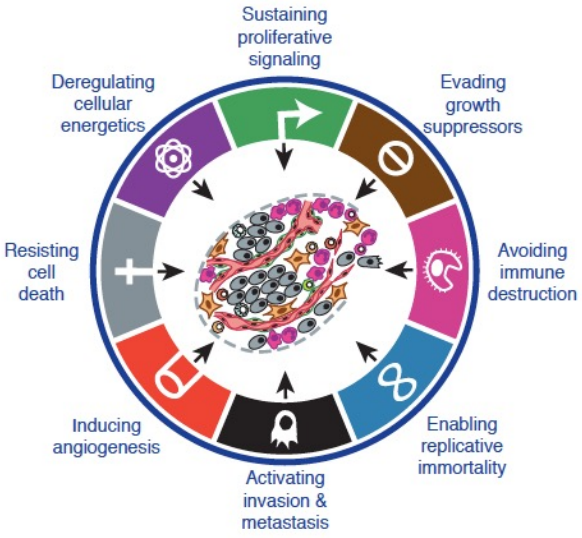
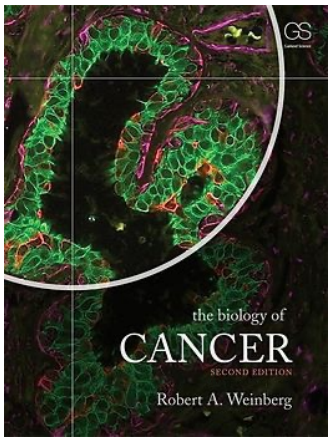
# The hallmarks of cancer - BIO-392

Hanahan & Weinberg, 2011
Cell 144:646-674
(see Moodle, week 1)




Recommended textbook:

| | |
|---|---|
| Titel: | The Biology of Cancer<br>2nd edition, 2014<br>Garland Science |
| Autor: | Robert A. Weinberg |
| EAN: | 9780815345282 |
| ISBN: | 978-0-8153-4528-2 |






## Introduction to oncology: Outline Constam part

**Core hallmark capabilities:**

| | | |
|---|---|---|
| March 5: | Sustained proliferation I | *Today* |
| March 12: | Sustained proliferation II | |
| April 2: | Evading growth suppression | |
| April 9: | Establishing replicative immortality | |
| April 23: | Spring break | |
| May 7: | Activating invasion and metastasis | |
| May 14: | Evading apoptosis | |

## Proliferative *and* growth suppressive signals converge on the cell cycle clock

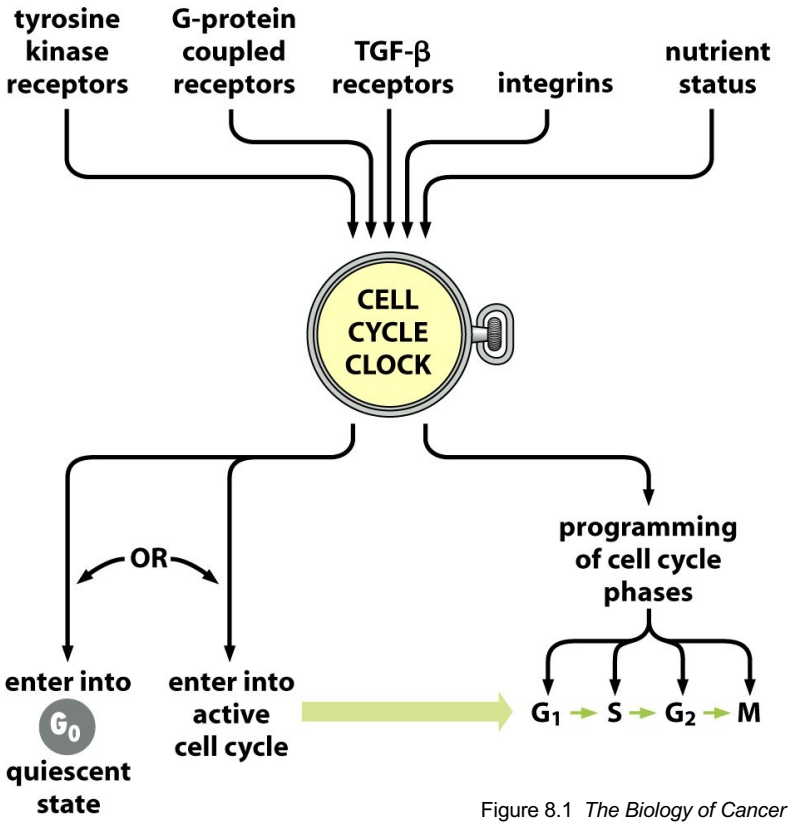
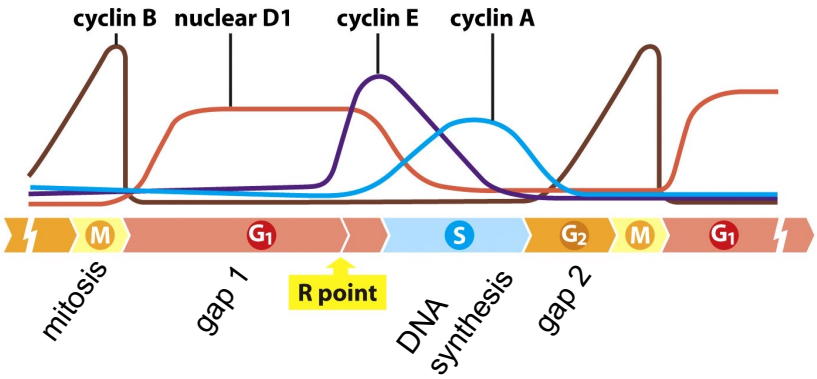



Figure 8.1 *The Biology of Cancer* (© Garland Science 2007)

## Cell cycle progression is governed by waves of cyclin expression




Cyclins bind and activate cyclin-dependent kinases (CDK):

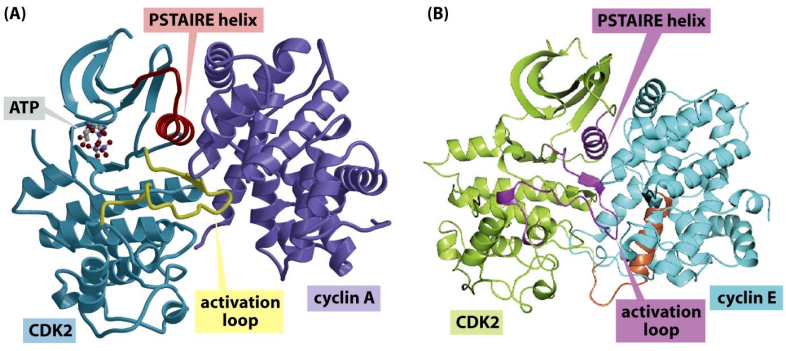
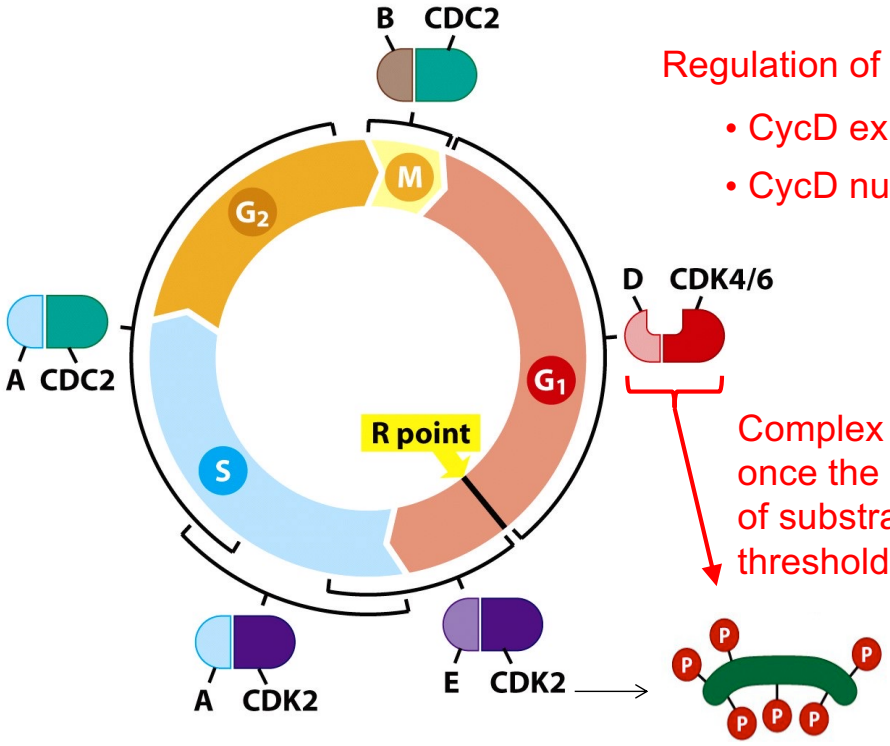



Figure 8.10 *The Biology of Cancer* (© Garland Science 2007)

# Phosphorylation by CyclinD/CDK4,6 complex inactivates RB1




Regulation of Cdk4,6 activity by:

- CycD expression levels
- CycD nuclear translocation

Complex launches S-phase once the hyperphosphorylation of substrate reaches a critical threshold (”restriction point”)

CDK2 activity: Necessary to then *complete* mitosis

Crncec et al. 2023, Nature 619:7969

# Multiple proliferative signals activate the promoters of cyclin D

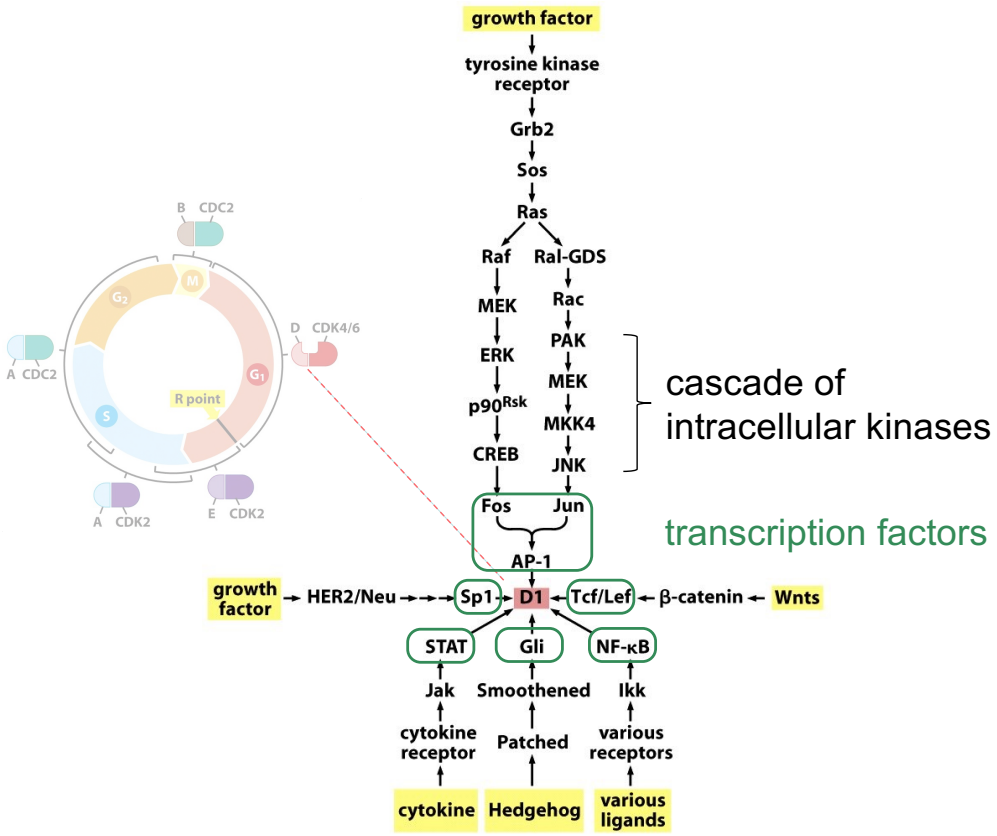



Figure 8.11b *The Biology of Cancer* (© Garland Science 2007)

## Multiple proliferative signals activate the promoters of cyclin D

- Pfizer (Palbociclib): >2016
- Eli Lilly (Abemaciclib): >2017
- Novartis (Ribociclib): >2017

**CDK4/6i(nhibitors):**
First-line treatment of advanced "ER+" breast cancers

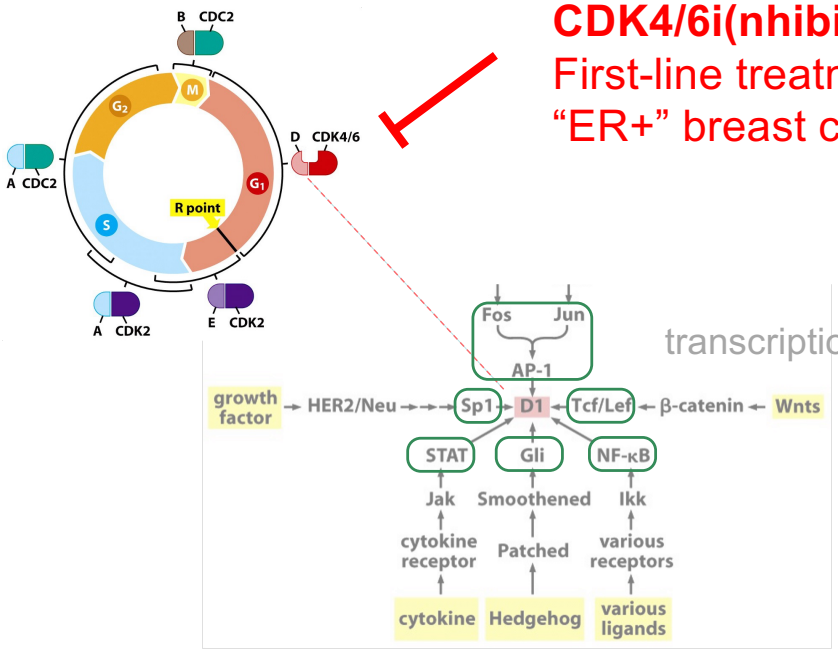



Figure 8.11b *The Biology of Cancer* (© Garland Science 2007)



## TODAY

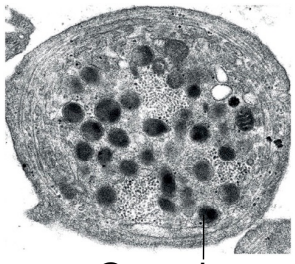
## Hallmark capability 1: Sustained proliferative signaling

Weinberg, selected parts of chapters 5 & 6

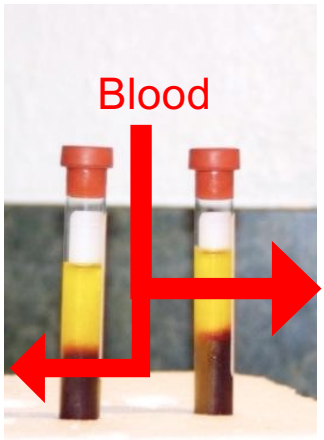

- ❑ Receptor tyrosine kinases (RTK)
  - Discovery
  - Oncogenic mutations
  - Therapeutic inhibitors
- ❑ RTK signal transduction
  - Ras family of small GTPases
  - Drugging oncogenic KRAS
  - PI3K/Akt signaling (Ras effectors)

# Discovery of “growth factors” in blood serum

blood clot (platelets)



α-Granules




Serum containing platelet-derived growth factor (PDGF)

Wounds trigger blood clotting:

➔ activated platelets precipitate blood cells, and release the content of their α-granules

➔ the liquid phase (serum) contains factors such as PDGF that activate and attract fibroblasts to initiate wound healing



# PDGF and many other growth factors stimulate the growth of healthy tissues

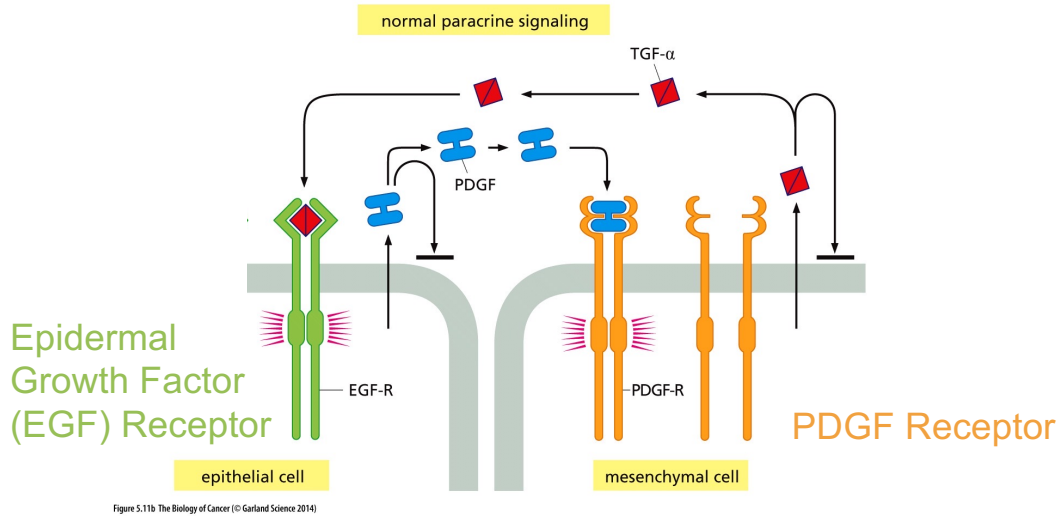



Figure 5.11b The Biology of Cancer (© Garland Science 2014)

*Healthy* growth typically relies on *paracrine* growth factors:
This reduces the risk of uncontrolled cancerous tissue growth.

## Receptor hyperactivation by ectopic production of its ligands

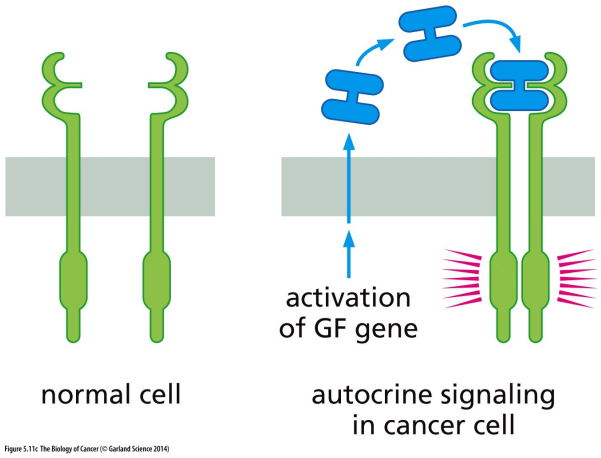
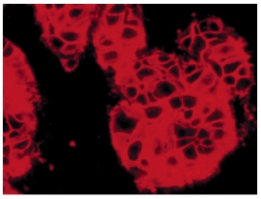



Figure 5.11c The Biology of Cancer (© Garland Science 2014)

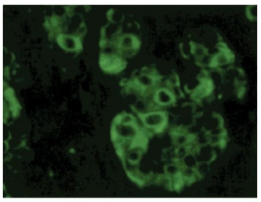
Many cancer cell types "ectopically" express growth factors (blue) that are absent in normal cells of the same lineage.

If such cancer cells also produce the cognate receptors, they can provide themselves with an "autocrine" growth stimulus.

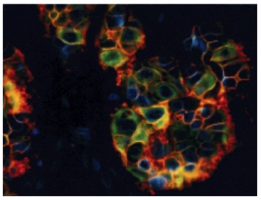
Invasive breast carcinoma



EGF-receptor



EGFR ligand (TGF-α)



overlay



## Concept: Different modes of growth factor signaling

*Systemic* signaling of *hormones* is called *endocrine*.

*Growth factor* signaling can be:

- autocrine
- juxtacrine
- paracrine

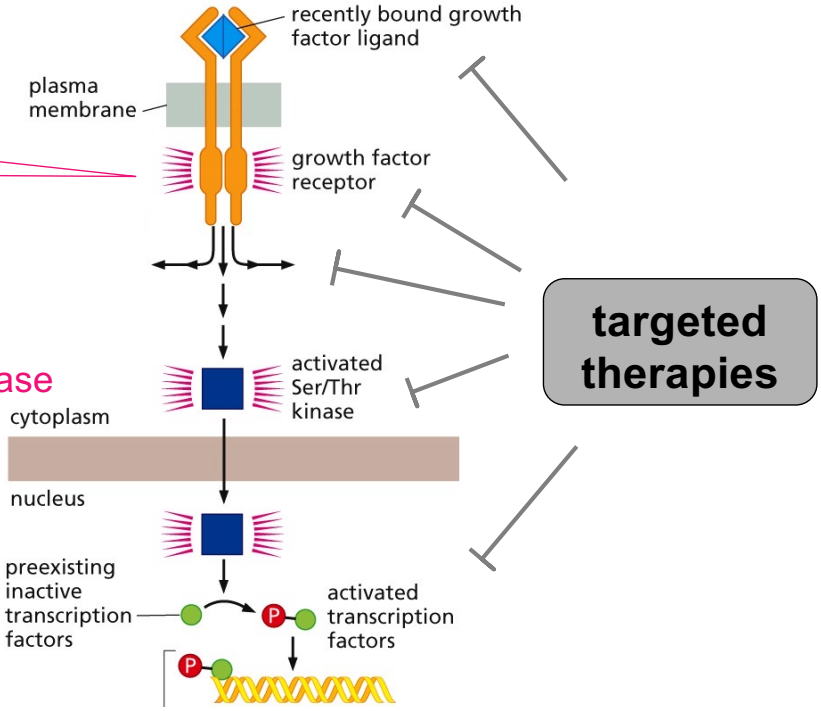
depending on the range of action.

The range of action determines their availability (also for cancer cells)

# Signal transduction and what we need to know about it

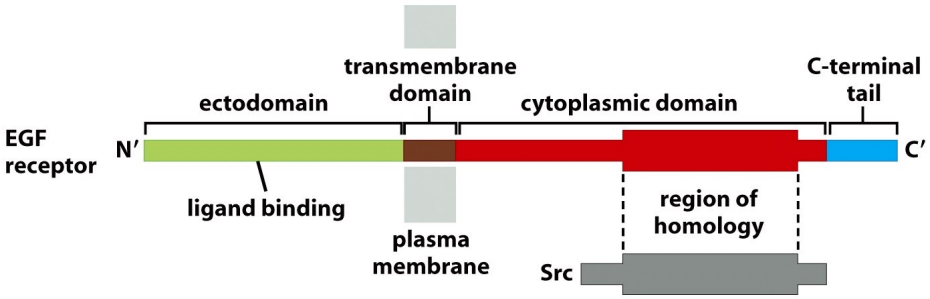
**How?**

- in normal tissues
- **in cancer**
- and any other disease



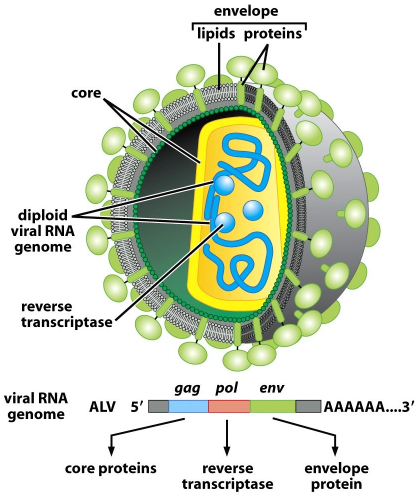


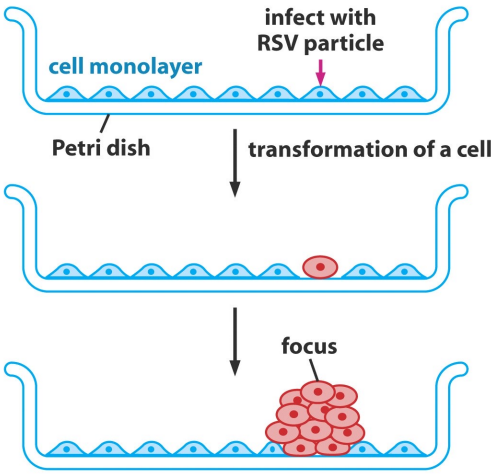

# The receptors for EGF and PDGF each resemble the viral oncoprotein Src




- Src-like sequences are found in their *cytoplasmic domain*
- Studying Src shed light on how such receptors signal

# v-Src is responsible for the tumorigenicity of RSV



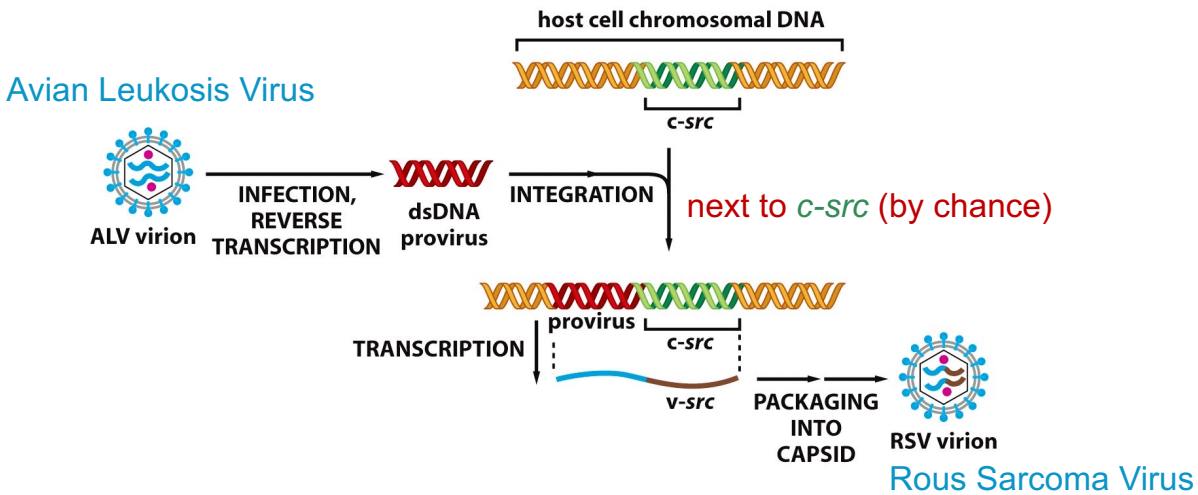

Rous Sarcoma Virus transforms the growth of infected chicken fibroblasts

A transformation-deficient mutant RSV was found to lack the *v-src* gene
Stehelin et al. 1976 J Mol Biol, 1976 Nature



# Origin of the v-src gene

- Hybridization of a *v-src* cDNA probe to DNA of uninfected cells revealed a cellular *c-src gene* (**1989 Nobel prize, Varmus & Bishop**)
- v-Src is thought to be a renegade viral version of the c-Src gene that arose during RSV evolution from an ALV:



## v-Src is called a viral *oncogene* because...

v-Src is sufficient to induce many features of a full blown tumor in cultured cells:

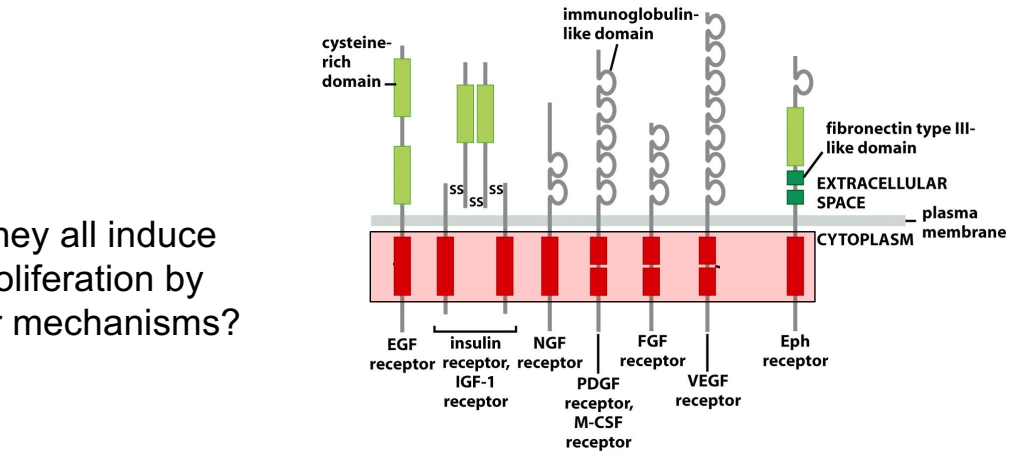
- cell shape changes
- loss of 'contact inhibition'
- anchorage-independent survival & growth

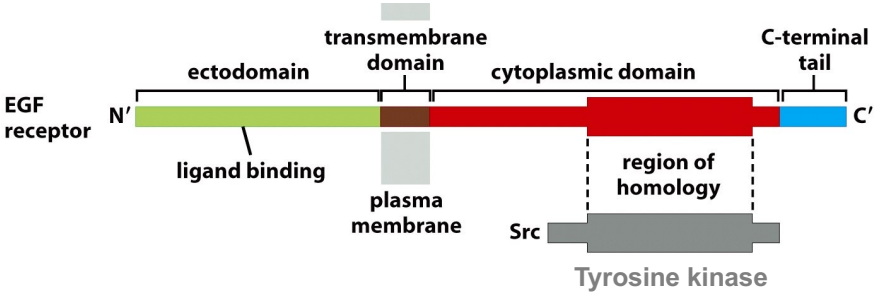
} = "transformed" growth



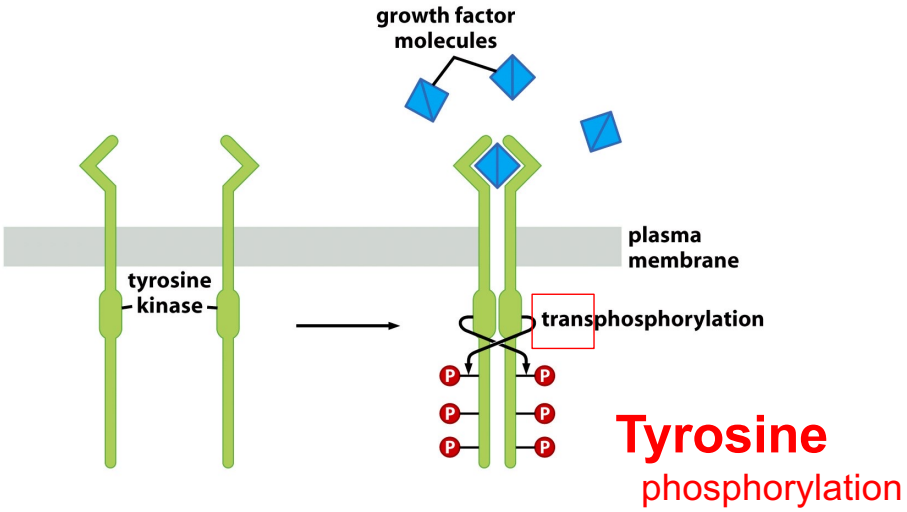
## PDGF and EGF receptors resemble the viral oncoprotein v-Src

=> Do they all induce cell proliferation by similar mechanisms?



## A Src-like cytosolic domain in the cytosolic domain of so-called Receptor Tyrosine Kinases (RTK) has tyrosine kinase activity




Dimerization by ligand stimulates RTK autophosphorylation in *trans*

→ Do cancer cells somehow *hyper*activate their RTKs, and if so how?



## TODAY

## Hallmark capability 1: Sustained proliferative signaling

Weinberg, selected parts of chapters 5 & 6


- ❑ Receptor tyrosine kinases (RTK)
  - ✓ Discovery
  - • Oncogenic mutations
  - • Therapeutic inhibitors
- ❑ RTK signal transduction
  - • Ras family of small GTPases
  - • Drugging oncogenic KRAS
  - • PI3K/Akt signaling (Ras effectors)

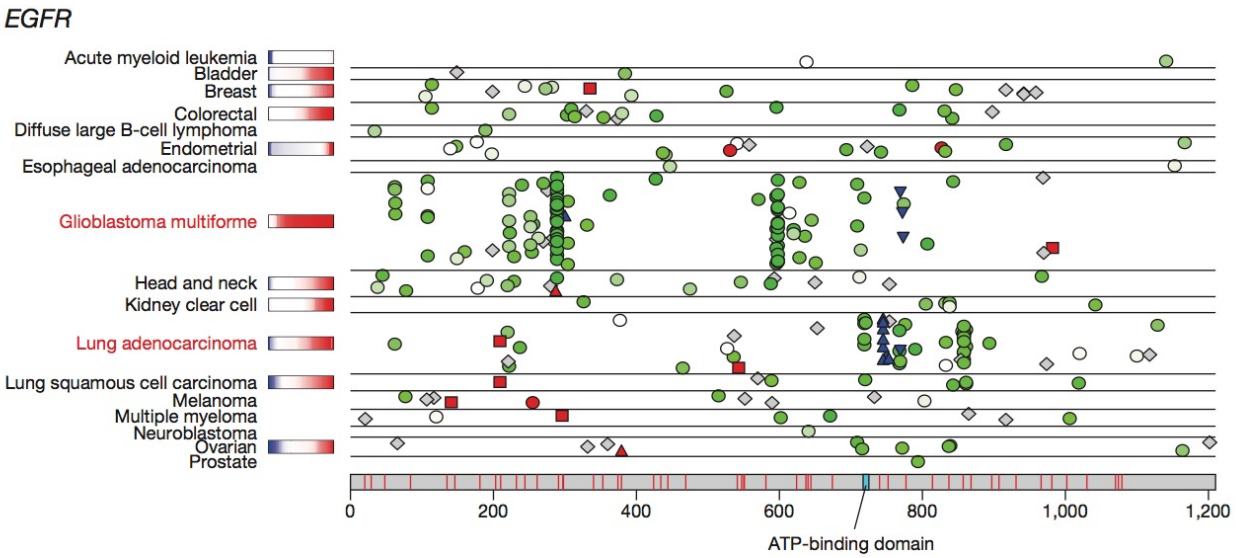
# Discovery and saturation analysis of cancer genes across 21 tumour types

Michael S. Lawrence[1], Petar Stojanov[1,2], Craig H. Mermel[1,3], James T. Robinson[1], Levi A. Garraway[1,2,4], Todd R. Golub[1,2,4,5], Matthew Meyerson[1,2,4], Stacey B. Gabriel[1], Eric S. Lander[1,4,6]* & Gad Getz[1,3,4]*

Nature 505:495-501 (2014)

Exome sequencing of >4700 human cancers:

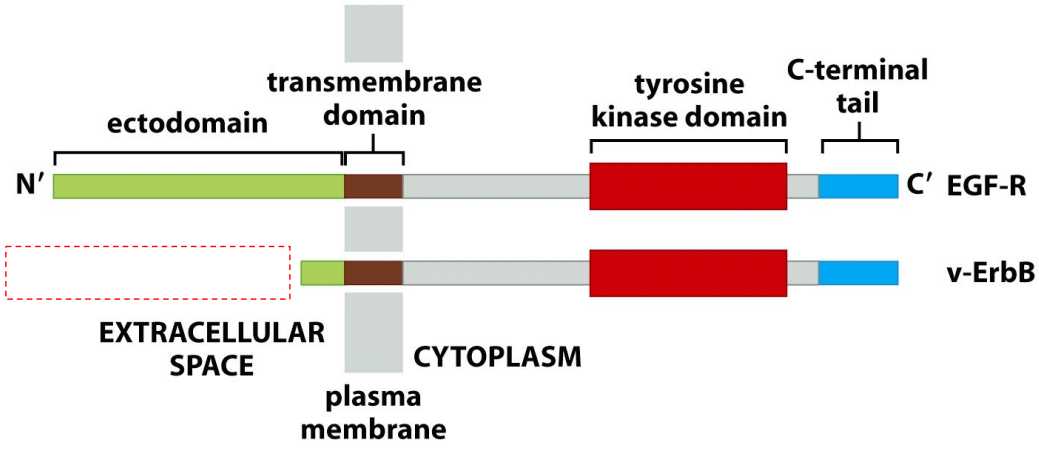
EGFR **mutation hot spots** differ in glioblastoma compared to lung cancer:






## v-ErbB has constitutive tyrosine kinase activity

- the v-ErbB oncogene from erythroblastosis virus induces leukemias of red blood cell precursors
- v-ErbB lacks an inhibitory extracellular domain:




- this suggested that RTKs may become oncogenic by hyperactivation

# RTKs can become hypersensitive to, or even independent of ligands by mutations *or* by overexpression

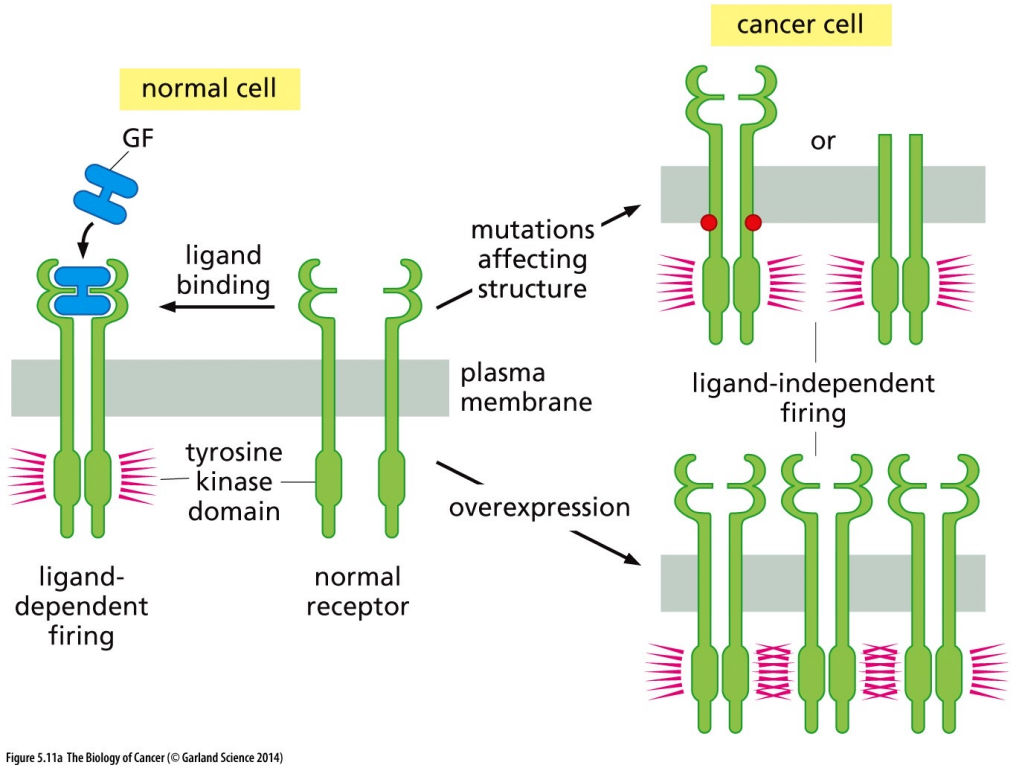



Figure 5.11a The Biology of Cancer (© Garland Science 2014)

# Mutation *or* overexpression of certain RTKs in cancer cells reduces their dependence on RTK ligands

| Type of Alteration | EGFR |
|---|---|
| *Overexpression* | |
| Gene amplification | SCC head & neck glioblastoma |
| *Mutation* | |
| Extracellular domain | Glioblastoma |
| Kinase domain | NSCLC |

Barrier: Limited growth factor supply

- Even seemingly disparate cancers may share some fundamental capabilities ("Hallmarks")
- Complexity reflects a spectrum of biological solutions to overcome tissue-specific and common barriers




# Mutation *or* overexpression of certain RTKs in cancer cells reduces their dependence on RTK ligands

**Table 5.2** Tyrosine kinase GF receptors altered in human tumors[a]

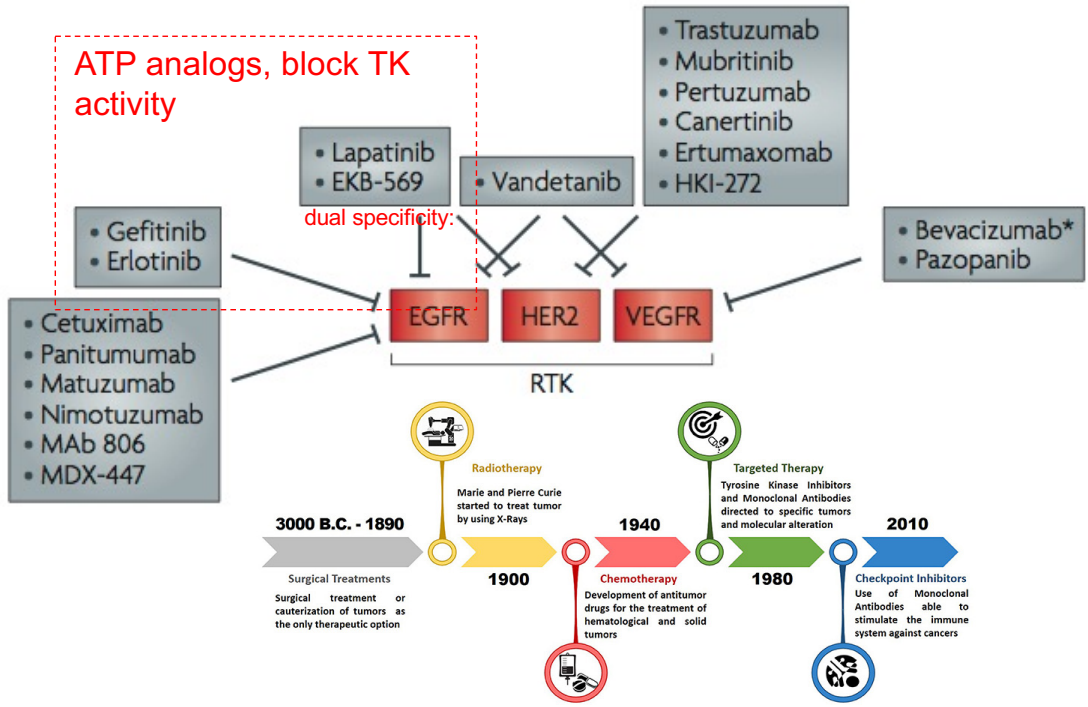
| Name of receptor | Main ligand | Type of alteration | Types of tumor |
|---|---|---|---|
| EGF-R/ErbB1 | EGF, TGF-α | overexpression | non-small cell lung cancer; breast, head and neck, stomach, colorectal, esophageal, prostate, bladder, renal, pancreatic, and ovarian carcinomas; glioblastoma |
| EGF-R/ErbB1 | | truncation of ectodomain | glioblastoma, lung and breast carcinomas |
| ErbB2/HER2/Neu | NRG, EGF | overexpression | 30% of breast adenocarcinomas |
| ErbB3, 4 | various | overexpression | oral squamous cell carcinoma |
| Flt-3 | FL | tandem duplication | acute myelogenous leukemia |
| Kit | SCF | amino acid substitutions | gastrointestinal stromal tumor |
| Ret | | fusion with other proteins, point mutations | papillary thyroid carcinomas, multiple endocrine neoplasias 2A and 2B |
| FGF-R3 | FGF | overexpression; amino acid substitutions | multiple myeloma, bladder and cervical carcinomas |

[a]See also Figure 5.17.

Overexpression of RTKs *frequently* results from *gene amplification*



# Therapeutic opportunities




Liu et al. 2009 Nat Rev Drug Discov

# 1st generation RTK inhibitors in the clinic

| Type of Alteration | EGFR | ErbB2 (a.k.a. HER2) | Targeted Drug |
|---|---|---|---|
| *Overexpression* | | | |
| Gene amplification | SCC head & neck glioblastoma | Breast, ovarian, gastric, salivary | ErbB2 antibody trastuzumab for breast cancer |
| *Mutation* | | | |
| Extracellular domain | Glioblastoma | Not found | |
| Kinase domain | NSCLC | NSCLC | EGFR TKI gefitinib and erlotinib for NSCLC |

- (Only) 30% of HER2+ patients respond to Trastuzumab (anti-HER2 Ab)
- Initial response rate of NSCLC to Gefitinib: 71%, but transient

→ Mechanisms of primary (innate) and acquired drug resistance?

Hynes 2009 Discovery Medicine

---

- 2nd generation EGFR/HER inhibitor (Afatinib): Irreversible
- Acquired resistance: New resEGFRm (e.g. T790M)

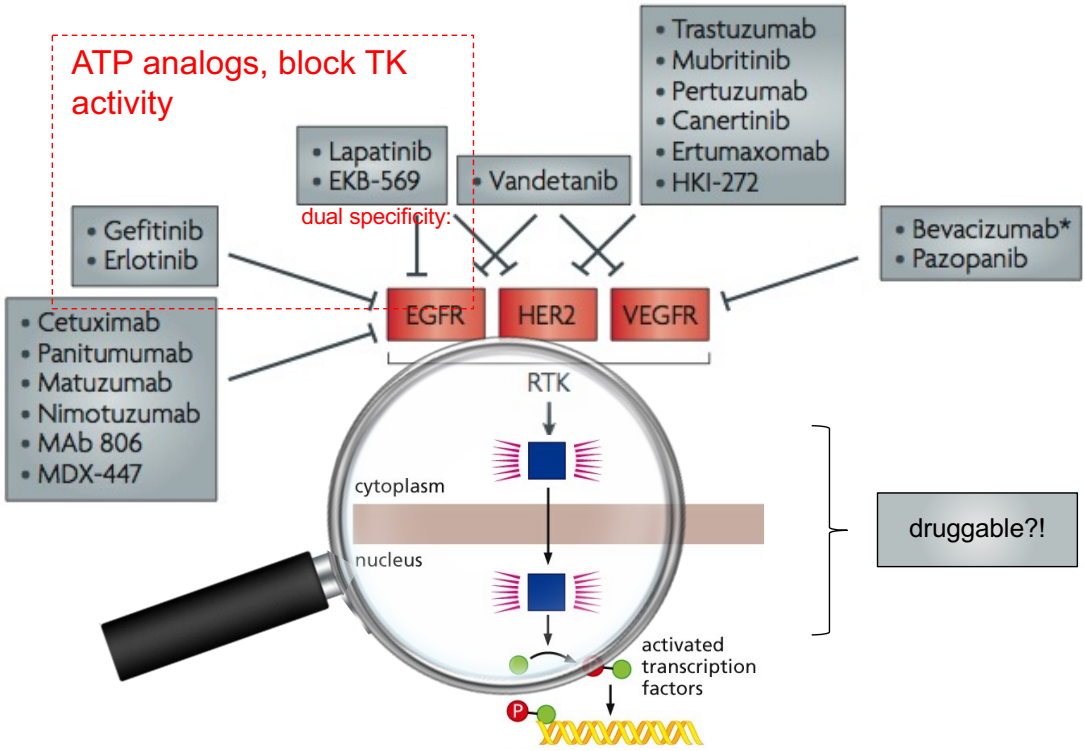
**Table 1** Generations of EGFR/HER-TKIs for NSCLC

| FDA approval | Generation | TKIs | Mechanism of action | Molecular targets |
|---|---|---|---|---|
| 2003 | First-generation EGFR/HER-TKIs | Gefitinib[22,24,25] | 4-Anilino-quinazoline; reversible | *EGFR*$^{L858R}$, *EGFR*$^{Del19}$ |
| | | | Resistance within <12 months (frequent: T790M) | |
| 2004 | | Erlotinib[24,25] | Problem: | |
| 2013 | Second-generation EGFR/HER-TKIs | Afatinib[25,26] | Anilino-quinazoline (with acrylamide group); covalent; irreversible | wt*EGFR* (Cys-797), *EGFR*$^{L858R}$, *EGFR*$^{L858R/T790M}$, *EGFR*$^{L858R/T854A}$, wt*HER2* (Cys805), *HER2* amplification, *HER4* (Cys803) |
| 2018 | | Dacomitinib[25,27] | Anilino-quinazoline (with electrophilic motif); covalent; irreversible | *EGFR*$^{L858R}$, *EGFR*$^{Del19}$, *EGFR*$^{T790M}$ wt*HER2*, mutant-*HER2*, *HER2* amplification, *HER4* |
| | | Neratinib[28–30] | Quinoline (with cyano group); covalent; irreversible | *EGFR*$^{L858R}$, *EGFR*$^{T790M}$, *HER2*, *HER4* |
| 2017 | Third-generation EGFR/HER-TKIs | Osimertinib[25,31] | Mono-anilino-pyrimidine; covalent, irreversible | *EGFR*$^{L858R}$, *EGFR*$^{Del19}$, *EGFR*$^{T790M}$ |

- Primary Gefitinib resistance (30%)
  - Pre-existing res*EGFR*m, or:
  - *KRAS* mutations, *PTEN* losses, *PIK3CA* mutations, *BIM* deletion, and 60% unknown factors

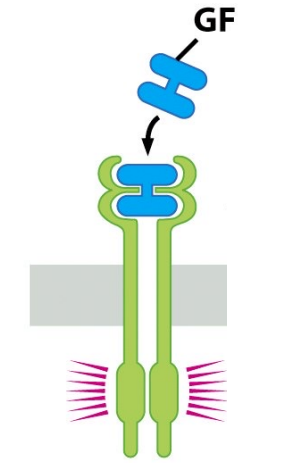
Wang et al., OncoTargets and Therapy 2016:9 5461–5473

# Therapeutic opportunities




Liu et al. 2009 Nat Rev Drug Discov

# How does RTK phosphorylation promote signal transduction ?




**ligand-dependent firing**

How?

TODAY

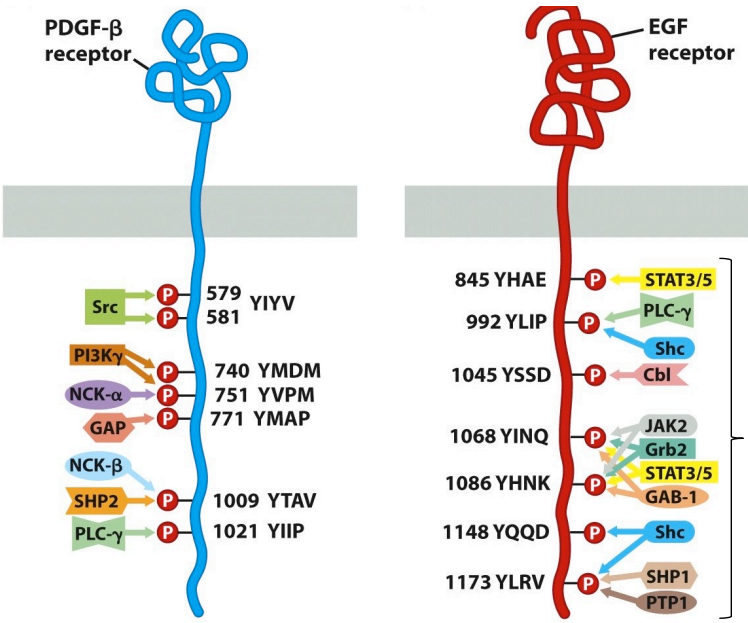
## Hallmark capability 1: Sustained proliferative signaling

Weinberg, selected parts of chapters 5 & 6


- ☑ Receptor tyrosine kinases (RTK)
  - ✓ Discovery
  - ✓ Oncogenic mutations
  - ✓ Therapeutic inhibitors
- ❑ RTK signal transduction
  - Ras family of small GTPases
  - Drugging oncogenic KRAS
  - PI3K/Akt signaling (Ras effectors)



## *Multiple* p-Tyr residues recruit *diverse* partner proteins

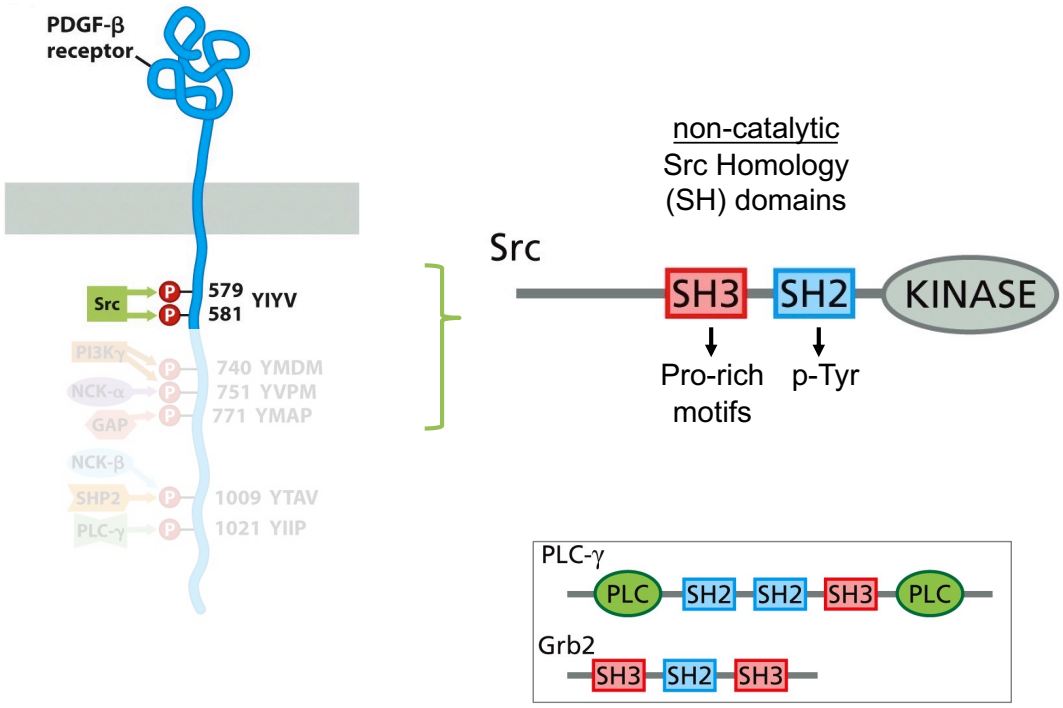



Docking sites for multiple proteins

=> opportunities to modulate signal transduction

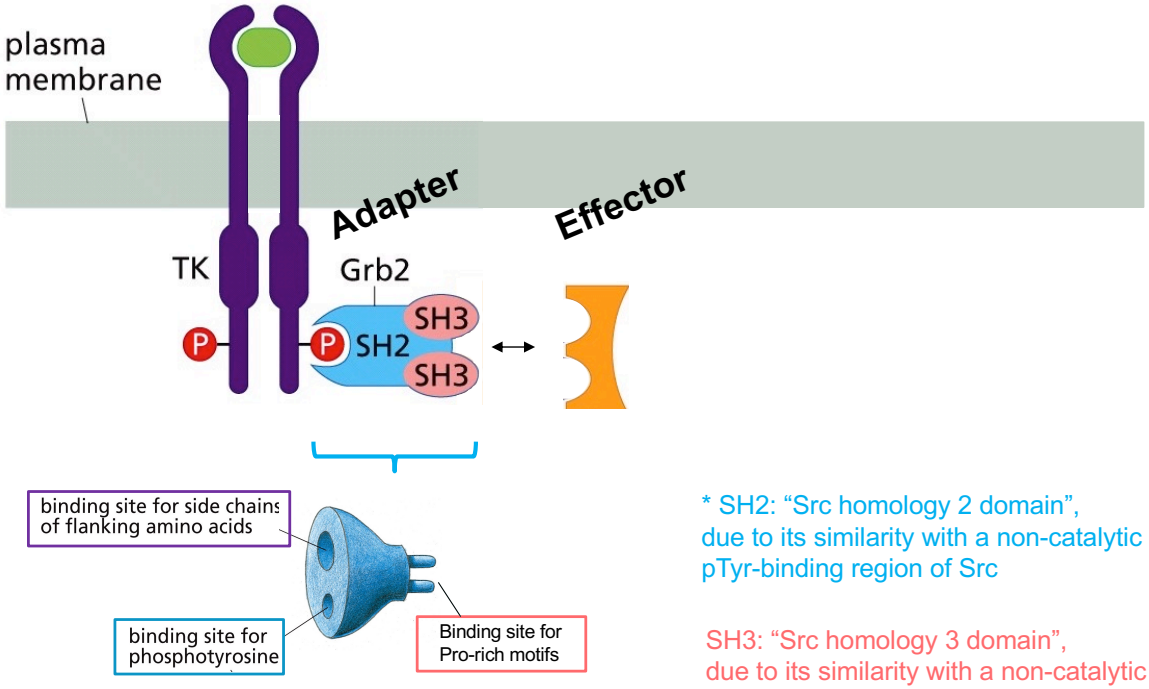
*Code* of p-Tyr modifications → signal specificity

# Protein domains that bind specific P-Tyr sequence motifs
## Example #1: SH2 domains of Src






## Example #2:
## Growth Factor Receptor Bound Protein 2 (Grb2)




* SH2: "Src homology 2 domain", due to its similarity with a non-catalytic pTyr-binding region of Src

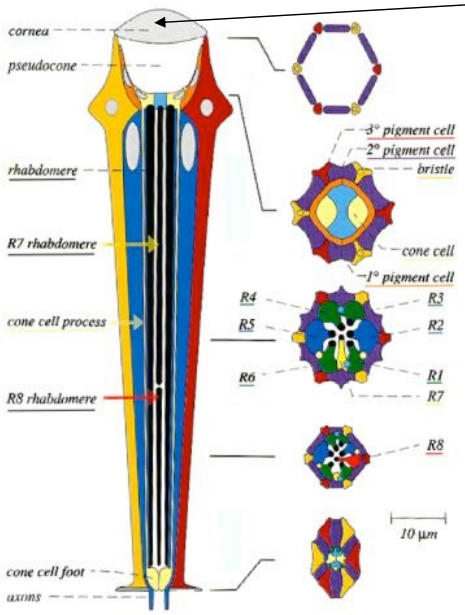
SH3: "Src homology 3 domain", due to its similarity with a non-catalytic Proline-binding region of Src

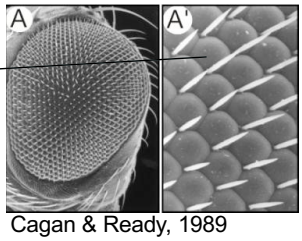


Figure 6.12 *The Biology of Cancer* (© Garland Science 2014)

# Genetic screening for RTK signal transduction components

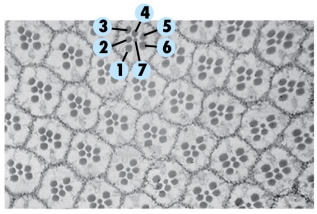
The *Drosophila* compound eye:
~800 ommatidia with 8 photoreceptor neurons each:




Cagan & Ready, 1989

Cross-section:

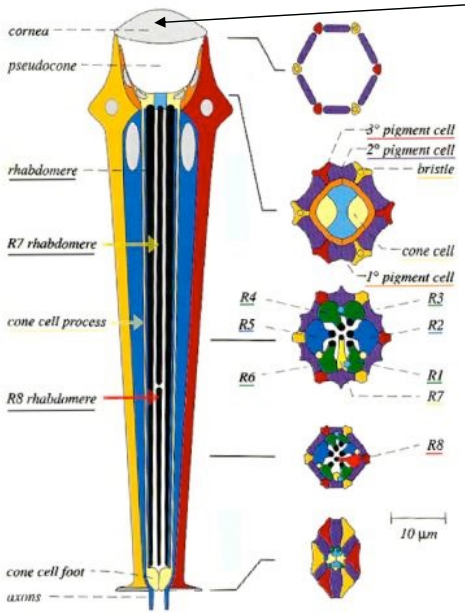


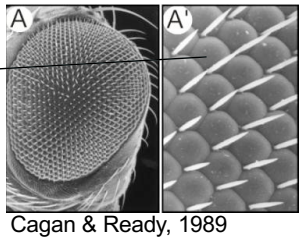

**wild type**



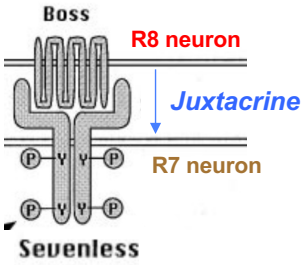
# Genetic screening for RTK signal transduction components

The *Drosophila* compound eye:
~800 ommatidia with 8 photoreceptor neurons each:



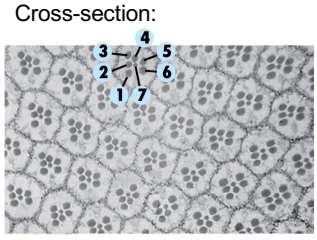



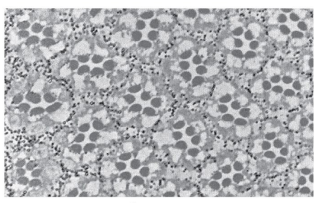

Cagan & Ready, 1989




Bride-of-sevenless (BOSS) binding to **Sevenless (RTK)** specifies R7 cell fate

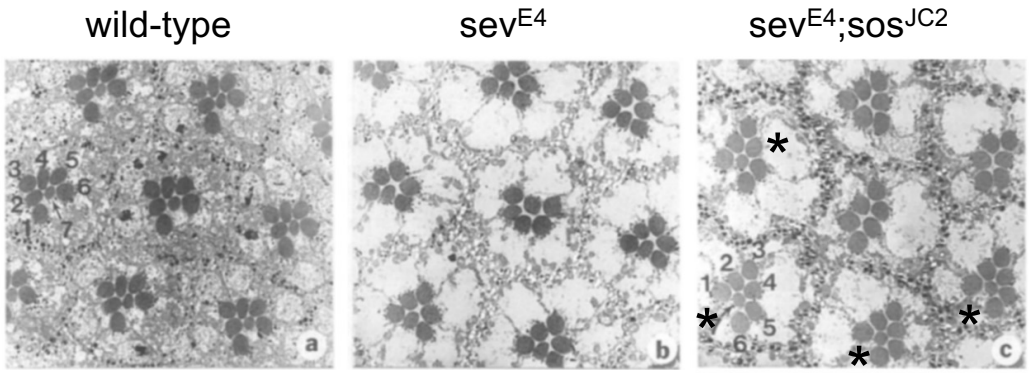
Cross-section:



**wild type** ***sevenless* mutant**

## Rescue of sevenless mutant ommatidia by Sos gain-of-function




Definition of *gain-of-function* mutations:
Increased or prolonged activity compared to wild-type

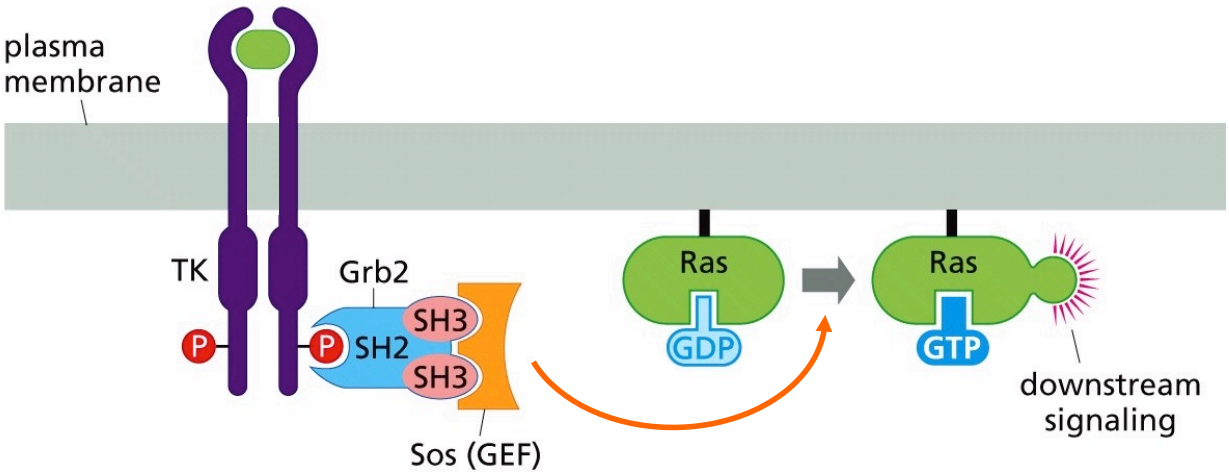
→ What does this rescue of the R7 fate prove about the role of Sos?

→ Sos was shown in the same study to also function in EGFR signaling

Rogge et al. (1991) Cell 1:39-48



## p-EGFR recruits Son-of-sevenless (Sos) to activate Ras

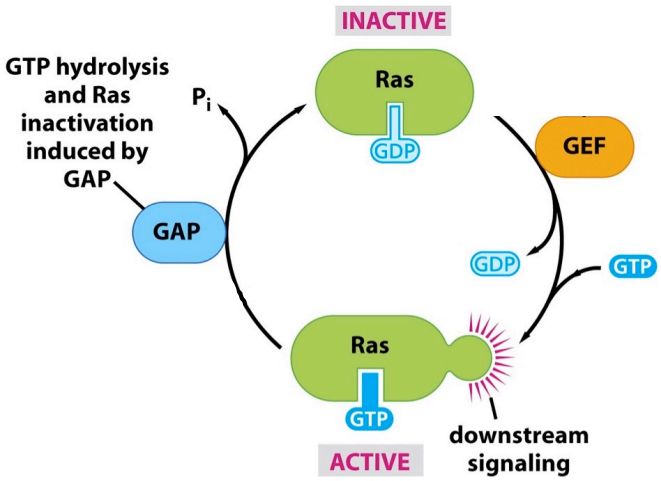



- Grb2 mediates recruitment of the ***guanine exchange factor Sos***
- The resulting proximity to Sos activates the membrane-anchored **small GTPase Ras**

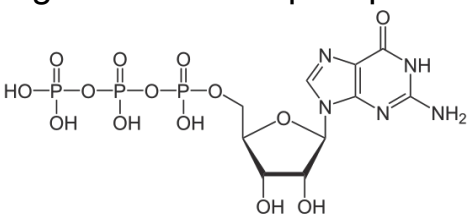


Figure 6.12 *The Biology of Cancer* (© Garland Science 2014)

# Sos activates Ras by exchanging GDP for GTP




guanosine-5'-triphosphate

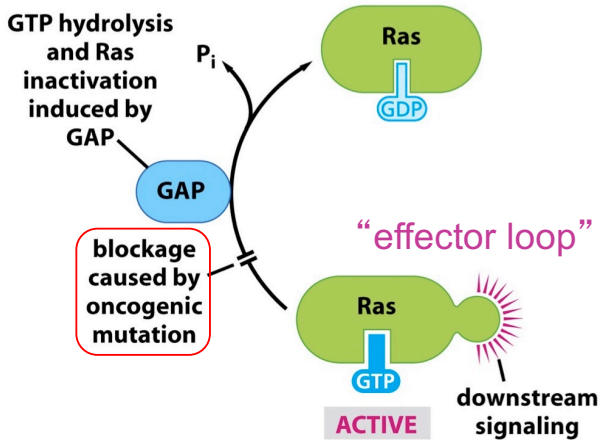


- Small GTPases are switched ON by Guanine Exchange Factors (GEF)
- Ras switches itself OFF when it binds GTPase-activating protein (GAP)
  => This ensures a defined, transient signal duration !



# Oncogenic mutations lock Ras in the GTP-bound, active form

*(most important!)*




Activating mutations in Ras are found in 20-25% of all human tumors and up to 90% in specific tumor types.

- Gly12 and Gln61 interact with GTP
- mutations in either of these residues block GTP *hydrolysis*

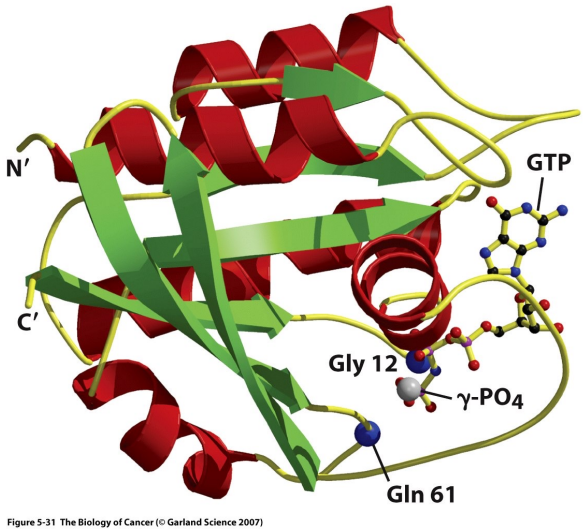



Figure 5-31 The Biology of Cancer (© Garland Science 2007)

## In the absence of ERBB signaling, G12 mutant KRAS fails to induce lung tumors

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

### Afatinib restrains K-RAS–driven lung tumorigenesis

Herwig P. Moll[1], Klemens Pranz[2], Monica Musteanu[3], Beatrice Grabner[2], Natascha Hruschka[2], Julian Mohrherr[2], Petra Aigner[2], Patricia Stiedl[2], Luka Brcic[4], Viktoria Laszlo[5,6], Daniel Schramek[7,8,9], Richard Moriggl[2,10,11], Robert Eferl[12], Judit Moldvay[13], Katalin Dezso[14], Pedro P. Lopez-Casas[3], Dagmar Stoiber[2,15], Manuel Hidalgo[3], Josef Penninger[7], Maria Sibilia[12], Balázs Győrffy[16], Mariano Barbacid[3], Balázs Dome[5,6,13,17], Helmut Popper[4], Emilio Casanova[1,2]*



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

### The ERBB network facilitates KRAS-driven lung tumorigenesis

Björn Kruspig[1]*, Tiziana Monteverde[1]*, Sarah Neidler[1], Andreas Hock[2], Emma Kerr[3], Colin Nixon[2], William Clark[2], Ann Hedley[2], Sarah Laing[1], Seth B. Coffelt[1], John Le Quesne[4], Craig Dick[1,5], Karen H. Vousden[2], Carla P. Martins[3], Daniel J. Murphy[1,2†]



See today's exercise, question 4

Cancer Cell. 2020 Jan 13;37(1):3-4. doi: 10.1016/j.ccell.2019.12.009.

### Sticking it to KRAS: Covalent Inhibitors Enter the Clinic

Frank McCormick [1]

(= phase I trials, 2019)

### KRAS inhibitors, approved

Rafael Rosell, Andrés Aguilar, Carlos Pedraz & Imane Chaib

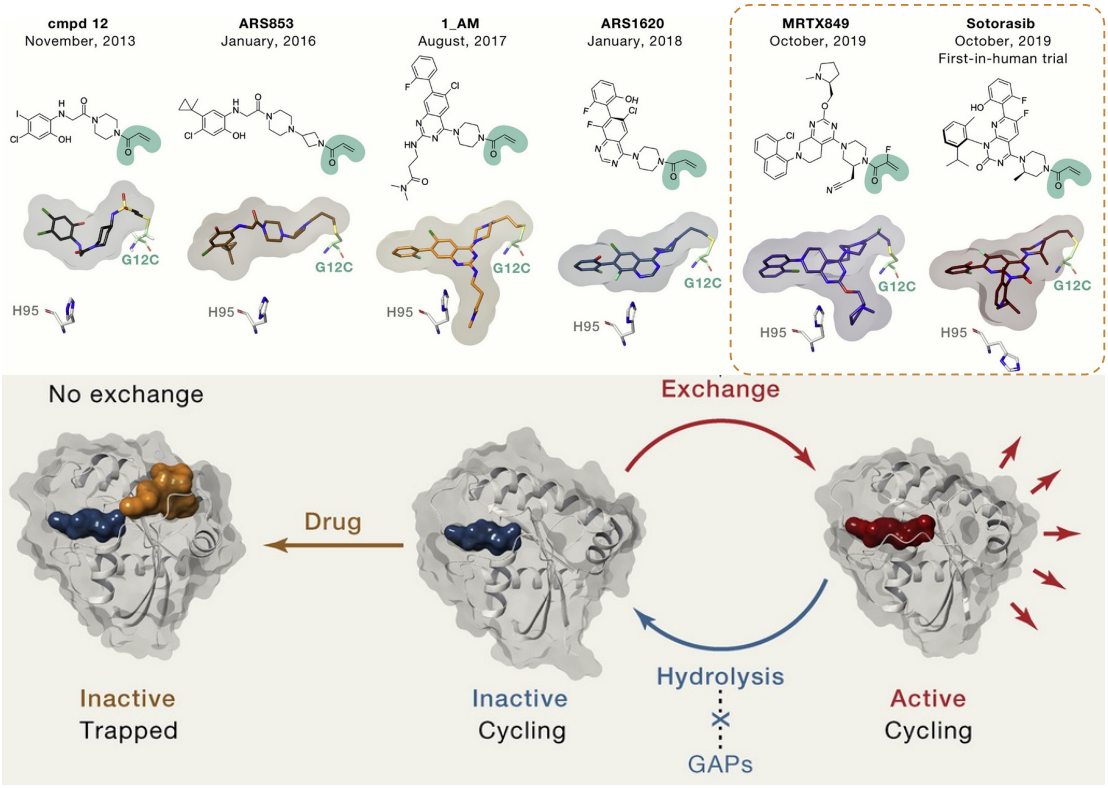
*Nature Cancer* **2**, 1254–1256 (2021) | Cite this article



**FDA approvals**

May 2021: sotorasib (Amgen)
February 2022: adagrasib (Mirati Therapeutics):

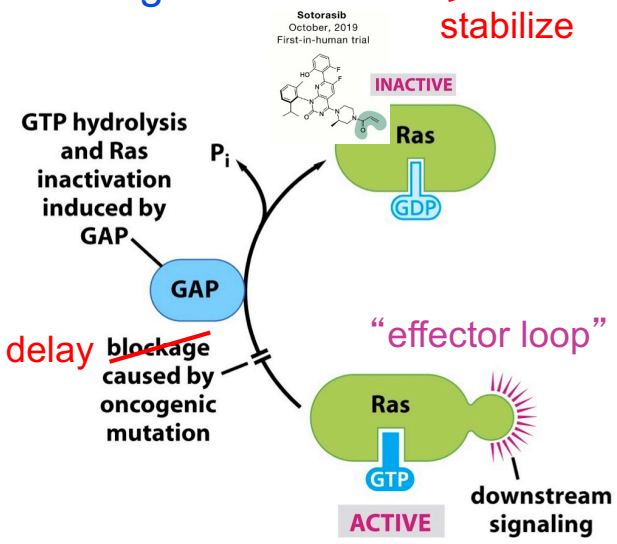
# Targeting G12>**C** mutant KRAS
# (found in 13% of Non-Small Cell Lung Cancer)



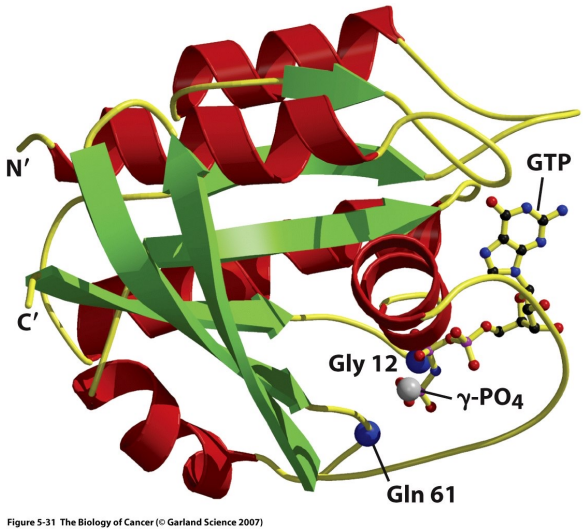

Kim et al. 2020, Cell 183:850-859

# Oncogenic mutations ~~lock~~ Ras in the GTP-bound, active form

stabilize




- Gly12 and Gln61 interact with GTP
- mutations in either of these residues ~~block~~ GTP *hydrolysis*
  delay




Activating mutations in Ras are found in 20-25% of all human tumors and up to 90% in specific tumor types.

## TODAY

# Hallmark capability 1: Sustained proliferative signaling

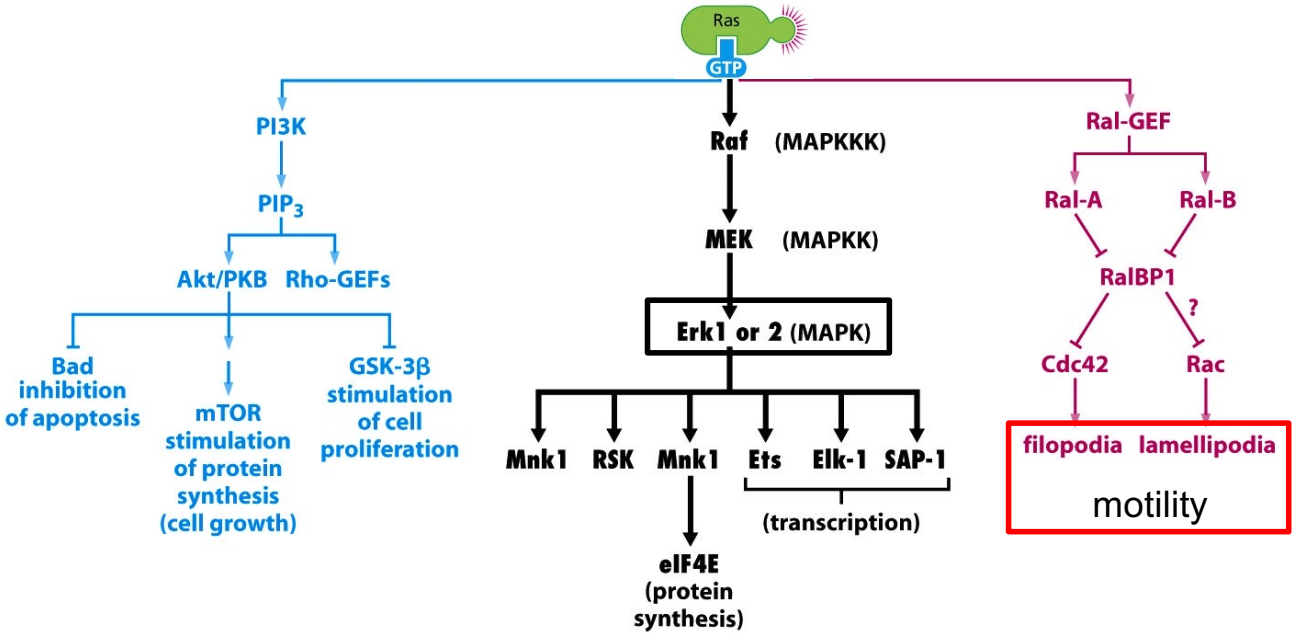
## Weinberg, selected parts of chapters 5 & 6


- ☑ Receptor tyrosine kinases (RTK)
  - ✓ Discovery
  - ✓ Oncogenic mutations
  - ✓ Therapeutic inhibitors
- ❑ RTK signal transduction
  - ✓ Ras family of small GTPases
  - ✓ Drugging oncogenic KRAS
  - • PI3K/Akt signaling (Ras effectors)



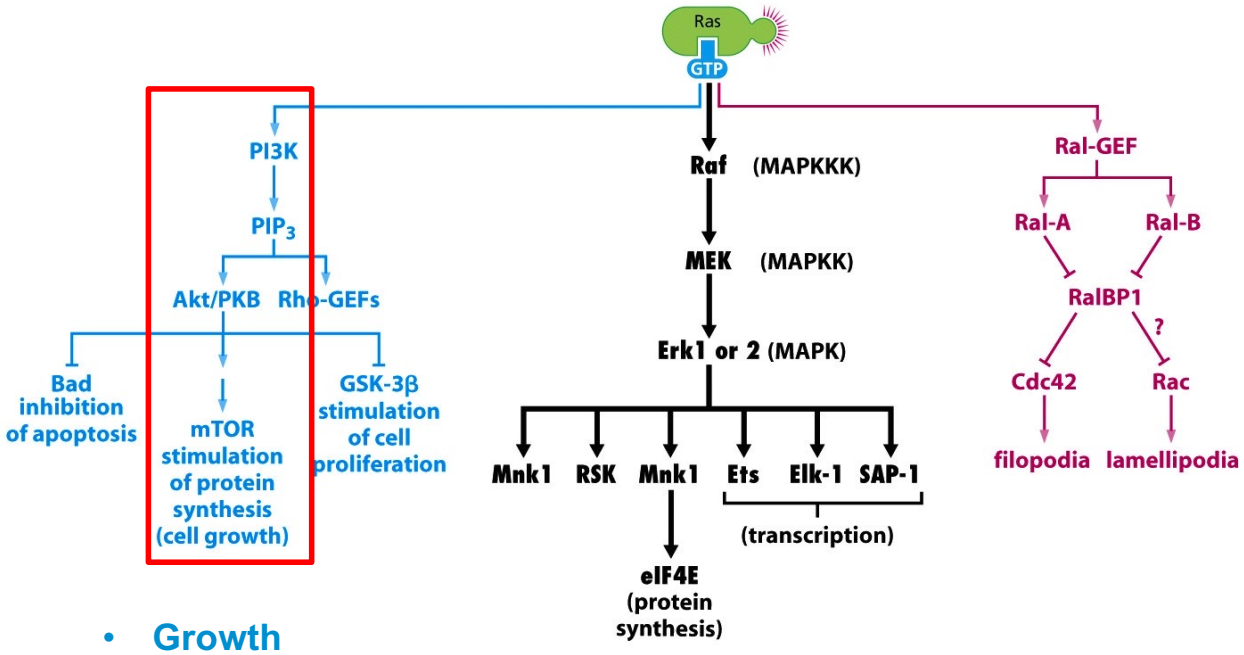
## Active Ras binds and stimulates at least 3 important effectors

*(Of prime importance to understand diverse RTK signaling outputs!)*




ERKs: extracellular-signal-regulated kinases
➔ Cell differentiation and/or proliferation
➔ Oncogene-induced senescence (protective)

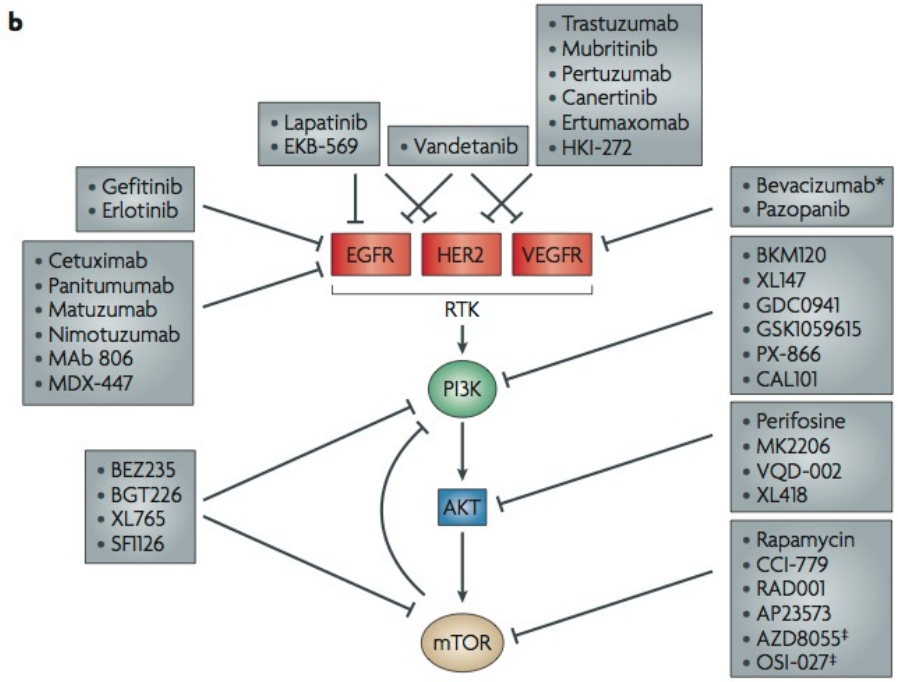
# PI3K/Akt signaling branch




- **Growth**
- **Proliferation**
- **Survival**



# Therapeutics: e.g. RTK/PI3K/mTOR pathway inhibitors

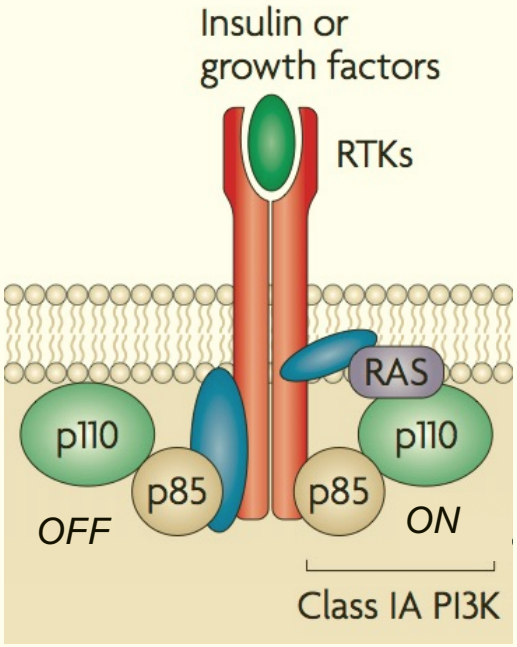



Liu et al. 2009 Nat Rev Drug Discov

# Activation of PI3K by p-RTK and Ras at the plasma membrane

**p110α (*PIK3CA* gene)**

- inhibited by p85 subunit
- p-RTK and Ras overcome inhibition by p85
- p110α is uncoupled from p85 inhibition in many cancers by activating mutations




⇒ is PI3K a good drug target?

⇒ What side effects need to be ruled out?



Liu et al. 2009 Nat Rev Drug Discov

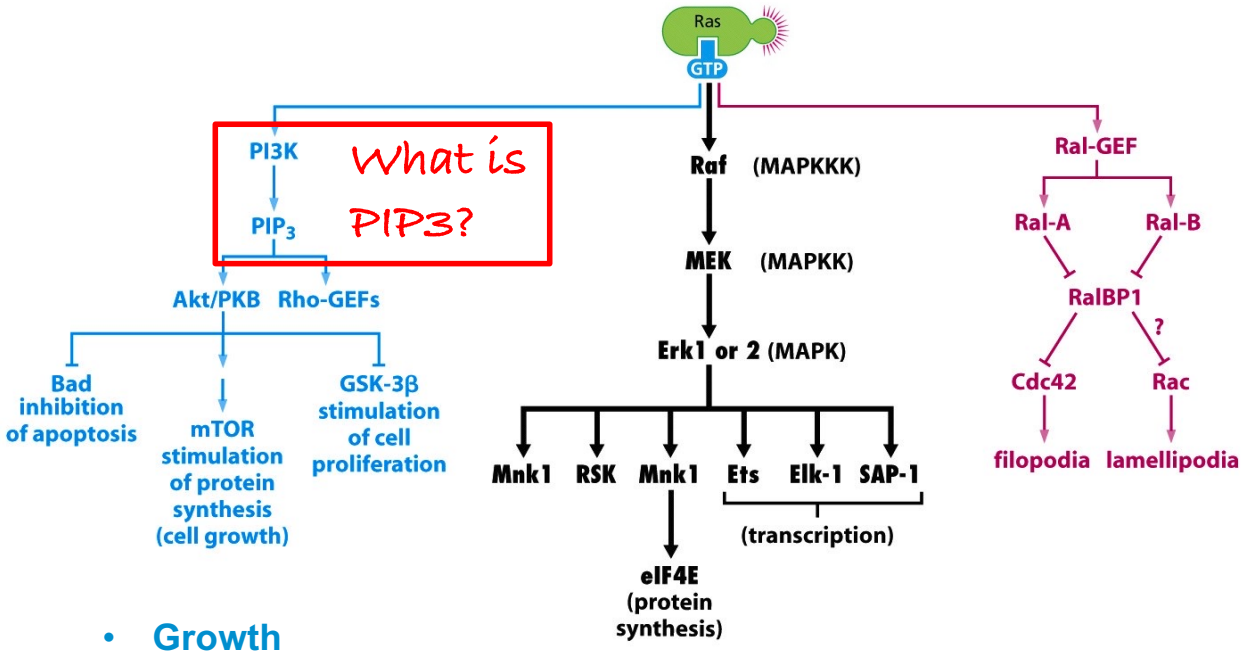
**Table 1** Completed randomized trials of PI3K and AKT inhibitors in breast cancer

| Trial | Phase | Treatment | Targeted therapy | Patient population | Outcomes (therapy vs placebo) |
|---|---|---|---|---|---|
| BELLE-2 | III | Buparlisib or placebo + fulvestrant | Pan-PI3K inhibitor | HR+/HER2− locally advanced or MBC, resistant to AI ($n = 1147$) | PFS 6.9 months vs 5 months (HR 0.78; $p = 0.00021$)<br>PFS 6.8 months vs 4 months in PI3K mutated (HR 0.76; $p = 0.014$) |
| BELLE-3 | III | Buparlisib or placebo + fulvestrant | Pan-PI3K inhibitor | HR+/HER2− locally advanced or MBC, resistant to mTOR inhibitor ($n = 432$) | PFS 3.9 months vs 1.8 months (HR 0.67; $p = 0.0003$) |
| BELLE-4 | II/III | Buparlisib or placebo + paclitaxel | Pan-PI3K inhibitor | HER2− locally advanced or MBC ($n = 416$) | PFS 8.0 months vs 9.2 months (HR 1.18)<br>PFS 9.1 months vs 9.2 months in PI3K mutated (HR 1.17) |
| FERGI | II | Pictilisib or placebo + fulvestrant | Pan-PI3K inhibitor | Advanced or MBC, resistant to AI | PFS 6.6 months vs 5.1 months (HR 0.74; $p = 0.096$)<br>PFS 6.5 months vs 5.1 months in PI3K mutated (HR 0.74; $p = 0.268$)<br>PFS 5.8 months vs 3.6 months in non-PI3K mutated (HR 0.72; $p = 0.23$) |
| PEGGY | II | Pictilisib or placebo + paclitaxel | Pan-PI3K inhibitor | HR+/HER2− locally recurrent or MBC ($n = 183$) | PFS 8.2 months vs 7.8 months (HR 0.95; $p = 0.83$)<br>PFS 7.3 months vs 5.8 months in PI3K mutated (HR 1.06; $p = 0.88$) |
| SOLAR-1 | III | Alpelisib or placebo + fulvestrant | PI3Kα inhibitor | HR+/HER2− advanced BC, resistant to AI ($n = 572$) | PFS 11.1 months vs 3.7 months (HR 0.48)<br>PFS 11.0 months vs 5.7 months in PI3K mutated (HR 0.65; $p = 0.00065$) |
| LORELEI | II | Taselisib or placebo + letrozole | PI3Kα inhibitor | HR+/HER2− early-stage BC, neoadjuvant ($n = 334$) | ORR 50% vs 39.3% (OR 1.55; $p = 0.049$)<br>ORR 56.2% vs 38% in PI3K mutated (OR 2.03; $p = 0.033$)<br>No significant difference in pCR |
| NEO-ORB | II | Alpelisib or placebo + letrozole | PI3Kα inhibitor | HR+/HER2− early-stage BC, neoadjuvant ($n = 257$) | ORR 43% vs 45% (*PIK3CA* mutant), 63% vs 61% (*PIK3CA* wildtype)<br>pCR rates low in all groups |
| SANDPIPER | III | Taselisib or placebo + fulvestrant | PI3Kα inhibitor | HR+/HER2− locally advanced or MBC, resistant to AI ($n = 516$) | PFS 7.4 months vs 5.4 months (HR 0.70; $p = 0.0037$) |
| FAKTION | II | Capivasertib or placebo + fulvestrant | AKT inhibitor | HR+/HER2− advanced BC, resistant to AI ($n = 140$) | PFS 10.3 months vs 4.8 months (HR 0.57; $p = 0.0035$) |
| I-SPY2 | | MK-2206 or placebo + chemotherapy | AKT inhibitor | Invasive BC ≥ 2.5 on exam or ≥ 2 cm on imaging | Improved pCR rate |
| LOTUS | II | Ipatasertib or placebo + paclitaxel | AKT inhibitor | TNBC locally advanced or metastatic ($n = 124$) | PFS 6.2 months vs 4.9 months (HR 0.60; $p = 0.037$)<br>PFS 6.2 months vs 3.7 months in *PTEN*-low tumors (HR 0.59; $p = 0.18$) |

*AI* aromatase inhibitor, *BC* breast cancer, *HR+* hormone receptor-positive, *HER2−* HER2-negative, *HR* hazard ratio, *MBC* metastatic breast cancer, *OR* odds ratio, *ORR* overall response rate, *pCR* pathologic complete response, *PFS* progression-free survival, *TNBC* triple negative breast cancer (estrogen receptor negative, progesterone receptor negative, and HER2 negative)

Ellis & Ma, 2019, Curr Oncol Rep Dec 11;21(12):110. doi: 10.1007/s11912-019-0846-7

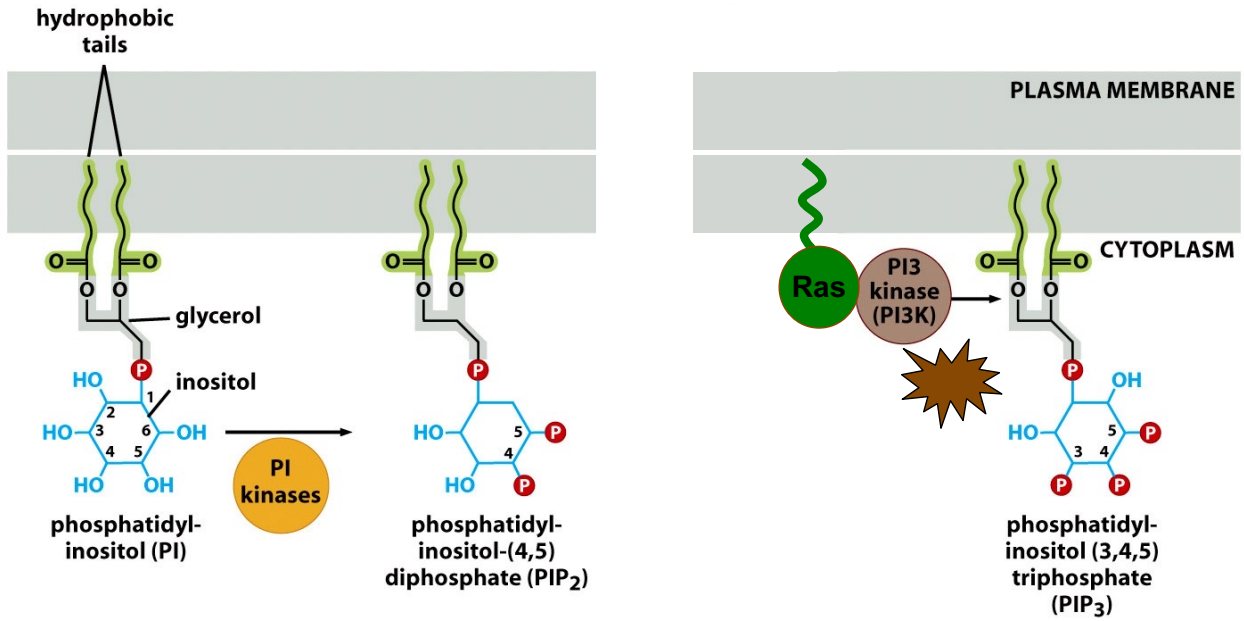
# PI3K/Akt signaling branch




- **Growth**
- **Proliferation**
- **Survival**



# Ras-activated PI3K phosphorylates the phospholipid PIP2

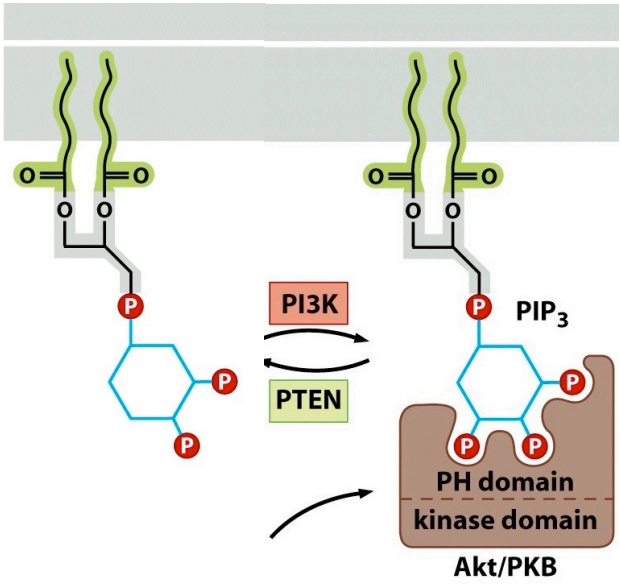



- Binding to active Ras stimulates PI3K activity
- PI3K: The phospho*lipid* kinase that converts PIP2 into PIP3

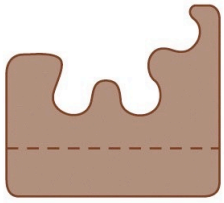


Figure 6.16b *The Biology of Cancer* (© Garland Science 2007)

# PIP3 allows membrane docking of PH-domain proteins




Pleckstrin Homology



3-Phosphoinositide-dependent kinases

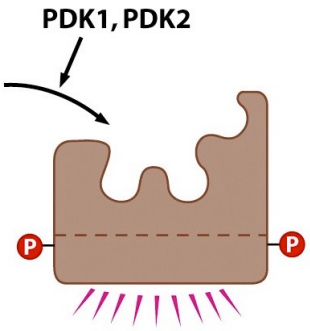
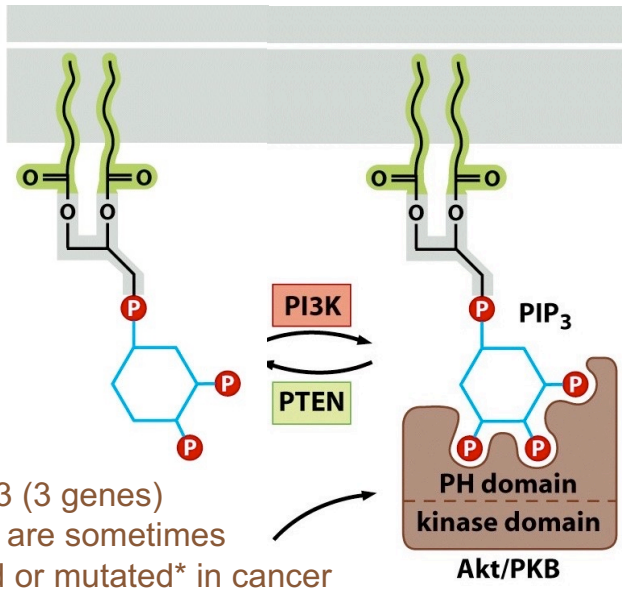





Figure 6.19a *The Biology of Cancer* (© Garland Science 2007)

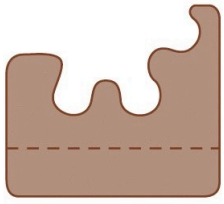
# Affinity of AKTs for PIP3 is rate-limiting for their phosphorylation





- Akt1, 2, 3 (3 genes)
- Akt1 & 2 are sometimes amplified or mutated* in cancer

Pleckstrin Homology



* e.g. E17K mutation increases the affinity of the Akt PH domain for PIP3

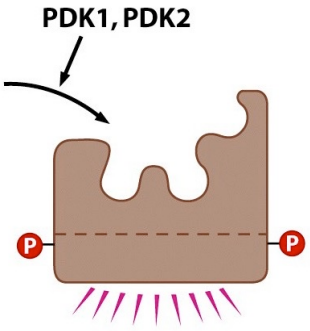





Figure 6.19a *The Biology of Cancer* (© Garland Science 2007)

# P-Akt phosphorylates *multiple* cancer-relevant substrates

**Table 6.3 Effects of Akt/PKB on survival, proliferation, and cell growth**

| Biological effect | Substrate of Akt/PKB | Functional consequence |
|---|---|---|
| *Anti-apoptotic* | | |
| | Bad (pro-apoptotic)[a] | inhibition |
| | caspase-9 (pro-apoptotic)[b] | inhibition |
| | IκB kinase (anti-apoptotic)[c] | activation |
| | FOXO1 TF (pro-apoptotic)[d] | inhibition |
| | Mdm2 (anti-apoptotic)[e] | activation |
| *Proliferative* | | |
| | GSK-3β (anti-proliferative)[f] | inhibition |
| | FOXO4 (anti-proliferative)[g] | inhibition |
| | $p21^{Cip1}$ (anti-proliferative)[h] | inhibition |
| *Growth* | | |
| | Tsc2 (anti-growth)[i] | inhibition |



Table 6.3 *The Biology of Cancer* (© Garland Science 2007)

# Questions?

## Summary I

RTKs can be dimerized by ligands, mutations or overexpression

RTK dimers transmit mitogenic signals through autophosphorylation

RTKs recruit Sos and other factors through SH domain adapters

Sos is a GEF that activates Ras

Effectors of Ras:GTP induce protein synthesis, proliferation, survival and cell shape changes:

1. PI3K (a phospholipid kinase) - Akt pathway
2. Raf (a Ser/Thr kinase) – MEK – ERK pathway
3. Ral-GEF – Ral – Rac/Cdc42 pathway

Several RTKs and some key effectors have become druggable, but efficacy and durability of targeted monotherapies remain limited



## Next week…



RTK/Ras/PI3K pathway, though frequently involved, is not the only “cyclist” that drives sustained proliferation signaling:

- ❑ JAK/STAT signaling & inhibitors
- ❑ Wnt/β-catenin signaling in colon cancer