KRAS, Function,mutation and Frequency in Cancer

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Discovery

Discoveries of the potently oncogenic viruses

1964: Harvey murine sarcoma virus
1967: Kirsten murine sarcoma virus

their ability to cause rat sarcomas after their name as H-*ras* and K-*ras*

H-*ras* and **K-*ras***, with their protein names cited as **H-Ras** and or **K-Ras**

1973-1976: **viral *src* oncogene is a normal chicken gene transduced by the virus into its own genome, thereby converting a normal gene into a potent oncogenic agent**

1979-: NIH/3T3 cells become morphologically and growth-transformed by a DNA obtained from tumor have been infected Kirsten murine sarcoma virus.

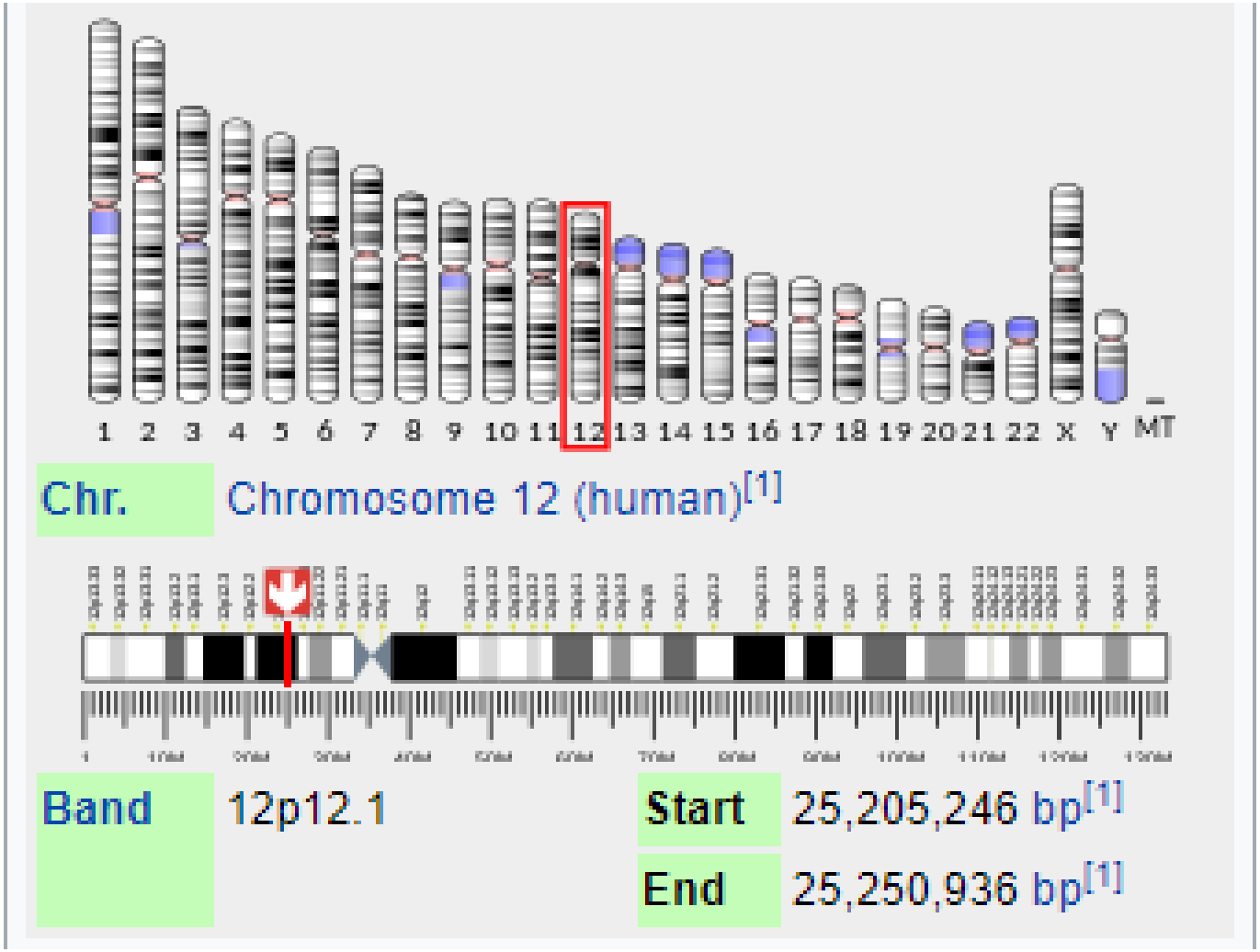
1982: Three groups made the discovery that the transforming genes identified in the NIH/3T3 DNA transfection assays were the same RAS genes identified earlier in Kirsten and Harvey sarcoma viruses

1983: **An abnormal form of the p21 protein expressed by colon and lung carcinoma cell lines showed that the gene encoding this protein is able to transform NIH3T3 cells .**

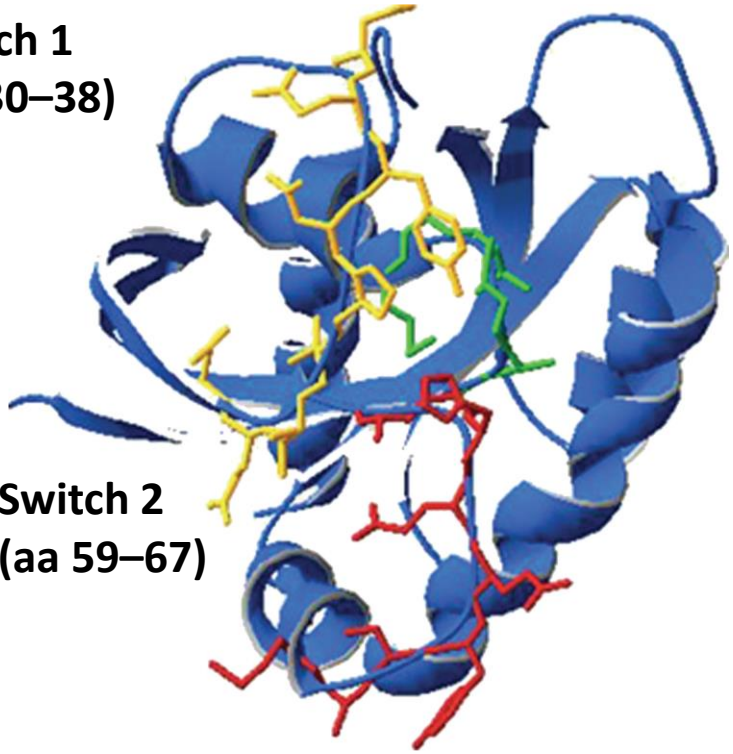
:1985 The transformation of NIH3T3 cells by an activated aberrant p21 proteins were encoded by the altered KRAS gene and their expression in carcinoma tissue was causally linked to an abnormal state of activation

Since then, it has been accepted that KRAS is one of front-line sensors that initiate the activation of an array of signaling that lead to cell transformation

45690 bp Gene location (Human)



K-Ras protein

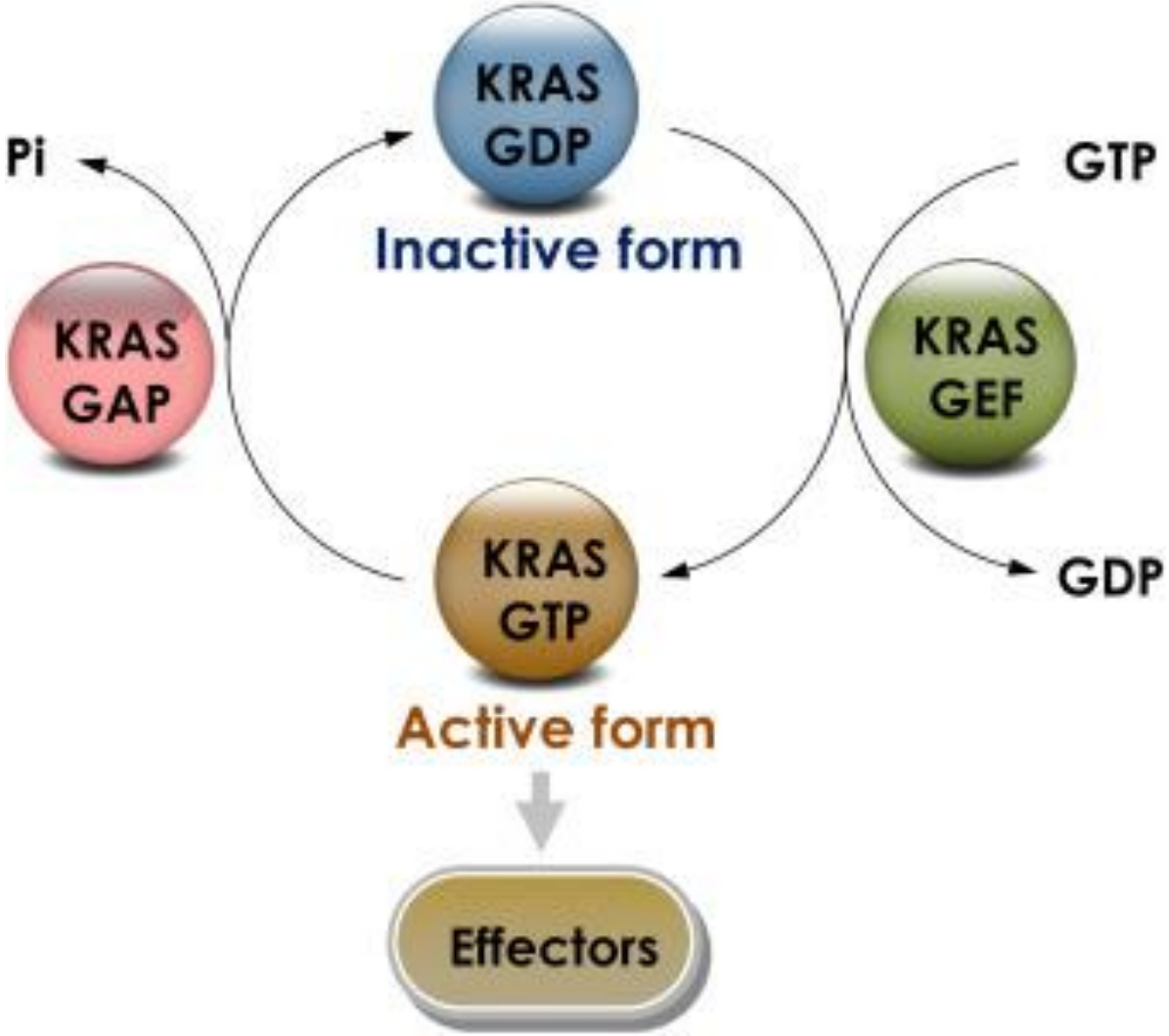


KRAS protein, contains 188 amino acid residues with a molecular mass of 21.6 kD

KRAS belongs to a group of small GTP-binding proteins, it's a GTPase

The KRAS protein is a plasmamembrane-localized molecular, regulating multiple signal transduction pathways

There are two important regions in RAS protein known as Switch 1 (amino acids 30–38) and Switch 2 (aminoacids 59–67) which form an effector loop, controlling the specificity of the binding of this protein to GTP molecules.

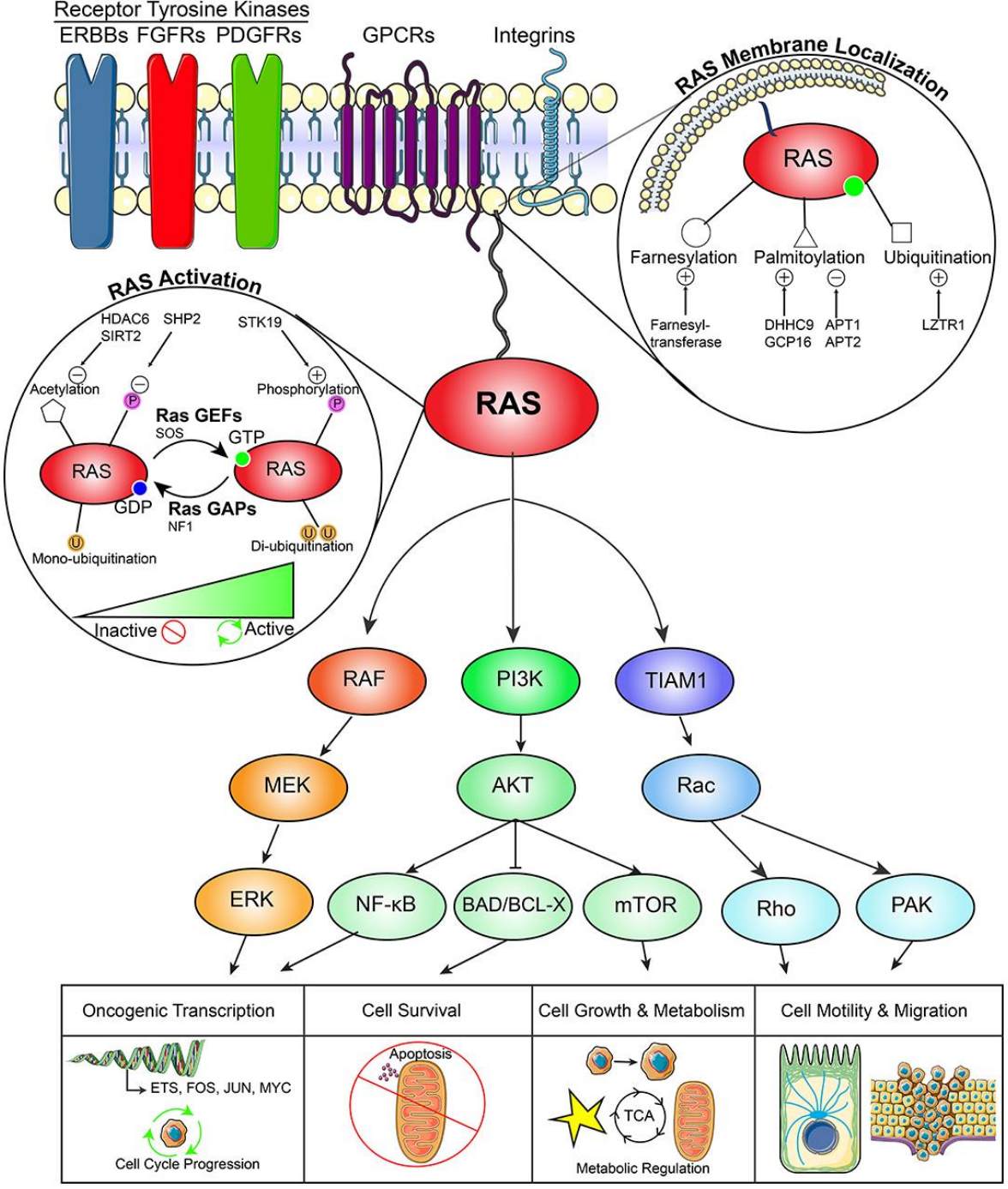


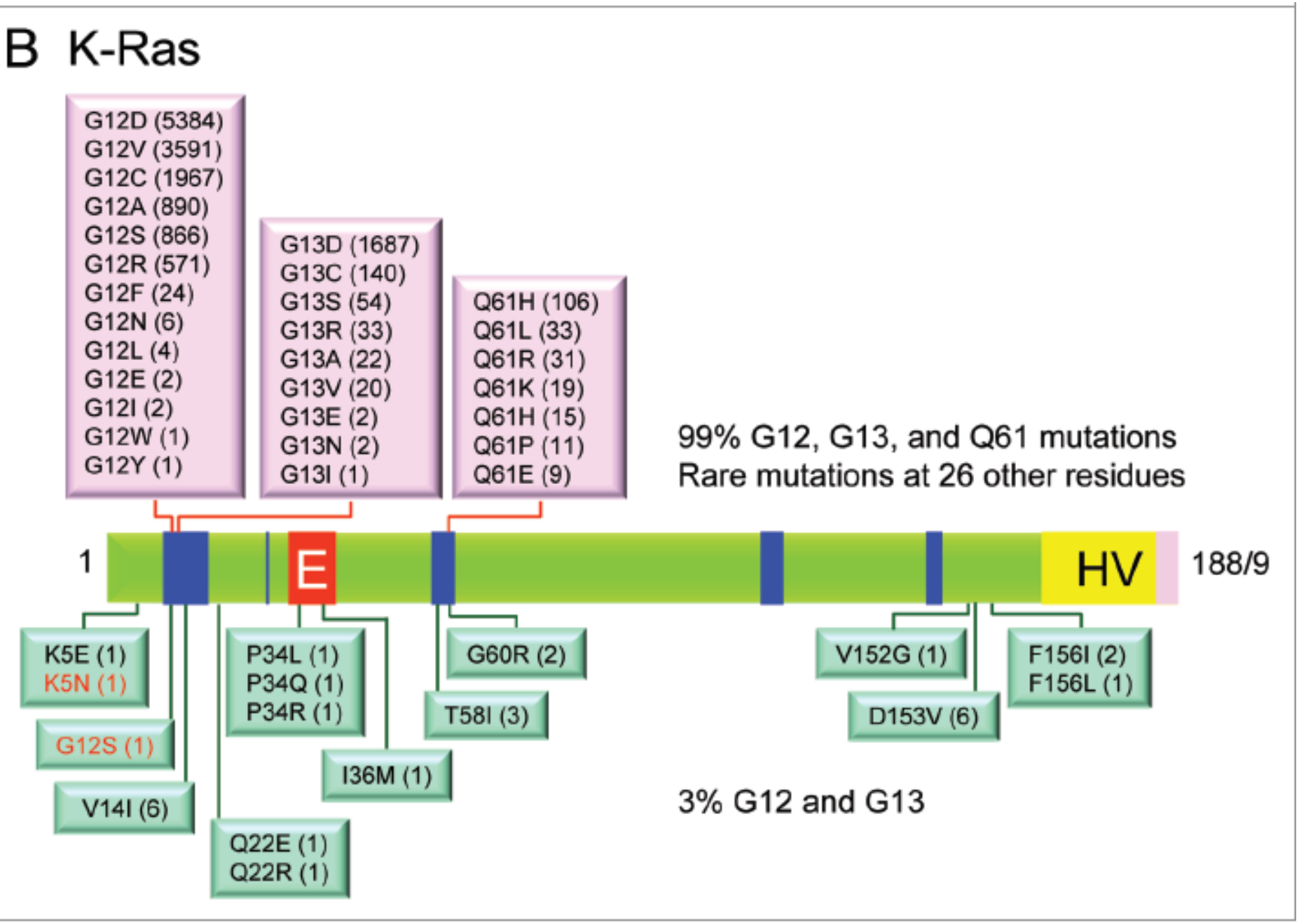
GTPase-activating proteins (GAPs)— amplify the GTPase activity of the RAS protein 100,000-fold

Mutations found in an oncogenic form of the RAS p21 protein impair GTPase activity and make the KRAS protein unresponsive to GAP proteins.

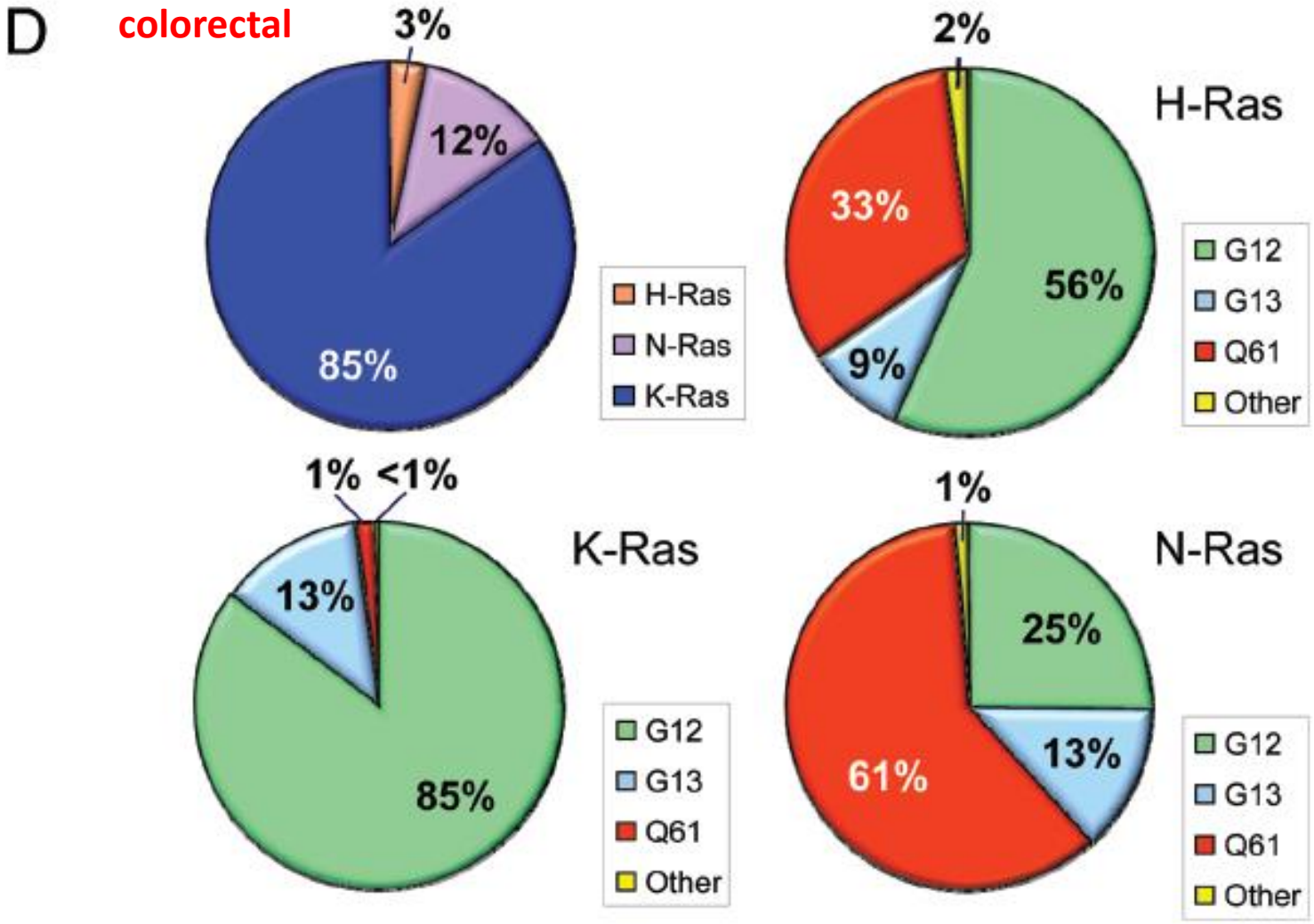
Mutated forms of p21 rapidly exchange GDP for GTP, which it prefers as a substrate, thus inducing the active state.

Such aberrant forms of KRAS protein deregulate many effectors, thus affecting several important cellular pathways


Receptor Tyrosine Kinases
ERBBs FGFRs PDGFRs
GPCRs
Integrins
RAS Membrane Localization
RAS
Farnesylation
Palmitoylation
Ubiquitination
Farnesyl-transferase
DHHC9 GCP16
APT1 APT2
LZTR1
RAS Activation
HDAC6 SIRT2
SHP2
STK19
Acetylation
Phosphorylation
Ras GEFs
SOS
GTP
RAS
GDP
Ras GAPs
NF1
Mono-ubiquitination
Di-ubiquitination
Inactive
Active
RAS
RAF
PI3K
TIAM1
MEK
AKT
Rac
ERK
NF-κB
BAD/BCL-X
mTOR
Rho
PAK
Oncogenic Transcription
Cell Survival
Cell Growth & Metabolism
Cell Motility & Migration
ETS, FOS, JUN, MYC
Cell Cycle Progression
Apoptosis
TCA
Metabolic Regulation


B K-Ras
G12D (5384)
G12V (3591)
G12C (1967)
G12A (890)
G12S (866)
G12R (571)
G12F (24)
G12N (6)
G12L (4)
G12E (2)
G12I (2)
G12W (1)
G12Y (1)
G13D (1687)
G13C (140)
G13S (54)
G13R (33)
G13A (22)
G13V (20)
G13E (2)
G13N (2)
G13I (1)
Q61H (106)
Q61L (33)
Q61R (31)
Q61K (19)
Q61H (15)
Q61P (11)
Q61E (9)
99% G12, G13, and Q61 mutations
Rare mutations at 26 other residues
1
E
HV
188/9
K5E (1)
K5N (1)
G12S (1)
V14I (6)
Q22E (1)
Q22R (1)
P34L (1)
P34Q (1)
P34R (1)
I36M (1)
T58I (3)
G60R (2)
V152G (1)
D153V (6)
F156I (2)
F156L (1)
3% G12 and G13

Distribution of Ras mutation in cancer



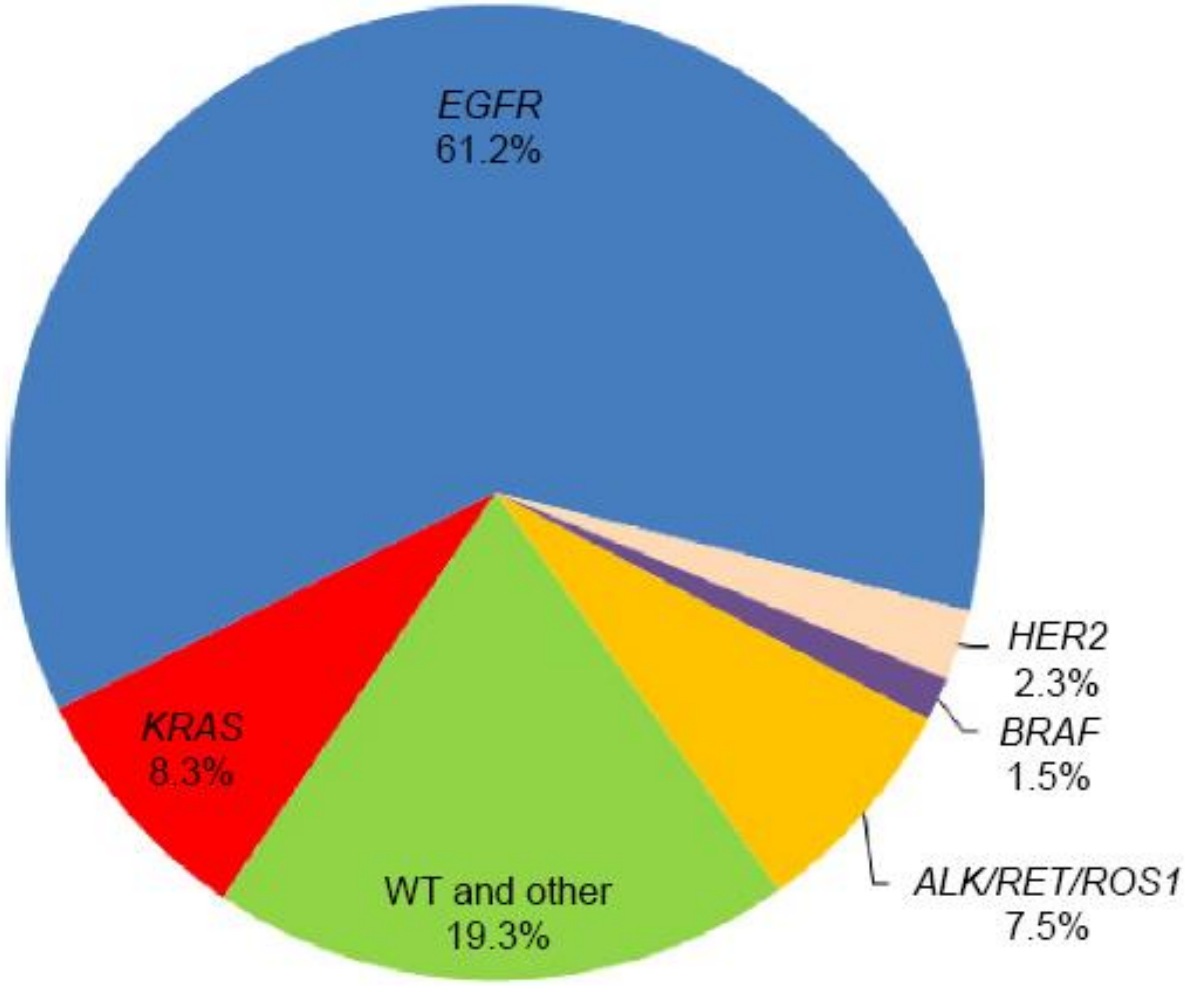


Figure 1 Frequency of gene mutations in 1,368 patients with lung adenocarcinoma.
Abbreviation: WT, wild type.

Table 1 Promising metabolic targets for *KRAS*-driven cancers

Metabolic change	Targets[a]	Cancer type[b]	Pathway[c]
Glucose-related	GFPT1	PDCA	HBP
	RPIA	PDCA	Non-oxidative PPP
	RPE	PDCA	Non-oxidative PPP
	GLUT1	CRC	Glycolysis
	Vitamin C	CRC	Redox/glycolysis
	HK2	NSCLC	Glycolysis
Amino acid-related	GOT1	PDCA	Glutaminolysis
	GLUD1	PDCA/CRC	Glutaminolysis
	MDH1	PDCA	Glutaminolysis
	ASNS	CRC	Glutaminolysis
	SLC25A22	CRC	Glutaminolysis
	SLC25A13	CRC	Glutaminolysis
Lysosome-related	Hydroxychloroquine	PDCA	Macropinocytosis/autophagy
	EIPA	PDCA	Macropinocytosis
	ATG7	NSCLC	Autophagy
Lipid-related	ACSL3	NSCLC	Lypogenesis
	FASN	NSCLC	Lypogenesis

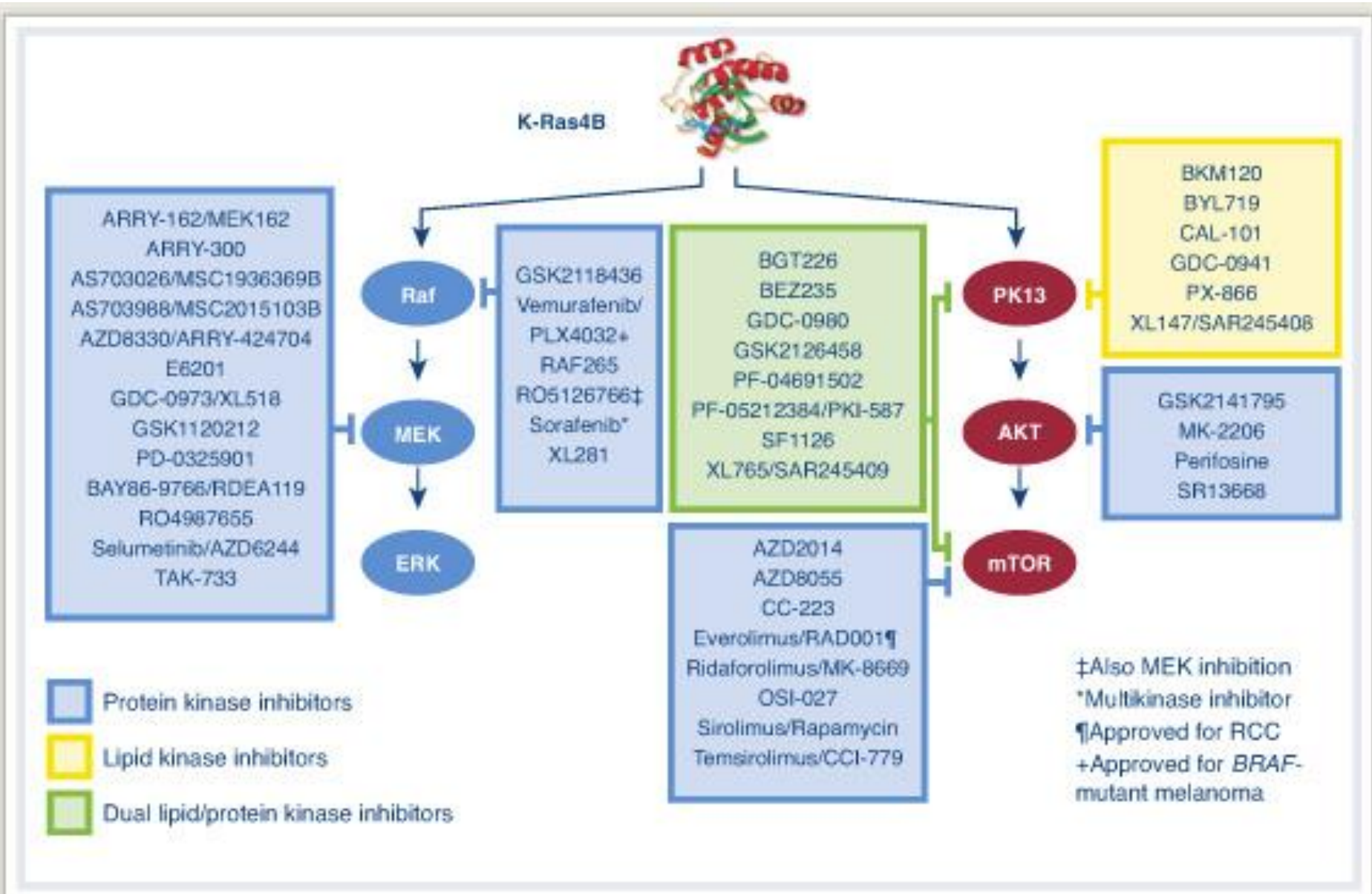


Fig. 1: Inhibitors of Raf or PI3K effector signaling under phase 1-III clinical evaluation. Courtesy of Channing J. Der, PhD.


Thank you