Tutorial Session 2:
Basic Cancer Biology

Oncogenes, tumor suppressor genes, and signaling pathways involved in tumor initiation and progression

NCI Nanotechnology Alliance Investigators Meeting

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Chapel Hill, NC

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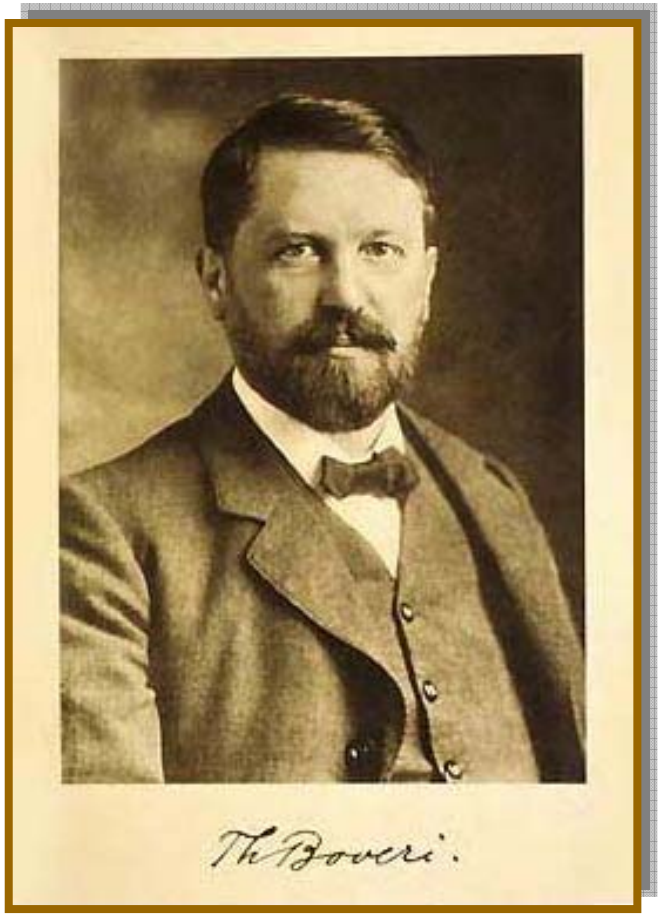
Overview

- Cancer genetics and signal tranduction - the big picture
- Cancer is a genetic disease
  - Classes of cancer genes
  - Discovery of cancer genes
- Signal transduction
  - The key players
  - The processes
- Cancer treatment - target-based signal transduction inhibitors

Cancer is a genetic disease

The big picture

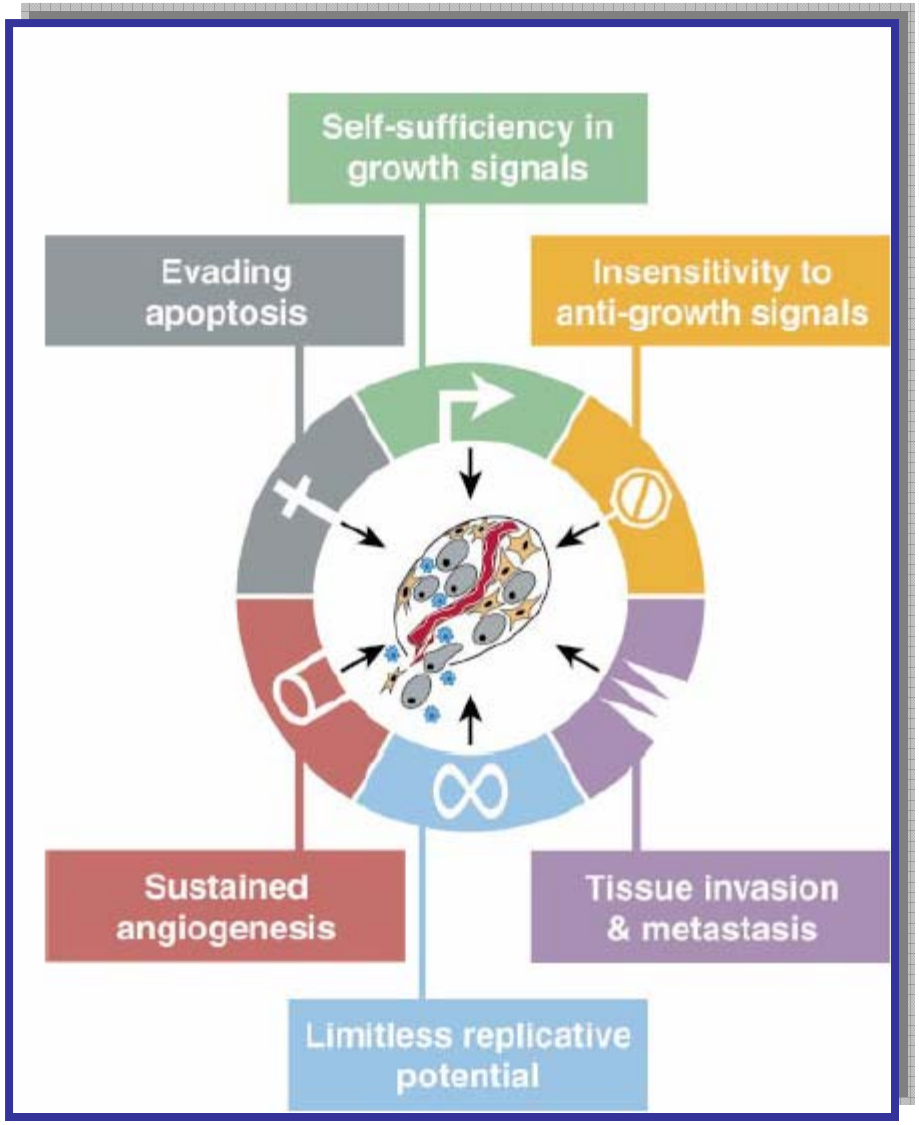
Cancer is a genetic disease



In 1914, German biologist Theodor Boveri postulated that abnormal chromosome number, or aneuploidy, might be a root cause of cancer.

By the numbers

- How many genetic mutations are required to convert a normal cell to a malignant tumor cell?
- How many cancer genes are there?
- How many protein kinases are mutated in human cancers?
- Human many cancer genes are “druggable” targets?



We suggest that the vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology…shared in common by…perhaps all types of human tumors."

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

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University of California at San Francisco
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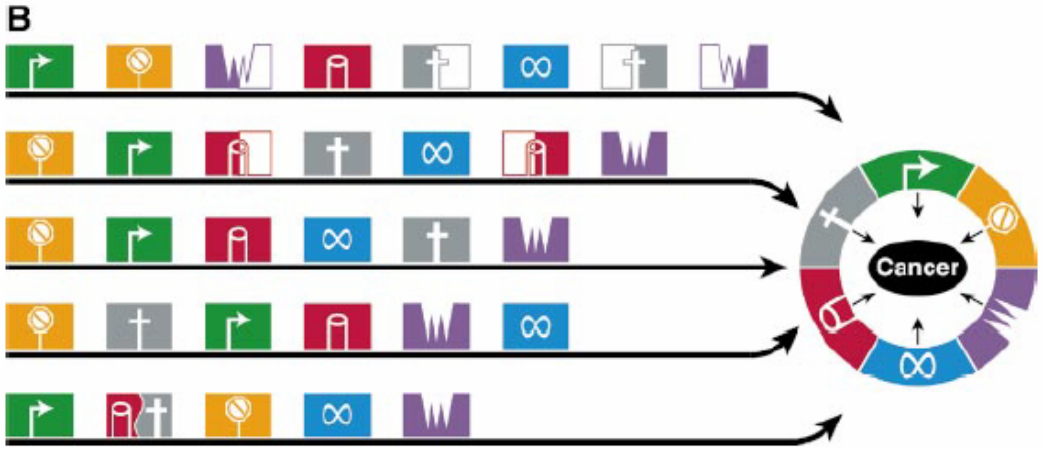
Parallel pathways of tumorigenesis

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin



- The order may differ.
- Some lesions may contribute to more than one capability (e.g., p53 mutation).
- Some capabilities may require the cooperation of multiple genetic events.

p53*

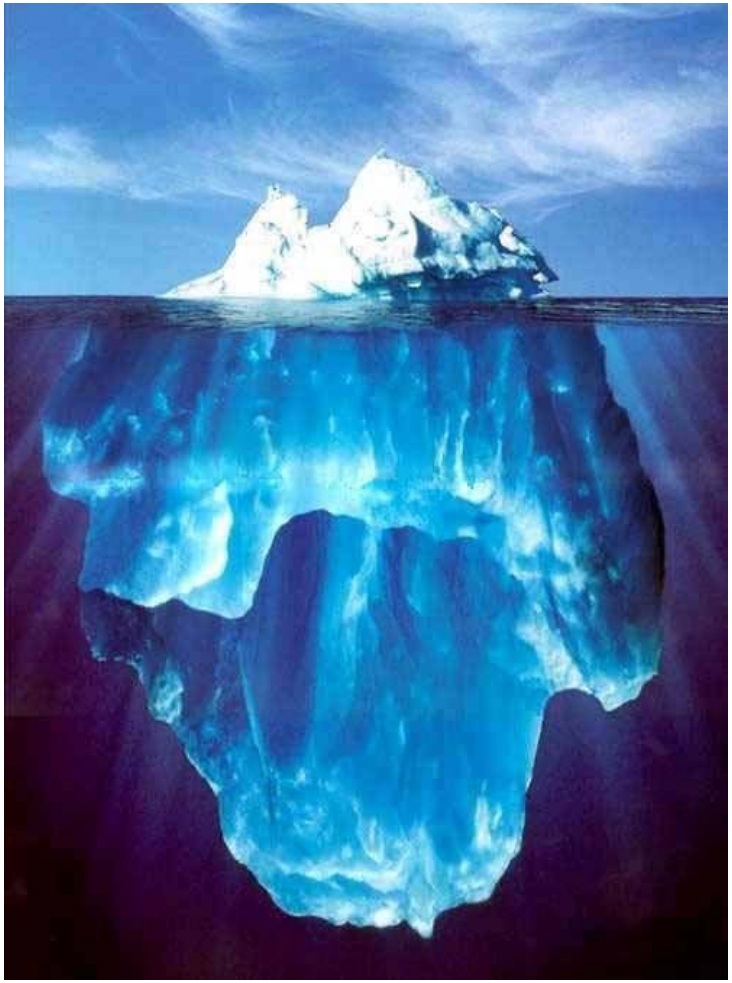
Cancer gene census

Amplification	7
Frameshift mutation	66
Large deletion	27
Missense mutation	87
Nonsense mutation	63
Other mutation	10
Splicing mutation	42
Translocation	271

Currently, more than 1% of all human genes (363) for which mutations have been causally implicated in cancer. Of these, approximately 90% have somatic mutations in cancer (326), 20% bear germline mutations (68) that predispose to cancer and 10% show both somatic and germline mutations.

http://www.sanger.ac.uk/genetics/CGP/Census/

Genetic complexity of cancer: yet more cancer targets?

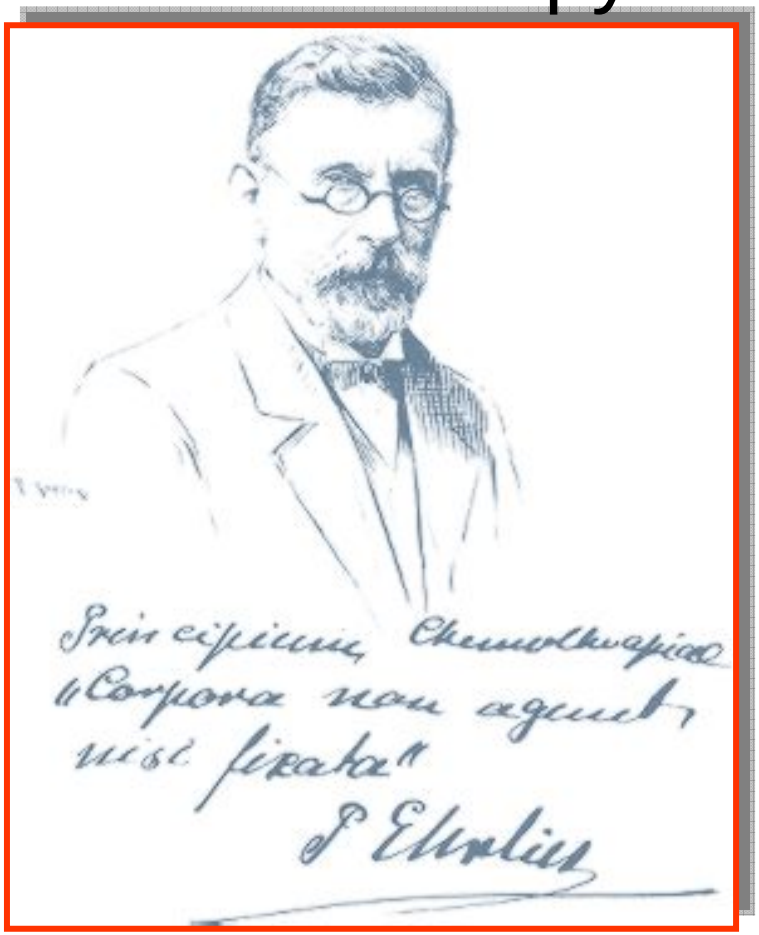


Somatic mutations represent only a subset of genetic defects in cancer cells

- Altered gene expression
- Altered protein posttranslational processing
- Alternative gene splicing
- Promoter methylation and loss of gene expression

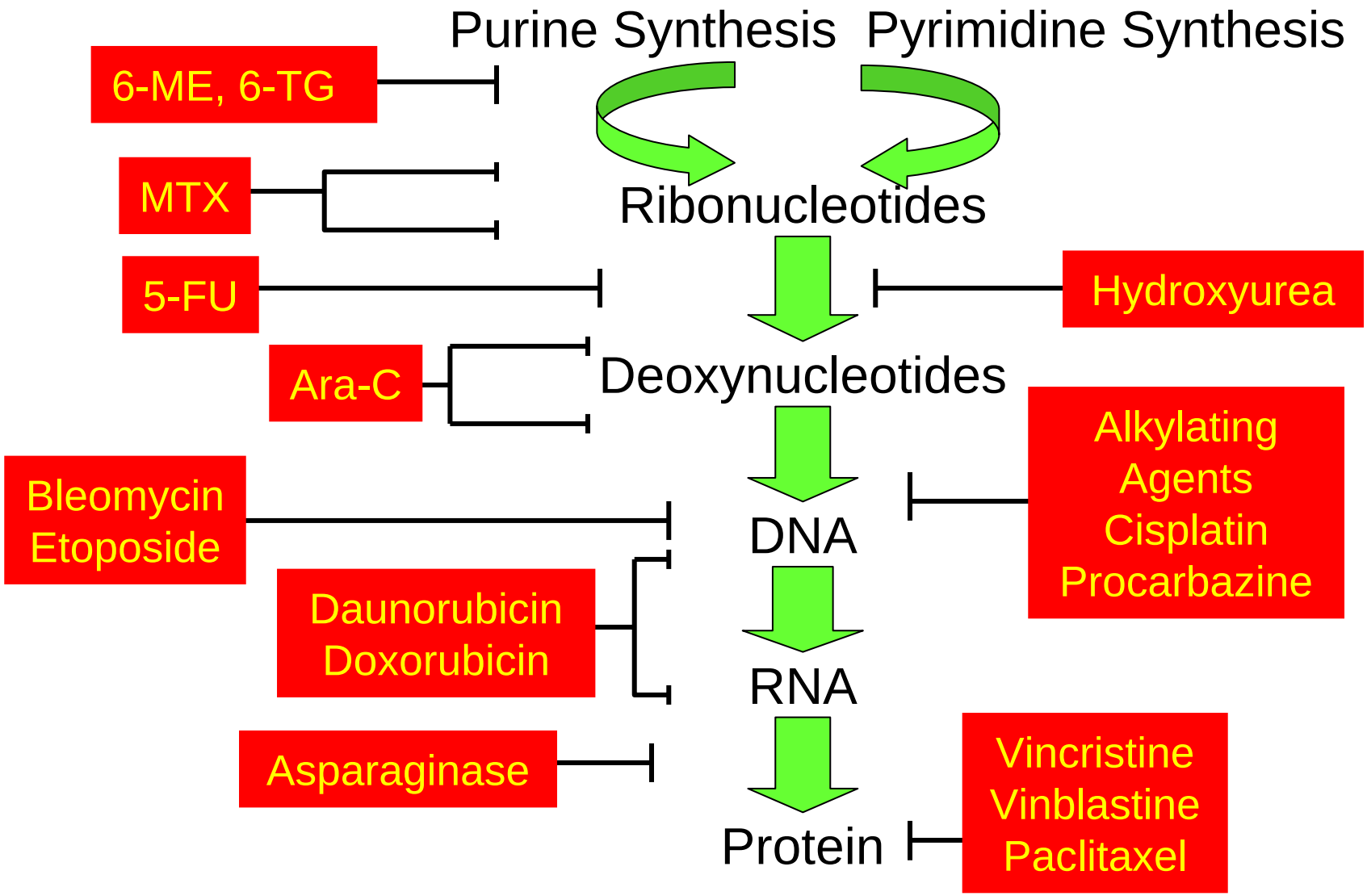
German bacteriologist was a pioneer in modern chemotherapy and hematology (Nobel Prize in 1908). He spent years studying the effects of chemicals on tissue and in search of “magic bullets” that kill the microbe or cancer cell but not the person with the disease.

"Father of Chemotherapy"



Paul Ehrlich

Targeting DNA,RNA and protein synthesis



Anticancer drugs target proliferating cells - I

- Anticancer drugs are NOT magic bullets. Ideally they should target only the cancer cells. However, they target proliferating cells whether normal or neoplastic.
- Not all cancer cells are rapidly proliferating. Of the four major types of tumors, the faster growing hematological (nonsolid) types (leukemias and lymphomas) are more responsive to treatment than the slower growing solid types (carcinomas and sarcomas).

Anticancer drugs target proliferating cells - II

- Normal cells of the hair follicles, bone marrow and intestinal epithelium are rapidly dividing and are especially sensitive to inhibition by anti-neoplastic drugs. This results in the toxic side effects common to most anticancer drugs.

FDA approval of signal transduction inhibitors: targeting protein kinases

1998 Trastuzumab inhibitor of HER2 in breast cancer

2001 Imatinib inhibitor of BCR-Abl in CML

2003 Gefitinib inhibitor of EGFR in NSCLC

2004 Cetuximab inhibitor of EGFR in CRC

2004 Bevacizumab inhibitor of VEGF CRC

2004 Erlotinib inhibitor of EGFR in NSCLC

2005 Sorafenib multi-kinase inhibitor (Raf, VEGFR, PDGFR) in renal cell cancer

2006 Sunitinib multi-kinase inhibitor (Flt3, VEGFR, PDGFR) for gastrointestinal and kidney cancer

2006 Dasatinib multi-kinase inhibitor (BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2 and PDGFR) for CML

2006 Panitumumab inhibitor of EGFR in colon cancer

2007 Lapatinib inhibitor of EGFR/HER2 for the treatment of advanced or metastatic breast cancer

Classes of FDA-approved of signal transduction inhibitors

Monoclonal antibody

Trastuzumab (Herceptin) inhibition of HER2

Cetuximab (Erbitux) inhibitor of EGFR

Bevacizumab (Avastin) inhibition of VEGF

Panitumumab inhibitor of EGFR

Small molecule

Imatinib (Gleevec) inhibition of BCR-Abl, Kit, and PDGF

Gefitinib (Iressa) inhibition of EGFR

Cetuximab (Erbitux) inhibitor of EGFR

Erlotinib (Tarceva) inhibition of EGFR

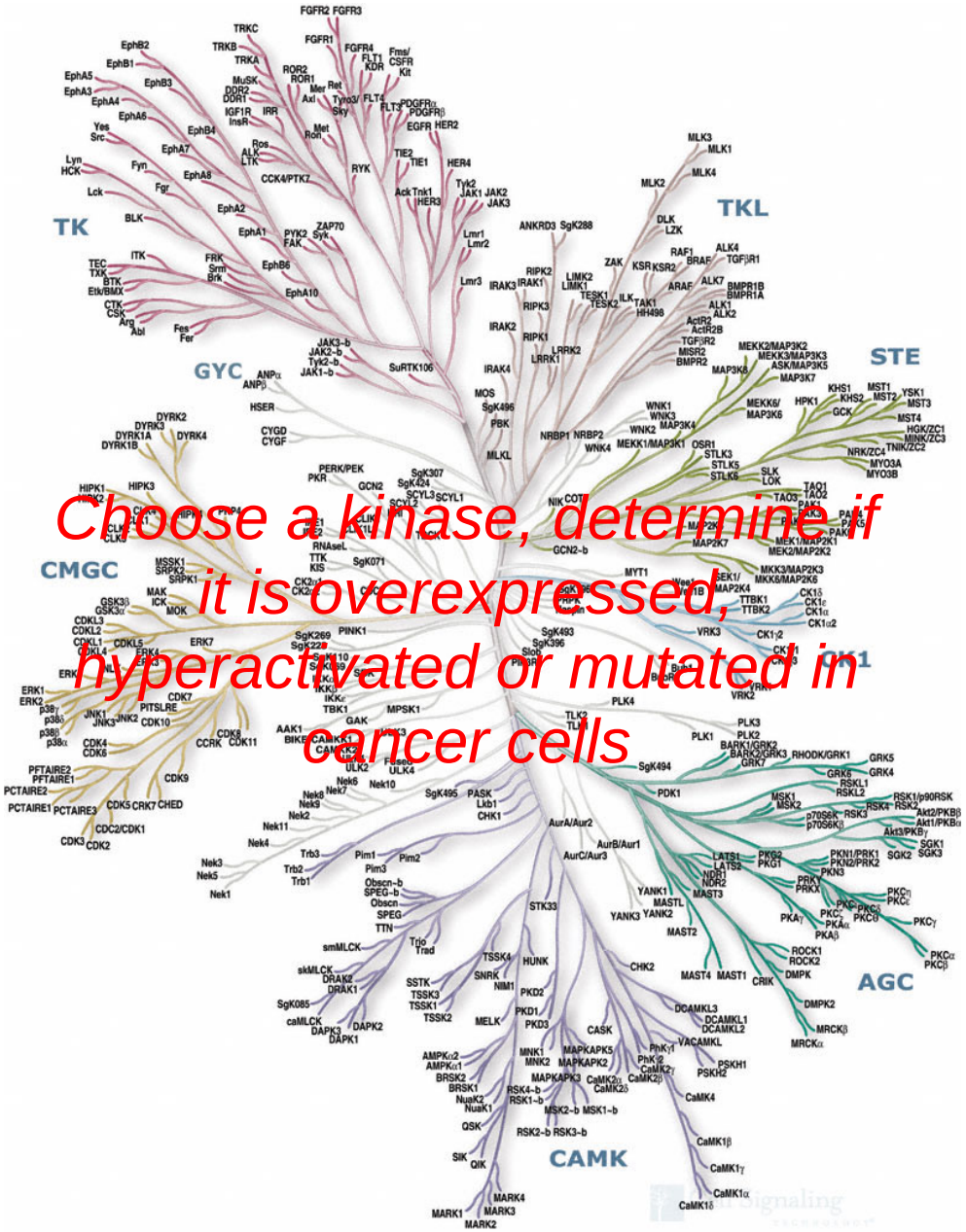
Sorafenib inhibition of c-Raf-1, B-Raf, VEGFR, PDGFR, FLT3, Kit,

Sunitinib (Vectibix) inhibition of FLT3, VEGFR, PDGFR, Kit

Dasatinib (Sprycell) inhibitor of BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2 and PDGFR

Lapatinib inhibition of EGFR, HER2

The human kinome



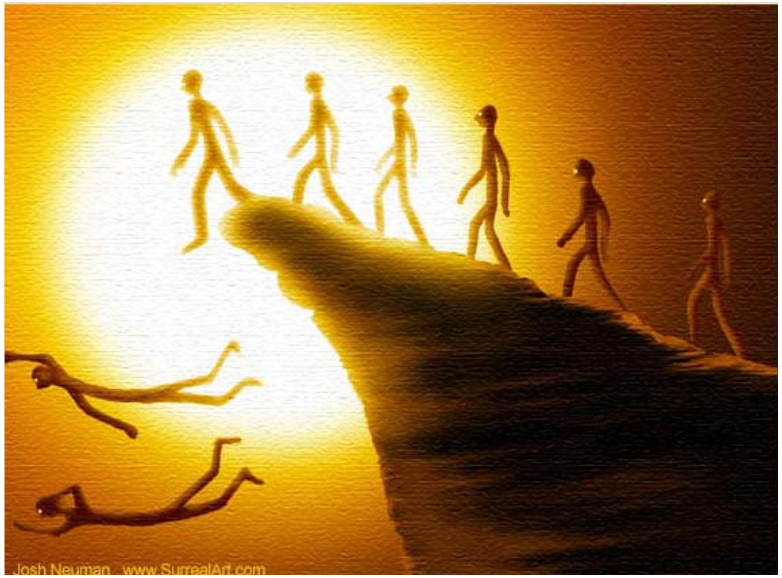
Choose a kinase, determine if it is overexpressed, hyperactivated or mutated in cancer cells

We have catalogued the protein kinase complement of the human genome (the "kinome") using public and proprietary genomic, complementary DNA, and expressed sequence tag (EST) sequences. This provides a starting point for comprehensive analysis of protein phosphorylation in normal and disease states, as well as a detailed view of the current state of human genome analysis through a focus on one large gene family. We identify 518 putative protein kinase genes…

Manning et al., The Protein Kinase Complement of the Human Genome, *Science* 2002 298: 1912-1934

http://www.cellsignal.com/reference/kinase/kinome.jsp

Protein kinases are considered the most “druggable” targets for anti-cancer drug development



Are other classes of proteins, besides cell surface receptors and ligands, and protein kinases, druggable targets?

Cancer is a genetic disease

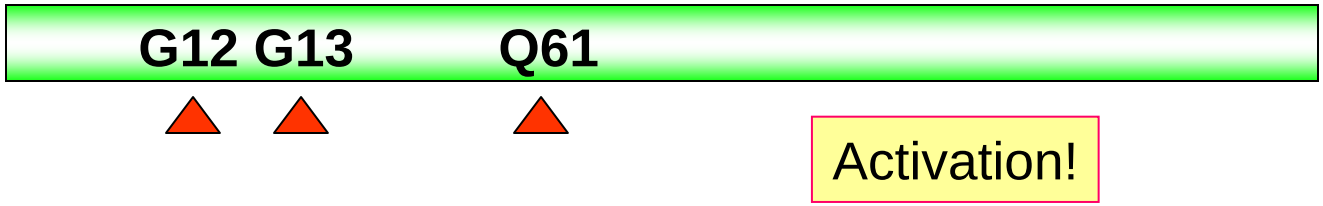
The players

Cancer genes defined

- Oncogene – gain-of-function, dominant acting (Ras, Raf, Myc, EGFR, Abl, PDGFR)
- Tumor suppressor – loss-of-function, require loss of both alleles (p53, Rb, BRCA, PTEN, NF1, Tsc2)

Ras is activated by missense mutations in 30% of human cancers

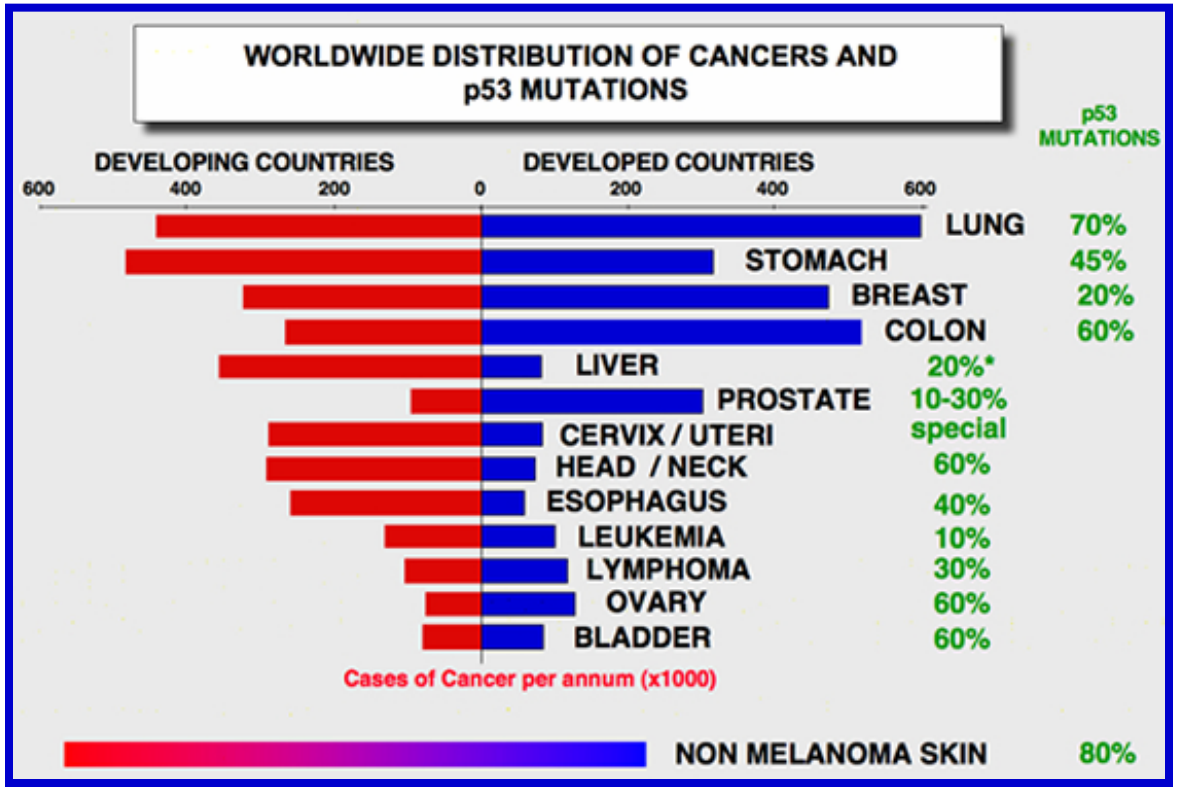
Human Tumor Cell Line	*Gene*	*Codon*	*Mutation*	
EJ bladder carcinoma	H	12	GTC	Gly-Val
Hs242 lung carcinoma	H	61	CTG	Gln-Leu
Calu-1 lung carcinoma	K	12	TGT	Gly-Cys
PR310 colon carcinoma	K	61	CAT	Gln-His
PA1 teratocarcinoma	N	12	GAT	Gly-Asp
HT54 gastric carcinoma	N	61	CGA	Gln-Arg
DLD1 colon carcinoma	K	13	GAT	Gly-Asp



Activation!

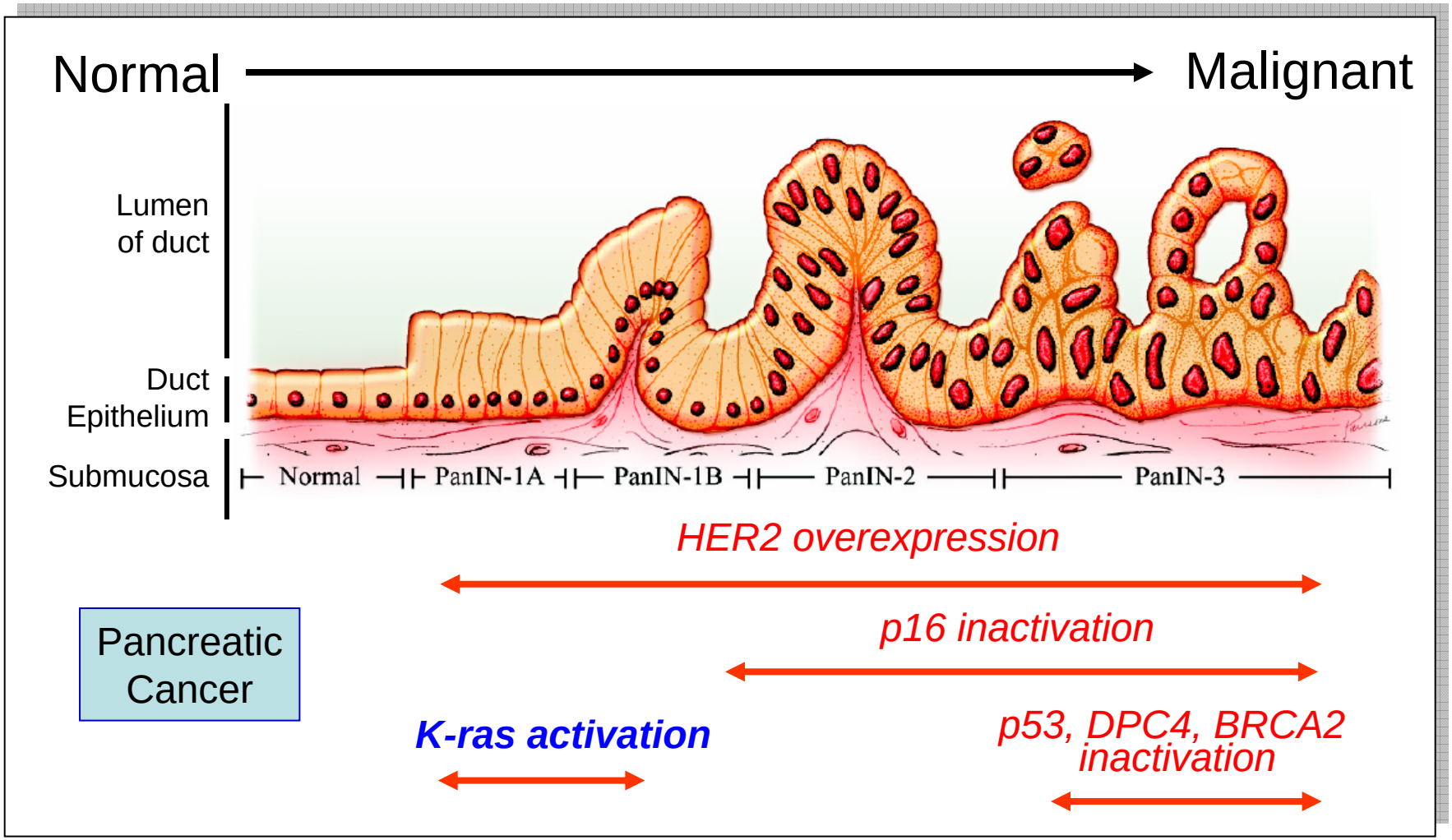
p53 tumor suppressor mutation in 50% of human cancers

http://p53.free.fr/index.html



Inactivation of the p53 gene is essentially due to small mutations (missense and nonsense mutations or insertions/deletions of several nucleotides), which lead to either expression of a mutant protein (90% of cases) or absence of protein (10% of cases)

Cancer is a multistep genetic process



Adapted from Hruban et al. (2000) Clin Cancer Res. 6:2969

Cancer is a genetic disease

How were cancer genes discovered?

Target Identification - Past

- Virology
  - RNA tumor viruses
    - Acutely transforming
    - Chronic transforming
- Gene transfer biological assays
- Chromosome abnormalities
  - Translocations
  - Gene amplification

RNA tumor viruses established the foundation for cancer genetics and signal transduction

- Acutely transforming retroviruses – transduction of cellular genes into viral genome, conversion of normal genes into viral oncogenes (e.g., Src).
- Weakly oncogenic retroviruses – integration into host genome, causing deregulation of host gene function.

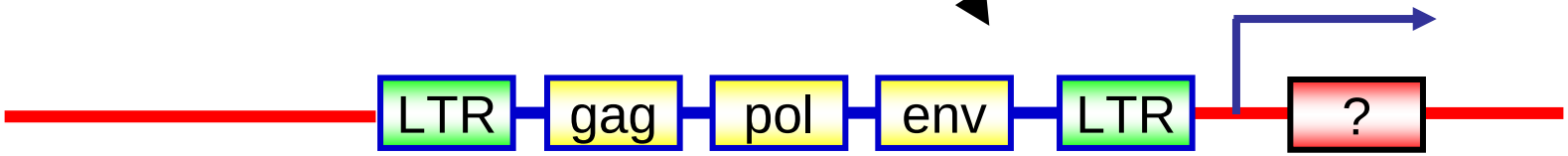
Retroviruses

Non-transforming Virus

Acutely Transforming Virus

Transduction of cellular gene

Chronic Transforming Virus

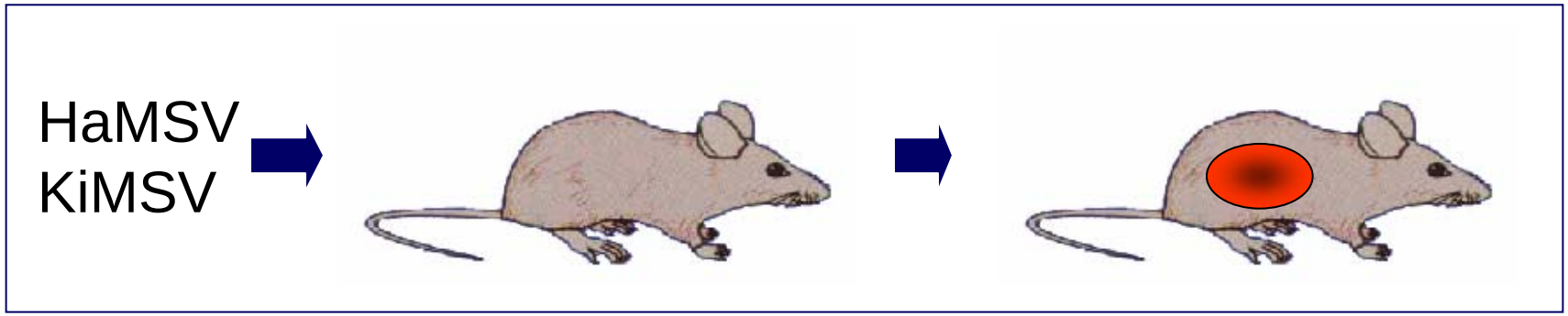


Viral integration activation of cellular gene

Ras history begins

An unidentified virus which causes the rapid production of tumors in mice.

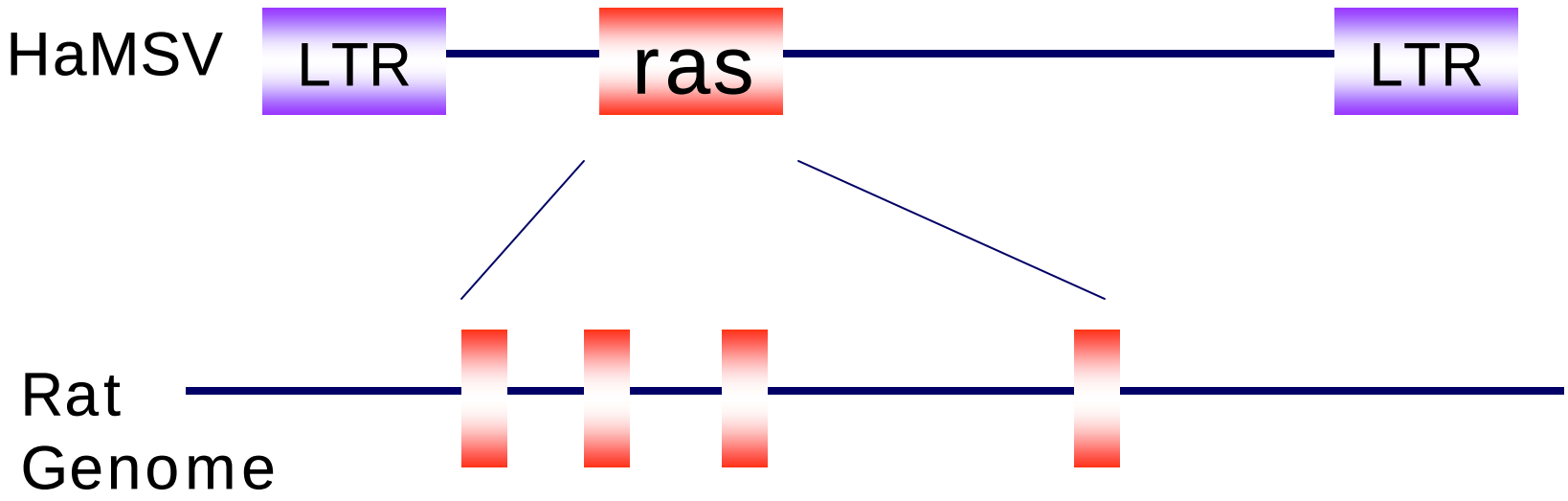
Harvey (1964) Nature 204:1104.



- 100% of mice develop tumors in weeks
- Rapid development of sarcomas and erythroleukemias

Somers & Kirsten (1967) Science 40:1053

H-*ras* Aand K-*ras* were first identified as viral oncogenes



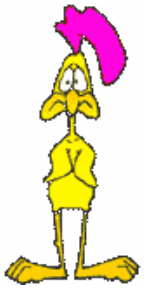
Like *src*, the viral *ras* genes were acquired from normal cellular genes

Scolnick and colleagues (1974)

Key discovery: cancer-causing viruses

The Nobel Prize in Physiology or Medicine 1966

"for his discovery of tumour-inducing viruses"



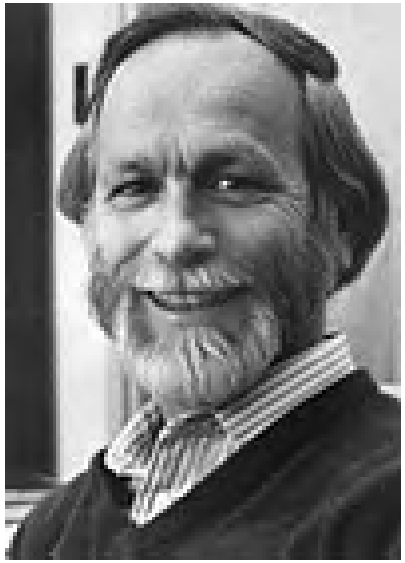
Peyton Rous

Avian Sarcoma Virus → Viral Src Oncogene

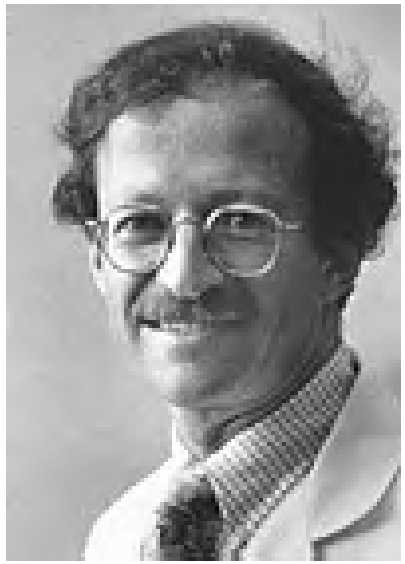
Key discovery: viral oncogenes arose from normal cellular genes

The Nobel Prize in Physiology or Medicine 1989

"for their discovery of the cellular origin of retroviral oncogenes"



J. Michael Bishop



Harold Varmus

Retroviral oncogenes: many are important players in human cancers

- Abl
- Akt
- Cbl
- ErbA
- ErbB[1]
- Ets
- Fes

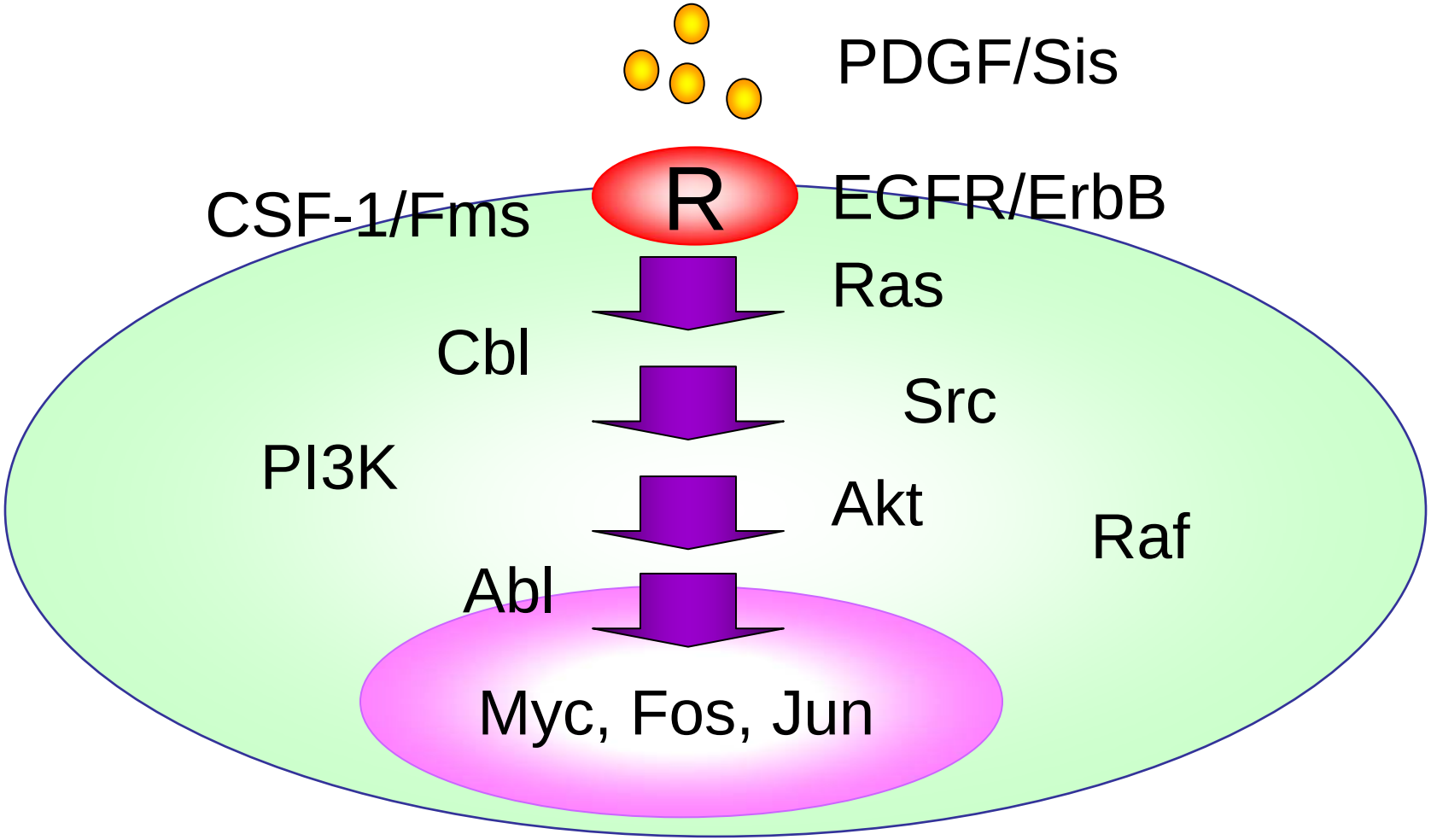
- Fgr
- Fms[2]
- Fos
- Fps
- Jun
- Kit
- Maf
- Mos

- Mpl
- Myb
- Myc
- P3K[3]
- Qin
- Raf
- H-Ras
- K-Ras

- Rel
- Ros
- Sea
- Sis[4]
- Ski
- Src
- Yes

[1]EGFR; [2]CSF-1R; [3]PI3-Kinase; [4]PDGF

Retrovirus oncoproteins have provided the foundation for defining signaling networks



Target Identification - Past

- Virology
  - RNA tumor viruses
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    - Chronic transforming
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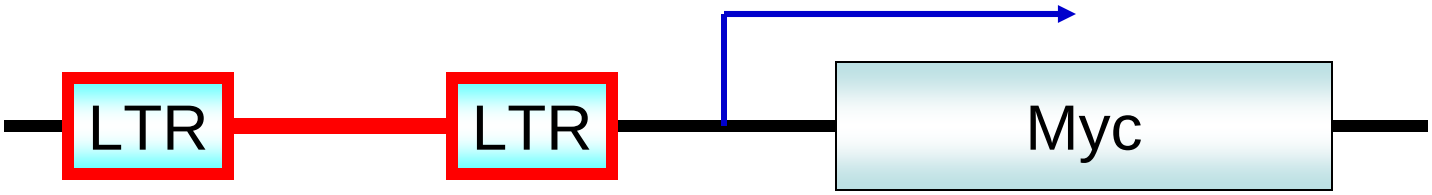
- Chromosome abnormalities
  - Translocations
  - Gene amplification

Retrovirus integration activation of oncogenes

Avian Leukosis Virus →

→ B-cell lymphomas



Hayward et al. (1981) Nature 295:209

Oncogene activation by retrovirus integration

Myc*	Wnt-1	Fli-1
N-Myc	Wnt-2	Bmi-1
ErbB*	Int-2 (FGF-3)	Tpl-2
H-Ras*	Pim-1	Nov
K-Ras*	Lck	IL-2
Fos*	Evi-1	IL-3
Myb*	Hox 2.4	CM-CSF
Fms*	Spi-1	CSF-1

*Identified previously as retrovirus oncogenes

“The enemy within”

- Viruses can manipulate normal cellular genes and convert them into potent oncogenes
- Suggests that cellular genes have the potential, if mutated, to promote cancer. Does it really happen?

Initially, no evidence was found to support this. So, interest in the study of retrovirus oncogenes rapidly diminished.

But finally, in 1982, beginning with Ras, many of these virus-identified oncogenes were implicated in human cancers

Cancer genes come of age

1982 Mutated ras oncogenes identified in bladder, lung and colon cancer

1982 Myc onco[illegible] overexpressed in Burkitt[illegible]

1984 Abl oncogene[illegible] and rearranged in Philadelphia chromosome positive CMLs

1984 ErbB2 oncogene overexpressed in breast and other cancer cells

1987 Rb tumor[illegible] in retinoblast[illegible]

1987 p53 established as tumor suppressor lost in many human cancers

1994 BRCA1 familial breast cancer gene cloned

"The enemy within"

Magic bullet design?

Target Identification - Past

- Virology
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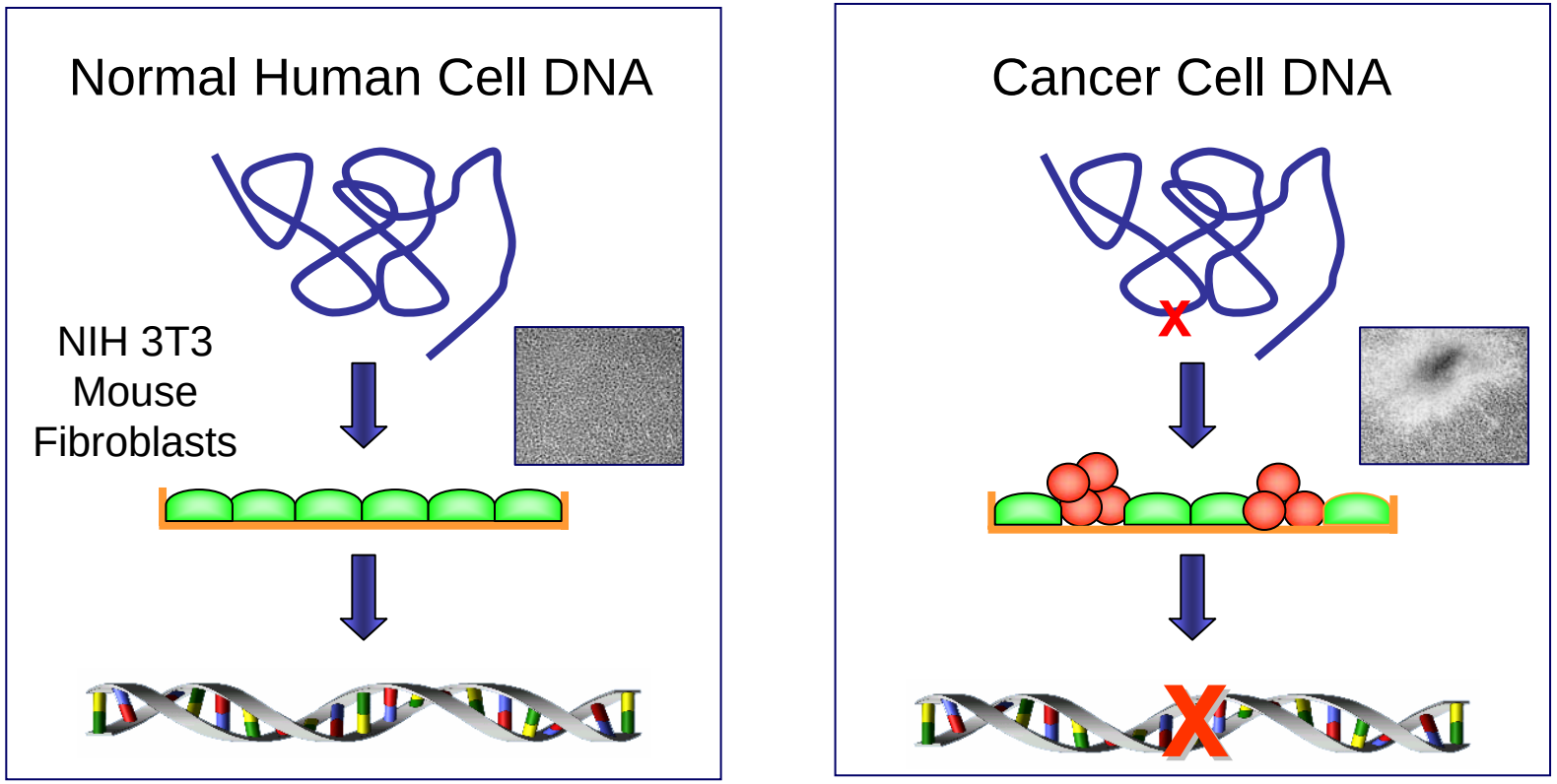
Key discovery: transforming genes are present in human tumor cells



Krontiris & Cooper (1981) PNAS 78:1181

What are these activated oncogenes?

Ras is mutated in 30% of all human cancers

Pancreatic carcinoma	90%
Cholangiocarcinoma	55%
Colon adenocarcinoma	50%
Thyroid carcinoma	30%
Seminoma	40%
Embryonal rhabdomyosarcoma	35%
Acute myelogenous leukemia	35%
Myeloblastic syndromes	30%
Lung carcinoma	30%

NIH 3T3 gene transfer assay for oncogene discovery

Tumor-Associated	Transfection-Associated*	
H-Ras	Raf-1	Cot
K-Ras	B-Raf	Ove
N-Ras	Ret	Tre
Neu/ErbB2	Ros	Hst
Met	Dbl	FGF-5
Ret	Vav	Mas
TrkA		

*Activated during the transfection assay

Target Identification - Past

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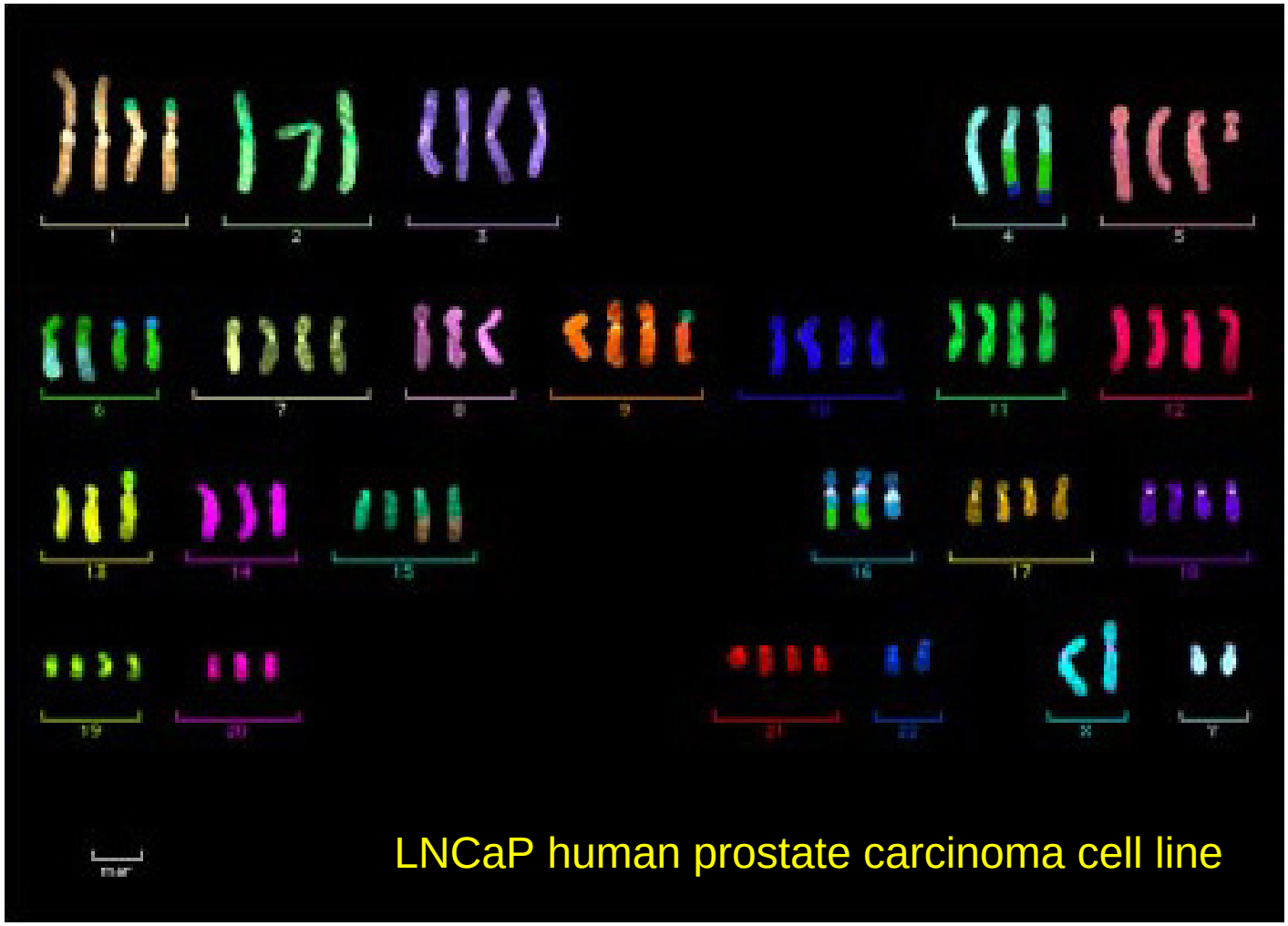
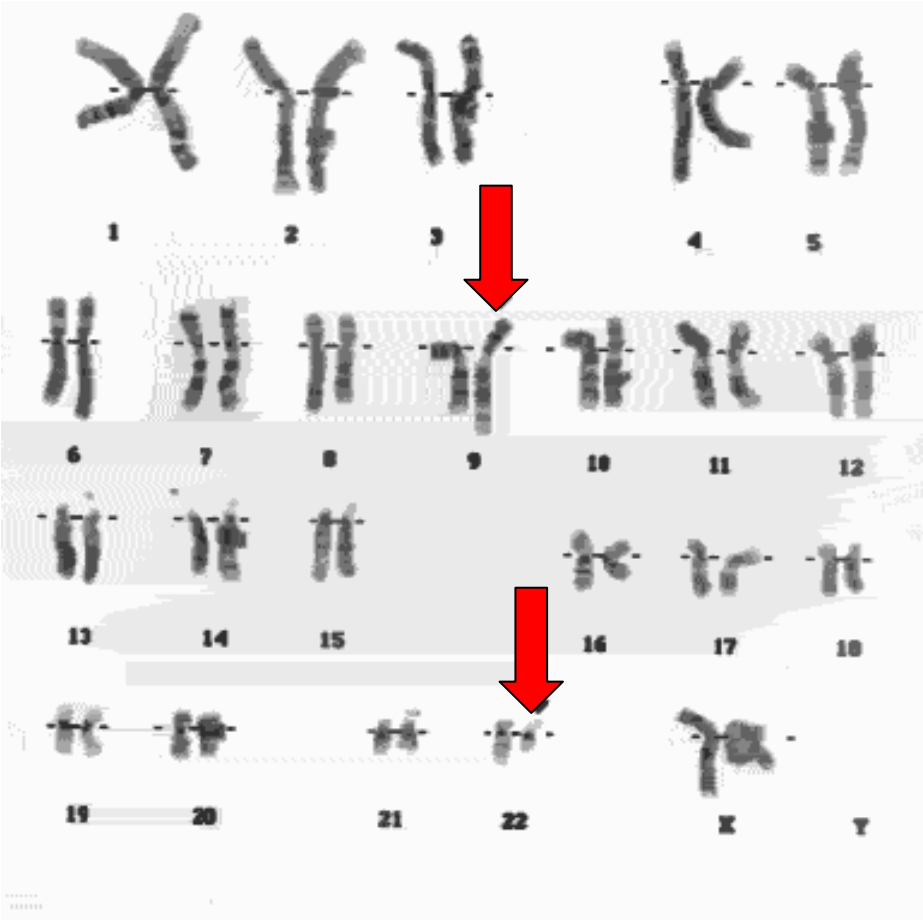
Cancer cells exhibit many cytogenetic alterations



FISH (www.prostatecanceruk.org)

Do they cause altered function of specific genes?

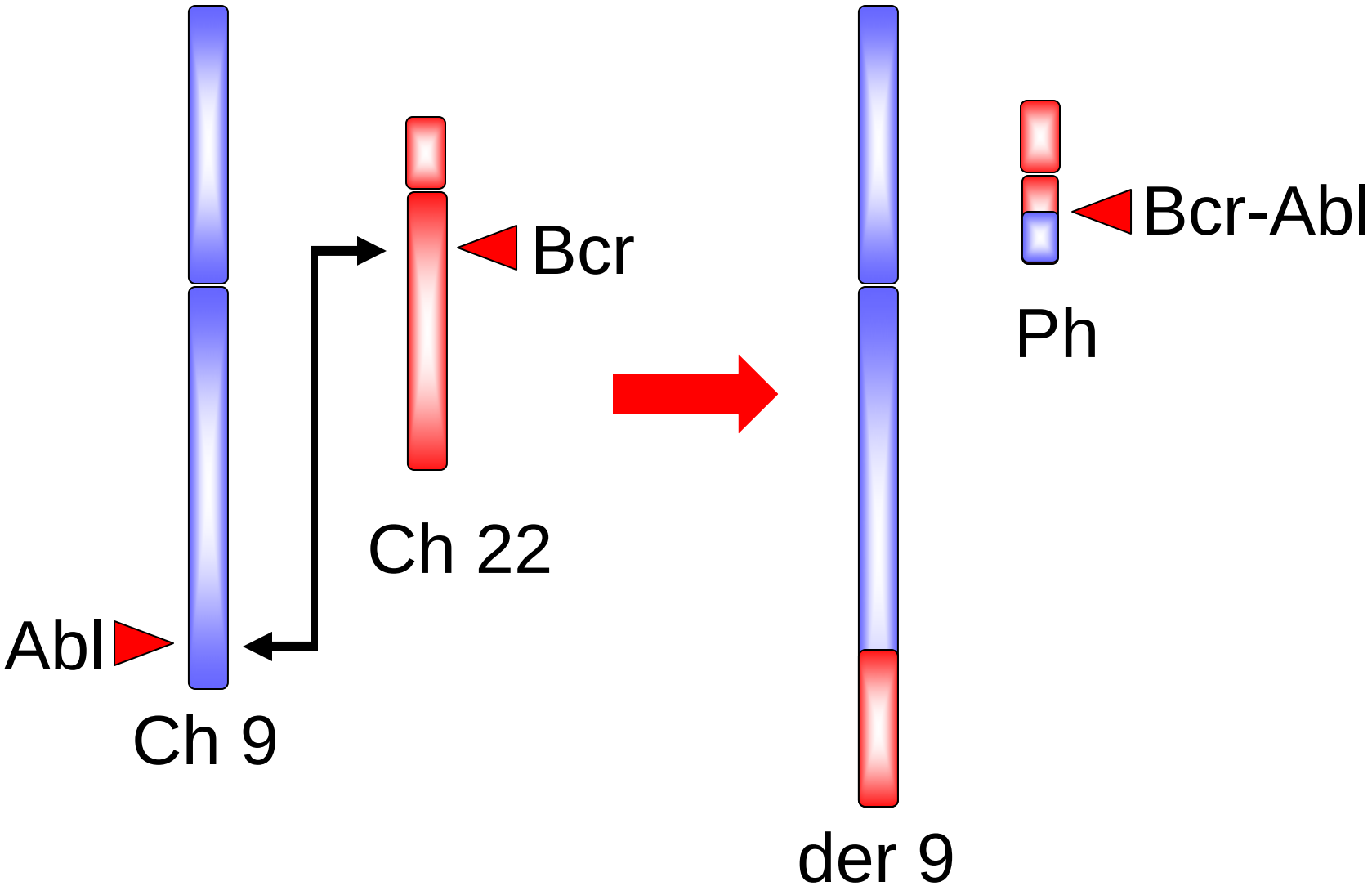
Philadelphia Chromosome and chronic myelogenous leukemia



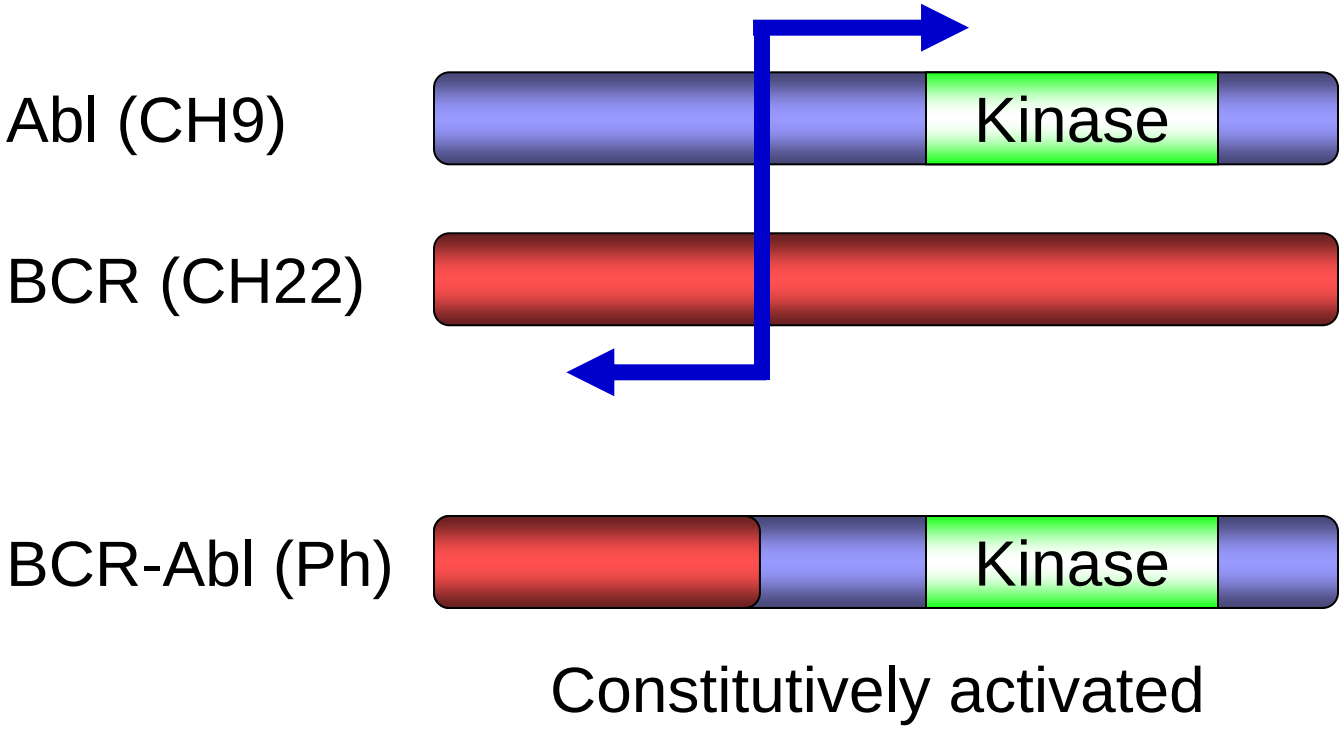
Reciprocal Translocation of Chromosomes 9 and 22

Identified in 1960, but molecular consequence not known

Formation of Ph Chromosome



BCR-Abl: activated mutant of Abl



Ph translocation present in 95% of human CMLs

Oncogenes activated by chromosome translocation

Myc	Lyl-1	Tan-1	CBFβ/MYH11
Bcl-2	PRAD-1	**Bcr-Abl**	Ews/Fli1
Bcl-3	Rhom-1	Dek/Can	Lyt-10/Cα1
Bcl-6	Rhom-2	E2A/Pbx1	Hrx/Enl
Hox11	Tal-1	PML/RAR	Hrx/Af4
IL-3	Tal-2	C16/Erg	Aml1/Mtg8
		Rel/Nrg	NPM/ALK

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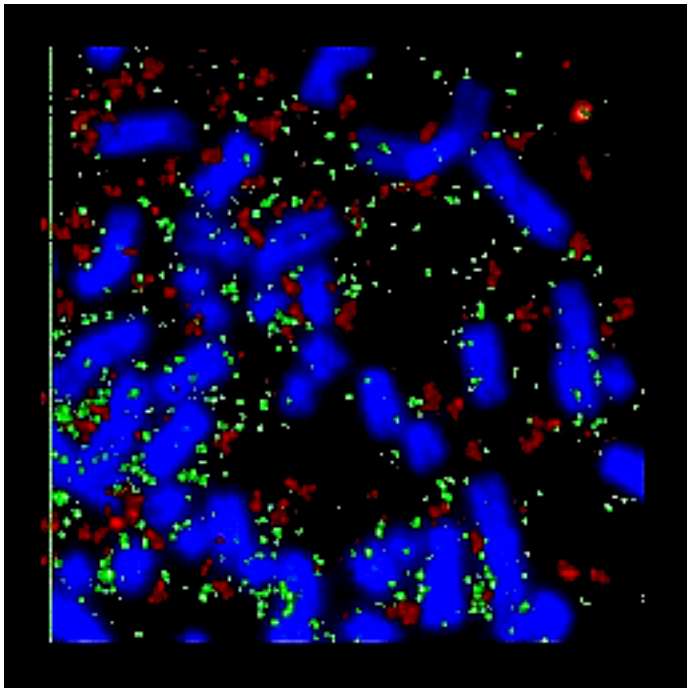
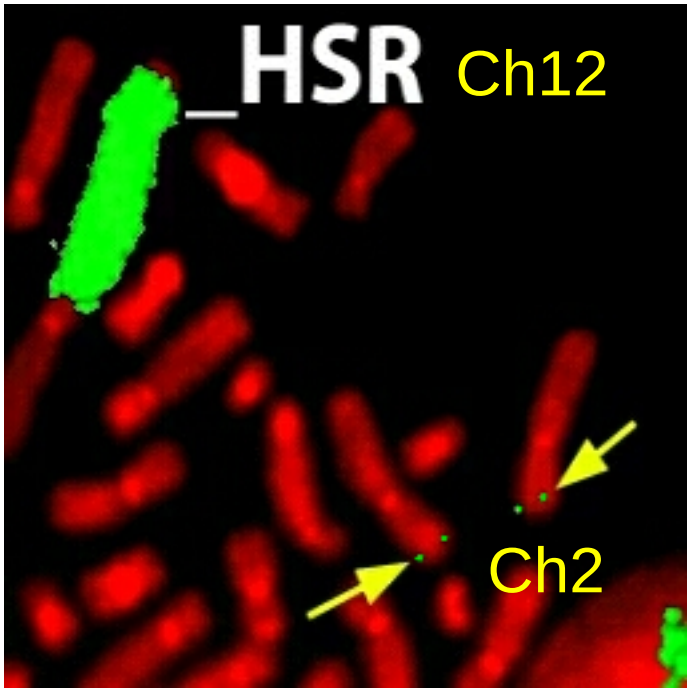
A Myc-related gene (N-Myc) is amplified in human neuroblastomas

Double Minutes



N-Myc and Mdm2 Amplification

Homogeneous Staining Region



N-Myc Amplification

Amplified oncogenes in human cancers

Myc*
N-Myc
L-Myc
ErbB*
ErbB2
Int-2
Hst
PRAD-1
Abl*

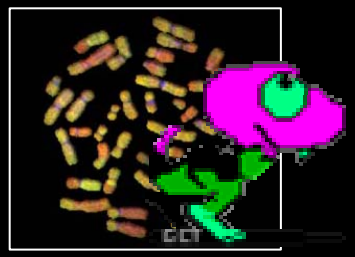
Myb*
Ets-1*
H-Ras*
K-Ras*
N-Ras
Gli
K-Sam
Mdm-2

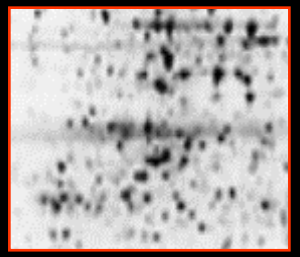
*Identified previously as retrovirus oncogenes

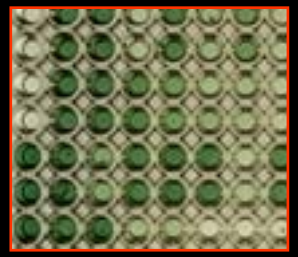
Cancer is a genetic disease

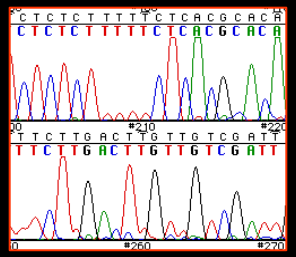
Cancer discovery, now and the future

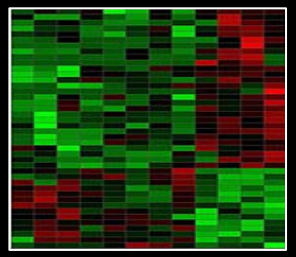
From looking where the light is to genome-wide approaches for genetic dissection of diseases











Genome sequencing: megabases of information available

Aedes aegpti
Anopheles gambiae
Bos taurus
Caenorhabditis elegans
Canis familiaris
Ciona intestinalis
Ciona savignyi
Danio rerio
Dasypus novemcinctus
Drosophila melanogaster
Echinops telfairi
Gallus gallus
Gasterosteus aculeatus
Homo sapiens
Loxodonta africana
Macaca mulatta
Monodelphis domestica
Mus musculus
Ornithorhynchus anatinus
Oryctolagus cuniculus
Oryzias latipes
Pan troglodytes
Rattus norvegicus
Saccharomyces cerevisiae
Takifugu rubripes
Tetraodon nigroviridis
Xenopus tropicalis

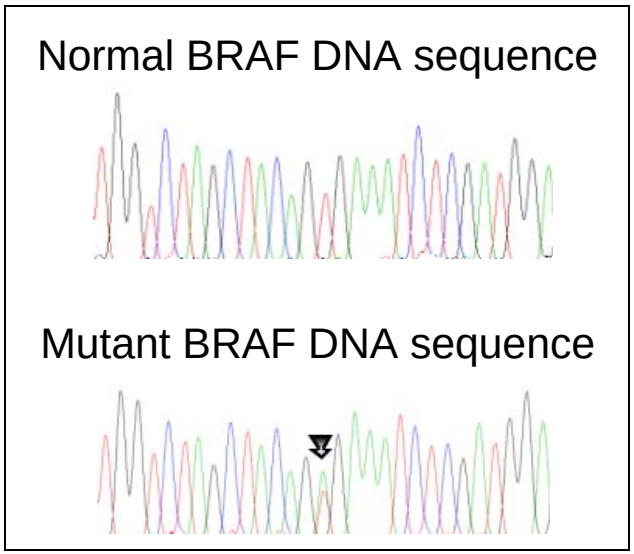
This wealth of information has contributed to our rapid advances in discovering yet more cancer genes

Cancer genome project

http://www.sanger.ac.uk/genetics/CGP/

Cancer genome project: strategy

- Sequencing coding exons and flanking splice junctions of all genes in the human genome for somatically acquired small intragenic mutations in human cancer.
- DNA from primary tumours and normal genomic DNA from the same individuals, in addition to cancer cell lines.
- The first sets of genes included protein kinases and other genes that are potential therapeutic targets.



70% of melanomas with mutated BRAF

Brute force sequencing of logical suspects

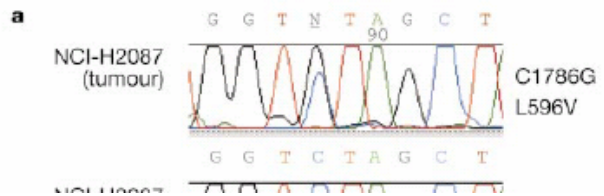
letters to nature

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

[1]*Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, CB10 1SA, UK*
[3]*Cancer Research UK Centre for Cell and Molecular Biology, Chester Beatty Labs, Institute of Cancer Research, London SW3 6JB, UK*

phoblastoid cell lines from the same individuals were screened for sequence variants through the coding exons and intron–exon junctions of the *BRAF* gene using a capillary-based modified heteroduplex method followed by direct sequencing of polymerase chain reaction products. (Exon 1, containing 135 base pairs (bp) of coding sequence, failed to amplify despite the use of five different primer sets.) Three single-base substitutions were detected. Two were in *BRAF* exon 15: T1796A leading to a substitution of valine by glutamic acid at position 599 (V599E) in the melanoma cell line Colo-829, and C1786G leading to L596V in the NSCLC cell line NCI-H2087 (Fig. 1). A further mutation was found in exon 11: G1403C leading to G468A in the NSCLC cell line NCI-H1395. None of the three changes were present in the lymphoblastoid cell lines from the same individuals, indicating that the variants were somatically acquired mutations.



>20 single amino acid substitutions found in B-Raf; most result in activated and transforming proteins.

Unbiased, large-scale sequence analyses of cancer cells: the wave of the future

- Sequencing of all sequence verified genes (13,023) in 11 breast and 11 colorectal carcinoma cell lines (Sjoblom et al., 2006)
- Sequencing of 518 protein kinase genes in 210 cancers (210 primary tumors, 2 early cultures, 39 cell lines), including lung, stomach, ovary, colon, kidney, testes, breast, etc. (Greenman et al., 2007).
- NCI and NHGRI Human Cancer Genome Project – will sequence 2,000 genes implicated in cancer in 12,500 tumor samples (250 each from 50 different cancers.

*Can*didate *can*cer genes (*CAN*-genes)

- 13,023 genes evaluated
- 1,149 genes mutated
- 242 *CAN*-genes

- 122 breast *CAN*-genes (12 per tumor)
- 69 CRC *CAN*-genes (9 per tumor)
- No more than 6 in common with other cancers

Sequencing the kinome

- Sequence analyses of exons of 518 protein kinase genes in 210 cancers (210 primary tumors, 2 early cultures, 39 cell lines).
- Number of mutations varied widely both with and between class of cancer.
- 1,007 total mutations identified (83% passenger mutations), with 158 driver mutations identified in 120 kinases.
- 73 tumors with no mutations, 66 with at least one driver mutations – not just kinases

If mutated kinases are required for effective targets, these results suggests that we need to also consider other protein classes.

Greenman et al. (2007) Nature 446:153

Target validation: cause or consequence of cancer?

- Does the altered function promote oncogenesis?
- Will “correction” of the gene defect reverse oncogenesis?

AND YET THE QUESTION REMAINED: "WHO CAME FIRST?"

RNAi silencing of putative oncogenes: the latest, greatest tool for target validation?

The Nobel Prize in Physiology or Medicine 2006

Andrew Z. Fire

Craig C. Mello

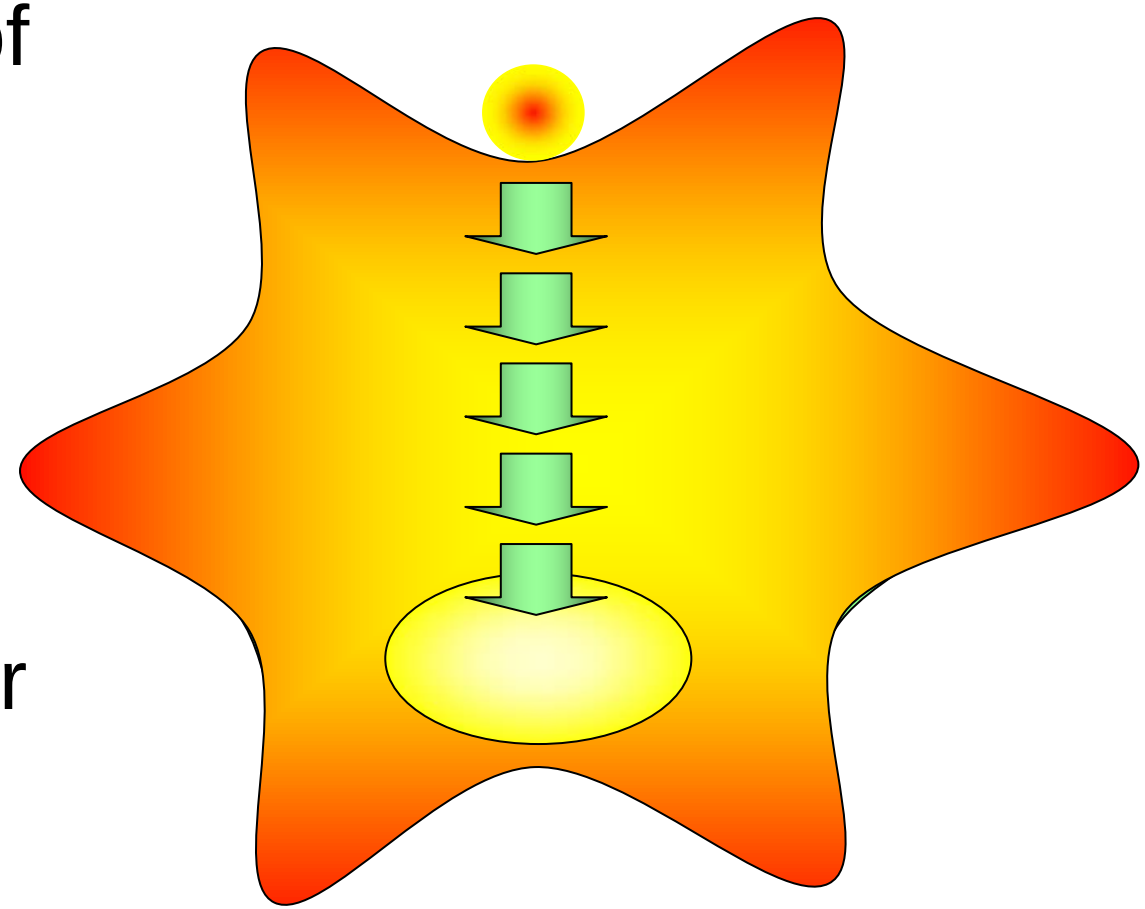
"Faster than a speeding bullet. More powerful than a locomotive."

Signal transduction

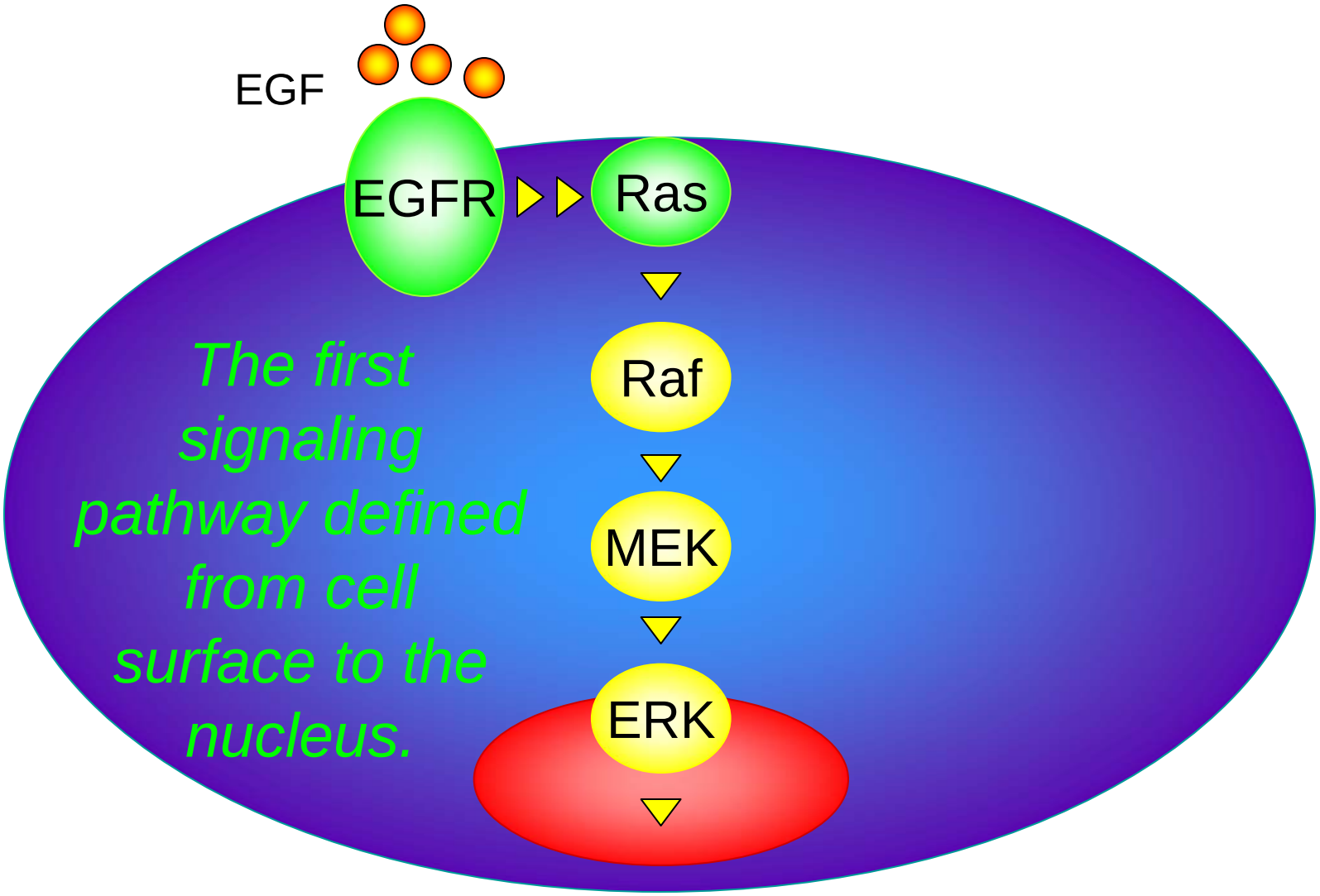
The players

Signal transduction defined

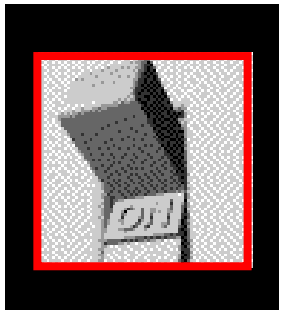
The cascade of molecular events that allow a cell to convert extracellular signals into specific cellular responses.



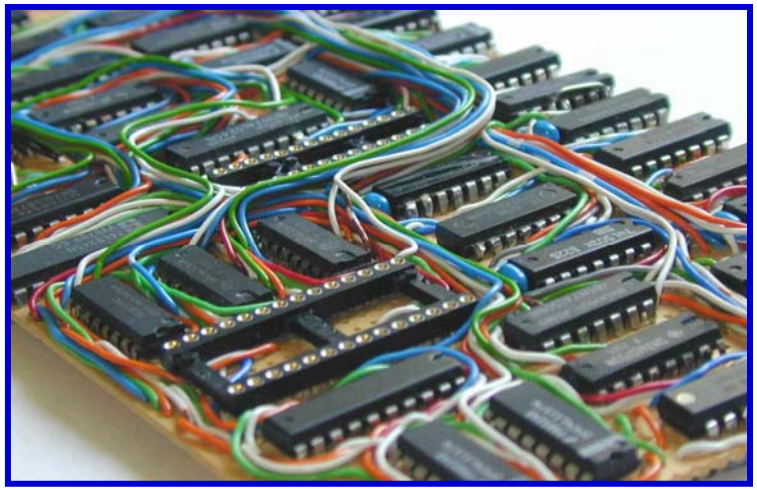
1993 - a signaling achievement: Ras activates a kinase cascade

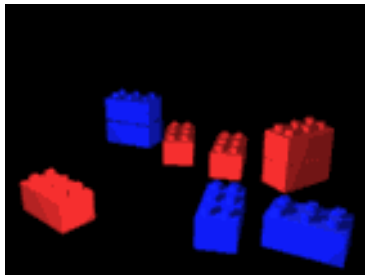


Signal transduction involves the complex interplay of diverse enzymatic processes and protein-protein interactions



Signaling on-off switches



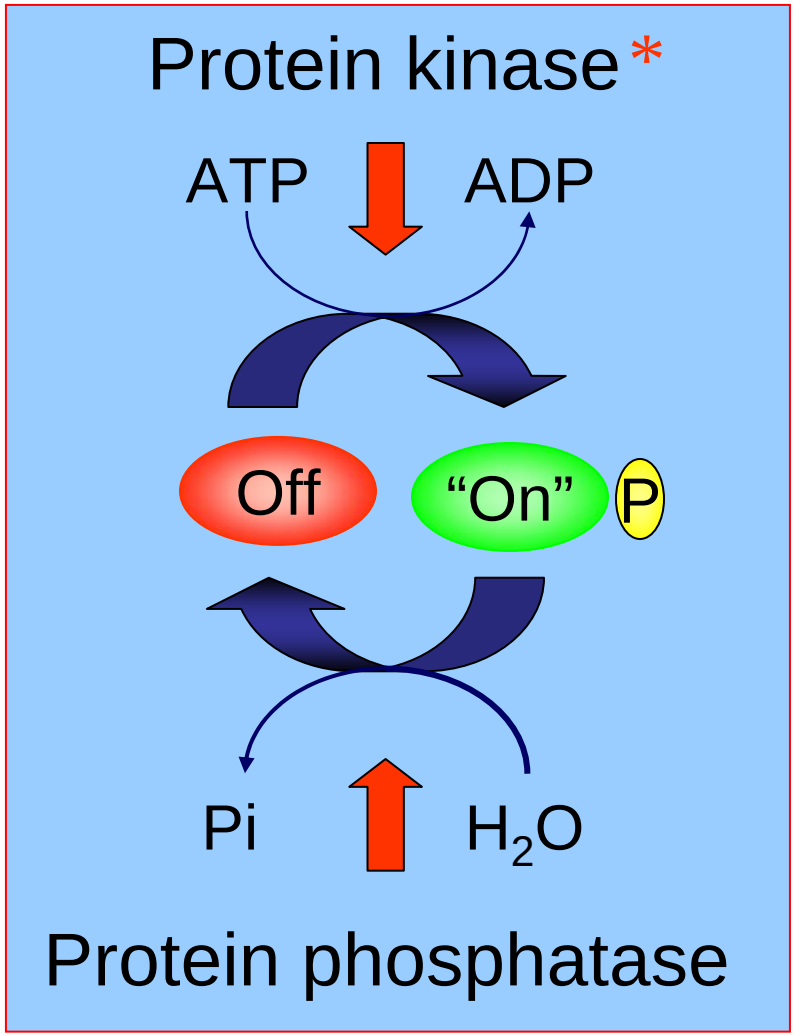


Signaling connectors

Regulation of signaling protein function

- Protein phosphorylation – protein kinases and phosphatases
- GTPases – guanine nucleotide (GDP and GTP) binding proteins
- Protein-protein/lipid interaction domains – modular domains that determine signaling specificity of interactions.

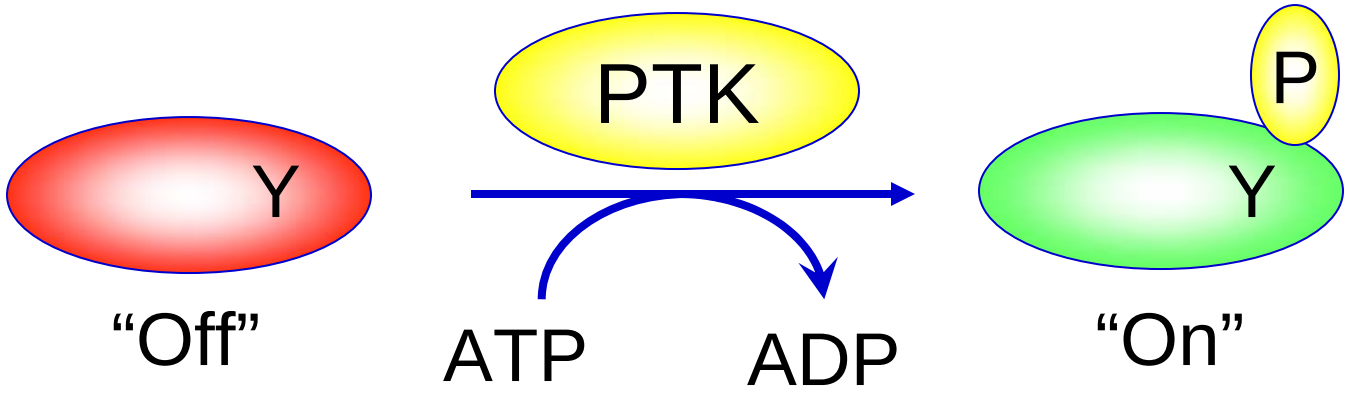
Reversible Protein Phosphorylation



- Regulation of protein:protein interaction
- Regulation of subcellular location
- Regulation of catalytic activity

*HER2, EGFR, Raf, MEK, ERK, Akt

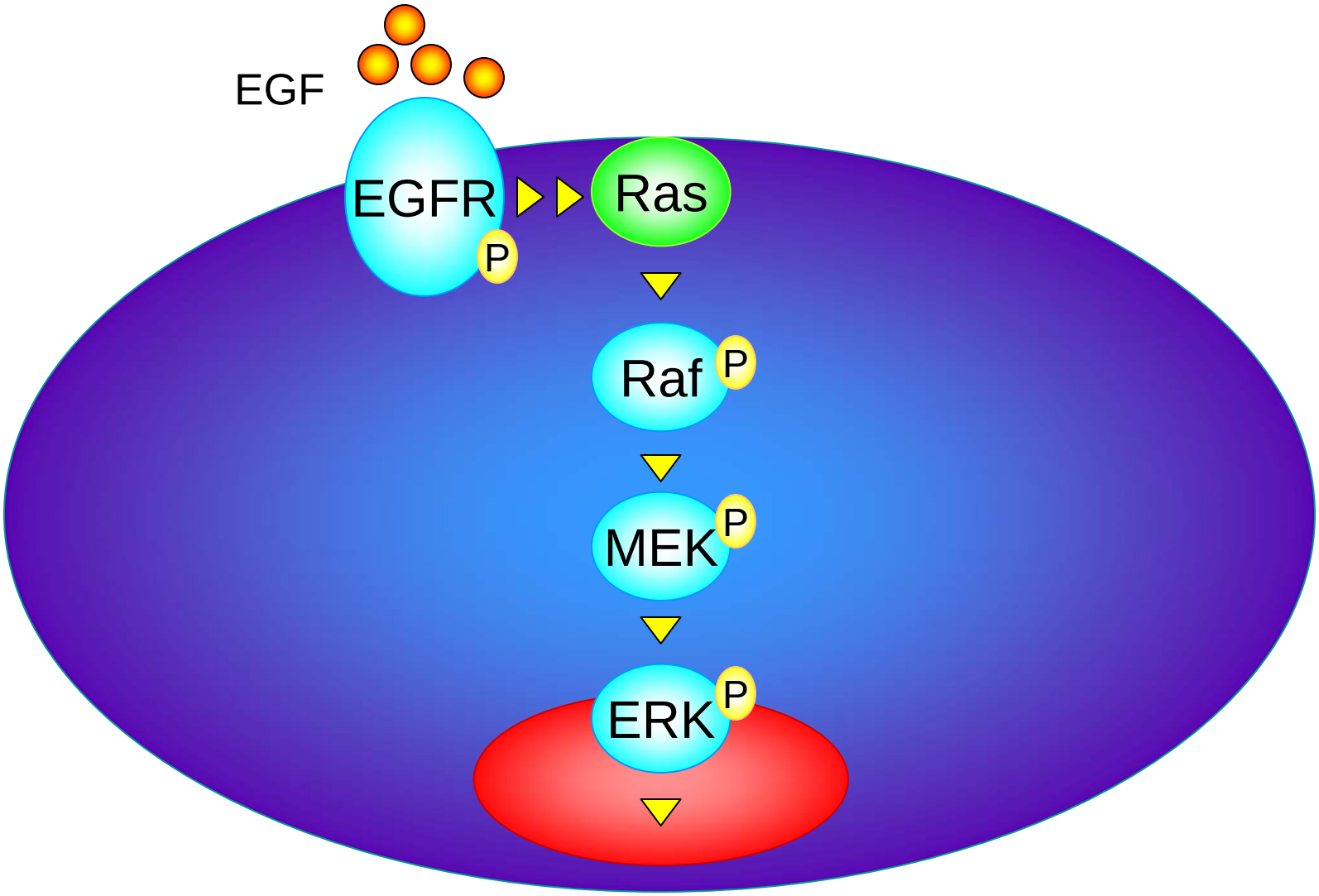
Protein kinases: key regulators of signal transduction



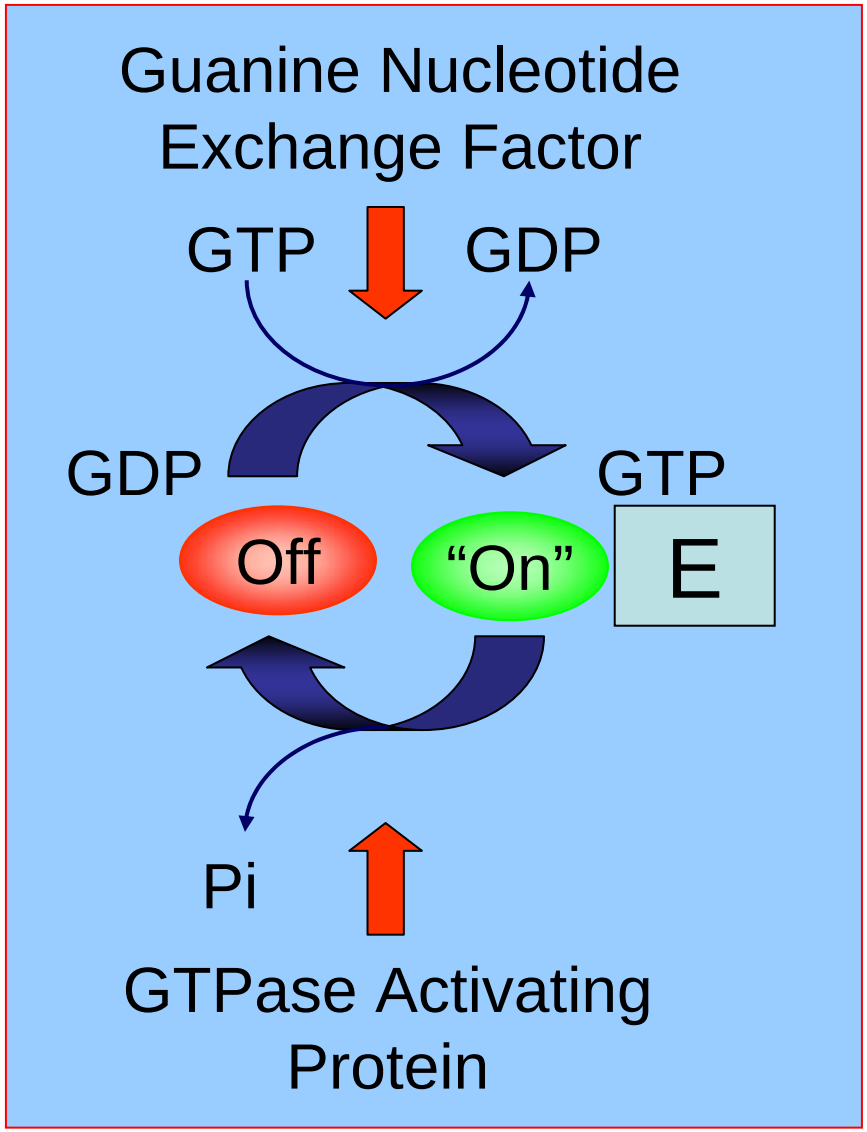
- Of the 31,000+ human genes, ~2.5% are devoted to protein phosphorylation.
- There are 518 human protein kinases, of which 90 are protein tyrosine kinases (PTKs).
- Examples: EGFR, HER2, BCR-ABL, VEGFR

Manning et al. (2002) Science 298:1912

Protein kinases upstream and downstream of Ras

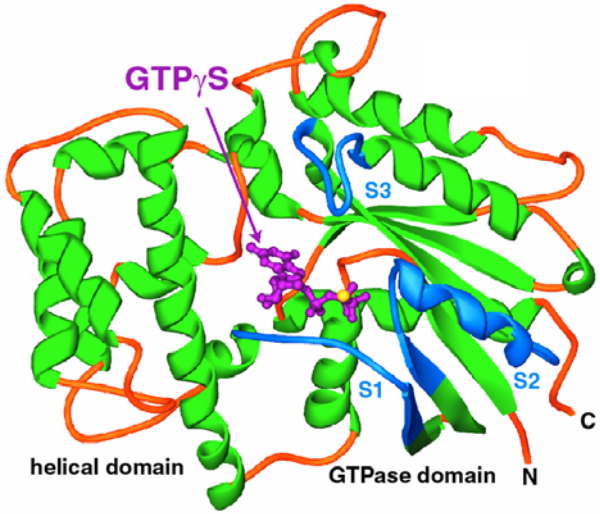


Reversible GDP/GTP Binding

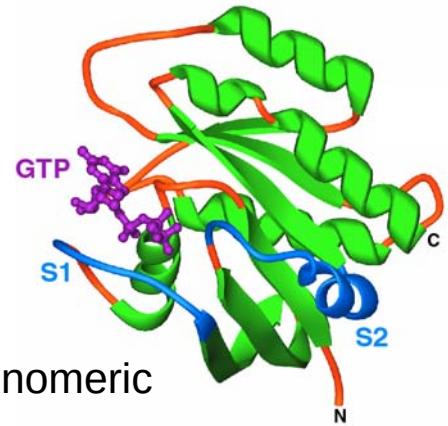


- Large GTPases and GPCRs
- Small GTPases – e.g. Ras, Rho
- Regulation of protein:protein interaction

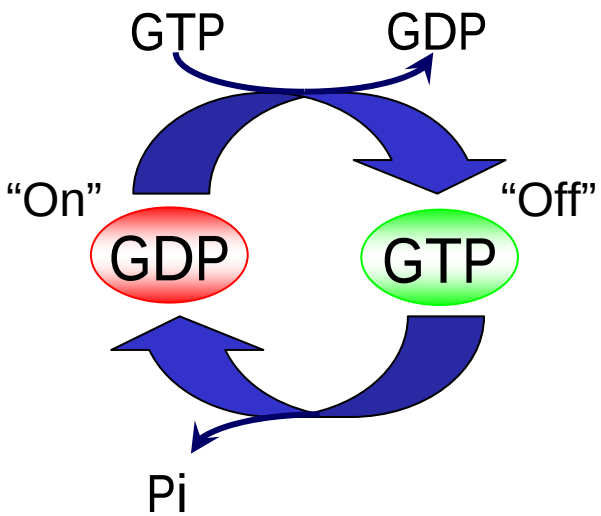
GTPases everywhere!

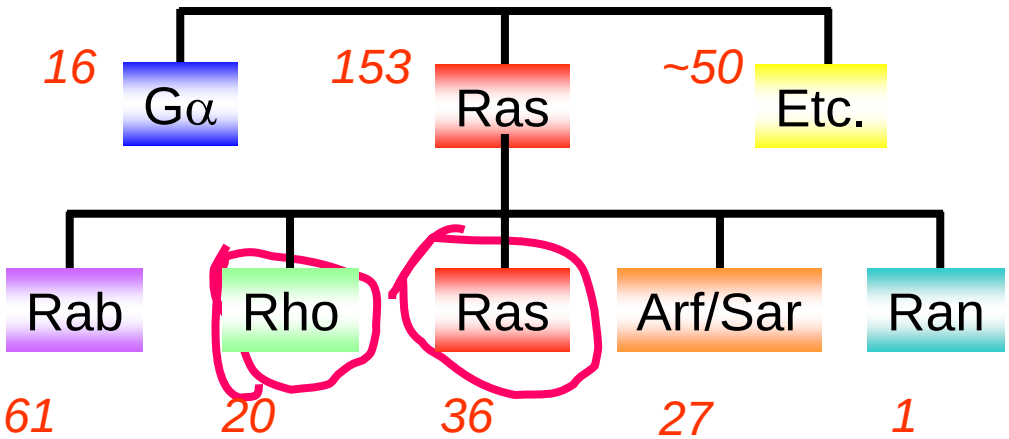


Gα: heterotrimeric

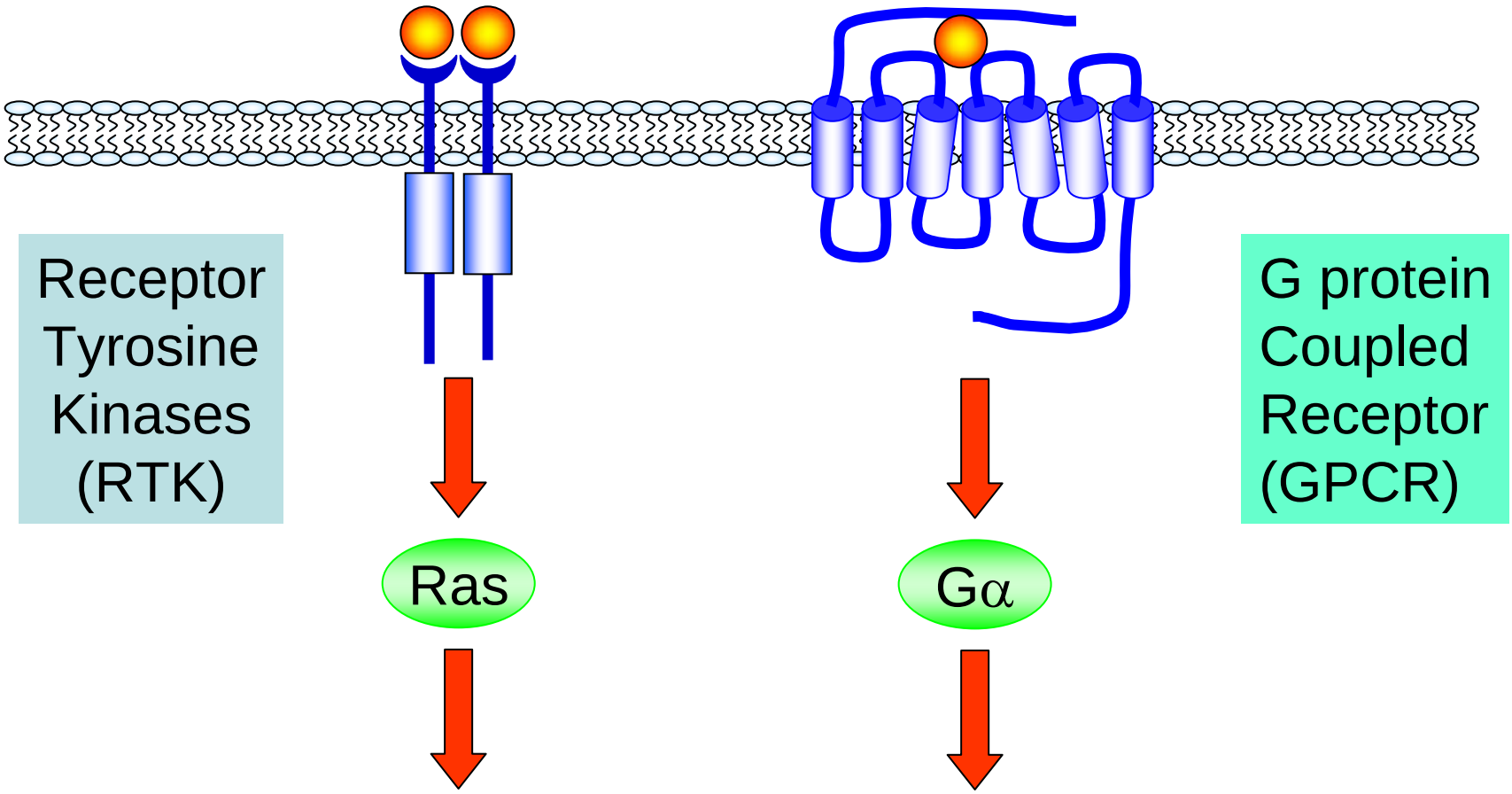


Ras: monomeric





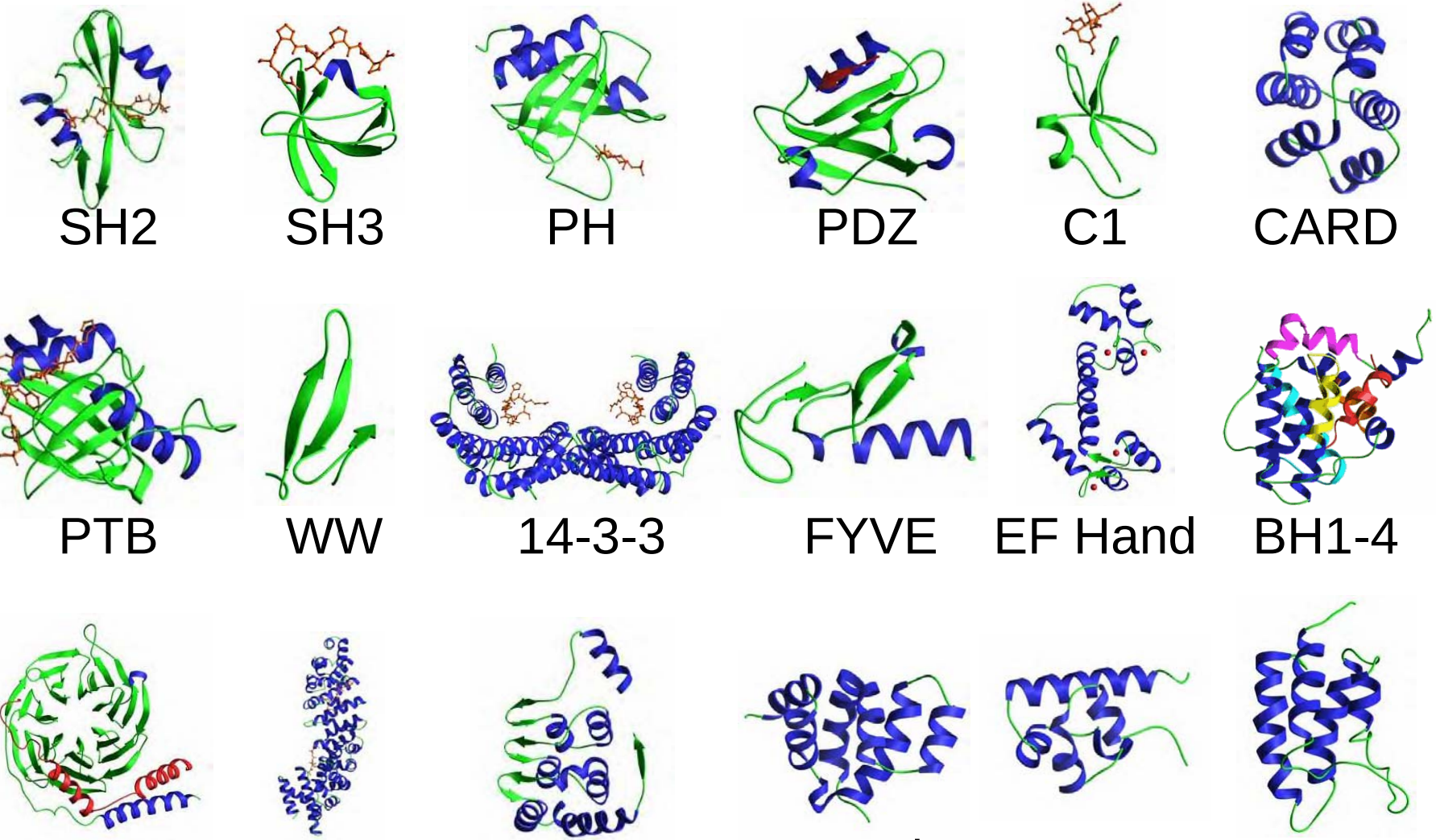
Receptor signaling causes downstream activation of GTPases



Signaling specificity: how do signaling proteins find each other?

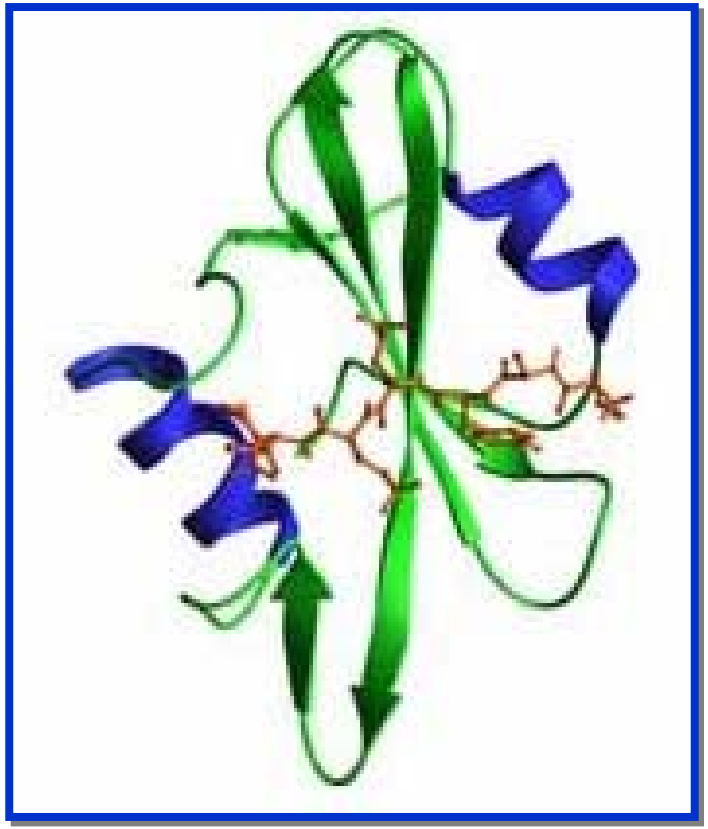
Signaling proteins are modular

Protein-protein/lipid interaction domains



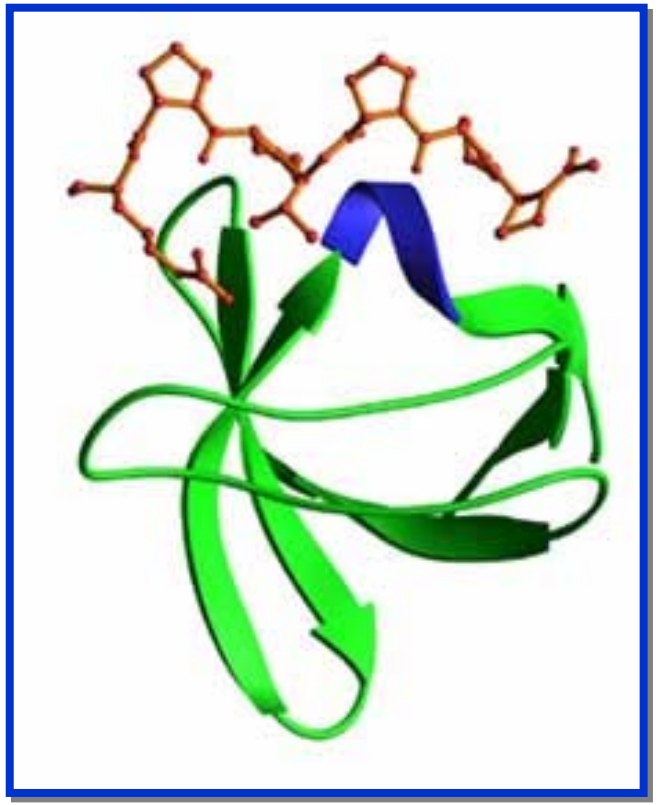
SH2 domains

- Src homology 2, first identified in Src family kinases
- ~100 amino acid protein module, found in >500 eukaryotic proteins
- phosphotyrosine residue-containing peptides in the context of 3-6 C-terminal residues
- Phosphorylation regulates reversible interaction

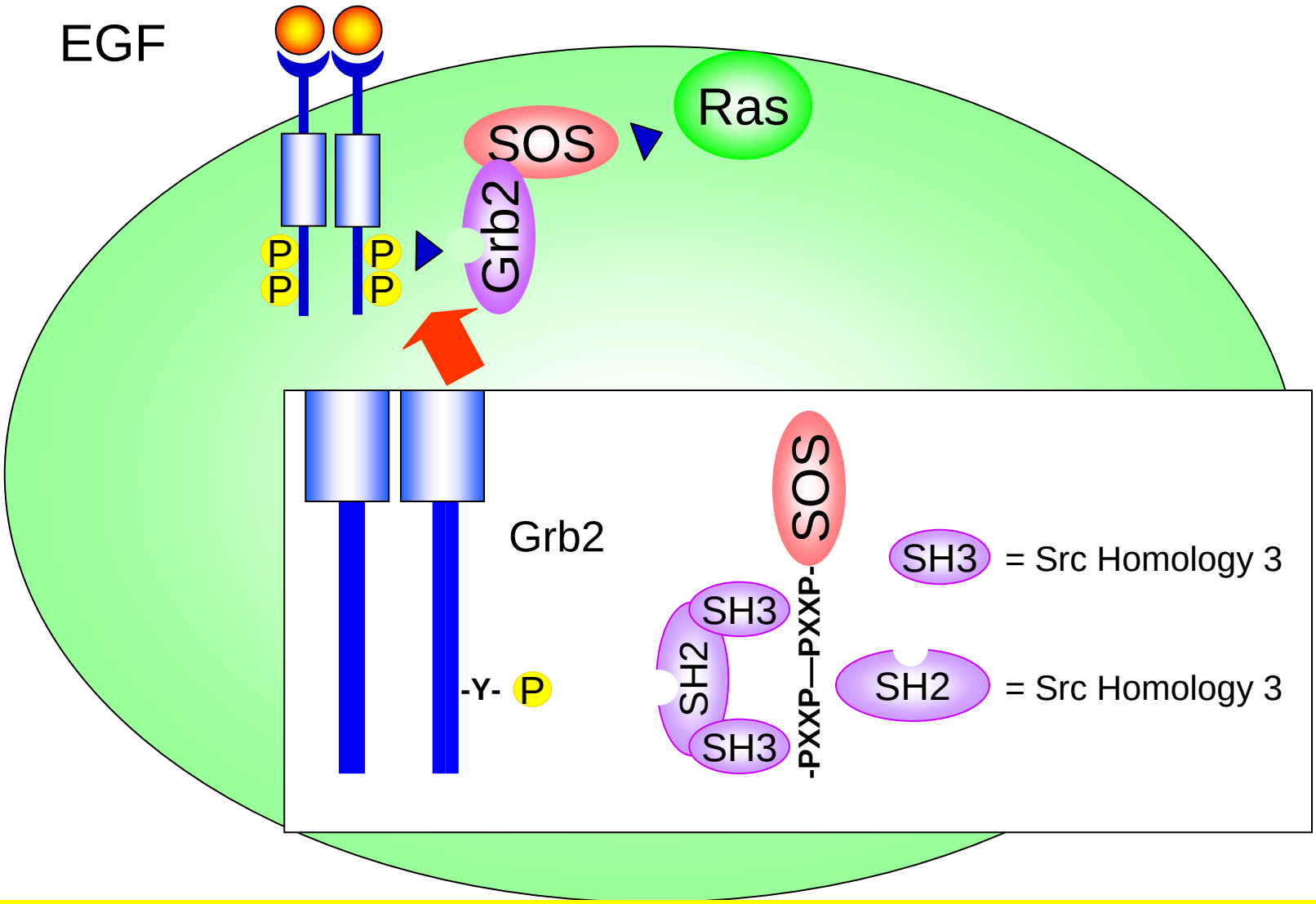


SH3 domains

- Src homology 3 domain, first identified in Src family kinases
- Found in >800 eukaryotic proteins
- Bind to proline-rich peptides with the minimal consensus P-X-X-P

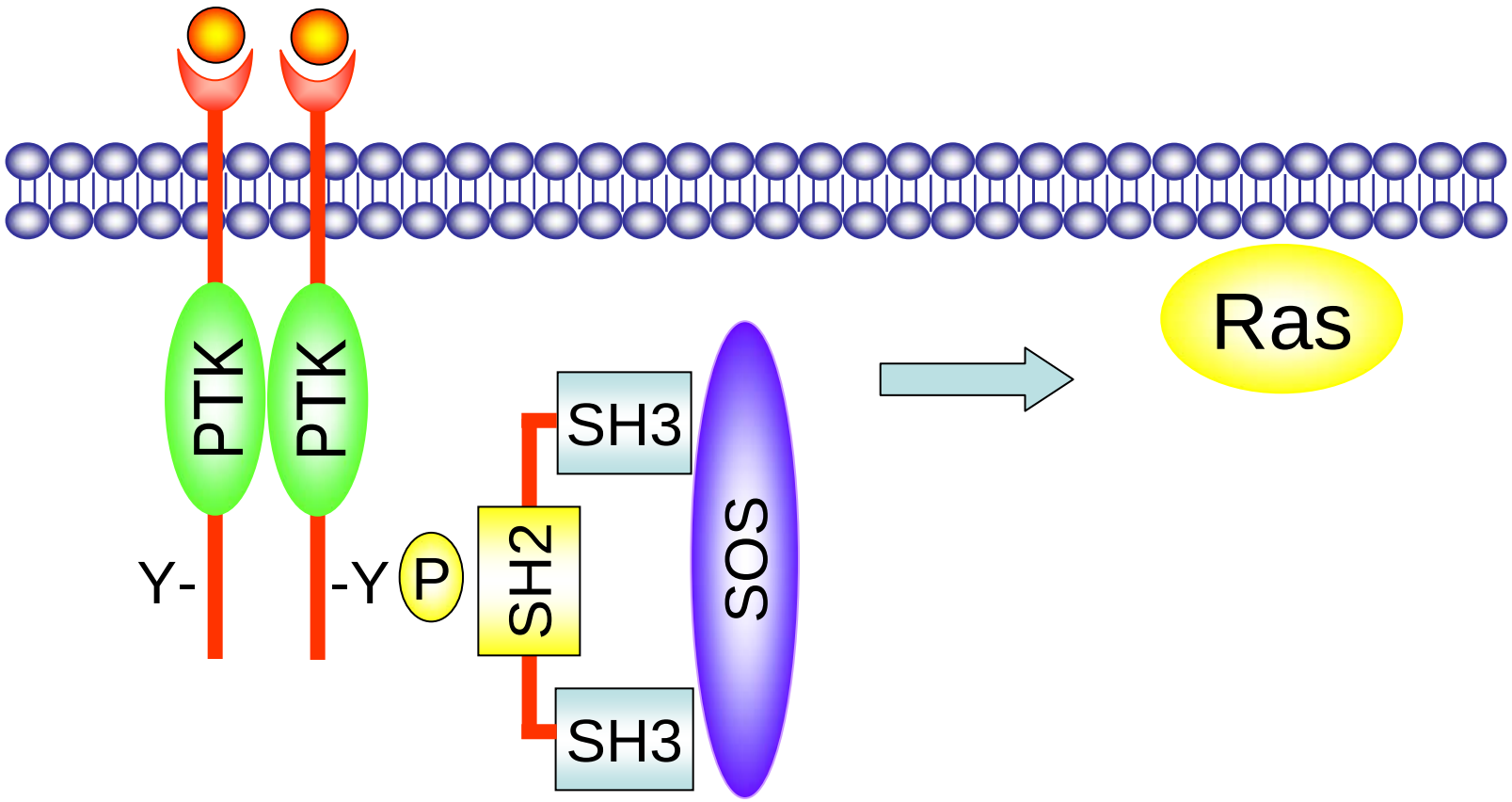


Ras signal transduction - 1993



Grb2 adaptor recruits the Sos RasGEF to the plasma membrane to activate Ras

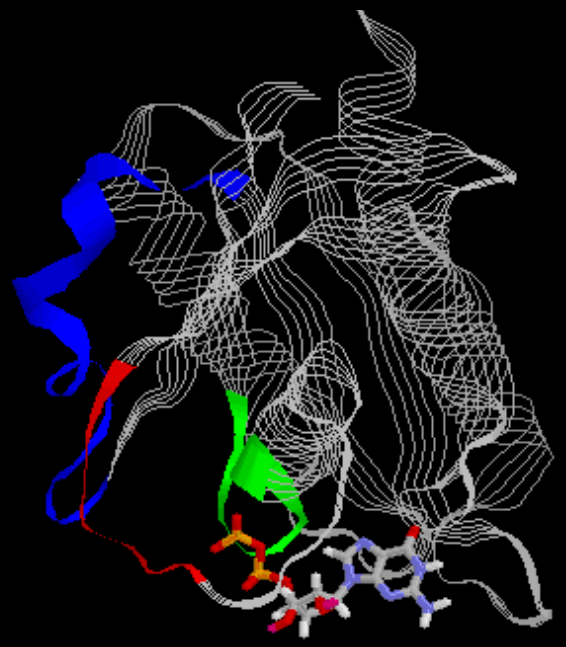
Grb2 SH2 domain protein causes activation of Ras



Grb2 adaptor protein – translocation of Sos to plasma membrane to activated membrane-associated Ras

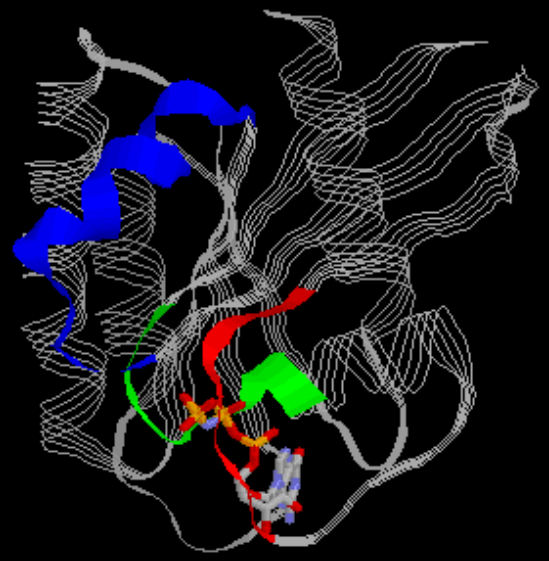
The Ras GDP/GTP switch: how does it work?

"Off"



Ras-GDP

"On"

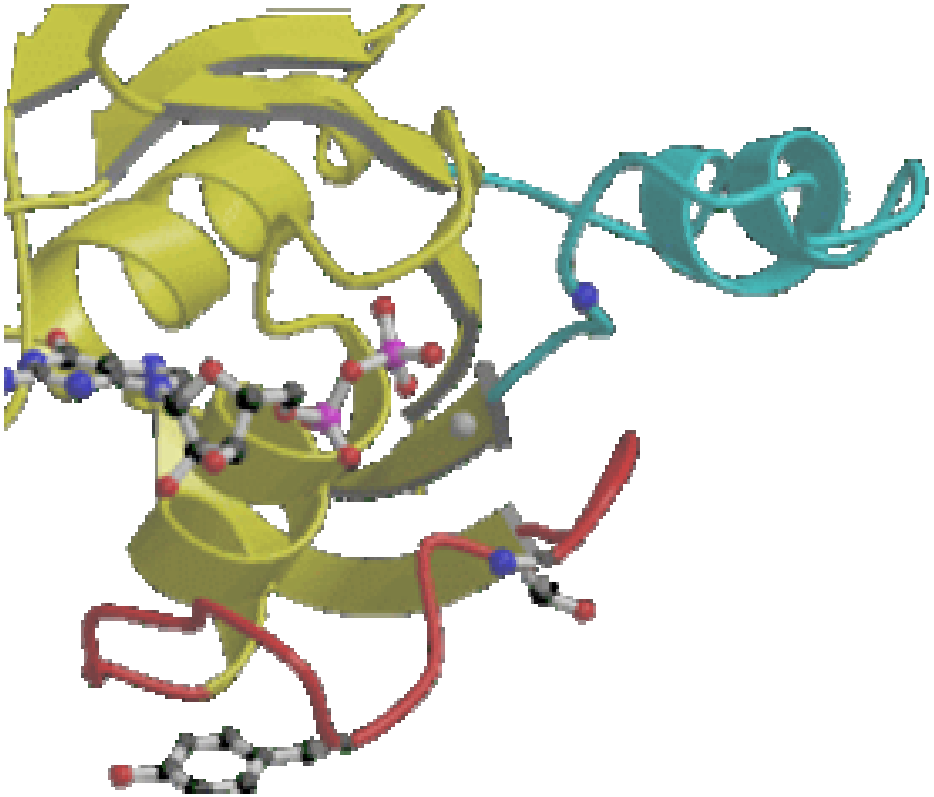


Ras-GTP

http://www.qub.ac.uk/bb/people/jnelson/jnelson/teaching.html

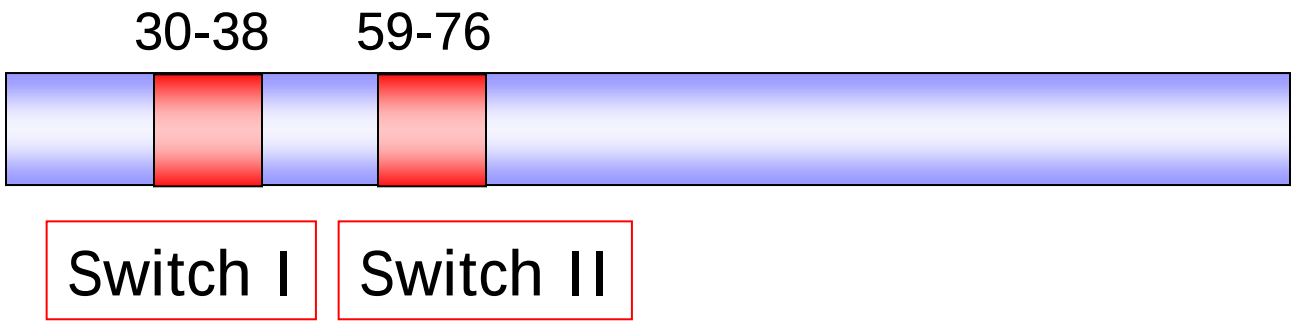
GTP hydrolysis flips the switch

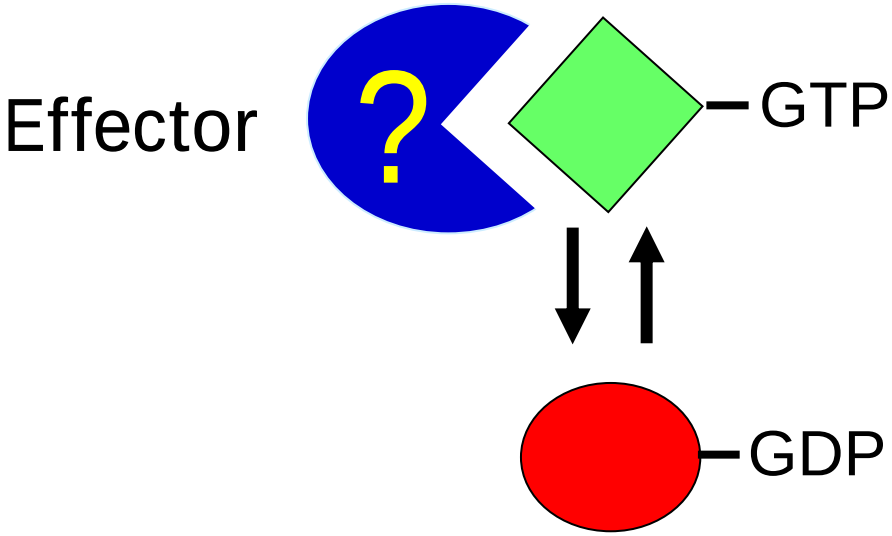
SI
SII



http://www.mpi-dortmund.mpg.de/departments/dep1/gtpase/gtpase_detail.php3

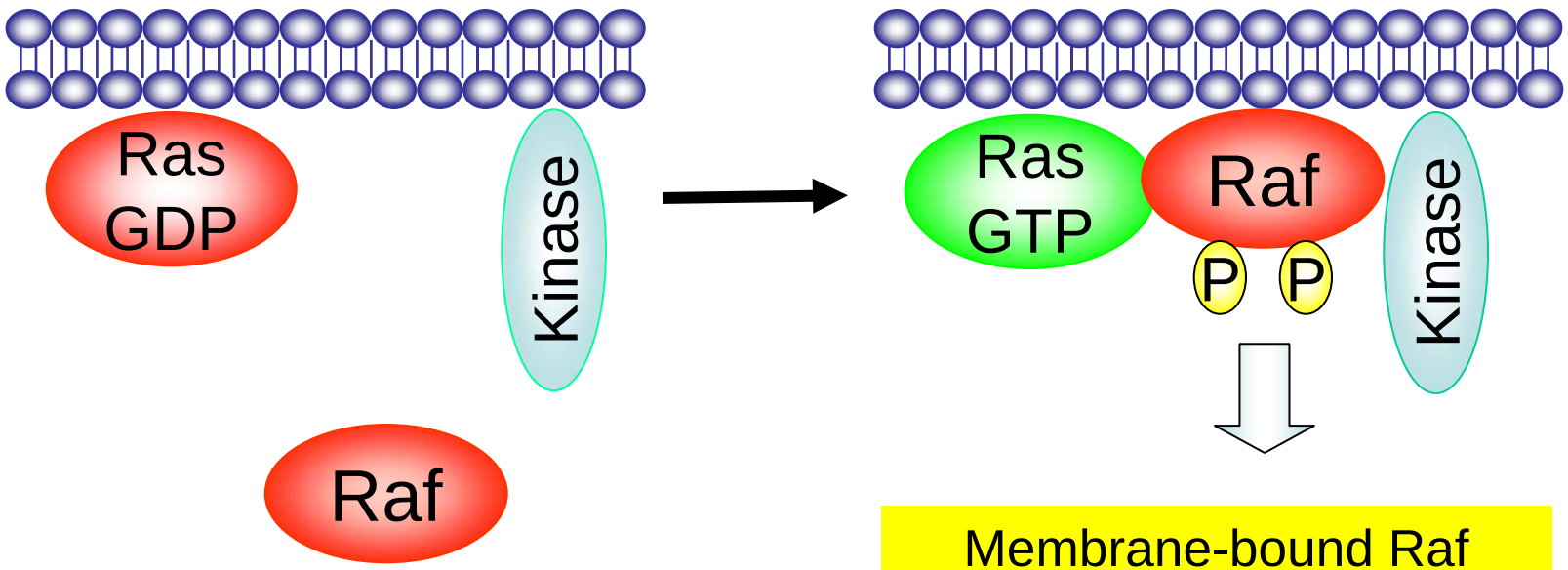
GTP-bound Ras interaction with downstream effectors





Preferential Binding to GTP-bound Ras

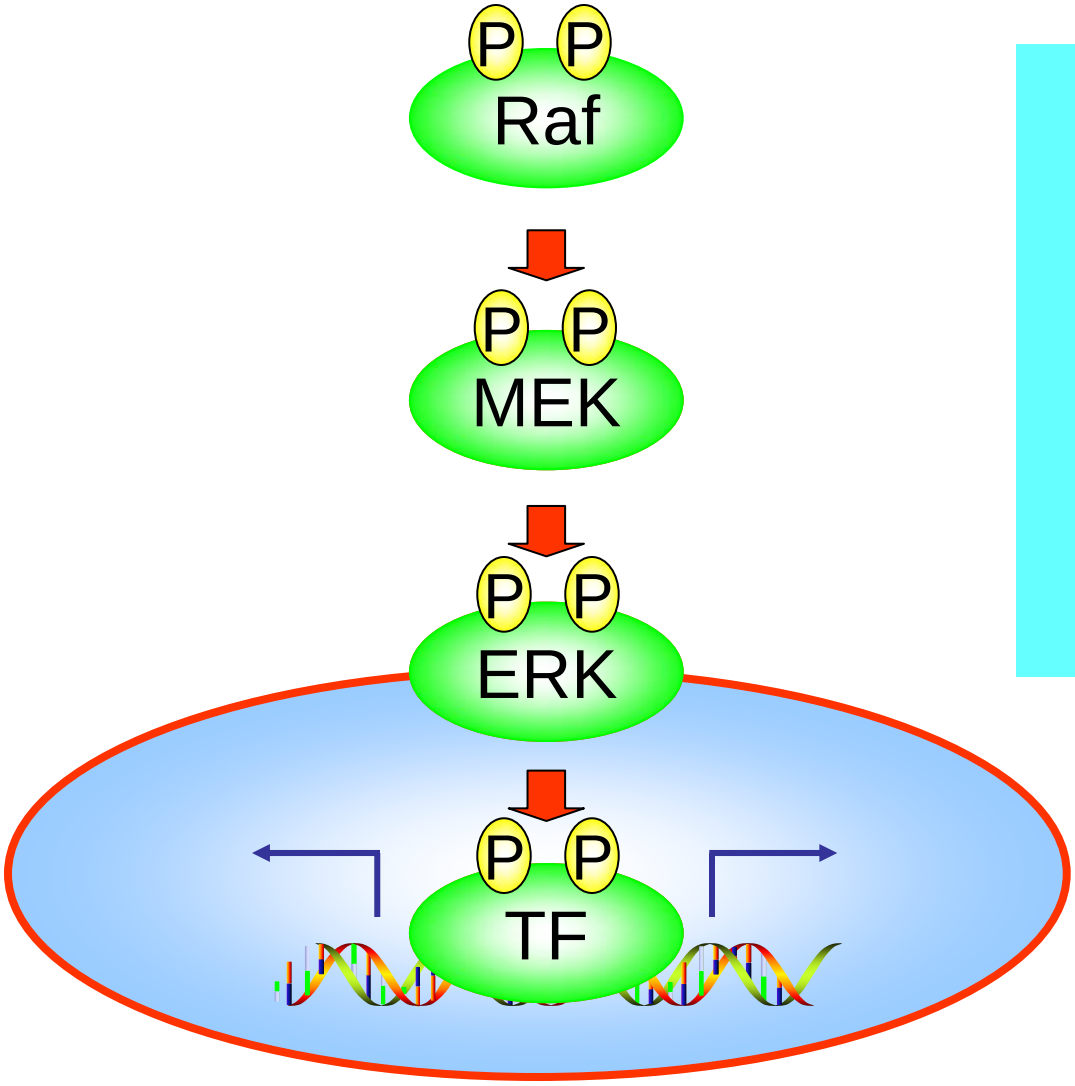
Activated Ras promotes Raf translocation to the plasma membrane



Cytosolic Raf is inactive

Membrane-bound Raf becomes phosphorylated and activated

The Raf-MEK-ERK protein kinase cascade

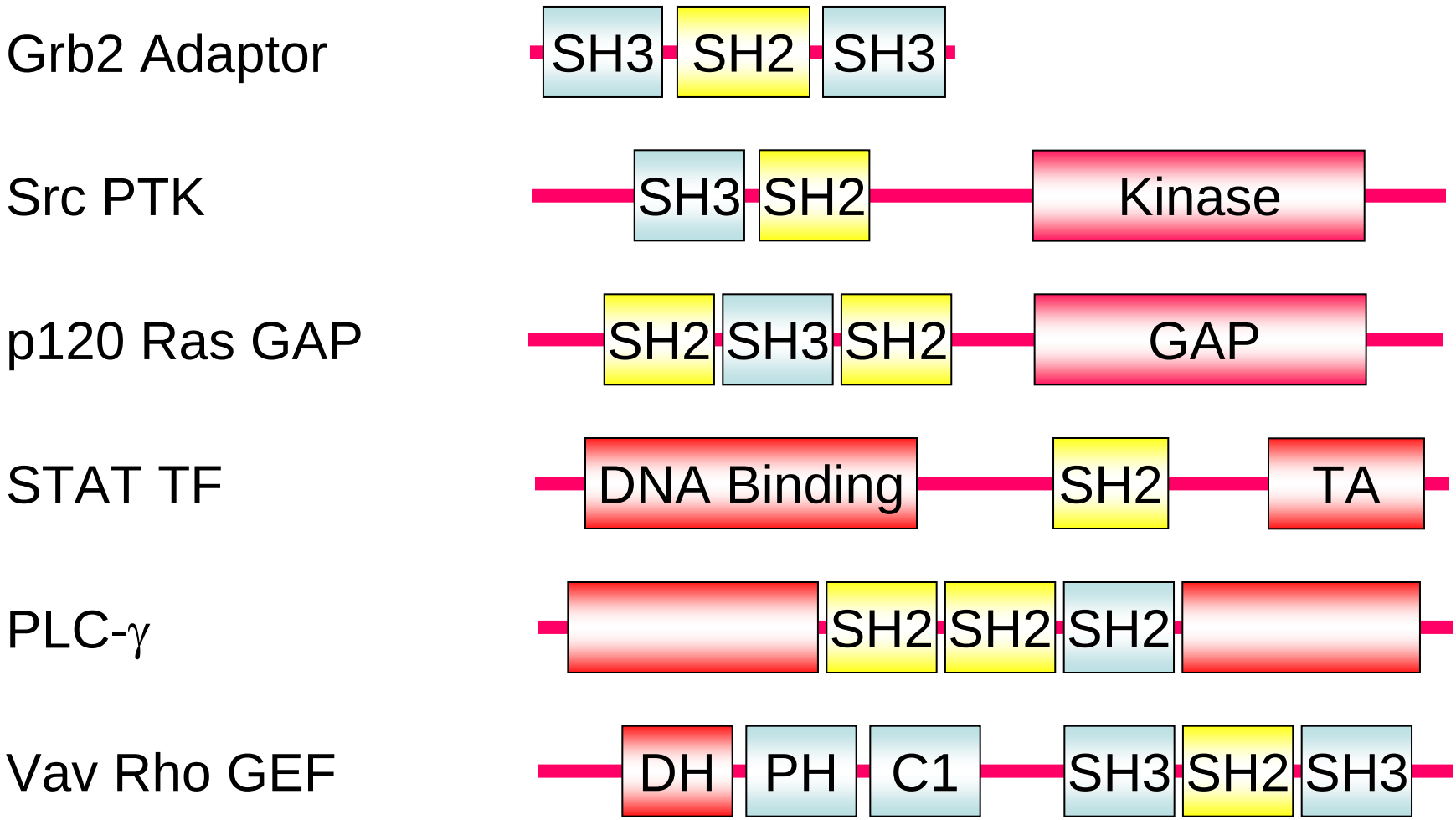


Activated ERK translocates to the nucleus and phosphorylates and activates transcription factors, stimulating changes in gene expression

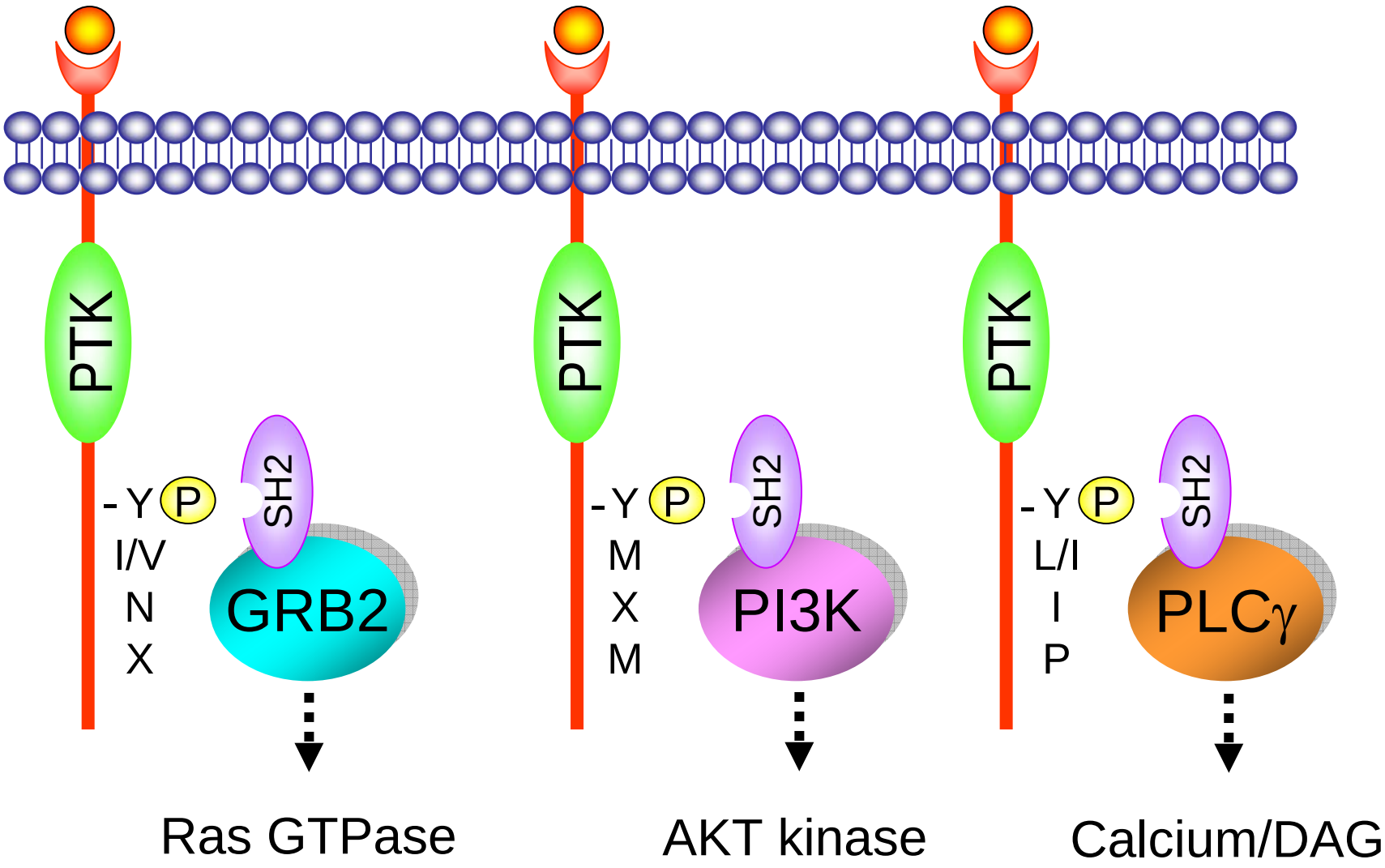
Signaling pathways are not linear

Signaling networks are complex

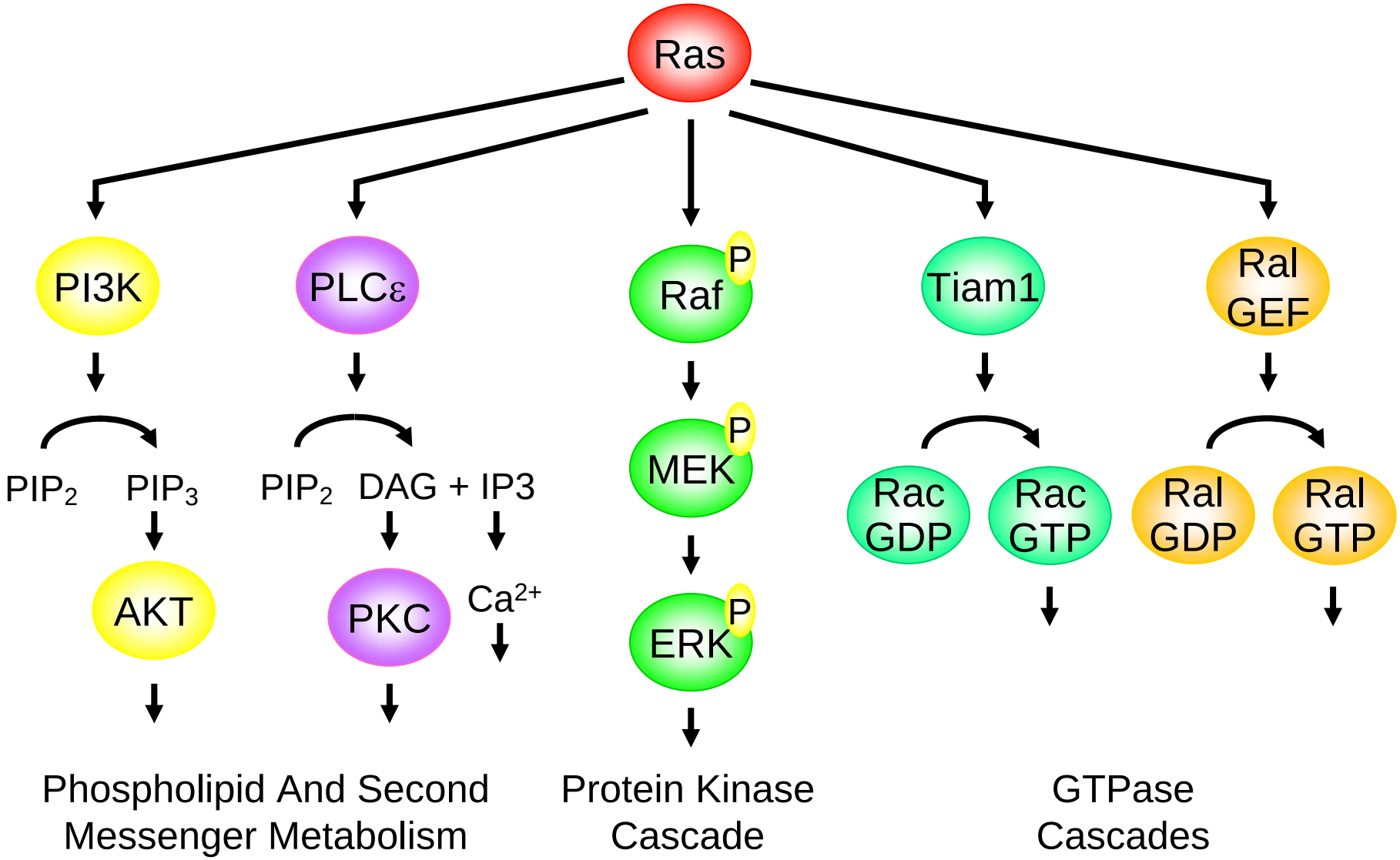
SH2 domain-containing proteins: proteins of diverse functions



Other SH2 domain-containing proteins bind activated EGFR



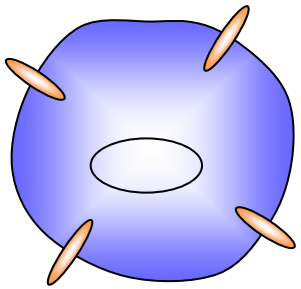
Ras activates multiple downstream effectors



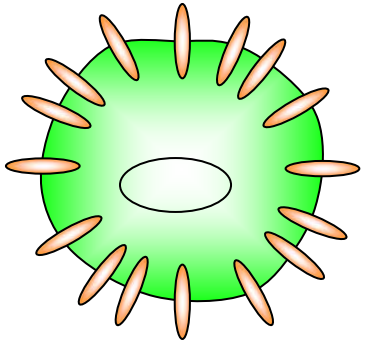
Cancer treatment

Signaling inhibitors

EGFR overexpression in cancer cells



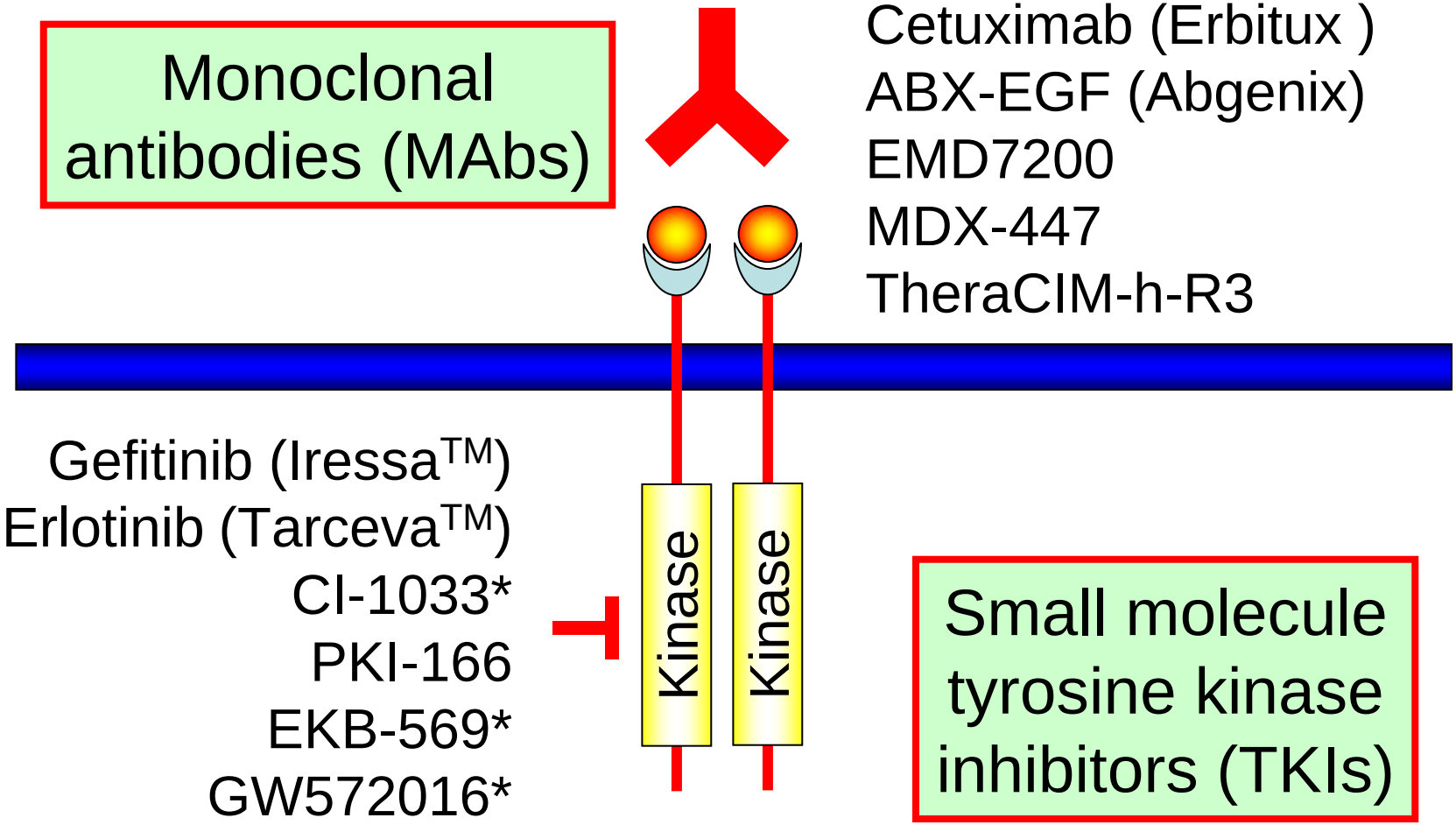
Normal cells with low levels of EGFR expression



Cancer cells overexpress EGFR, leading to uncontrolled growth

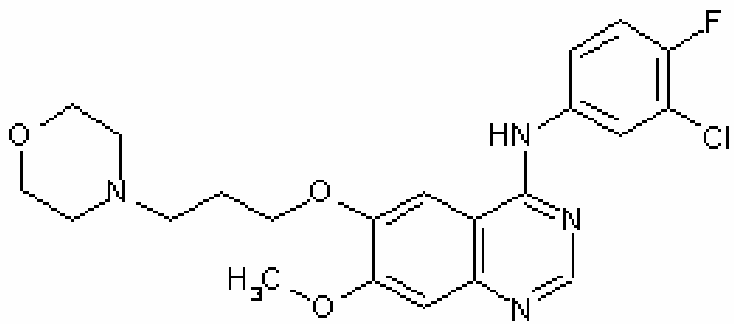
Head & Neck	80-100%
Colorectal	25-77%
Pancreatic	30-50%
Lung	40-80%
Esophageal	43-89%
Renal Cell	50-90%
Prostate	65%
Bladder	31-48%
Cervical	90%
Ovarian	35-70%
Breast	14-91%

EGFR inhibitors: two classes

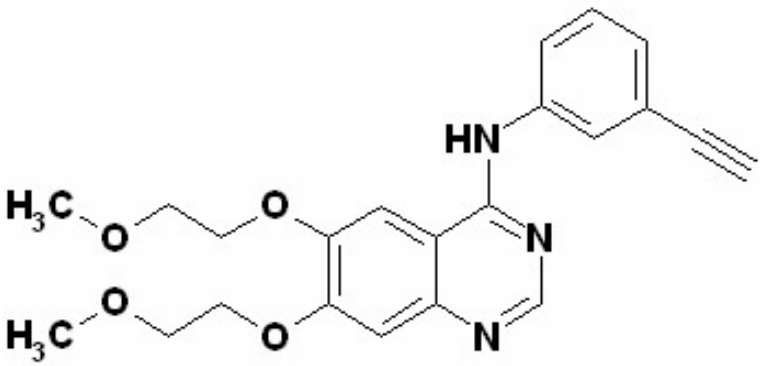


*Also inhibit HER2

EGFR tyrosine kinase inhibitors



Gefitinib (Iressa)



Erlotinib (Tarceva)

- ATP competitive inhibitors
- Oral bioavailability
- Most common toxicities are an acneiform rash and diarrhea, with severe adverse effects rare

Iressa approved for NSCLC treatment in 2003

- Treatment for patients whose cancer has continued to progress despite treatment with platinum-based and docetaxel chemotherapy.
- Clinical trial results of a study of NSCLC patients unresponsive to two prior treatments: 10% response rate (defined as at least 50% tumor shrinkage lasting at least one month).

Iressa (Gefitinib) failed to increase overall survival - 2004

- Despite initial tumor response, overall patient survival was not increased (5.6 v. 5.1 months for gefitinib and placebo, respectively).
- However, overall survival for patients of Asian origin (9.5 v. 5.5) or never-smokers (8.9 v. 6.1) was seen.

Tarceva approved for NSCLC treatment In 2004

- Approved as a treatment for NSCLC patients whose cancer has continued to progress despite other treatments, including at least one prior chemotherapy regimen.
- The median overall survival was 6.7 months in the Tarceva group compared with 4.7 months in the placebo group.

Erbitux approved for treatment of colon cancer in 2004

- For advanced colorectal cancer, in combination with irinotecan, or alone if patients cannot tolerate irinotecan.
- For patients unresponsive to irinotecan, the combination treatment of Erbitux and irinotecan shrank tumors in 22.9% of patients and delayed tumor growth by 4.1 months.
- For patients who received Erbitux alone, the tumor response rate was 10.8% and tumor growth was delayed by 1.5 months.

Anti-EGFR drug discovery

1960

1965 – Epidermal growth factor is identified

1967 – AEV is isolated from chicken with erythroblastosis

1970

1978 – EGFR determined to function as a protein kinase

1980

1983 – EGFR overexpression in human cancers

1983 – C225 anti-EGFR monoclonal antibody is described

1984 – EGFR identified as cellular homolog of viral ErbB oncogene

1984 – C225 blocks EGFR-overexpressing tumor cell growth in nude mice

1990

1988 – C225 evaluation in phase I clinical trials begin

2000

2002 – Iressa approved for use in Japan

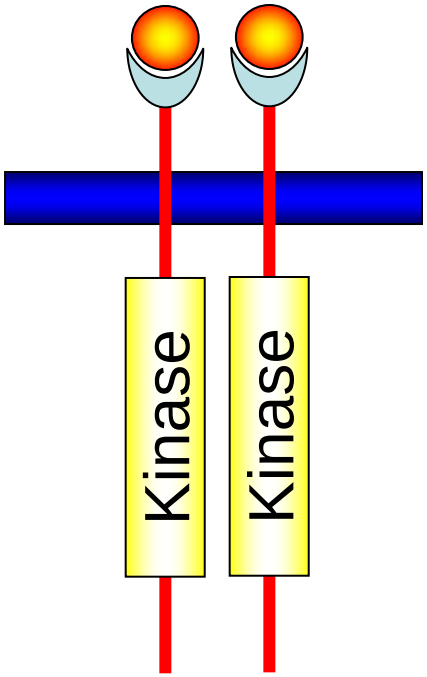
2003 – FDA approves Iressa for treatment of NSCLC

2004 – FDA approves Erbitux for treatment of colon cancer

>20 years from bench to clinic

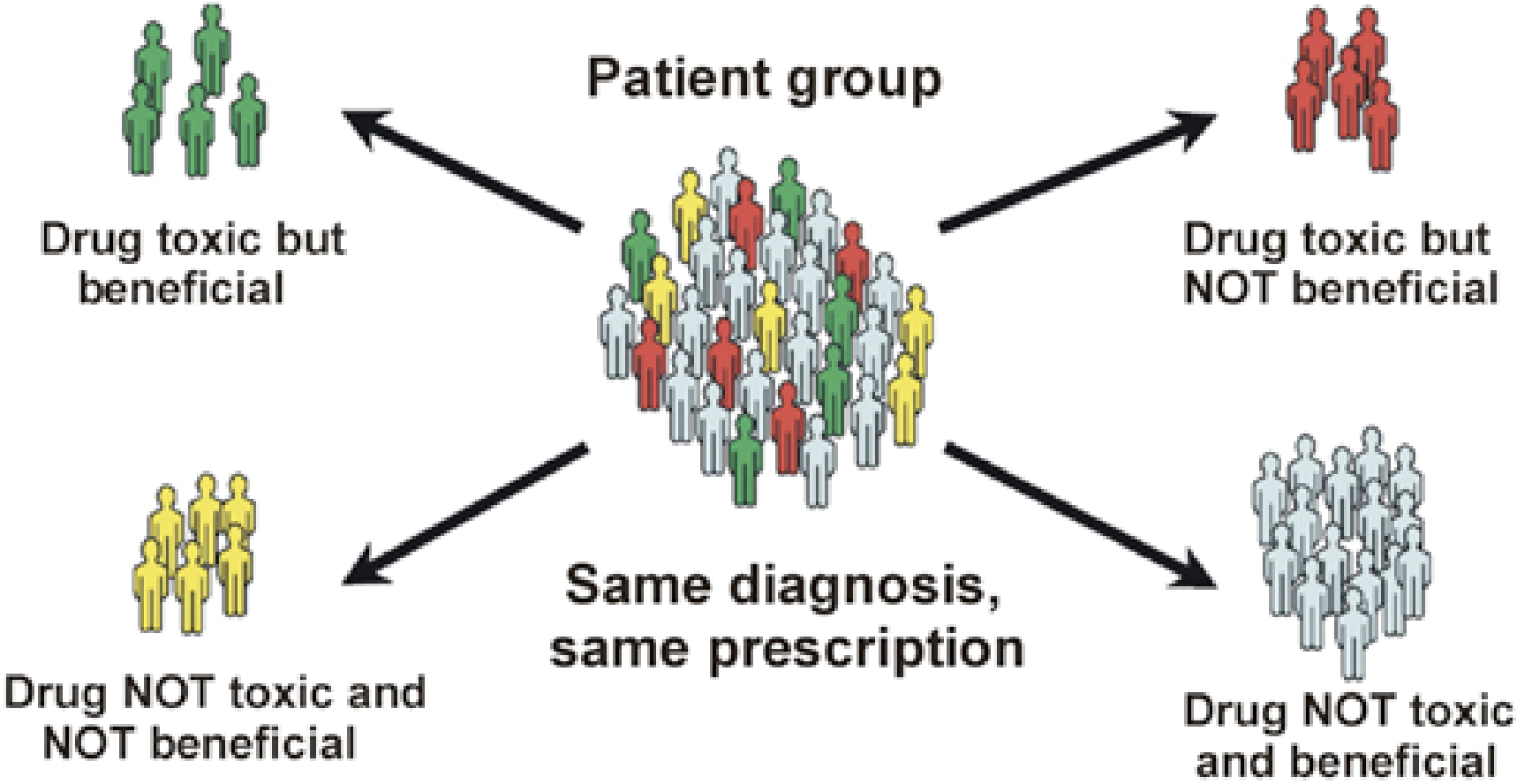
EGFR mutations define patients that respond to Iressa?

- Response rate of only 10-15% for EGFR positive NSCLC patients.
- 13/14 responders with EGFR mutations, 0/11 nonresponders with no EGFR mutations.



*Missense and deletion mutations in kinase domain

Pharmacogenomics: genetic markers to identify patients who will benefit



www2.eur.nl/fgg/ch1/cellbiology/patrinos/

Oncogenes involve gain of function

Tumor suppressors involve loss of function

Cancer is a multi-step genetic process

Protein kinases regulate signaling

GTPases are signaling regulators

Protein/lipid interaction domains are modular

Signaling is NOT linear: networks

FDA approval of protein kinase inhibitors

Target-based inhibitors with limited success

Pharmacogenomics for patient treatment