

# HER receptor family and pathways: a system biology perspective

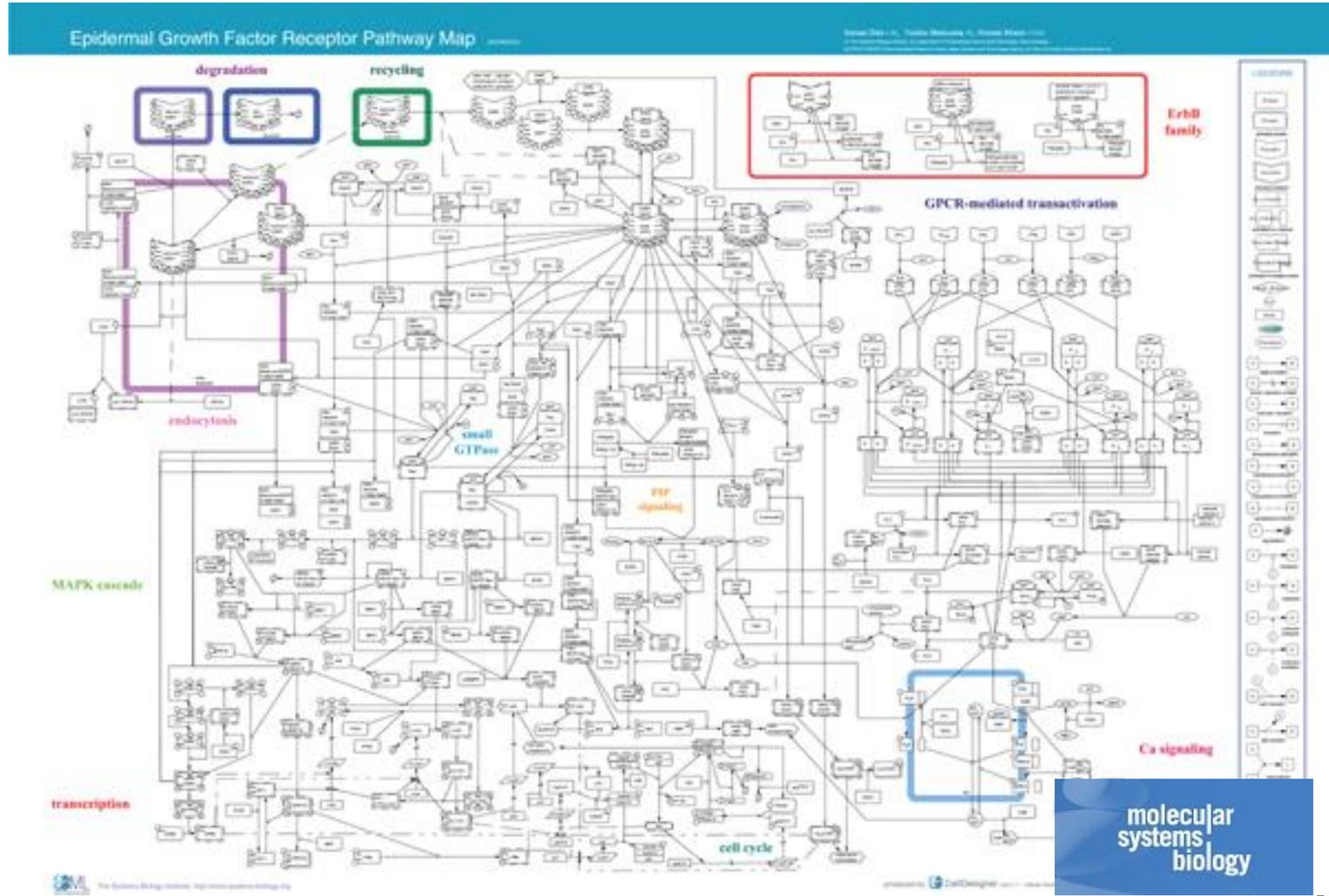
*Mattia Lauriola, Ph.D*

*4<sup>th</sup> International Conference*

*TRANSLATIONAL RESEARCH IN ONCOLOGY*

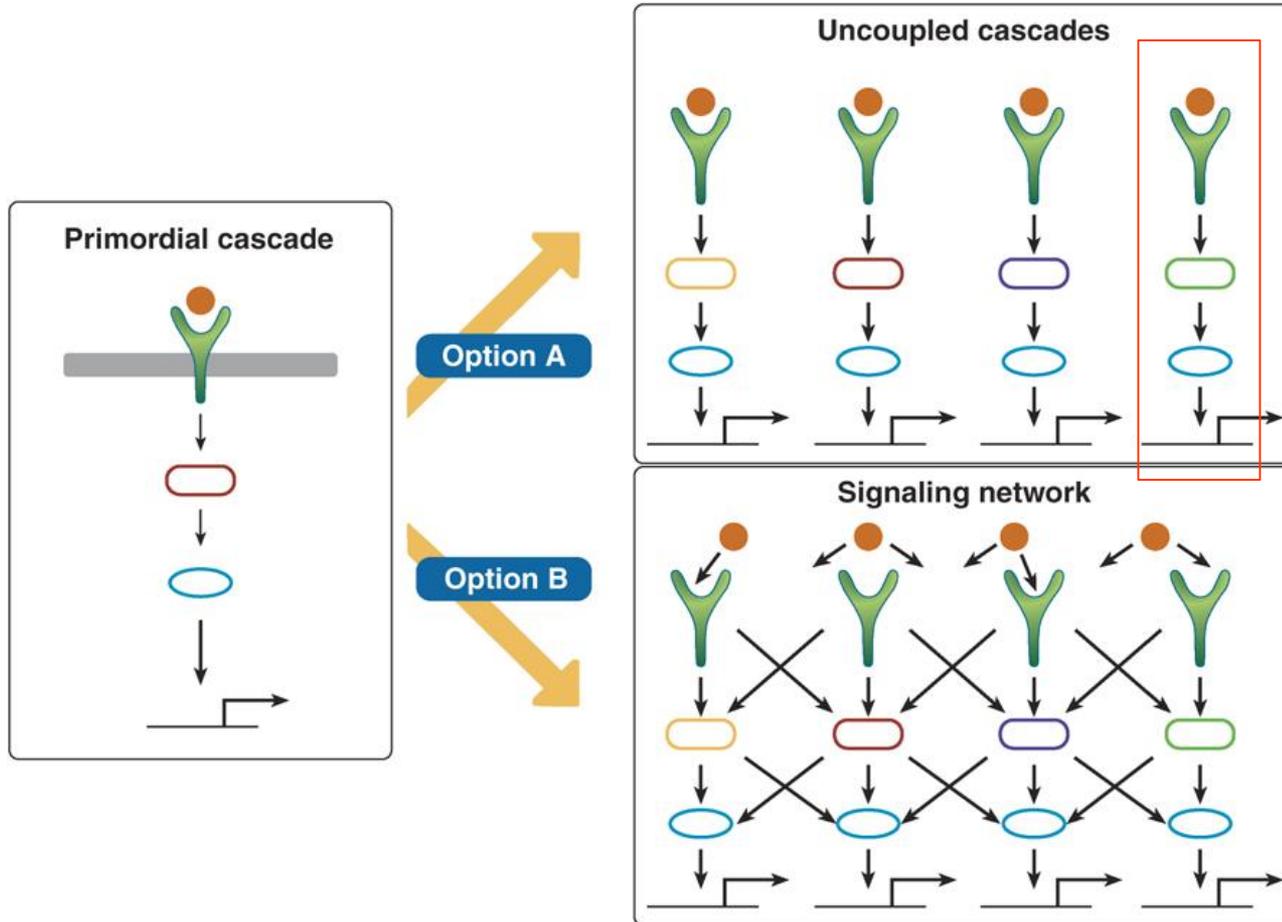
*Forli, November 9<sup>th</sup>*

# Signaling Complexity: The engineering perspective



adapted from Kanae Oda et al. Mol Syst Biol 2005;1

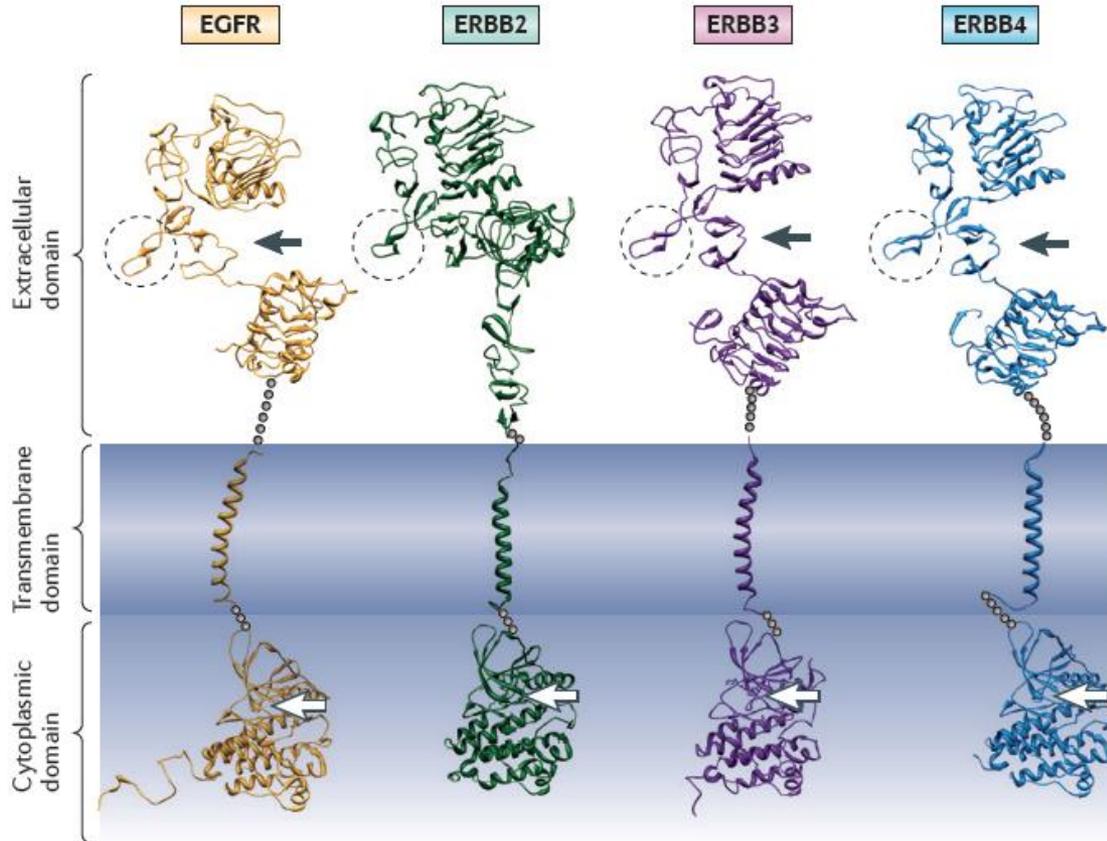
# From a vertical ERBB cascade to a signaling network: the evolution road



Imparts  
robustness  
and  
guarantees  
output  
reproducibility.

adapted from Ido Amit et al. Mol Syst Biol 2007

# The ERBB family

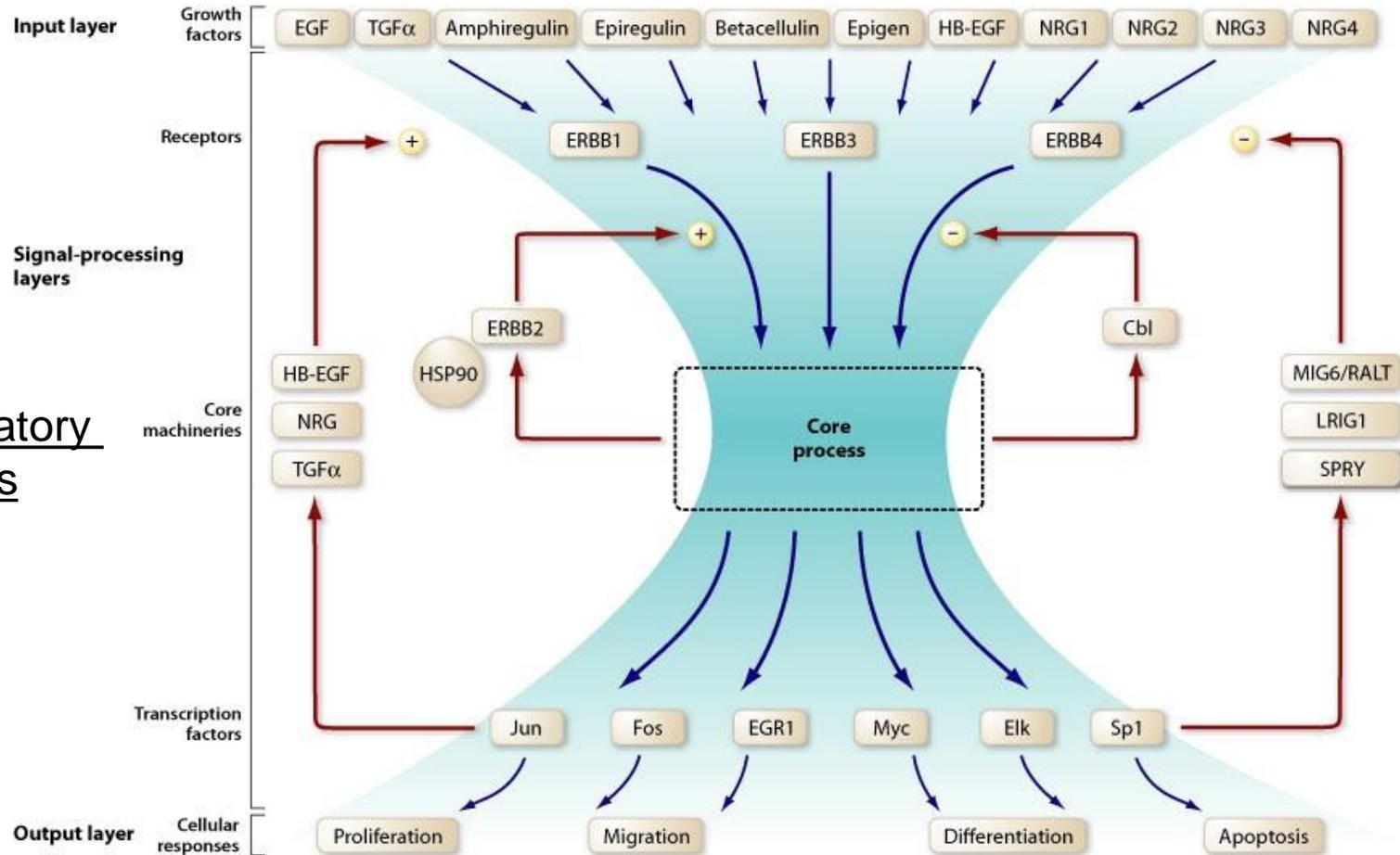


ERBB2 is a ligand-less receptor, which amplifies and prolongs signalling by forming functional hetero dimers

ERBB3 is a catalytically defective receptor

adapted from Pines & Yarden Y, *Nat Rev Mol Cell Biol.* 2006

# The ERBB family network



Inflammatory cytokines

adapted from Citri A & Yarden Y *Nat Rev Mol Cell Biol.* 2006



# Mechanisms Ensuring **Robustness** of Signaling Networks

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Modularity: Organization in Units that enable damage containment

Redundancy: Multiple input and output diversity

System Control: Bi-stability switch between negative and positive feedback control loops

Plasticity: flexibility in pathway switching



# Feedback



## LETTER

doi:10.1038/nature10868

### Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Prahallad<sup>1\*</sup>, Chong Sun<sup>1\*</sup>, Sidong Huang<sup>1\*</sup>, Federica Di Nicolantonio<sup>2,3\*</sup>, Ramon Salazar<sup>4</sup>, Davide Zecchin<sup>2</sup>, Roderick L. Beijersbergen<sup>1</sup>, Alberto Bardelli<sup>2,3</sup> & René Bernards<sup>1</sup>

Cancer Cell  
**Article**

CellPress

The up-front  
poly-therapy.

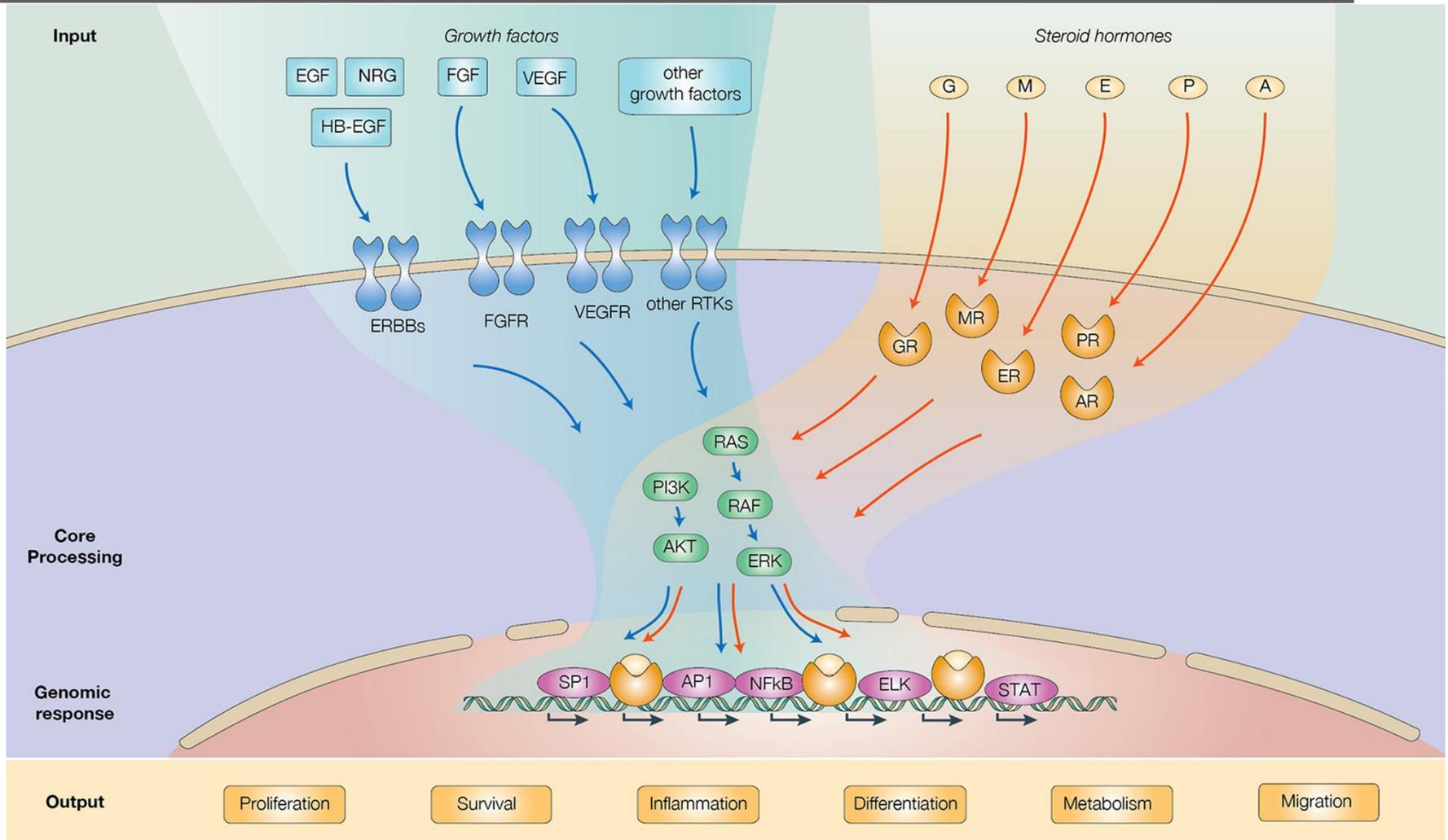
#### Drug Resistance via Feedback Activation of Stat3 in Oncogene-Addicted Cancer Cells

Ho-June Lee,<sup>1</sup> Guanglei Zhuang,<sup>1</sup> Yi Cao,<sup>2</sup> Pan Du,<sup>2</sup> Hyo-Jin Kim,<sup>1</sup> and Jeff Settleman<sup>1\*</sup>

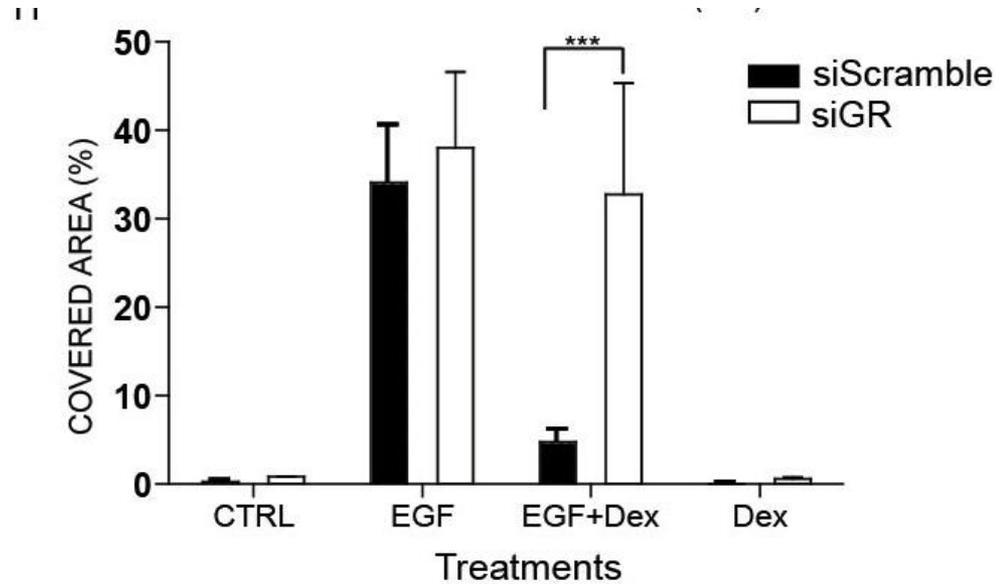
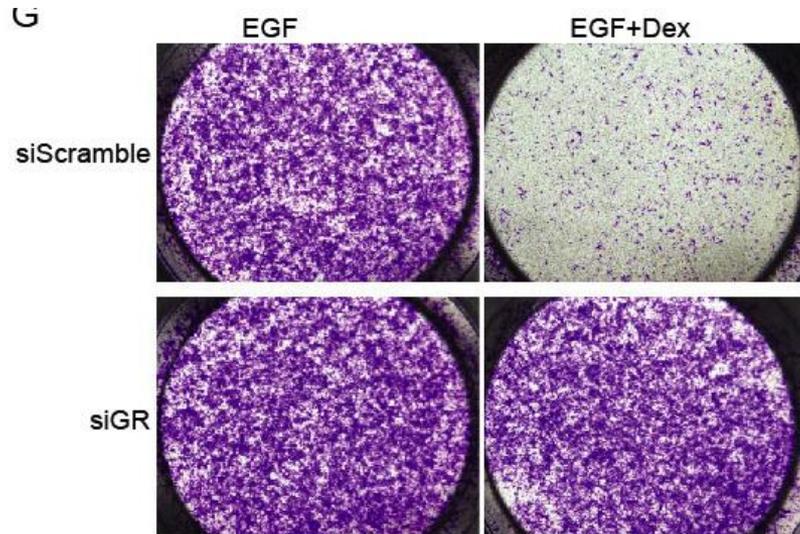
Feedback regulation of EGFR signalling: decision making by early and delayed loops

*Roi Avraham and Yosef Yarden*

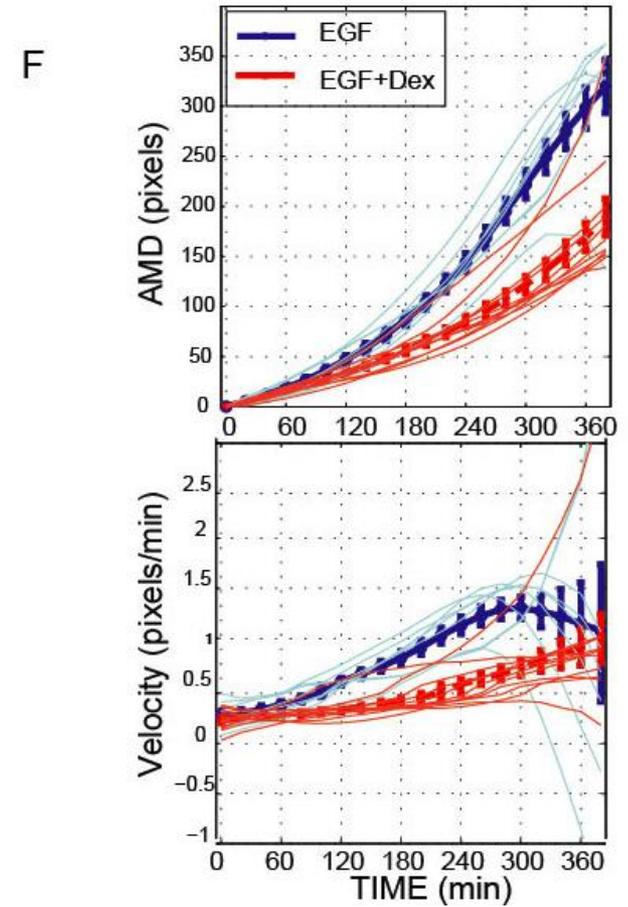
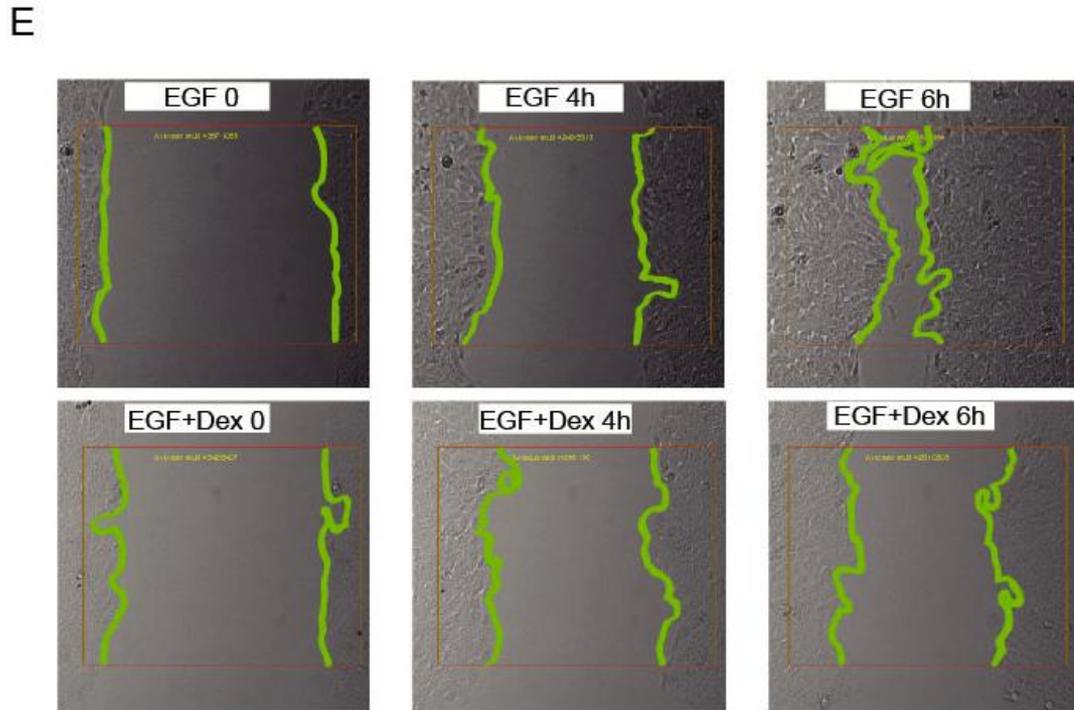
# Towards the emerging cross-talk: ERBB family and steroid hormones



# Ligand-activated GRs inhibit EGF-induced motility of mammary cells

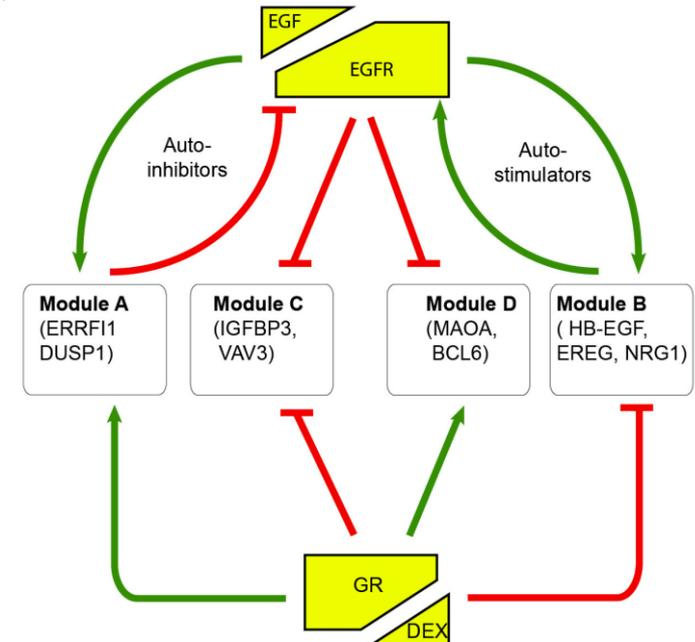
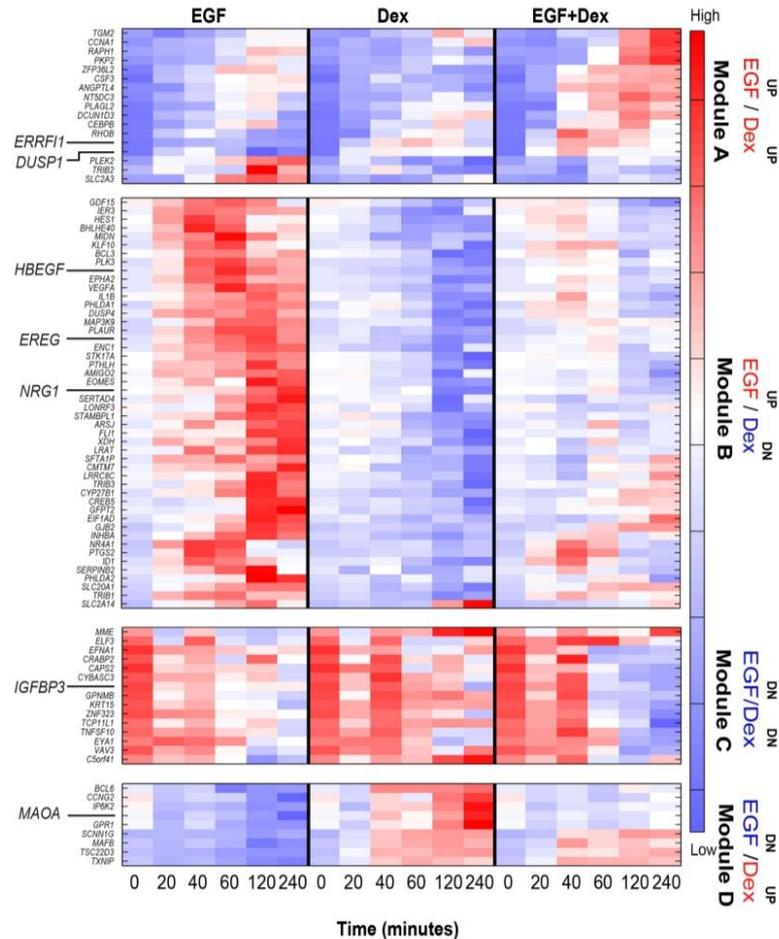


# Ligand-activated GRs inhibit EGF-induced motility of mammary cells

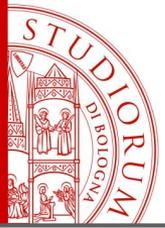


Lauriola et al, Nature Communications, 2014

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

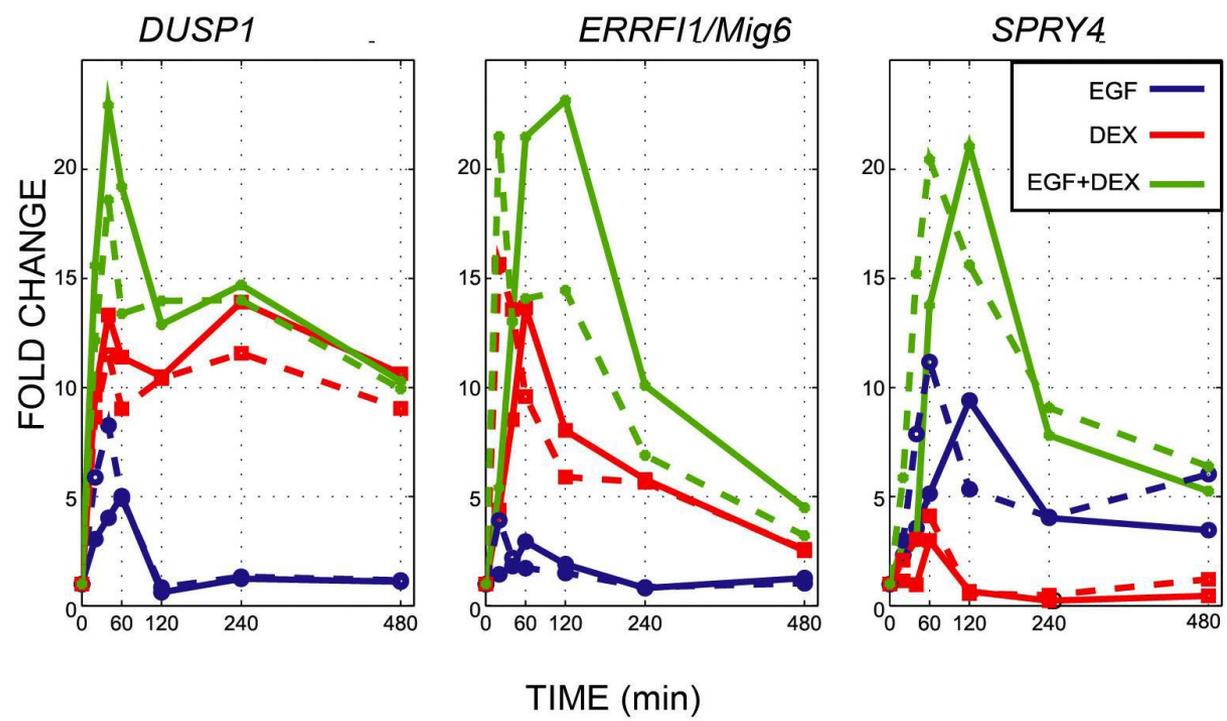


Lauriola et al, Nature Communications, 2014

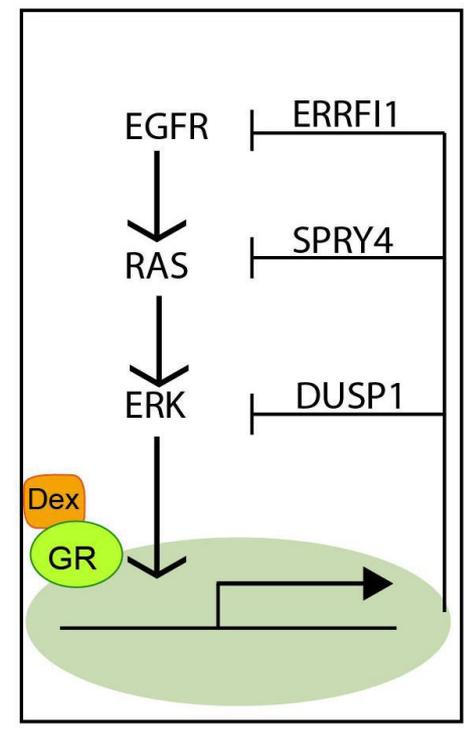


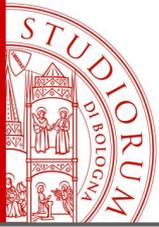
# GR exploits the EGFR gene program by activating the feedback inhibitors

A

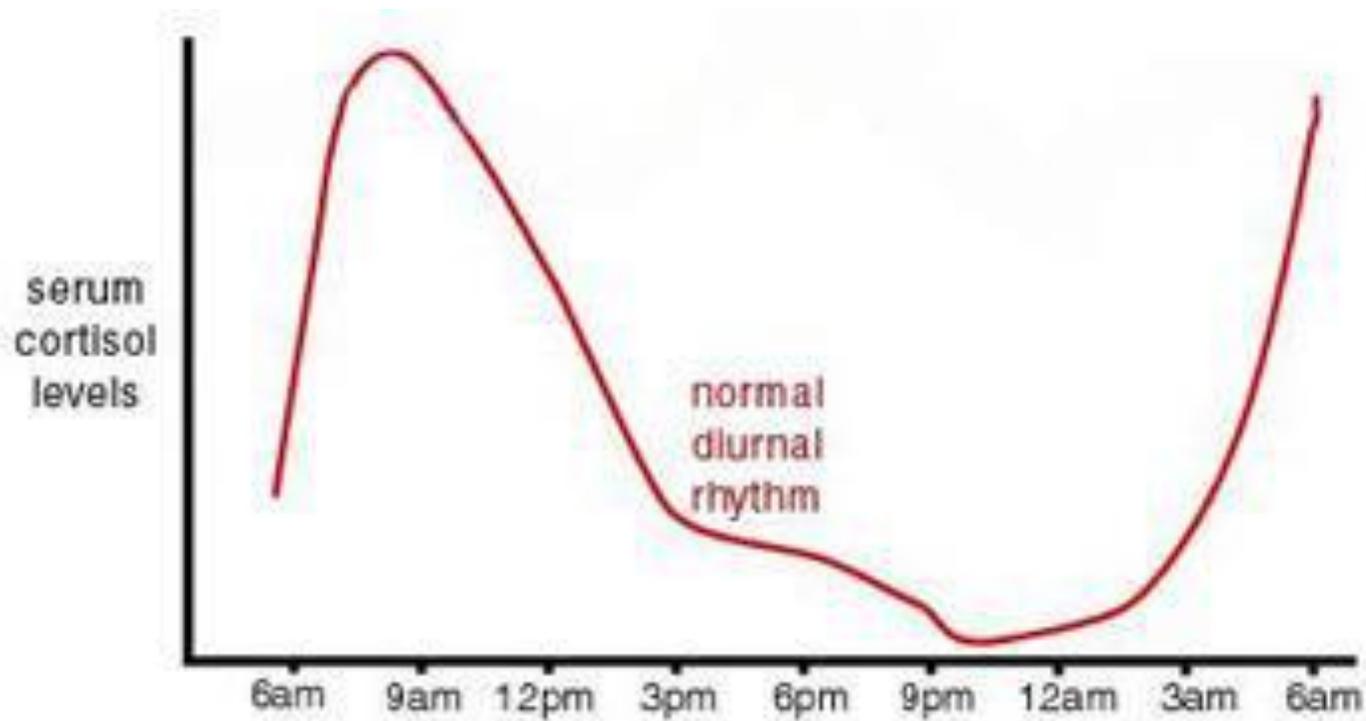


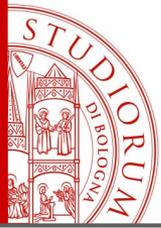
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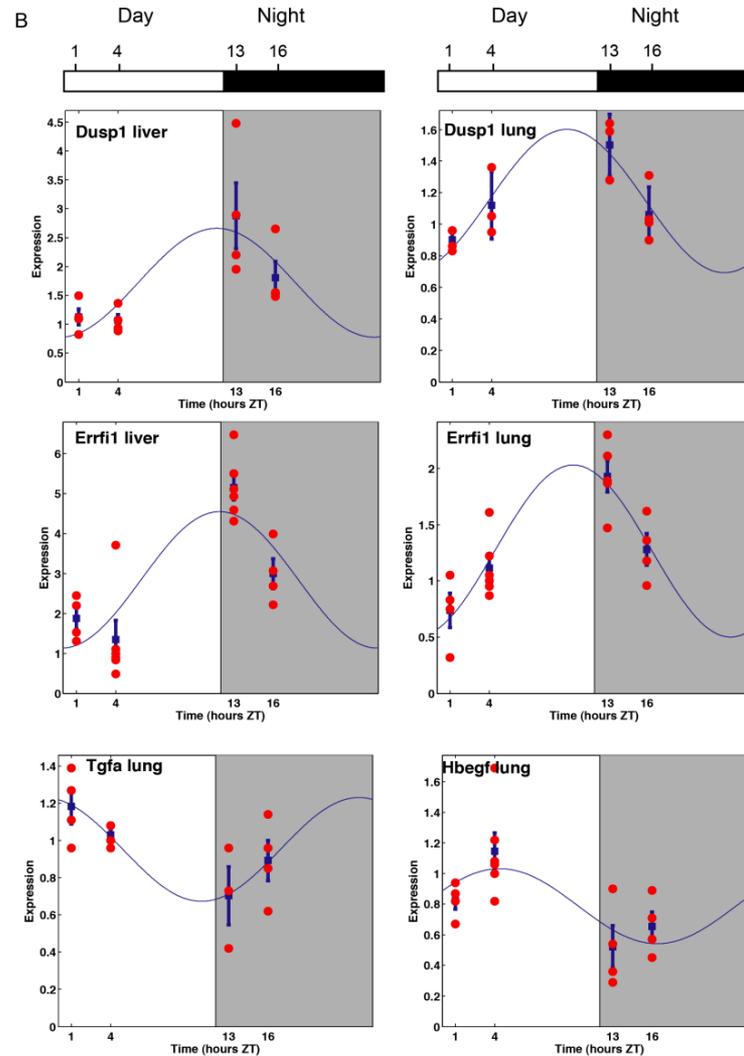


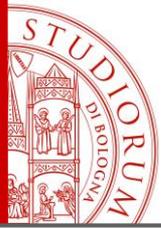
# Circadian Oscillations of Serum Cortisol Levels in Human





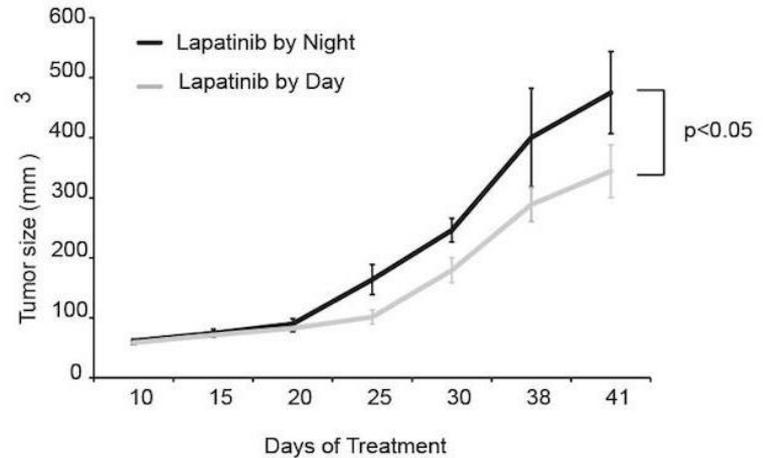
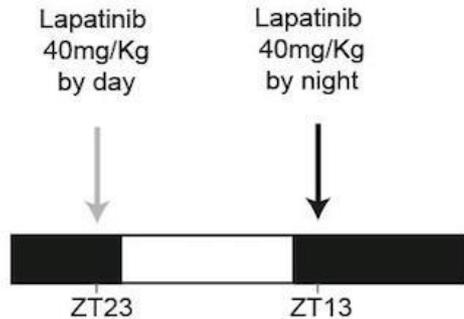
# Circadian regulation of EGFR feedback genes (liver and lung; WT mice)



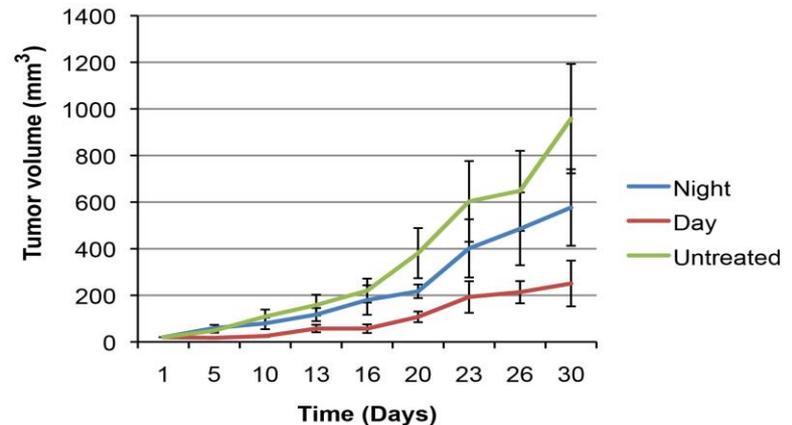


# EGFR inhibitors display potentiated activity when administrated during the resting phase

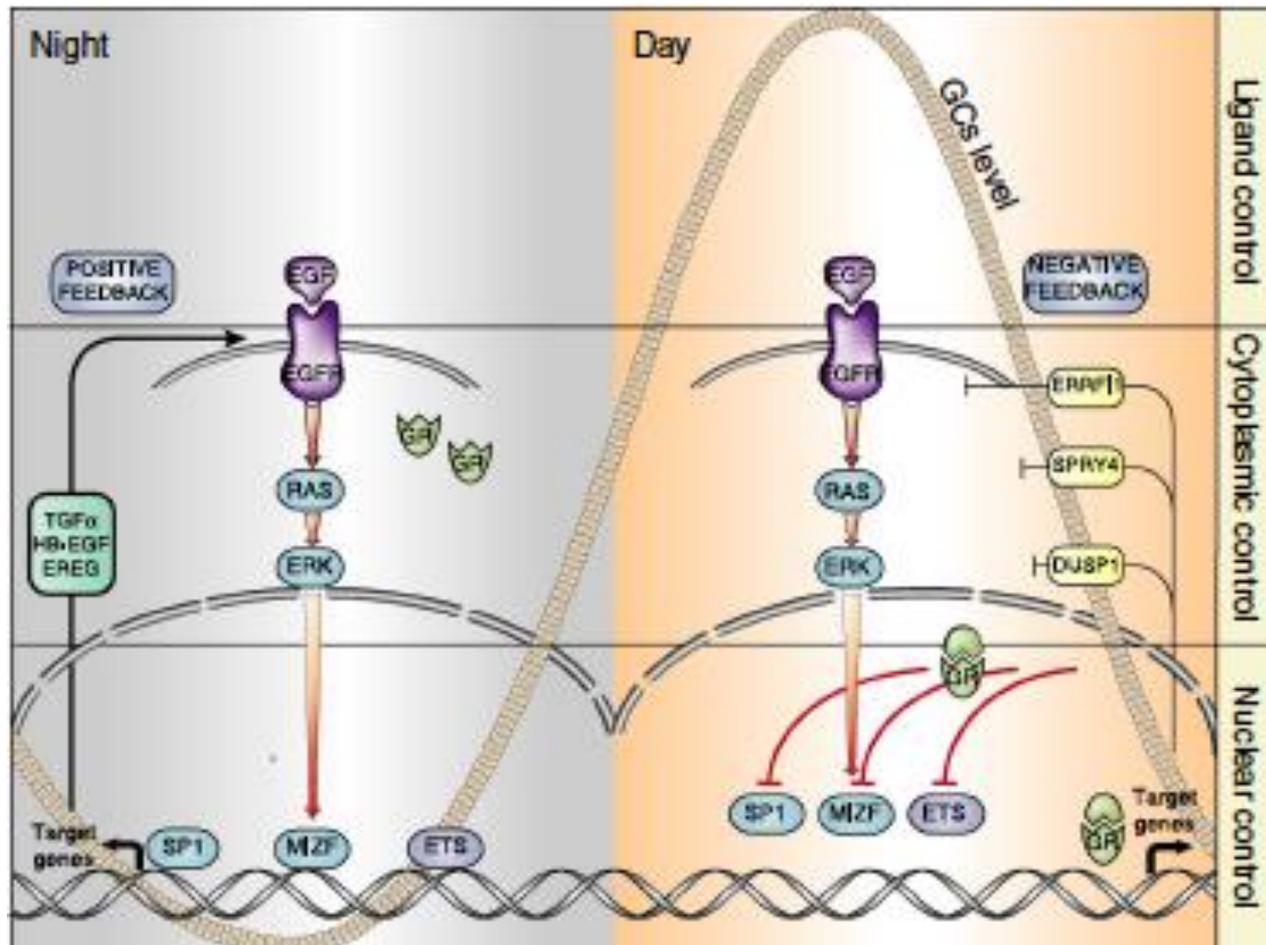
D



60 mg/kg/day



# EGFR inhibitors display potentiated activity when administrated during the resting phase





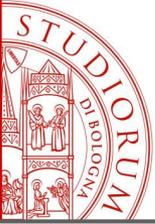
## Take Home Message #1

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Glucocorticoids block EGFR pathway, by suppressing the positive feedback and activating the negative feedback, 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.



# A module of positive feedback defines resistance to Cetuximab in colorectal cancer

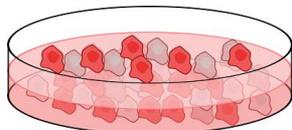
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- mCRC are EGFR dependent and anti EGFR monoclonal antibodies represent the first line treatment. Unfortunately, resistance typically occurs within 3–18 months after treatment initiation.
- Primary Resistance: tumors are refractory to therapy, can be explained by resistance-conferring factors preexisting in the bulk of tumor cells (e.s genomic mutations)
- Acquired Resistance: refers to disease progression in the face of ongoing treatment that was initially effective and can be caused by mutations arising during treatment as well as through other various **adaptive nongenetic responses**.

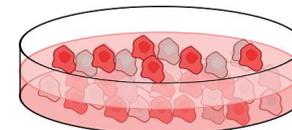
**The field of acquired resistance has received preclinical and clinical attention very recently**

# Establishment of a cells system resistant to cetuximab

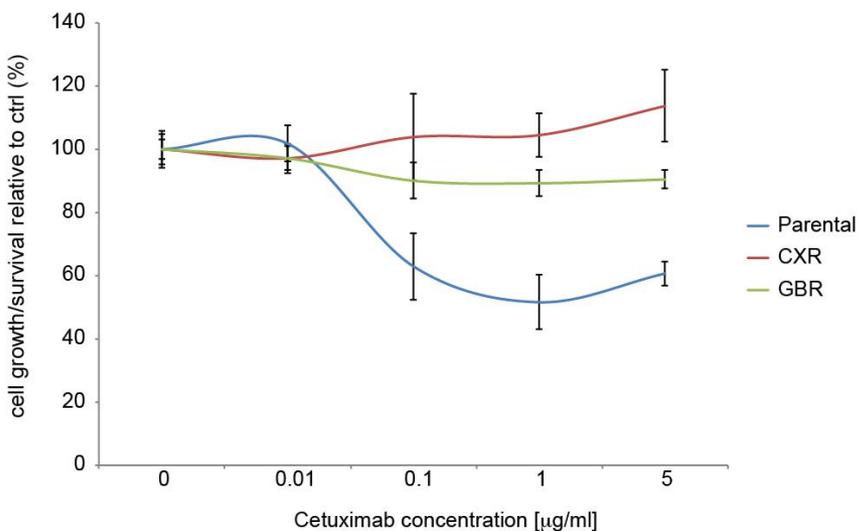
Caco-2



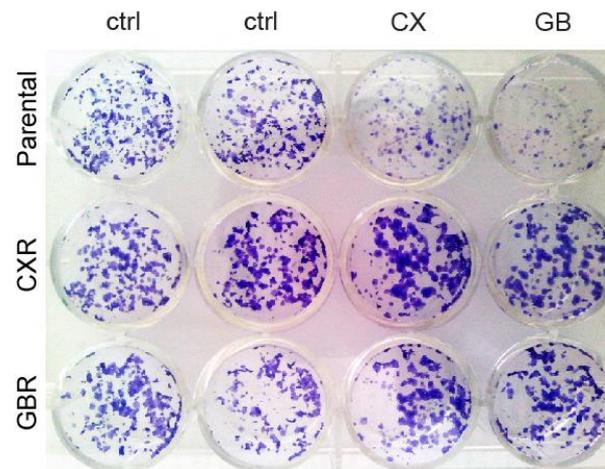
Caco-2 Resistant: CXR, GBR



Cetuximab and gefitinib exposure  
over 5 months

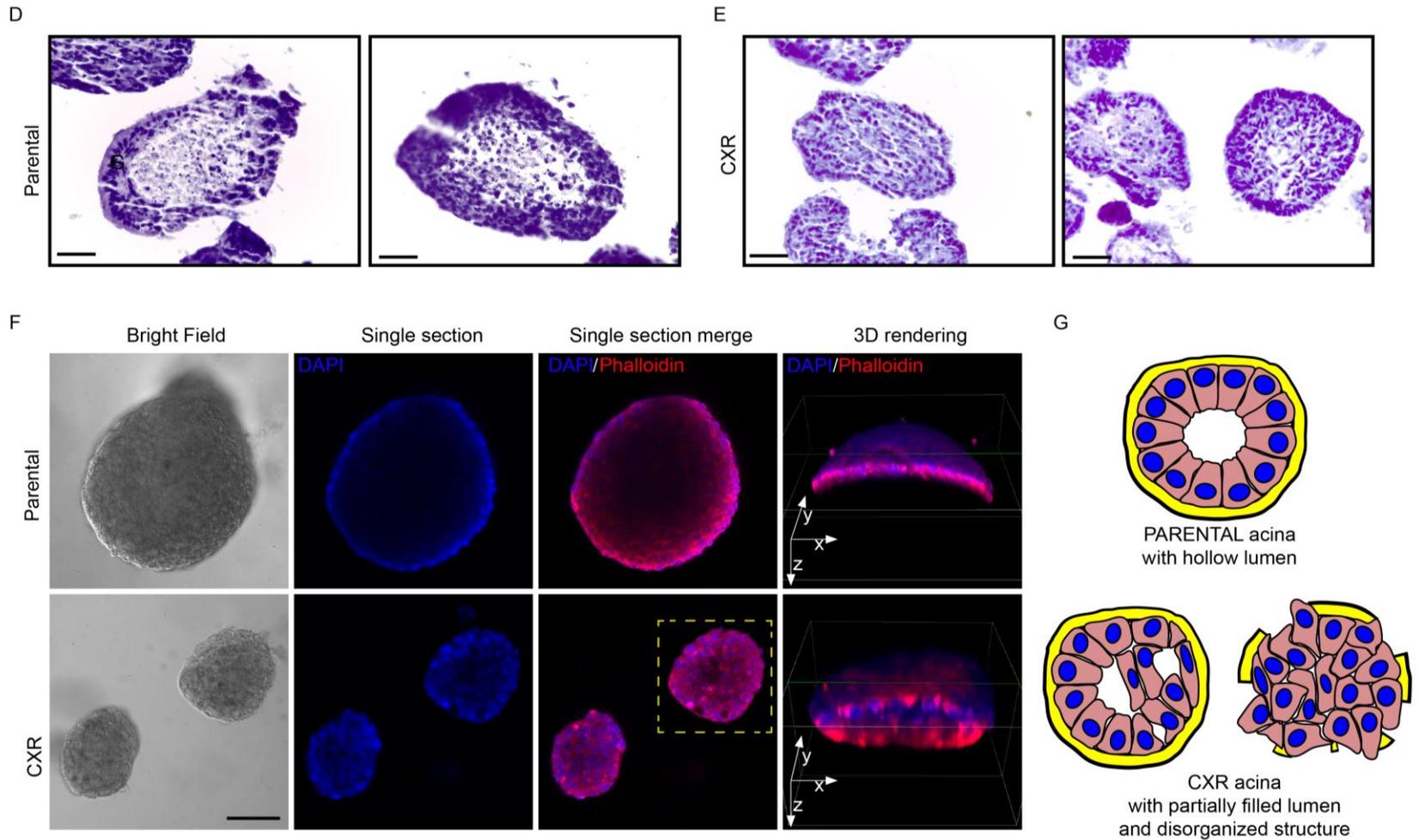


B



Gelfo V. et al, Oncotarget, 2016.

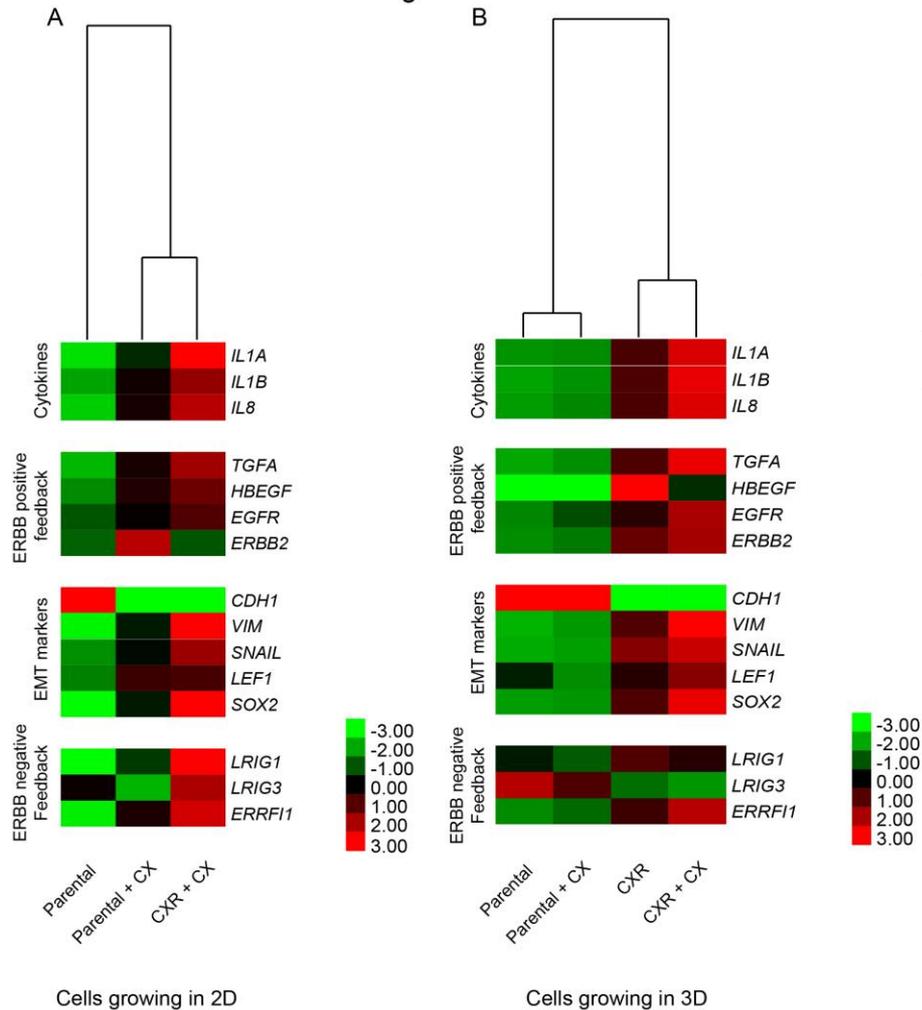
# Resistant clones displayed ability to growth in suspension as spheres



Gelfo V. et al, Oncotarget, 2016.

# Gene expression analysis of parental and CXR clones

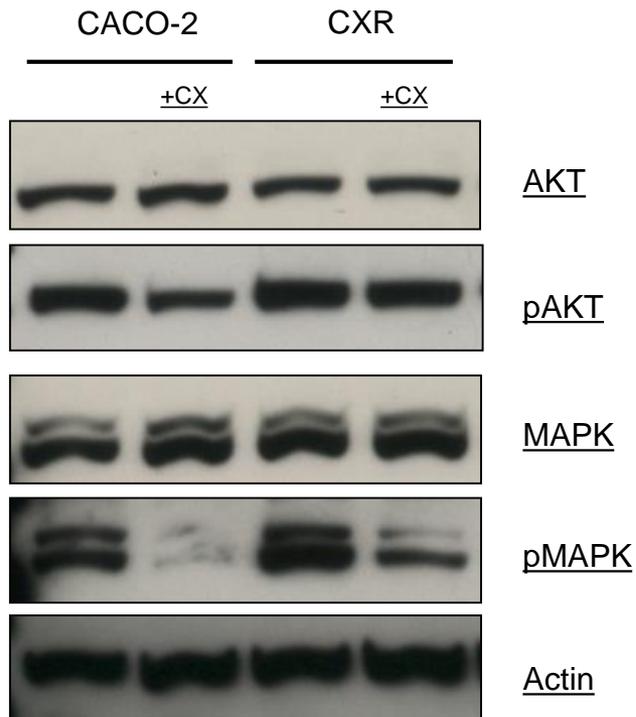
Figure 3



- ✓ Increase in Inflammatory cytokines
- ✓ Increase in EGFR ligands
- ✓ EMT markers

Gelfo V. et al, Oncotarget, 2016.

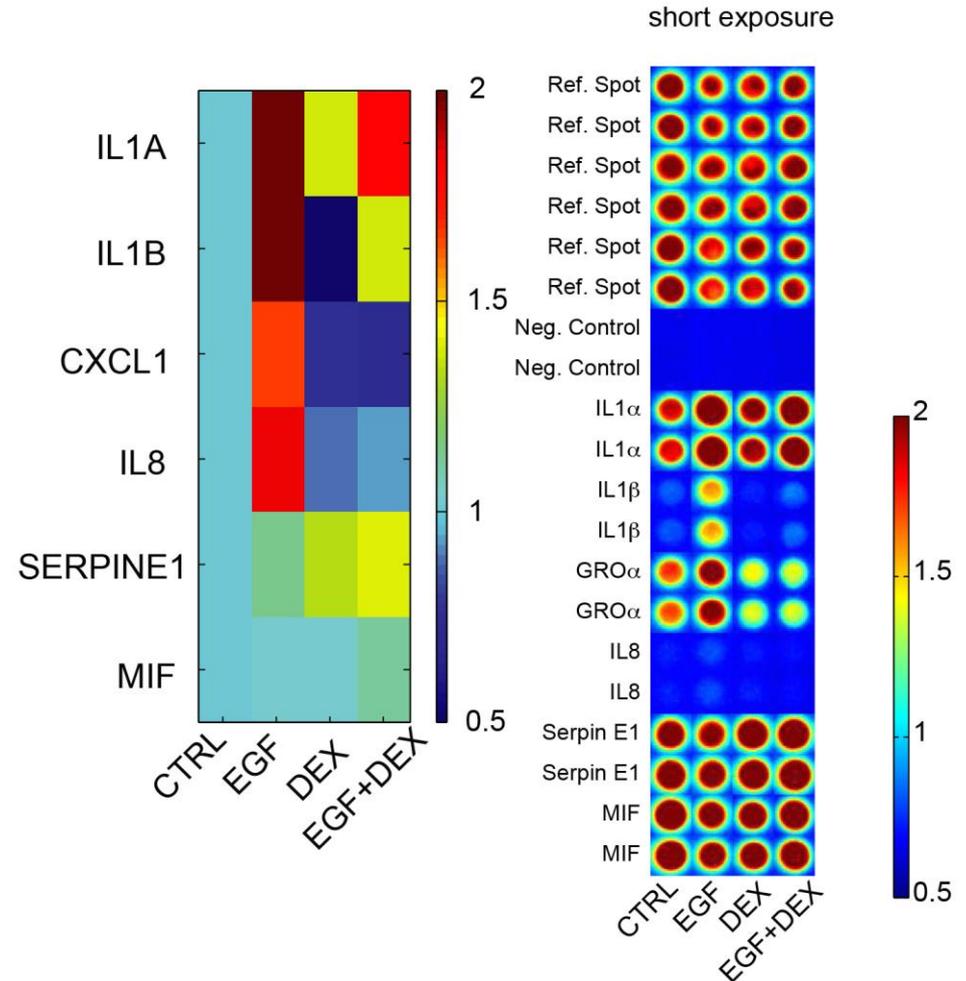
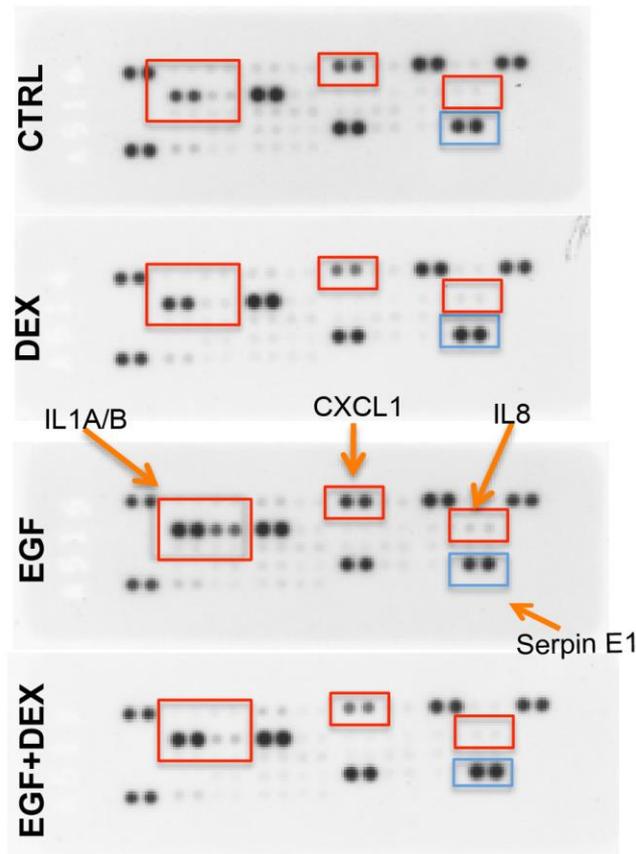
## Signaling pathways downstream to EGFR blockage



Resistant cells display higher level  
Activated ERK and AKT

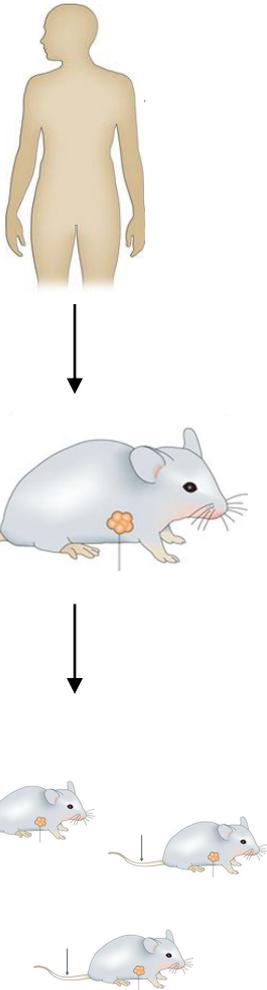
Gelfo V. et al, Oncotarget, 2016.

# EGFR activation controls the production of a module of inflammatory cytokines

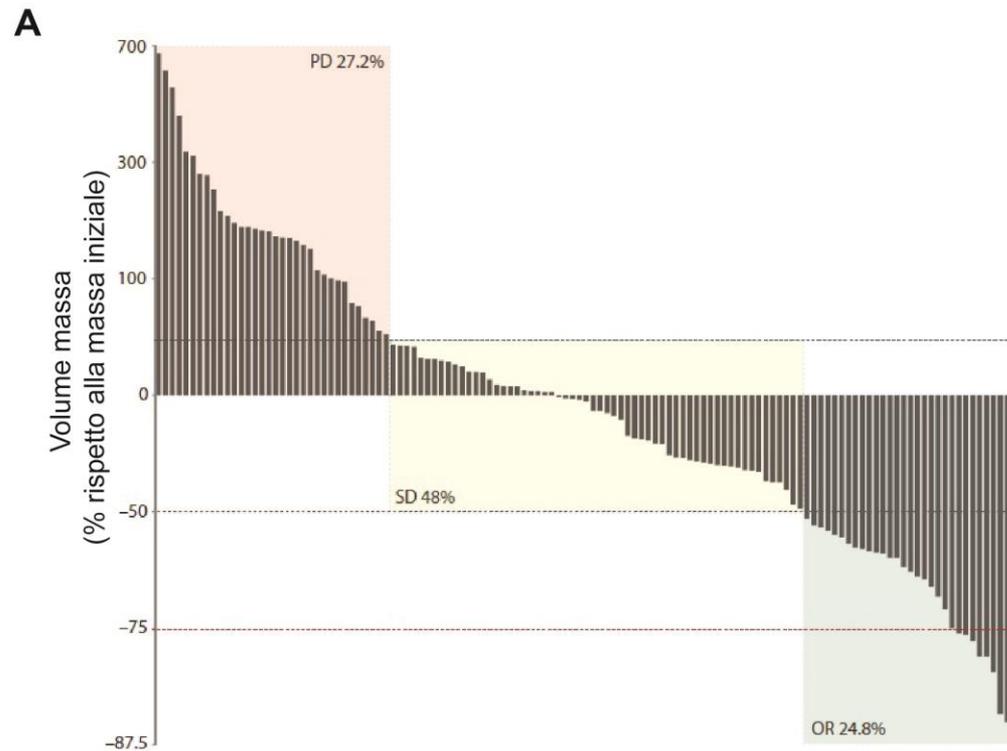


Gelfo V. et al, Oncotarget, 2016.

# The panel of inflammatory cytokines correlate with cetuximab response in colorectal patients



PD: Progressive Disease, 35% increase  
SD: Stable Disease, 35% increase and 50% reduction  
OR: Overall Response, more then 50% reduction

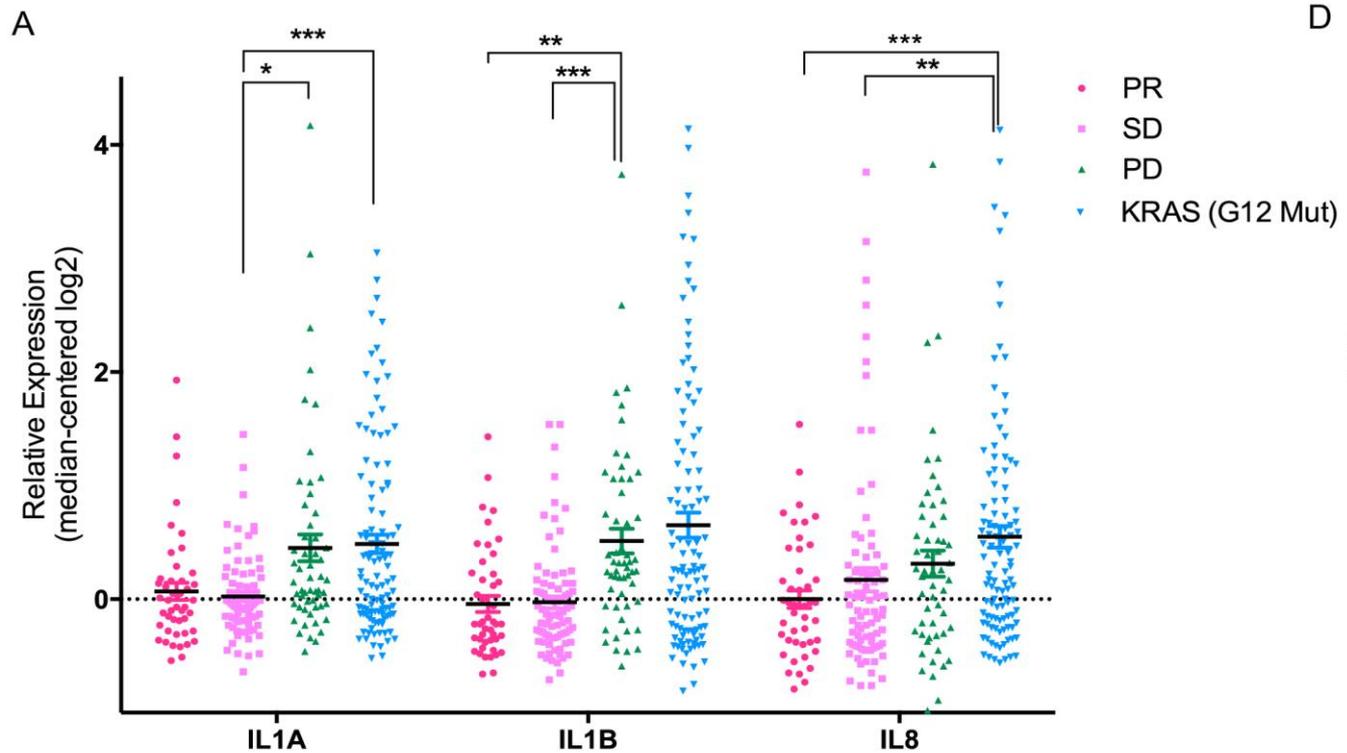


PD:  
SD: malattia stabile  
OR: regressione

adapted from Bertotti et al, *Cancer Discov.* **2011**



# The inflammatory cytokines IL1A/B and IL8 correlates with cetuximab response



Gelfo V. et al, Oncotarget, 2016.



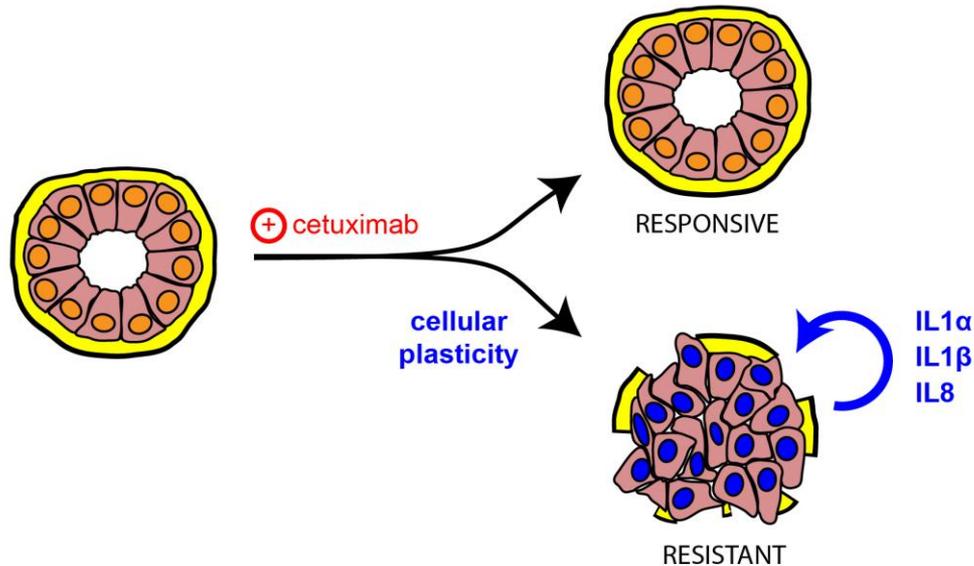
## To sum up

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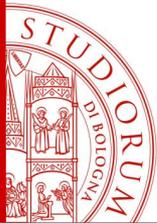
- ✓ The Caco-2 in vitro model suggests a mechanism of resistance to EGFR blockage shared by monoclonal antibody and small tyrosine kinase inhibitors
- ✓ Resistant clones permit phenotypic changes toward a more malignant phenotype, which enable the cells to grow in suspension
- ✓ Resistant phenotype is accompanied by increased expression of inflammatory cytokines and EGF-like growth factors as well as EMT/stem-like features

## Take Home Message #2

EGFR blockade might induce tumor plasticity, with up-regulation of a module of EGFR positive feedback loop, such as IL1A, IL1B and IL8, which might activate a compensatory pathway, thus overcoming EGFR inhibition.



**Poster #1**  
Valerio Gelfo



## Collaborators



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**Eitan Domani**

Amit Zeisel

Yeoshua Enuka

Silvia Carvalho

Moshit Lindzen

Lee Roth



**Gabriele D'Uva**



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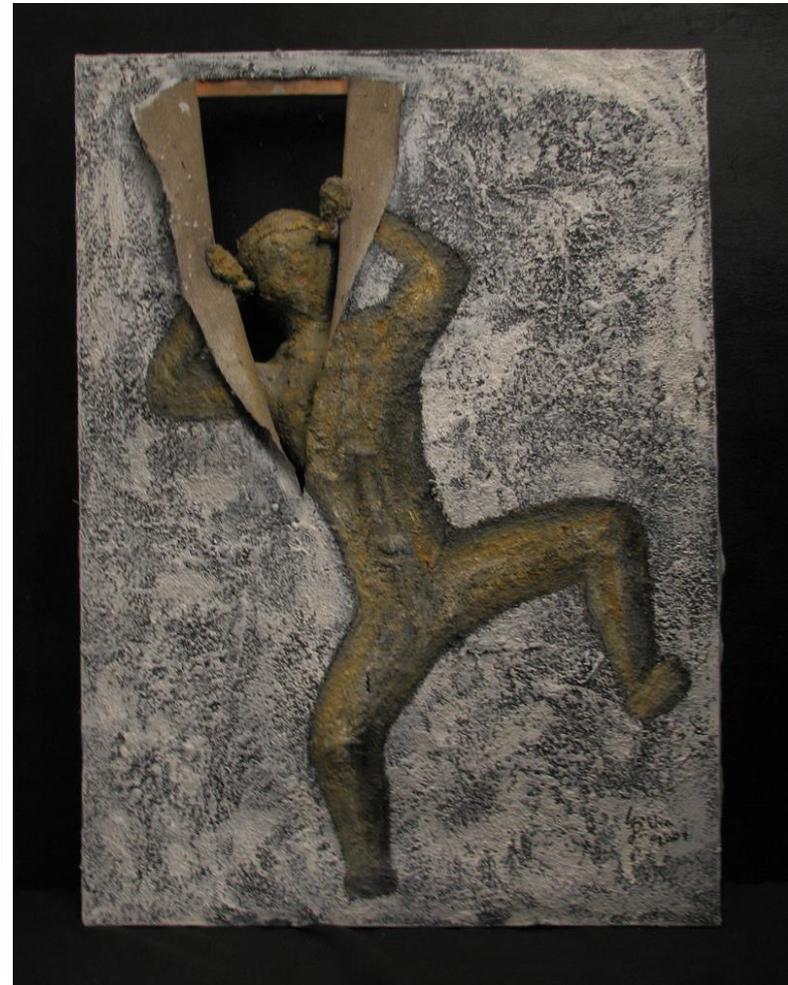
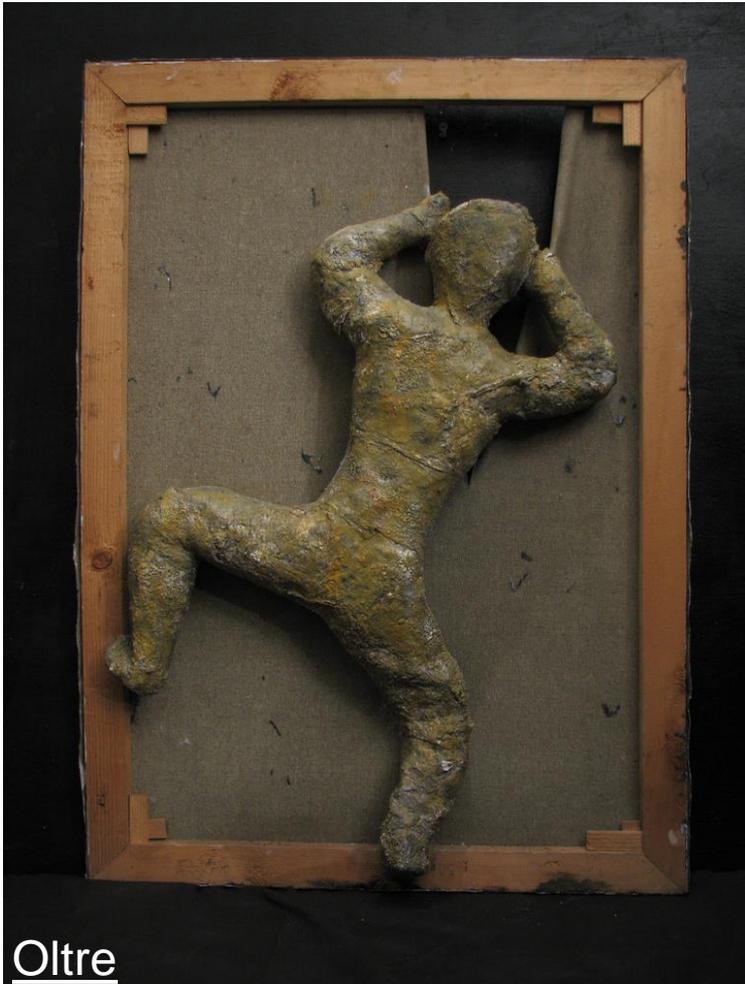


GERMAN  
CANCER RESEARCH CENTER  
IN THE HELMHOLTZ ASSOCIATION

Stefan Wiemann

Kirti Sharma

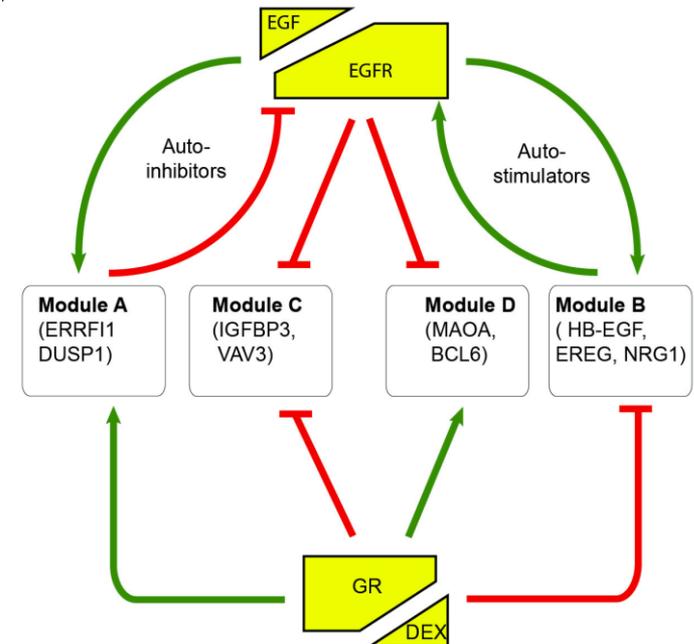
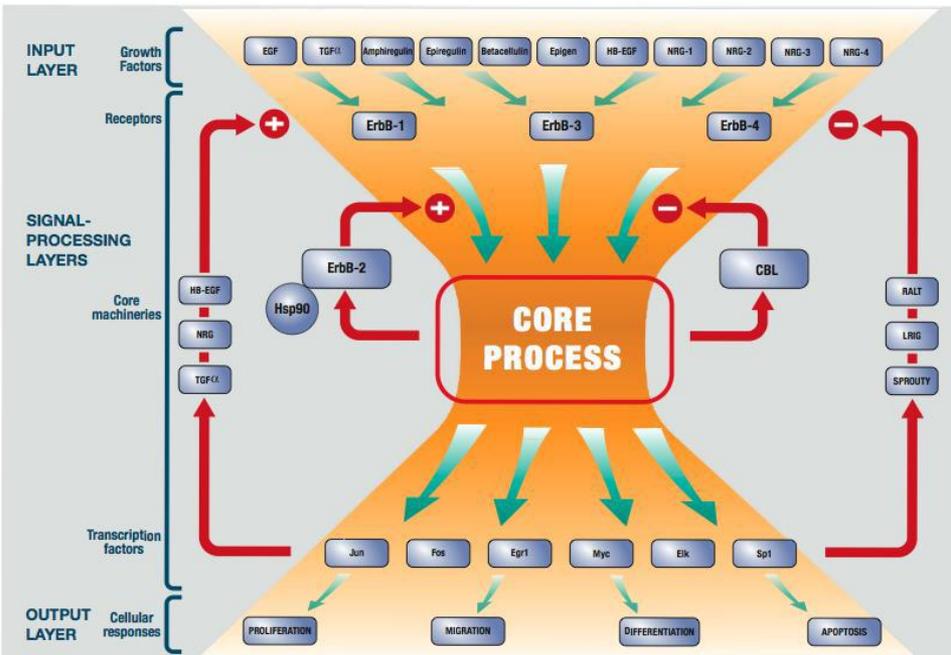
# Thanks for the attention



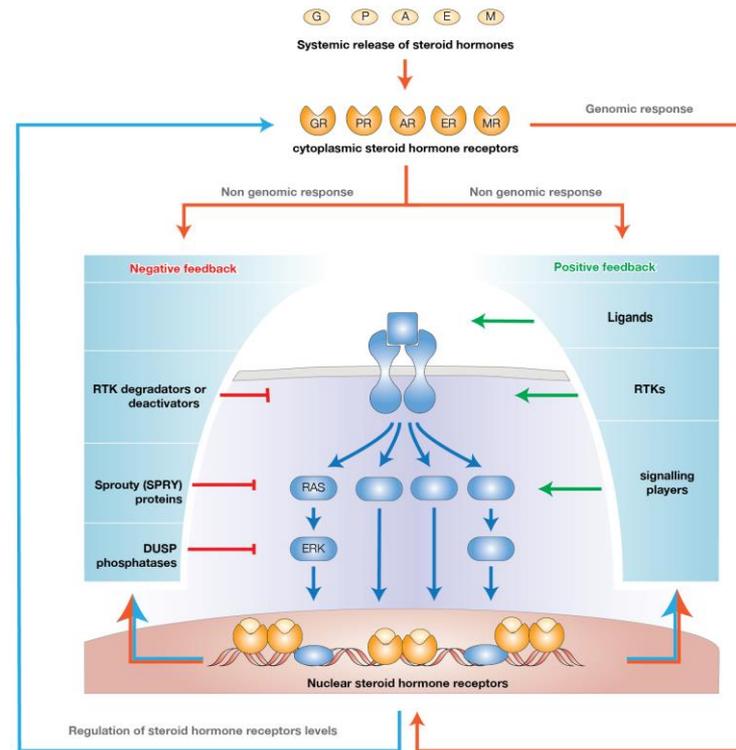
Oltre

Gabriele D'Uva  
Bologna 2008

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



# Towards the emerging cross-talk: ERBB family and steroid hormones



D'Uva G, Lauriola M, Semin Cell Dev Biol. 2016 Feb

Schematic diagram showing that a systemic release of steroid hormones regulates ERBB (and RTK) signalling by modulation of either positive and negative feedback mechanisms, at genomic and non genomic levels.