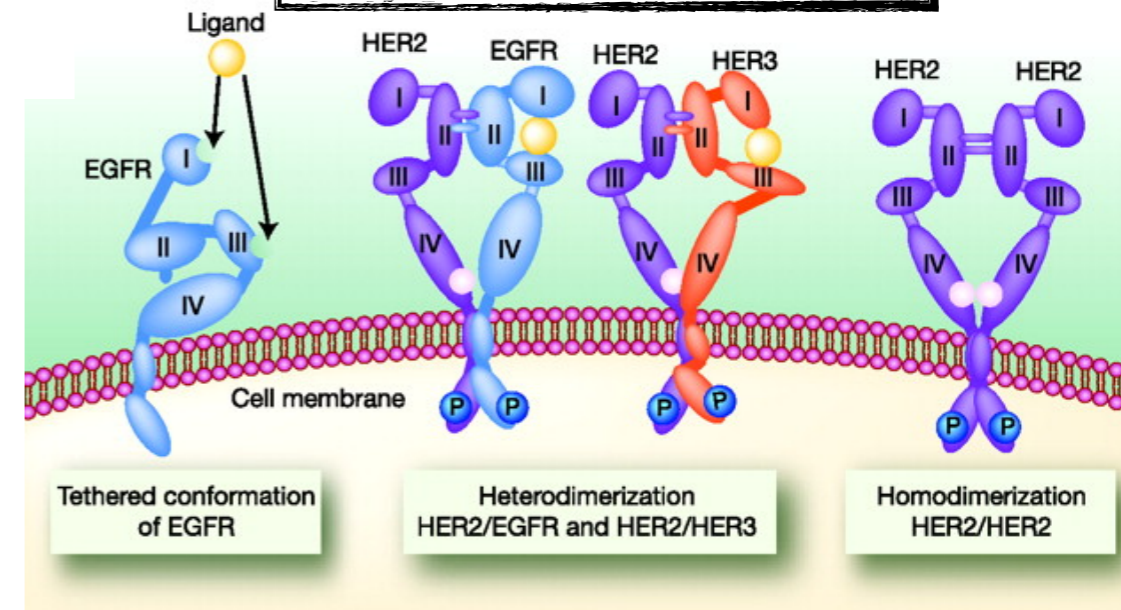# Module 2: Systems Engineering

- Revisit Module 2 goals & expectations

- M2D1 rewind

- EGFR fooled you, NSCLC!

- How mutations are detected in the clinic

- Some M2D2 lab plans
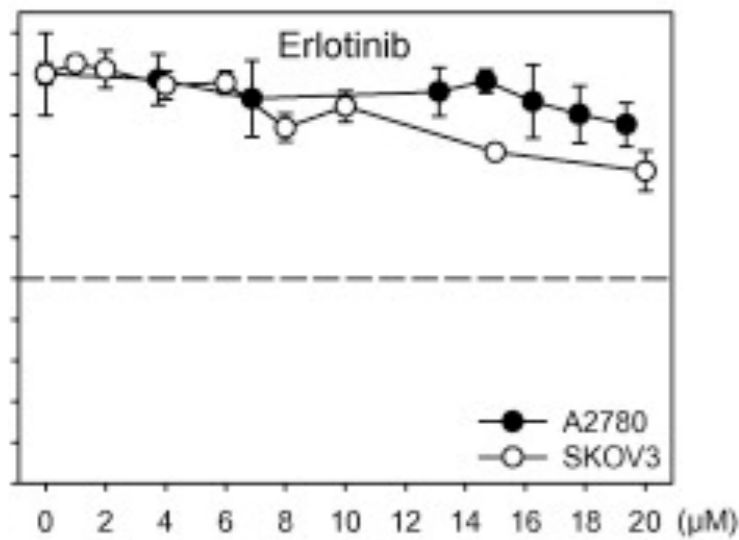
- Looking ahead

Module 2: Systems Engineering

Experimental Context: **EGFR System**

Module 2: Systems Engineering

Experimental Context: EGFR System

Design Goal:

Grunt et al. Biochem. Biophys. Res. Commun.
385:454-459(2009)

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

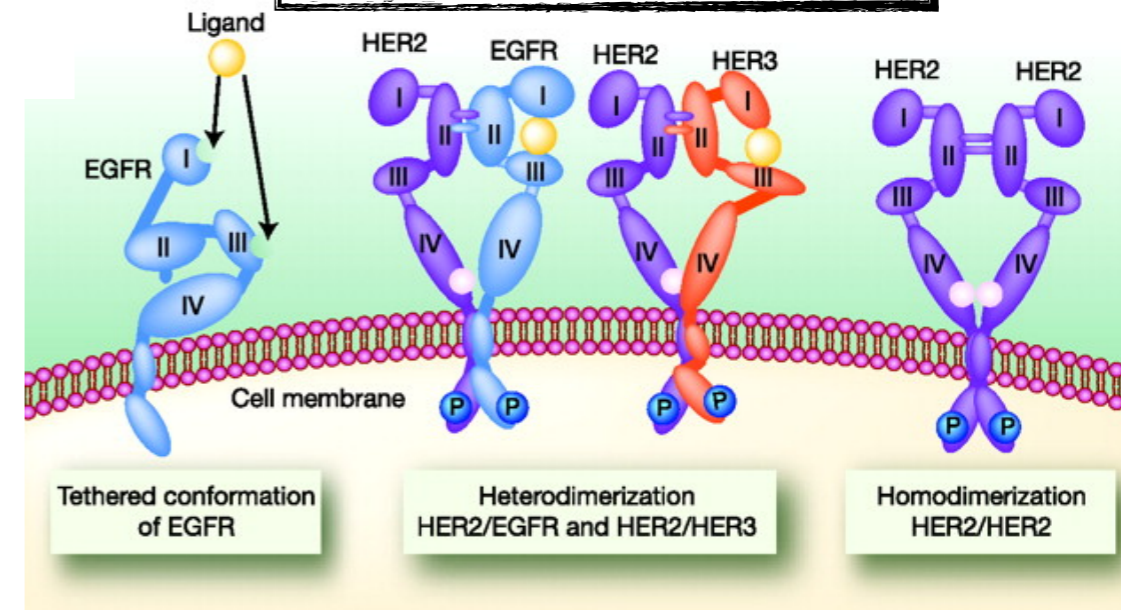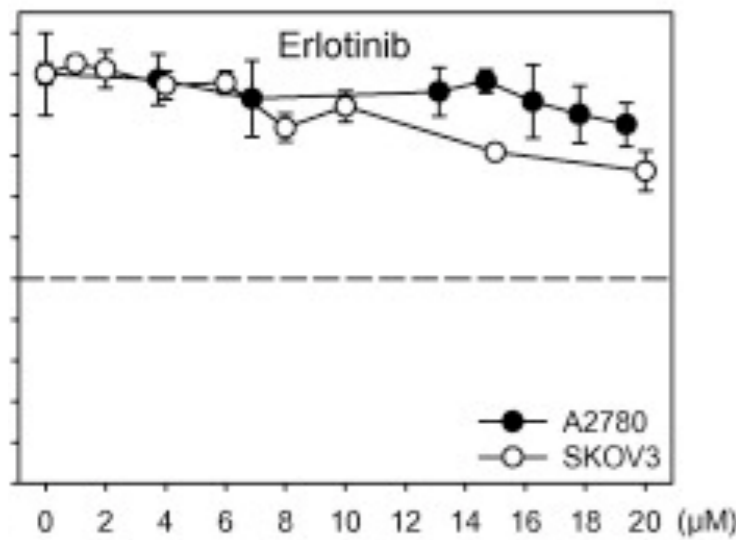# Module 2: Systems Engineering

Experimental Context: EGFR System

Design Goal:

Grunt et al. Biochem. Biophys. Res. Commun. 385:454-459(2009)

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.

Module 2: Systems Engineering

Experimental Context: EGFR System

Design Goal:

Erlotinib

● A2780
○ SKOV3

0 2 4 6 8 10 12 14 16 18 20 (μM)

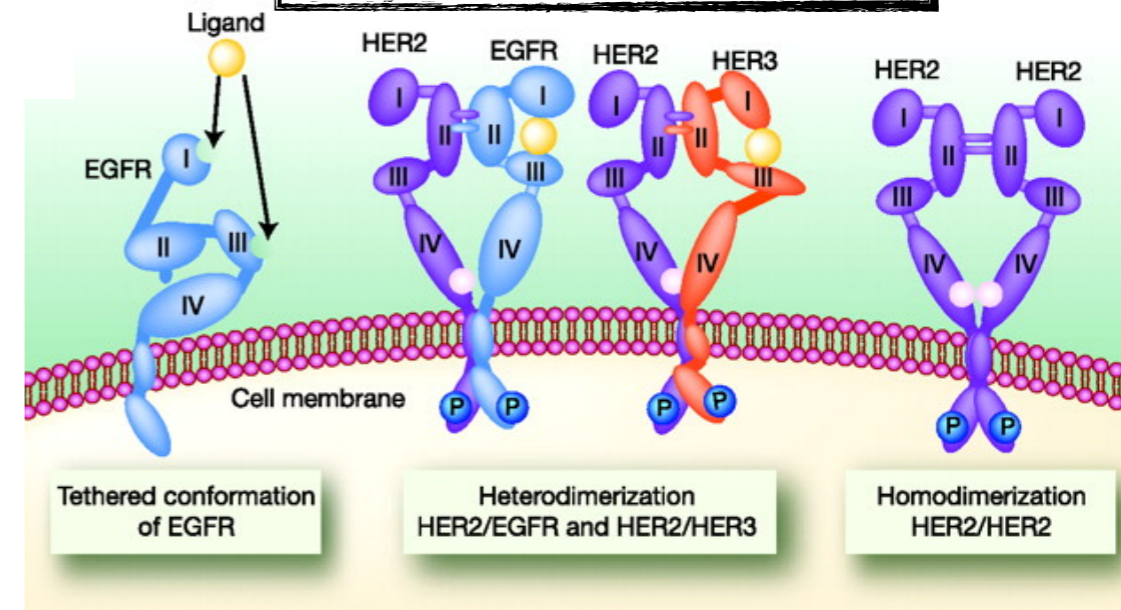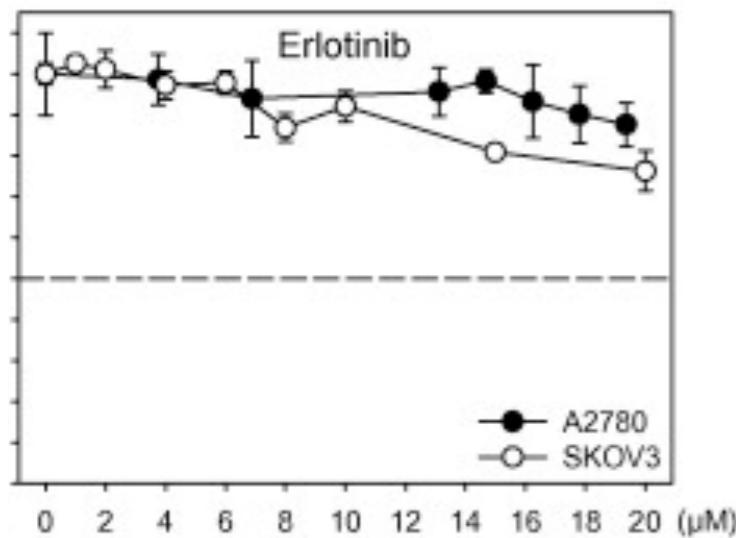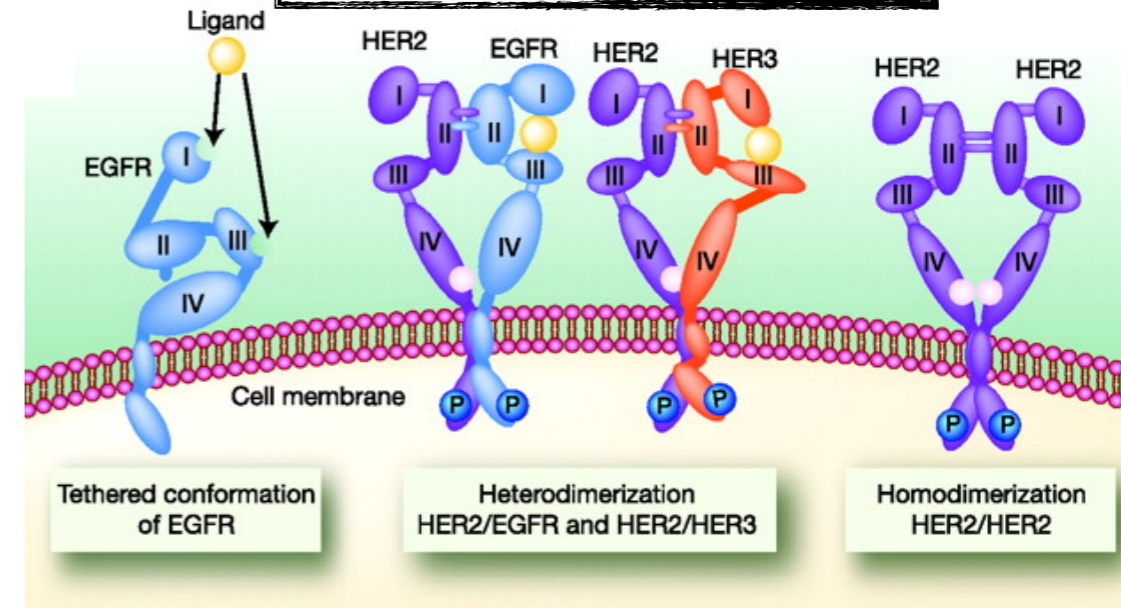Grunt et al. Biochem. Biophys. Res. Commun.
385:454-459(2009)

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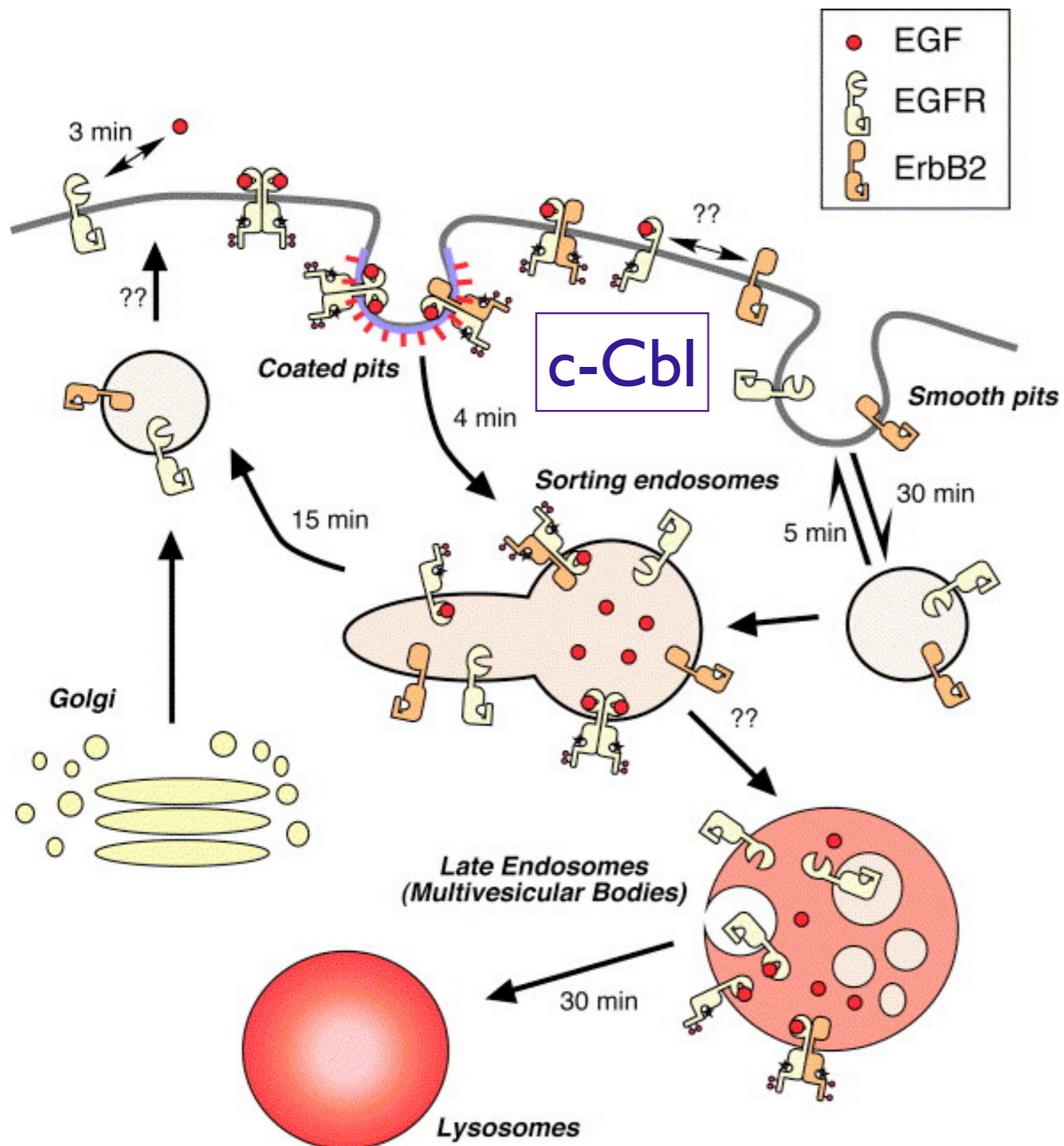

Approach:

Use mathematical models to make predictions and 'high throughput' experiments to test hypothesis.
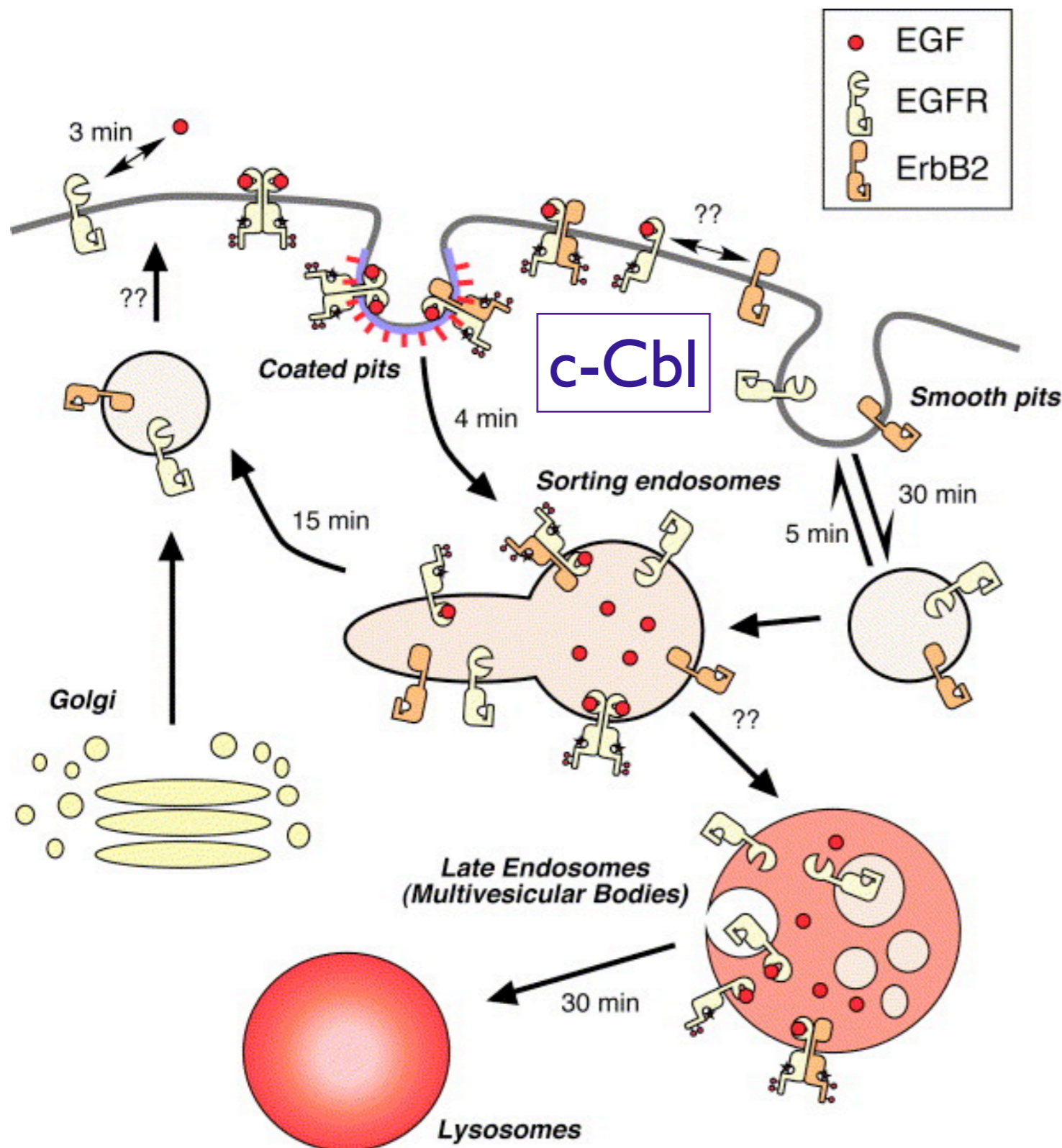
Themes of the module:

Cancer Systems Biology
High Throughput Screening Technologies

Bidkhori et al. model revisited.

Our simulation = 1000 sec ~ 17 min
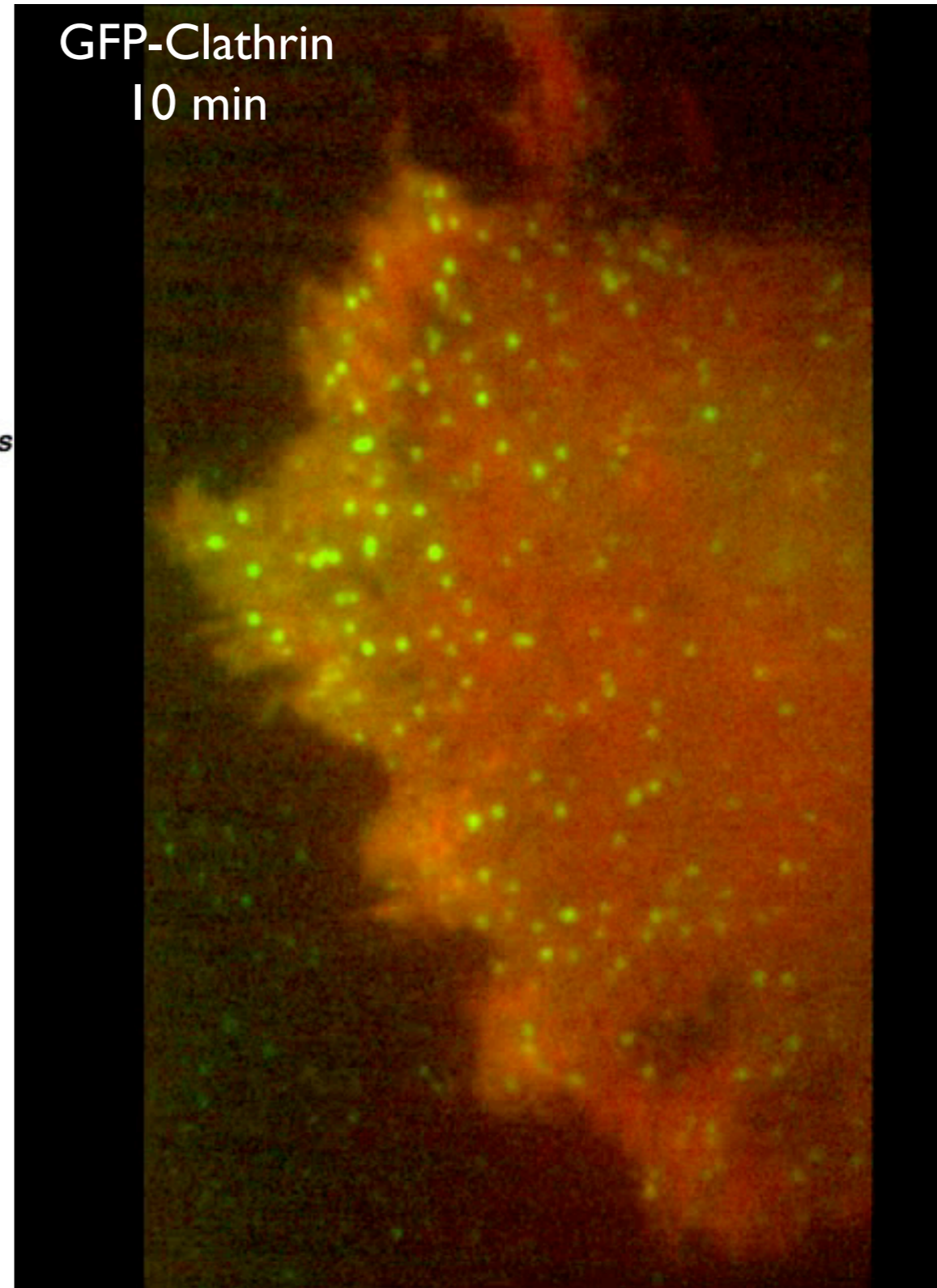
Bidkhori et al. model revisited.

GFP-Clathrin
10 min

c-Cbl

Our simulation = 1000 sec ~ 17 min

Bidkhori et al. model revisited.
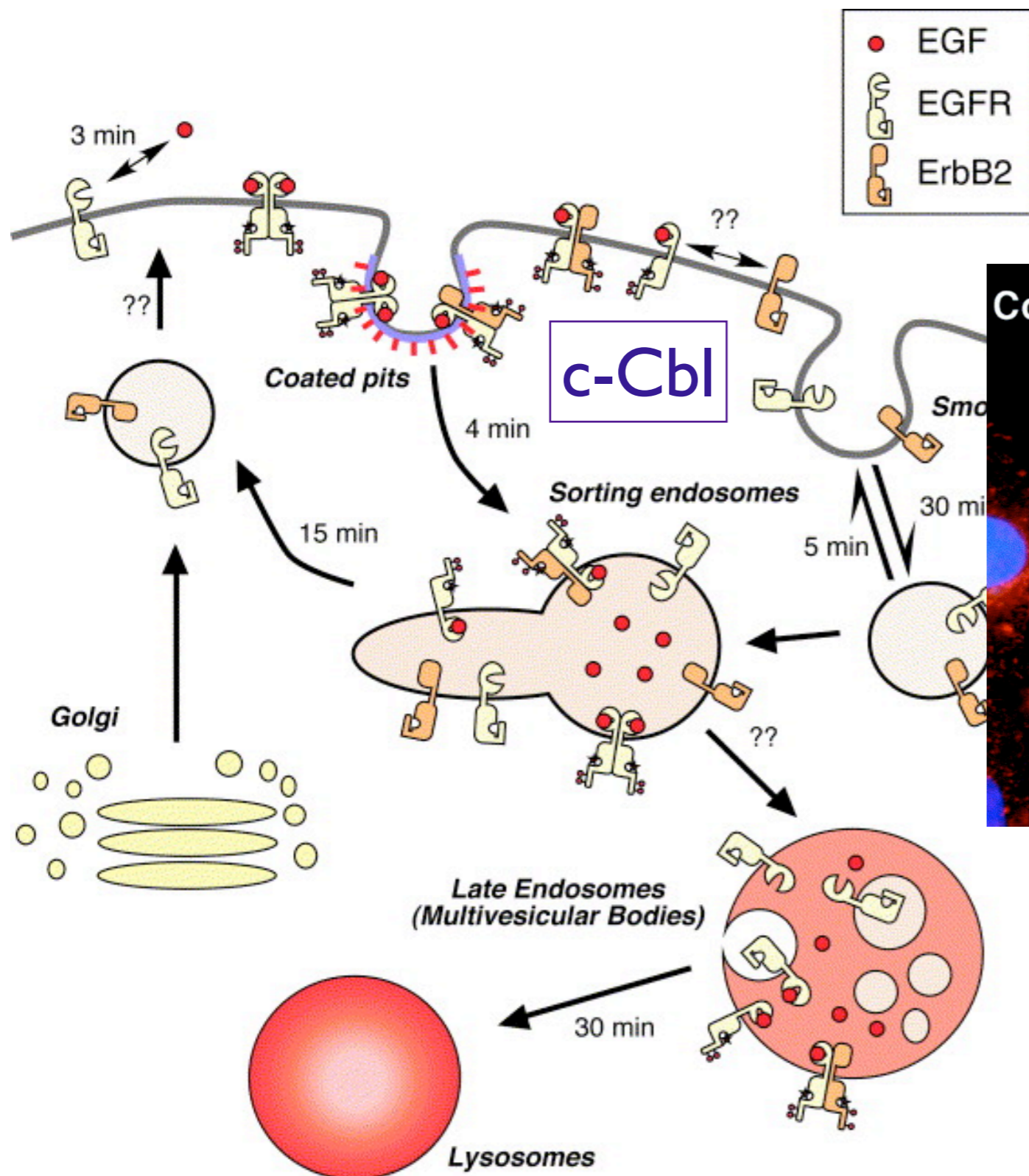
Red = anti-EGFR Ab

Green = anti-EGF Ab

20 min

Our simulation = 1000 sec ~ 17 min

Ras/ERK pathway

'Normal'

'Cancer'

[pShc]|Time   [Ras-GTP]|Time   [ppERK]|Time

Ras/ERK

Shankaran et al. Molecular Systems Biology **5** Article number: 332

PTEN

$$PTEN \dashv$$

$$PIP2 \rightleftharpoons PIP3$$

'Cancer'

'Cancer + no PTEN'
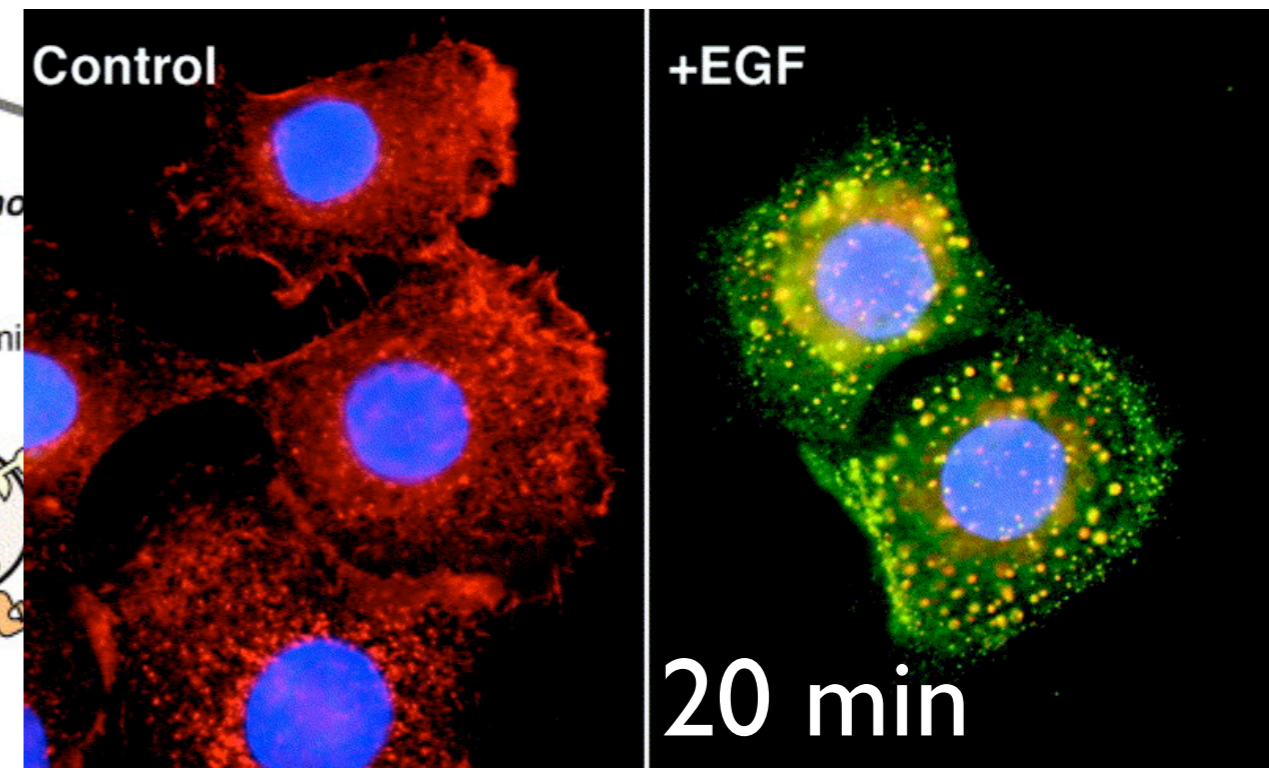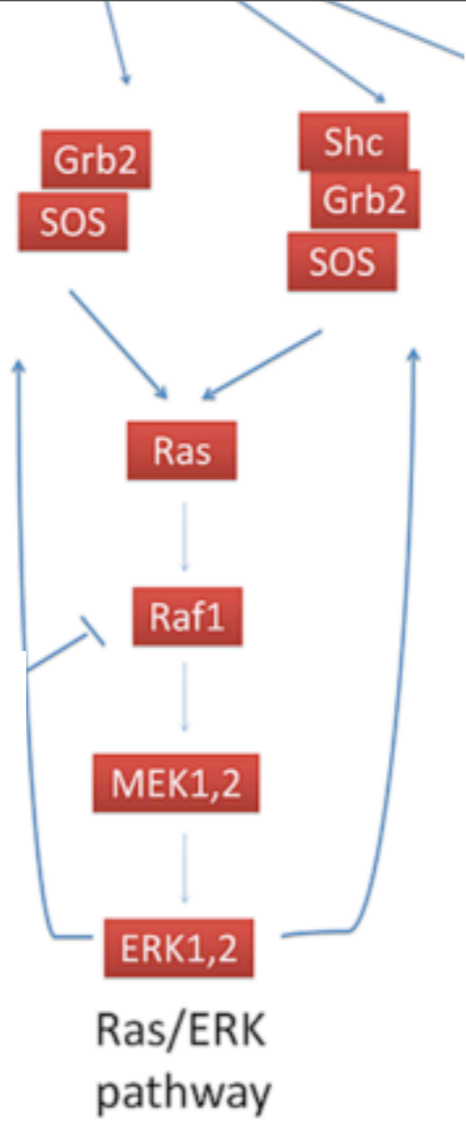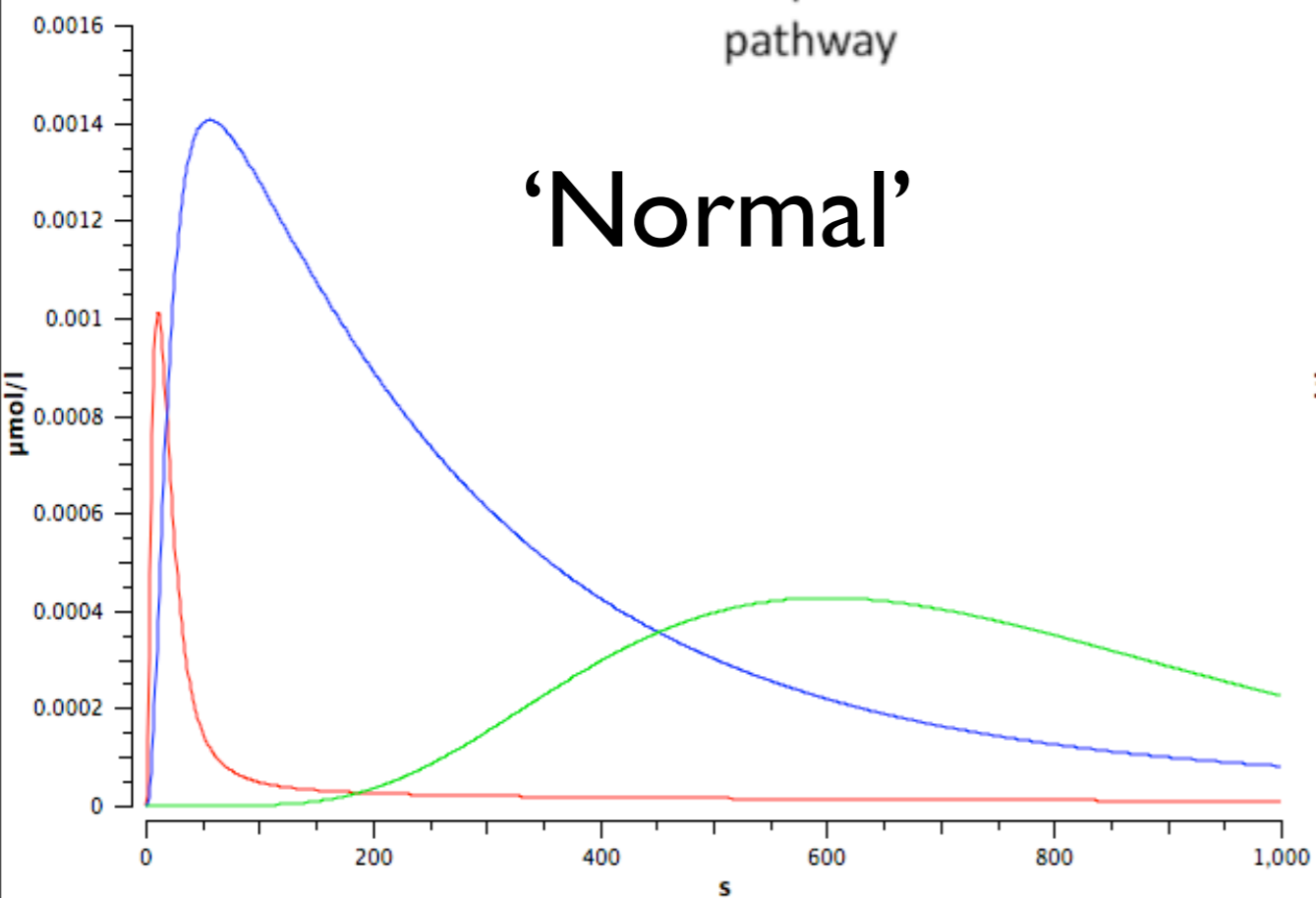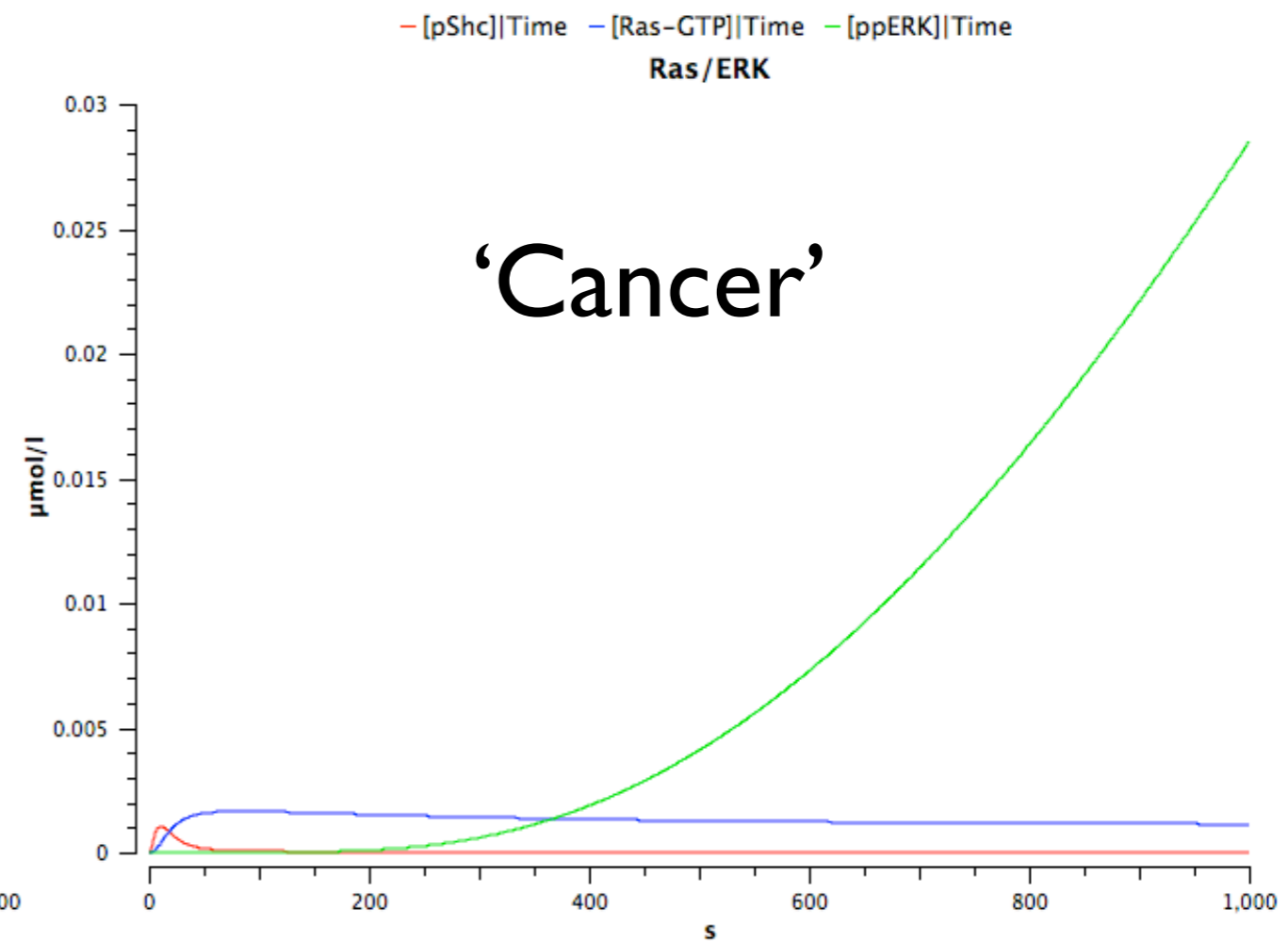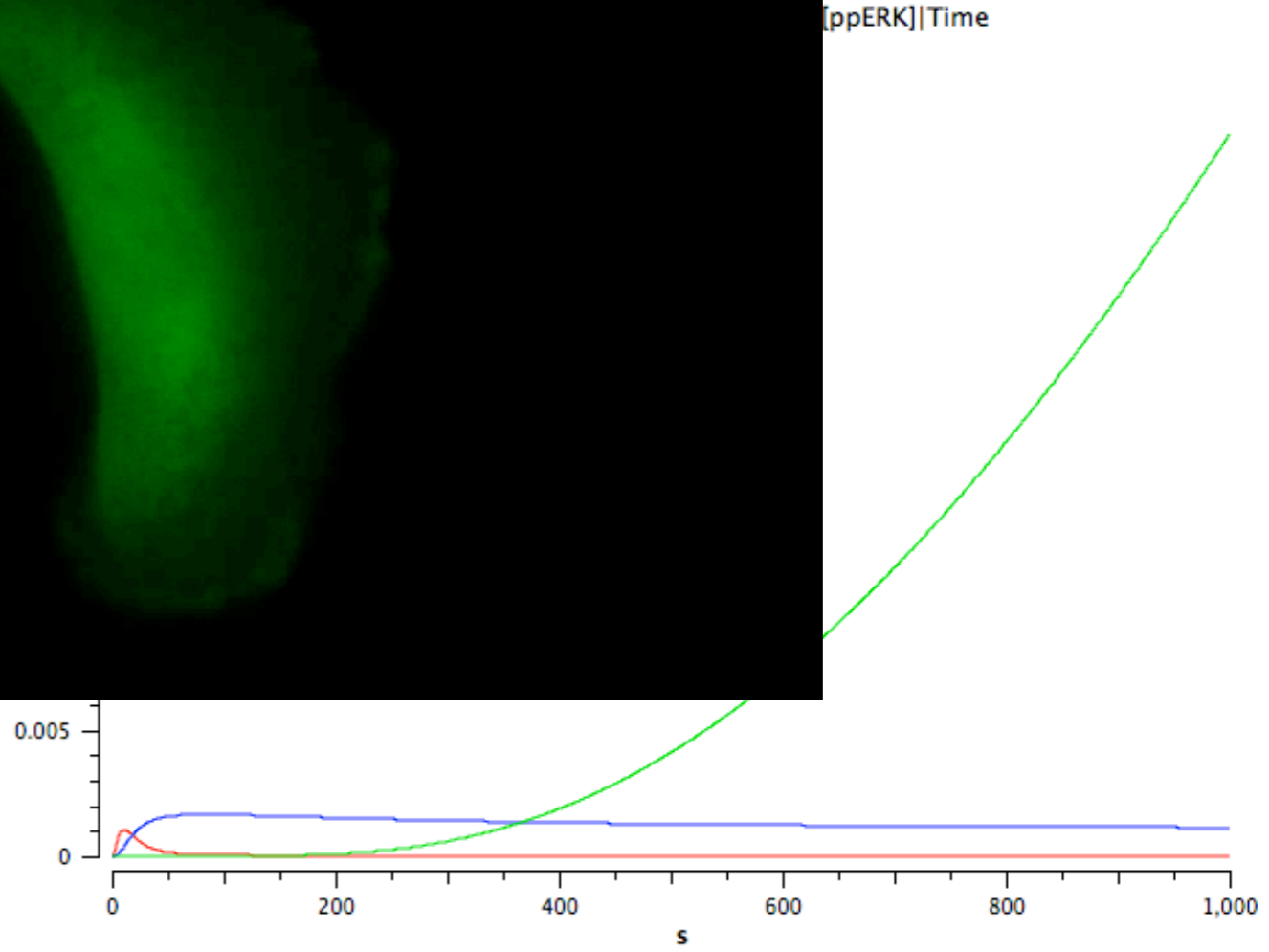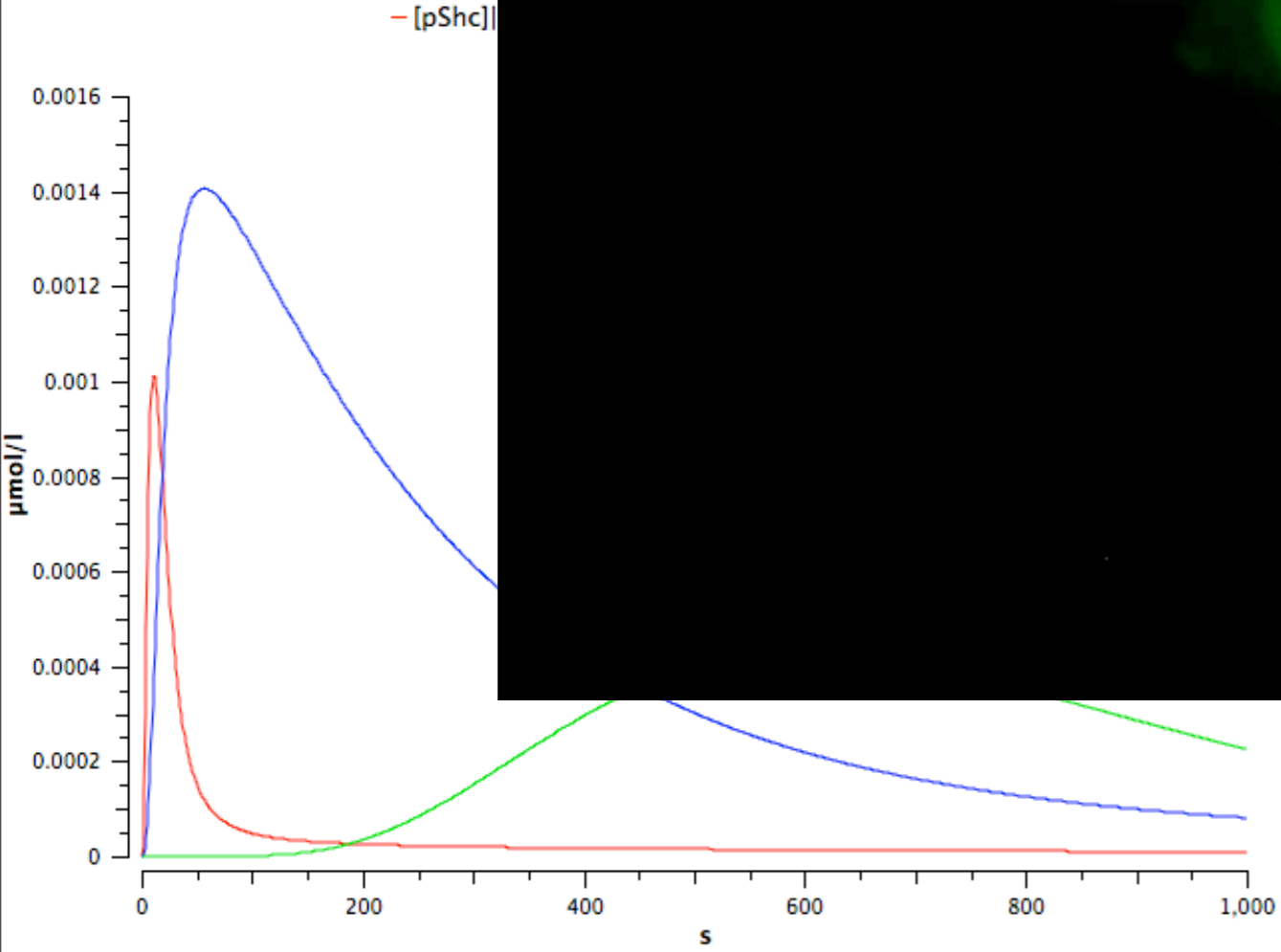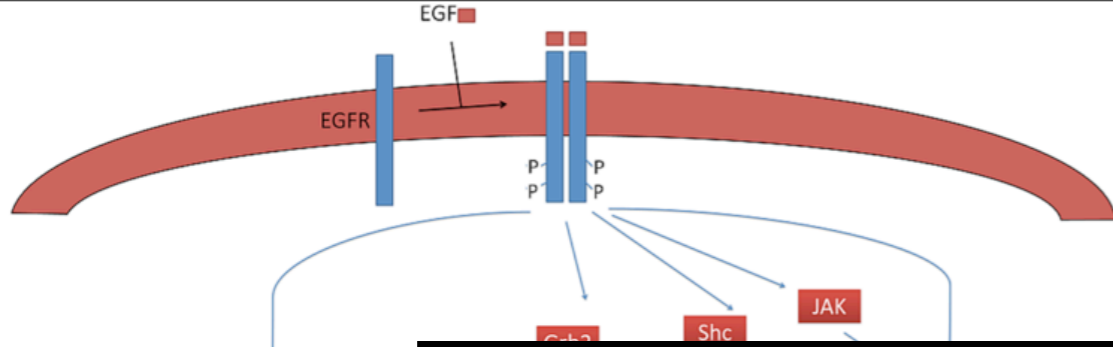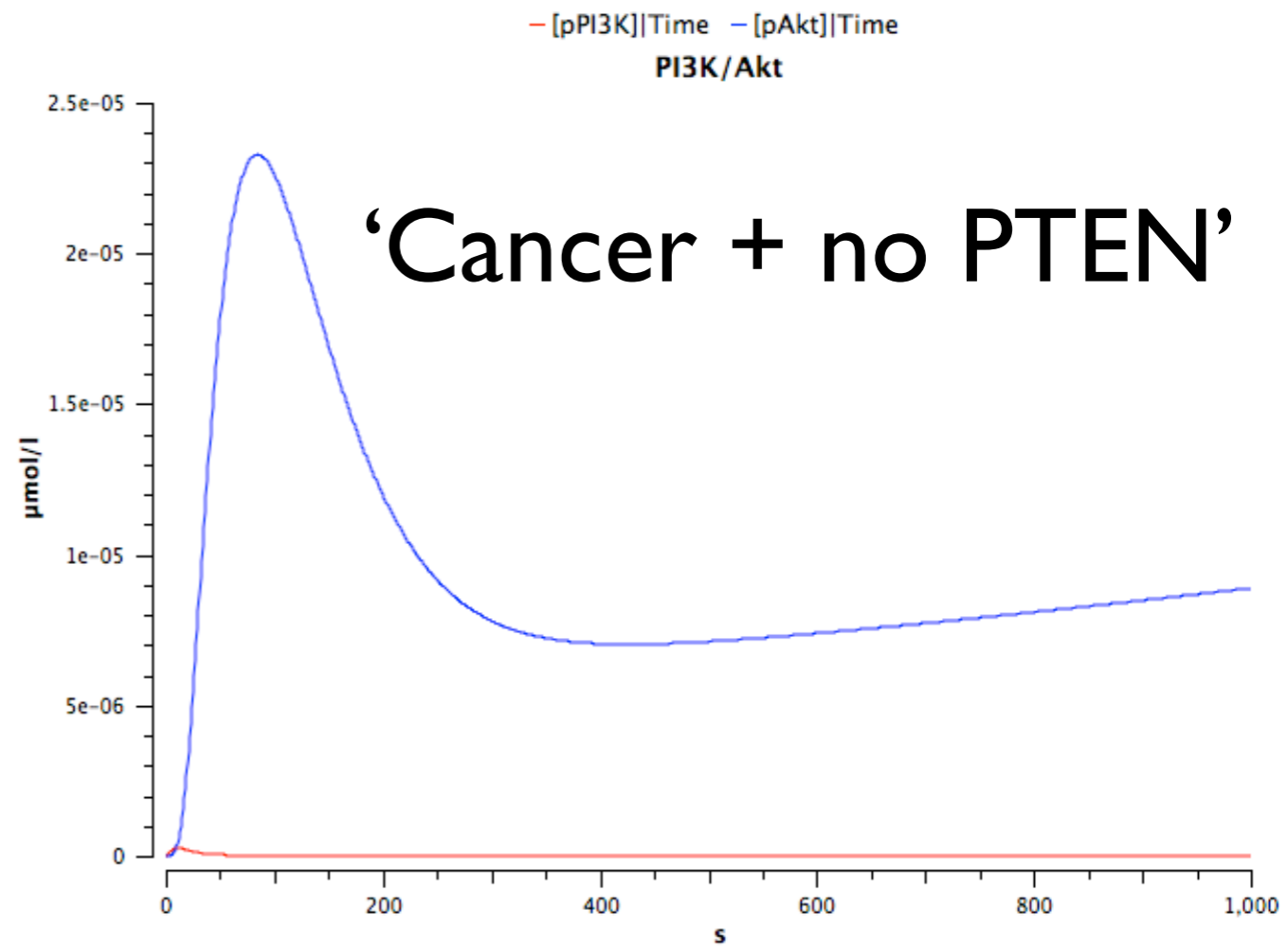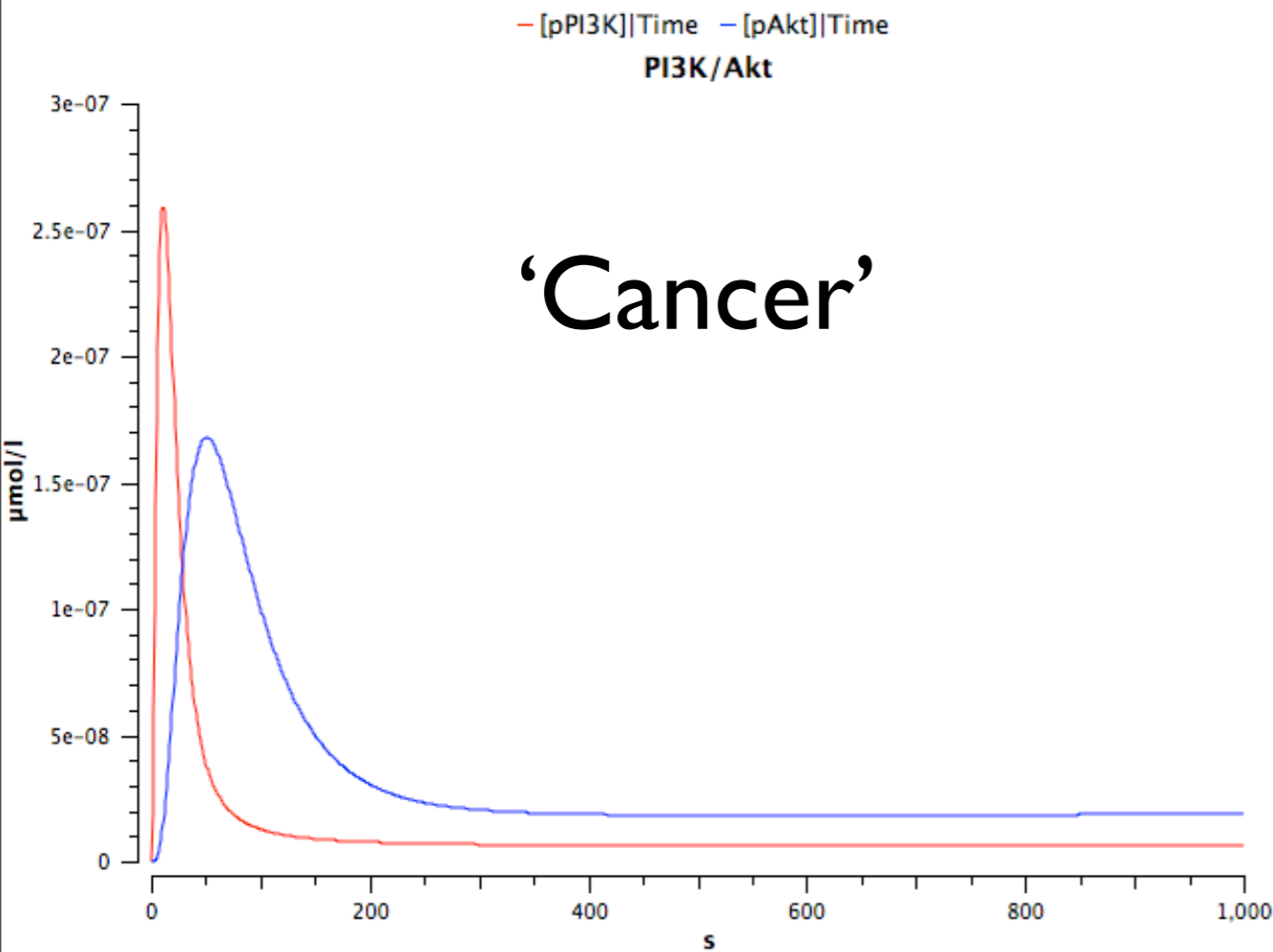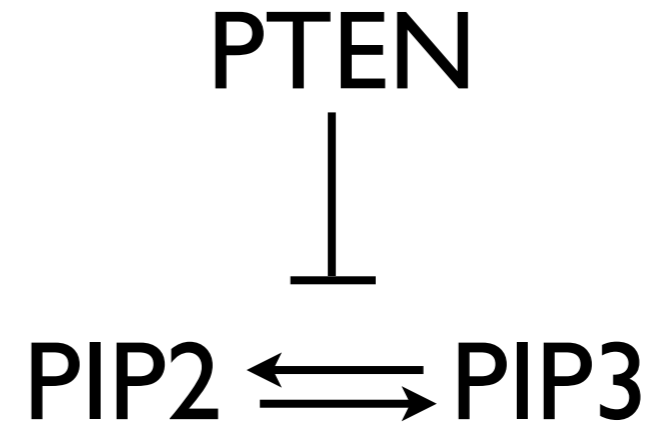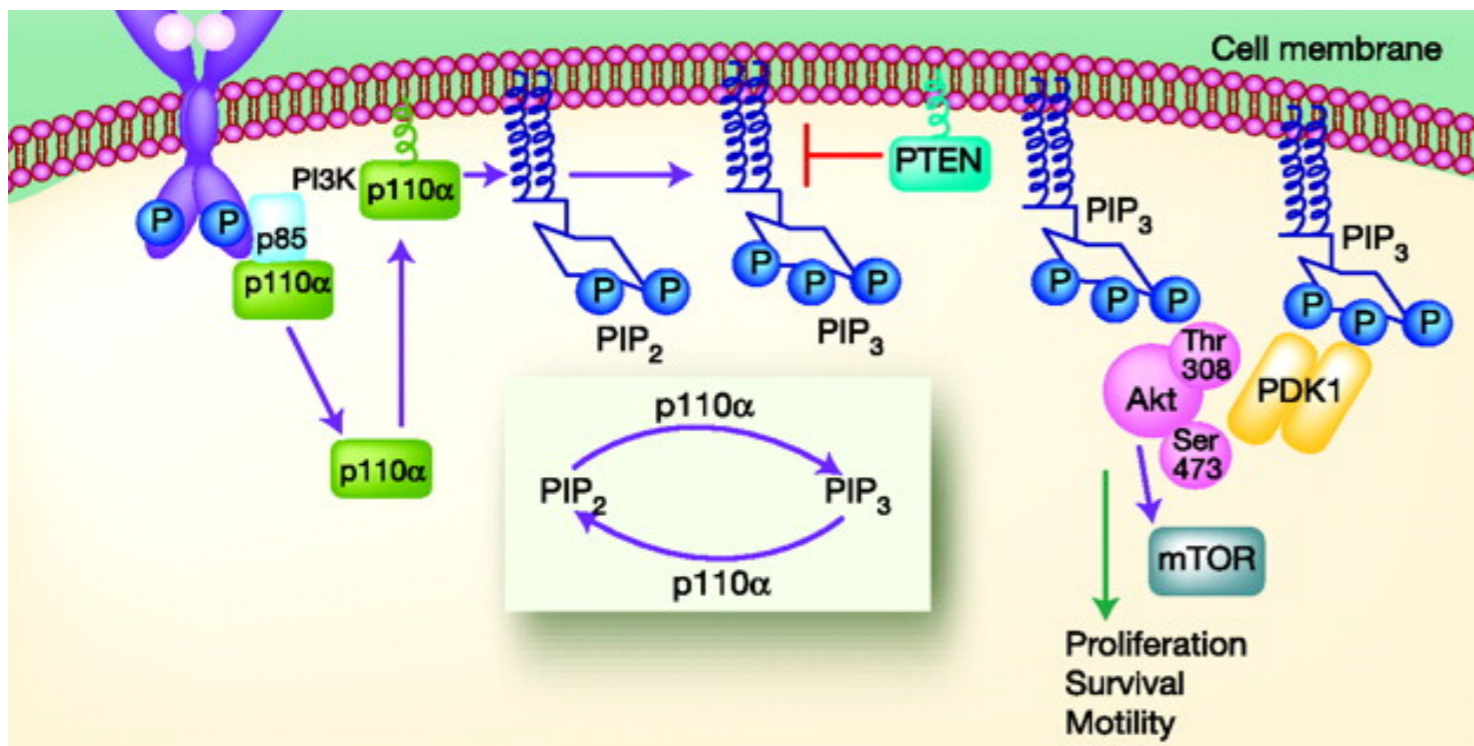
Not all models can simulate longer time points
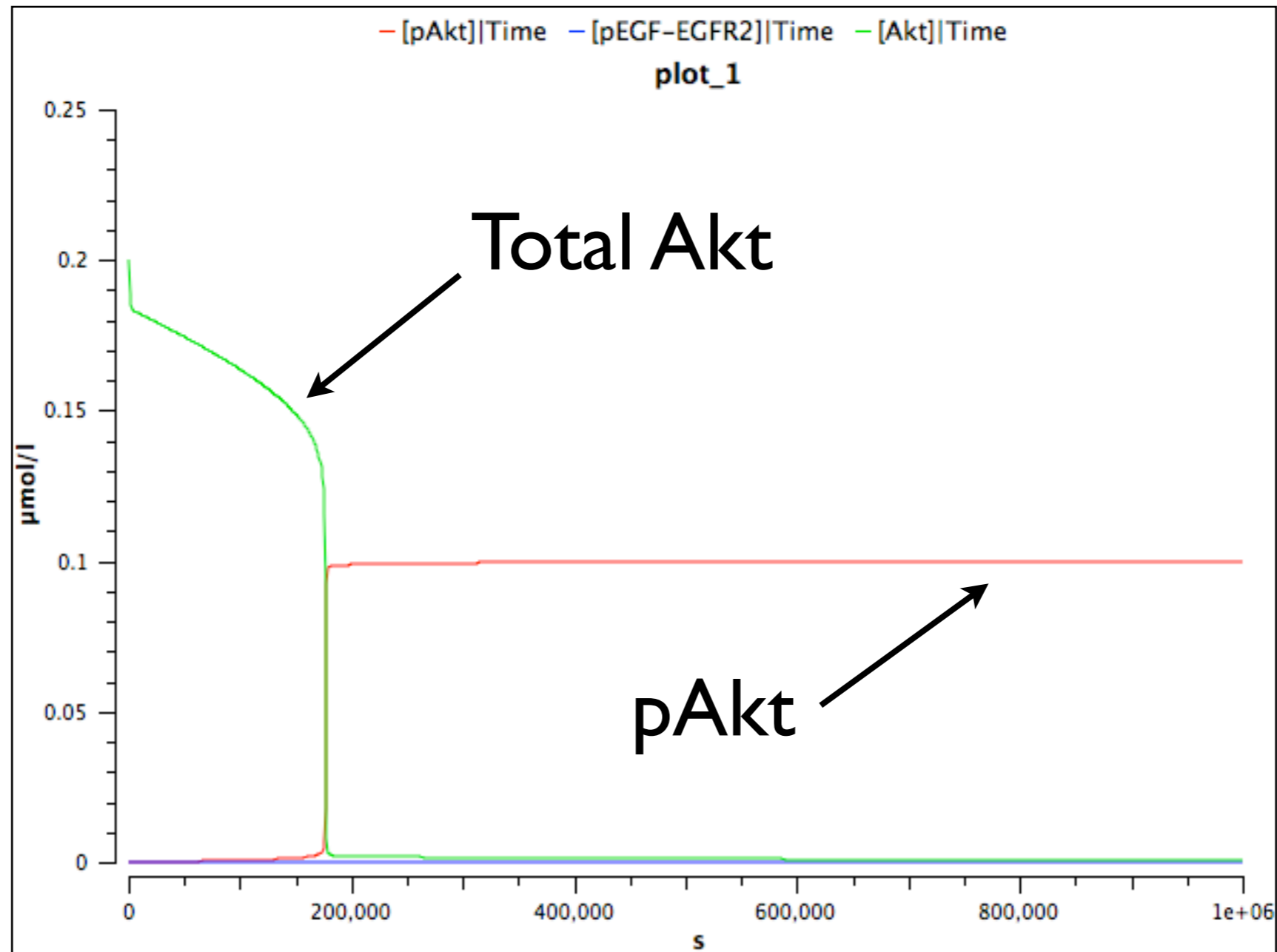
200,000 sec ~ 55.5 hrs

We can't predict everything from 1000 sec.
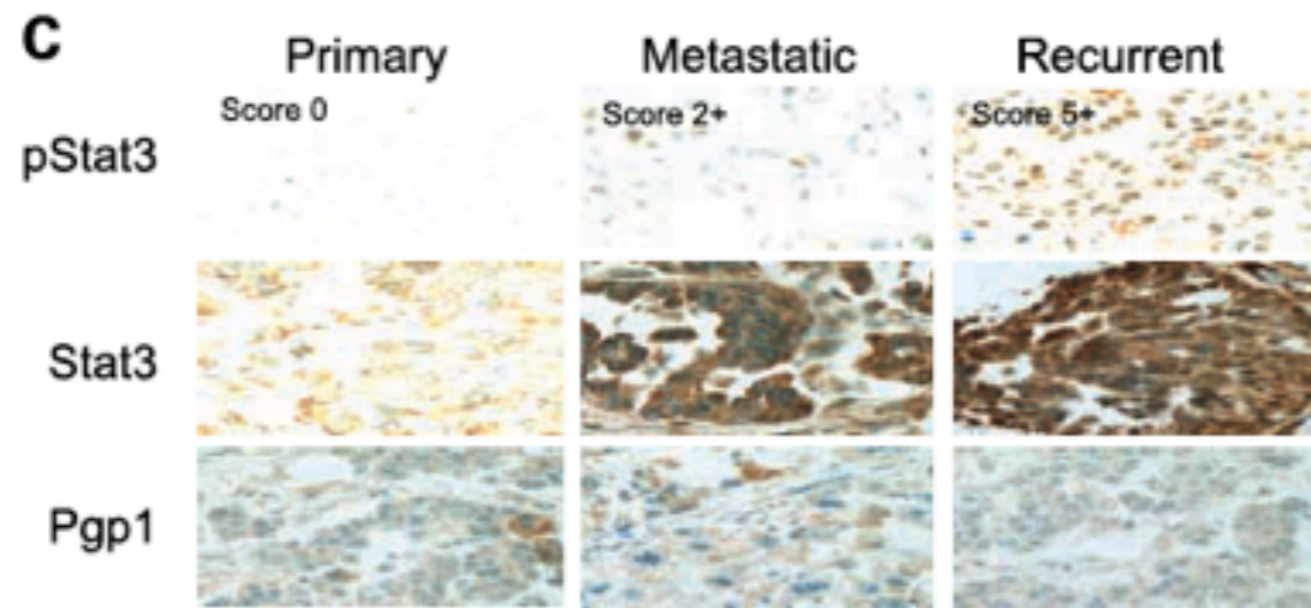
Clin Cancer Res September 1, 2006 12; 5055

'Normal'

'Cancer'

A face to the disease.

Let's go back to our popular friend, the EGFR

Number of Publications per Year / Total Publications vs Year (1980–2012)

Approval of:

Herceptin

Tarceva
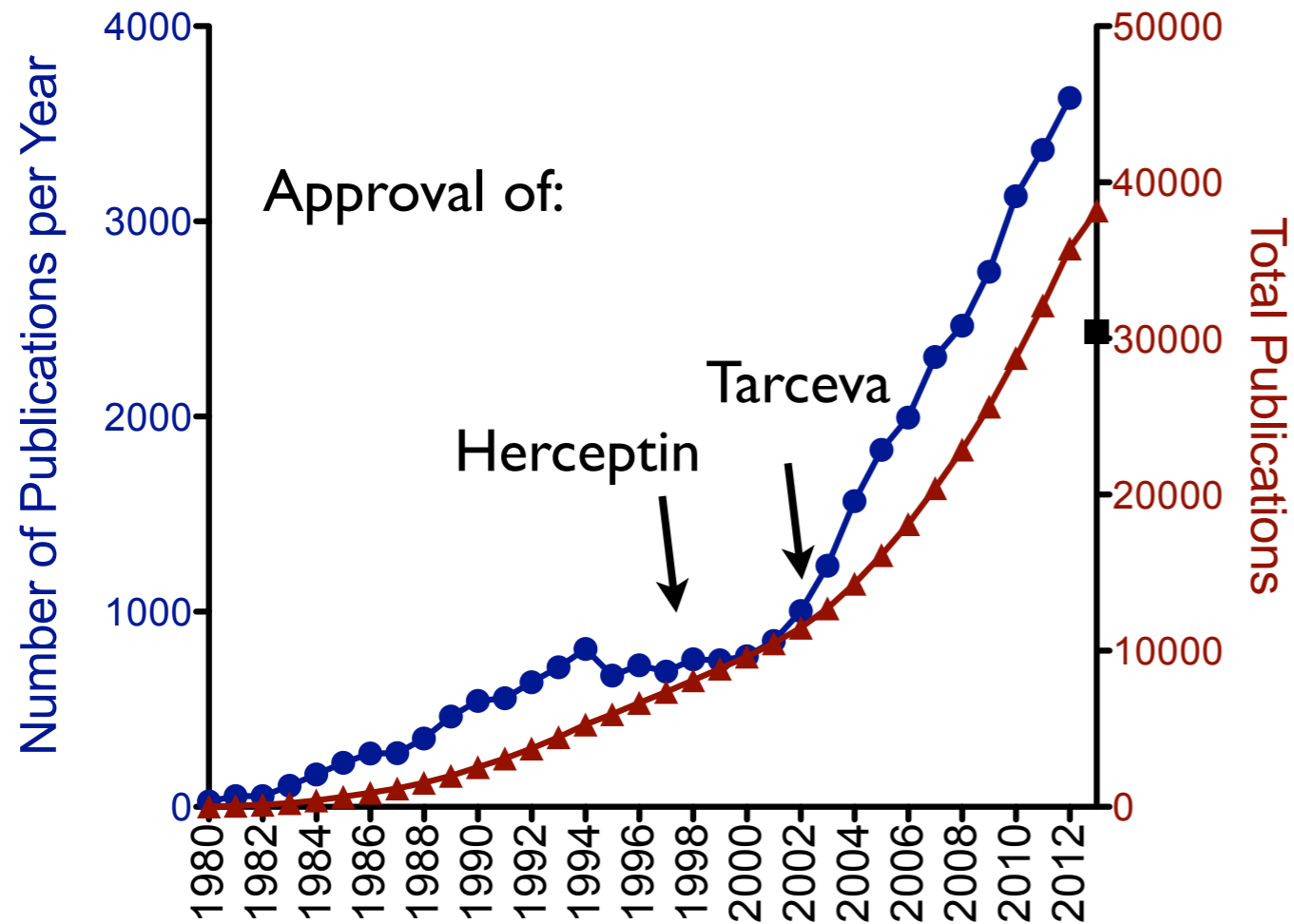
Pubmed search for "epidermal growth factor receptor"

Image credit: http://news.vanderbilt.edu/2011/12/stanley-cohen-nobel-prize/

Not all EGFR inhibitors are the same.
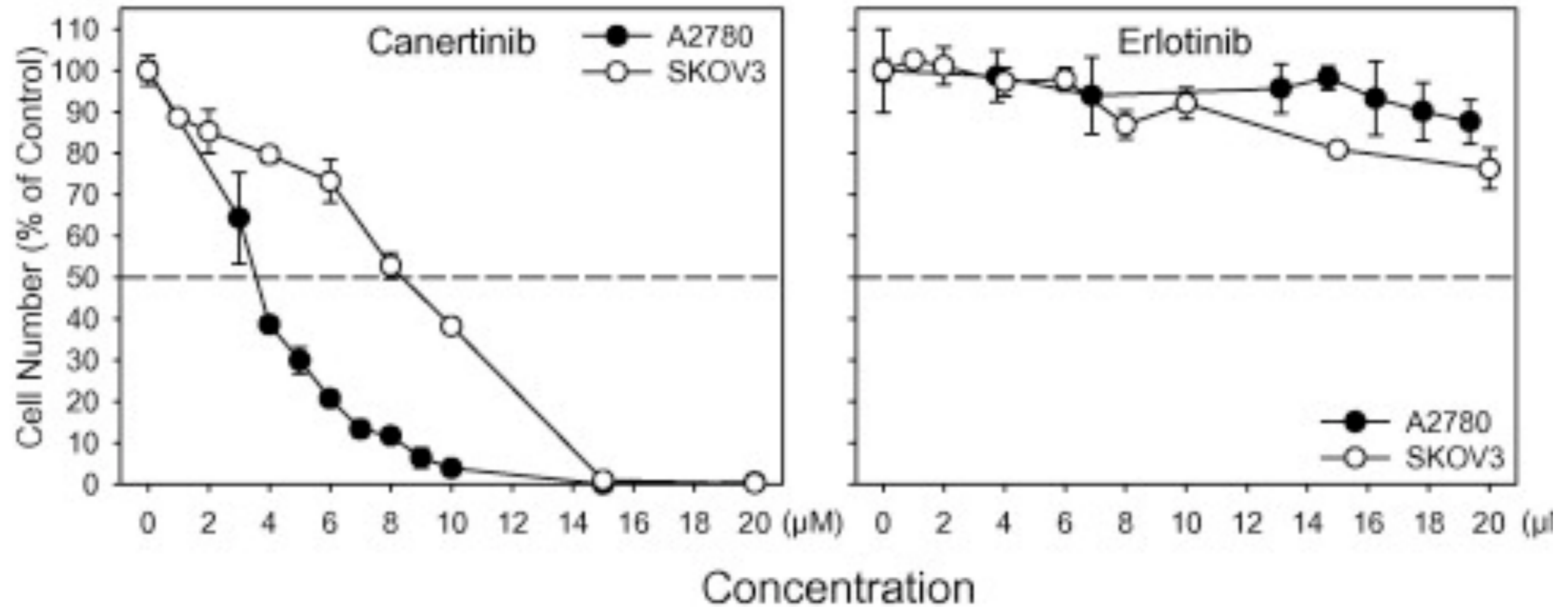
Canertinib = irreversible, promiscuous

Erlotinib = reversible, EGFR specfic

Grunt et al. Biochem. Biophys. Res. Commun. 385:454-459(2009)

Not all EGFR inhibitors are the same.
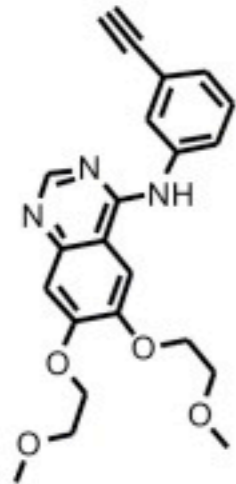
Erlotinib
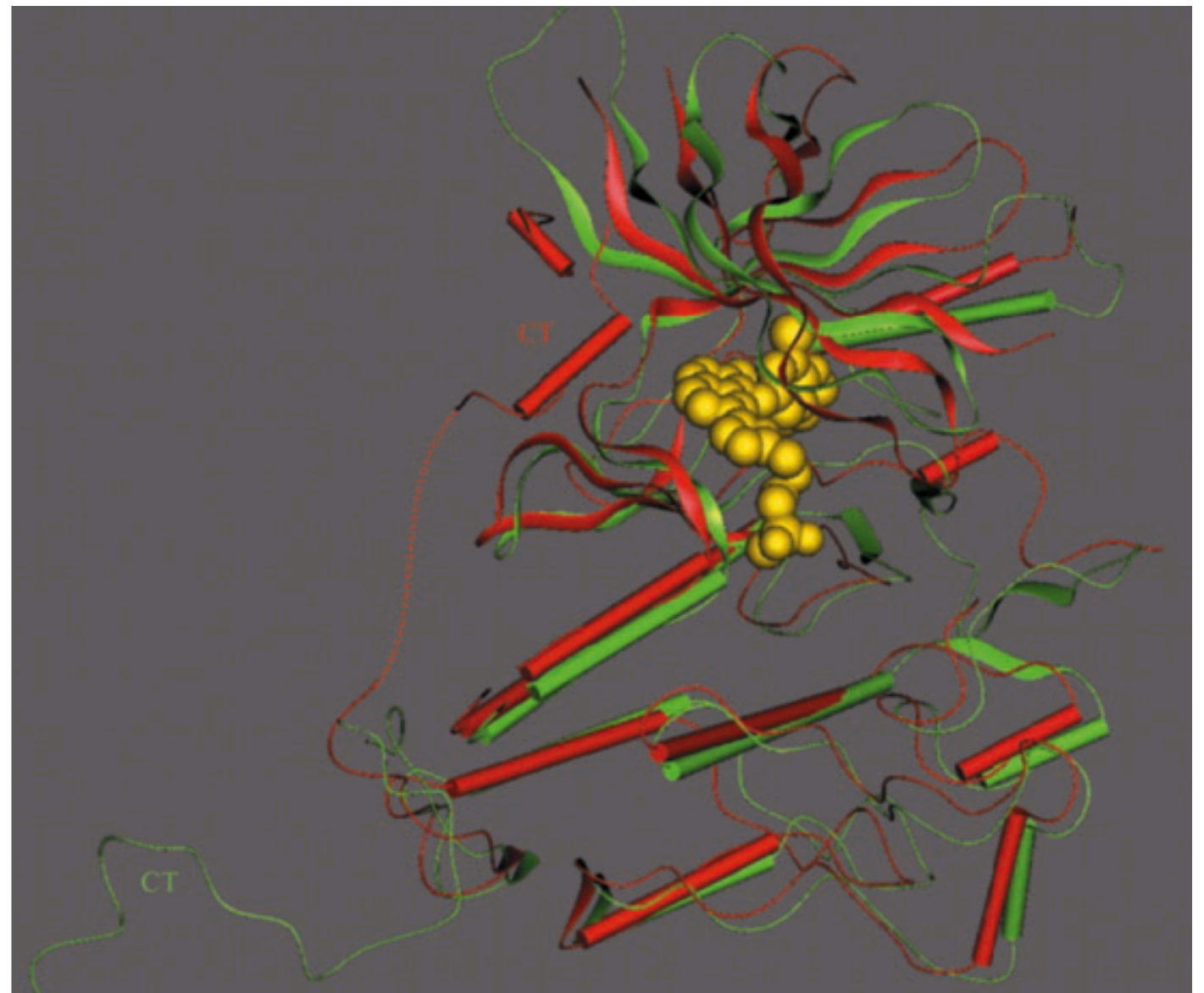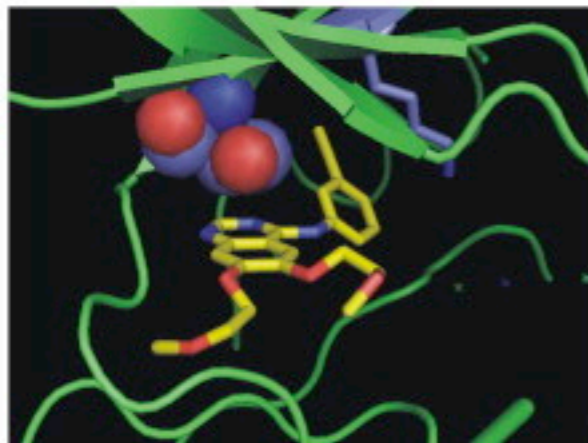
Green = Erlotinib bound
Red = Lapatinib bound

Thursday, October 10, 13

EGFR inhibition is *very* effective (?) in a subset of patients.

Table 1. Select Phase III Clinical Trials in Lung Cancer Involving EGFR TKIs

Trial	Year	Line	No. of Participants	Race	EGFR Mutant (%)	EGFR TKI	Reference Arm	TKI v Reference			
								RR (%)	CR (%)	PFS (months)	OS (months)
ISEL[27]	2005	Second to third	1,692	White, 75%; Asian, 21%*	12.1†	Gefitinib	Placebo	8.0 v 1.3	NA	3.0 v 2.6	5.6 v 5.1
BR.21[28]	2005	Second to third	731	Asian, 12%; other, 88%	23‡	Erlotinib	Placebo	8.9 v < 1	0.7 v 0	2.2 v 1.8	6.7 v 4.7
INTEREST[29]	2008	Second	1,433	White, 75%; Asian, 21%*	14.8§	Gefitinib	Docetaxel	9.1 v 7.6	NA	2.2 v 2.2	7.6 v 8.0
IPASS[4,30]	2009	First	1,217	East Asian, 100%	59.7‖	Gefitinib	Platinum doublet	43.0 v 32.2	NA	5.7 v 5.8	18.8 v 17.4
IPASS subgroup[4,30]	2009	First	261	East Asian, 100%	100	Gefitinib	Platinum doublet	71.2 v 47.3	NA	9.5 v 6.3	21.6 v 21.9
WJTOG3405[6,31]	2009	First	172	East Asian, 100%	100	Gefitinib	Platinum doublet	62.1 v 32.2	NA	9.2 v 6.3	35.5 v 38.8
NEJ002[7]	2009	First	224	East Asian, 100%	100	Gefitinib	Platinum doublet	73.7 v 30.7	4.4 v 0	10.8 v 5.4	30.5 v 23.6
OPTIMAL[8,32]	2011	First	165	East Asian, 100%	100	Erlotinib	Platinum doublet	82 v 36	2 v 0	13.1 v 4.6	22.7 v 28.9
EURTAC[9]	2012	First	174	White, 100% (Hispanic)	100	Erlotinib	Platinum doublet	64 v 18	3 v 0	9.7 v 5.2	19.3 v 19.5

Abbreviations: CR, complete response; EGFR, epidermal growth factor receptor; EURTAC, European Tarceva Versus Chemotherapy; INTEREST, IRESSA Non-Small-Cell Lung Cancer Trial Evaluating Response and Survival Against Taxotere; IPASS, Iressa Pan-Asia Study; ISEL, IRESSA Survival Evaluation in Lung Cancer; NA, not applicable; OPTIMAL, Open Label, Phase III Study Comparing First Line Tarceva vs Cisplatin Plus Gemcitabine in Chinese Advanced/Metastatic Non-Small-Cell Lung Cancer Patients With EGFR Activating Mutations; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.
*Excludes people of Indian origin.
†26 positive in 215 tested samples.
‡40 positive in 177 tested samples.
§44 positive in 297 tested samples.
‖261 positive in 437 tested samples.

Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. Ohashi K, Maruvka YE, Michor F, Pao W. J Clin Oncol. 2013 Mar 10;31(8):1070-80.

EGFR mutation drives drug response.
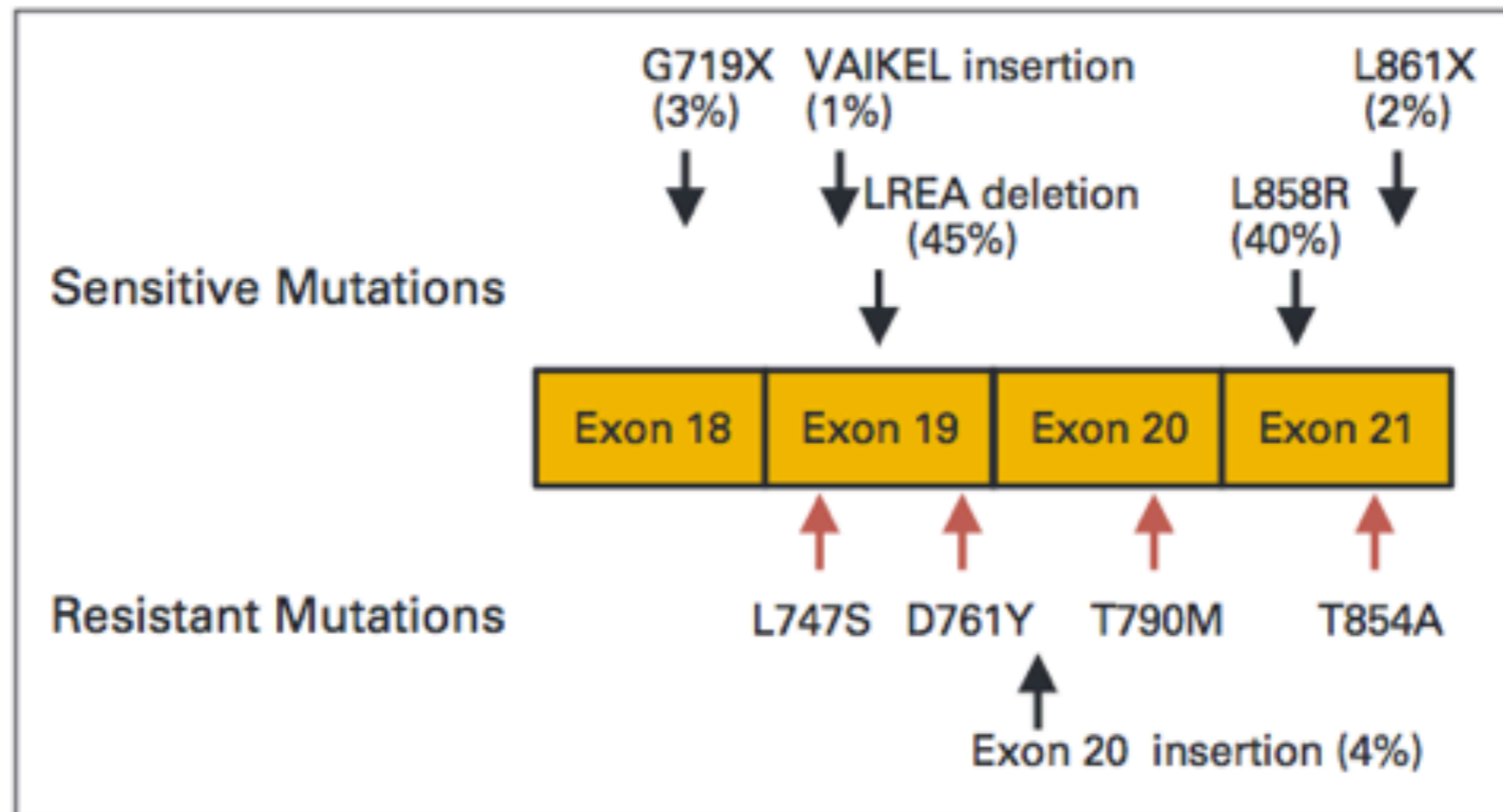
We will sequence Exons 19 & 21.

Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. Ohashi K, Maruvka YE, Michor F, Pao W. J Clin Oncol. 2013 Mar 10;31(8):1070-80.

Targeted inhibitors affect disease statistics.
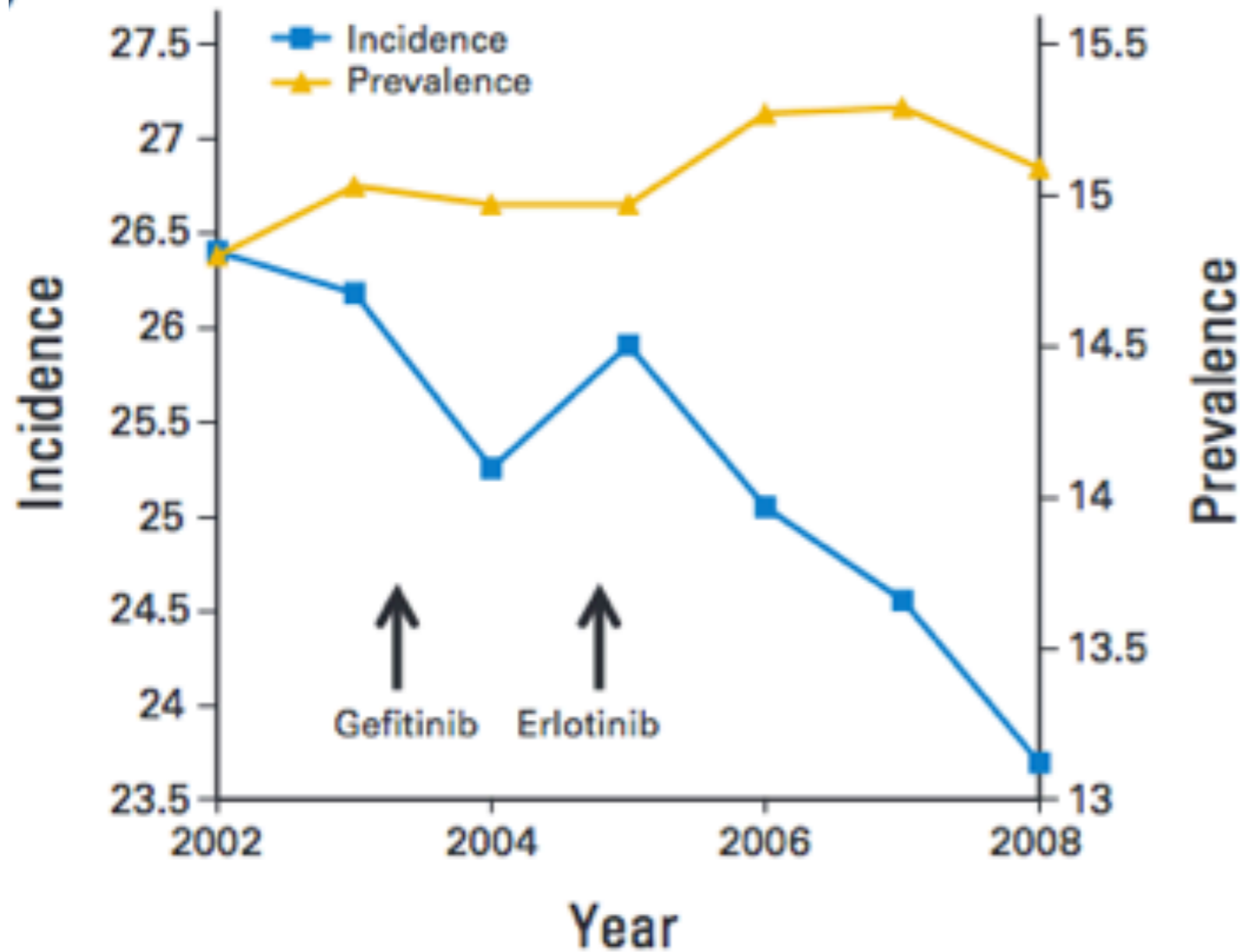
SEER database

How does lung cancer incidence decrease, but disease prevalence increase?

Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. Ohashi K, Maruvka YE, Michor F, Pao W. J Clin Oncol. 2013 Mar 10;31(8):1070-80.

Detecting EGFR Mutation -- PCR + Sequencing
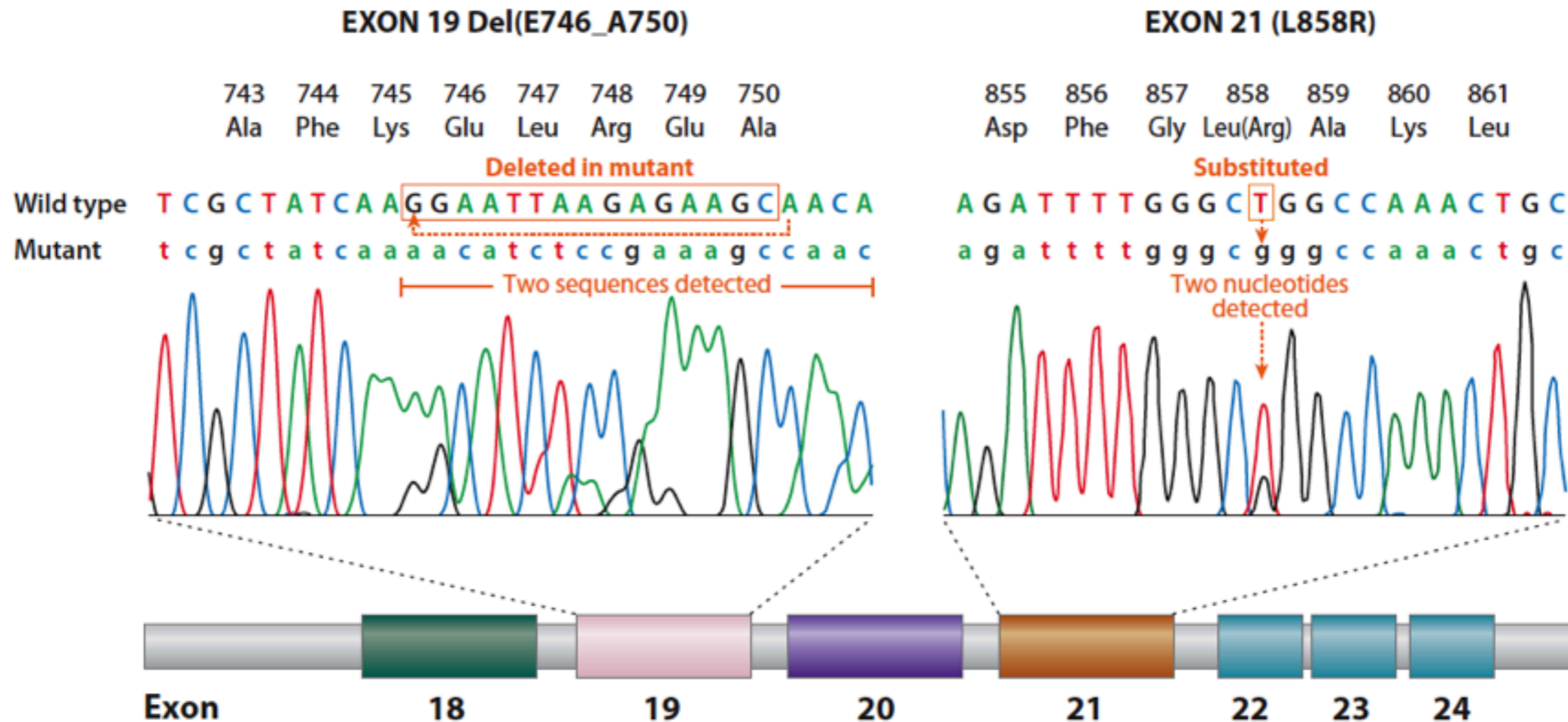
Figure 2

Amino acid and nucleotide sequence changes in exon 19 deletion and exon 21 L858R mutations involving the tyrosine kinase domain of epidermal growth factor receptor.

Santos et al. Annu. Rev. Pathol. Mech. Dis. 2011. 6:49–69

Acquired mutations end EGFR RTKi efficacy.
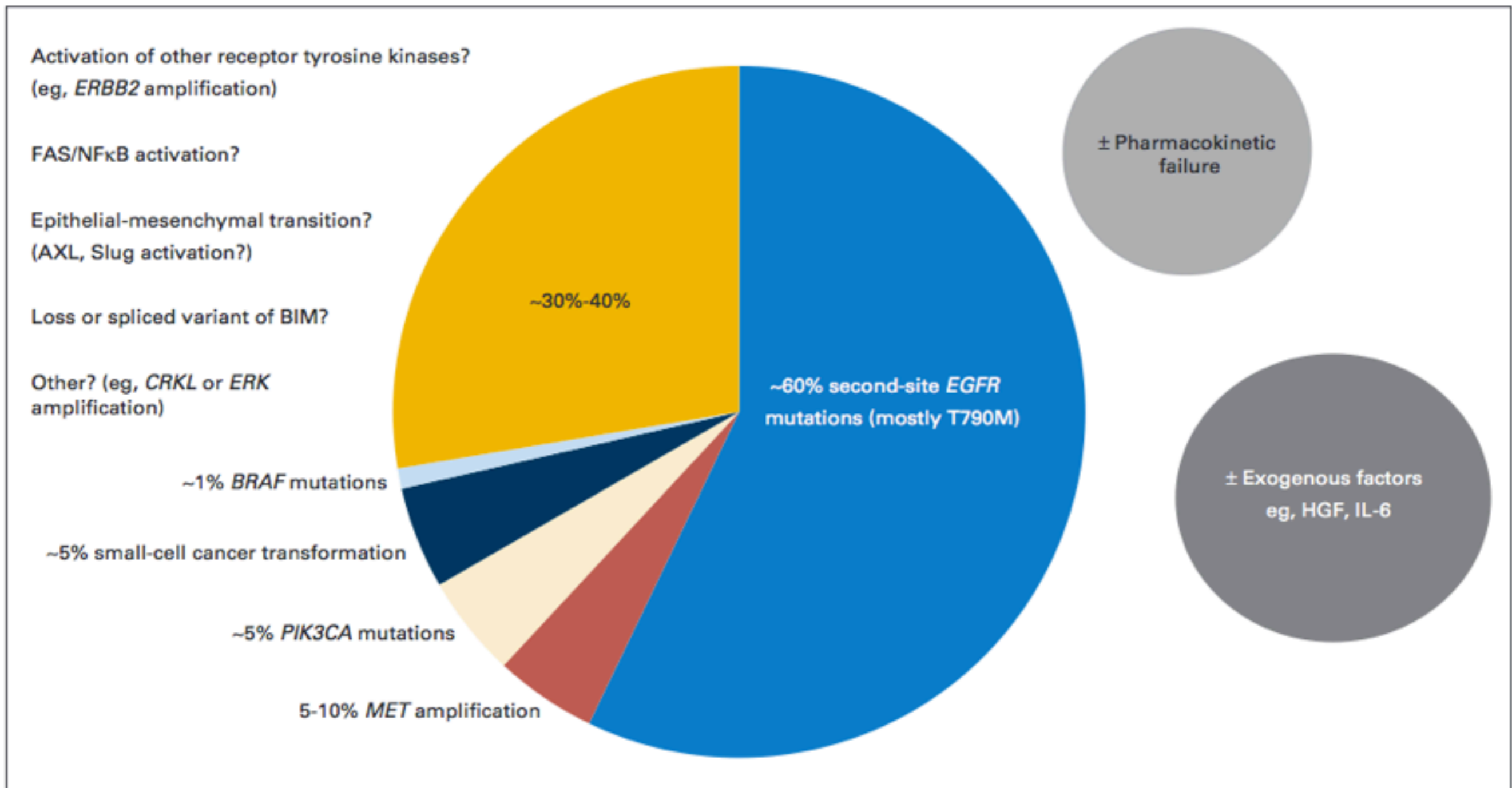
Fig 4. Mechanisms of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Multiple mechanisms have been elucidated in human samples and preclinical models. Some factors may overlap. HGF, hepatocyte growth factor; IL-6, interleukin-6.

Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. Ohashi K, Maruvka YE, Michor F, Pao W. J Clin Oncol. 2013 Mar 10;31(8):1070-80.

Systems biology applied to drug resistance -- modeling of T790M and dosing schedule.

A
PC-9/ER cells
Growth inhibition (%) vs Erlotinib (nM)
PC-9 parental, PC-9/ER

B
PC-9/BR cells
Growth inhibition (%) vs BIBW-2992 (nM)
PC-9 parental, PC-9/BR

C
PC-9 parental — EGFR ex20F, EGFR ex20R
PC-9/ER — EGFR ex20F, EGFR ex20R
PC-9/BR — EGFR ex20F, EGFR ex20R

PC-9 cells develop resistance upon chronic exposure to erlotinib or afatinib.

A higher percentage of cells harbor a T790M mutation.

RESEARCH ARTICLE

CANCER

Optimization of Dosing for EGFR-Mutant Non–Small Cell Lung Cancer with Evolutionary Cancer Modeling

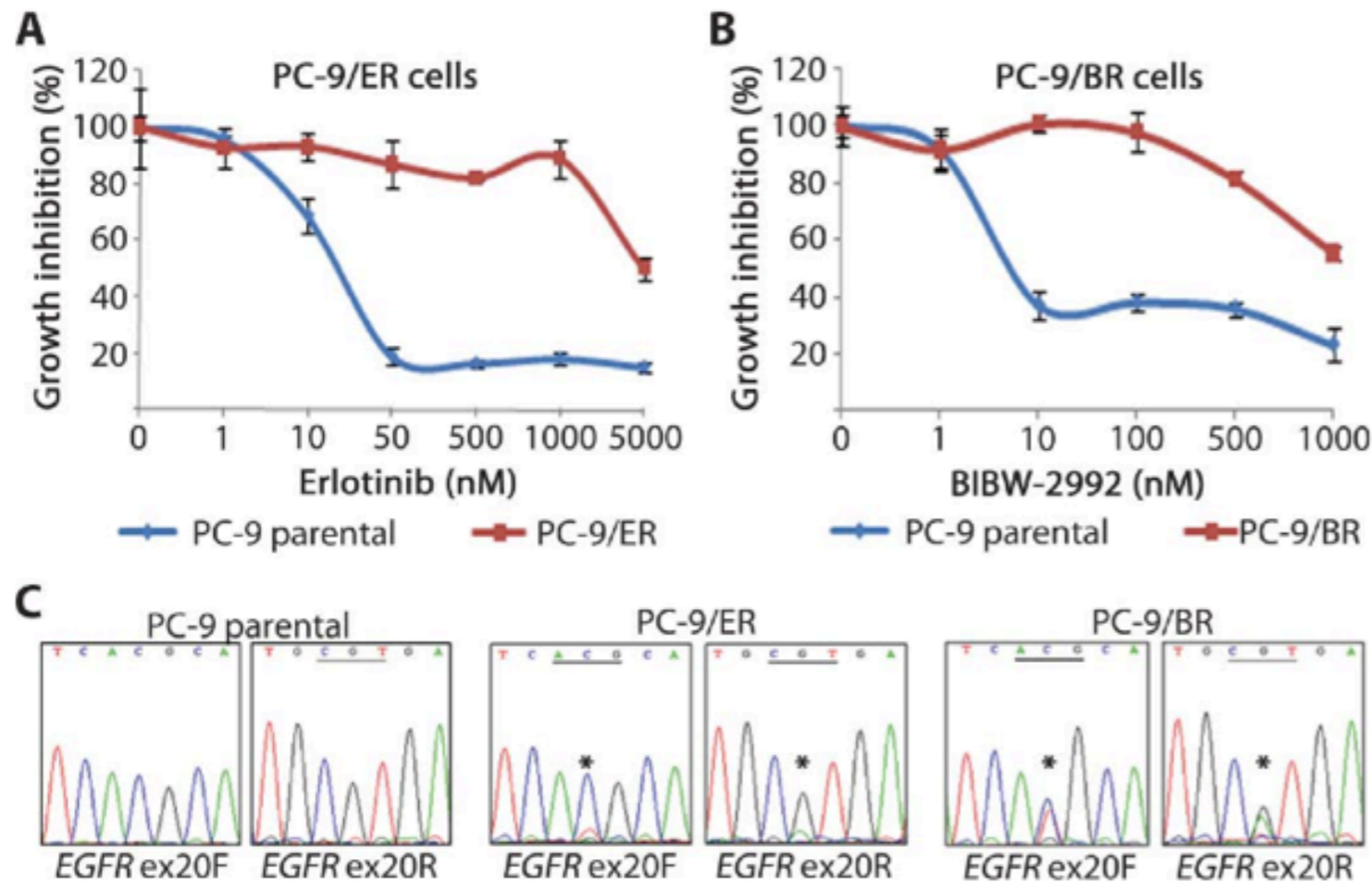Juliann Chmielecki,[1] Jasmine Foo,[2] Geoffrey R. Oxnard,[3] Katherine Hutchinson,[4] Kadoaki Ohashi,[4] Romel Somwar,[5] Lu Wang,[6] Katherine R. Amato,[4] Maria Arcila,[6] Martin L. Sos,[7] Nicholas D. Socci,[8] Agnes Viale,[9] Elisa de Stanchina,[10] Michelle S. Ginsberg,[11] Roman K. Thomas,[7,12,13] Mark G. Kris,[3] Akira Inoue,[14] Marc Ladanyi,[6,15] Vincent A. Miller,[3] Franziska Michor,[2]* William Pao[4]*

Systems biology applied to drug resistance -- modeling of T790M and dosing schedule.

When drug is removed:
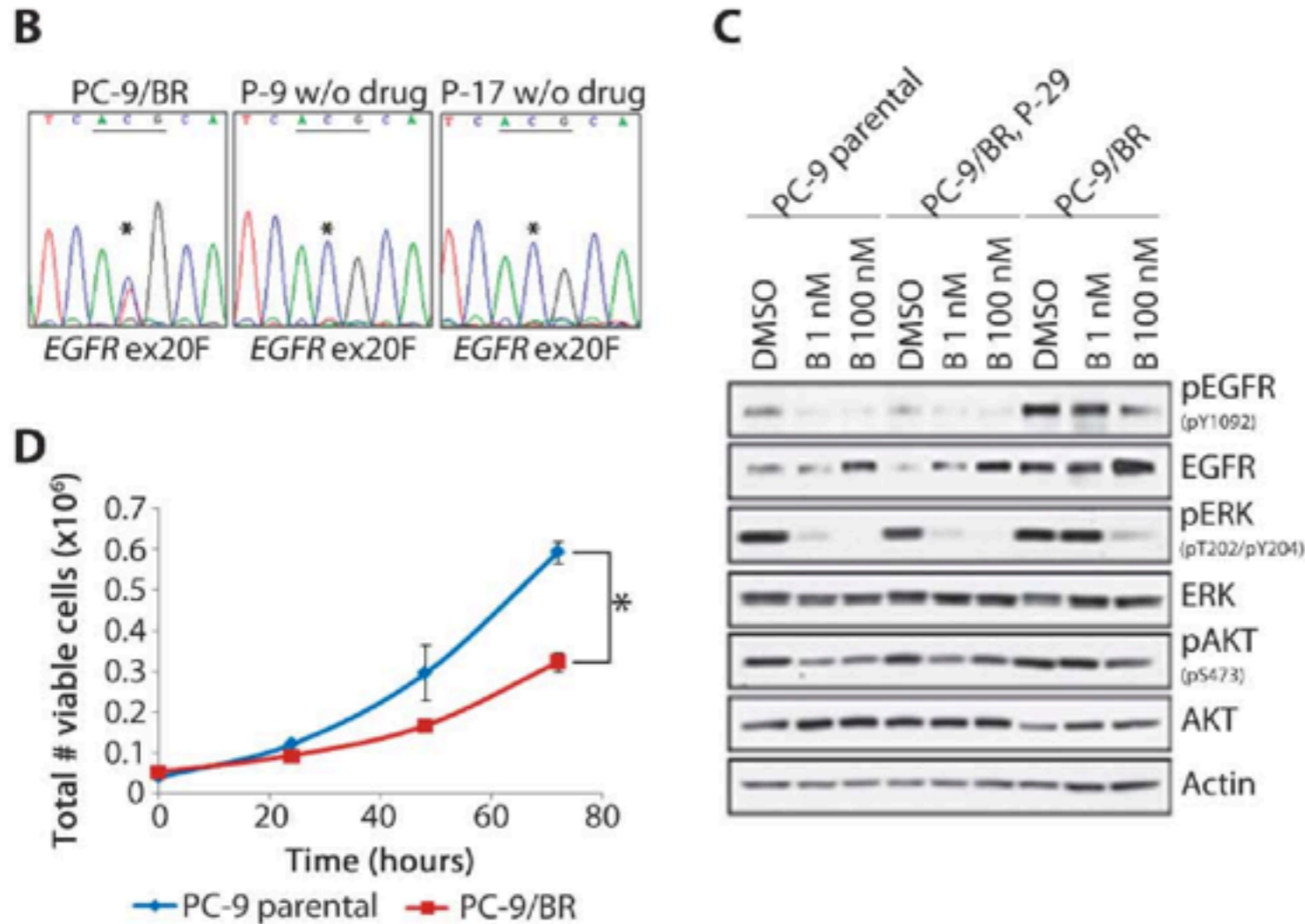
Mutation rate decreases

Signaling normalizes

*Growth rate is slower

Optimization of Dosing for EGFR-Mutant Non–Small Cell Lung Cancer with Evolutionary Cancer Modeling

Juliann Chmielecki,[1] Jasmine Foo,[2] Geoffrey R. Oxnard,[3] Katherine Hutchinson,[4] Kadoaki Ohashi,[4] Romel Somwar,[5] Lu Wang,[6] Katherine R. Amato,[4] Maria Arcila,[6] Martin L. Sos,[7] Nicholas D. Socci,[8] Agnes Viale,[9] Elisa de Stanchina,[10] Michelle S. Ginsberg,[11] Roman K. Thomas,[7,12,13] Mark G. Kris,[3] Akira Inoue,[14] Marc Ladanyi,[6,15] Vincent A. Miller,[3] Franziska Michor,[2*] William Pao[4*]

Systems biology applied to drug resistance -- modeling of T790M and dosing schedule.

H

Heterogeneous population: only some cells have T790M

Homogeneous population: all cells have T790M

+E → -E →

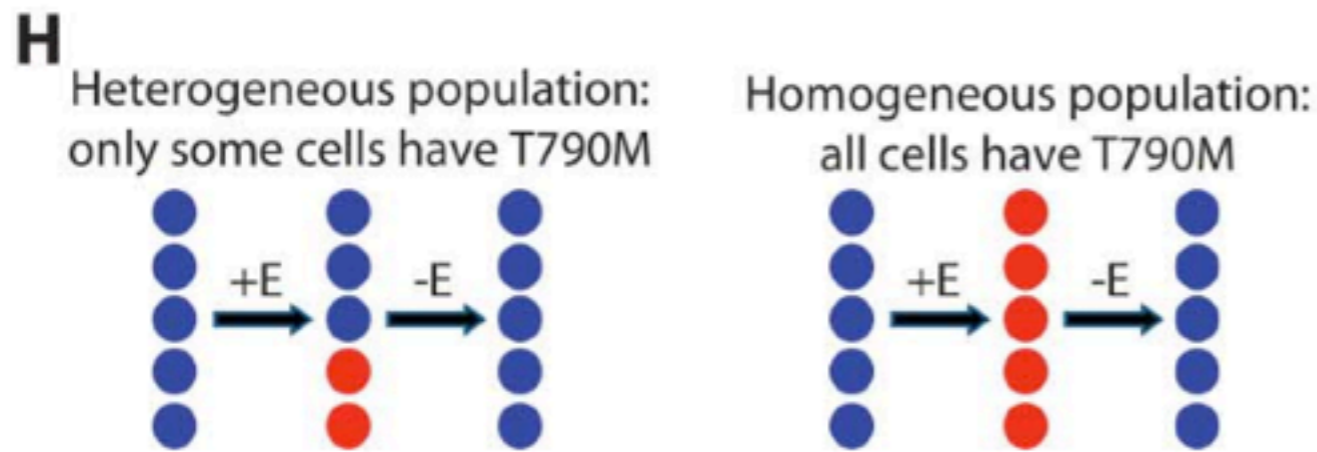## When drug is removed:

Mutation rate decreases

Signaling normalizes

*Growth rate is slower

Optimization of Dosing for EGFR-Mutant Non–Small Cell Lung Cancer with Evolutionary Cancer Modeling

Juliann Chmielecki,[1] Jasmine Foo,[2] Geoffrey R. Oxnard,[3] Katherine Hutchinson,[4] Kadoaki Ohashi,[4] Romel Somwar,[5] Lu Wang,[6] Katherine R. Amato,[4] Maria Arcila,[6] Martin L. Sos,[7] Nicholas D. Socci,[8] Agnes Viale,[9] Elisa de Stanchina,[10] Michelle S. Ginsberg,[11] Roman K. Thomas,[7,12,13] Mark G. Kris,[3] Akira Inoue,[14] Marc Ladanyi,[6,15] Vincent A. Miller,[3] Franziska Michor,[2]* William Pao[4]*

Systems biology applied to drug resistance -- modeling of T790M and dosing schedule.

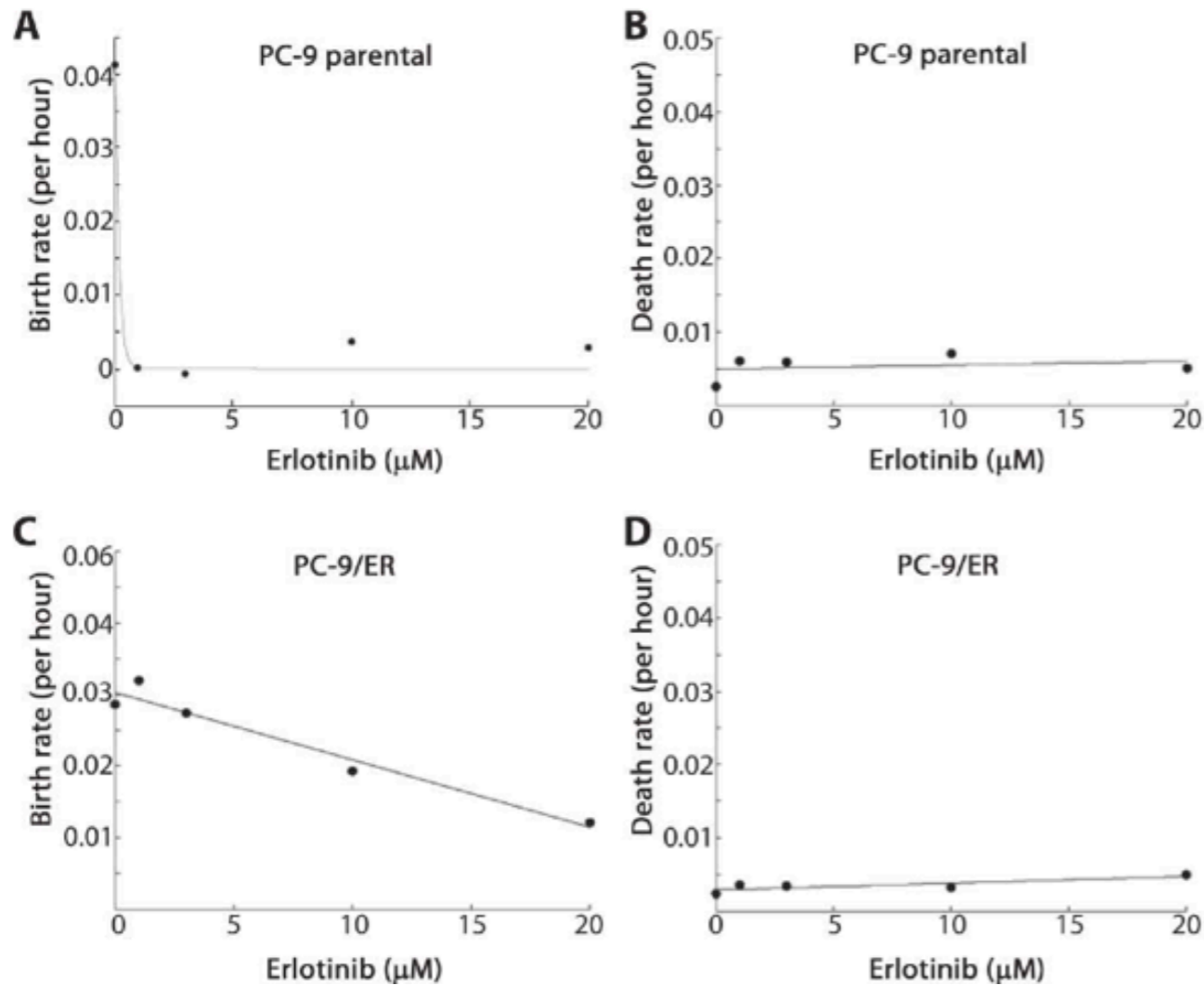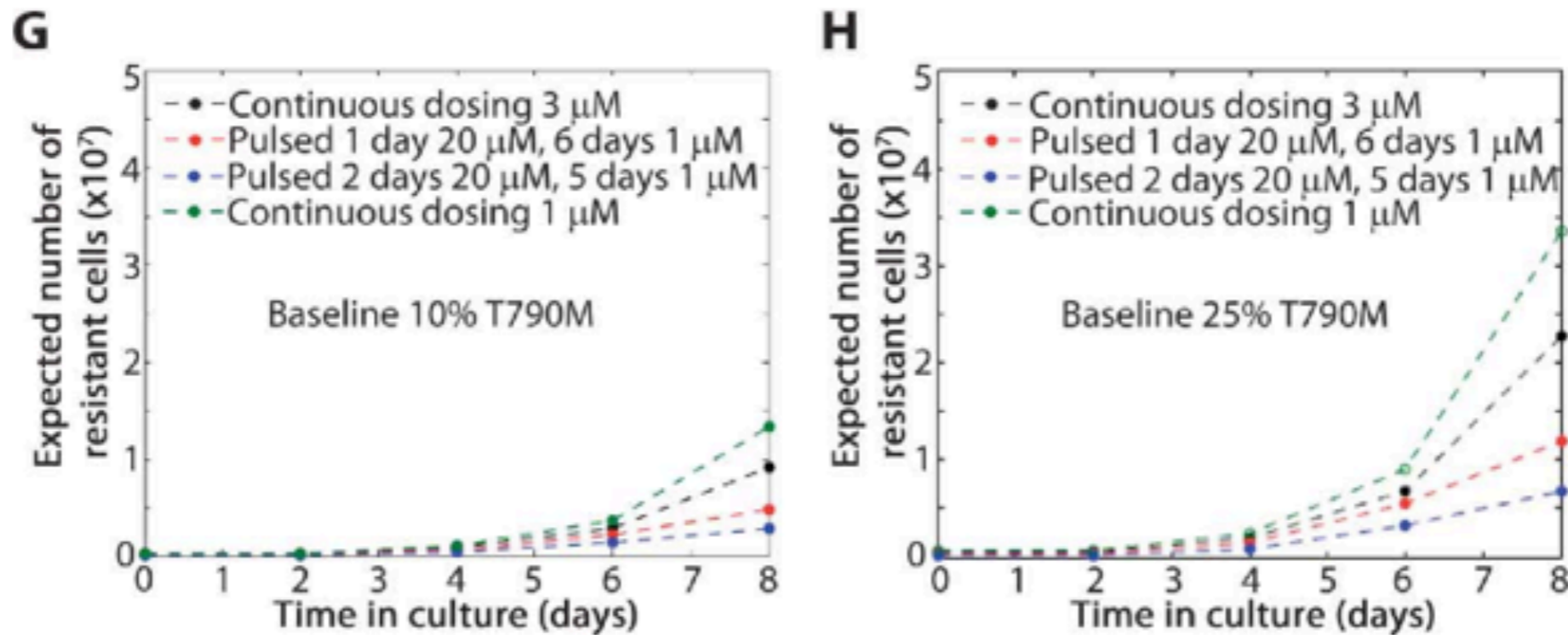A very simple and elegant mathematical model was employed using simple cell viability data & knowledge of mutation rate.

CANCER

Optimization of Dosing for EGFR-Mutant Non–Small Cell Lung Cancer with Evolutionary Cancer Modeling

Juliann Chmielecki,[1] Jasmine Foo,[2] Geoffrey R. Oxnard,[3] Katherine Hutchinson,[4] Kadoaki Ohashi,[4] Romel Somwar,[5] Lu Wang,[6] Katherine R. Amato,[4] Maria Arcila,[6] Martin L. Sos,[7] Nicholas D. Socci,[8] Agnes Viale,[9] Elisa de Stanchina,[10] Michelle S. Ginsberg,[11] Roman K. Thomas,[7,12,13] Mark G. Kris,[3] Akira Inoue,[14] Marc Ladanyi,[6,15] Vincent A. Miller,[3] Franziska Michor,[2*] William Pao[4*]

Systems biology applied to drug resistance -- modeling of T790M and dosing schedule.

High pulsed doses of Erlotinib keeps fast growing sensitive cells in check.

Optimization of Dosing for EGFR-Mutant Non–Small Cell Lung Cancer with Evolutionary Cancer Modeling

Juliann Chmielecki,[1] Jasmine Foo,[2] Geoffrey R. Oxnard,[3] Katherine Hutchinson,[4] Kadoaki Ohashi,[4] Romel Somwar,[5] Lu Wang,[6] Katherine R. Amato,[4] Maria Arcila,[6] Martin L. Sos,[7] Nicholas D. Socci,[8] Agnes Viale,[9] Elisa de Stanchina,[10] Michelle S. Ginsberg,[11] Roman K. Thomas,[7,12,13] Mark G. Kris,[3] Akira Inoue,[14] Marc Ladanyi,[6,15] Vincent A. Miller,[3] Franziska Michor,[2]* William Pao[4]*

Module 2: Systems Engineering

- Revisit Module 2 goals & expectatations

- M2D1 rewind

- EGFR fooled you, NSCLC!

- How mutations are detected in the clinic

- Some M2D2 lab plans

- Looking ahead