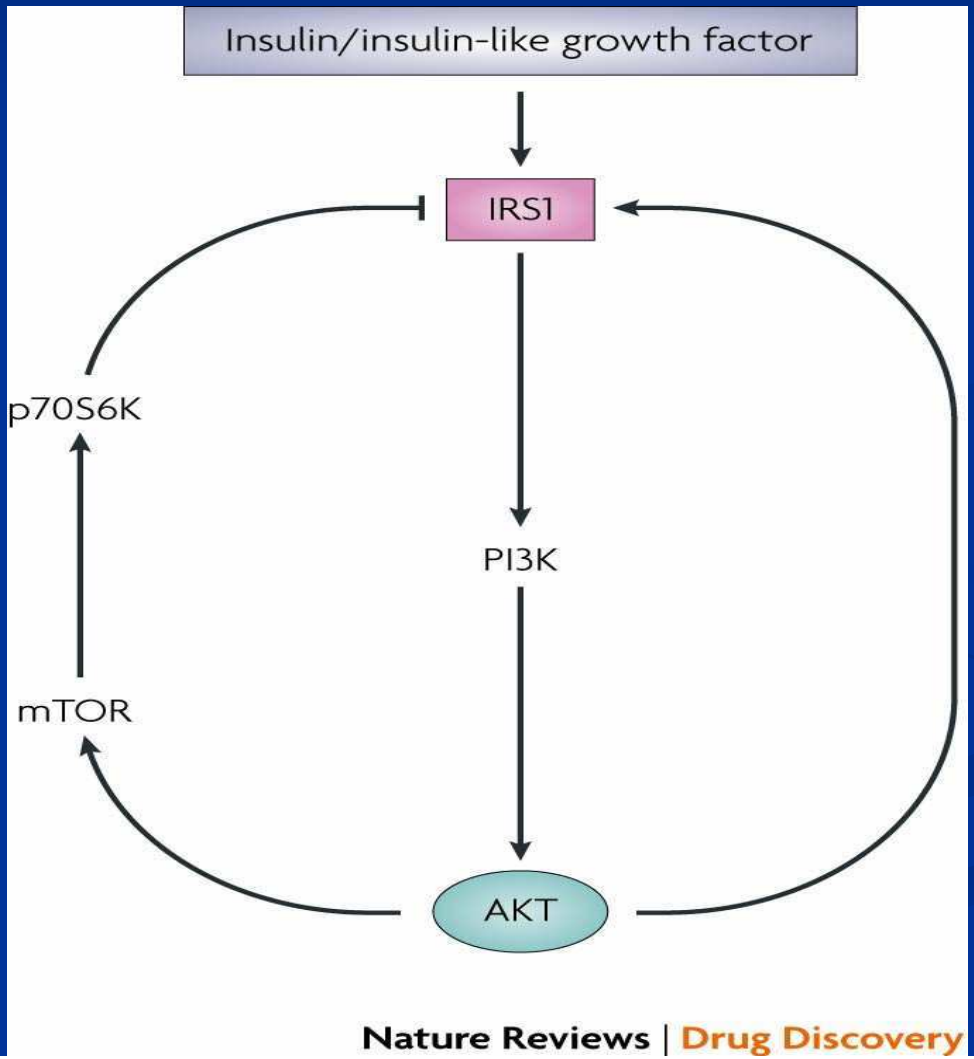
inhibitor gefitinib (Iressa; AstraZeneca) for patients with non-small-cell lung cancer (NSCLC)[13–16]. Even the problem of tumour recurrence in these responsive NSCLC and CML tumour types reveals that the majority of relapses involve resistance mutations in the target ('addictive') kinase, rather than a novel oncogenic expedient, which suggests that room for evolutionary manoeuvre in surviving tumour cells is highly constrained, even in the face of genomic instability[9,17–20]. This characteristic, in turn, increases the likelihood of overcoming the problem of resistance through future pathway-directed combination therapies[2,21–24].

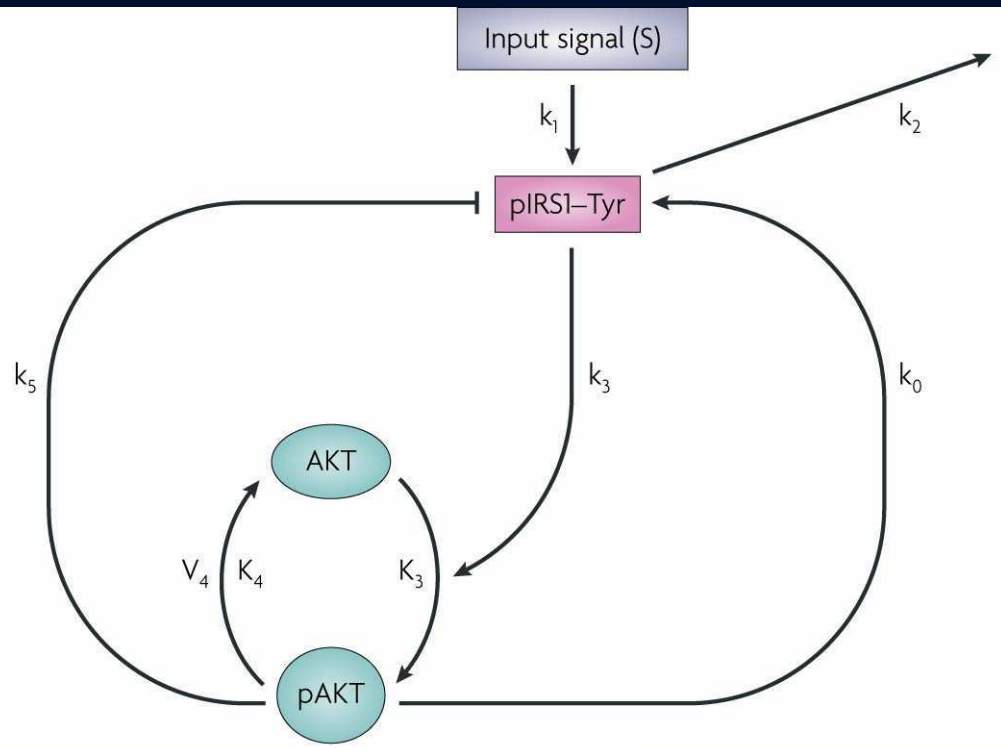
In this article, we focus on the particularly challenging realm of cancer drug discovery and treatment, as emerging evidence continues to corroborate the notion that each patient's tumour is unique

R.P Araujo, L.A. Liotta and E.F. Petricoin, 2007. Proteins, drug targets and the mechanisms they control: the simple truth about complex networks. *Nat. Rev. Drug Discov*. **6(11):**871-880

Feedback loops and targeted therapies: a case study using the mTOR pathway

Feedback loops and targeted therapies: a case study using the mTOR pathway





$$\frac{d}{dt}[pIRS1\text{-}Tyr] = k_1 S + (k_0 - k_5)[pAkt] - k_2[pIRS1\text{-}Tyr]$$

$$[pAkt] = G_K(Akt) = \frac{(V_A - 1) - K_4(K_A + V_A) + \sqrt{(V_A - 1 - K_4(K_4 + V_A))^2 + 4K_4(V_A - 1)V_A}}{2(V_A - 1)}$$

$$K_A = \frac{K_3}{K_4} \qquad V_A = \frac{k_3[pIRS1\text{-}Tyr]}{V_4}$$

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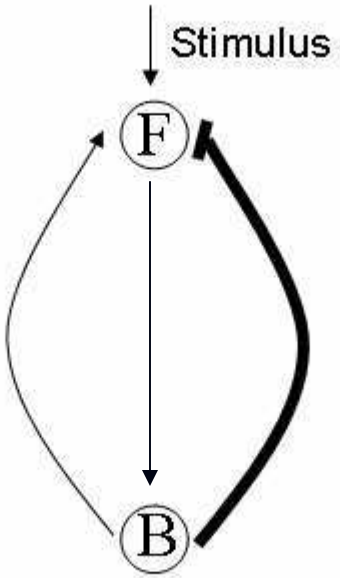
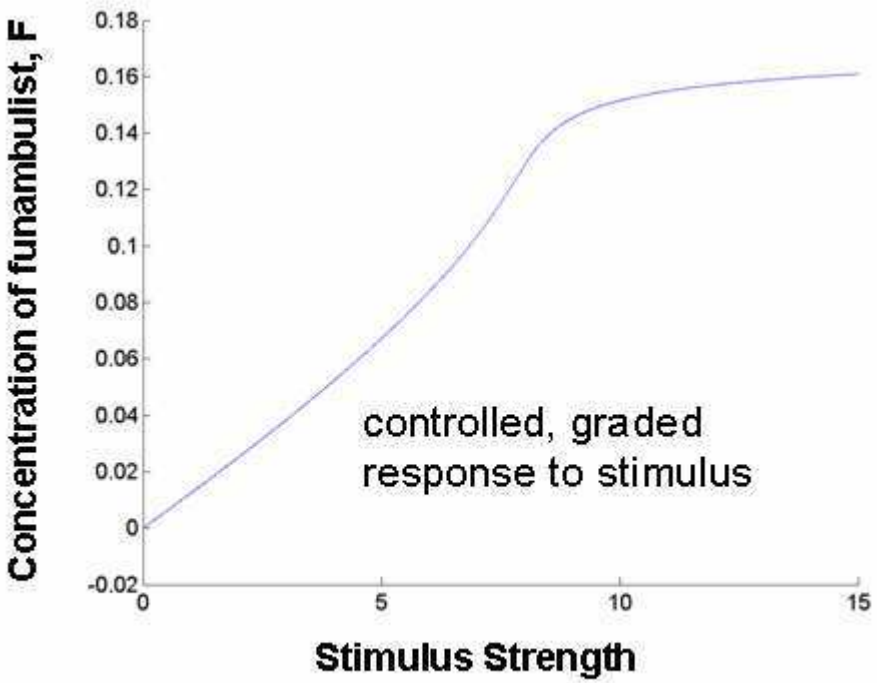
(a)



NORMAL



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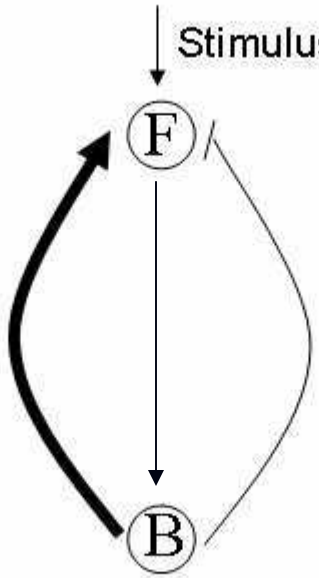
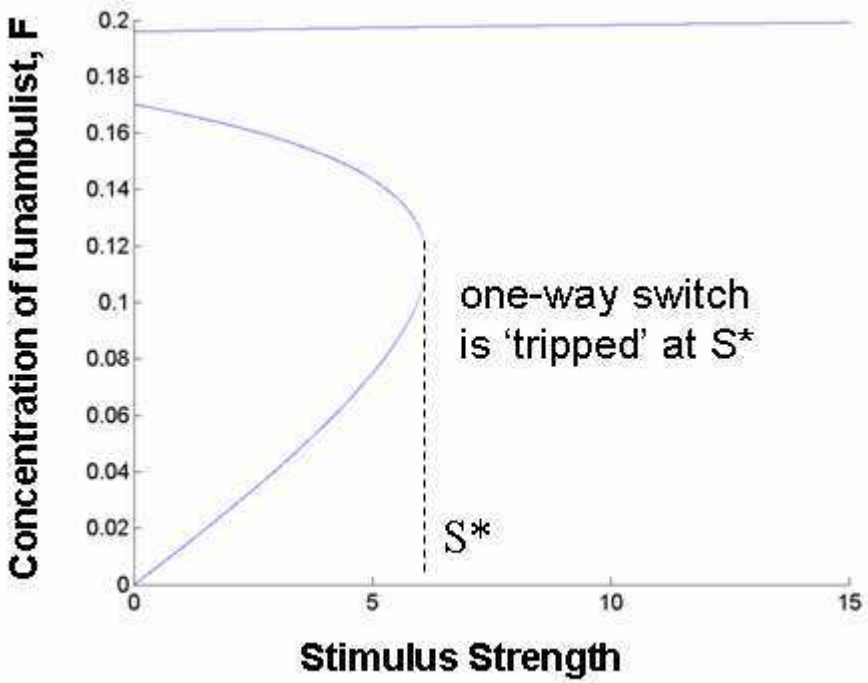
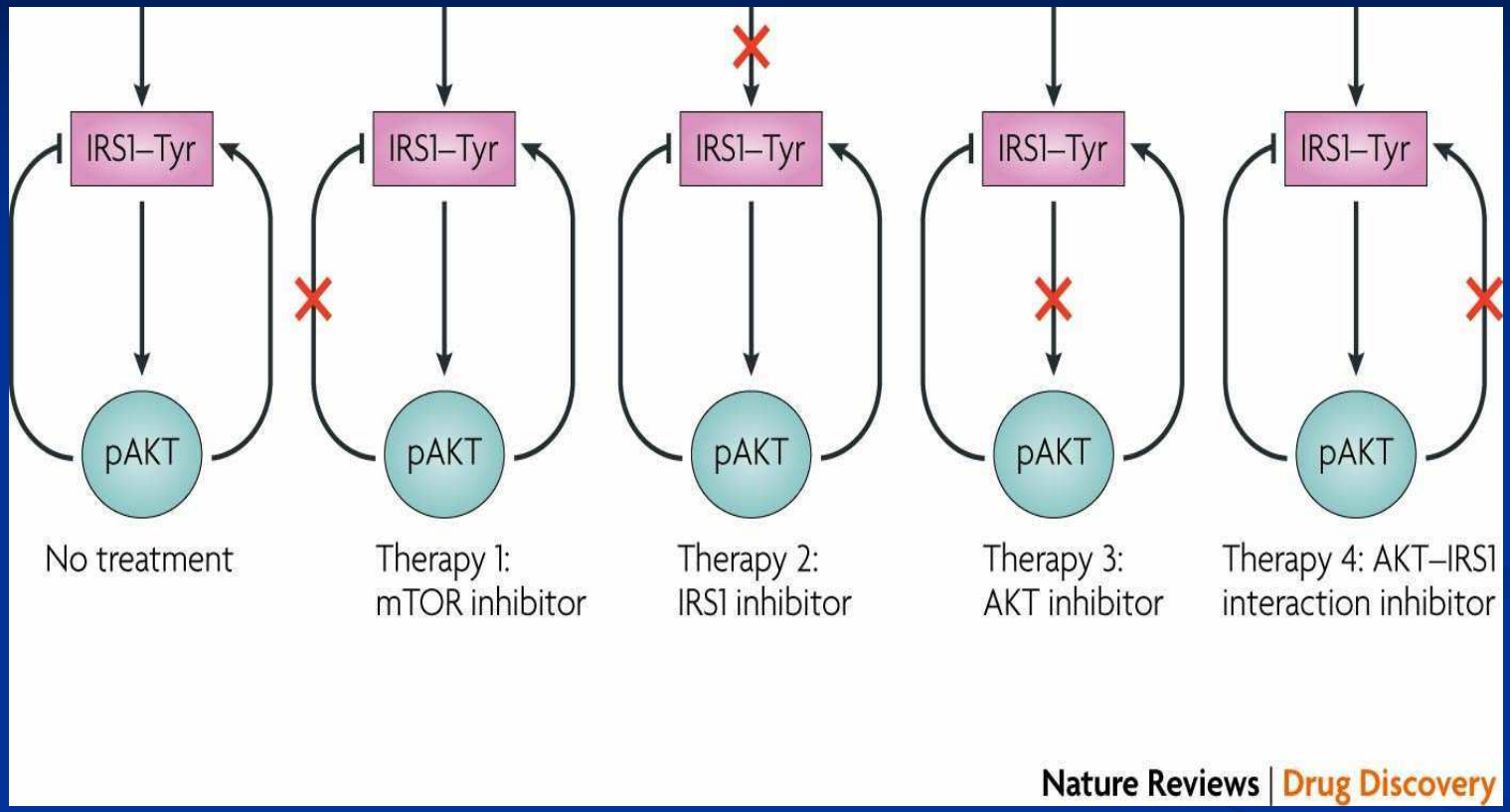


TUMOR




IRS1–Tyr
pAKT
No treatment
Therapy 1:
mTOR inhibitor
Therapy 2:
IRS1 inhibitor
Therapy 3:
AKT inhibitor
Therapy 4: AKT–IRS1
interaction inhibitor
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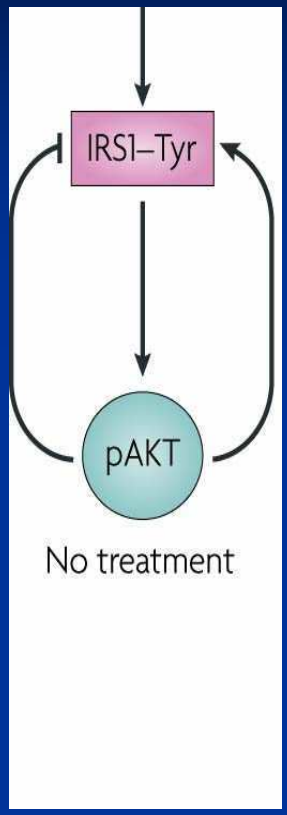
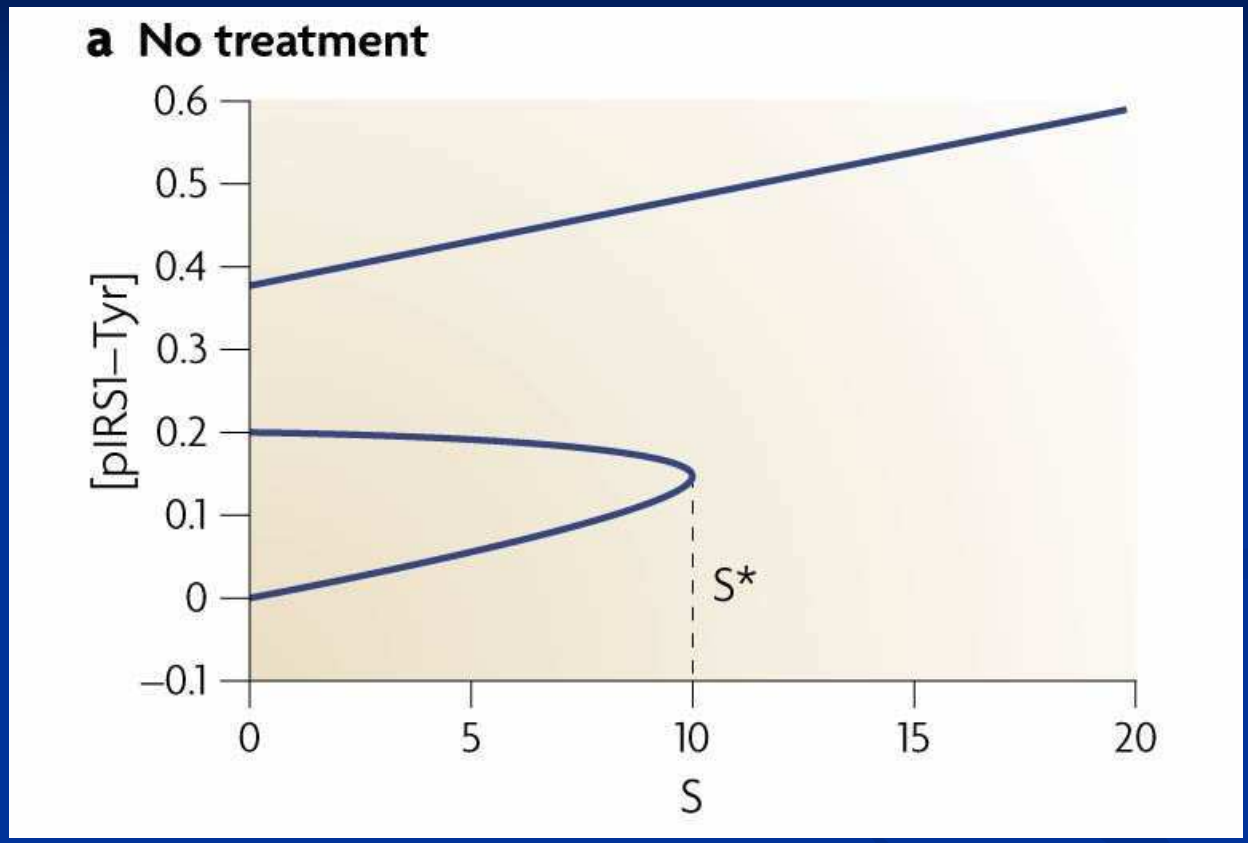
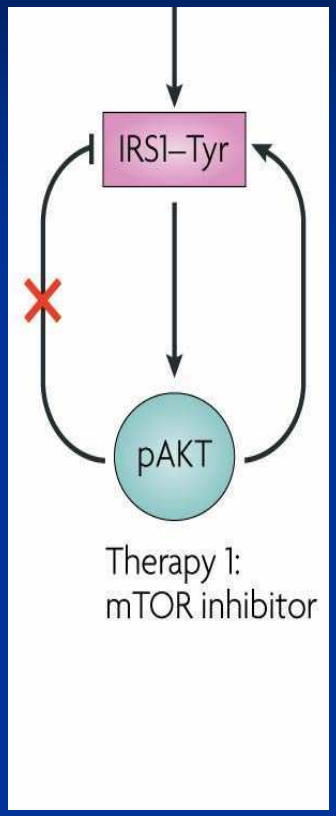
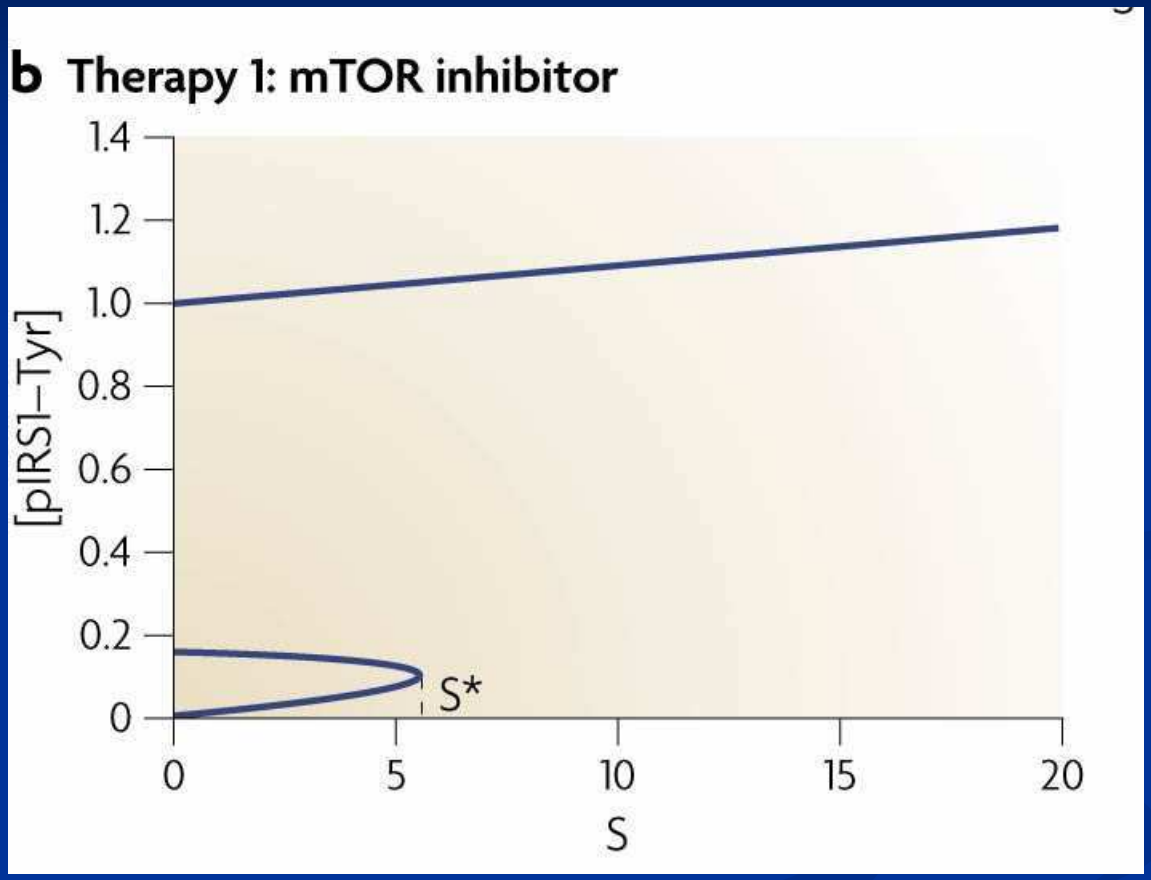
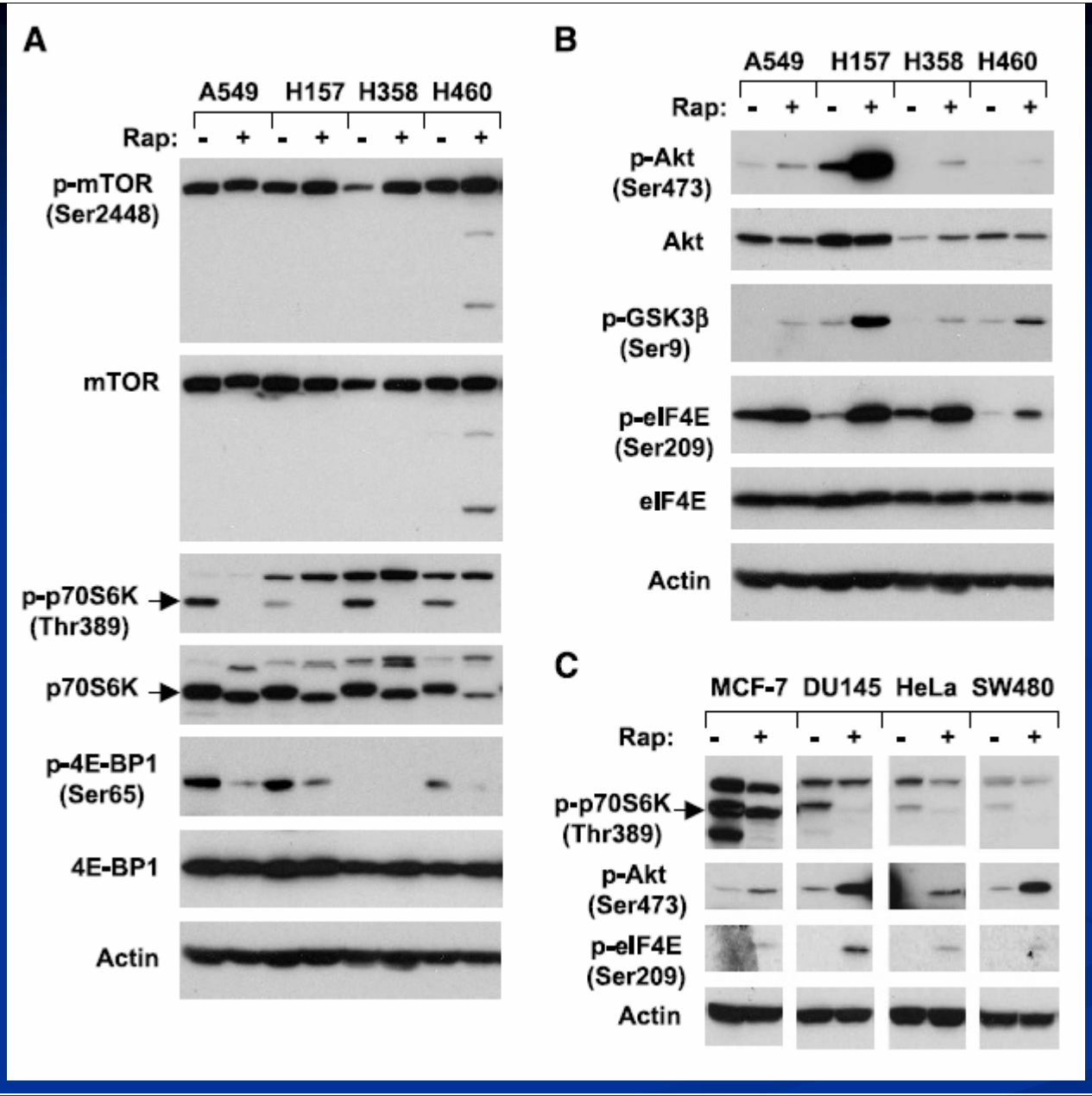

IRS1–Tyr
pAKT
No treatment


a No treatment
0.6
0.5
0.4
0.3
0.2
0.1
0
–0.1
[pIRS1–Tyr]
S*
0
5
10
15
20
S


IRS1–Tyr
pAKT
Therapy 1:
mTOR inhibitor


b Therapy 1: mTOR inhibitor
[pIRS1–Tyr]
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
S*
0
5
10
15
20
S



Sun, S.Y. et al., 2005. Activation of Akt and eIF4E survival pathways by rapamycin-mediated mammalian target of rapamycin inhibition. Cancer Research **65**, 7052-7058

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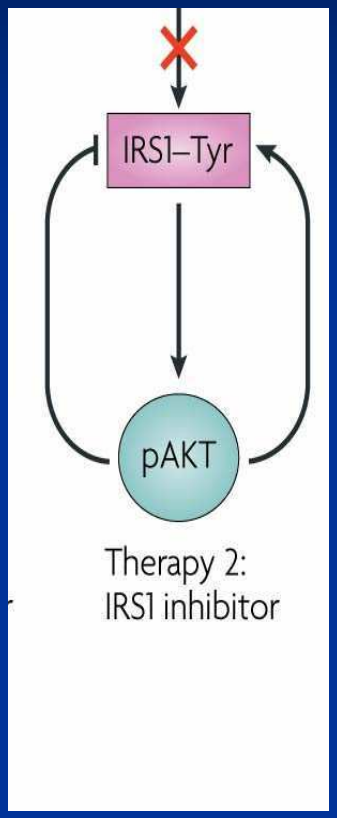
PLOS MEDICINE

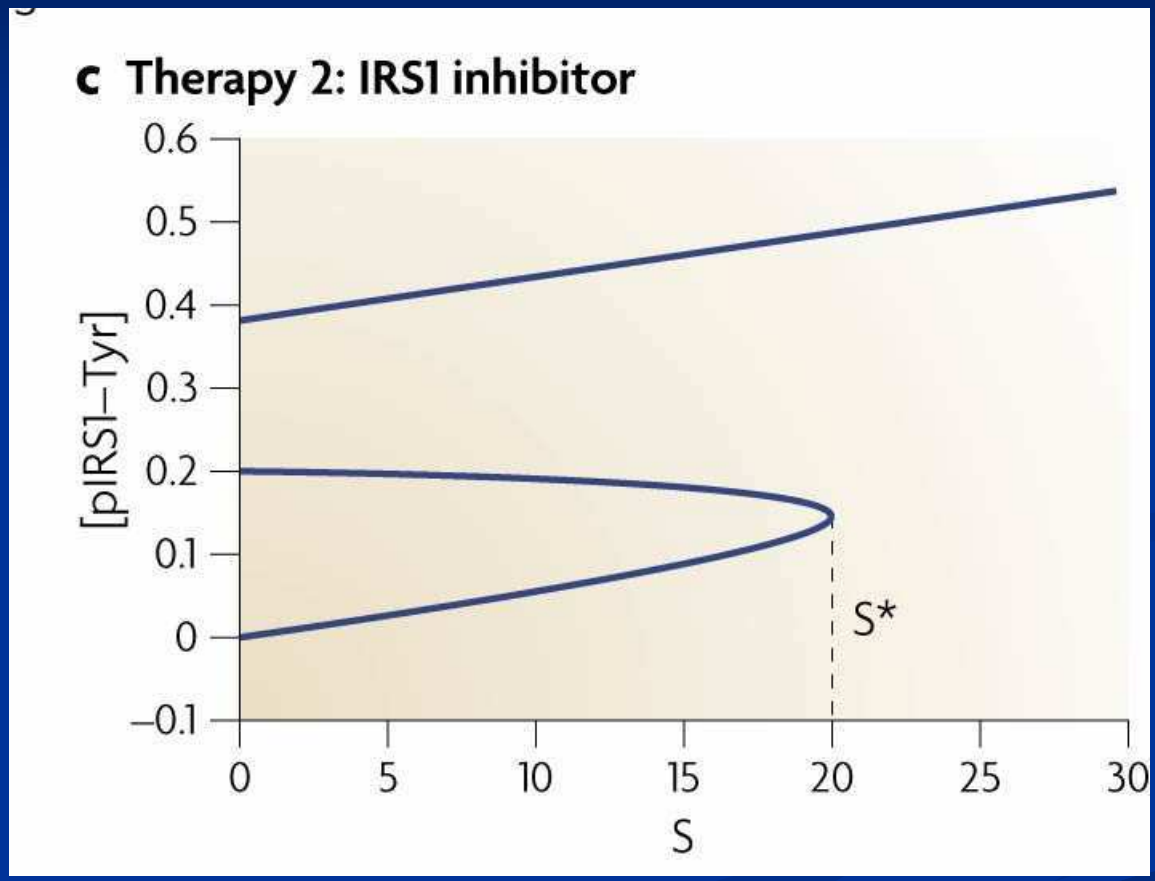
Antitumor Activity of Rapamycin in a Phase I Trial for Patients with Recurrent PTEN-Deficient Glioblastoma

Tim F. Cloughesy[1], Koji Yoshimoto[2¤], Phioanh Nghiemphu[1], Kevin Brown[3], Julie Dang[2], Shaojun Zhu[2], Teli Hsueh[4], Yinan Chen[4], Wei Wang[5], David Youngkin[3], Linda Liau[6], Neil Martin[6], Don Becker[6], Marvin Bergsneider[6], Albert Lai[1], Richard Green[7], Tom Oglesby[5], Michael Koleto[5], Jeff Trent[3], Steve Horvath[8], Paul S. Mischel[2,4], Ingo K. Mellinghoff[4], Charles L. Sawyers[9*]

1 Department of Neurology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America, 2 Department of Pathology and Laboratory Medicine, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America, 3 Translational Genomics Research Institute, Phoenix, Arizona, United States of America, 4 Department of Molecular and Medical Pharmacology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America, 5 Taylor Technology, Princeton, New Jersey, United States of America, 6 Department of Neurosurgery, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America, 7 Department of Neurology, Kaiser Permanente; Los Angeles, California, United States of America, 8 Department of Biostatistics and Human Genetics, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America, 9 Department of Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, New York, United States of America

T.F. Cloughsey et al. 2008. Antitumor activity of rapamycin in a phase I trial for patients With recurrent PTEN-deficient glioblastoma. PLOS Medicine, **5(1):** e8.


IRS1–Tyr
pAKT
Therapy 2:
IRS1 inhibitor


c Therapy 2: IRS1 inhibitor
[pIRS1–Tyr]
0.6
0.5
0.4
0.3
0.2
0.1
0
–0.1
S*
0
5
10
15
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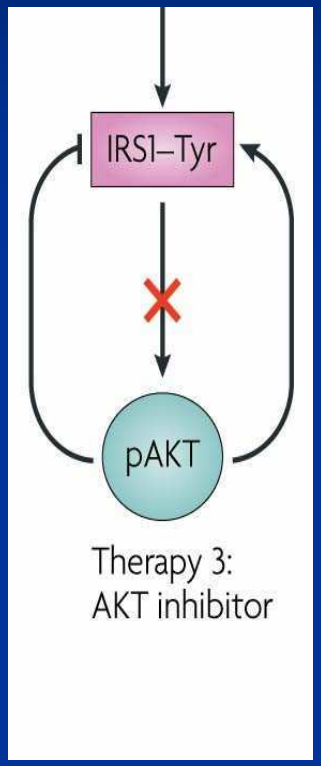
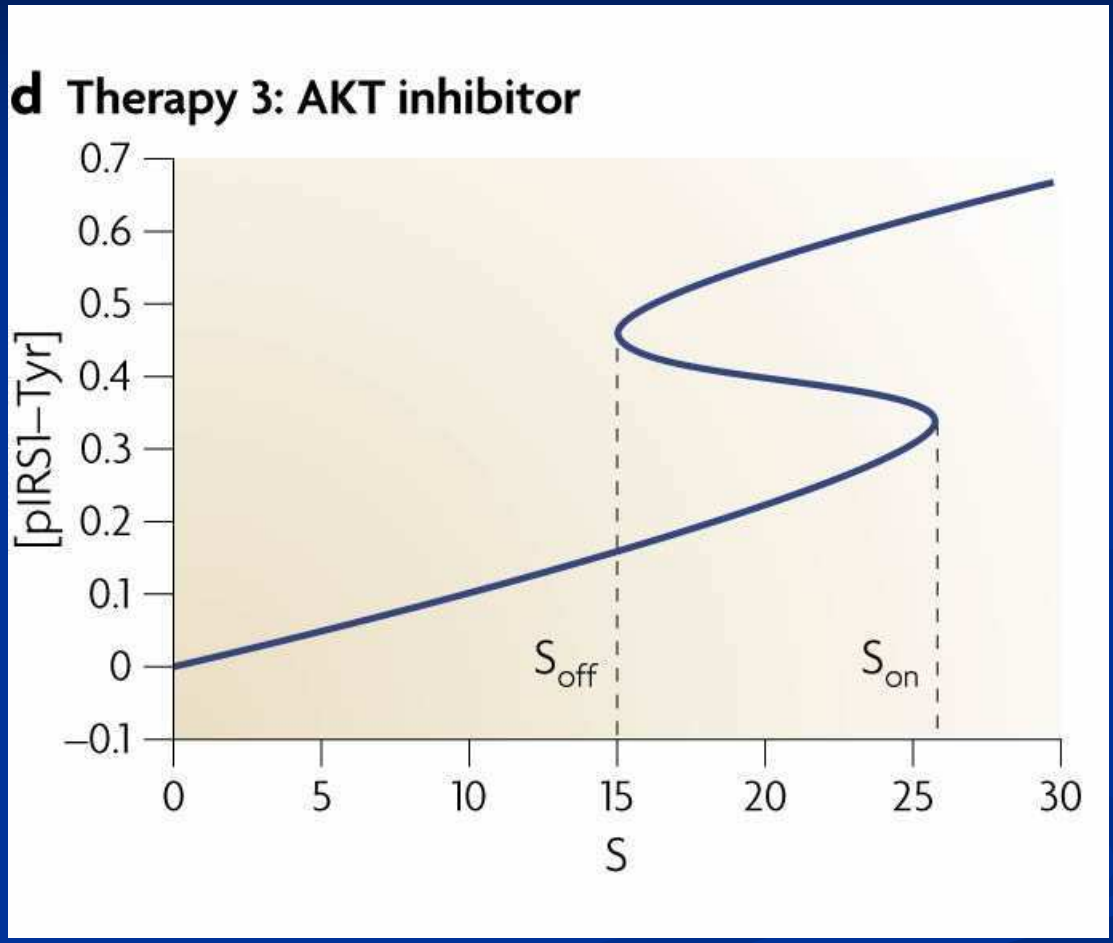
25
30
S


IRS1–Tyr
pAKT
Therapy 3:
AKT inhibitor


d Therapy 3: AKT inhibitor
[pIRS1–Tyr]
0.7
0.6
0.5
0.4
0.3
0.2
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–0.1
S_{off}
S_{on}
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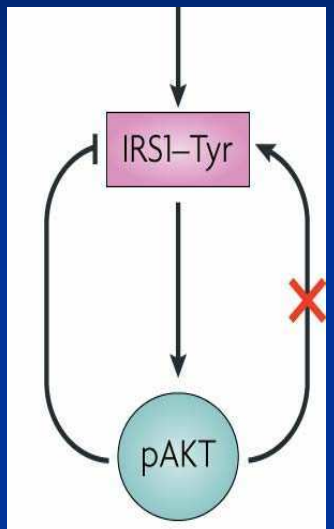
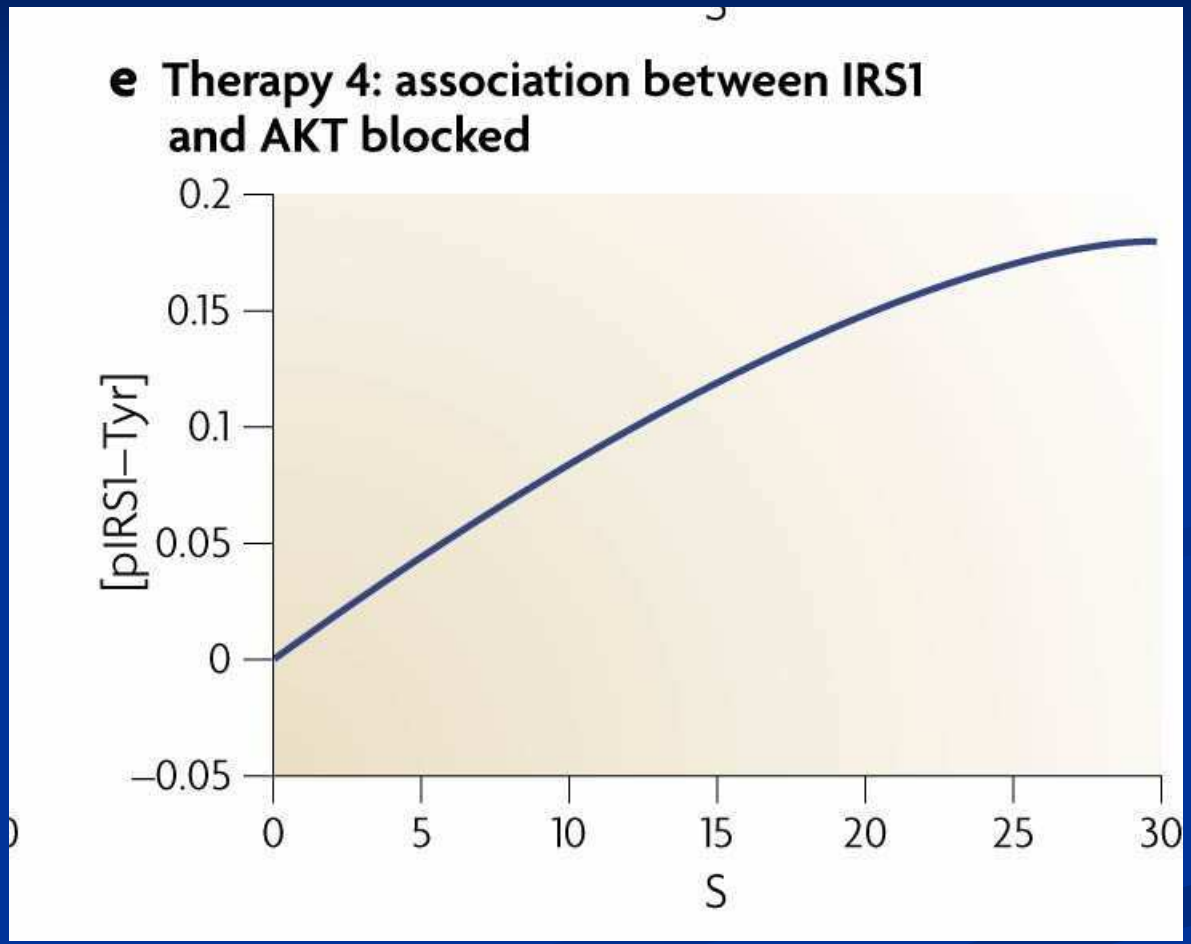
S



Therapy 4: AKT–IRS1 interaction inhibitor



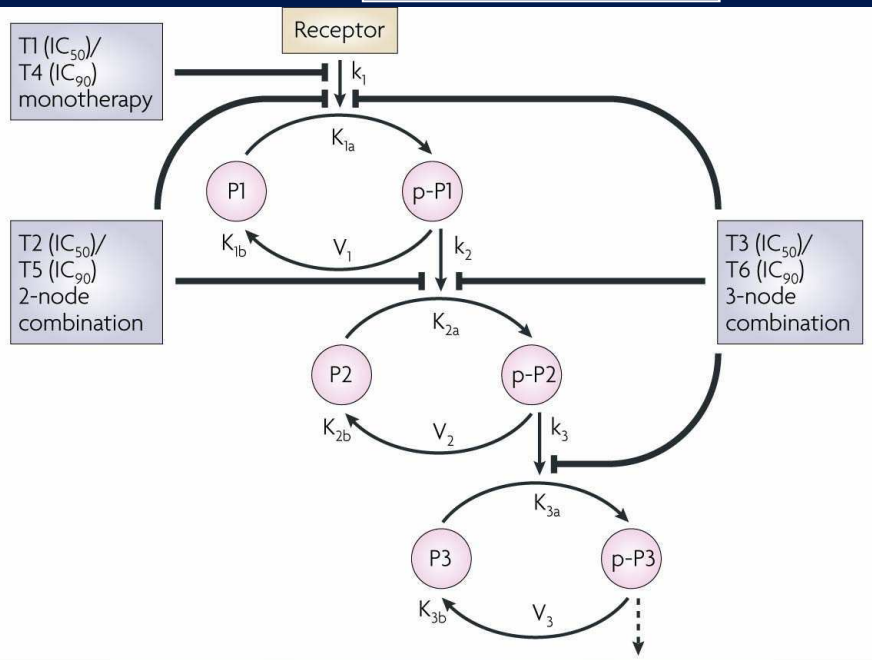
KEY CONCEPT:

A protein's suitability as a therapeutic target is determined by the nature of its contribution to the signaling network's control mechanisms, rather than by its aberrant activity.

'Network-Targeted' Combination Therapies and Overcoming Tumor Resistance to Targeted Therapeutics

Gefitinib/Erlotinib

EGFR$^{L858R/T790M}$



$$\frac{d}{dt}[pP1] = \frac{k_1[R]([P_{1TOT}] - [pP1])}{K_{1a} + [P_{1TOT}] - [pP1]} - \frac{V_1[pP1]}{K_{1b} + [pP1]}$$

$$\frac{d}{dt}[pP2] = \frac{k_2[pP1]([P_{2TOT}] - [pP2])}{K_{2a} + [P_{2TOT}] - [pP2]} - \frac{V_2[pP2]}{K_{2b} + [pP2]}$$

$$\frac{d}{dt}[pP1] = \frac{k_1[pP2]([P_{3TOT}] - [pP3])}{K_{3a} + [P_{3TOT}] - [pP3]} - \frac{V_3[pP3]}{K_{3b} + [pP3]}$$

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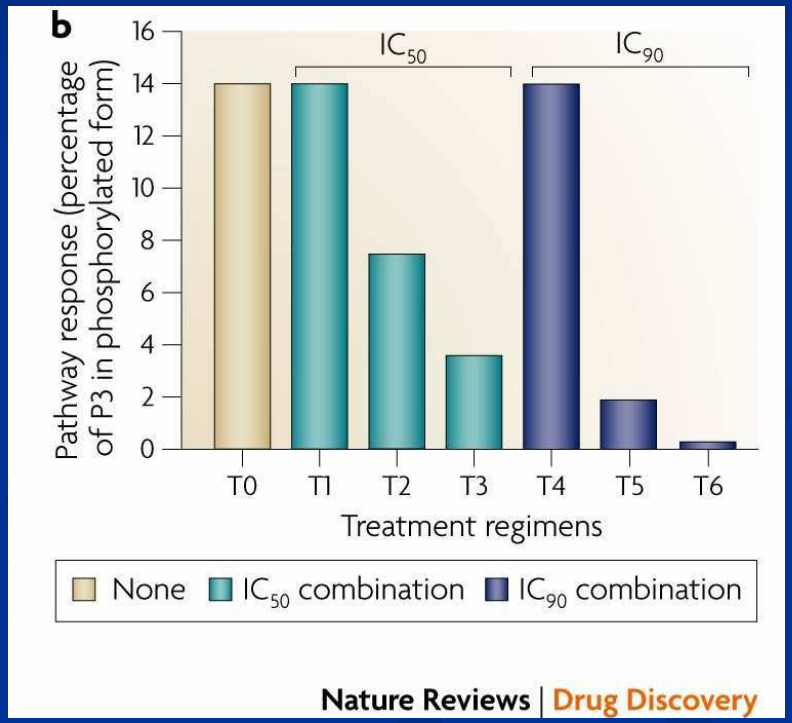

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Benefits of Combination Therapies

1. Potential to combat the problem of tumor resistance
2. Simultaneous inhibition of a cascade of proteins significantly enhances the potency of the therapy
3. Inhibition achieved with significantly lower drug doses
4. Potential for synergy in inhibition

Questions?

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