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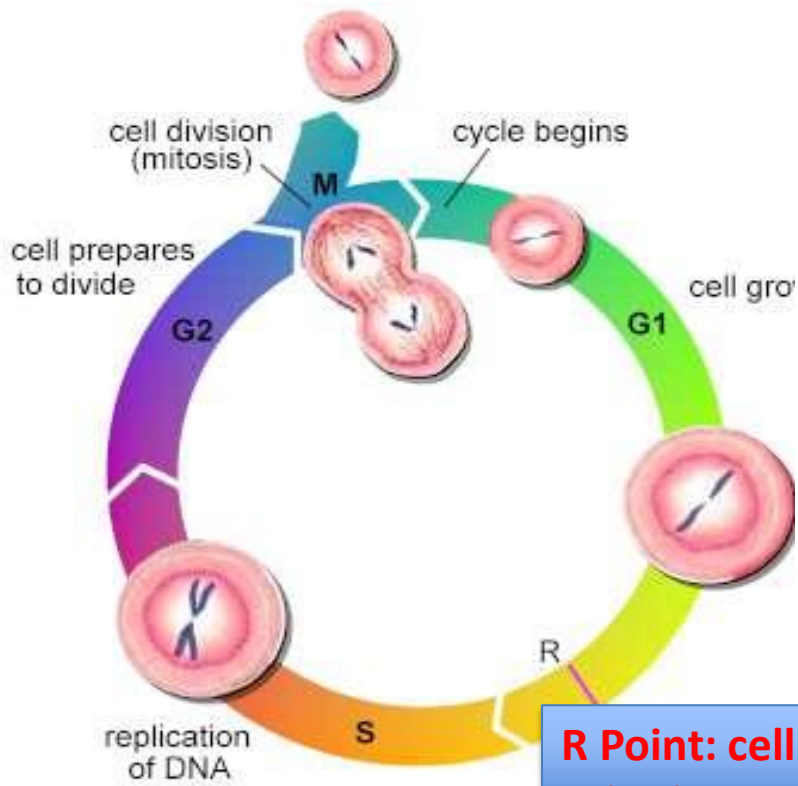
# ***Transcription-based Chronobiology of Receptor Tyrosine Kinases: Relevance to Cancer Progression***

**Yosef Yarden, PhD**

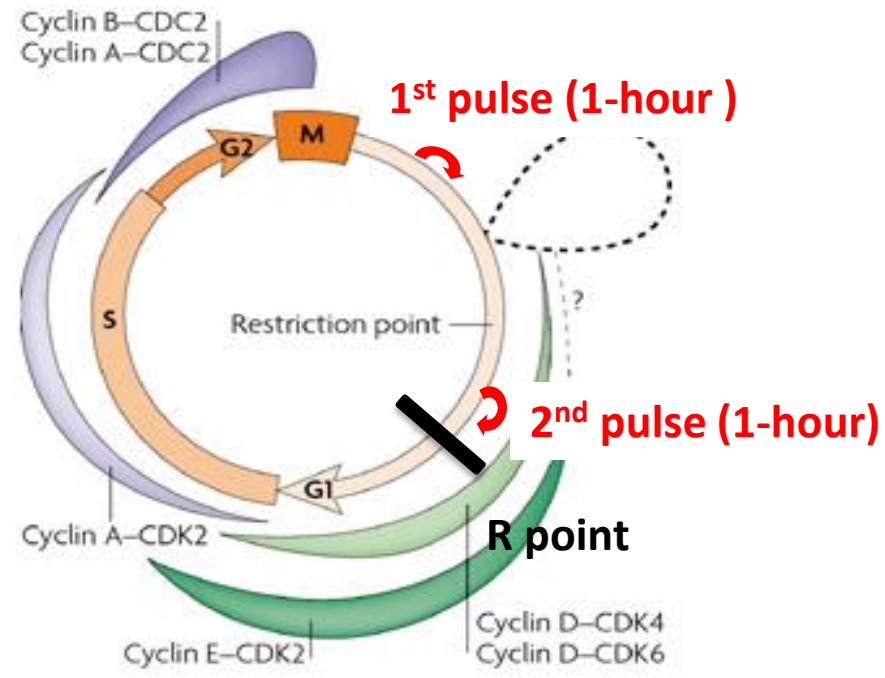
***Department of Biological Regulation  
The Weizmann Institute of Science  
Rehovot, Israel***

**International Conference on Transcriptomics  
Orlando; July 27, 2015**

# Part 1: EGF-induced proliferation of mammary cells (HMEC cells)

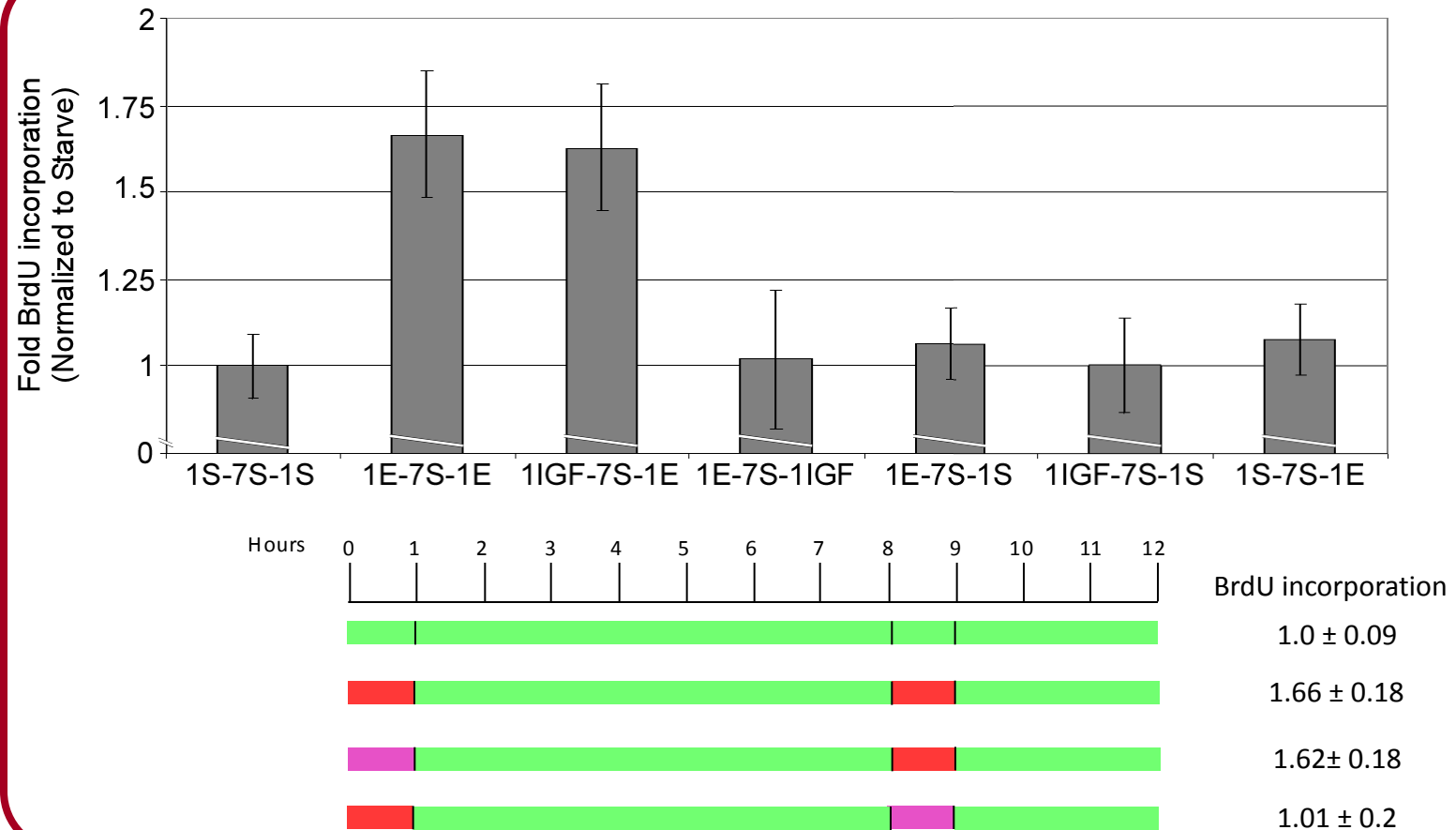


**R Point: cell decides  
Whether to continue**

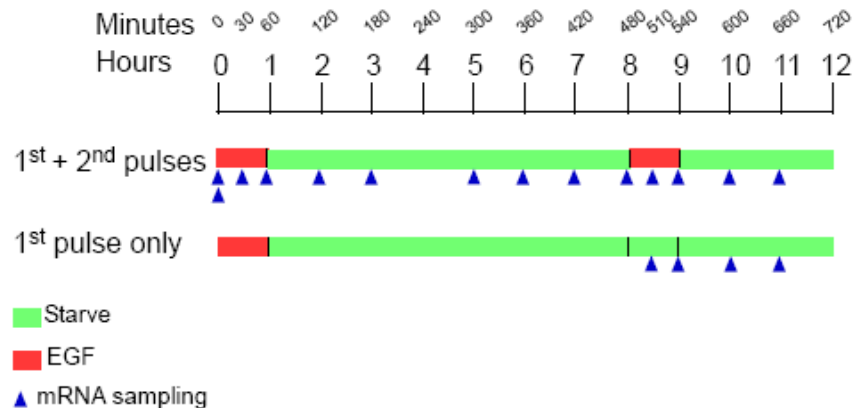
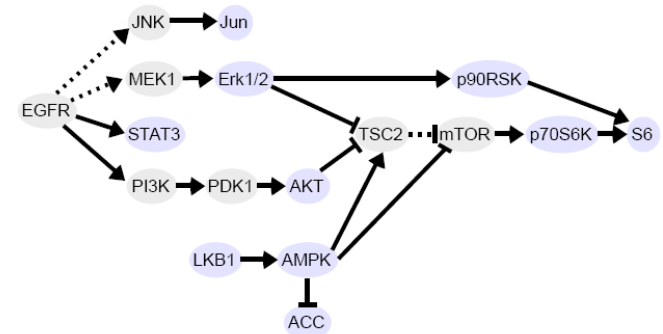
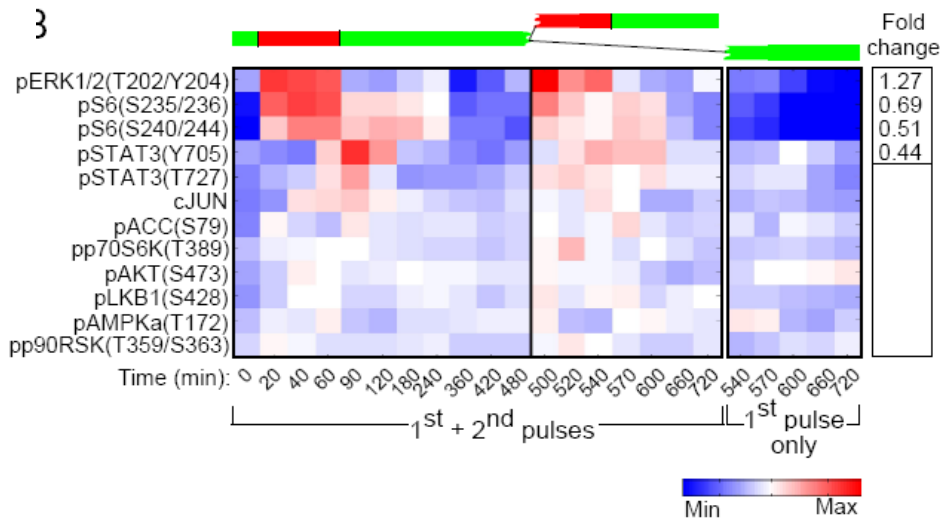


R crossing requires continuous (>6 hours) presence of growth factors, but might be replaced by 2 pulses of 1 hour each.

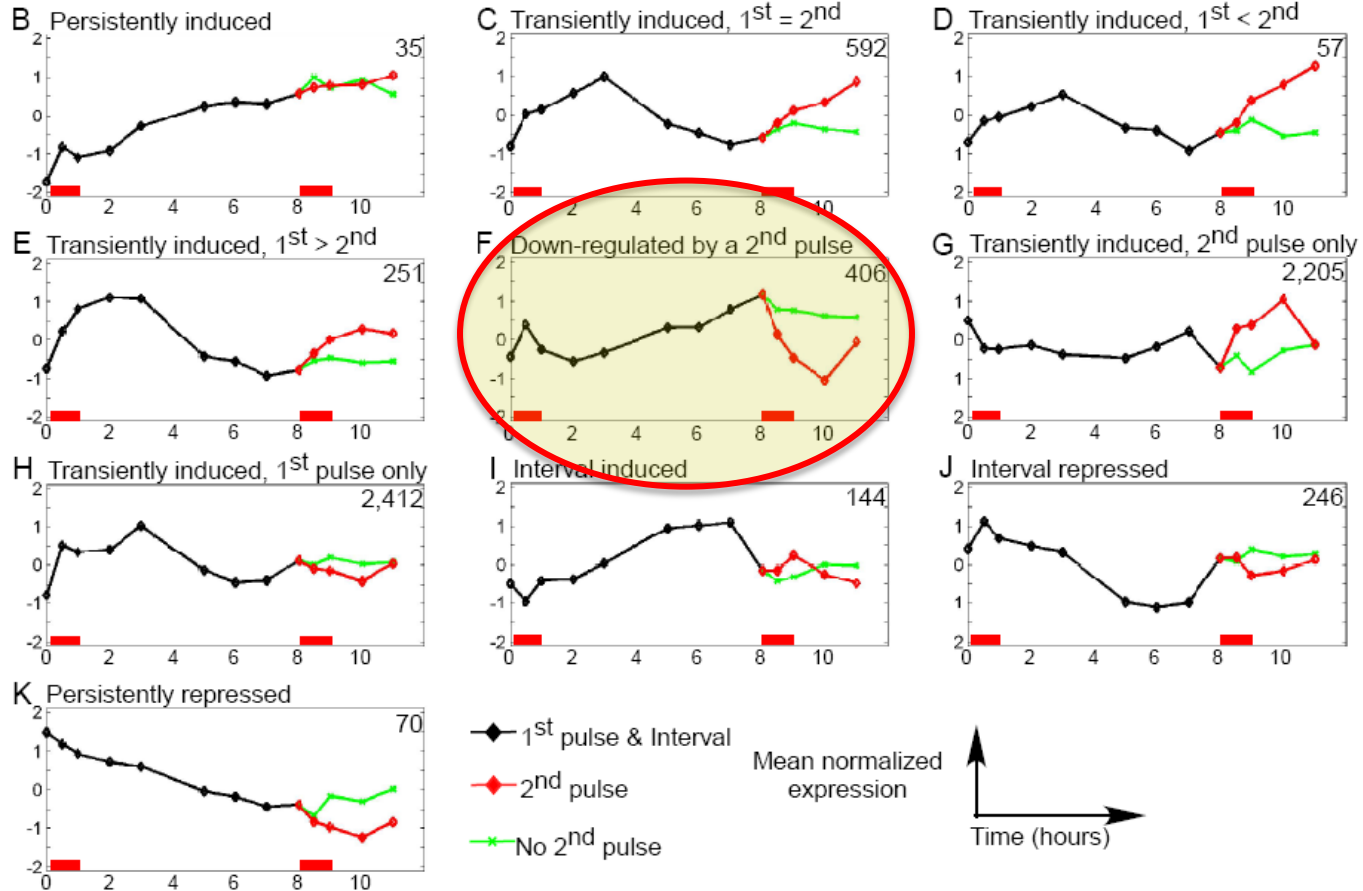
# IGF1 may replace EGF in the 1<sup>st</sup>, not in the 2<sup>nd</sup> pulse



# RPPA and Transcriptomic Analyses of the Two-Pulses

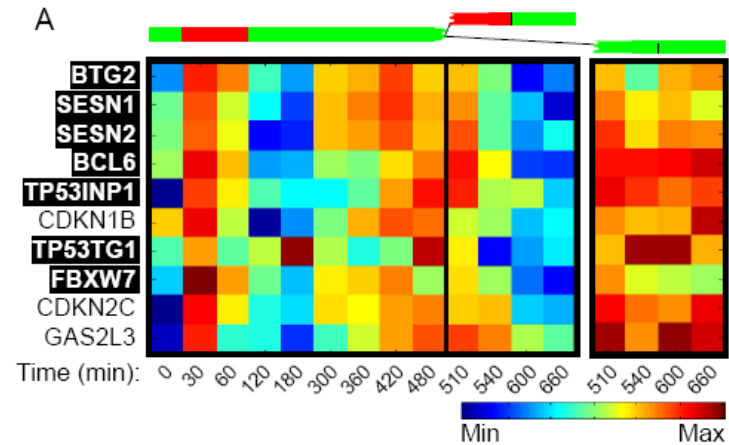


# 10 expression profiles are induced by EGF (two pulses)



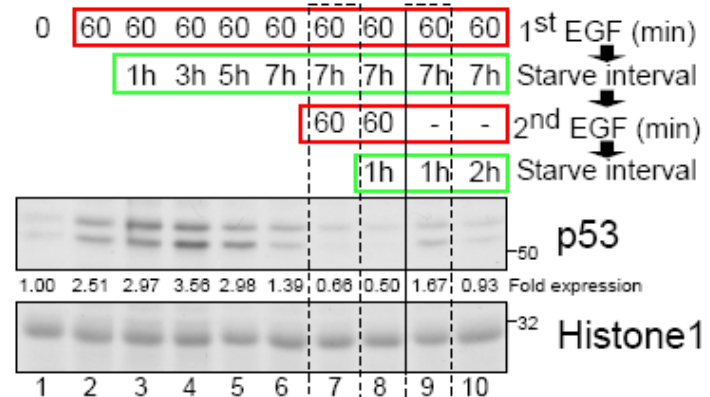
# The module “Down-regulated by 2<sup>nd</sup> Pulse” comprises several p53 regulated genes

The module includes well-established p53 target genes



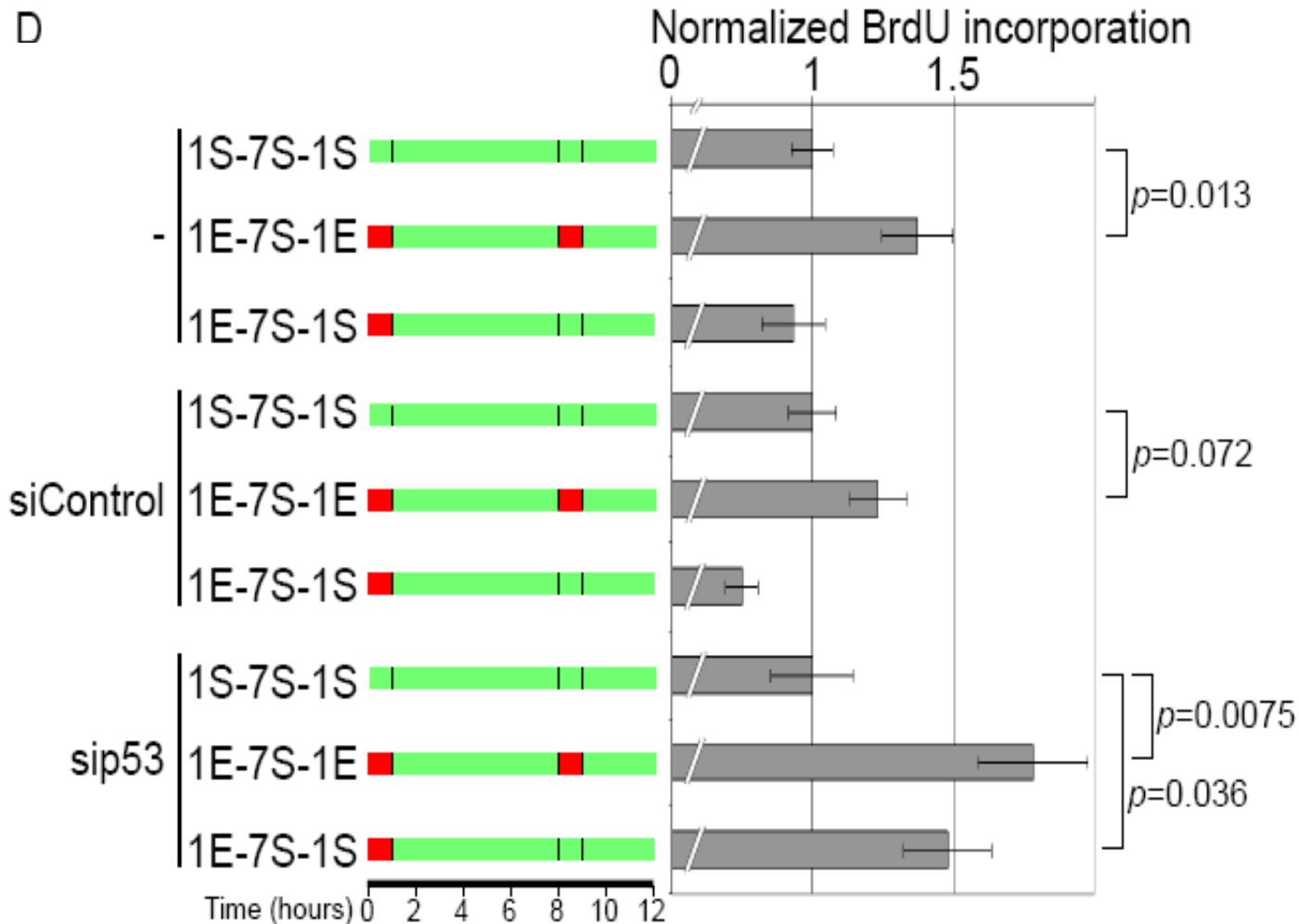
And

p53 associates with chromatin upon the 1<sup>st</sup> pulse, remains active during the interval and dissociates on the 2<sup>nd</sup> pulse

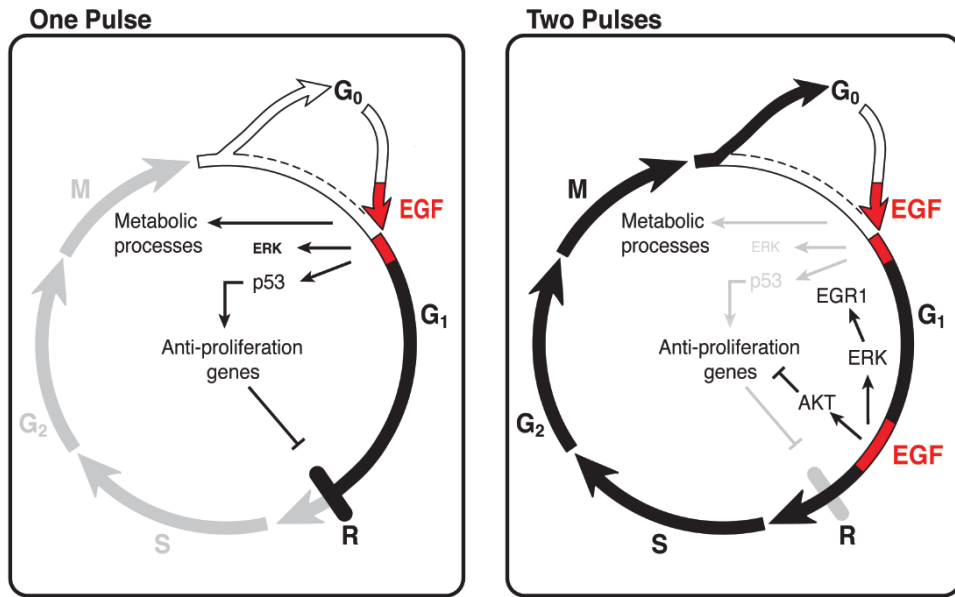




# Knockdown of p53 enables R-crossing in the absence of a second pulse



# The Paradigm of "Consistency Test"

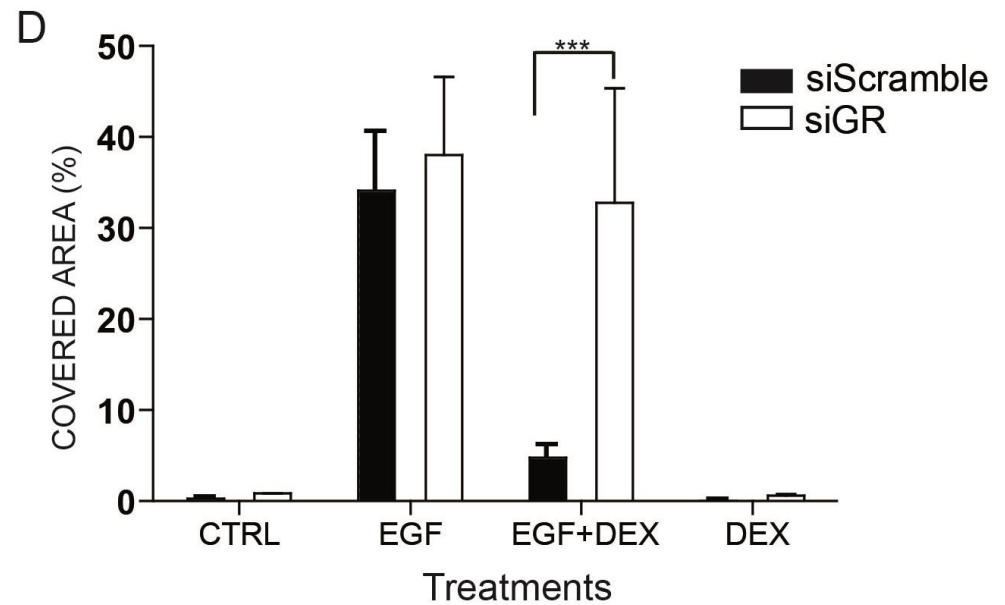
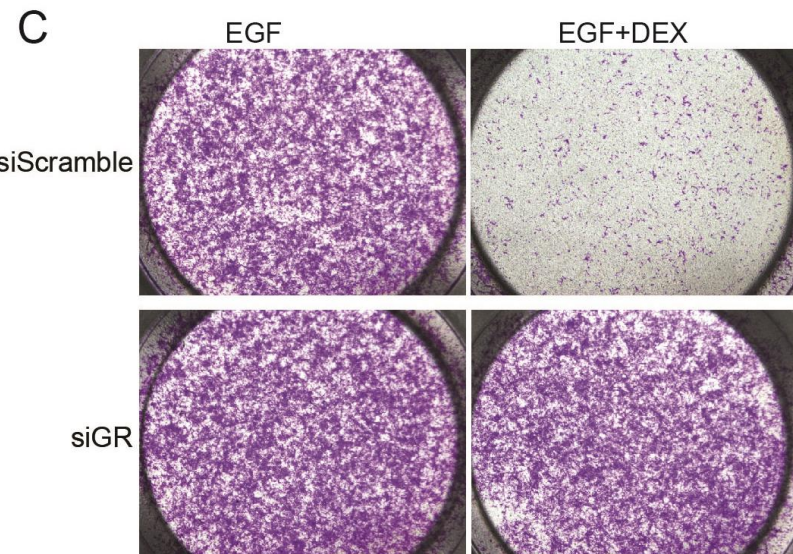


❑ The 2-pulse mode of commitment might filter the "noise" of growth factor bursts, which are often short and inconsistent

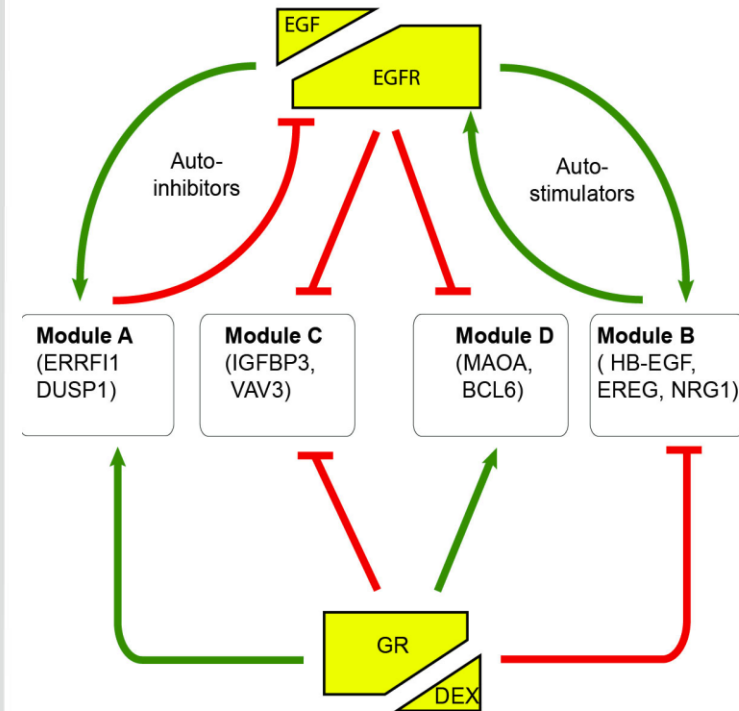
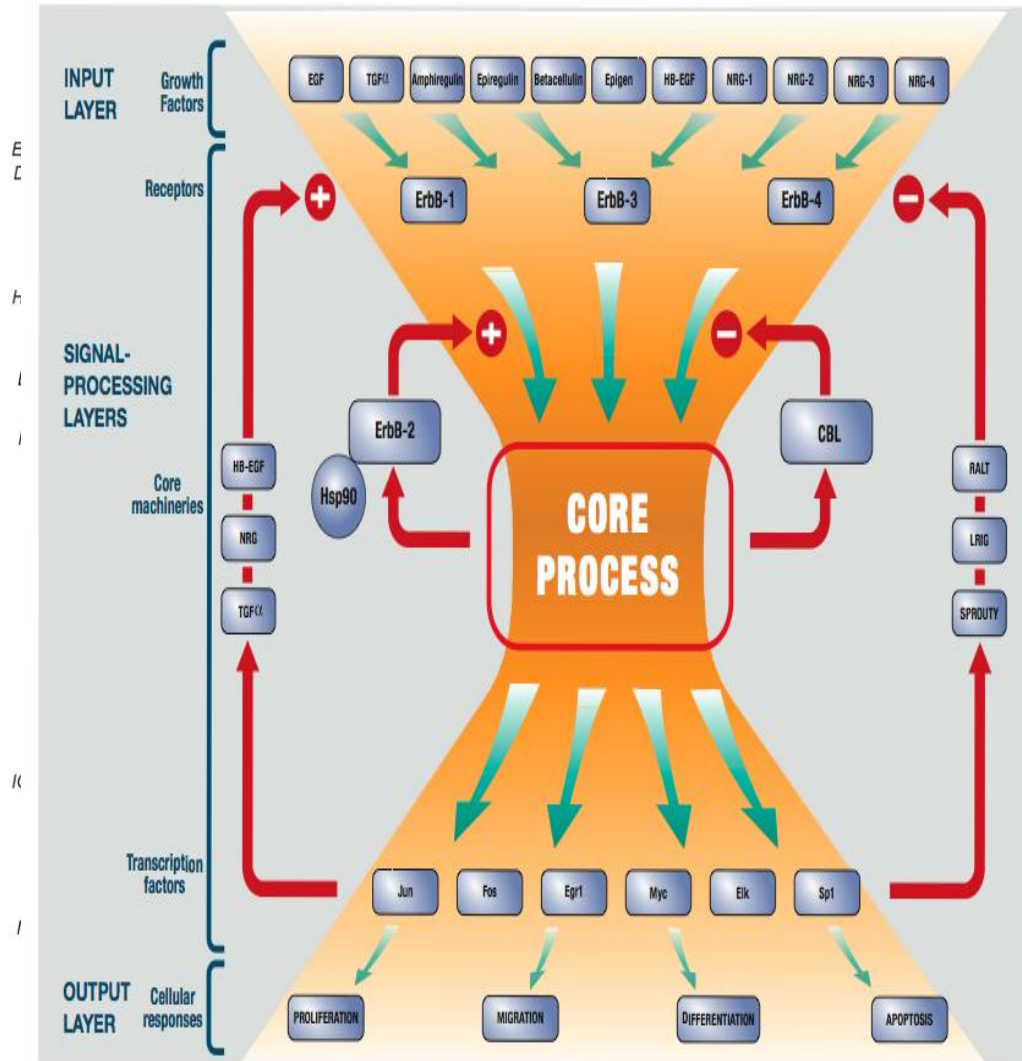
❑ In the absence of p53 (e.g., cancer cells), this filtering mechanism is defective

## Part 2: EGF-induced migration of mammary cells (MCF10A cells)

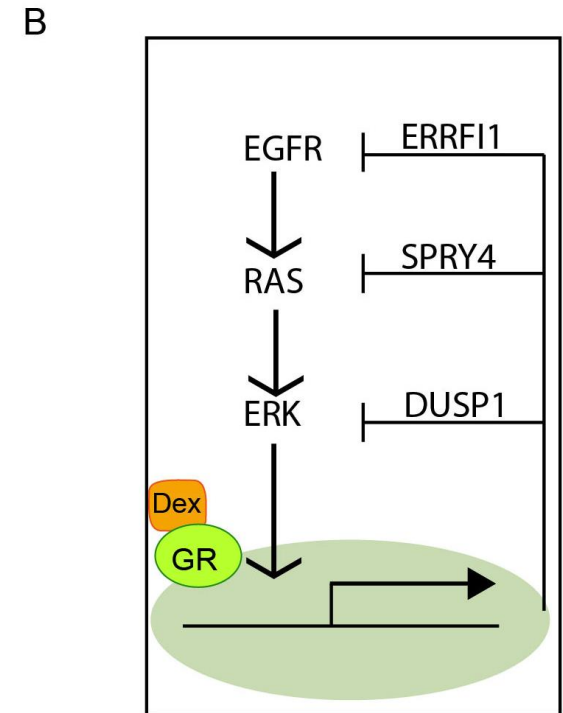
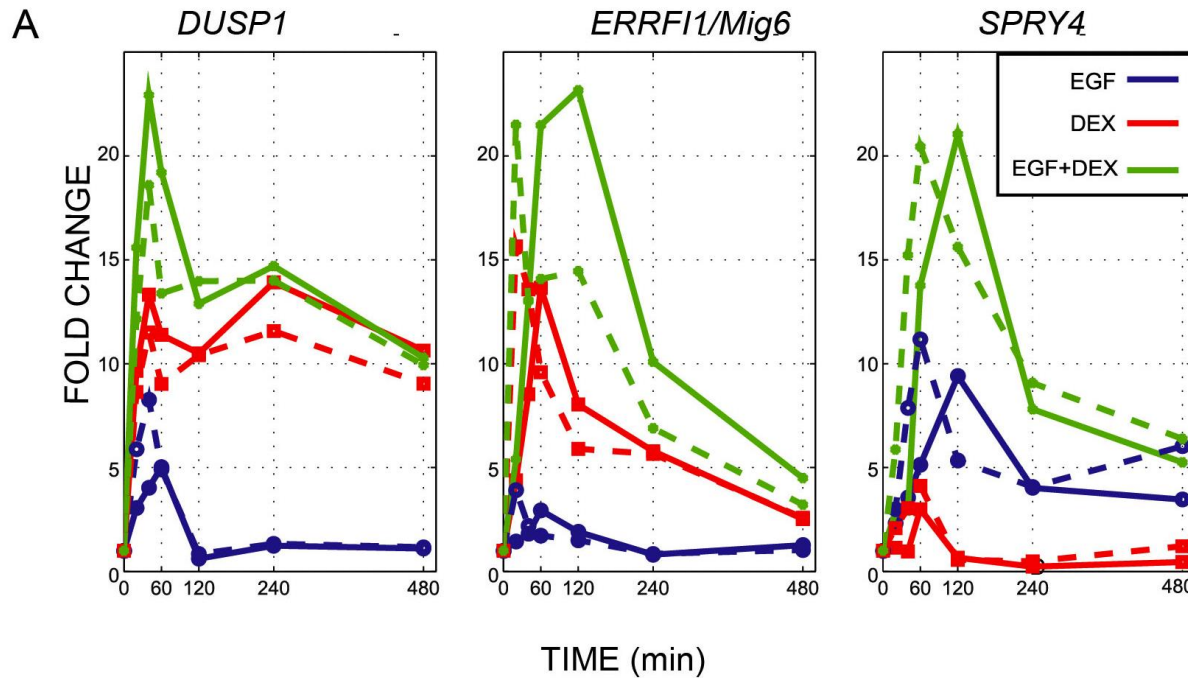
### GR Mediates the Inhibitory Effect of DEX on Cell Migration



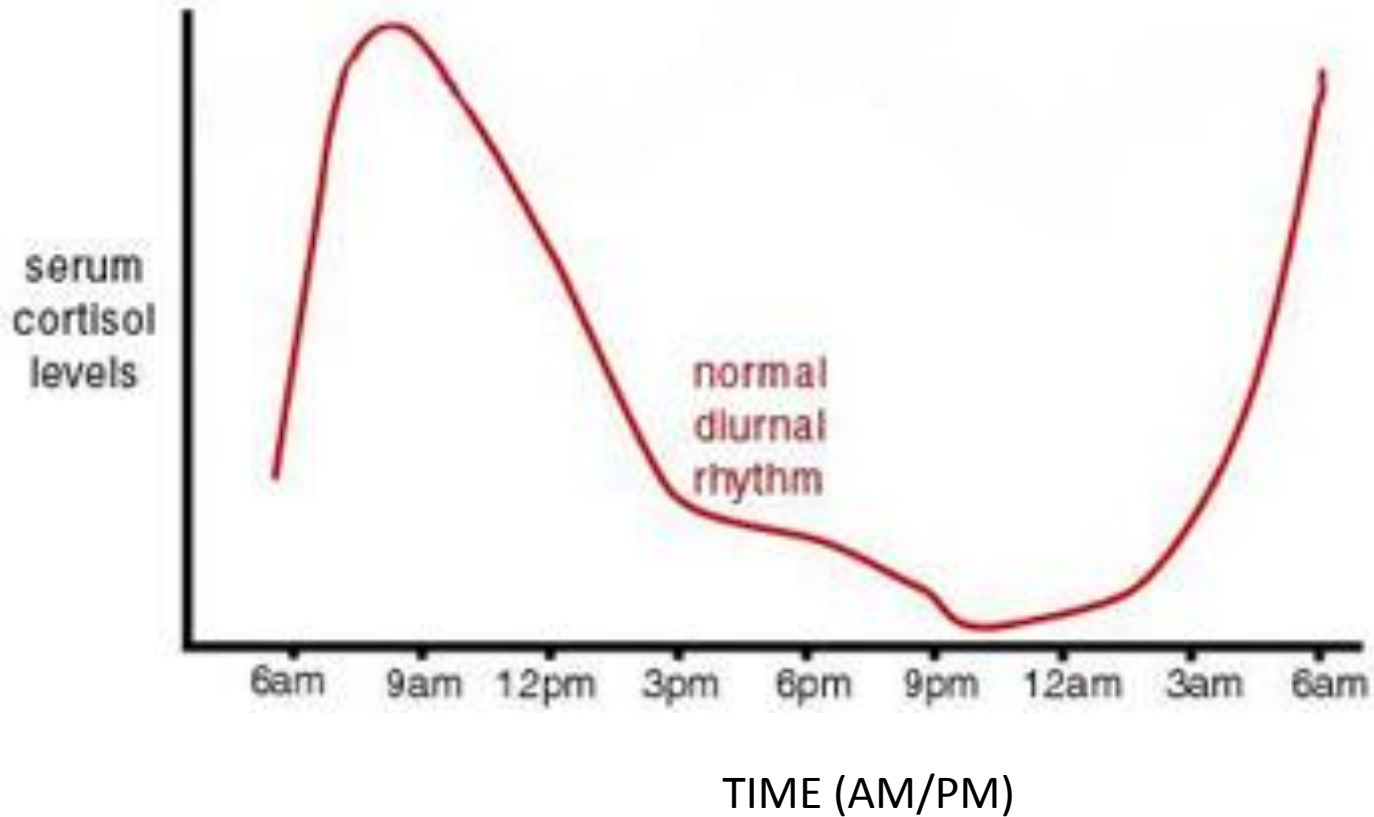
# GR exploits the EGFR gene program by inhibiting the feedback activators and activating the feedback inhibitors



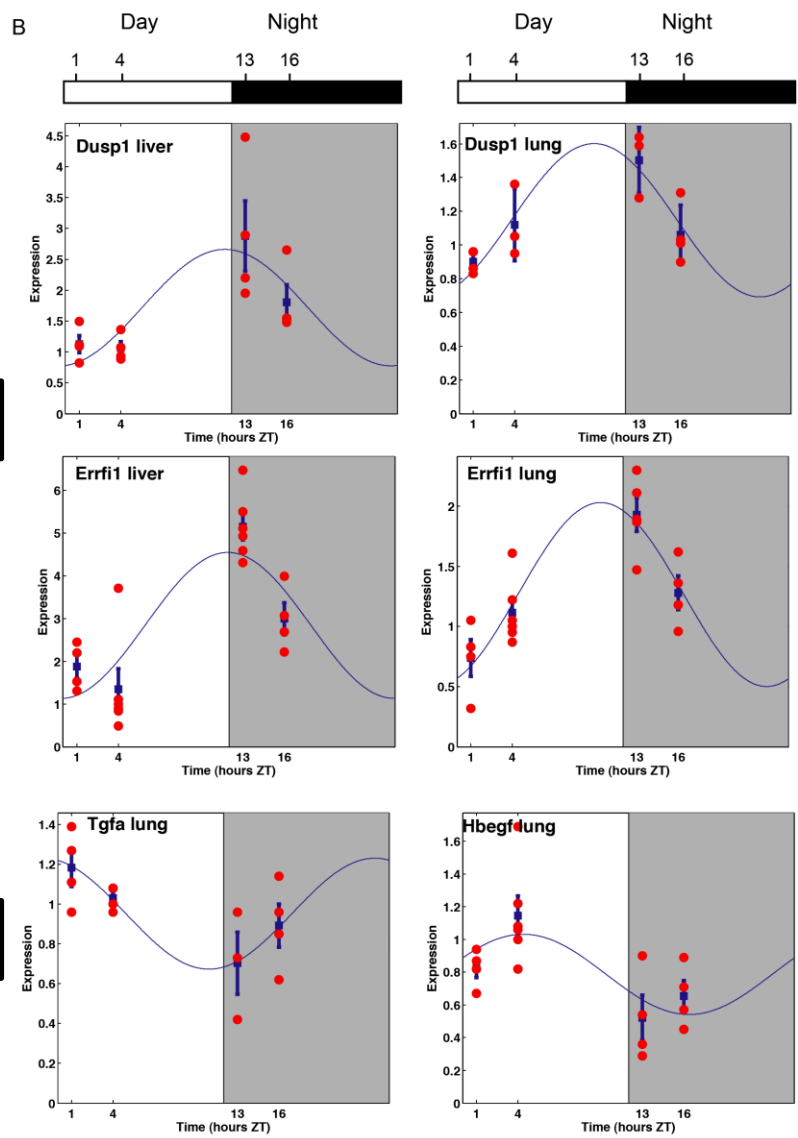
# Module A: GR enhances the expression of a set of negative regulators of EGFR signaling



# Circadian Oscillations of Serum Cortisol Levels in Human



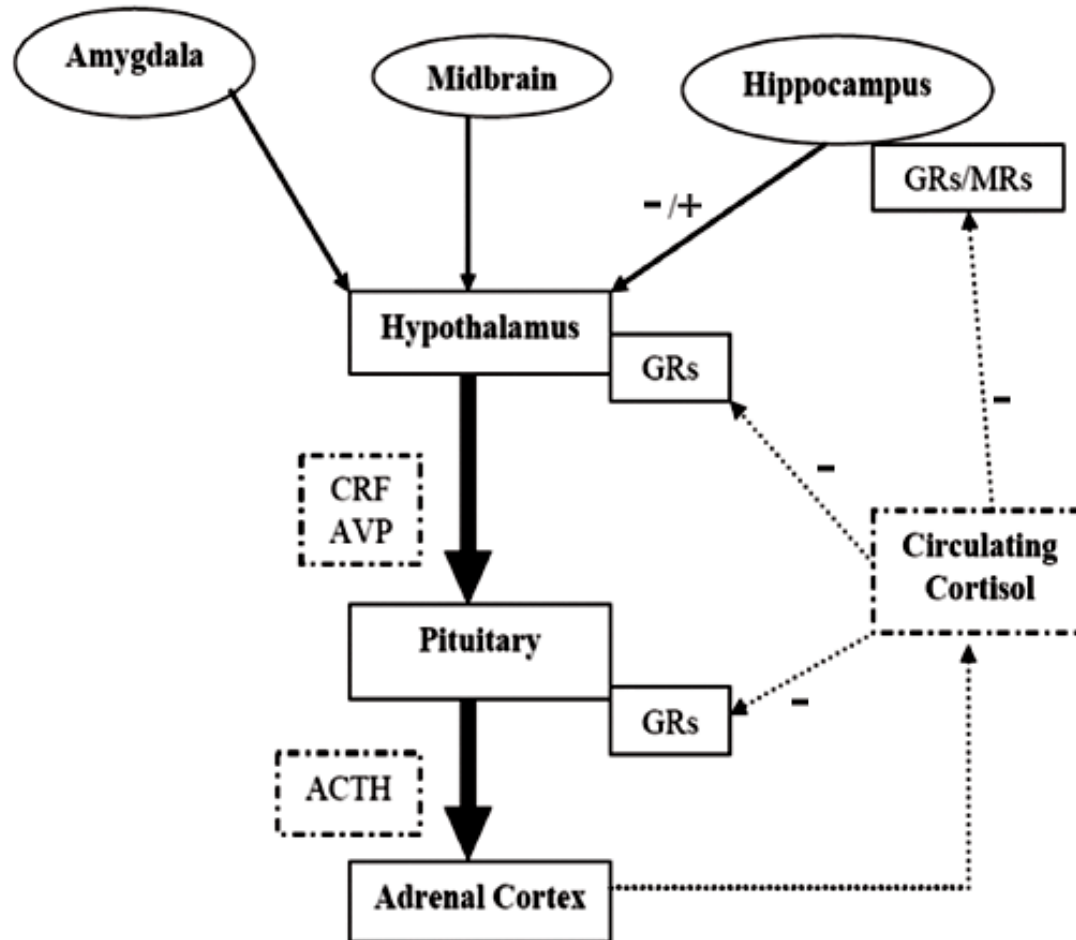
# Circadian regulation of EGFR feedback genes (liver and lung; WT mice)



Module A genes

Module B genes

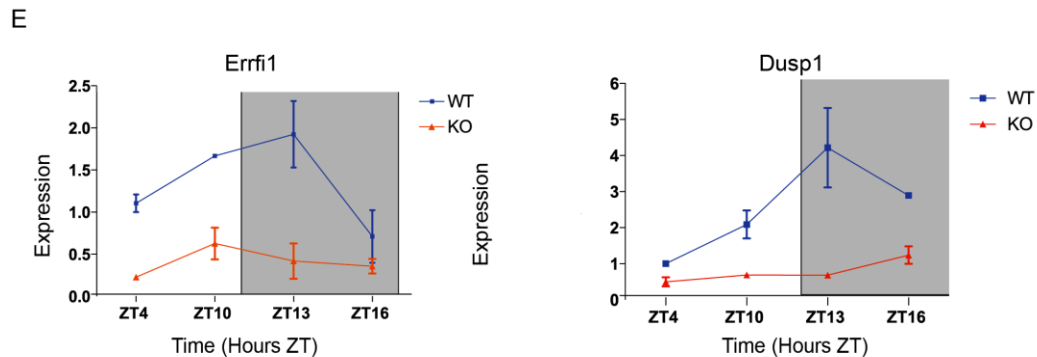
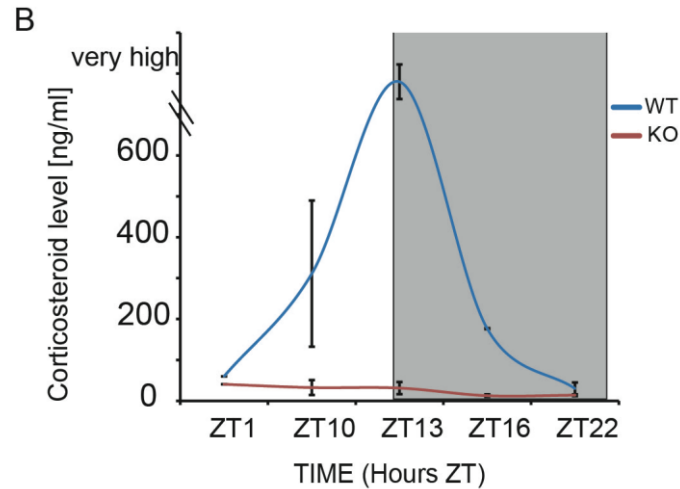
# The Hypothalamus-Pituitary-Adrenal (HPA) Axis





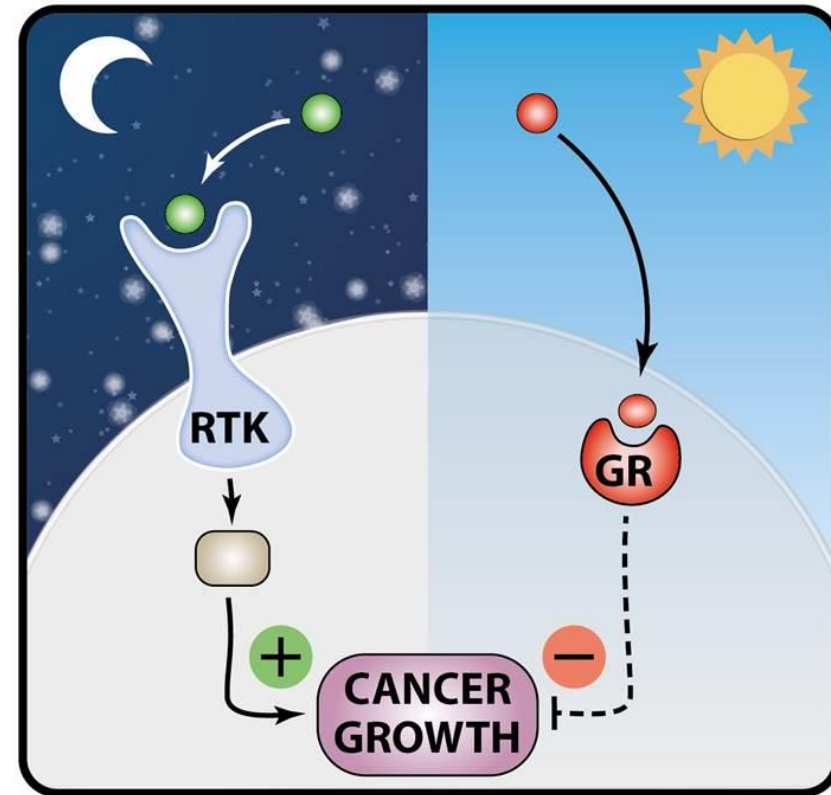
# Circadian regulation of EGFR negative regulators is defective in CRFR1-KO mice

In Red: CRFR1-depleted mice (CRFR1<sup>-/-</sup>)



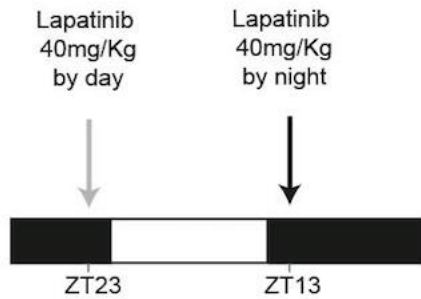
# Take-home Message #3: Circadian Regulation of EGFR

- **Glucocorticoid block EGF-induced migration of mammary cells by suppressing the activators and activating the inhibitors of EGFR.**
- **Our model predicts that EGFR is suppressed during daytime.**
- **If correct, EGFR's contribution to tumor progression might occur at night.**
- **Hence, inhibiting EGFR at night might be more beneficial than daytime treatments.**

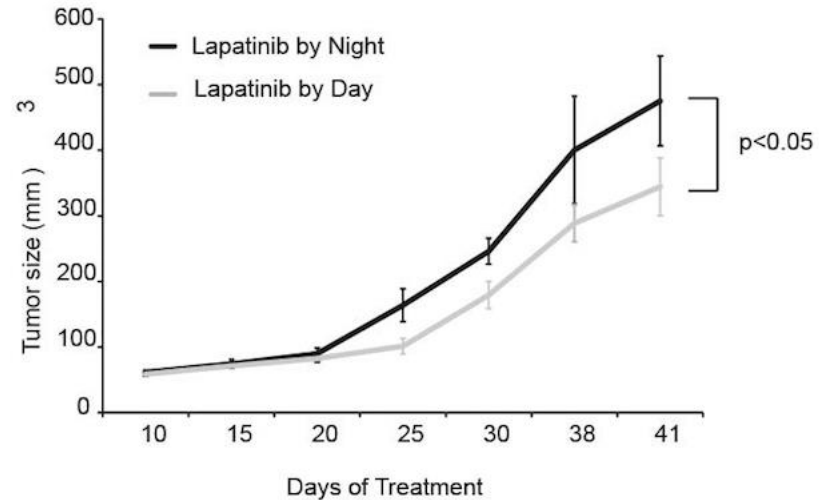


# HER2-overexpressing Gastric Cancer Xenografts: Superiority of Resting Phase Treatment with Lapatinib

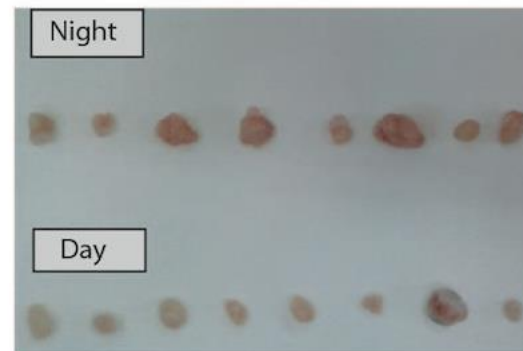
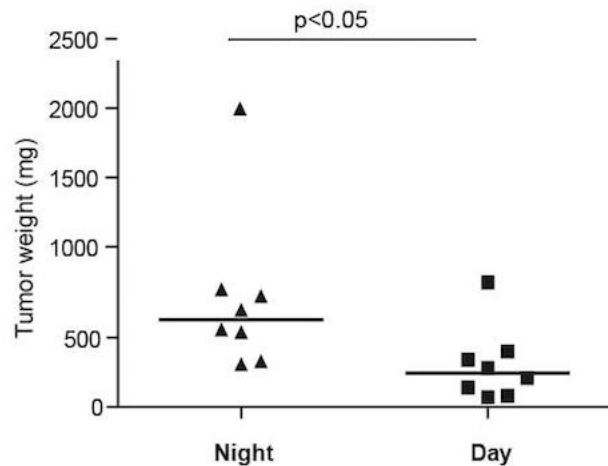
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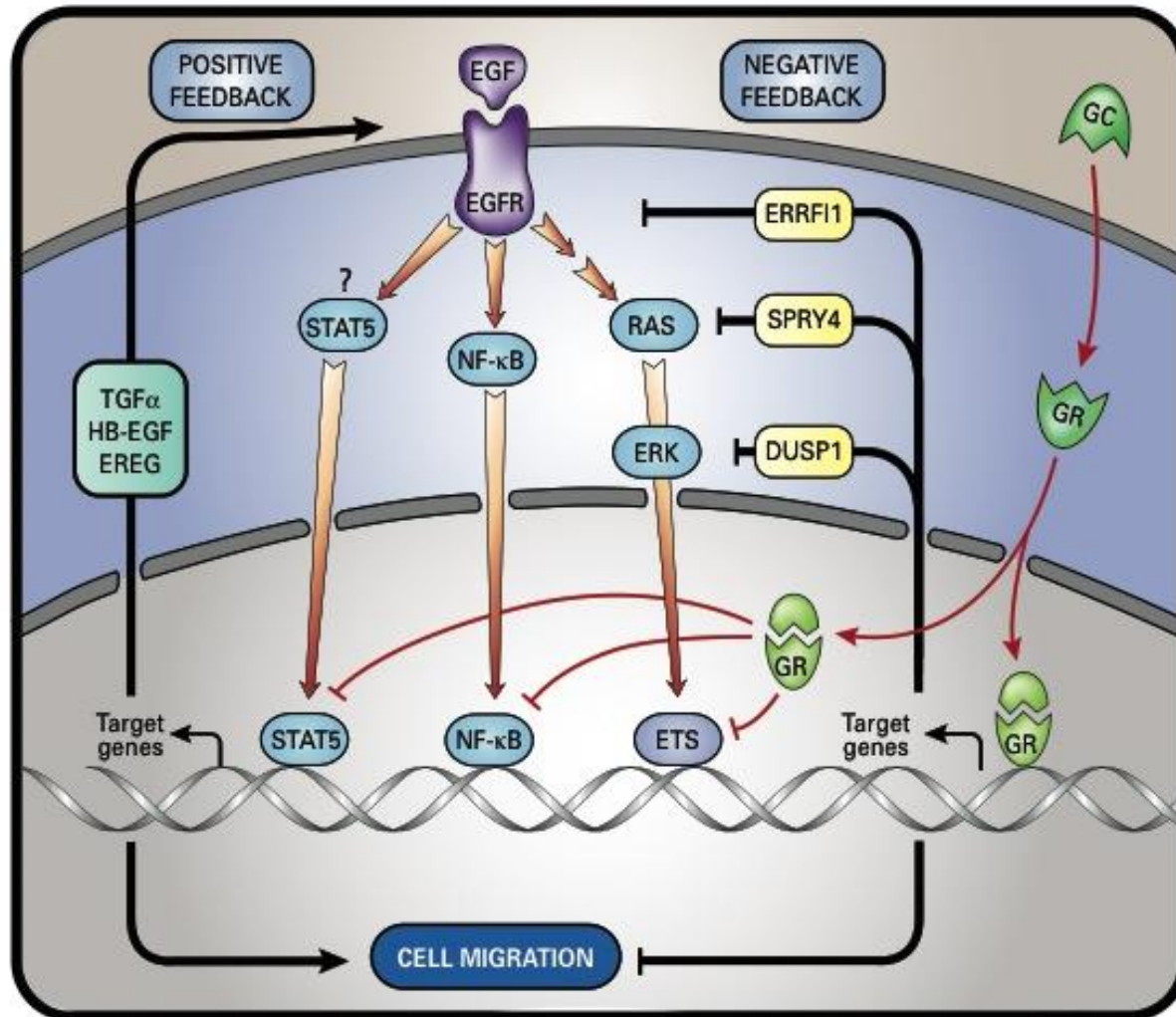
E



F



# GR Inhibits the EGFR Gene Program by Stimulating EGFR Negative Feedback and Suppressing Essential TFs



# Chronobiology of RTKs: Messages

1. Pulsatility of RTK signaling depends on wt-p53; it might be lost in tumors, leading to unregulated cellular proliferation.
2. Growth factor signaling is strongly suppressed by the glucocorticoid receptor, implying that some tumors might progress at the resting phase (night, in human).
3. Better understanding of the chronobiology of RTKs might improve cancer therapy.

# Acknowledgements



## My Group

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