HER2 and EGFR: at last, cancer therapy meets systems biology

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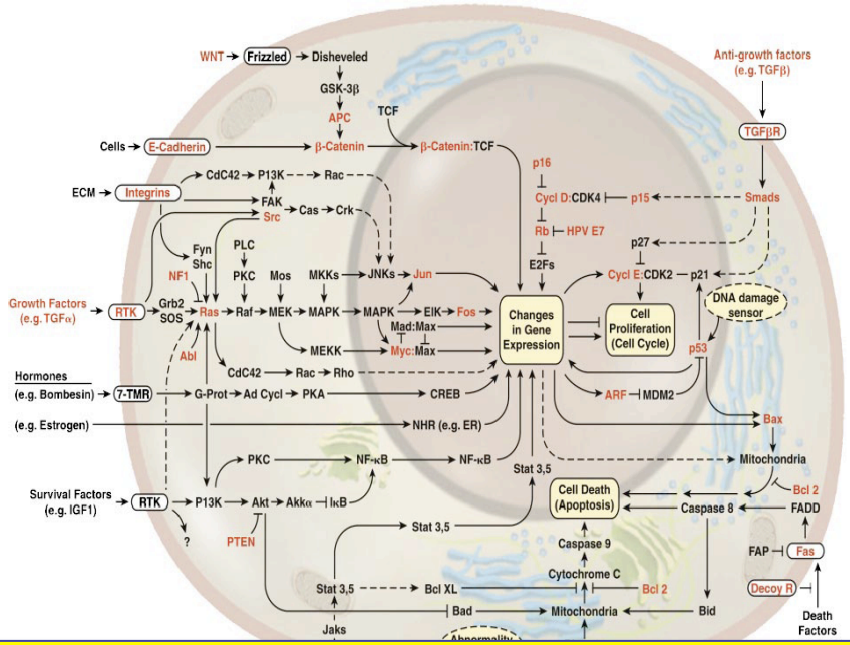
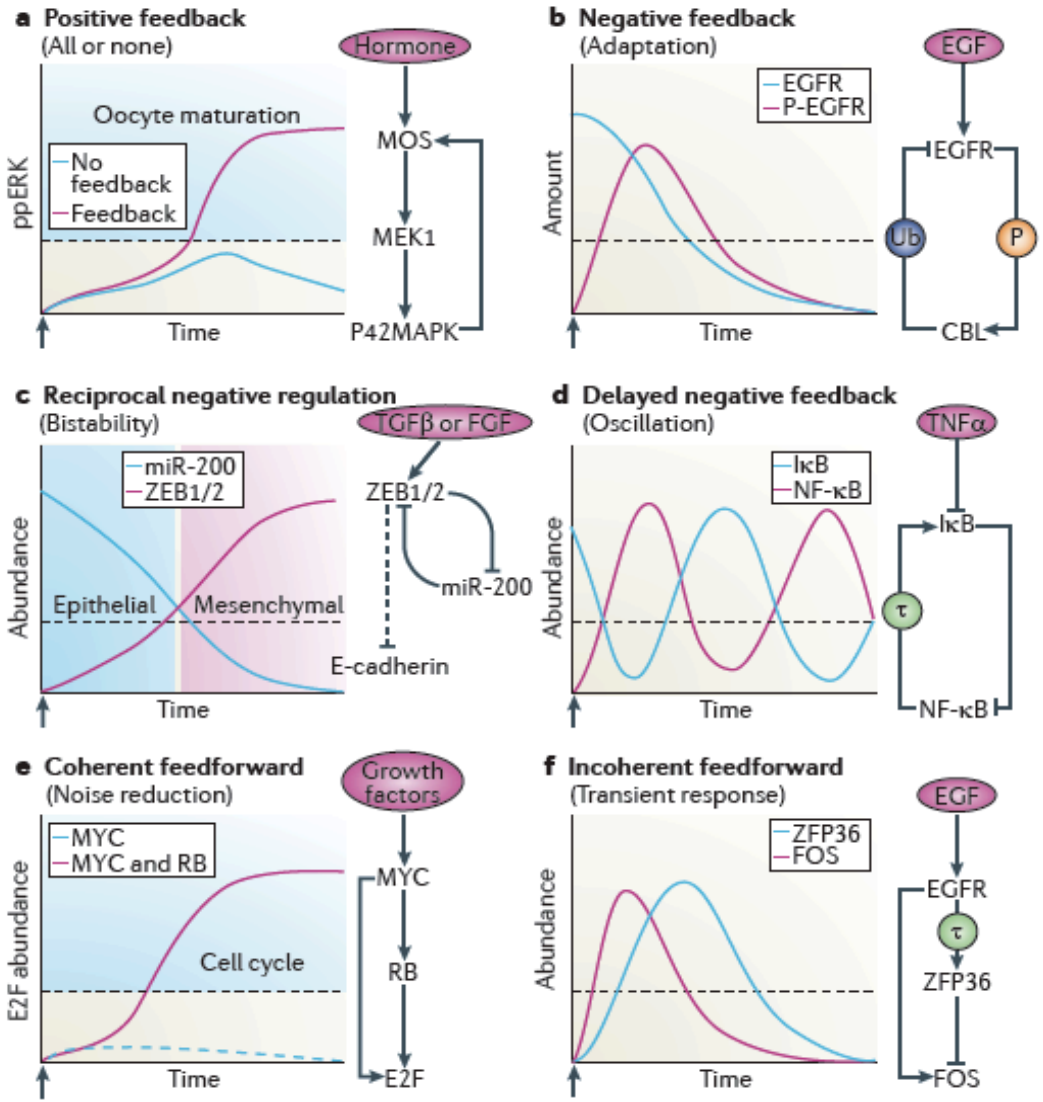
logical and engineered systems share structural and functional featu

- Component multiplicity
- Rich connectivity
- Fail-safe functioning



However, the single supervisory component of engineered systems is often replaced in biological systems by multiple control loops

Feedback Loops Carve Network's



Avraham & Yarden (2011) Nature Rev. Mol. Cell Biol.

Computational tasks of feedback regulatory loops

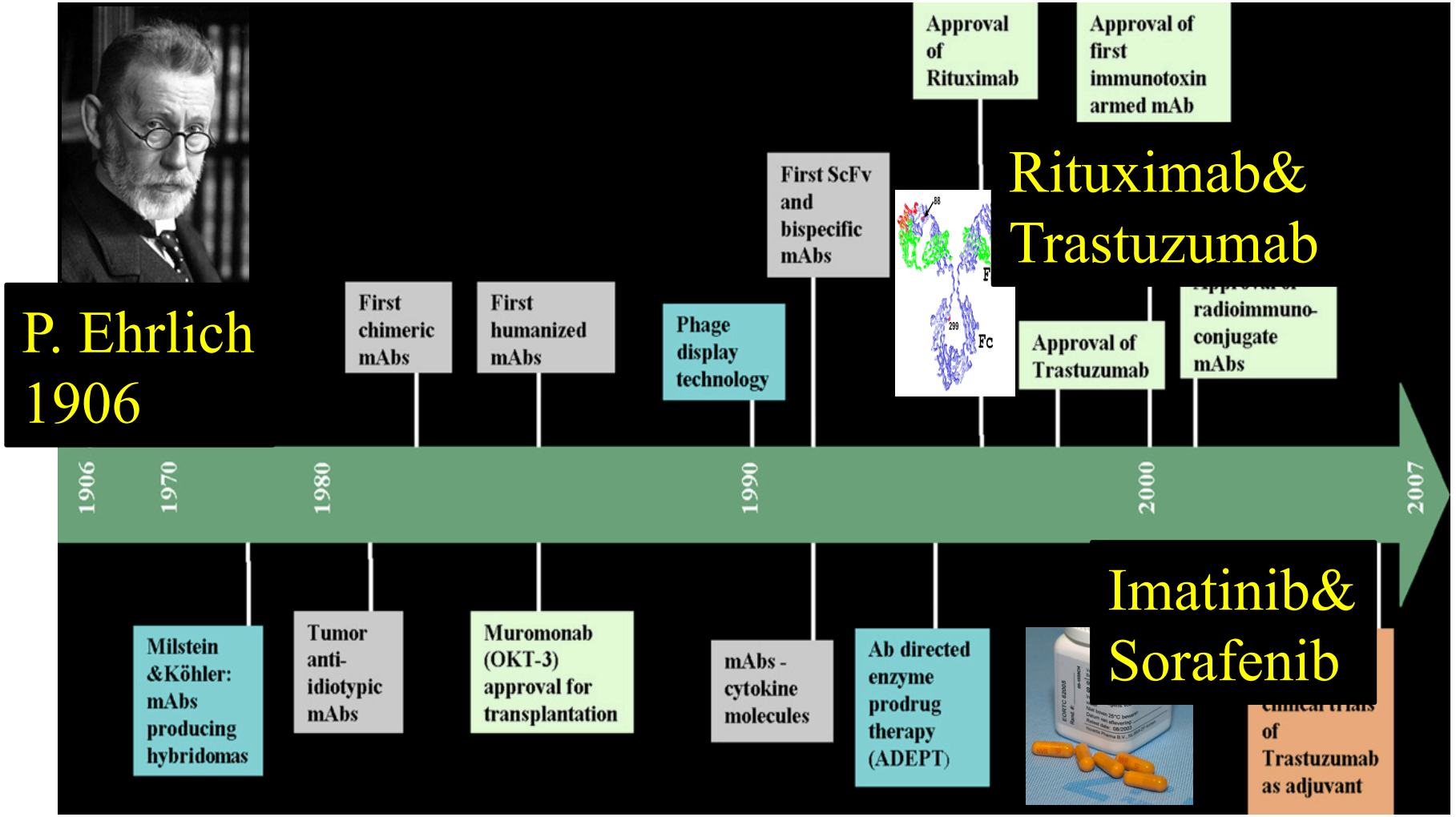
- **Fold change detection:** The output of a network depends on the relative change in input signal, rather than on the absolute levels.
- Reference: The incoherent feedforward loop can provide fold-change detection in gene regulation. Goentoro L., Shoval O.

Overall, feedback loops are the guardians of the cell's steady state. Hence, pharmacological interventions would eventually be restrained.

distinct phases of signalling. Jones SM and Kazlauskas A. *Nat Cell Biol* (2001)

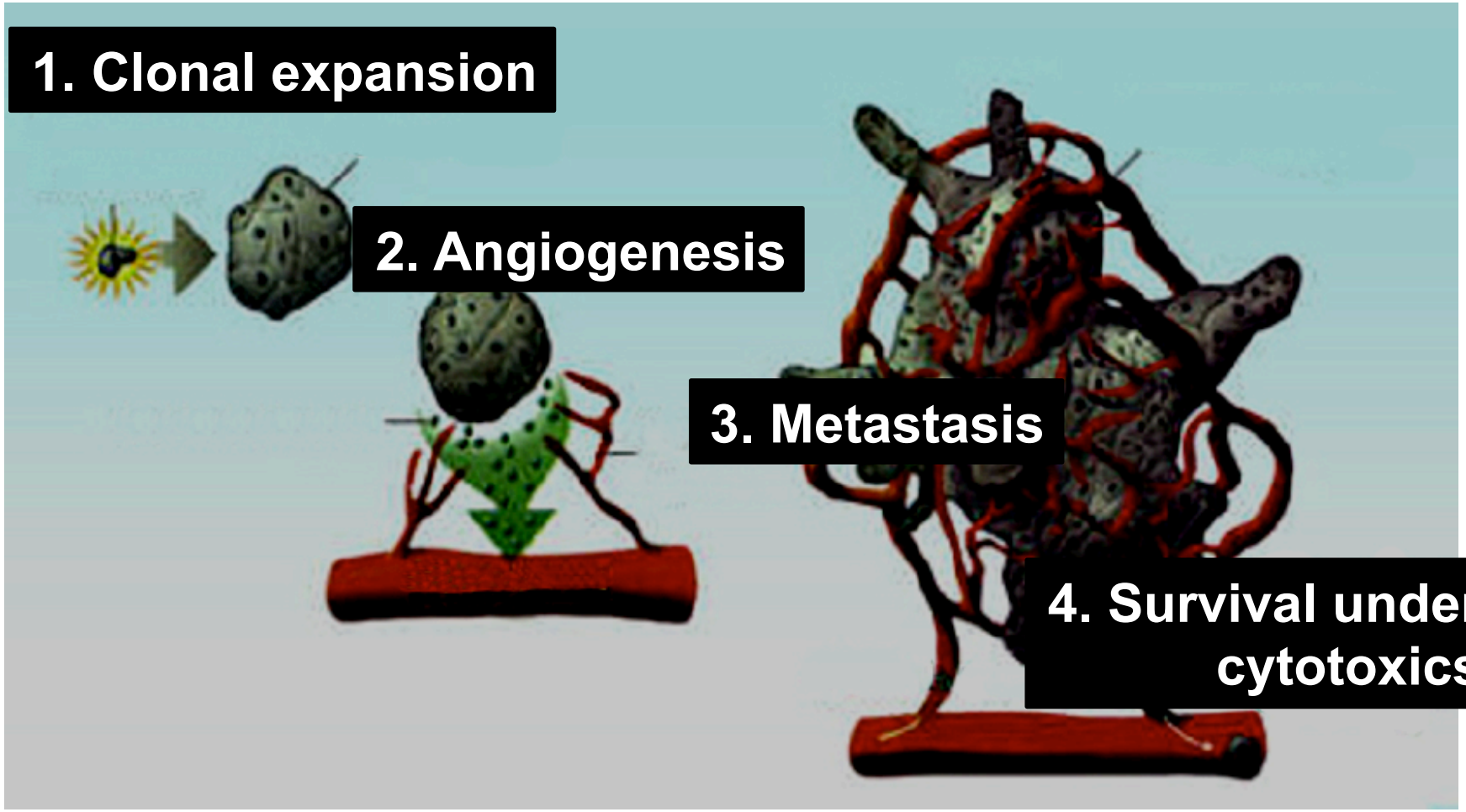
- **Decoding ligand specificity:** Although different signals are funneled into the same pathway, specificity is maintained by feedback regulation.
- Reference: Growth factor-induced MAPK network topology shapes Erk response determining PC-12 cell fate. Santos SD, Verveer PJ, and Bastiaens PI. *Nat Cell Biol* (2007)

The Era of Genome-Based Targeted Cancer Therapy



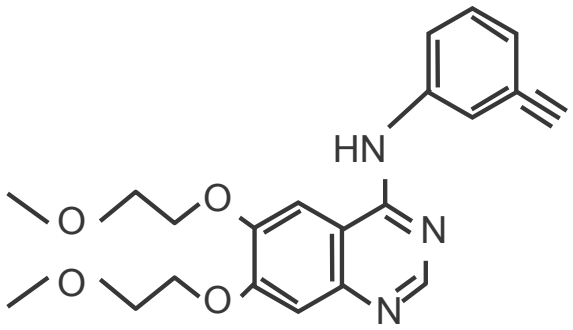
Ben-Kasus et al., (2007) Molecular Oncology

Growth Factors Control All Phases of Tumor Progression



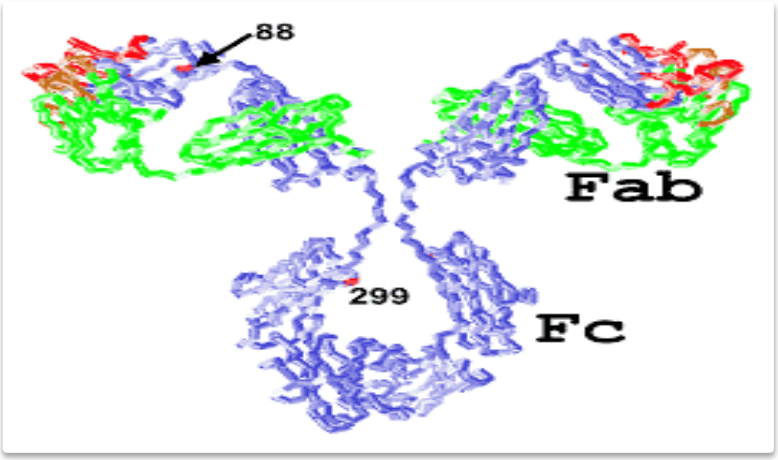
Two Major Therapeutic Strategies Targeting EGFR/HER2 Signaling

Kinase inhibitors



Gefitinib (lung CA)
Erlotinib (lung&pancreatic CA)
Afatinib (lung CA)
Lapatinib (breast CA)

Monoclonal antibodies

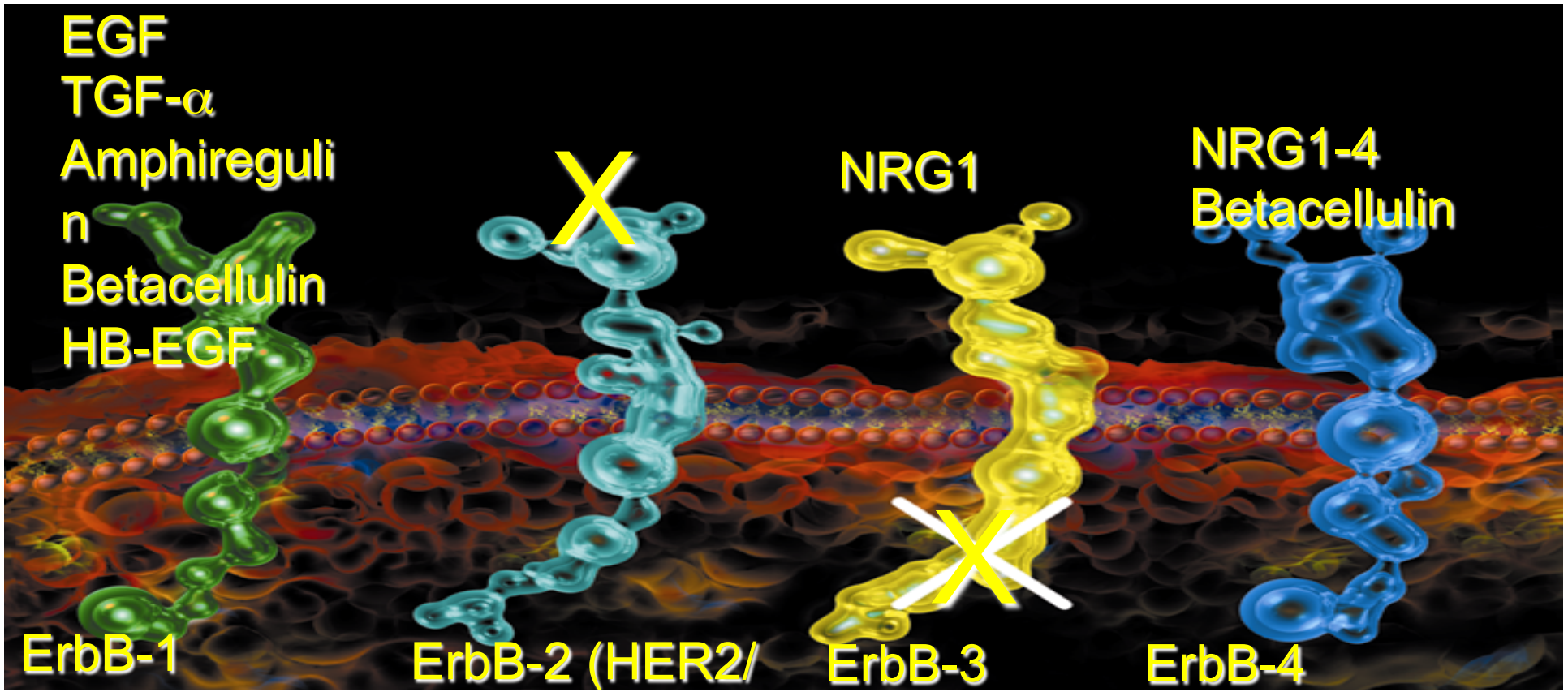


Trastuzumab (breast&gastric CA)
Cetuximab (colorectal&head CA)
Panitumumab (colorectal CA)
Pertuzumab (breast CA)

The EGFR/HER2 Family and the Double Enigma

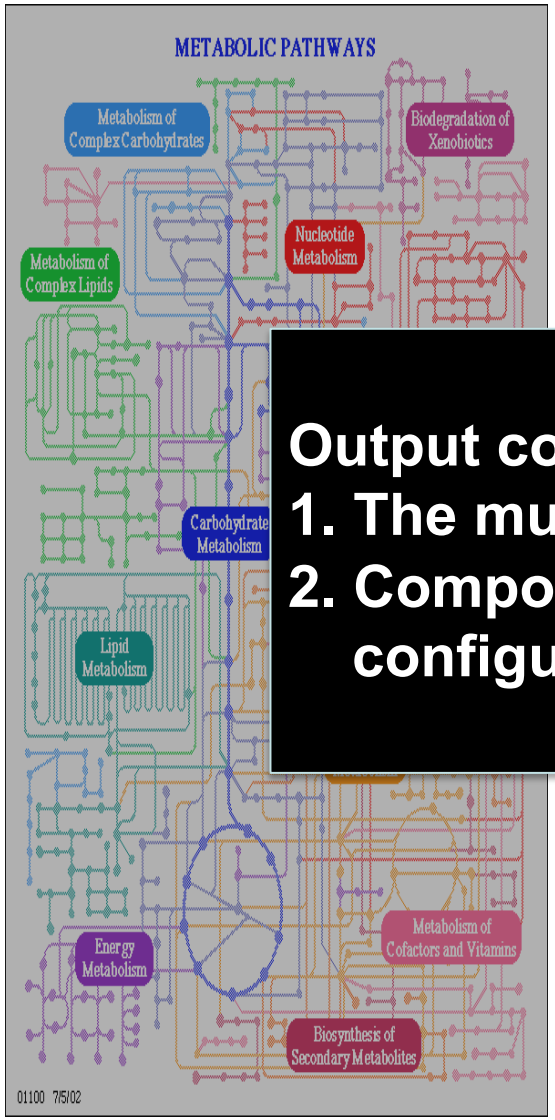
HER2, a strongly oncogenic kin of EGFR, binds no known ligand

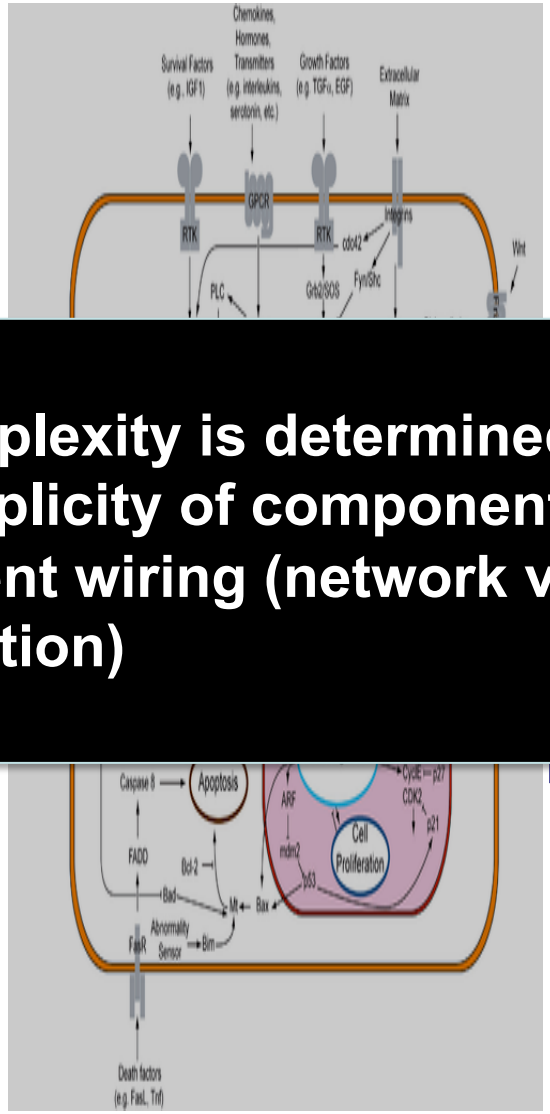
ERBB3 binds several ligands, but its kinase is inactive

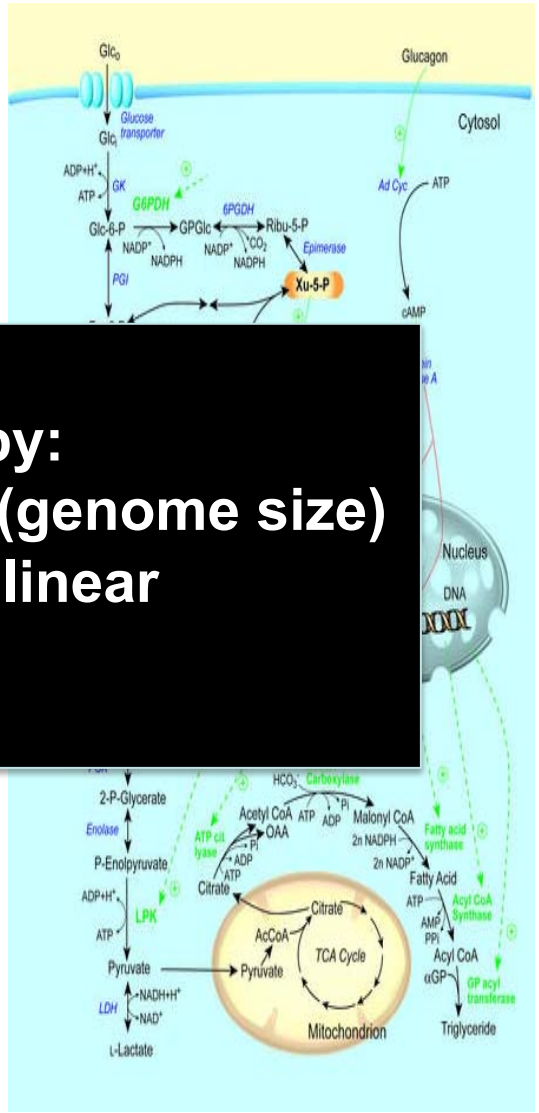


Systems biology of signal transduction: Integration of networks

Metabolism ***Information/signaling*** ***Energy***



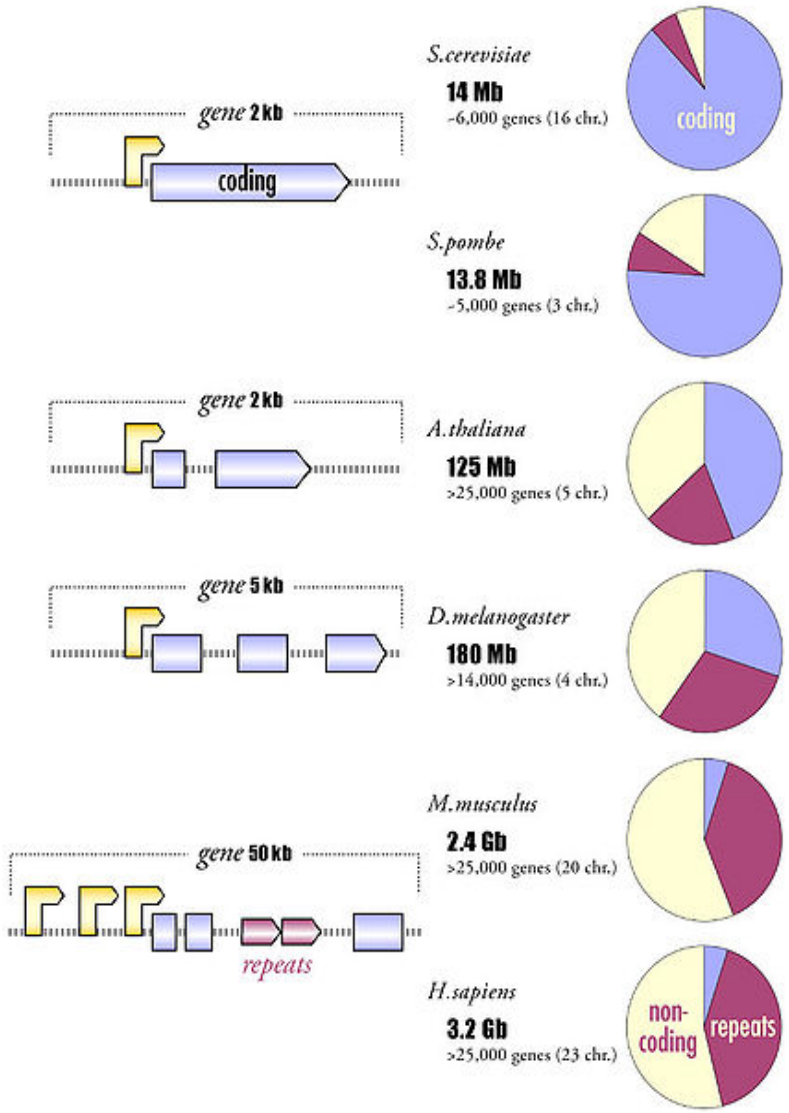




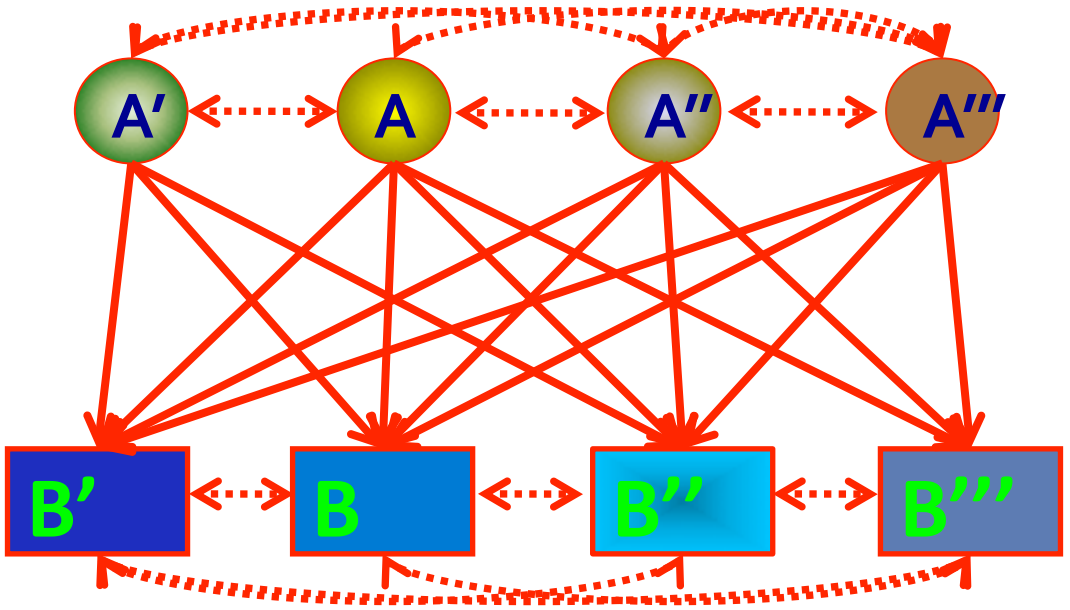
Output complexity is determined by:
1. The multiplicity of components (genome size)
2. Component wiring (network vs. linear configuration)

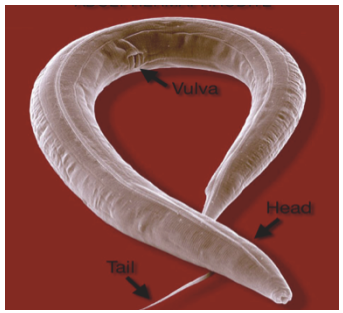
Networks evolved to compensate for the limited size of genomes

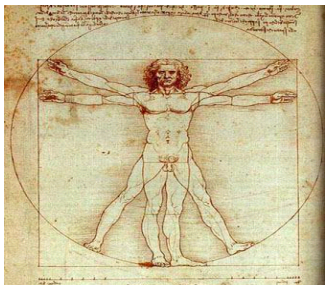
- Genomes expand by duplications
- Trade-offs of Mega-genomes:
  - Logistics of Replication
  - Challenges for DNA repair
  - Excessive regulatory sequences
- The alternatives:
  - Simple proteins-->multi-domain
  - Splice variants and PTMs
  - Pathways-->networks



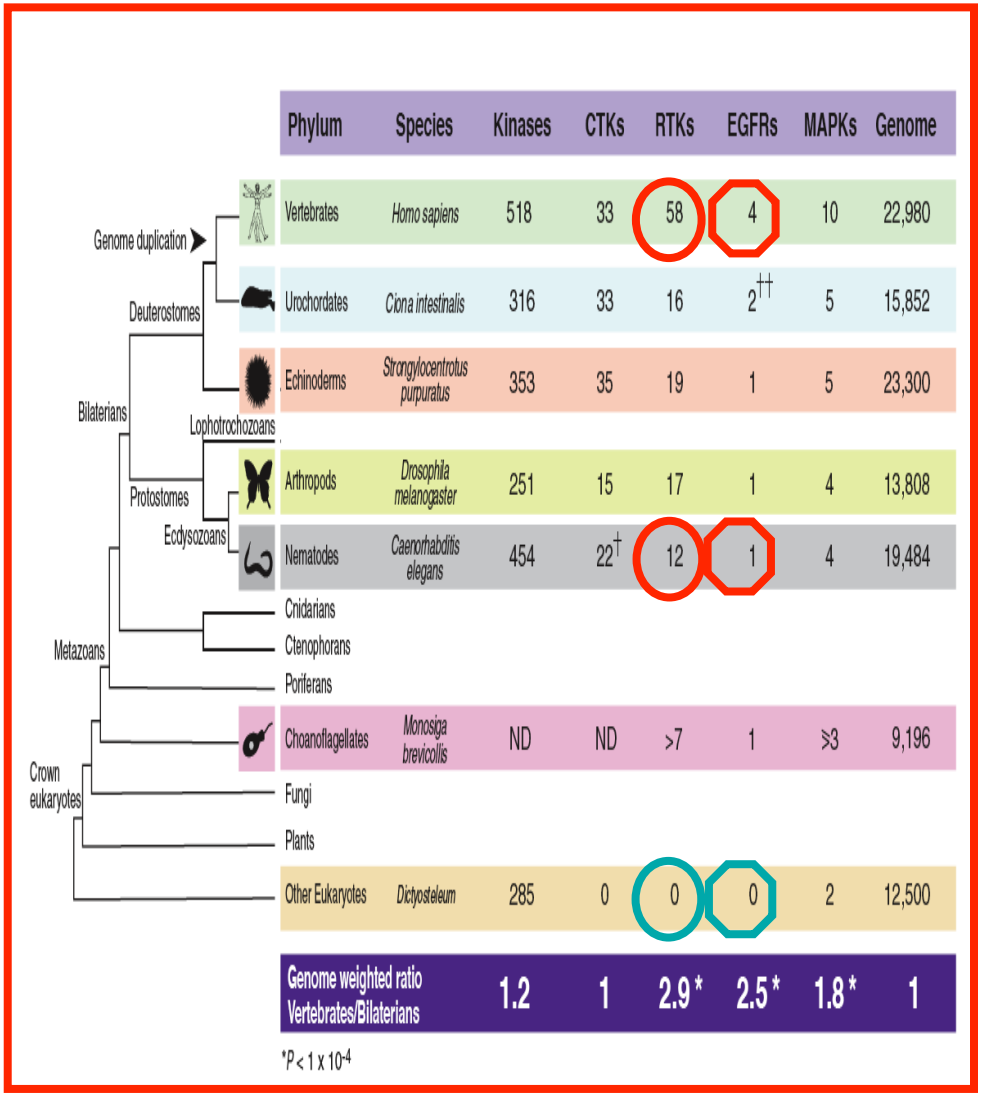
The Origin of Biological Complexity: Whole Genome and Chromosome Duplications







The Evolution of RTKs: Roles for Sub-Functionalization



Phylum	Species	Kinases	CTKs	RTKs	EGFRs	MAPKs	Genome
Vertebrates	*Homo sapiens*	518	33	58	4	10	22,980
Urochordates	*Ciona intestinalis*	316	33	16	2††	5	15,852
Echinoderms	*Strongylocentrotus purpuratus*	353	35	19	1	5	23,300
Arthropods	*Drosophila melanogaster*	251	15	17	1	4	13,808
Nematodes	*Caenorhabditis elegans*	454	22†	12	1	4	19,484
Cnidarians							
Ctenophorans							
Poriferans							
Choanoflagellates	*Monosiga brevicollis*	ND	ND	>7	1	⩾3	9,196
Fungi							
Plants							
Other Eukaryotes	*Dictyosteleum*	285	0	0	0	2	12,500
Genome weighted ratio Vertebrates/Bilaterians		1.2	1	2.9*	2.5*	1.8*	1

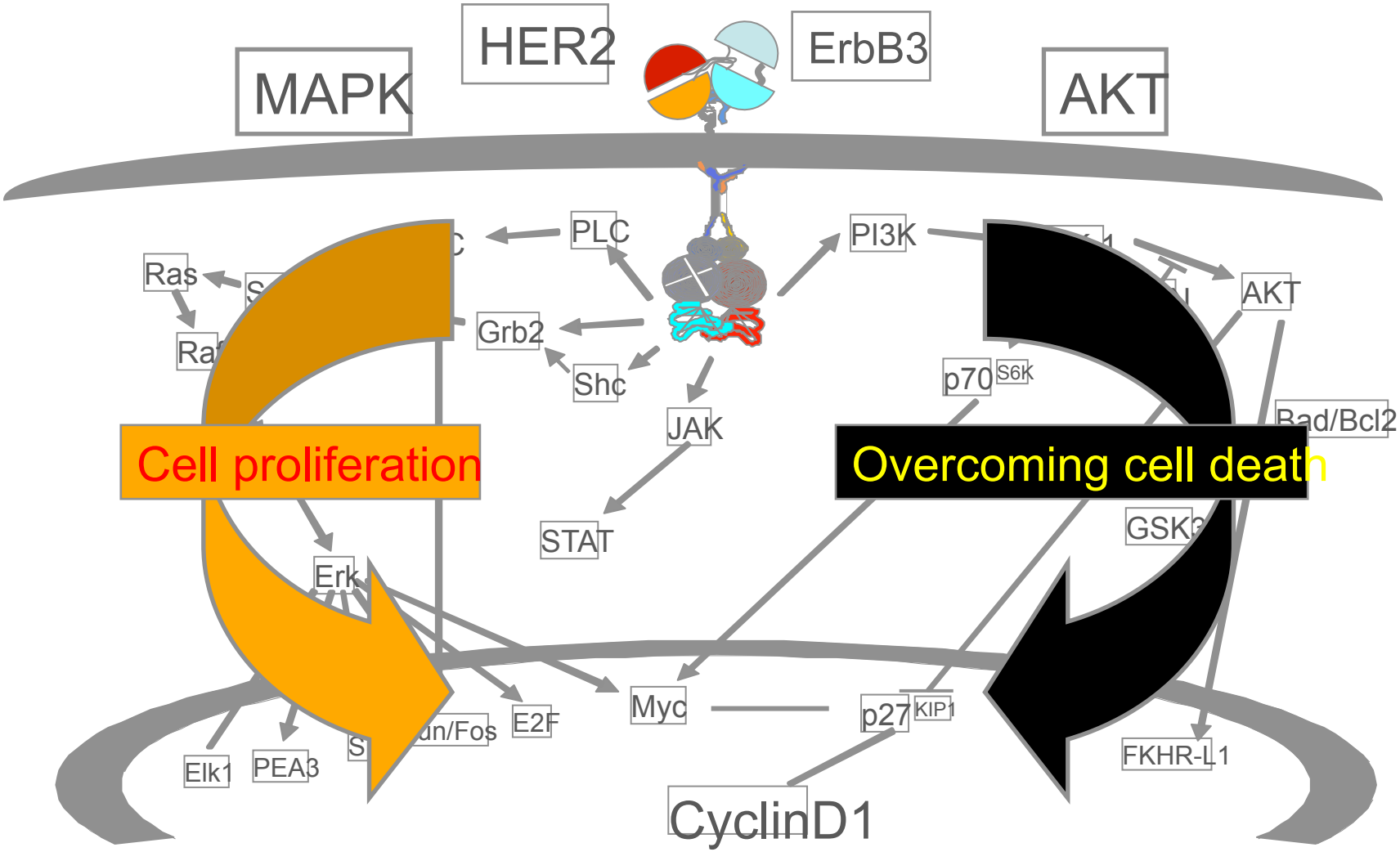
*$P < 1 \times 10^{-4}$

- There have been two genome- wide duplications and numerous smaller scale events

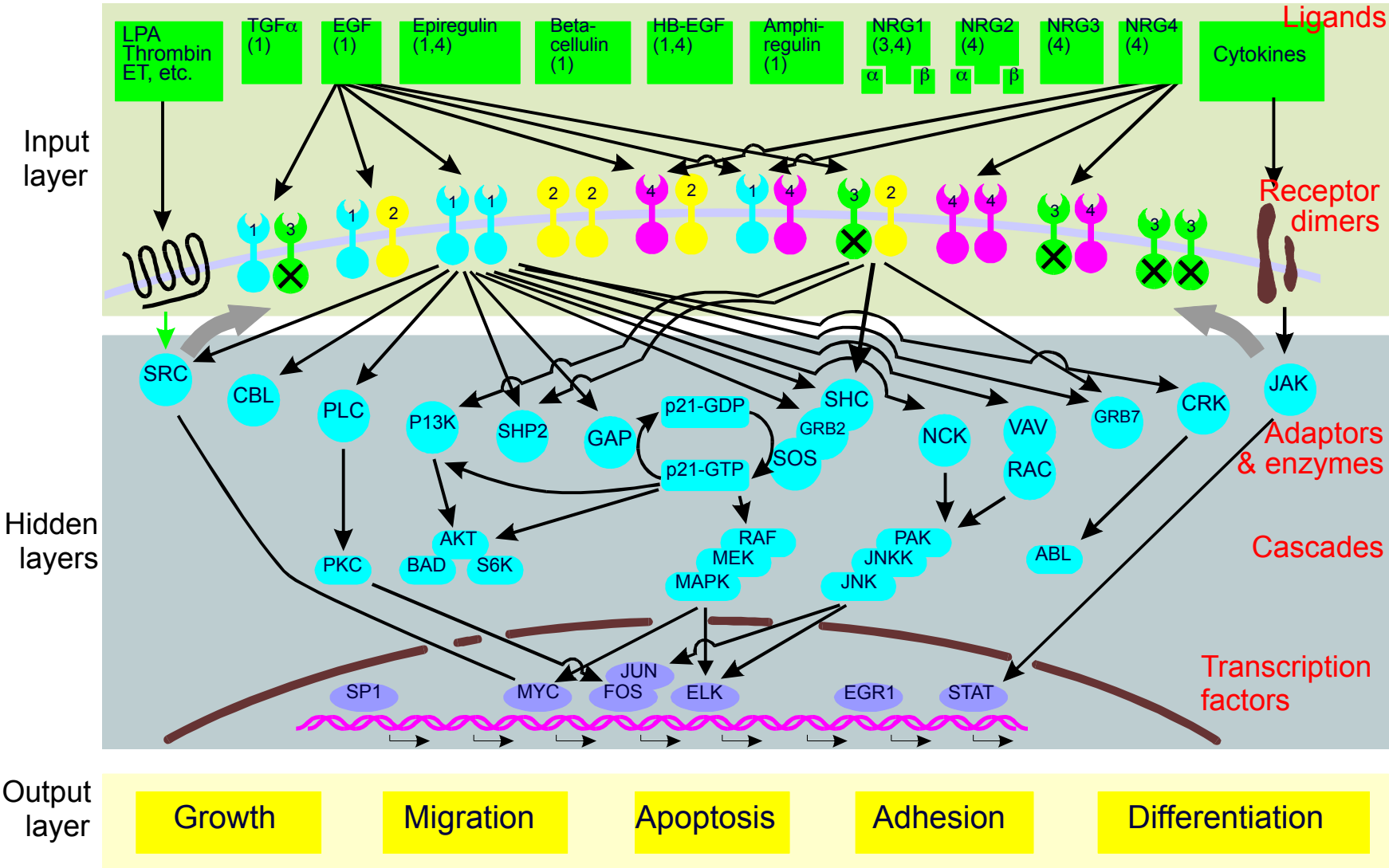
- Most duplicated genes are lost; sub-functionalization retains duplicated genes by enabling complementary functions

Amit, Wides &Yarden (2007) Molecular Systems Biology 3:151-163

Sub-functionalization: Heterodimers comprising ErbB3 (kinase-dead) and HER2 (ligand-less) are Highly Mitogenic

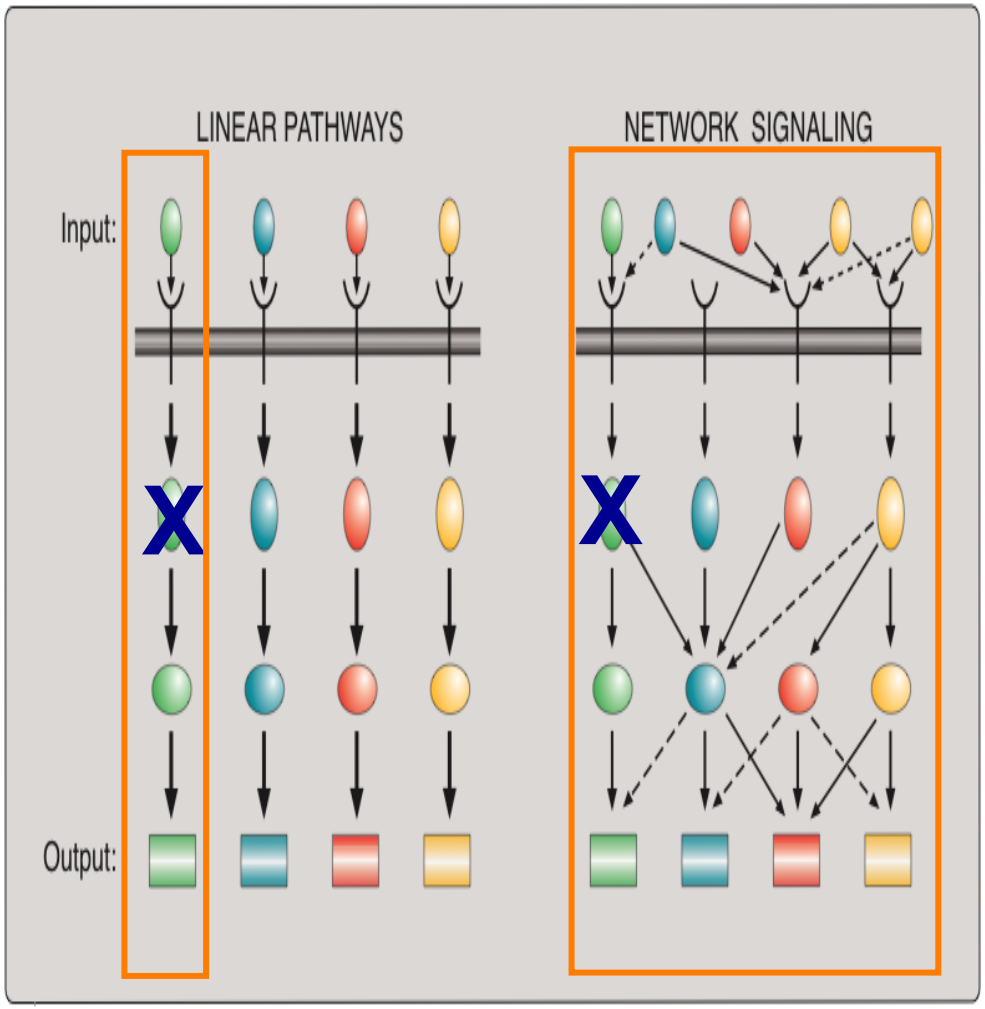


The EGFR/HER2 Signaling Network



Yarden and Sliwkowski (2001) Nature Rev. Mol. Cell Biol, 2:127-137.

Evolution Transformed a Pathway Into a Layered Signaling Network and Trained it to Resist Common Perturbations



Robustness is a property that enables a system to function despite external (environmental) and internal (genetic) perturbations.

Evolvability is the capacity of a system to generate stable variance.

Mechanisms that ensure robustness of engineered (and biological) systems

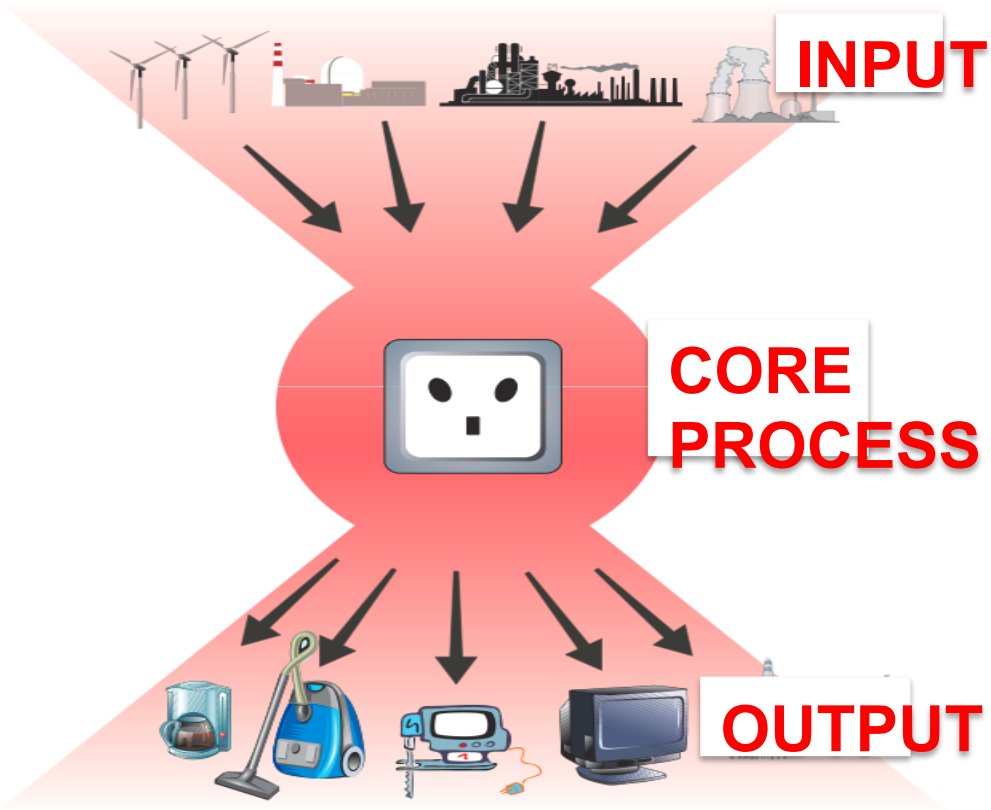
Modularity: ***Organization in units that enable damage containment***

Redundancy and diversity: ***input and output diversity and multiple pathways to achieve a specific function***

System controls:

Positive control leading to amplification and negative feedback control

System adaptability (training)



Citri and Yarden (2006) Nature Rev. Mol. Cell Biol. 7: 505

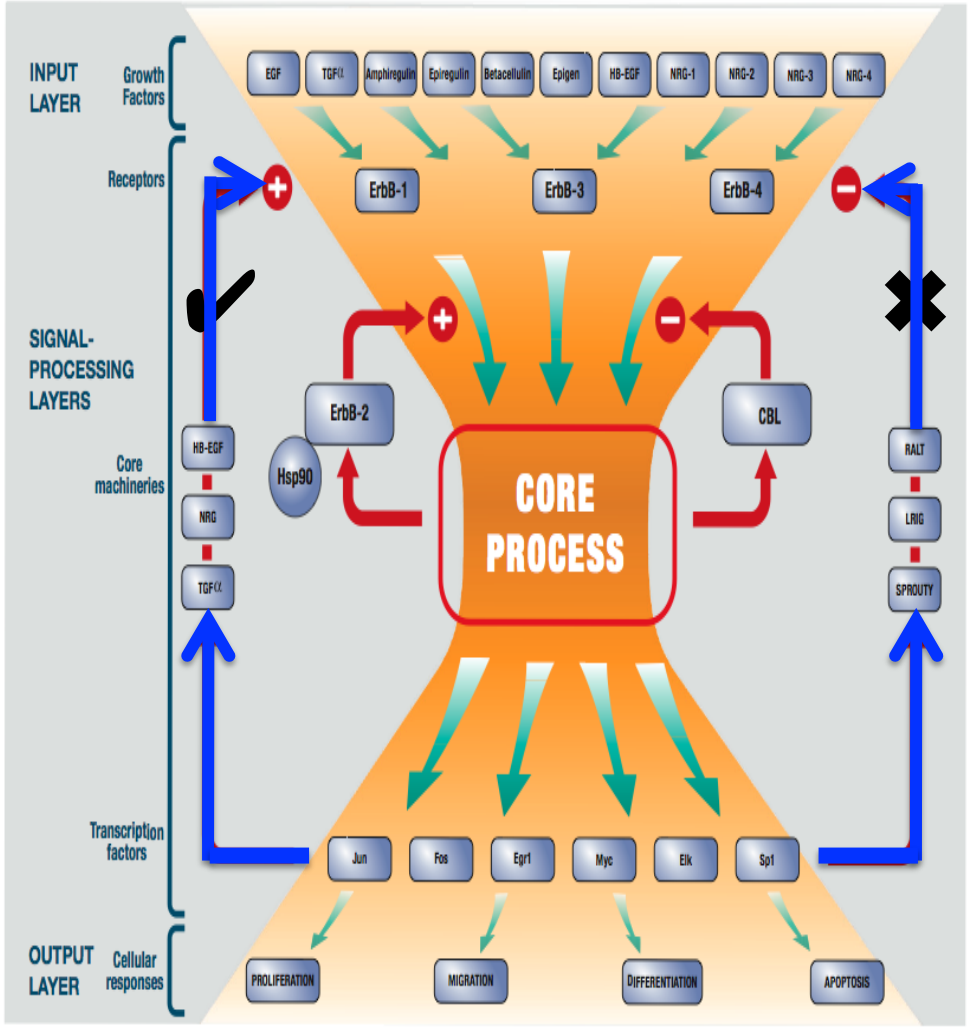
Control loops ensure robustness

Modularity: Organization in units that enable damage containment

Redundancy and diversity: input and output diversity and multiple pathways to achieve a specific function

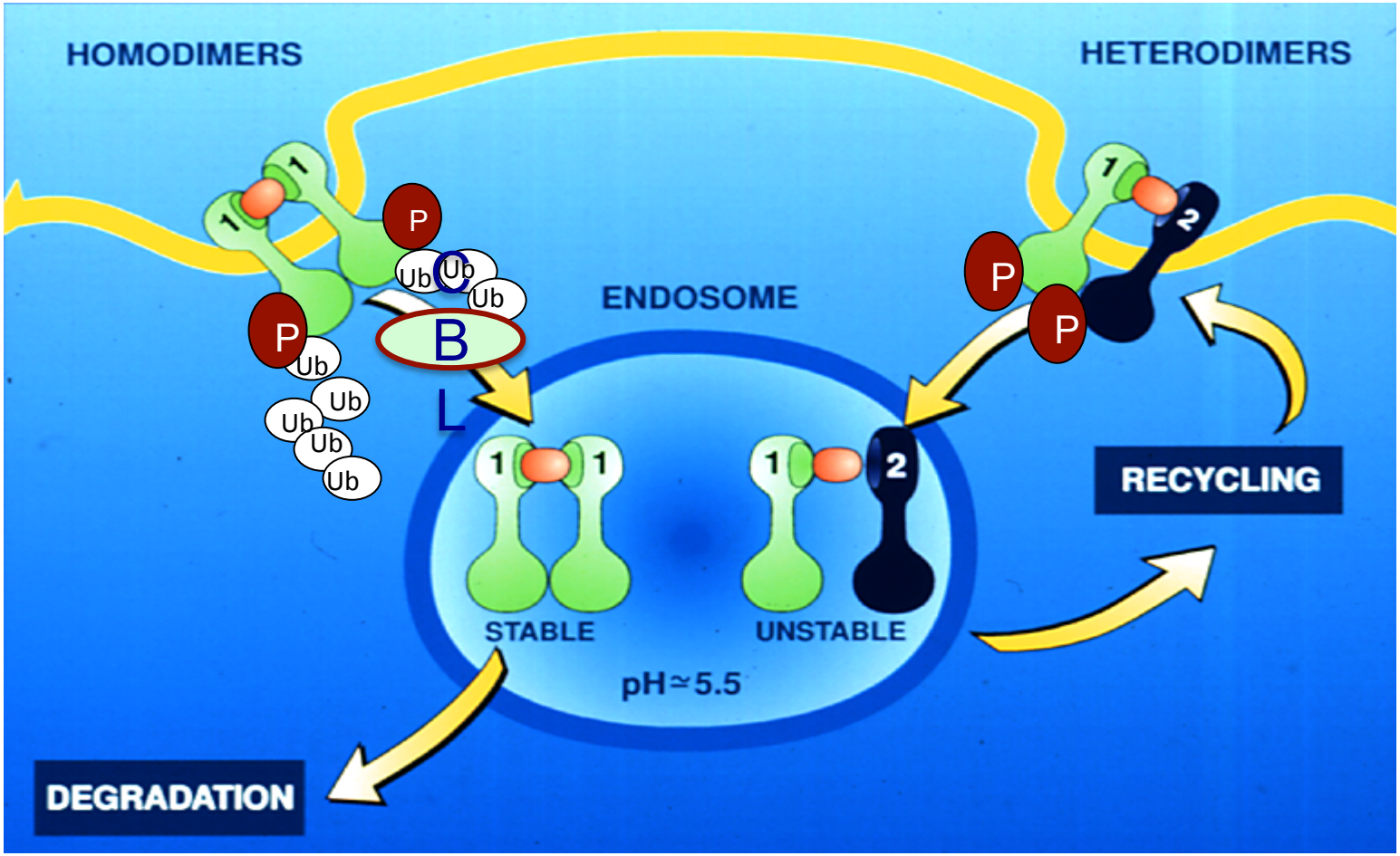
Positive and negative feedback control loops

Plasticity (short-term) and adaptability (long-term)



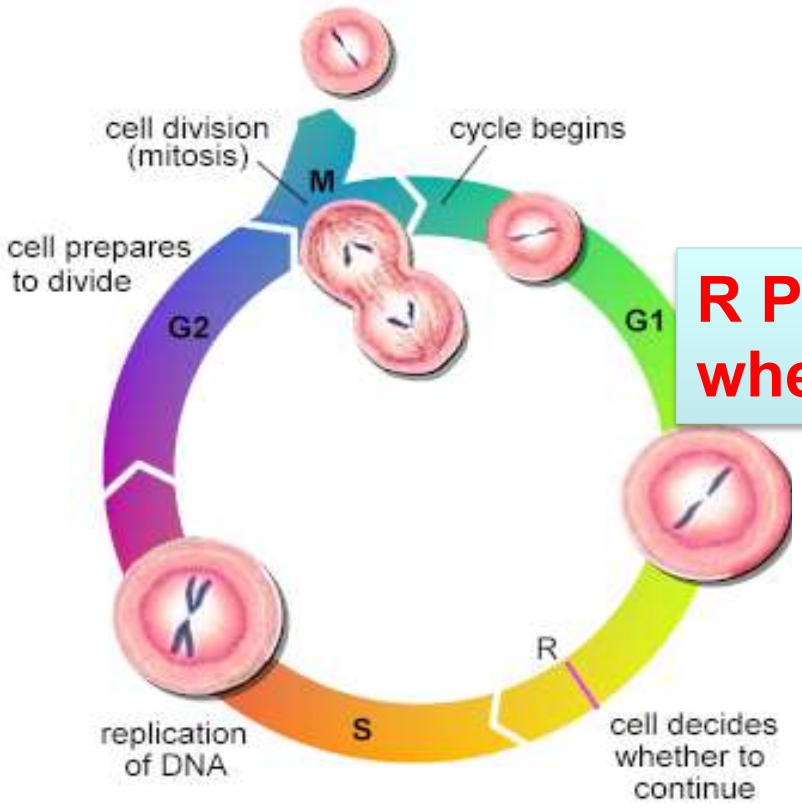
Citri and Yarden (2006) Nature Rev. Mol. Cell Biol. 7: 505

HER2 Recycles EGFR



Mosesson, Mills & Yarden (2008) Derailed endocytosis: an emerging feature of cancer. Nature Rev. Cancer 8;835-50

EGF-induced proliferation of mammary cells (HMECs)



R Point: cells decide whether to continue

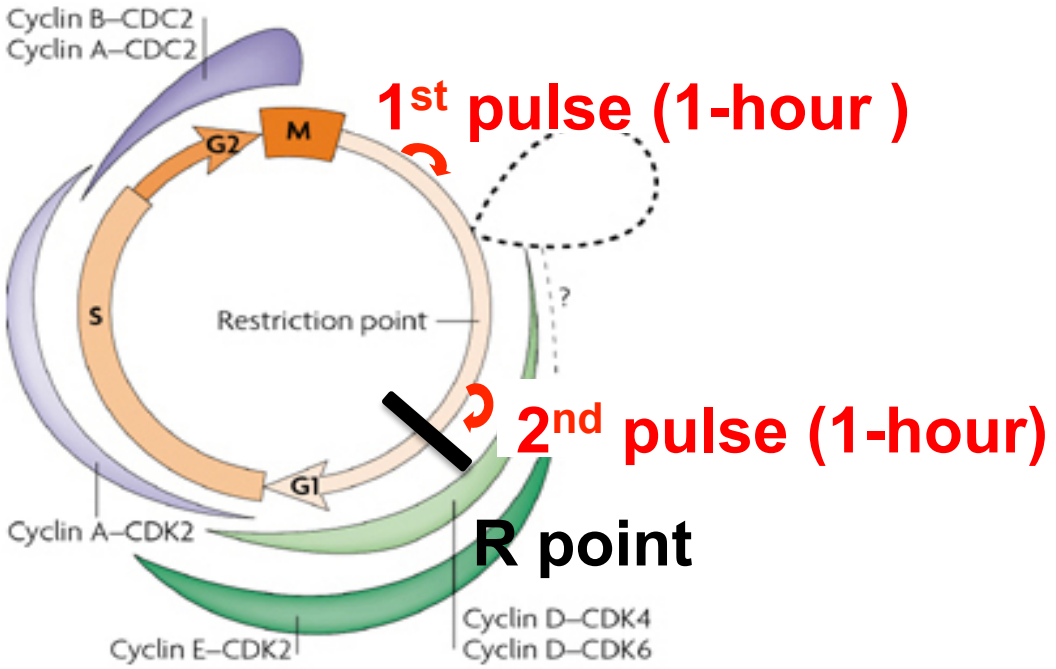
Yaara Zwang

R crossing requires continuous (>6 hours) presence of growth factors

Growth-factor-dependent mitogenesis requires two distinct phases of signalling

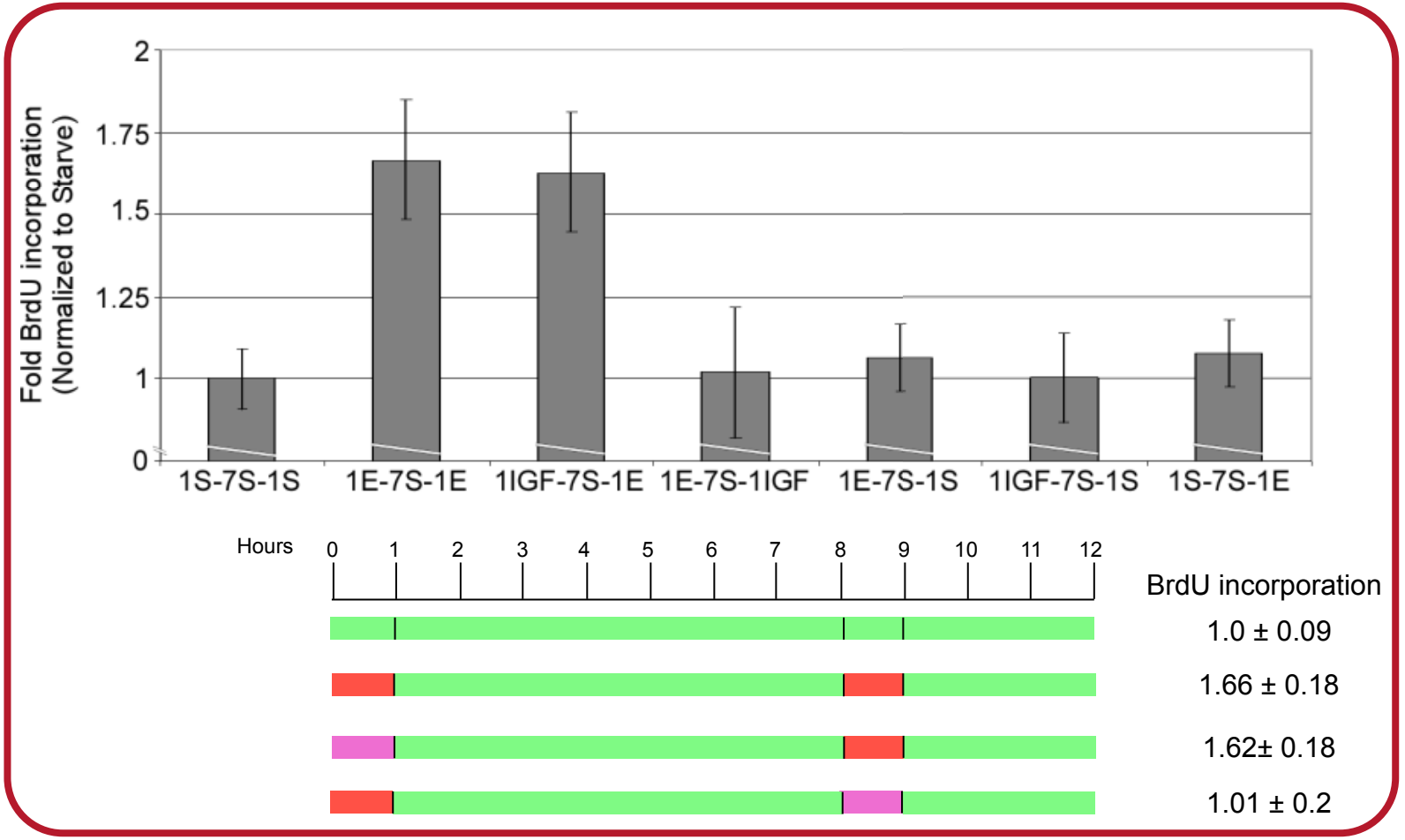
Steven M. Jones*† and Andrius Kazlauskas*‡§

NATURE CELL BIOLOGY | VOL 3 | FEBRUARY 2001



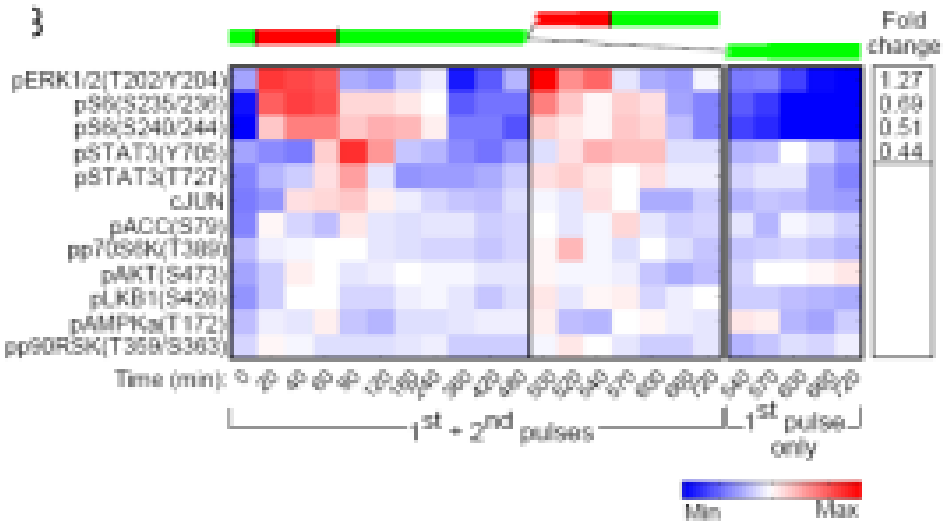
R-crossing is enabled by two short pulses of growth factors

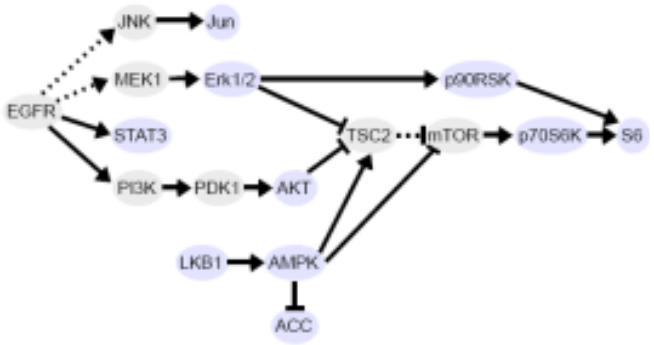
IGF1 may replace EGF in the 1st, not the 2nd pulse

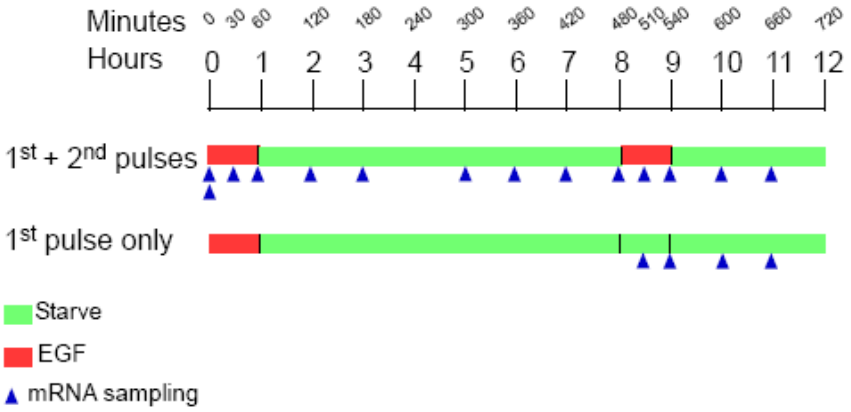


IGF-1 can substitute 1st pulse, but not 2nd pulse EGF.

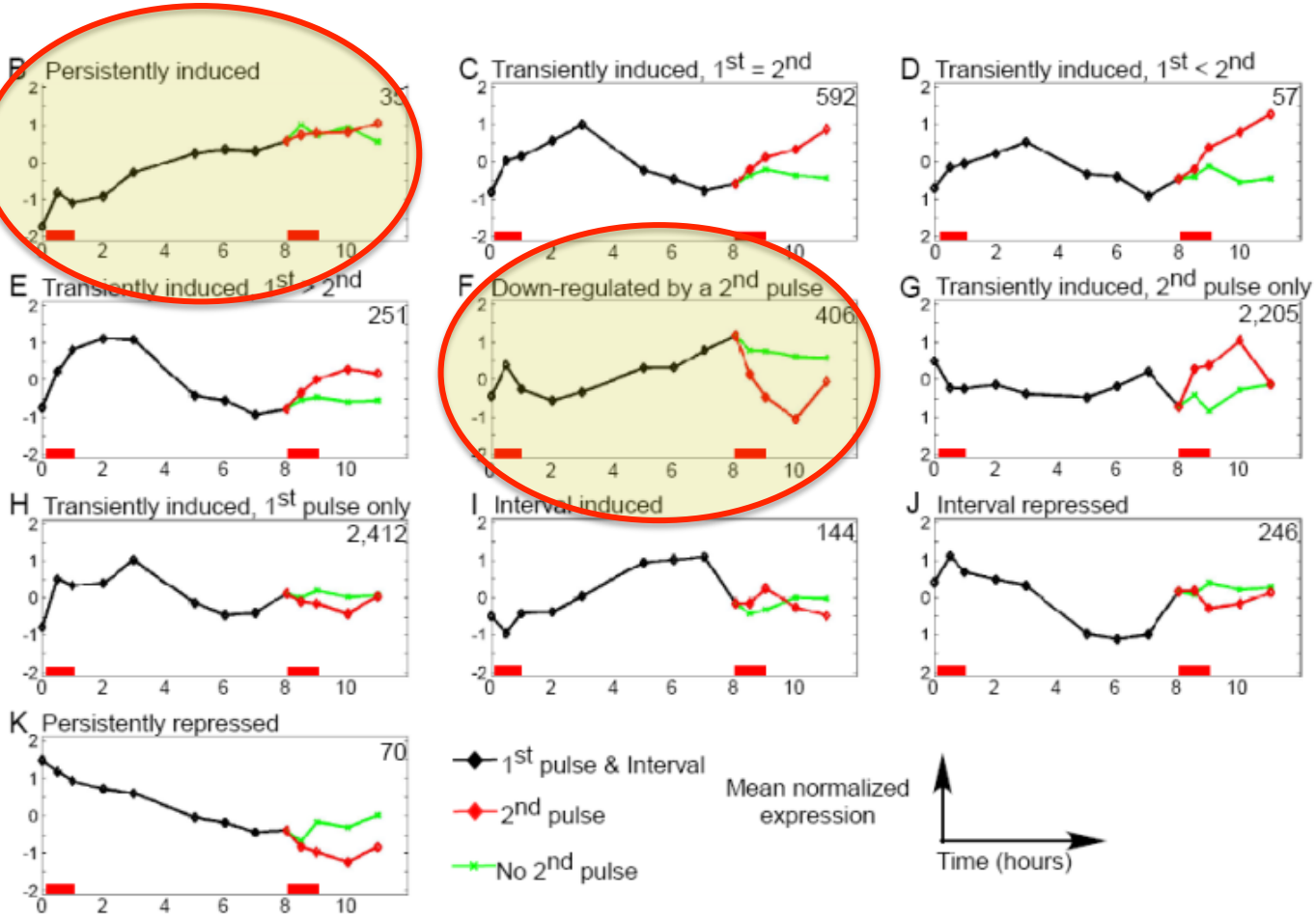
RPPA and Transcriptomic Analyses of the Two-Pulses



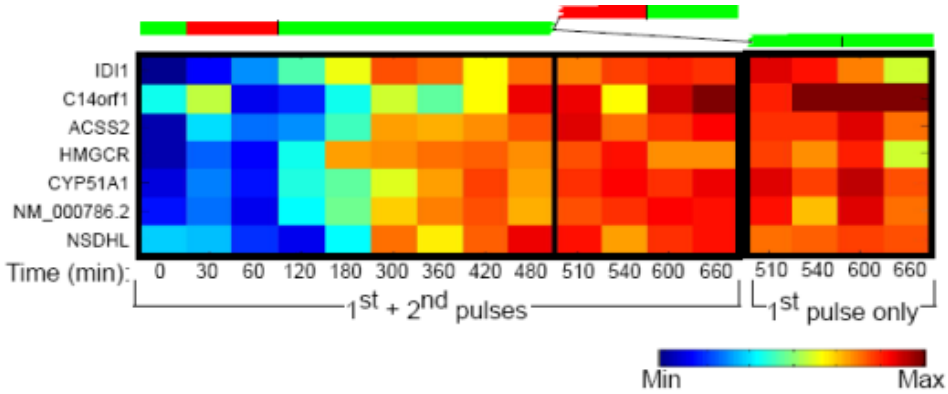


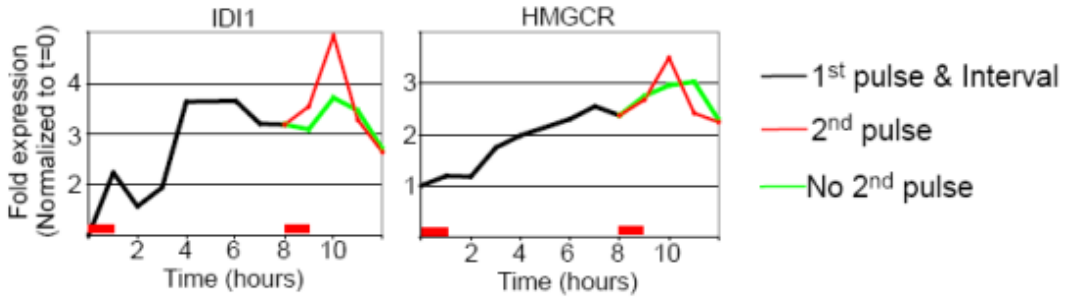


10 expression profiles are induced by EGF (two pulses)

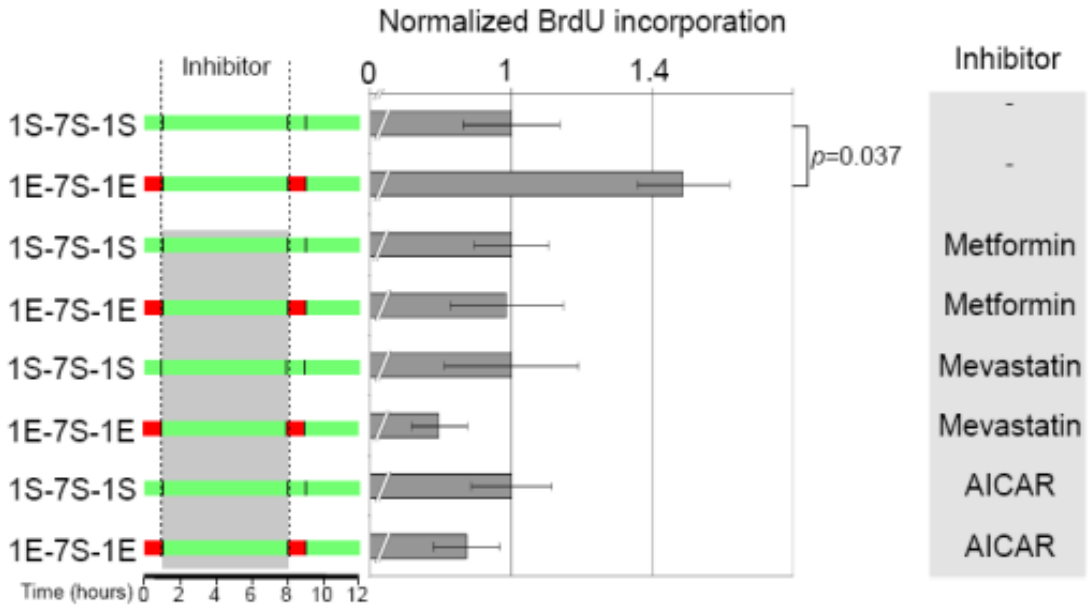


The *Persistently Induced* module is enriched for metabolic genes





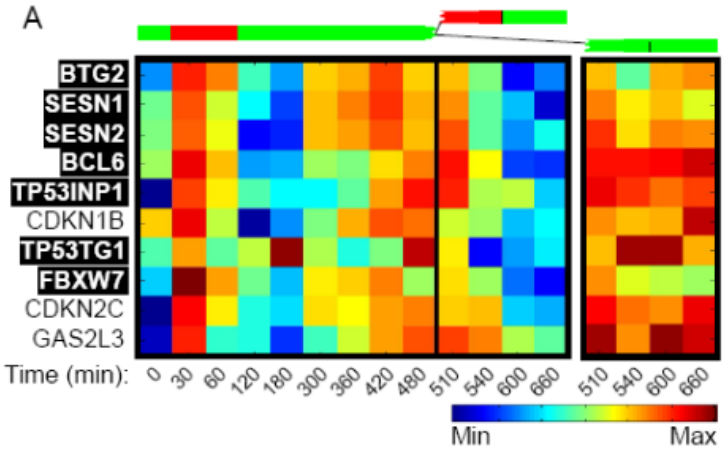
Induction of metabolic processes is essential for R-crossing



Lipid metabolism and membrane biogenesis initiate at the 1st pulse and might be essential for R crossing

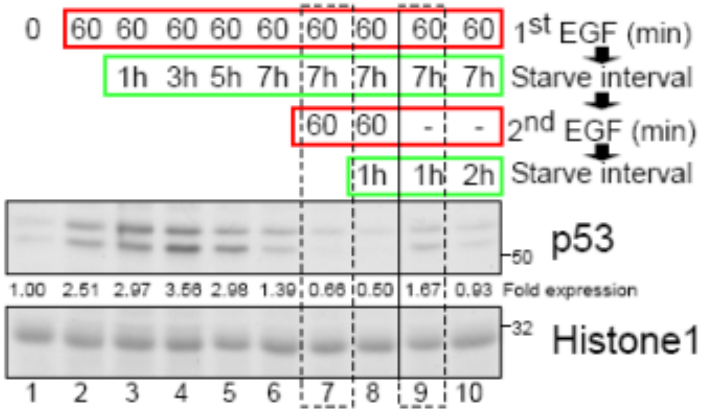
The module *"Down-regulated by 2nd Pulse"* comprises several p53 regulated genes

The module includes well-established p53 target genes

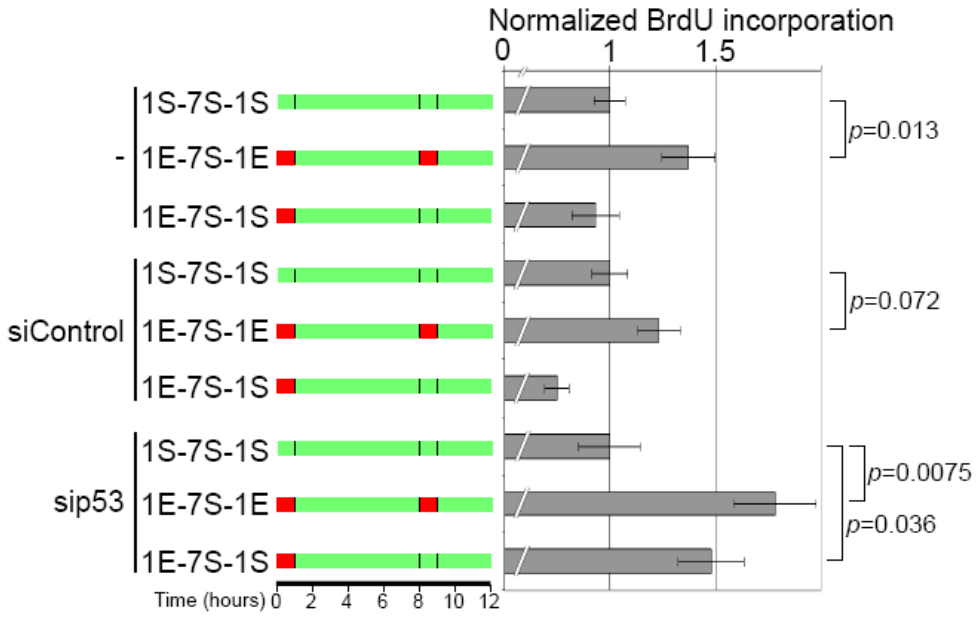


And

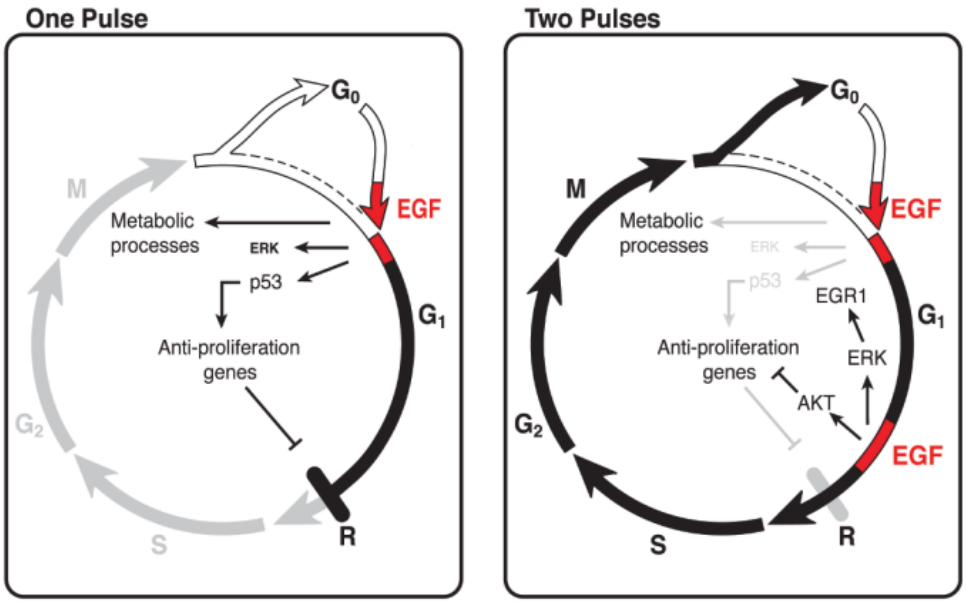
p53 associates with chromatin upon the 1st pulse, remains active during the interval and dissociates on the 2nd pulse



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



The Paradigm of “Consistency Test”



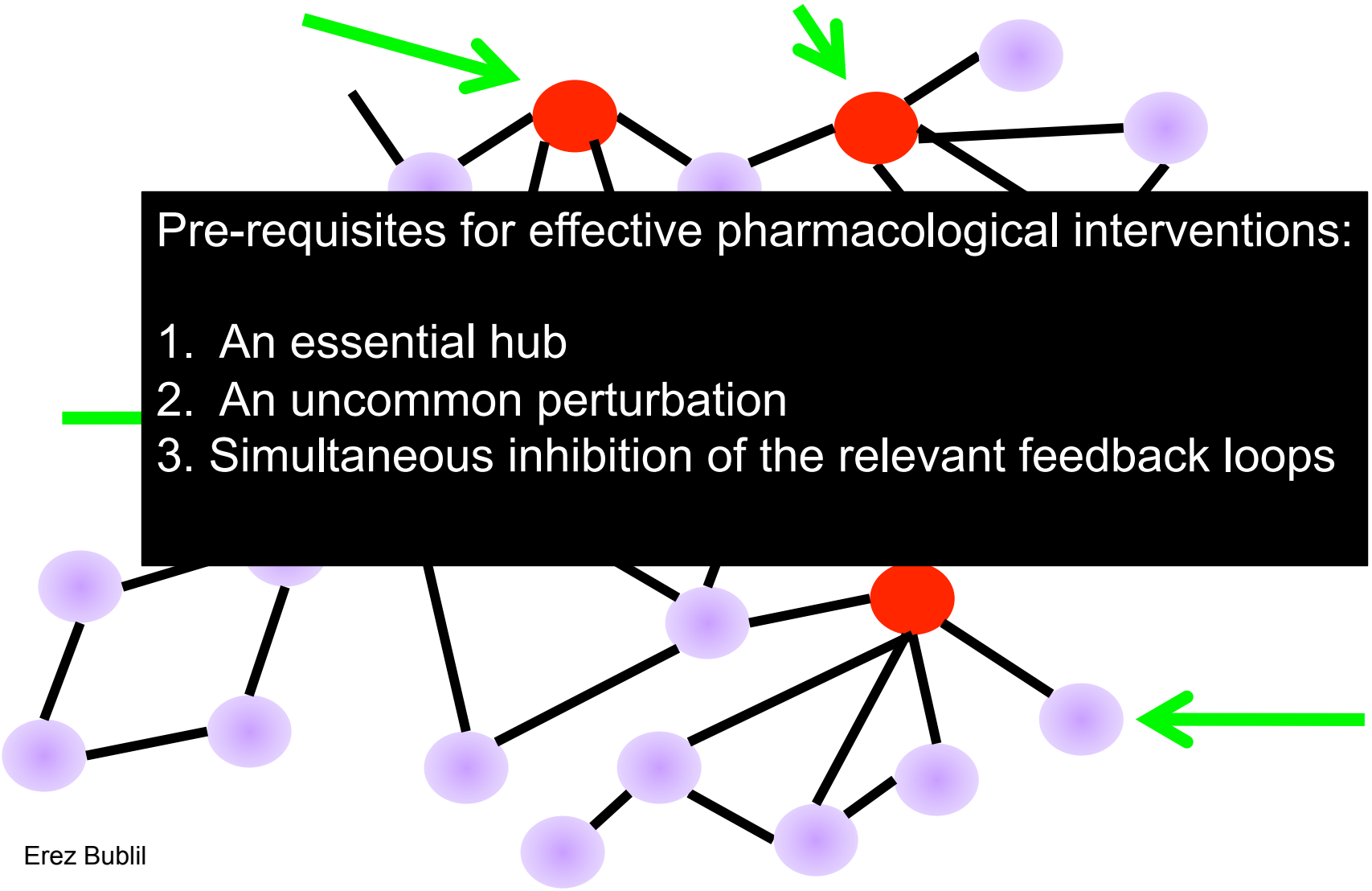
- The 2-pulse mode of commitment might filter the "noise" of growth factor bursts, which are often short and inconsistent
- In the absence of p53 (e.g., cancer cells), this filtering mechanism is defective

Back to Complexity: Lessons from Graph (Network) Theory

- While networks expand, rich nodes become richer[1]
- Networks are trained to resist common perturbations; they show extreme fragility to uncommon attacks (or double attacks)[2]
- Robust networks are hub-addicted, uncommon interceptors (drugs) targeting major hubs may collapse a network[3]
- Hub centrality breeds lethality[4]

1. A. Wagner, 2001; [2.] Carlson & Doyle, 2000; [3.]
2. I.B. Weinstein, 2002; [4.] Barbasi & Oltavi; 2001

Centrality-Lethality Principle



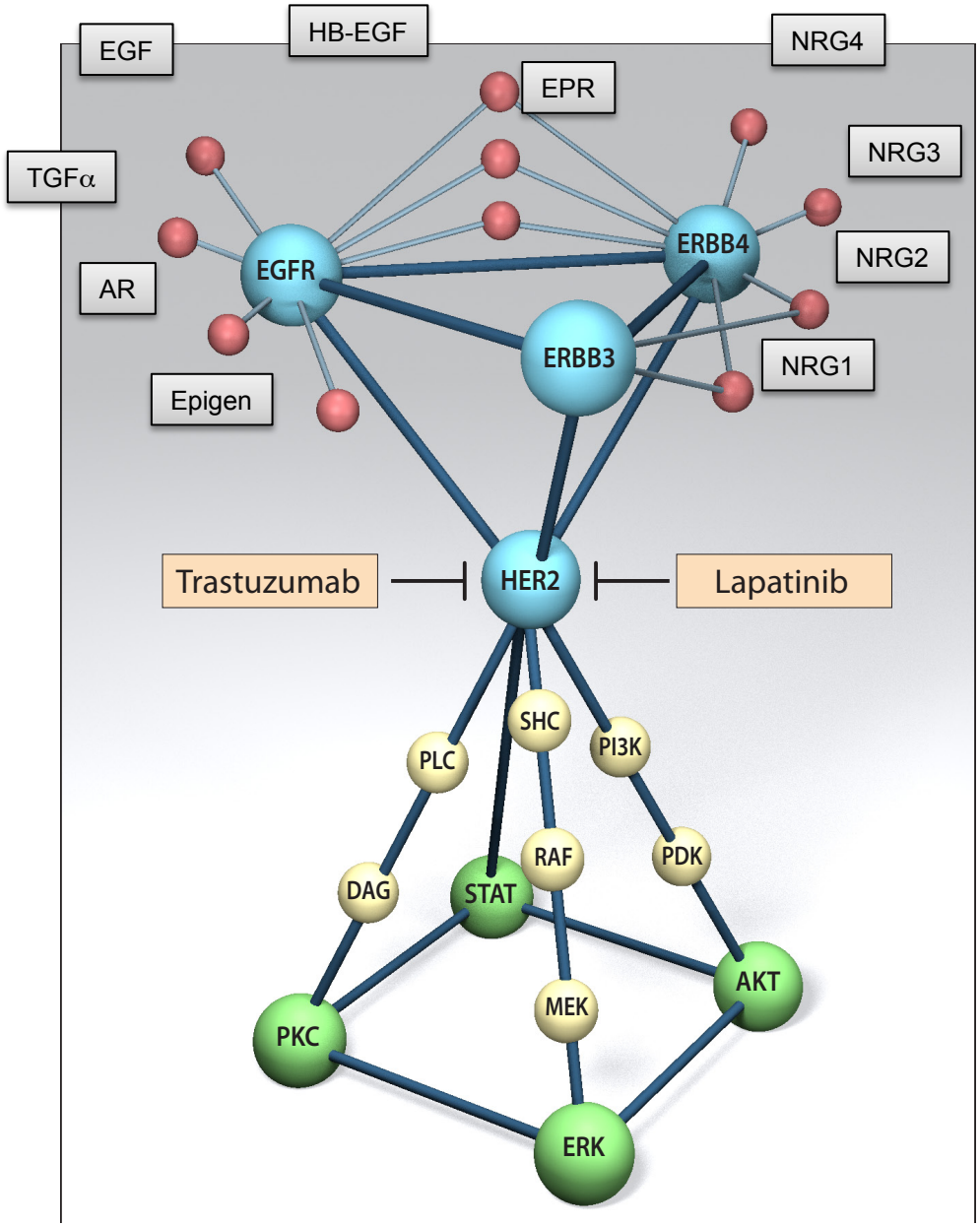
Pre-requisites for effective pharmacological interventions:

1. An essential hub
2. An uncommon perturbation
3. Simultaneous inhibition of the relevant feedback loops

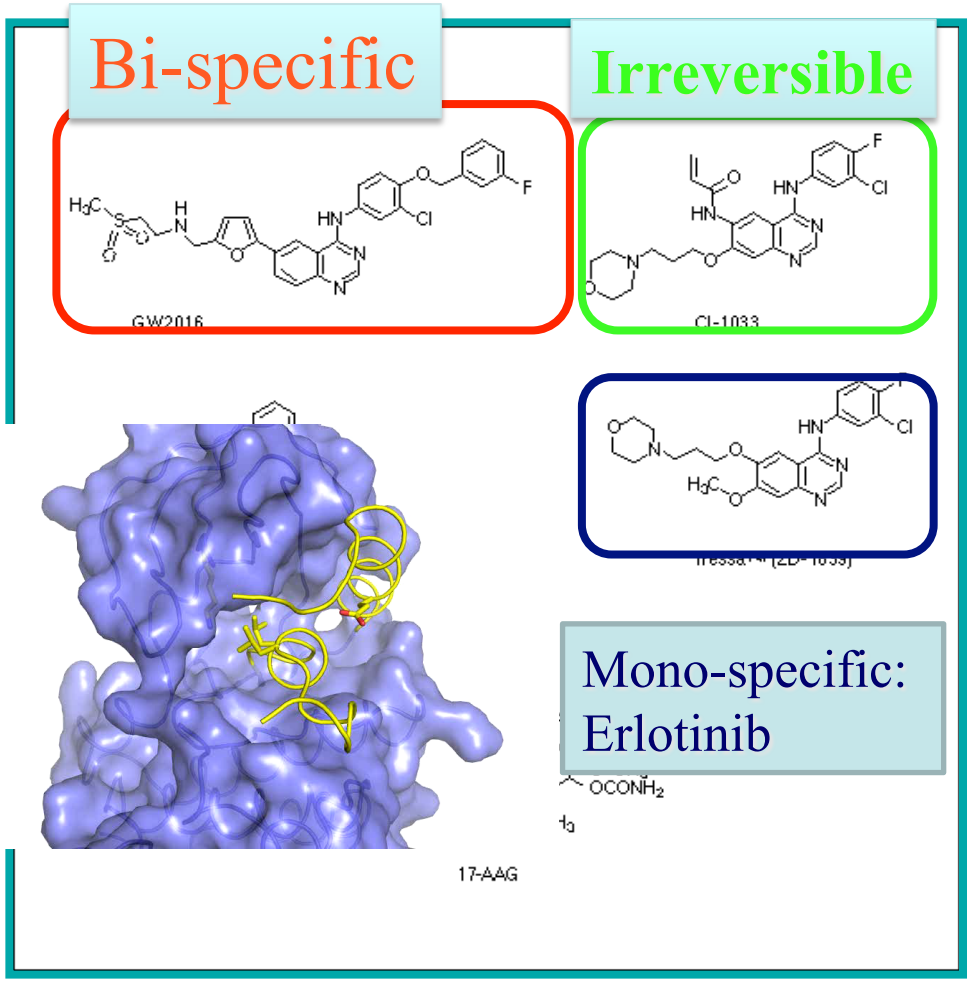
Erez Bublil

HER2+ Breast Tumors: excessive reliance (addiction) on heterodimers

I. Bernard Weinstein



Uncommon Perturbation #1: Double-hit drugs (e.g., Lapatinib)

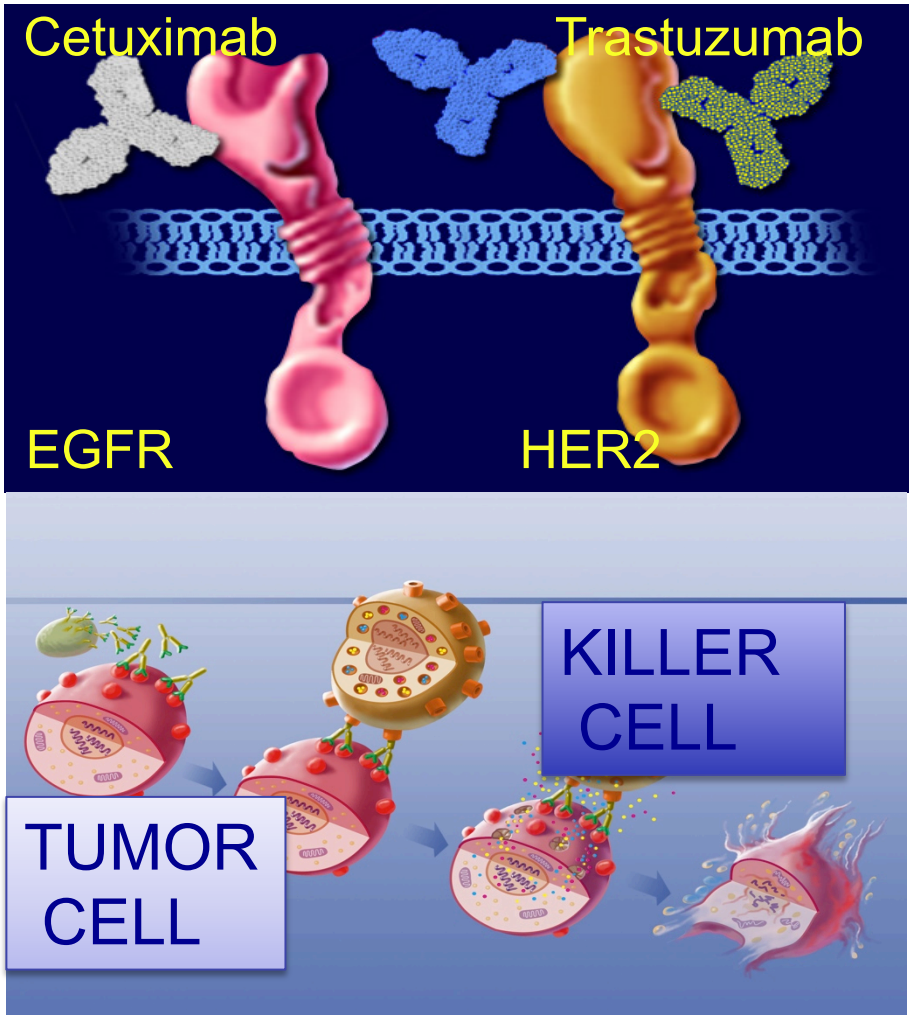


Burris HA, 3rd et al. J Clin Oncol 2005;23:5305

Title: Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas

Abstract: …. Heavily pretreated patients with ErbB1-expressing and/or ErbB2-overexpressing metastatic cancers were randomly assigned to one of five dose cohorts of lapatinib administered once daily……Four patients with trastuzumab-resistant metastatic breast cancer – two of whom were classified as having inflammatory breast cancer – had partial responses (PRs).

Uncommon Perturbation #2: Recruitment of the immune system by monoclonal antibodies



TUMOR CELL

Courtesy of Dr. Chris Bleackley (Univ. of Alberta)

Our Toughest Enemies

- ✓ **RAS and p53:** In combination, mutations in RAS and p53 are shred by >75% of human tumors, but both oncogenes are hardly druggable.

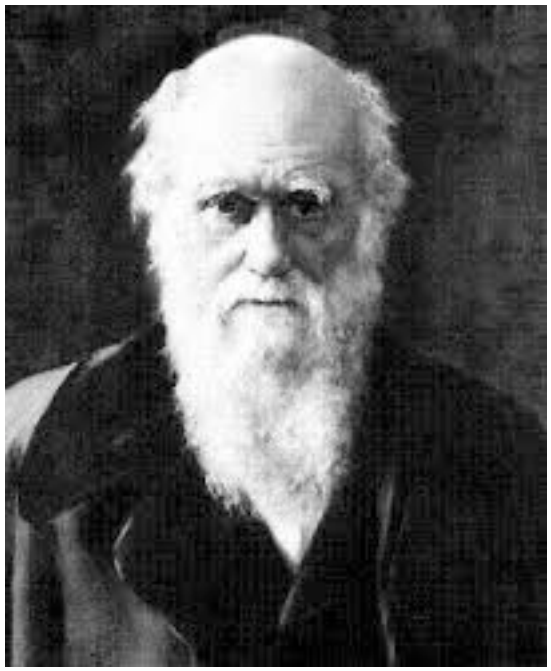
- ✓ **Micro-metasatses:** These small clusters of malignant cells evade all imaging technologies and remain most deadly.

- ✓ **Secondary (evolving) resistance to drugs:** Patients under treatment often develop resistance due to secondary mutations and other mechanisms.

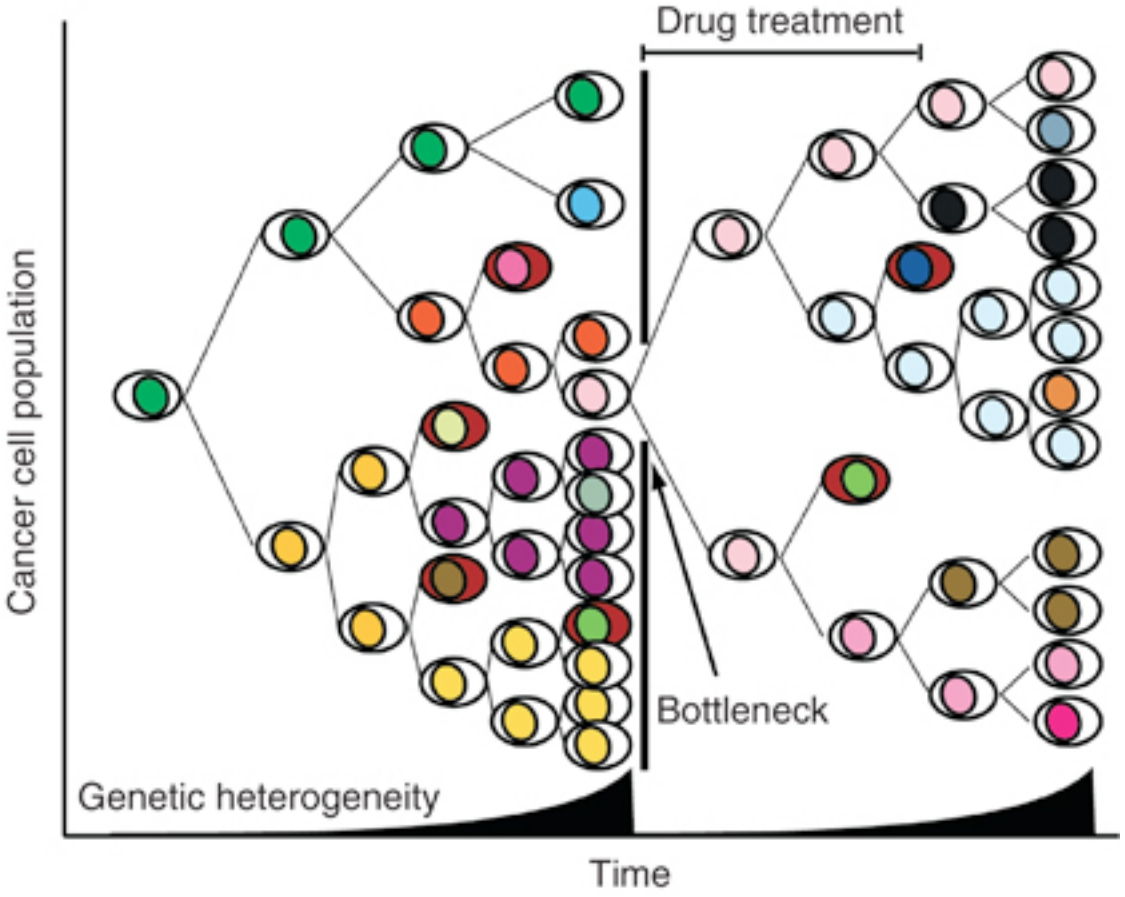
- ✓ **Tumor heterogeneity:** Intra-tumor and inter-metastases genetic heterogeneity underlie resistance to drugs and robust spreading throughout the body.

TUMOR HETEROGENEITY

Darwinian Bottlenecking Due to Treatment or Metastasis



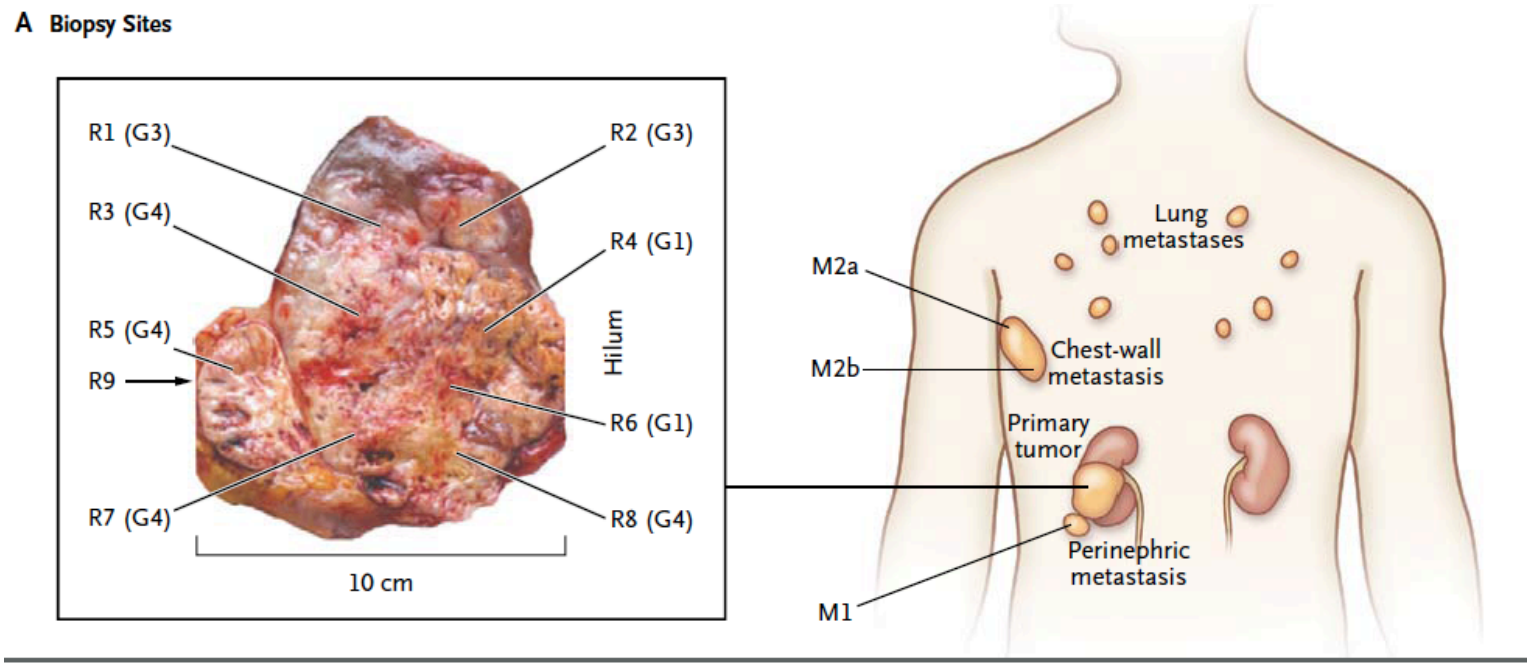
Charles Robert Darwin
(1809 – 1882)

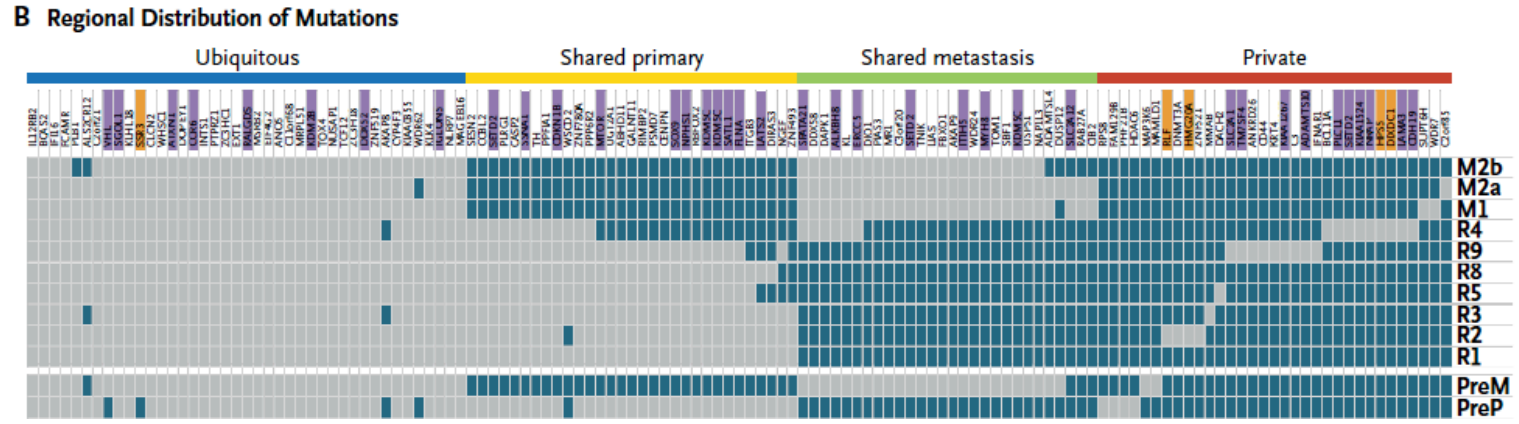


Intratumor Heterogeneity and Branched Evolution Revealed by Multi-region Sequencing (M. Gerlinger et al., 2012, NEJM)

- Used a primary RCC tumor and several metastases
- Performed exome sequencing, analysis of chromosome aberrations and ploidy profiling
- Observed branched evolutionary growth with 65% of all somatic mutations not shared by all tumor regions

Intra-tumour genetic heterogeneity





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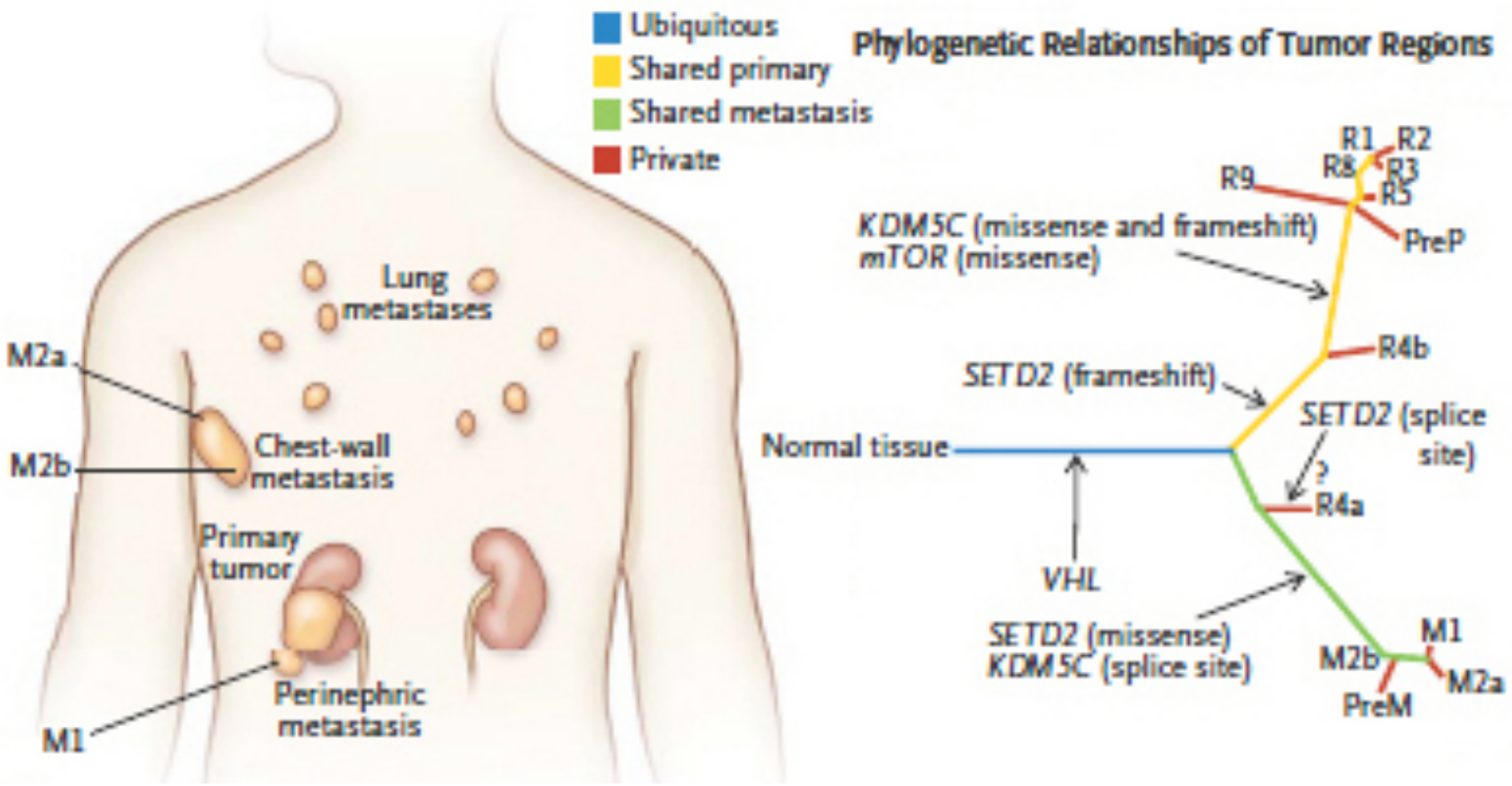
Philogenetic Relationships of Tumor Regions



Messages: Network Biology Provides a Conceptual Framework for Signal Transduction Therapies

- Networks evolved to compensate for the limited coding capacity of complex genomes
- While undergoing transformation from pathways to networks, biological systems gained robustness by means of training to withstand common, single perturbations (mono-therapies)
- Growth factors employ a pulsatile mode of regulation, which filters noise and ensures commitment to S-phase entry
- Feedback loops are the guardians of the cell's steady state; perturbing the steady state would invoke resistance, unless feedback loops are restrained
- In conclusion: Blocking a cancer network translates to:

-Targeting a major (addicting or survival) hub
-Using multiple or uncommon perturbations
-Restraining the respective feedback loop

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