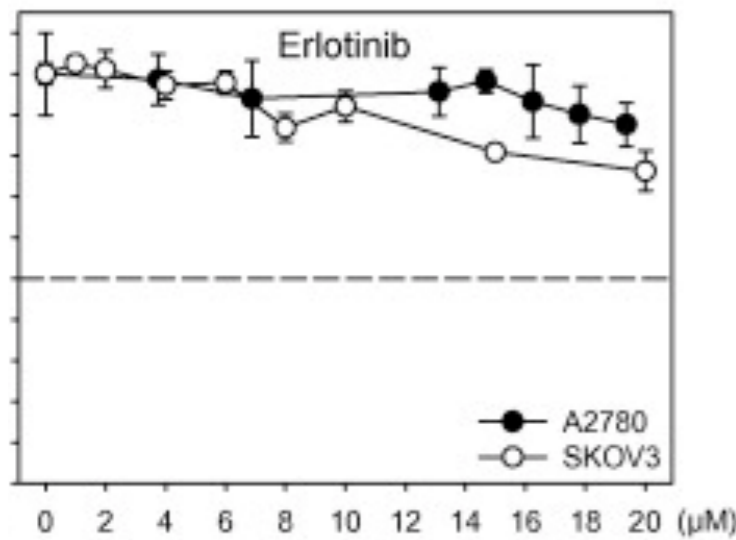# Module 2: Systems Engineering

- A few announcements -- JC & Report details

- Review Michor drug dosing model

- Clinical breast cancer subtypes

- Using systems biology to identify drug targets -- Kirouac et al.

- A look at your sequencing data
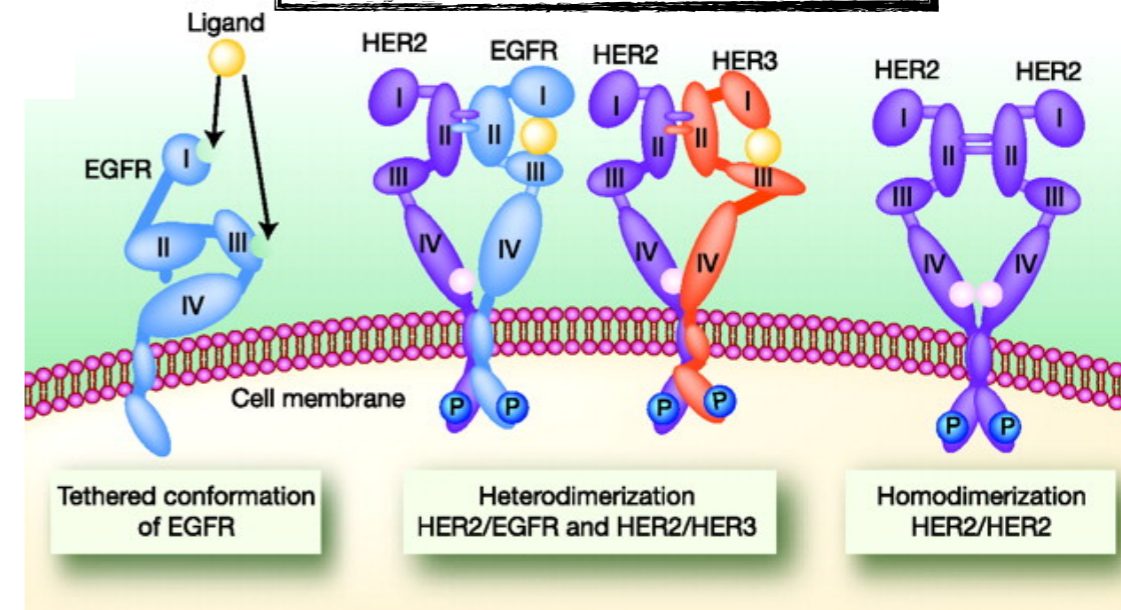
Module 2: Systems Engineering

Experimental Context: **EGFR System**

Design Goal:

Erlotinib

0 2 4 6 8 10 12 14 16 18 20 (μM)

● A2780
○ SKOV3

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

Overcome resistance to EGFR inhibition in SKOV3 human ovarian cancer cells.
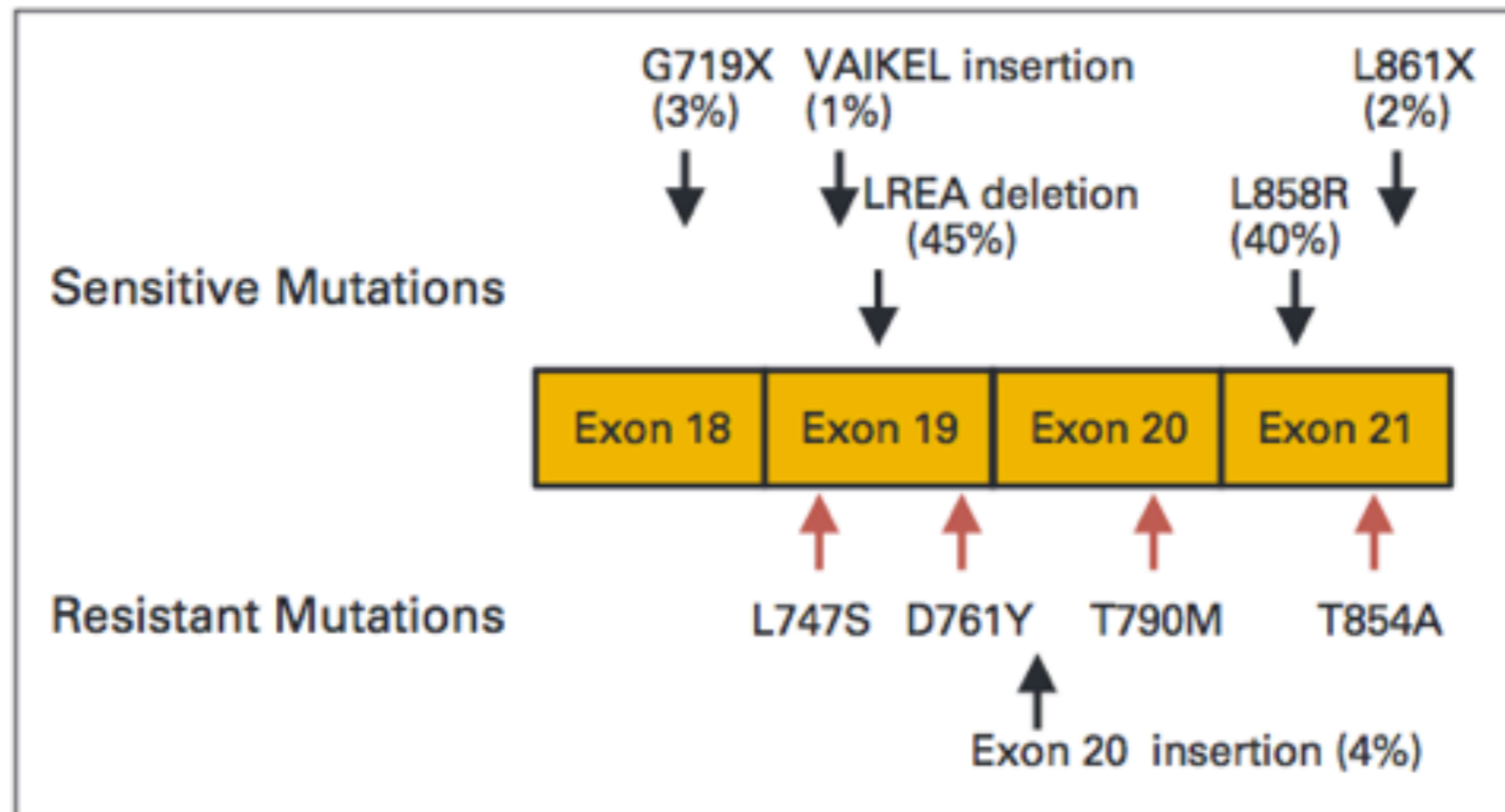
Approach: Use mathematical models to make predictions and 'high throughput' experiments to test hypothesis.

Themes of the module:

Cancer Systems Biology
High Throughput Screening Technologies

EGFR mutation drives drug response.

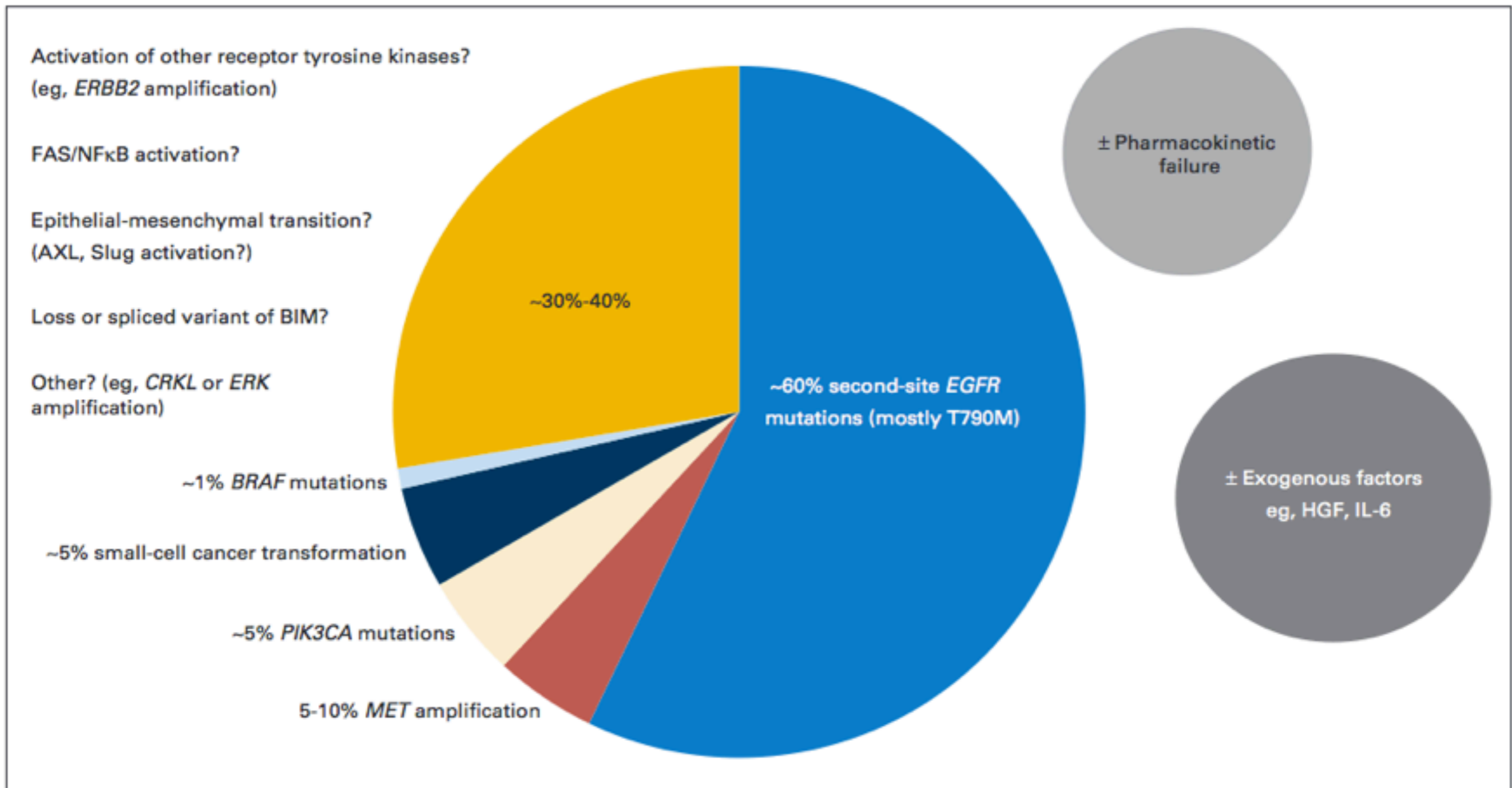We sequenced Exons 19 & 21.

Acquired mutations end EGFR RTKi efficacy.

Activation of other receptor tyrosine kinases? (eg, *ERBB2* amplification)

FAS/NFκB activation?

Epithelial-mesenchymal transition? (AXL, Slug activation?)

Loss or spliced variant of BIM?

Other? (eg, *CRKL* or *ERK* amplification)

~1% *BRAF* mutations

~5% small-cell cancer transformation

~5% *PIK3CA* mutations

5-10% *MET* amplification

~30%-40%

~60% second-site *EGFR* mutations (mostly T790M)

± Pharmacokinetic failure
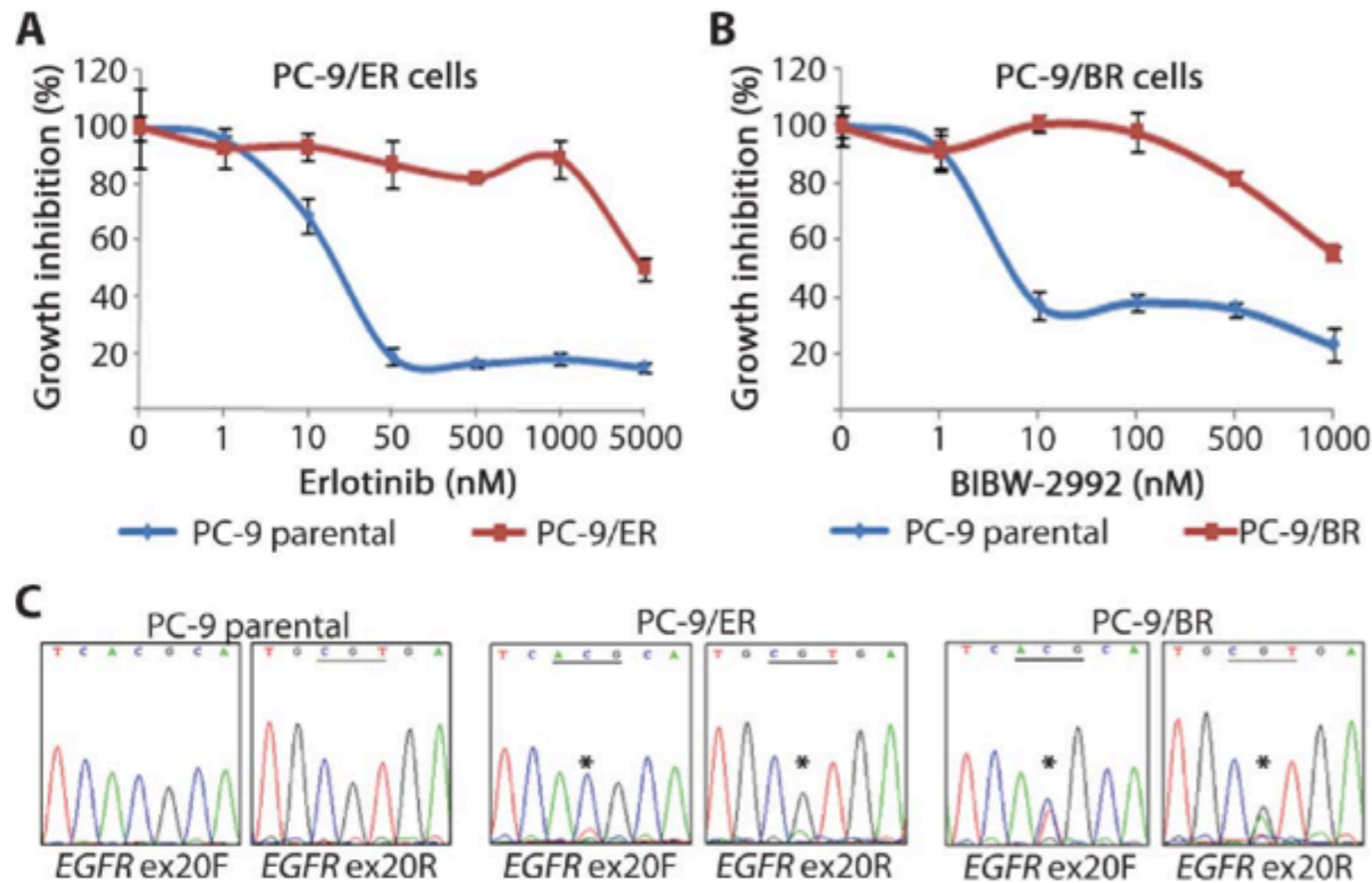
± Exogenous factors eg, HGF, IL-6

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

PC-9 cells develop resistance upon chronic exposure to erlotinib or afatinib (here BR).

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.
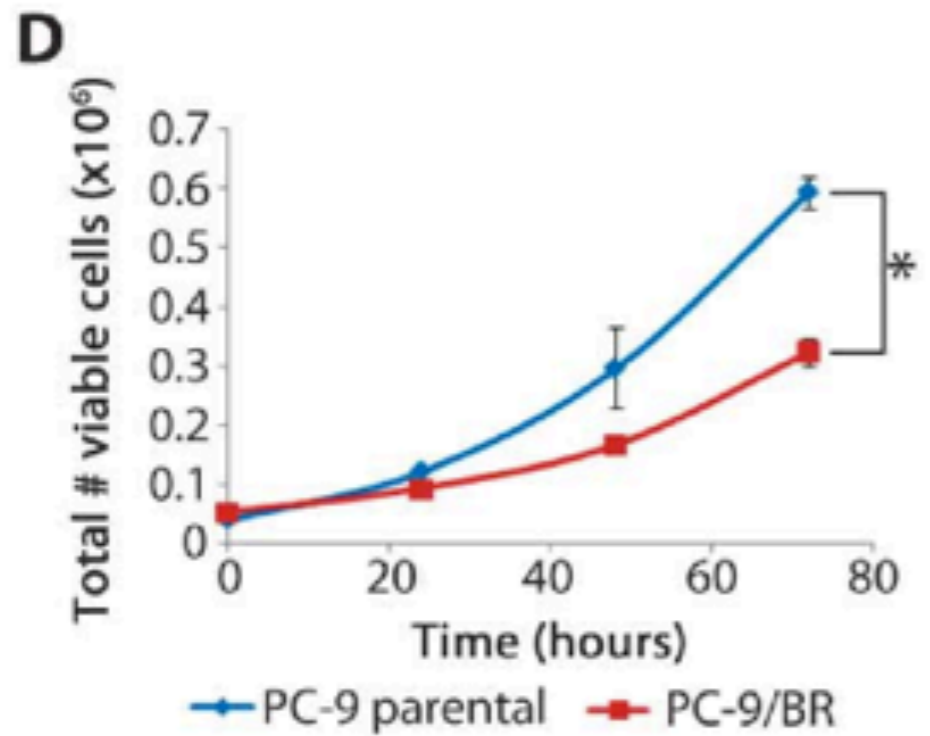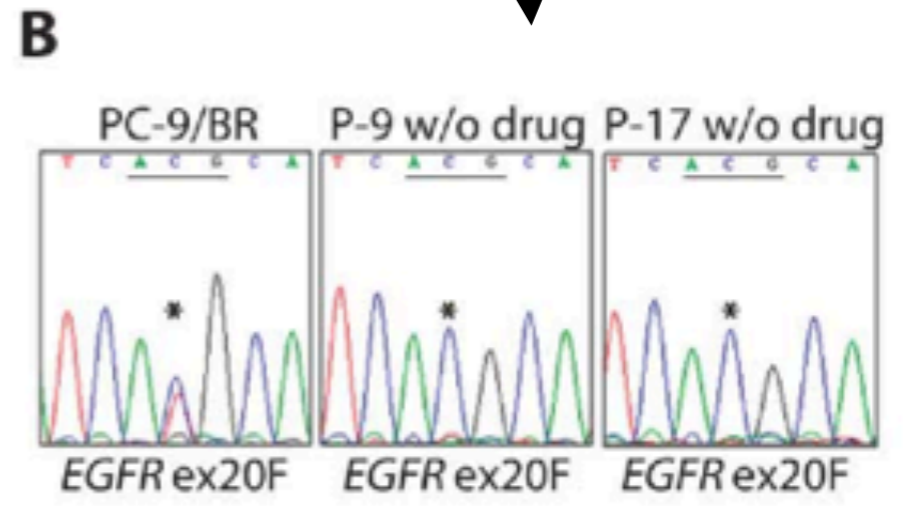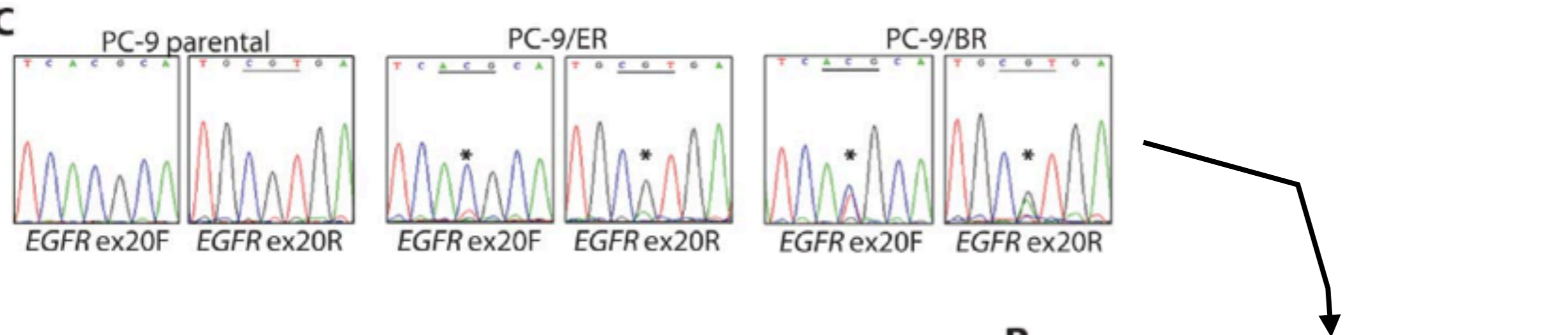
When drug is removed:
*Fewer mutant cells. Why?
*Growth rate is slower for mutant cells

Systems biology applied to drug resistance -- modeling of T790M and dosing schedule.
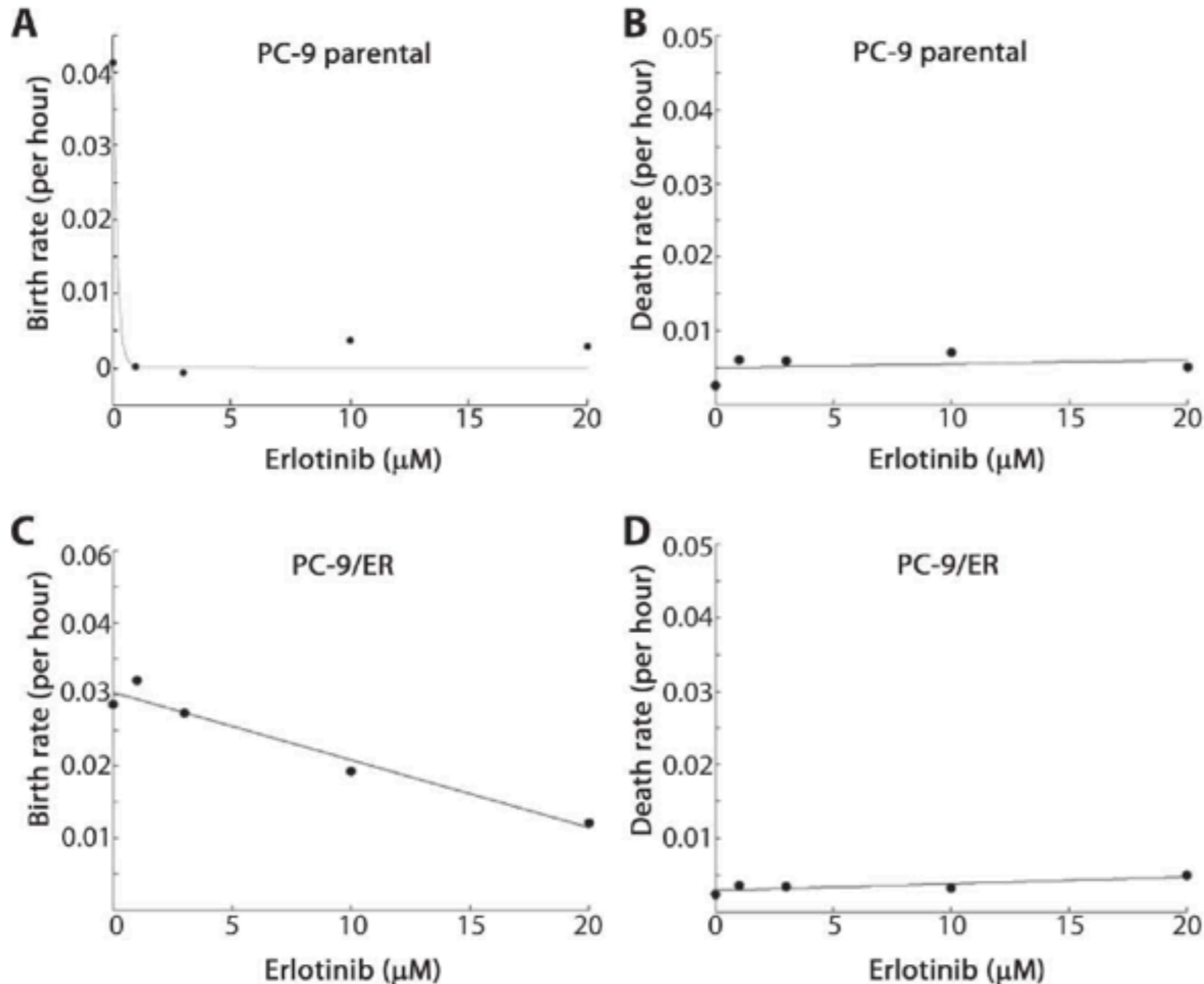
A simple and elegant mathematical model was employed using simple cell viability data & knowledge of mutation rate.

College study finds Oreo cookies are as addictive as drugs

"Even though we associate significant health hazards in taking drugs like cocaine and morphine, high-fat/ high-sugar foods may present even more of a danger because of their accessibility and affordability," Jamie Honohun said.

On a lighter note, Honohun says they also got a surprise when watching the rats eat the Oreos.

"They would break it open and eat the middle first," she said.

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39 Comments

Like 21k

lab rats.

The study ⧉ by students at Connecticut College found that when

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foxnews.com

A little bit of histology:
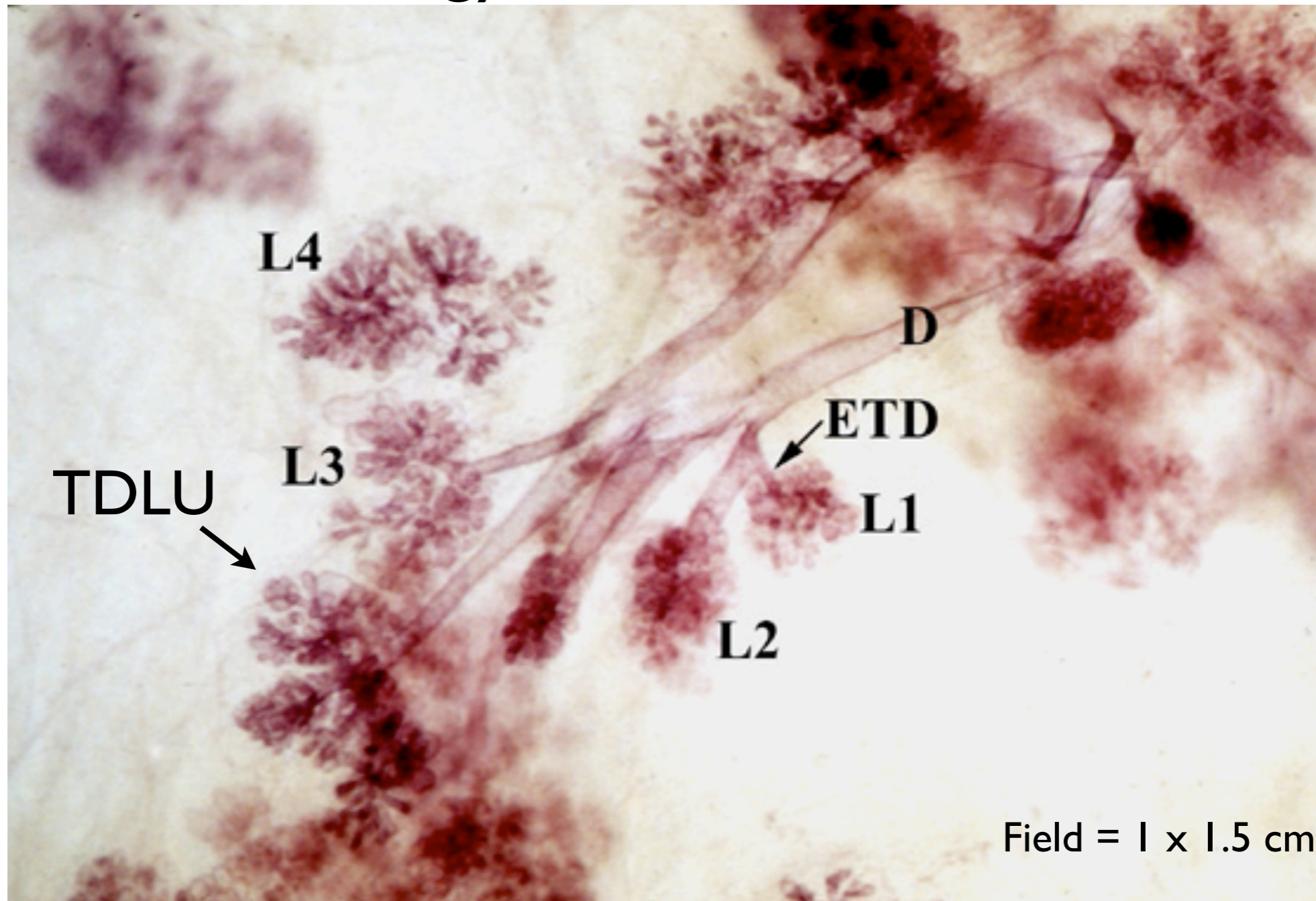
D = Duct   ETD = Extralobular Terminal Duct
L = Lobule TDLU = Terminal Ductal Lobular Unit
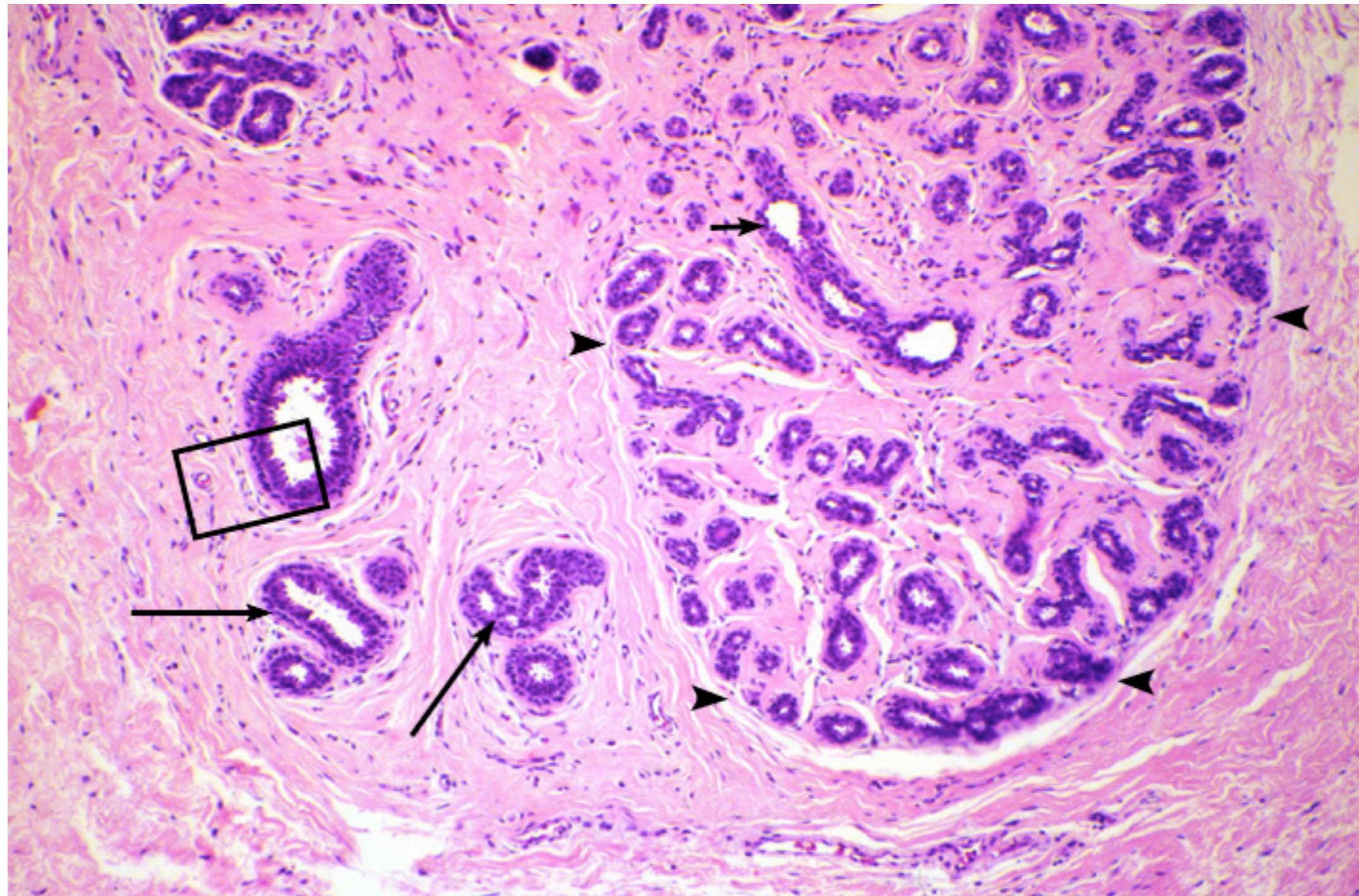
Field = 1 x 1.5 mm

Arrow heads delineate the lobule. The terminal ductule (short arrow) leads from the lobule to the duct system (larger arrows). Note how the pink fibrillar extracellular matrix material (mostly collagen) tends to wrap concentrically around the ducts and lobules
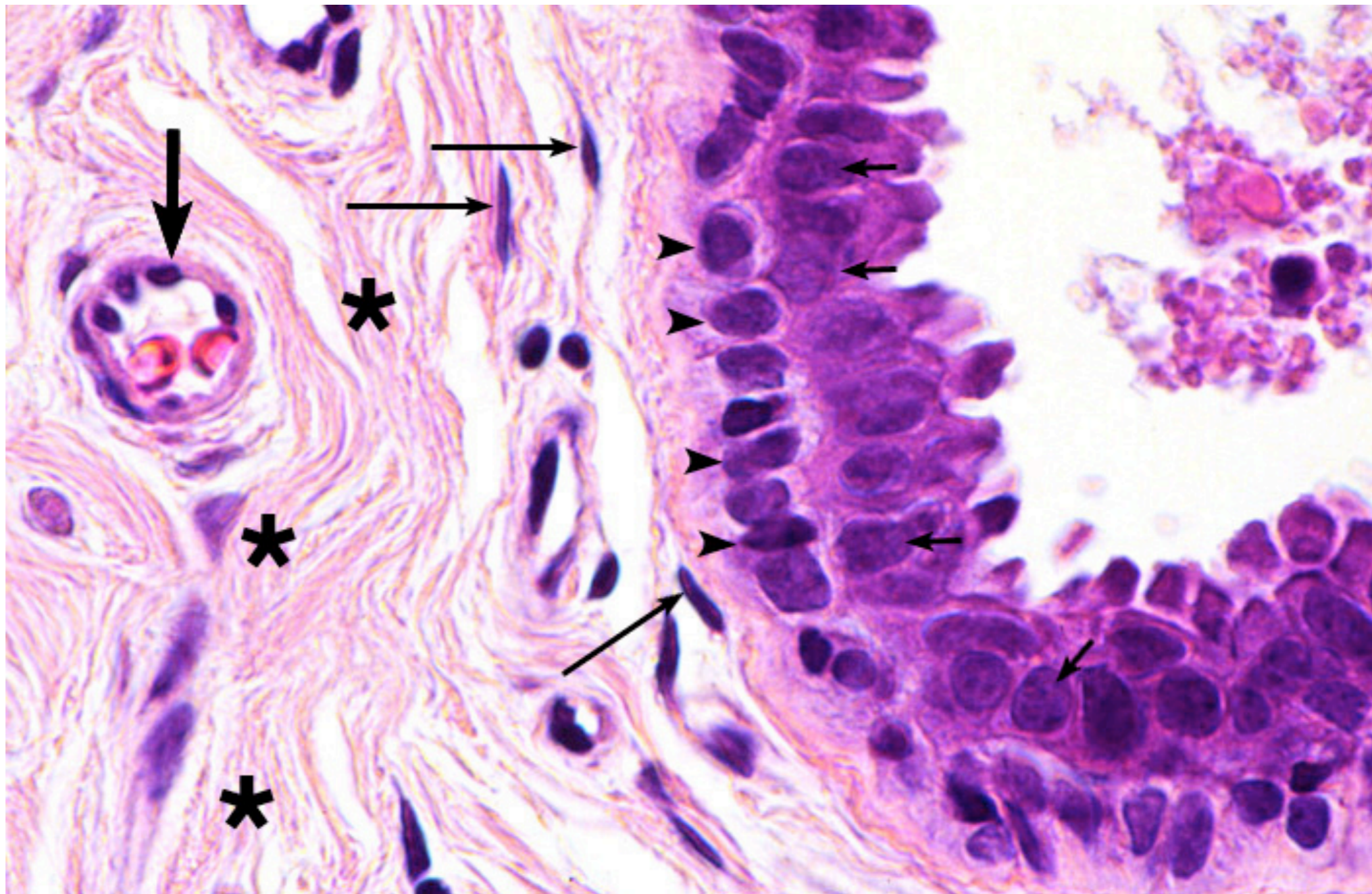
Field = 1 x 1.5 μm

Arrow heads show the myoepithelial cells apposed to the basal lamina. Ductal cells (short arrows) are partly overlapping in this section but form a single cell layer above the myoepithelium. Long thin arrows show several of the periductal fibroblasts. These have characteristic long pointed nuclei, they show a typical orientation of their long axis parallel with the basal lamina, and they appear inactive (heterochromatic nuclei) in this duct.

Breast cancer is a heterogeneous disease.

Breast cancer is a heterogeneous disease.

Genetic signatures define breast cancer subtypes.

Basal-like

HER2

Luminal A

Luminal B
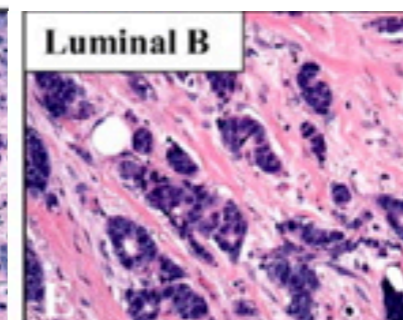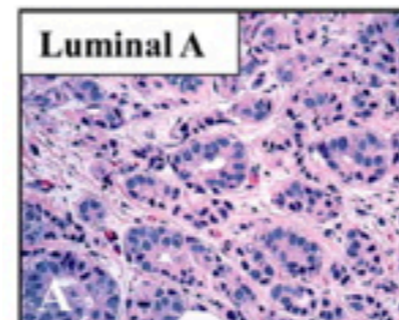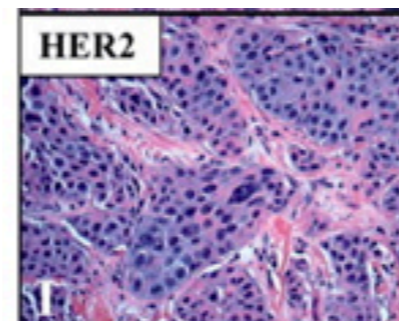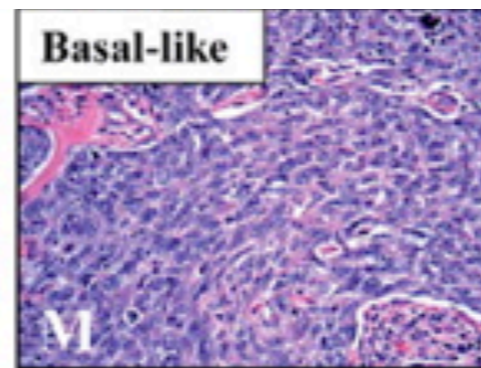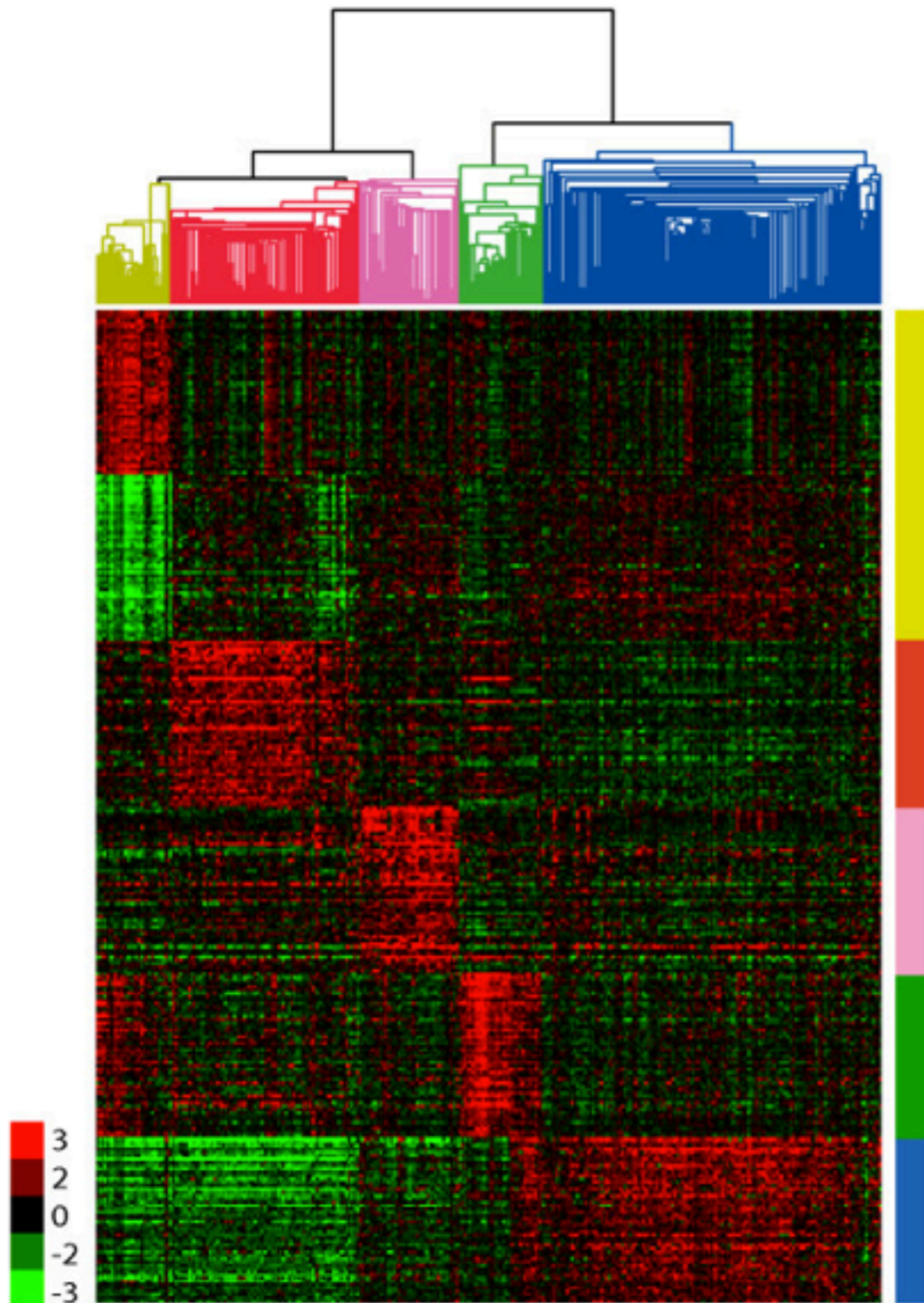
Prat et al. *Breast Cancer Research* 2010, **12**:R68

Sandu, LabMed June 2010 vol. 41 no. 6 364-372

EGFR family nomenclature can be confusing.

EGFR family nomenclature can be confusing.

Human / Mouse
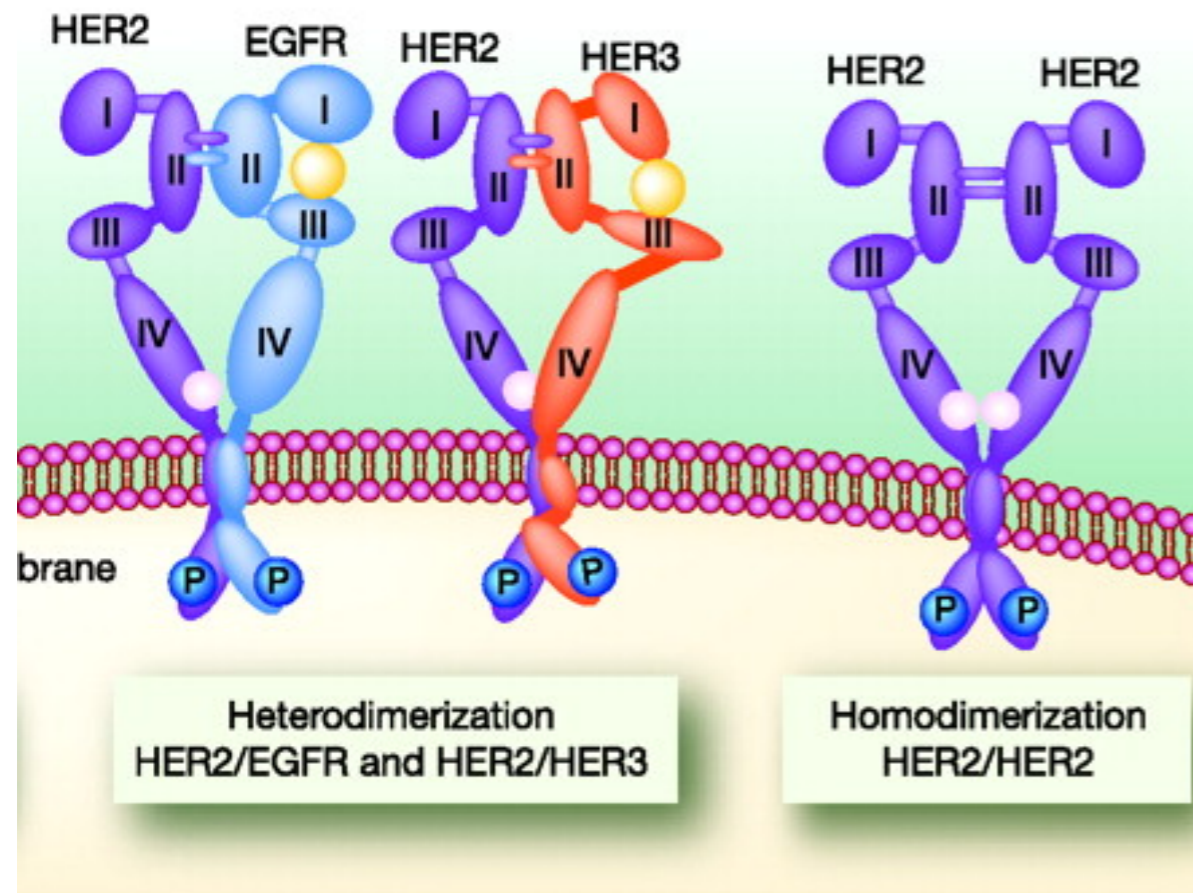EGFR = EGFR
HER 2 = ErbB2
HER 3 = ErbB3
HER 4 = ErbB4
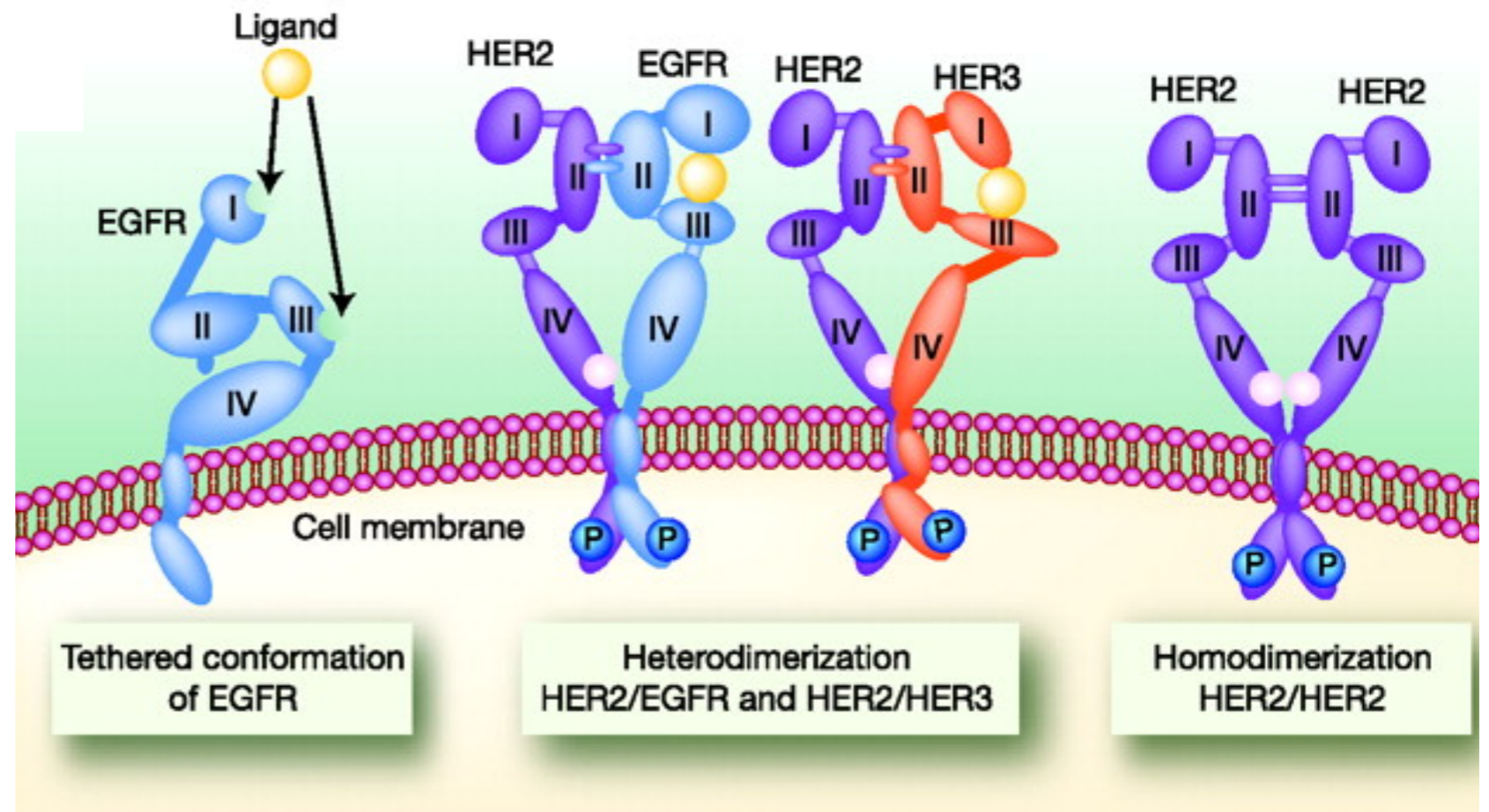
HER2 does not bind ligand.
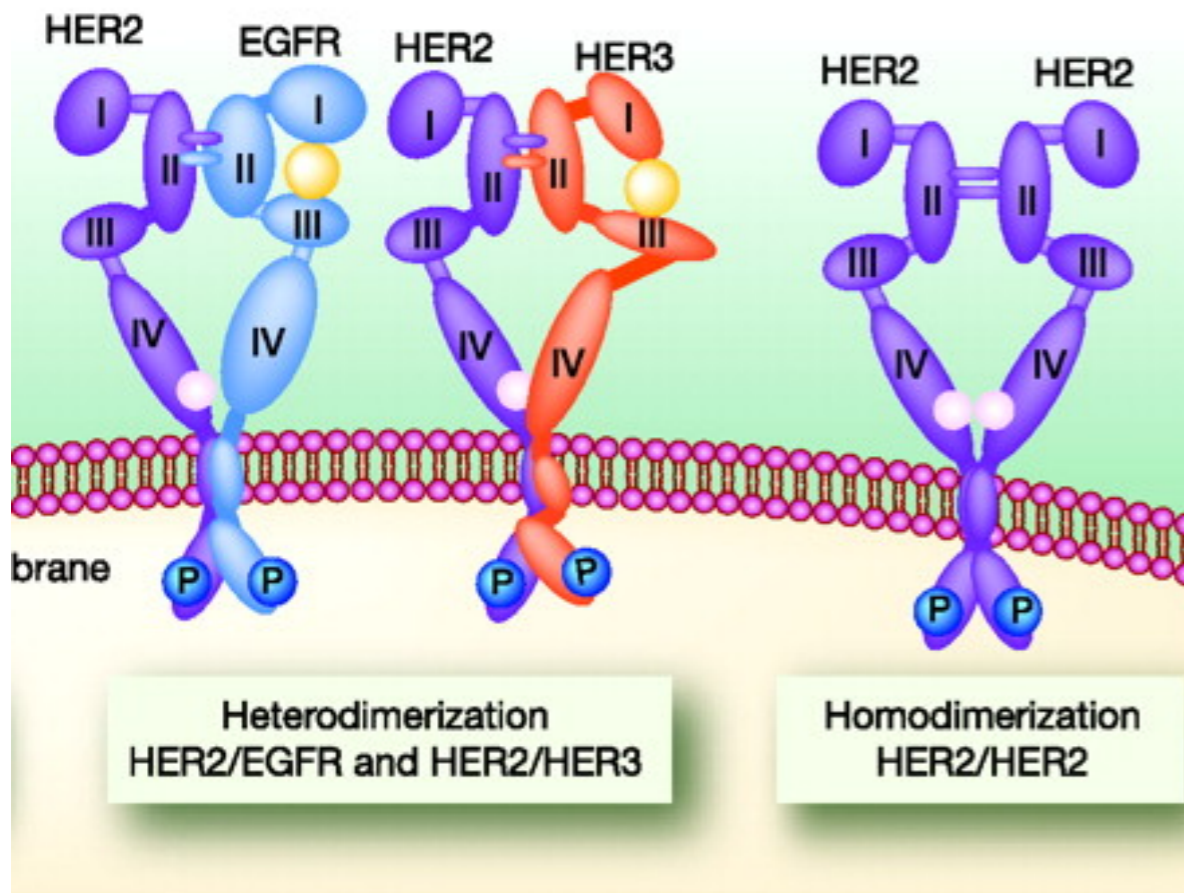
HER3 does not have a kinase domain -- must partner.

Heterodimerization
HER2/EGFR and HER2/HER3

Homodimerization
HER2/HER2

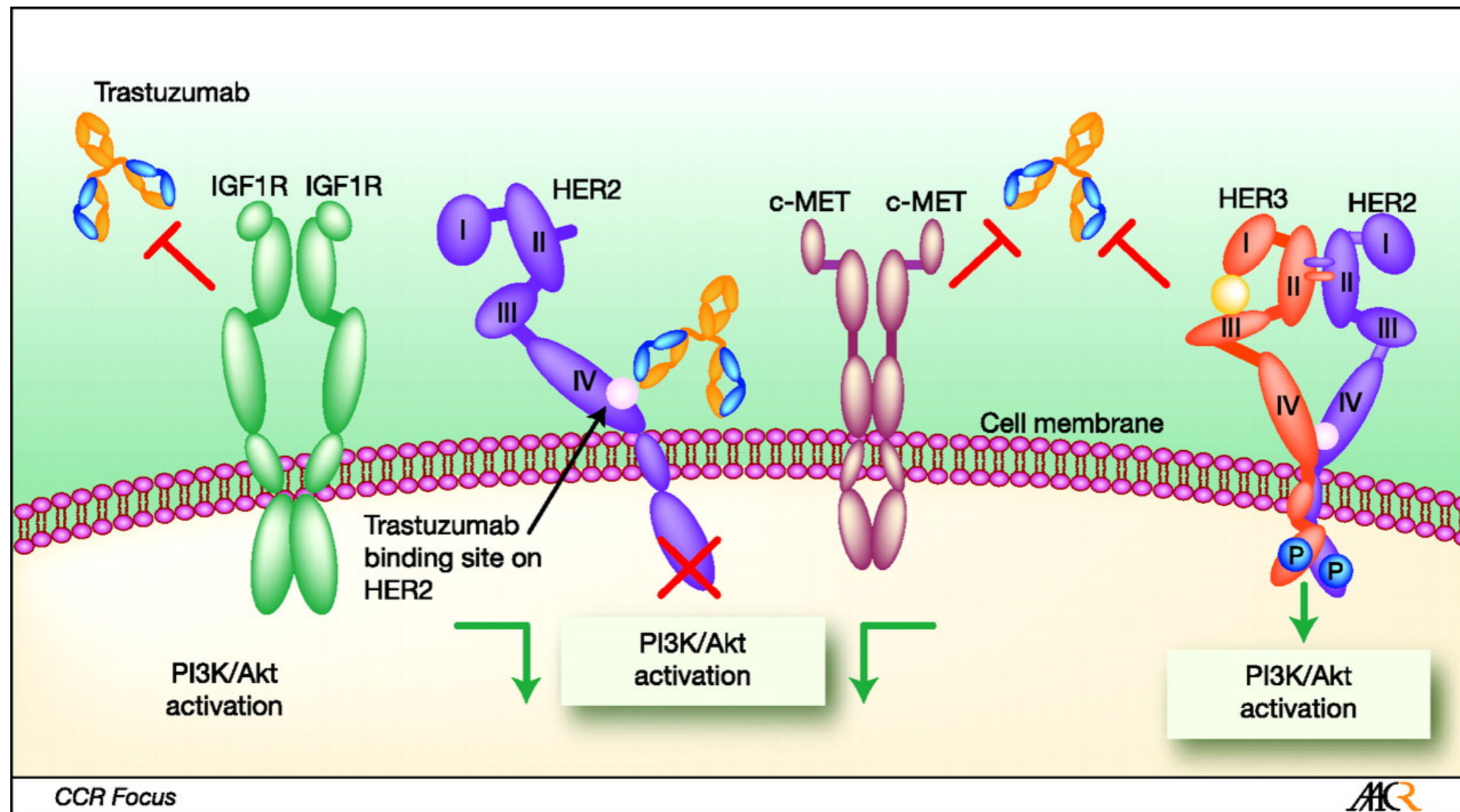# Consider the HER2+ subtype -- where EGFR is low.

>500,000 HER2 = homodimers

HER2-HER2 > HER2-EGFR

HER2-HER3 drives the Akt pathway

HER2-HER3 limited by HER3

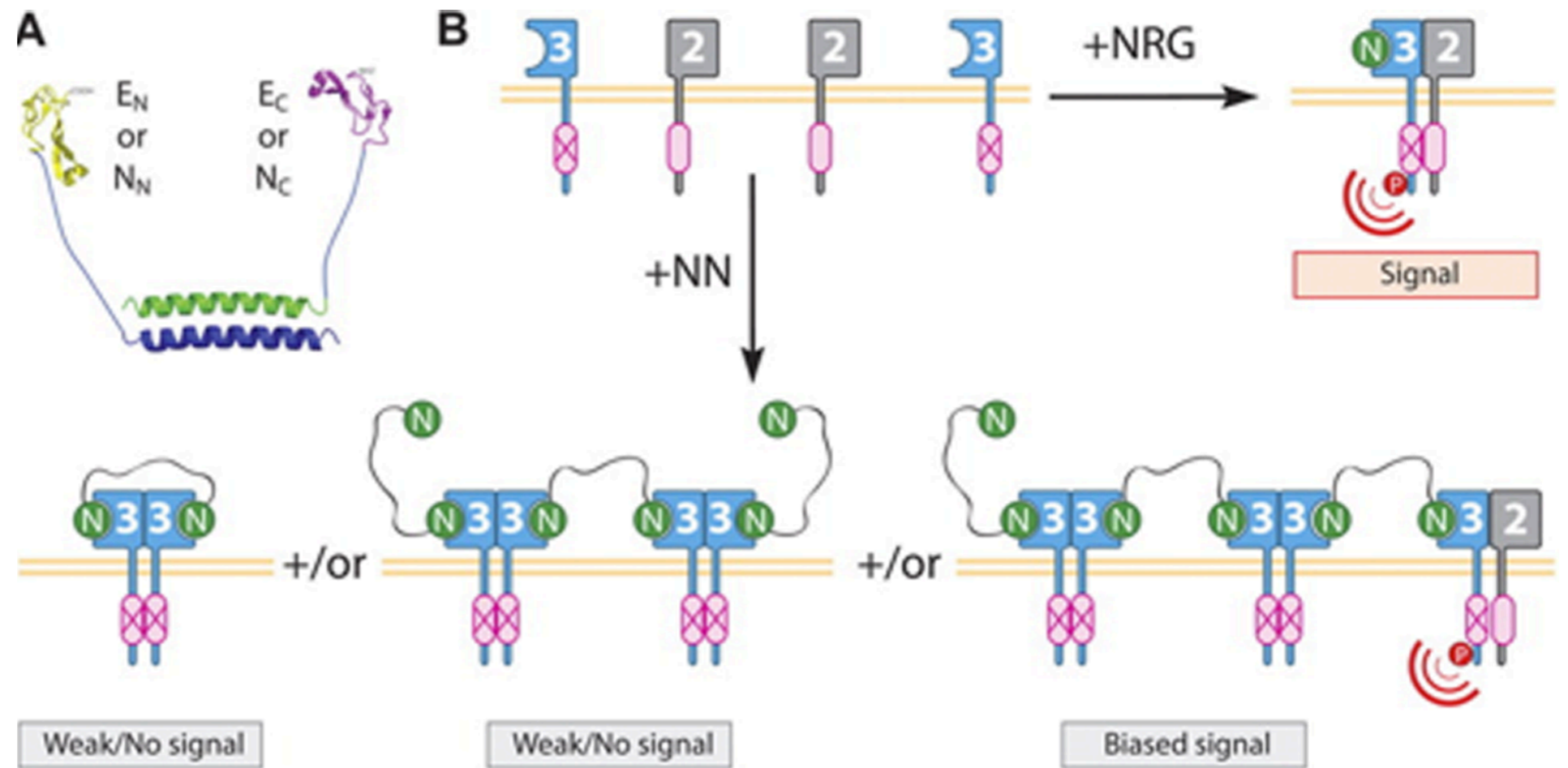Heregulin (HRG) = Neuregulin (NRG) = HER3 ligand
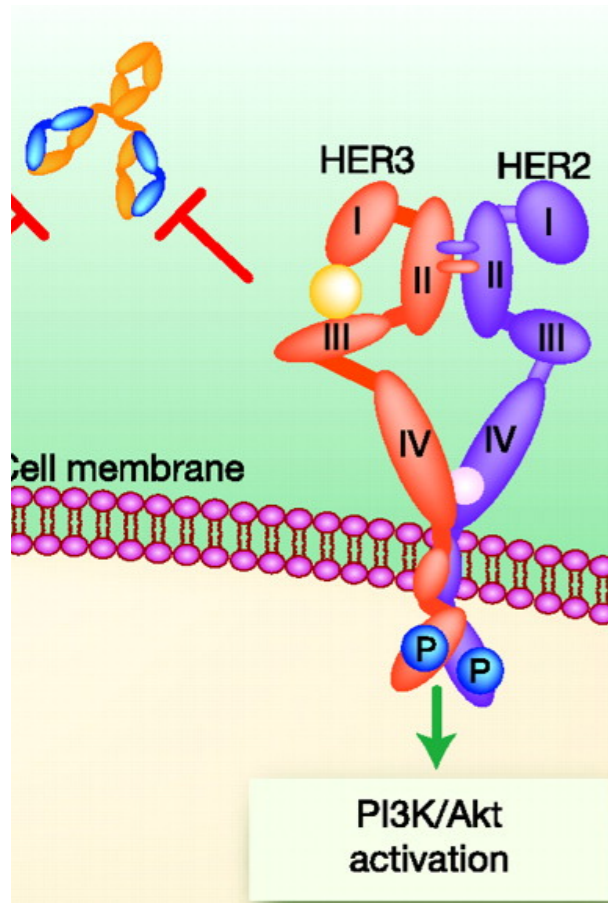
Recall: HER2-HER3 dimerization can offer escape from HER2 inhibition by Herceptin

Can you selectively target HER3 interactions to decrease incidence of HER2-HER3 heterodimers?

Target the HER3 homodimers to block signaling.

Modified from Jay et al. The Journal of Biological Chemistry August 5, 2011 286, 27729-27740.

Heregulin (HRG) = Neuregulin (NRG) = HER3 ligand

Target the HER3 heterodimers to block signaling.

Write this down -- can't go on wiki.

Target the HER3 heterodimers to block signaling.

Fab
(fragment antigen binding)

F(ab')₂

Fab'

scFv
(single-chain variable fragment)

di-scFv

sdAb
(single domain antibody)

trifunctional antibody

chemically linked F(ab')₂

BiTE
(bi-specific T-cell engager)
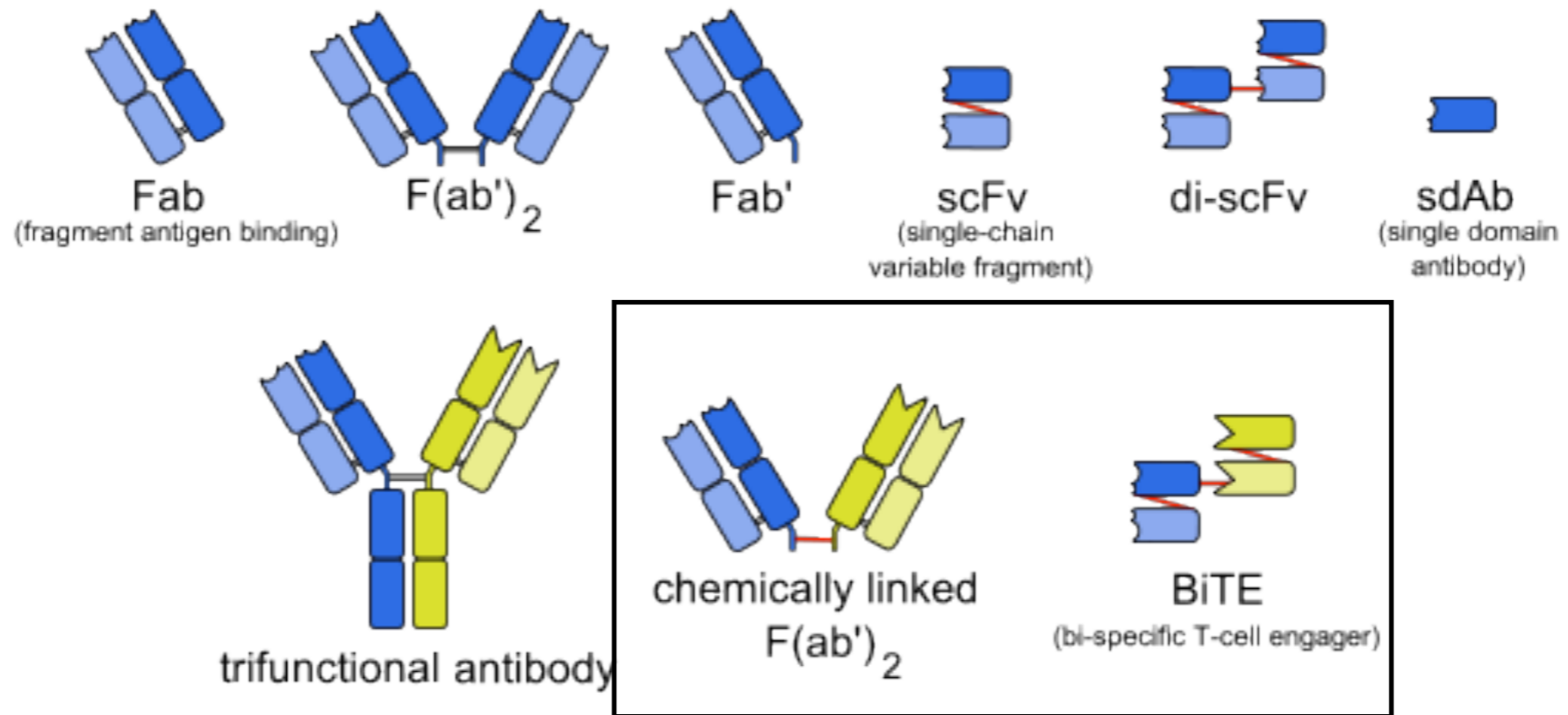
MM-111 is a bispecific antibody

Target the HER3 heterodimers to block signaling.
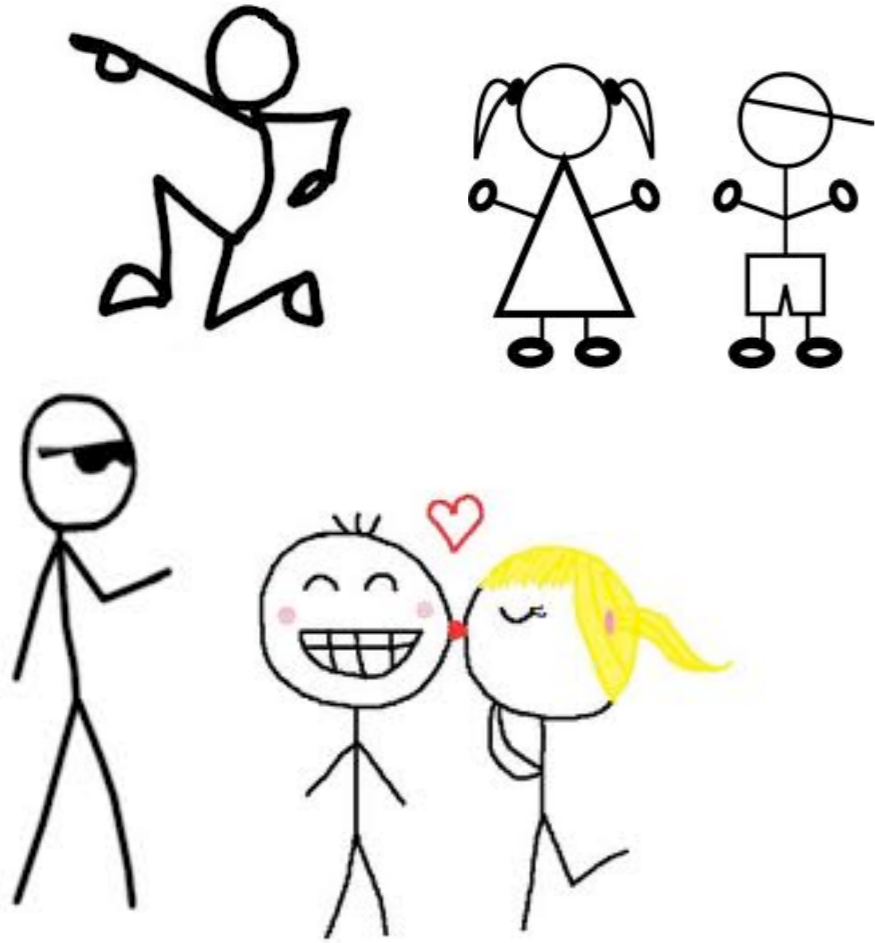
Compensation may require inhibition of multiple family members

MM-111

The Kirouac et al. paper uses MM-111 and Lapatinib as tools to interrogate the Akt and ERK pathways.

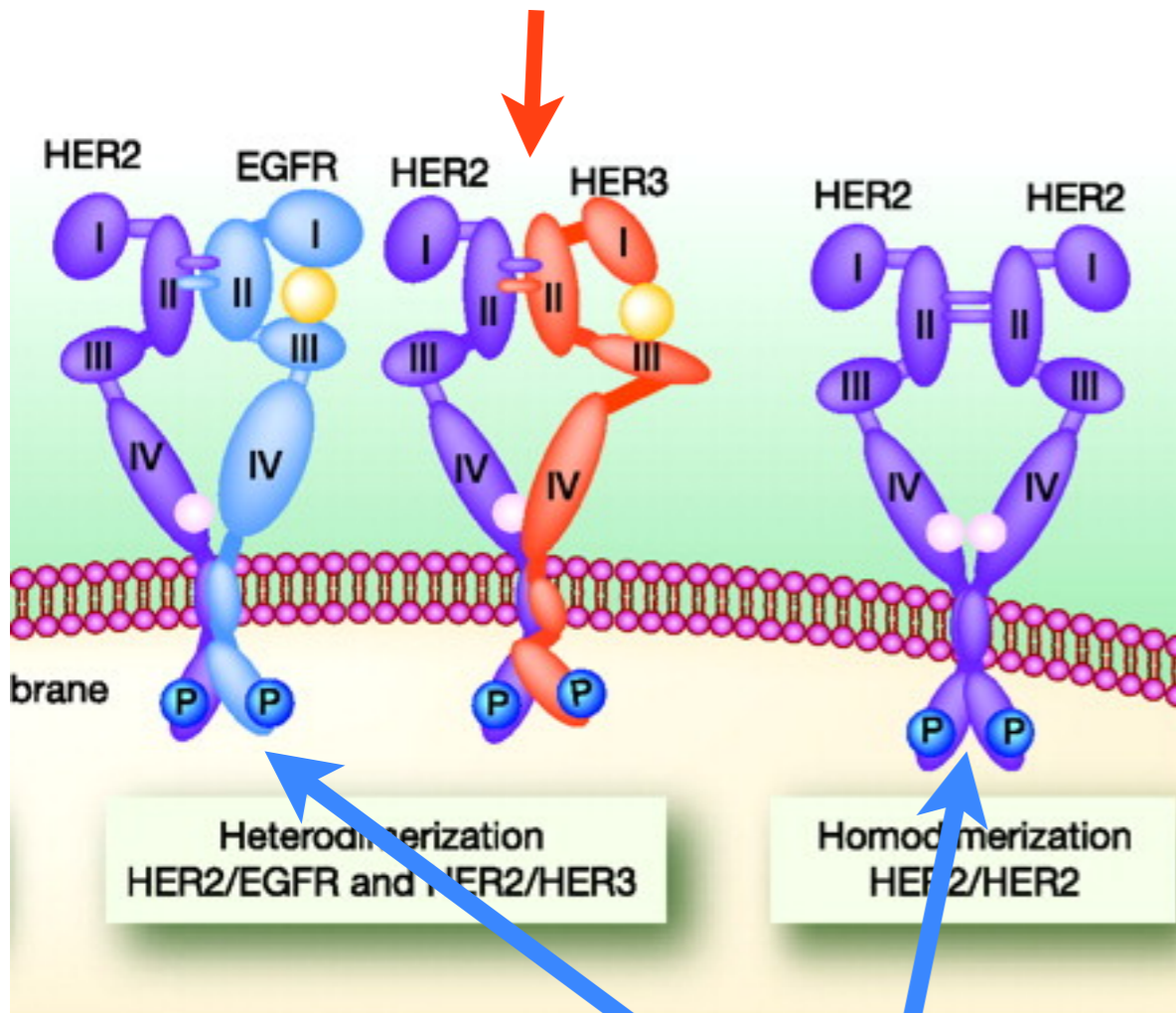Lapatinib

Modified from Pohlmann et al. Clin Cancer Res December 15, 2009 15; 7479
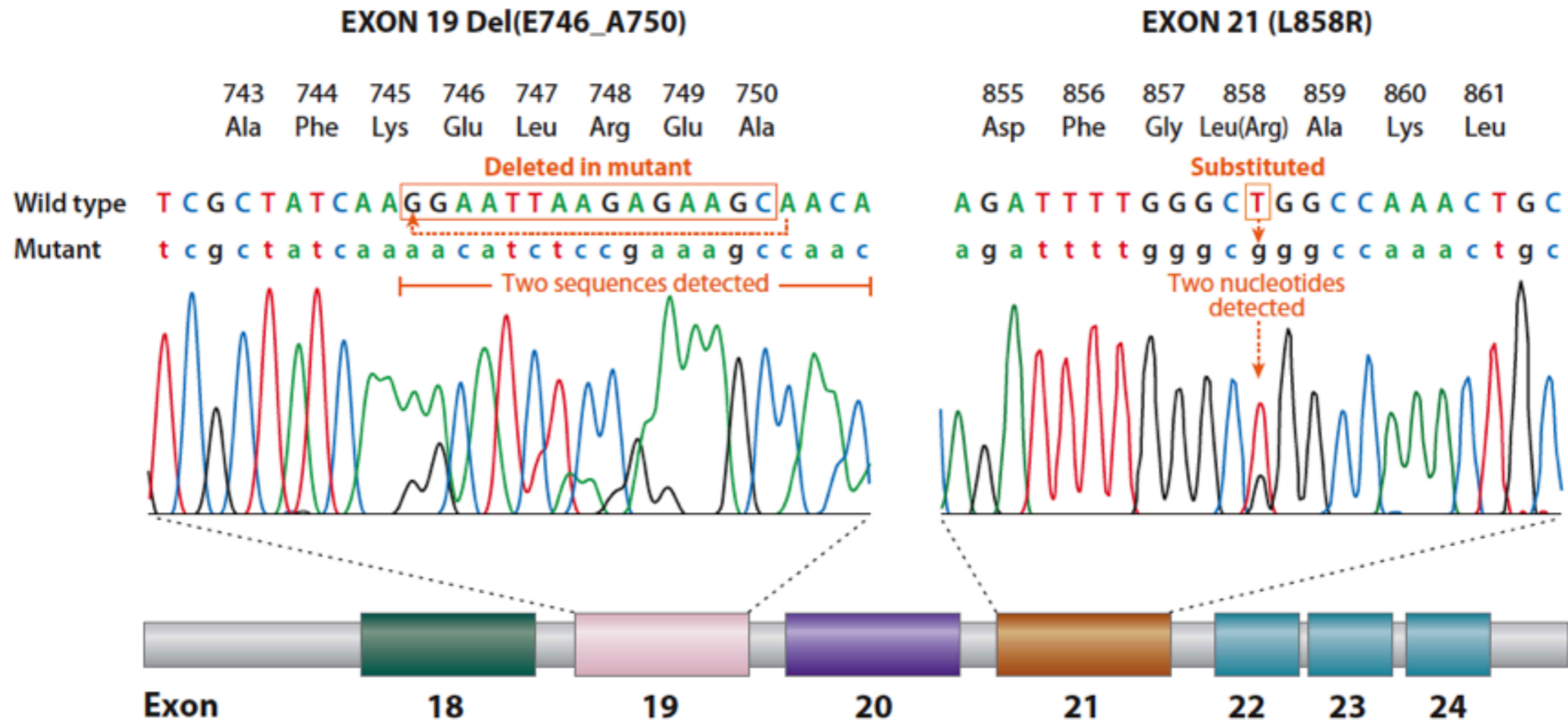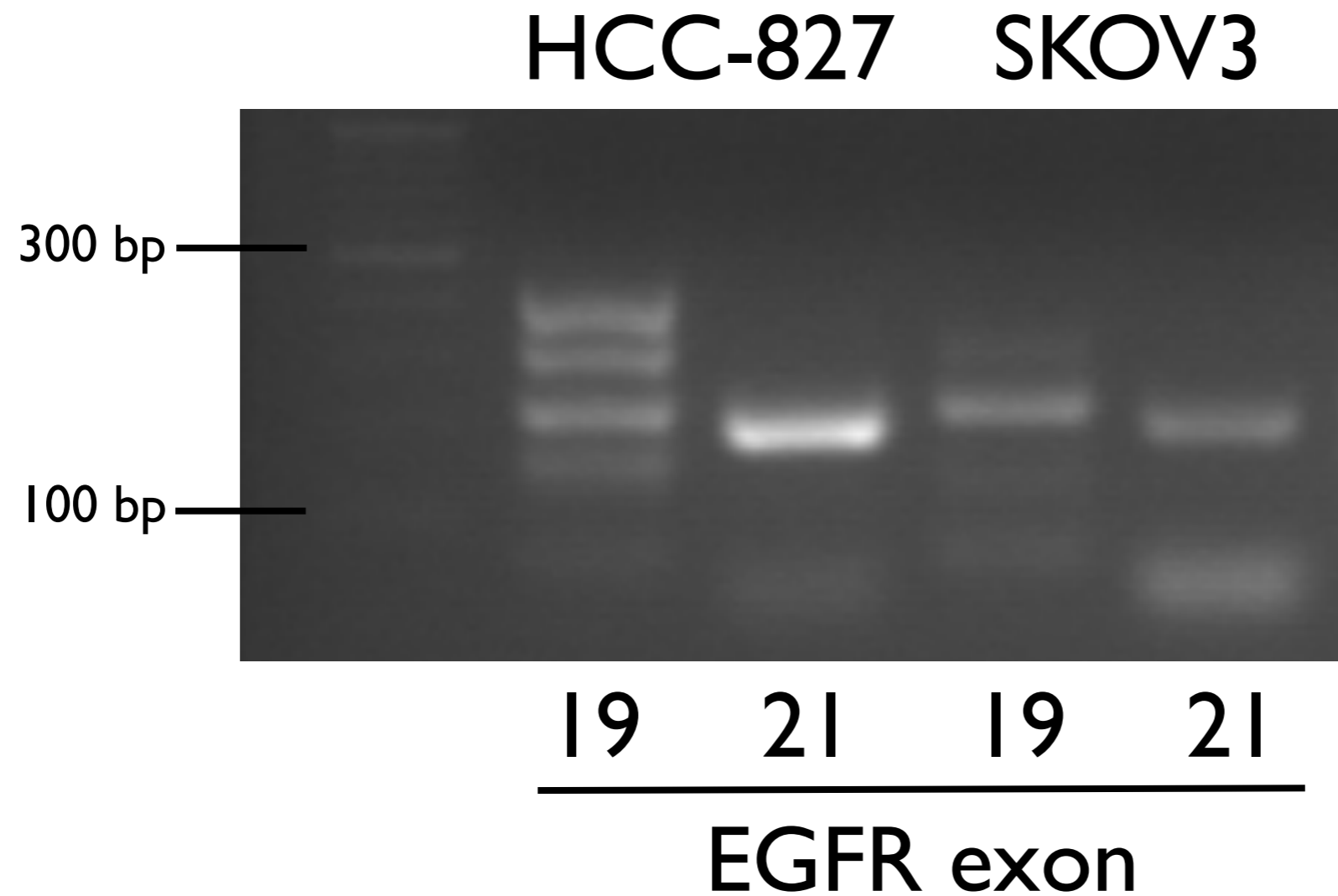
Detecting EGFR Mutation -- PCR + Sequencing

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

Detecting EGFR Mutation -- PCR + Sequencing

Expected amplicons ~ 150 bp

Primers bind outside exon

EXON 19 Del(E746_A750)

	743	744	745	746	747	748	749	750
	Ala	Phe	Lys	Glu	Leu	Arg	Glu	Ala

Deleted in mutant

Wild type   T C G C T A T C A A G G A A T T A A G A G A A G C A A C A

Mutant   t c g c t a t c a a a a c a t c t c c g a a a g c c a a c

Two sequences detected
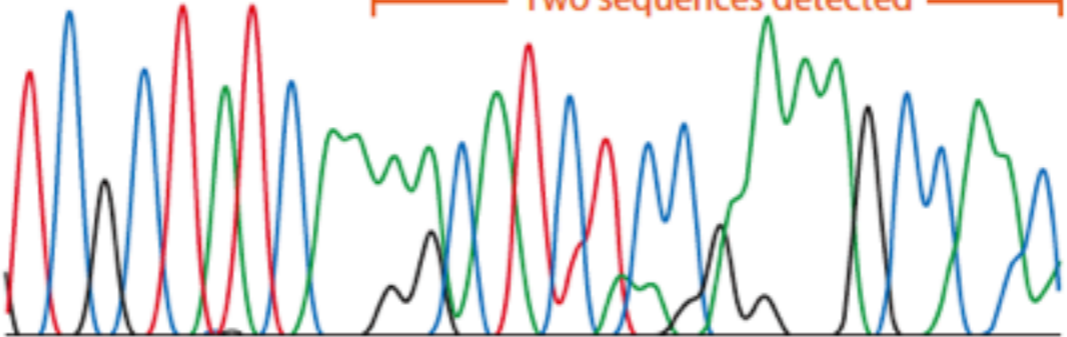
Trace File: Pink_19F_SKOV3-exon19F.ab1

Utilities	Next N	Find...	Data	Screen	H	2	V

C C G T C G C T A T C A A G G A A T T A A G A G A A G C

65   70   75   80   85   90

Pink_19F_SKOV3-exon19F
Pink_19F_SKOV3-exon19F_E05.ab1

900

675

450

225

Module 2: Systems Engineering

- A few announcements -- JC & Report details

- Review Michor drug dosing model

- Clinical breast cancer subtypes

- Using systems biology to identify drug targets -- Kirouac et al.

- A look at your sequencing data