

Module 2: Systems Engineering

Technical

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Module 2: Systems Engineering

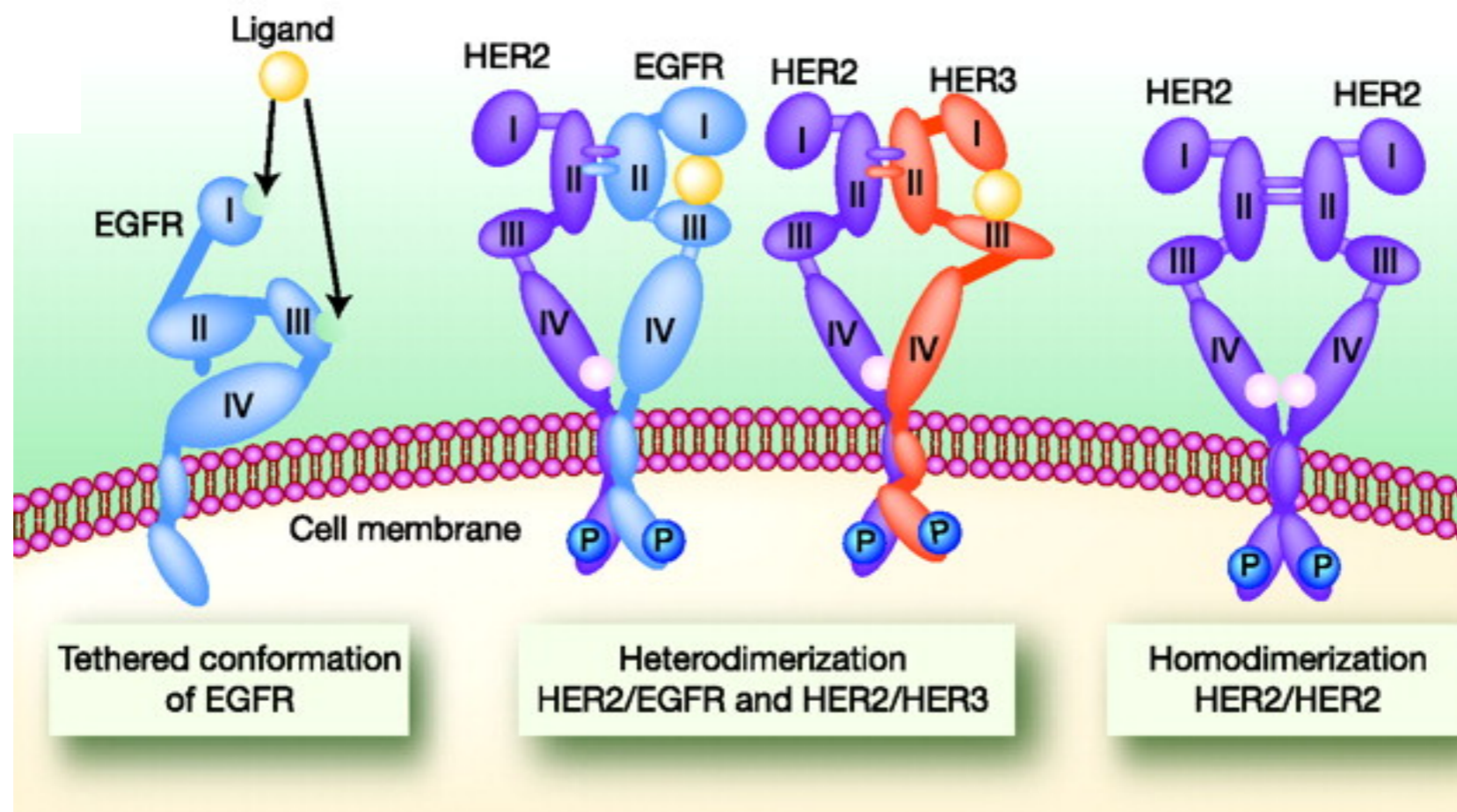
- A few words about 20.109 grading philosophy
- Brain break before thinking more about cell signaling
- Drug resistance & Systems Biology
- Module 2 overview -- in lecture & in the lab
- Short review of the EGFR system
- What we *are* going to do.
- What we *were* going to do (discuss M2D4).

Module 2: Systems Engineering

2012 AAAS: Dance your Thesis

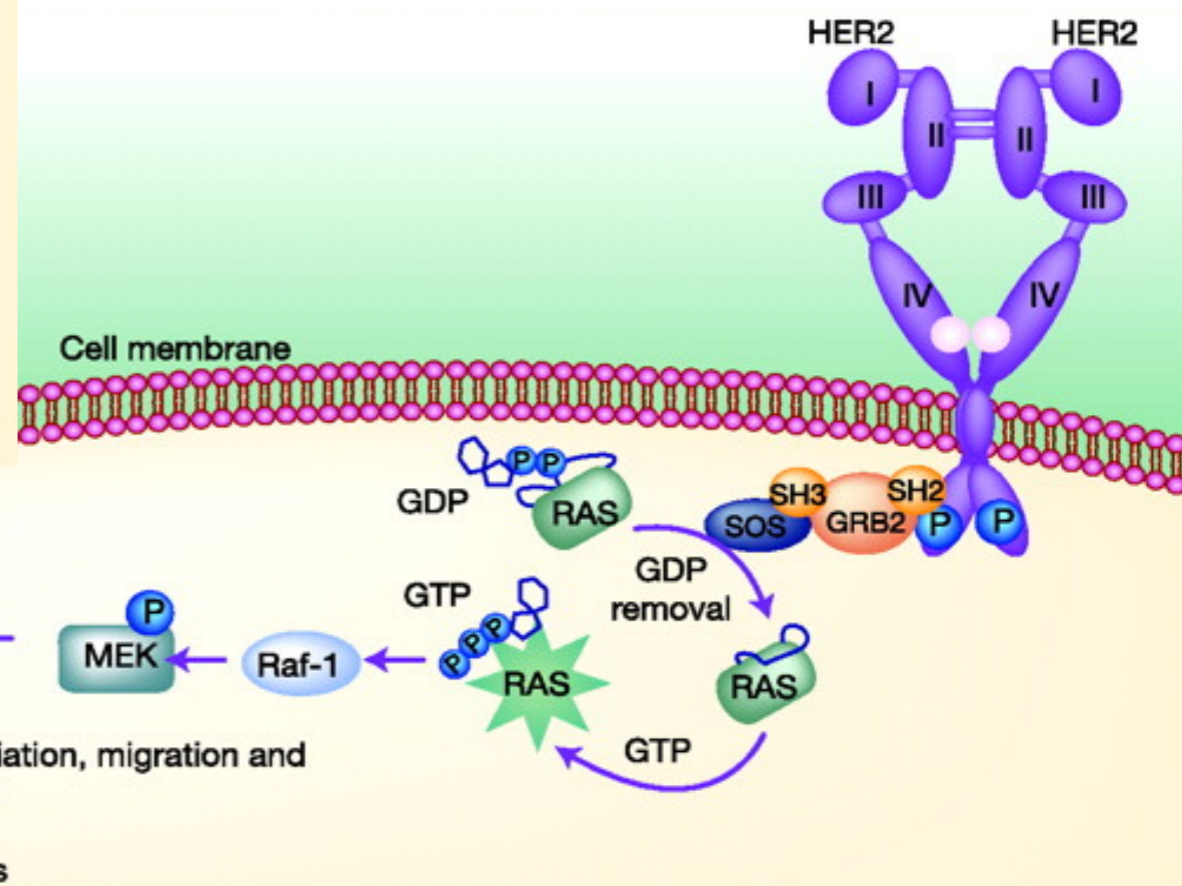
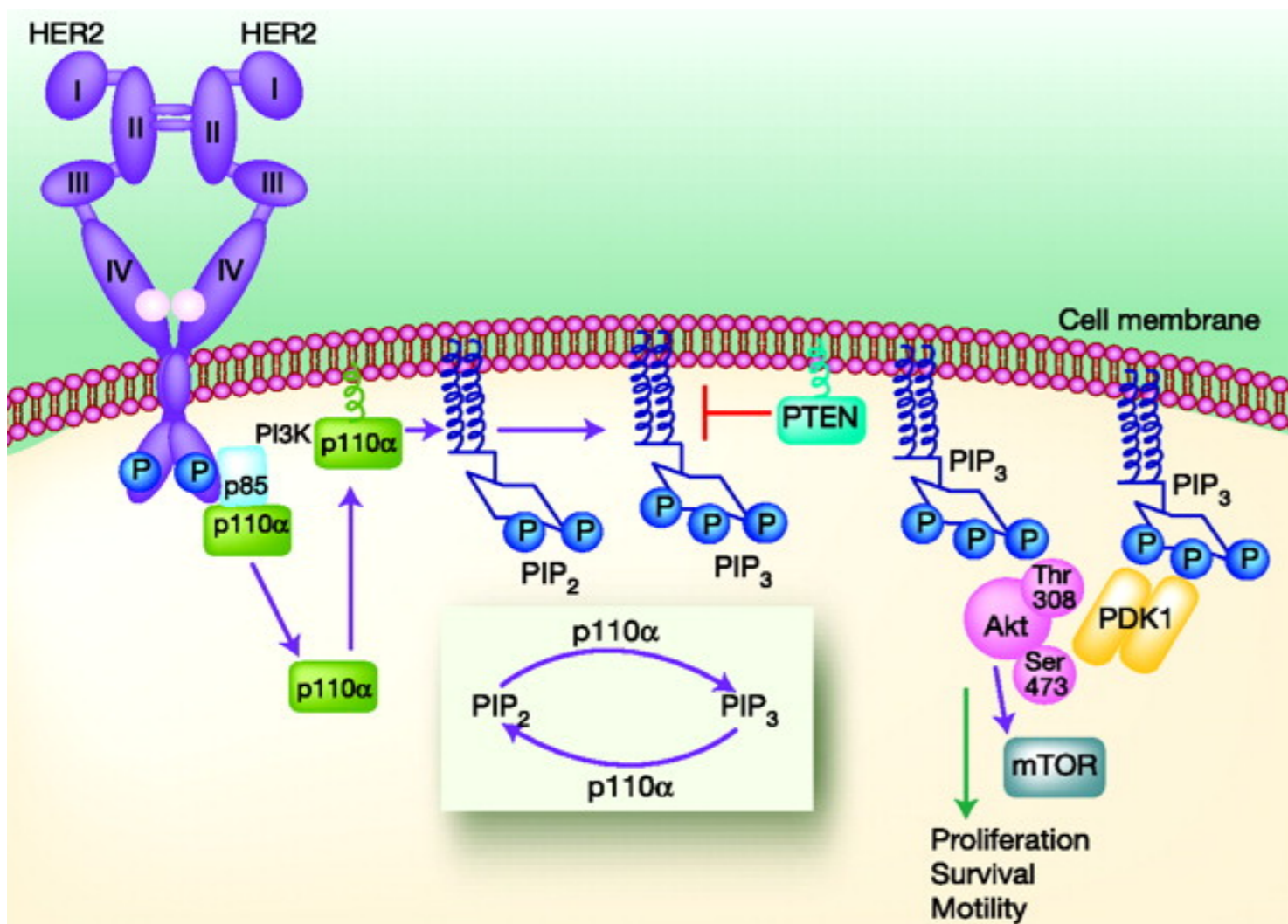
<http://vimeo.com/50490103>

Clinical application: Blocking HER2 signaling decreases breast cancer progression...



Modified from Pohlmann et al. Clin Cancer Res December 15, 2009 15; 7479

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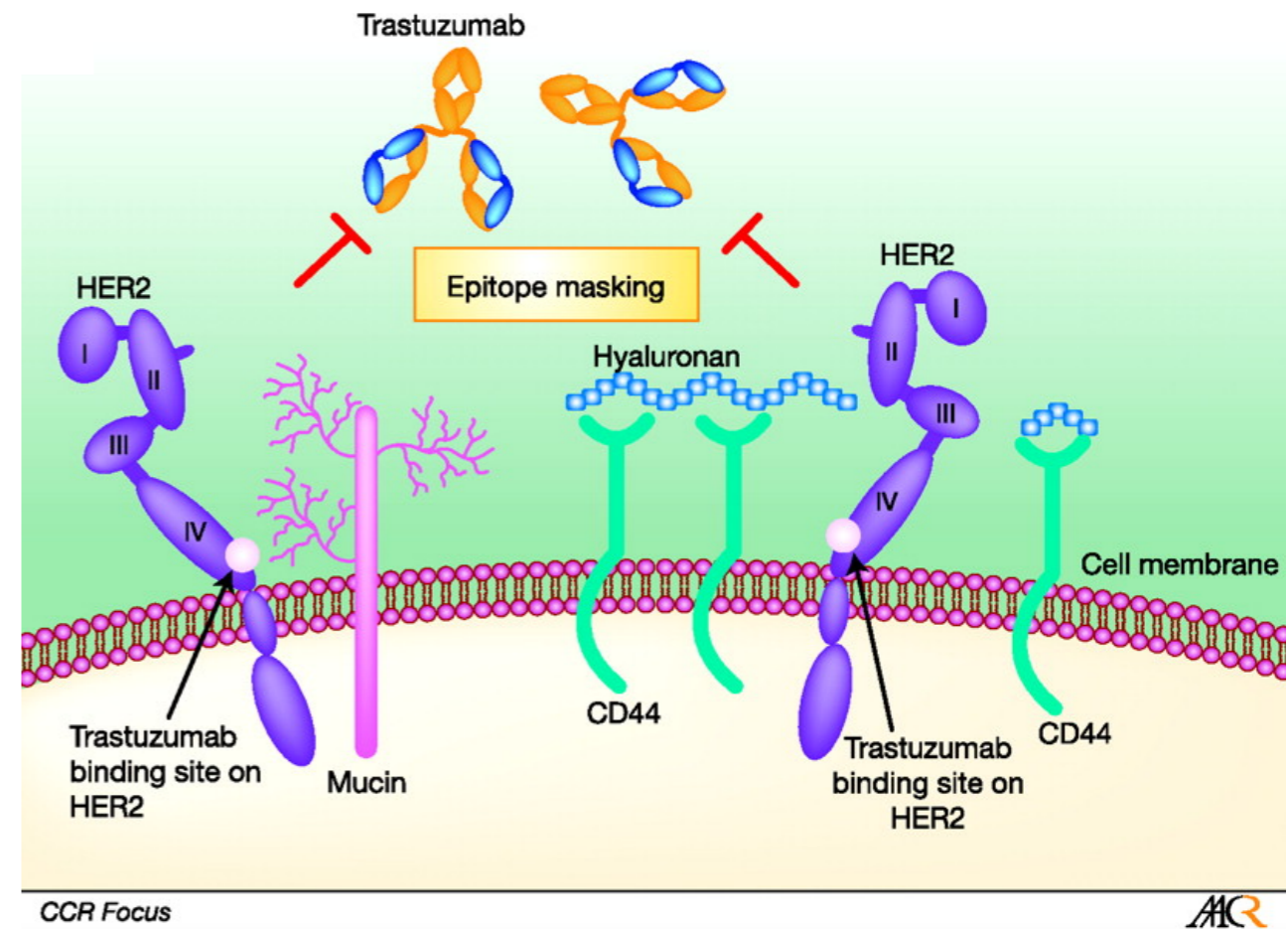
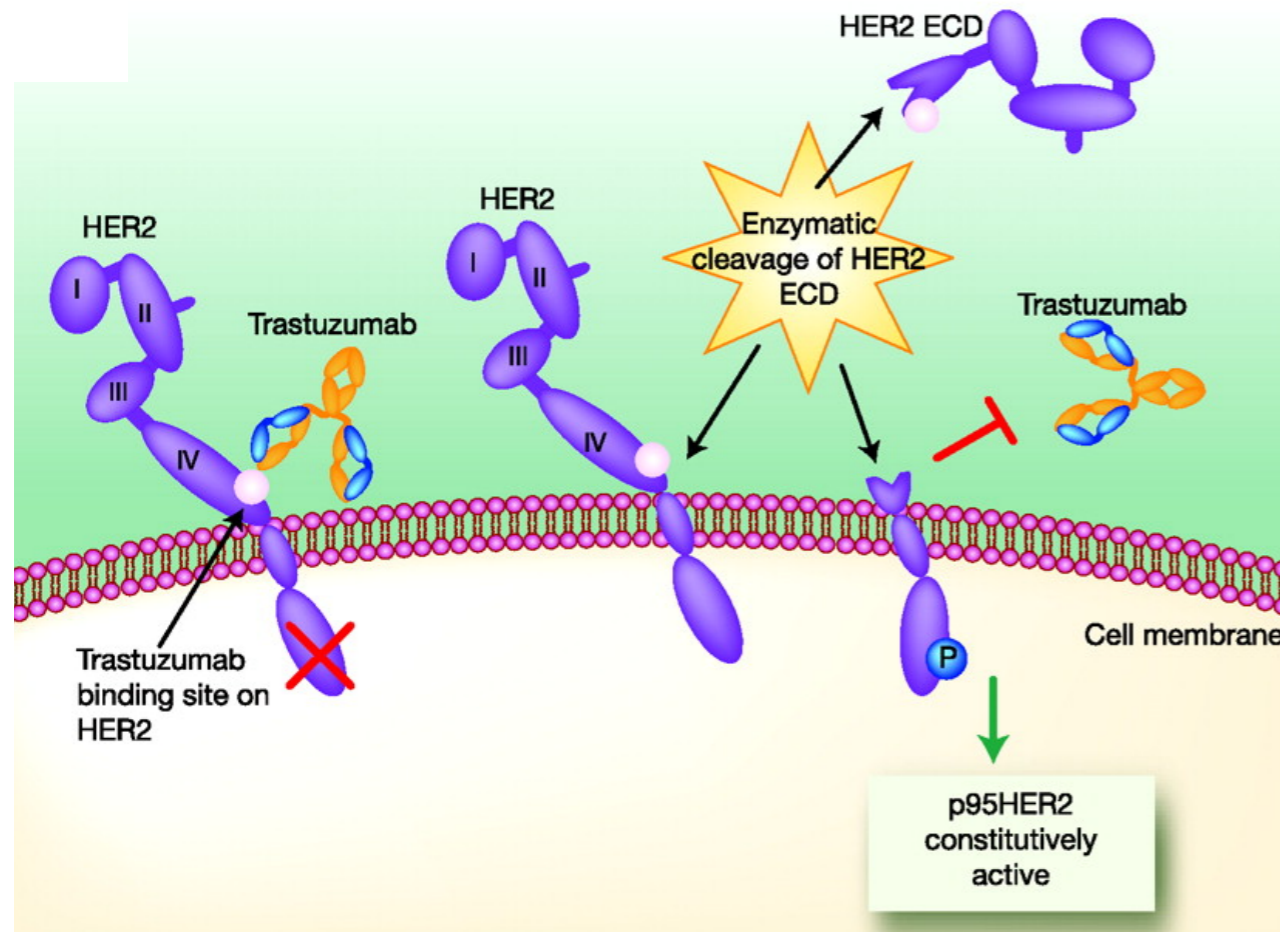


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The elephant in that dance:
What happens to patients who take an anti-HER2 drug?

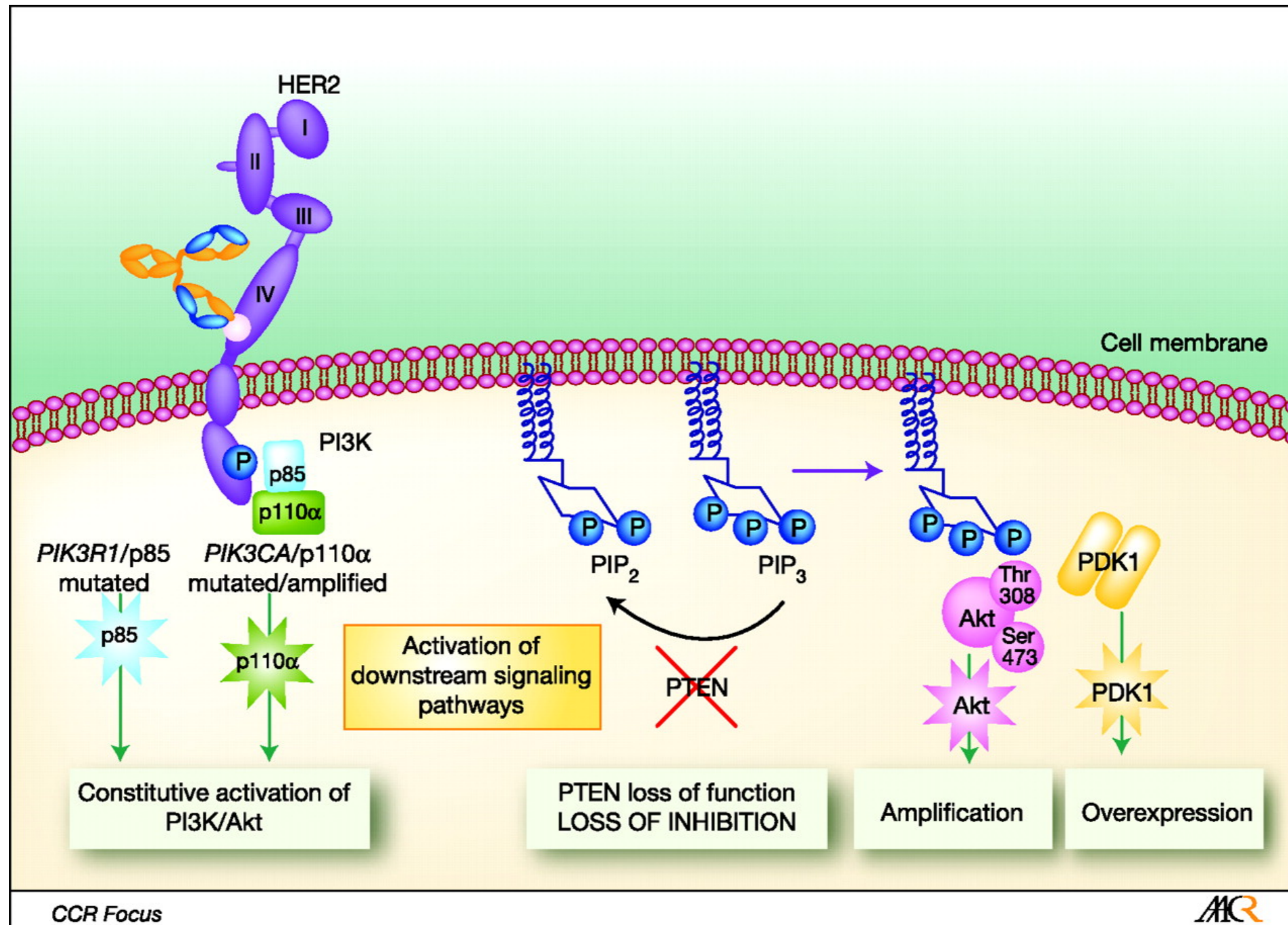
Disease progression resumes in ~ 1 year --
“acquired resistance”

The elephant in that dance: Mechanisms that mediate resistance.



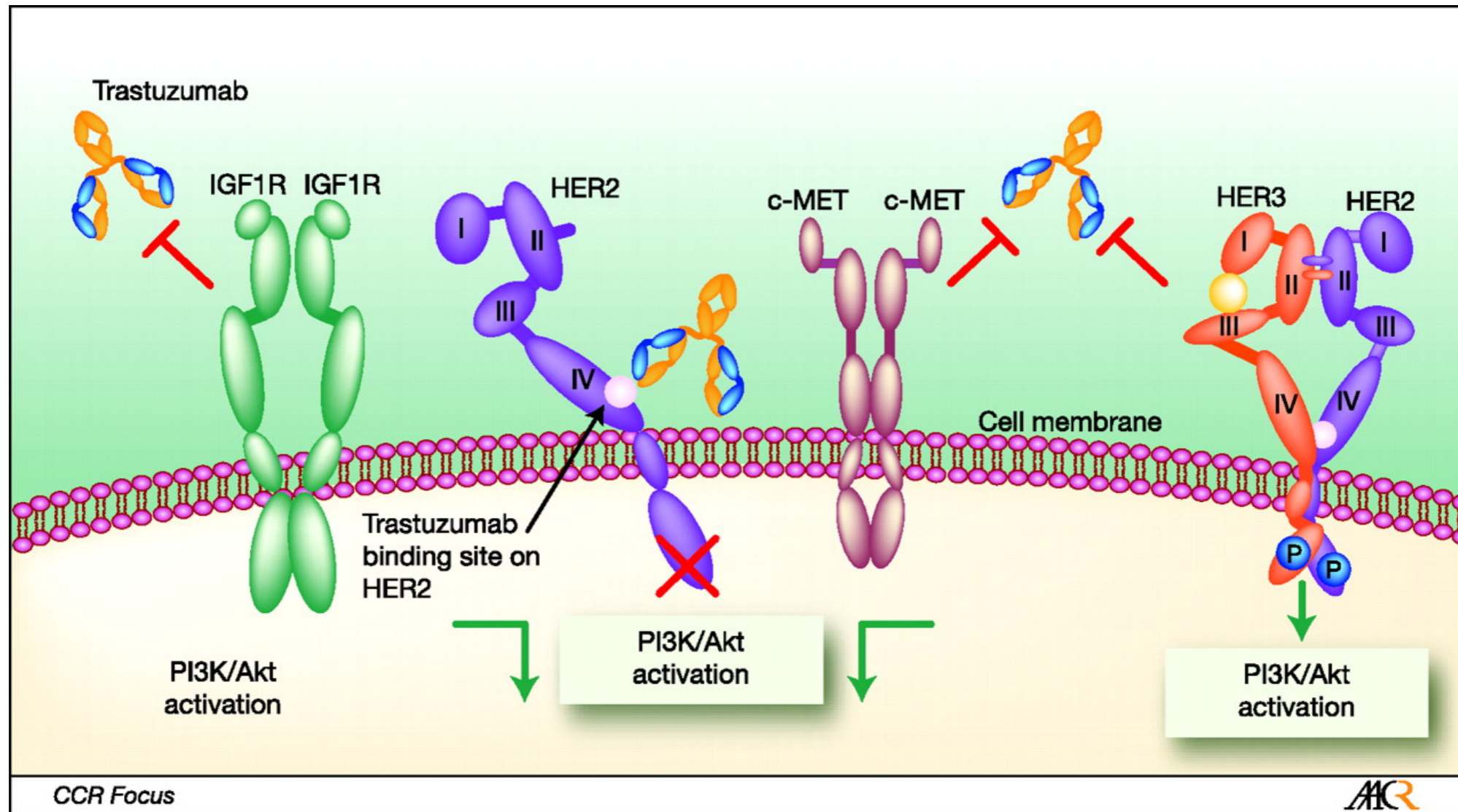
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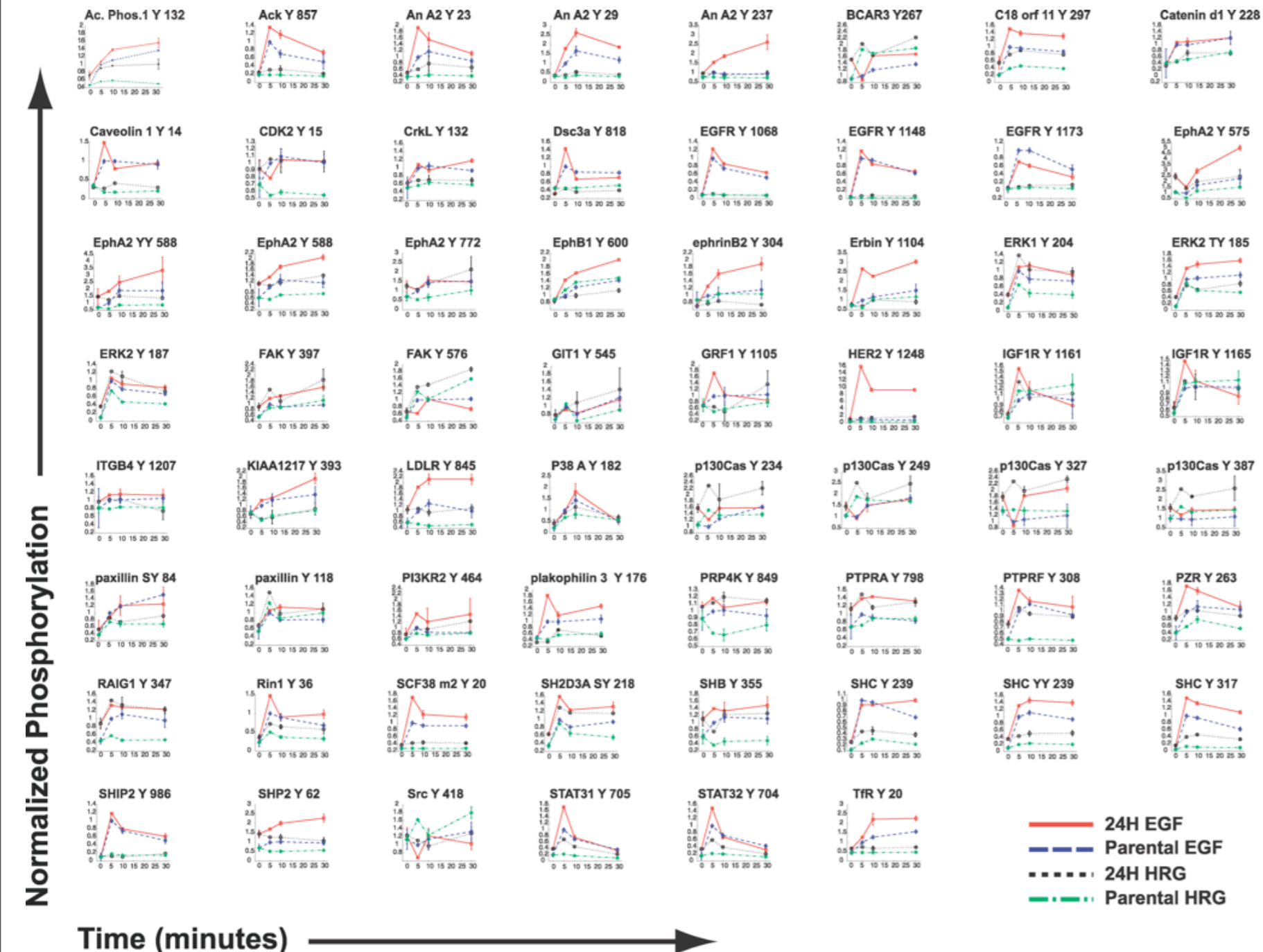
The elephant in that dance: Mechanisms that mediate resistance.



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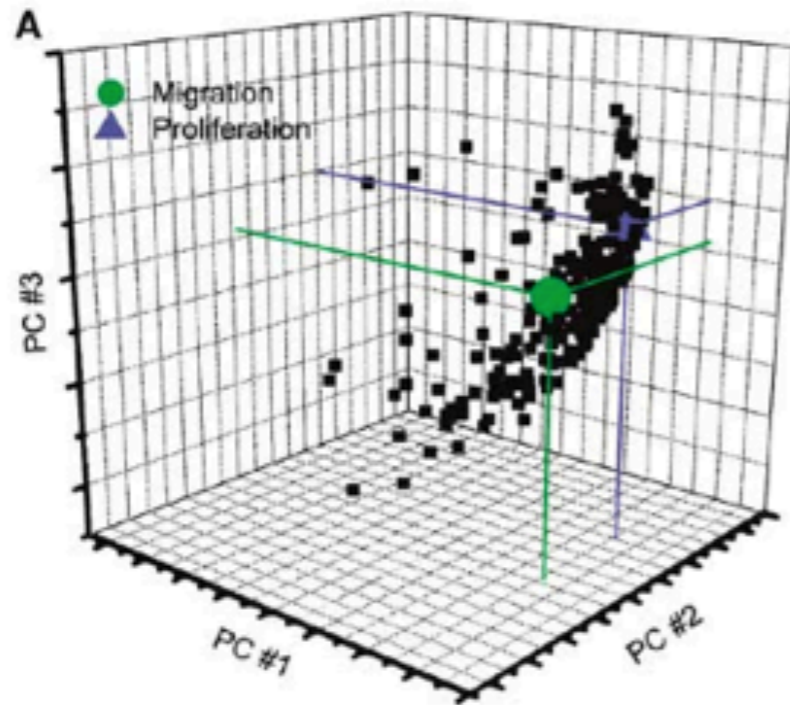
Systems biology aims to solve important problems like drug resistance through experiment + mathematical modeling.

How can we do better using a systems approach?



Kumar N, Wolf-Yadlin A, White FM, Lauffenburger DA (2007) Modeling HER2 Effects on Cell Behavior from Mass Spectrometry Phosphotyrosine Data. PLoS Comput Biol 3(1): e4.

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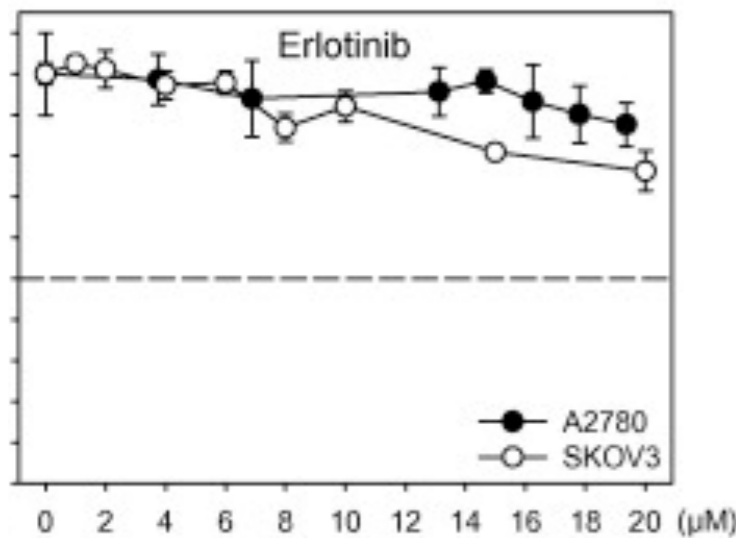
Migration		Proliferation	
Phosphorylation site	Measurement	Phosphorylation site	Measurement
SHP-2 Y 62	30 min	Dsc3a Y 818	10 min
An A2 Y 237	10 min	Dsc3a Y 818	30 min
An A2 Y 237	30 min	EGFR Y 1173	10 min
HER2 Y 1248	5 min	EGFR Y 1173	Integral
ErbB Y 1104	5 min	EGFR Y 1173	30 min
HER2 Y 1248	10 min	Dsc3a Y 818	Integral
HER2 Y 1248	30 min	IGF1R Y 1165	30 min
GRF1 Y 1105	5 min	EGFR Y 1173	5 min
LDLR Y 845	30 min	paxillin S/Y 84/88	30 min
HER2 Y 1248	Integral	CrkL Y 132	10 min
SHP-2 Y 62	10 min	GIT1 Y 545	5 min
An A2 Y 237	5 min	paxillin S/Y 84/88	5 min
SHB Y 355	5 min	Catenin d1 Y 228	30 min
LDLR Y 845	5 min	paxillin S/Y 84/88	Integral
EphA2 Y/Y 588/594	5 min	Src Y 418	Integral

Effects of **HER2** overexpression on cell signaling networks governing proliferation and migration. Wolf-Yadlin A, Kumar N, Zhang Y, Hautaniemi S, Zaman M, Kim HD, Grantcharova V, Lauffenburger DA, White FM. Mol Syst Biol. 2006;2:54. Epub 2006 Oct 3.

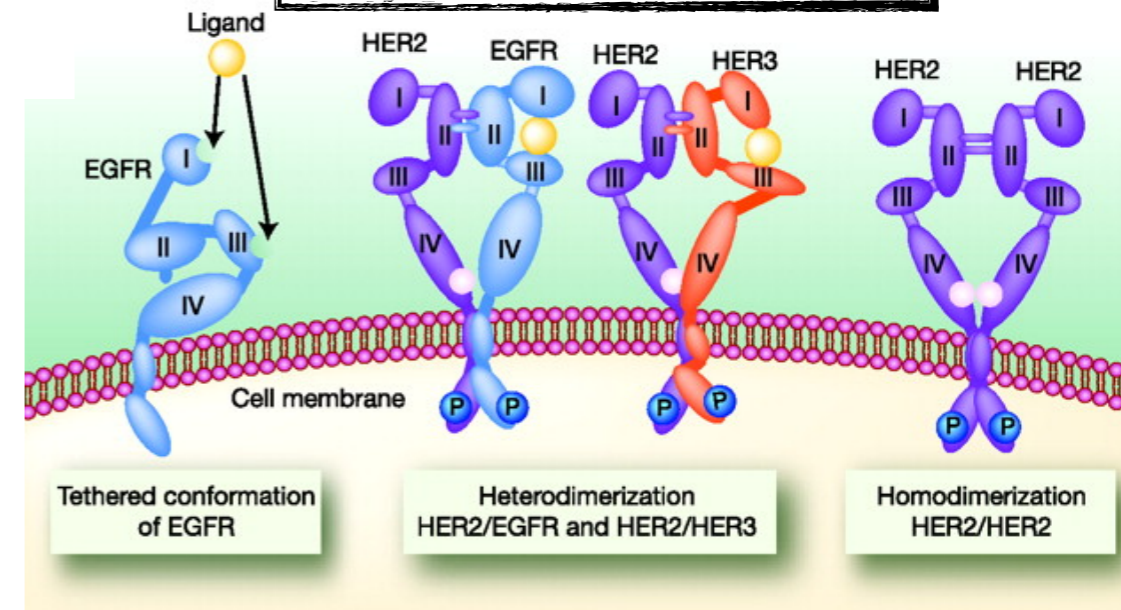
Module 2: Systems Engineering

Experimental Context: EGFR System

Design Goal:



Overcome resistance to EGFR inhibition in SKOV3 human ovarian cancer cells.



Approach:

Use mathematical models to make predictions and 'high throughput' experiments to test hypothesis.

Themes of the module:

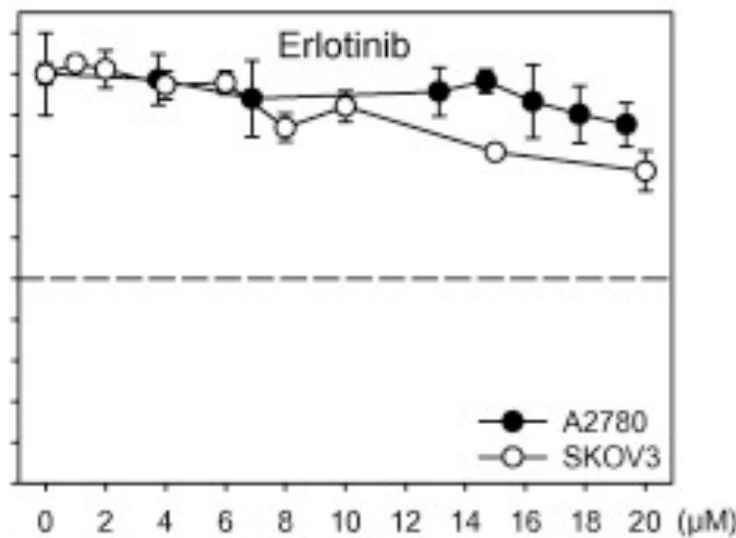
Cancer Systems Biology
High Throughput Screening Technologies

Cool Science Interlude

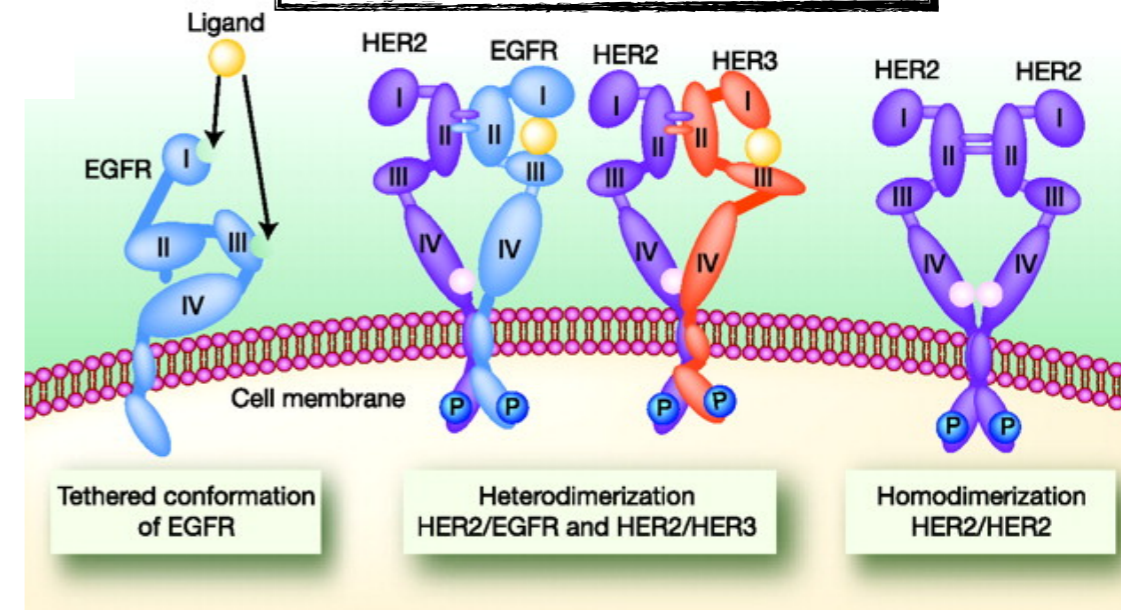
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Cancer Systems Biology
High Throughput Screening Technologies

Module 2: Systems Engineering

Experimental Techniques:

cDNA library prep + mutation analysis PCR
DNA sequencing
Drug/Inhibitor + Growth Factor Stimulation
Phosphotyrosine Western blot
High Throughput Cell Viability Assay -- Robots!

Data Analysis Techniques:

ODE model simulation
Sanger sequencing analysis
Densitometry -- IC50
Handling large data sets -- visualization & quantification

Module 2: Systems Engineering

A very communication intensive module:

In lab 'mock' Journal Club -- M2D3

Journal Club presentations (individual) -- M2D5/8

In lecture 'Design-your-own-HTS' -- M2D6

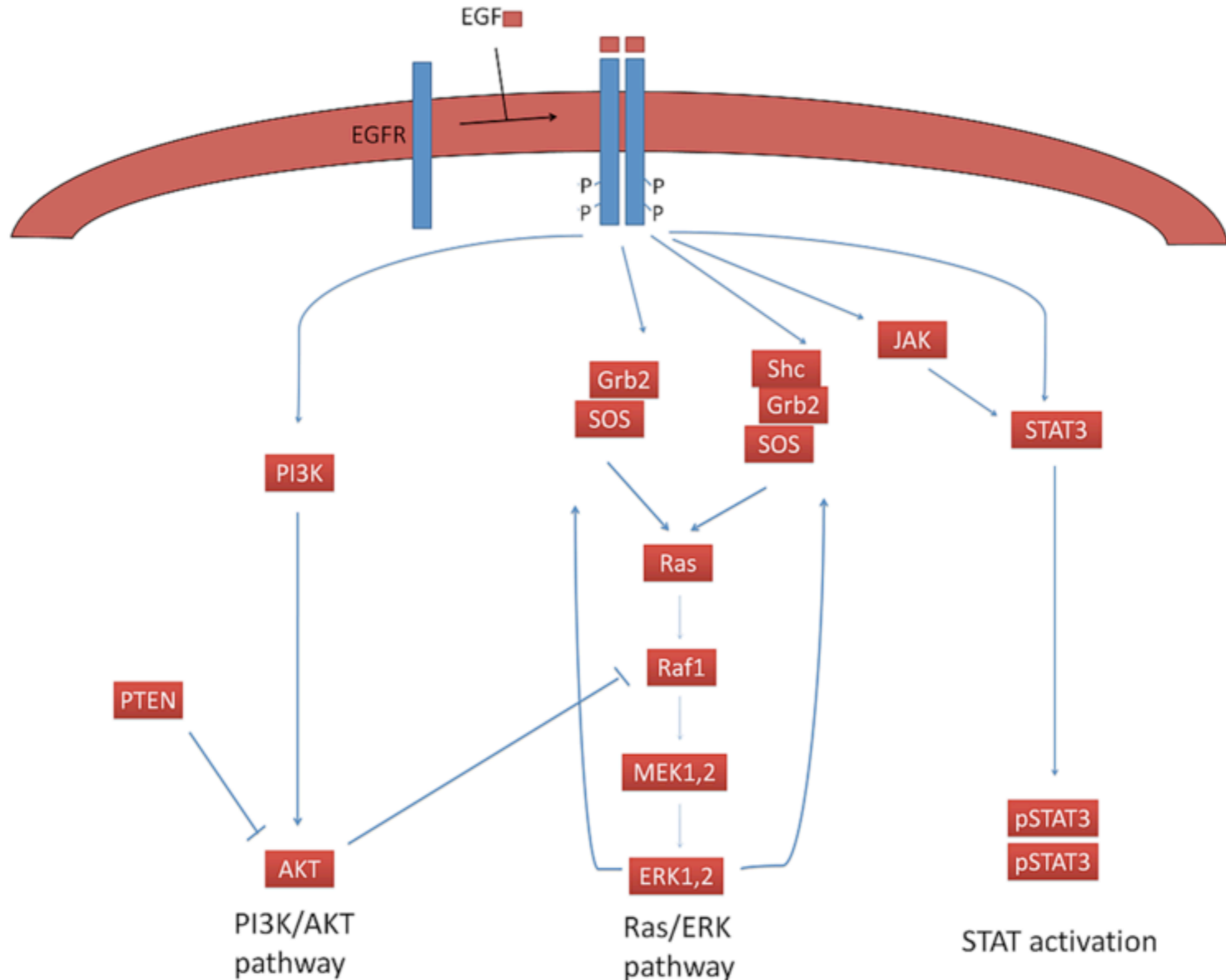
Full written research report + revision

+ mid-term evaluations (of us)

Module 2: Systems Engineering

Day:	Lab:	Lecture:
1	Explore the System	<i>Where does SB fit in?</i>
2	Do we have a mutant?	<i>SB & Mutation</i>
3	Analysis + Planning	<i>Math in drug design</i>
4	Low-throughput Screen	<i>(Semi)Quantifying activity</i>
5	Journal Club	<i>HTS Experimentation</i>
6	Analysis + Planning	<i>Design your own screen</i>
7	High-throughput Screen	<i>So much data!</i>
8	Journal Club	<i>HTS in industry</i>

Today in lab: EGFR pathway model



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