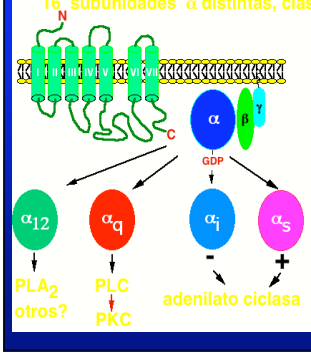
Ras family

G proteins

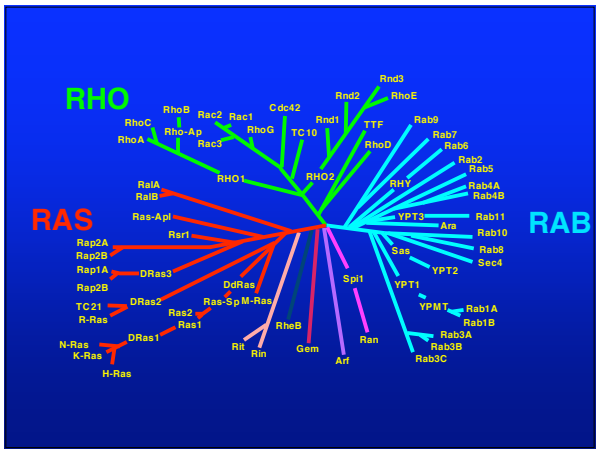
Receptores acoplados a proteínas G

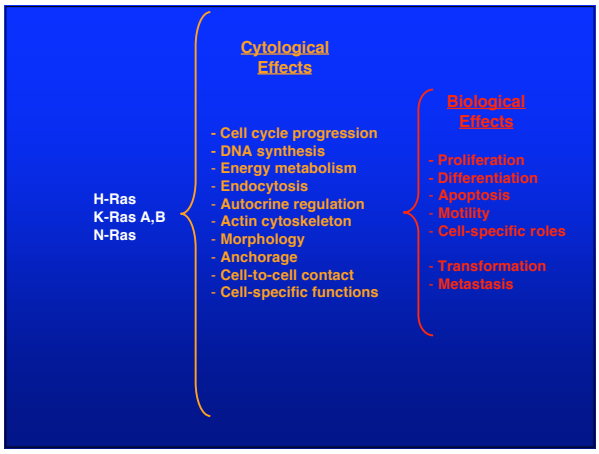
~1200 receptores identificados
(1% del genoma humano codifica este tipo de receptores)
Se expresan en todos los tejidos y clases de células
16 subunidades α distintas, clasificadas en 4 familias



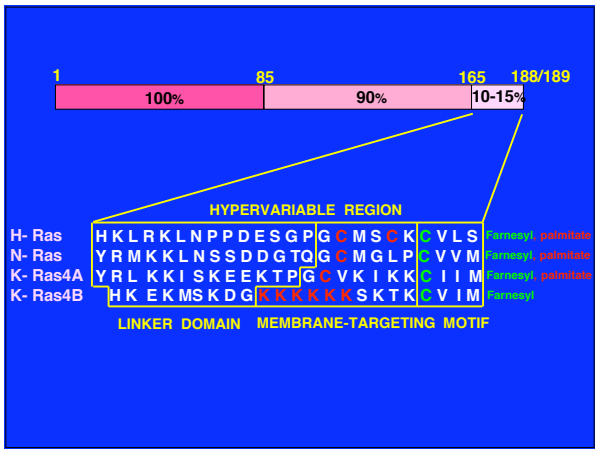
Funciones biológicas

gusto y olfato
(~1000 tipos de receptores)
fotorecepción
neurotransmisión
función de glándulas
endocrinas y paracrinas
quimiotaxis
exocitosis
control de la presión arterial
embriogénesis
desarrollo
proliferación y diferenciación celular



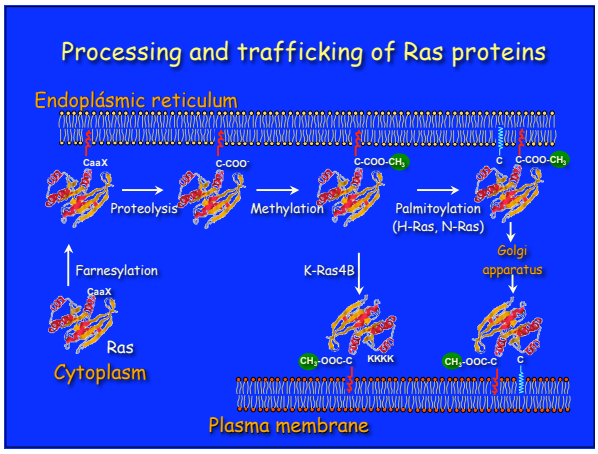


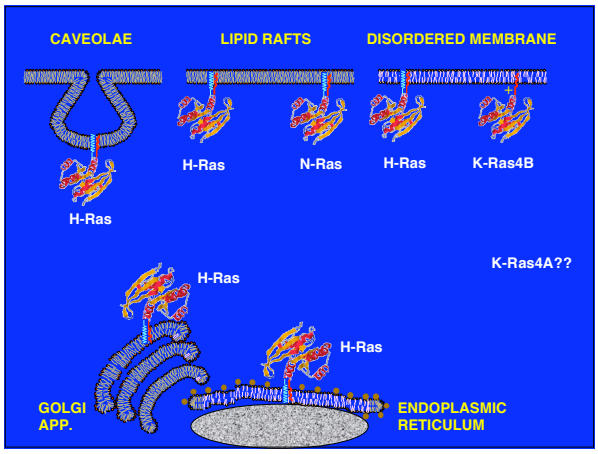
ONCOGEN	ORIGEN	GEN	CROMOSOMA (h)
H- *ras*	Retrovirus de sarcoma de rata (Harvey)	3 kb	11
K- *ras*	Retrovirus de sarcoma de rata (Kirstein)	35 kb	12
N- *ras*	Neuroblastoma humano (no retroviral)	7 kb	1

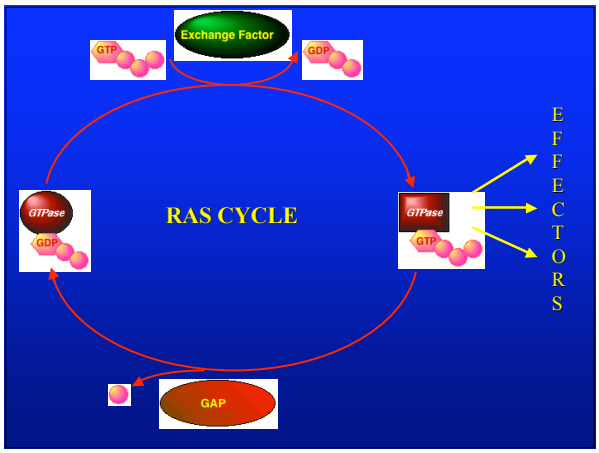


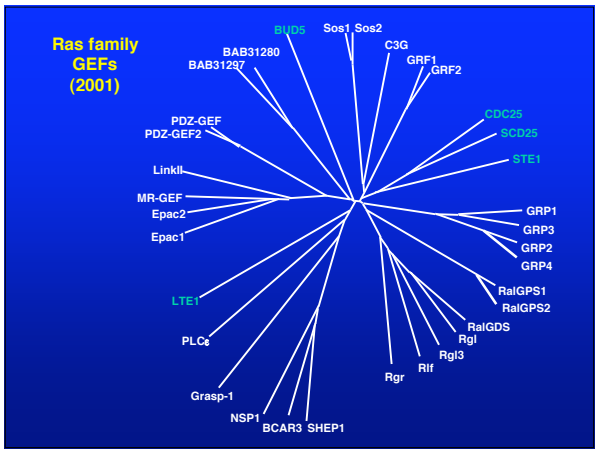
Main differences among H-, K-, and N-Ras

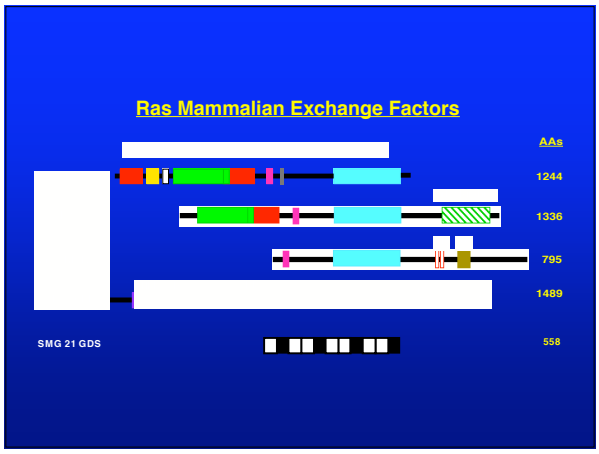
- Distinct patterns of expression in tissues and during development.
- Distinct involvement in human carcinogenesis.
- Distinct transforming potential in different cell types.
- Differences in their anti-apoptotic potential.
- Differences in their sensibility towards NF1- GAP.
- Differentially activated by some exchange factors.
- Quantitative differences in their ability to activate Raf and PI-3K.
- Distinct phenotypes of *ras* knock-out mice.

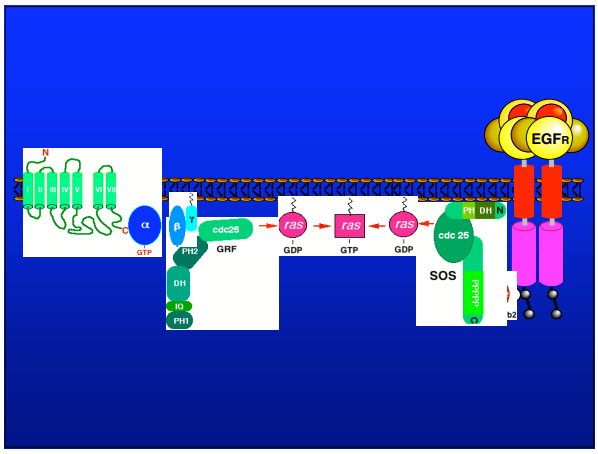

Processing and trafficking of Ras proteins
Endoplásmic reticulum
CaaX
C-COO⁻
C-COO-CH₃
C
C-COO-CH₃
Proteolysis
Methylation
Palmitoylation
(H-Ras, N-Ras)
Golgi
apparatus
Farnesylation
CaaX
Ras
Cytoplasm
K-Ras4B
CH₃-OOC-C
KKKK
CH₃-OOC-C
C
Plasma membrane

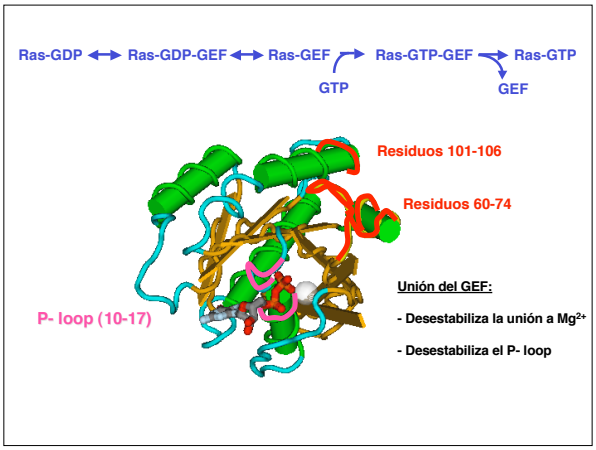

CAVEOLAE
LIPID RAFTS
DISORDERED MEMBRANE
H-Ras
H-Ras
N-Ras
H-Ras
K-Ras4B
K-Ras4A??
H-Ras
H-Ras
GOLGI
APP.
ENDOPLASMIC
RETICULUM

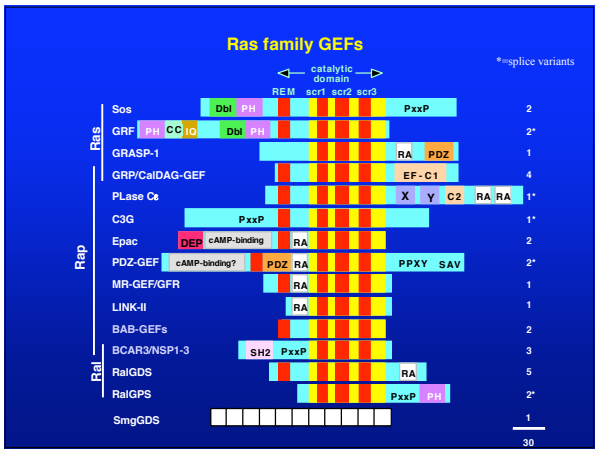

Exchange Factor
GTP
GDP
GTPase
GDP
RAS CYCLE
GTPase
GTP
E
F
F
E
C
T
O
R
S
GAP

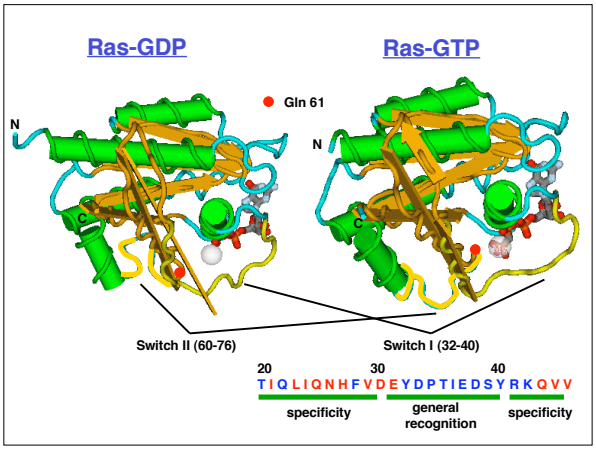

Ras family
GEFs
(2001)
BUD5
Sos1 Sos2
BAB31280
BAB31297
C3G
GRF1
GRF2
PDZ-GEF
PDZ-GEF2
CDC25
SCD25
STE1
LinkII
MR-GEF
Epac2
Epac1
GRP1
GRP3
GRP2
GRP4
RalGPS1
RalGPS2
LTE1
RalGDS
Rgl
PLCε
Rgl3
Rgr
Rlf
Grasp-1
NSP1
BCAR3
SHEP1

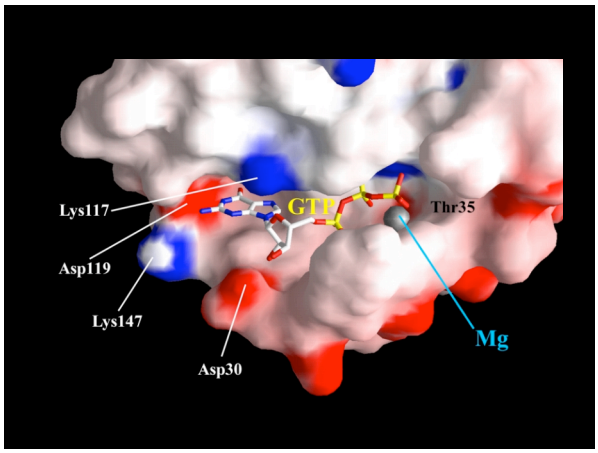

Ras Mammalian Exchange Factors
AAs
1244
1336
795
1489
SMG 21 GDS
558

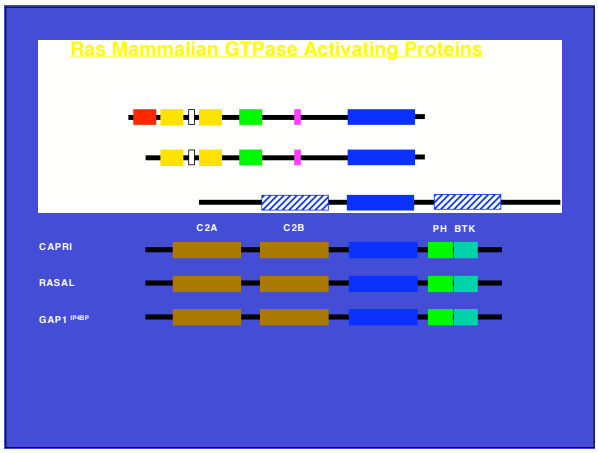

EGFR
cdc25
GRF
ras
GDP
GTP
GDP
cdc 25
SOS
PH
DH
PH2
DH
IQ
PH

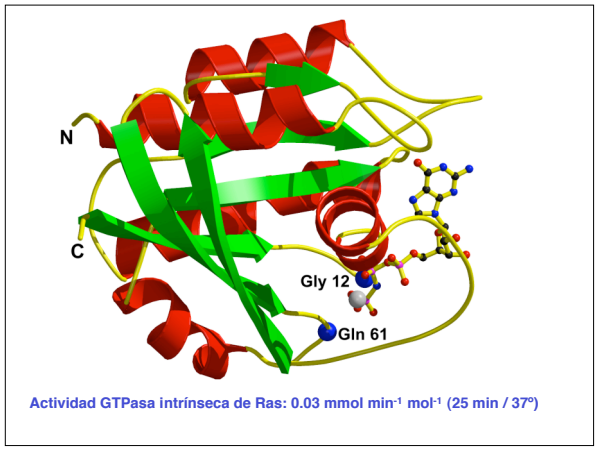

Ras-GDP
Ras-GDP-GEF
Ras-GEF
Ras-GTP-GEF
Ras-GTP
GTP
GEF
Residuos 101-106
Residuos 60-74
P- loop (10-17)
Unión del GEF:
- Desestabiliza la unión a Mg2+
- Desestabiliza el P- loop

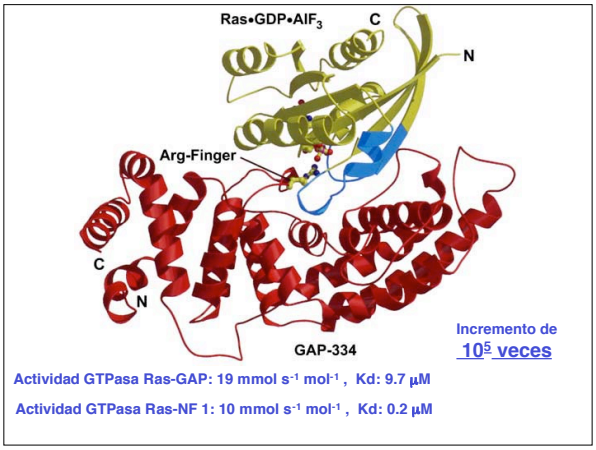

Ras family GEFs
*=splice variants
catalytic domain
REM
scr1
scr2
scr3
Ras
Rap
Ral
Sos
GRF
GRASP-1
GRP/CalDAG-GEF
PLase Cε
C3G
Epac
PDZ-GEF
MR-GEF/GFR
LINK-II
BAB-GEFs
BCAR3/NSP1-3
RalGDS
RalGPS
SmgGDS
30

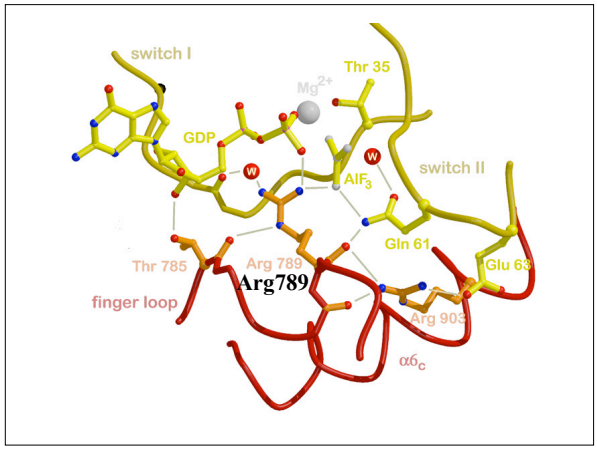

Ras-GDP
Ras-GTP
Gln 61
N
C
N
C
Switch II (60-76)
Switch I (32-40)
20
30
40
T I Q L I Q N H F V D E Y D P T I E D S Y R K Q V V
specificity
general recognition
specificity

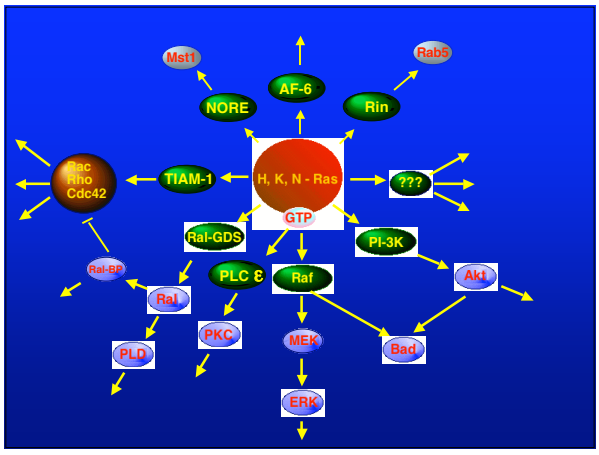

Lys117
GTP
Thr35
Asp119
Lys147
Asp30
Mg

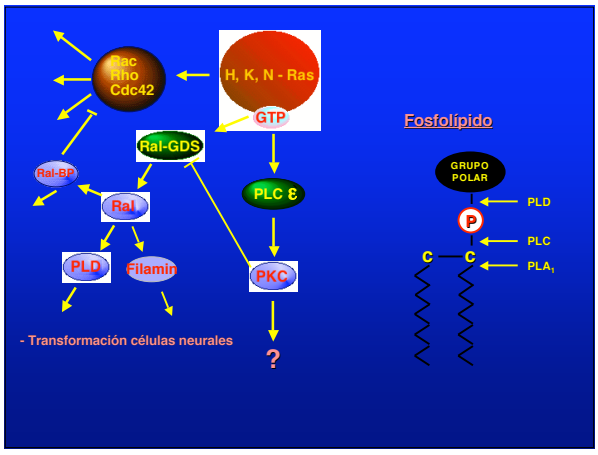

Ras Mammalian GTPase Activating Proteins
C2A
C2B
PH
BTK
CAPRI
RASAL
GAP1 IP4BP

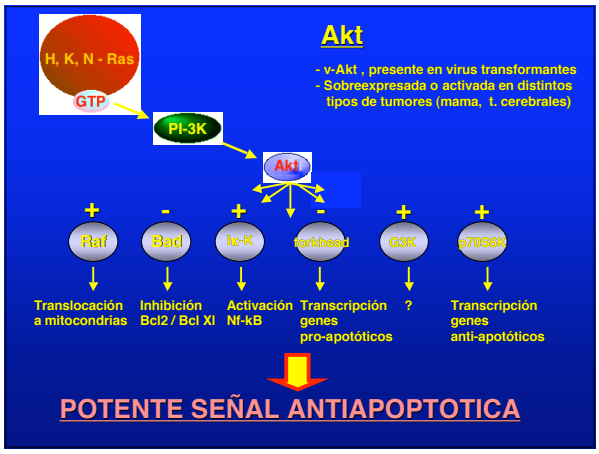

N
C
Gly 12
Gln 61
Actividad GTPasa intrínseca de Ras: 0.03 mmol min-1 mol-1 (25 min / 37º)

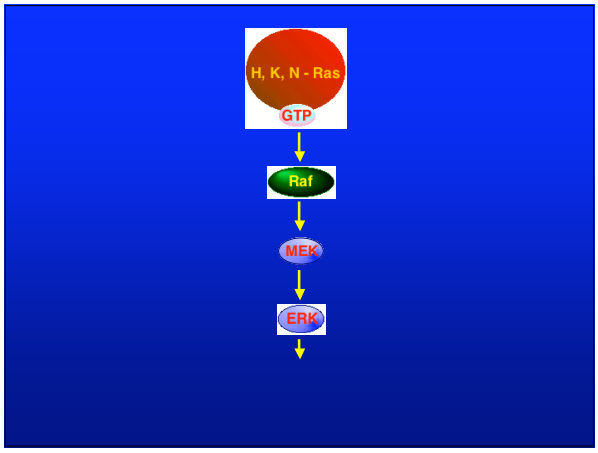

Ras•GDP•AlF3
C
N
Arg-Finger
C
N
GAP-334
Incremento de
10^5 veces
Actividad GTPasa Ras-GAP: 19 mmol s-1 mol-1 , Kd: 9.7 µM
Actividad GTPasa Ras-NF 1: 10 mmol s-1 mol-1 , Kd: 0.2 µM

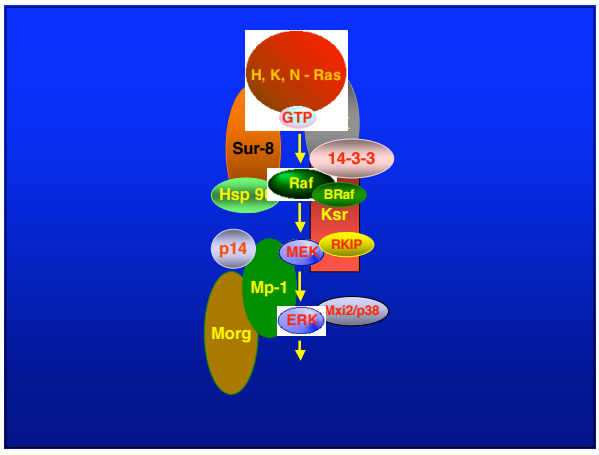

switch I
Thr 35
Mg2+
GDP
W
W
AlF3
switch II
Gln 61
Thr 785
Arg 789
Arg789
Glu 63
finger loop
Arg 903
α6c

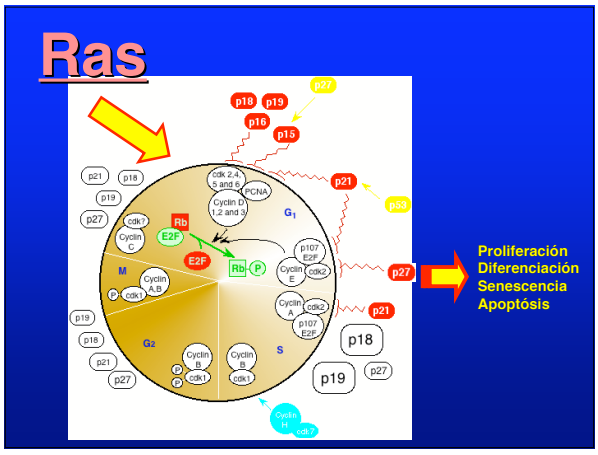

Mst1
Rab5
AF-6
NORE
Rin
Rac
Rho
Cdc42
TIAM-1
H, K, N - Ras
???
GTP
Ral-GDS
PI-3K
Ral-BP
PLC ε
Raf
Akt
Ral
PKC
MEK
Bad
PLD
ERK

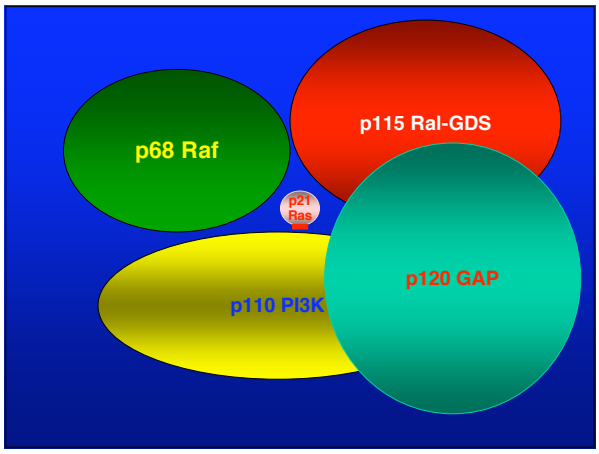

Rac
Rho
Cdc42
H, K, N - Ras
GTP
Ral-GDS
Ral-BP
Ral
PLC ε
PLD
Filamin
PKC
- Transformación células neurales
?
Fosfolípido
GRUPO POLAR
PLD
P
PLC
C
C
PLA1

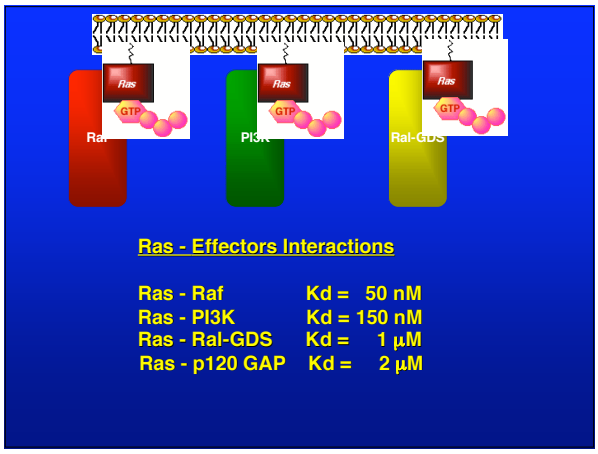

Akt
- v-Akt , presente en virus transformantes
- Sobreexpresada o activada en distintos tipos de tumores (mama, t. cerebrales)
H, K, N - Ras
GTP
PI-3K
Akt
+
Raf
-
Bad
+
Ik-K
-
forkhead
+
GSK
+
p70S6K
Translocación a mitocondrias
Inhibición Bcl2 / Bcl Xl
Activación Nf-kB
Transcripción genes pro-apotóticos
?
Transcripción genes anti-apotóticos
POTENTE SEÑAL ANTIAPOPTOTICA

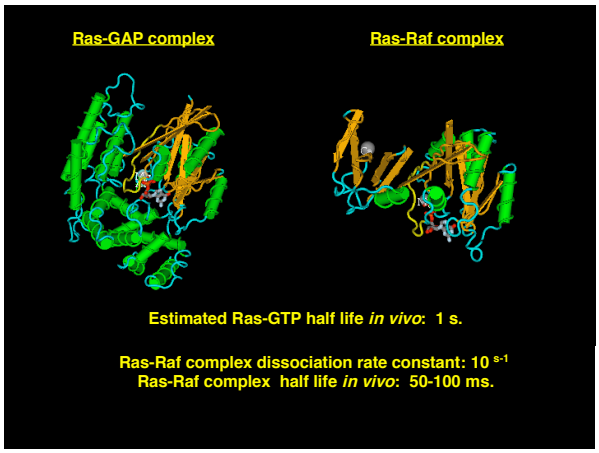

H, K, N - Ras
GTP
Raf
MEK
ERK

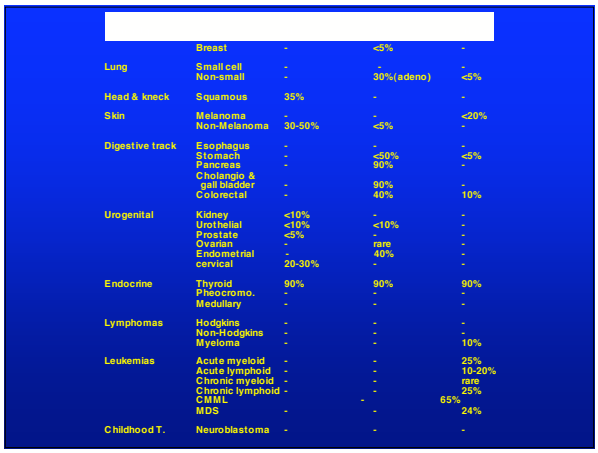

H, K, N - Ras
GTP
Sur-8
14-3-3
Hsp 9
Raf
BRaf
Ksr
p14
MEK
RKIP
Mp-1
ERK
Mxi2/p38
Morg


Ras
p18
p19
p16
p15
p27
p21
p18
p19
p27
cdk 2,4, 5 and 6
PCNA
Cyclin D 1,2 and 3
G1
cdk7
Cyclin C
Rb
E2F
M
Cyclin A,B
cdk1
p107
E2F
Cyclin E
cdk2
Cyclin A
G2
Cyclin B
S
p18
p19
p27
Cyclin H
cdk7
p53
Proliferación
Diferenciación
Senescencia
Apoptósis

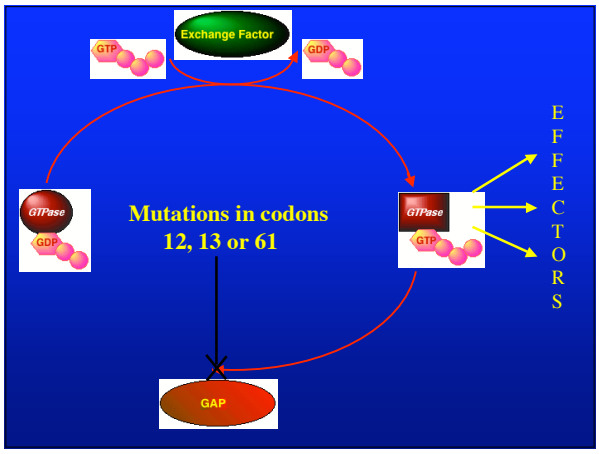


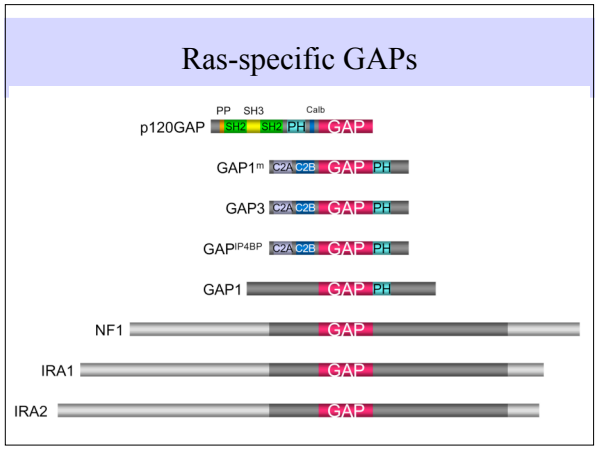


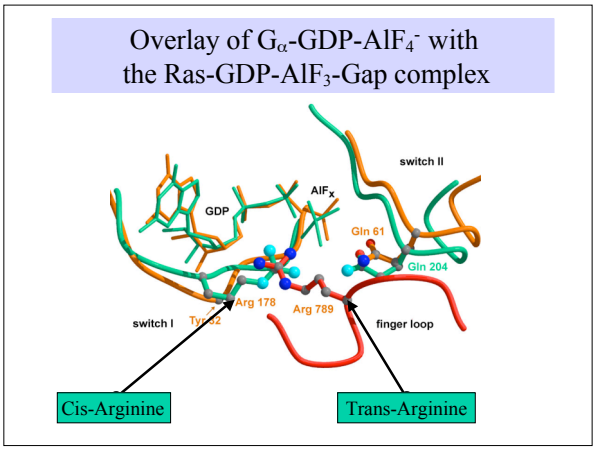


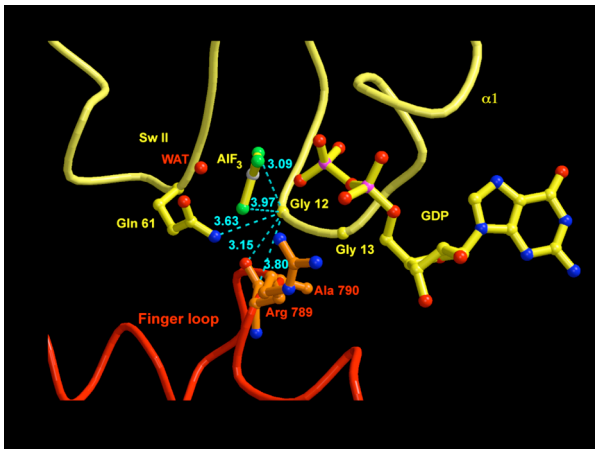


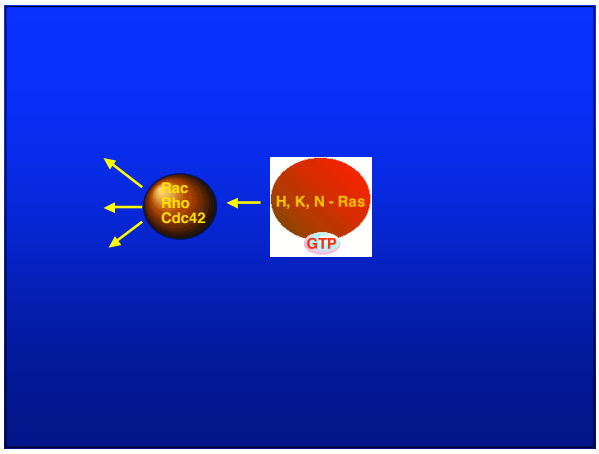
	Breast	-	<5%	-
Lung	Small cell	-	-	-
	Non-small	-	30%(adeno)	<5%
Head & kneck	Squamous	35%	-	-
Skin	Melanoma	-	-	<20%
	Non-Melanoma	30-50%	<5%	-
Digestive track	Esophagus	-	-	-
	Stomach	-	<50%	<5%
	Pancreas	-	90%	-
	Cholangio & gall bladder	-	90%	-
	Colorectal	-	40%	10%
Urogenital	Kidney	<10%	-	-
	Urothelial	<10%	<10%	-
	Prostate	<5%	-	-
	Ovarian	-	rare	-
	Endometrial	-	40%	-
	cervical	20-30%	-	-
Endocrine	Thyroid	90%	90%	90%
	Pheocromo.	-	-	-
	Medullary	-	-	-
Lymphomas	Hodgkins	-	-	-
	Non-Hodgkins	-	-	-
	Myeloma	-	-	10%
Leukemias	Acute myeloid	-	-	25%
	Acute lymphoid	-	-	10-20%
	Chronic myeloid	-	-	rare
	Chronic lymphoid	-	-	25%
	CMML	-	-	65%
	MDS	-	-	24%
Childhood T.	Neuroblastoma	-	-	-

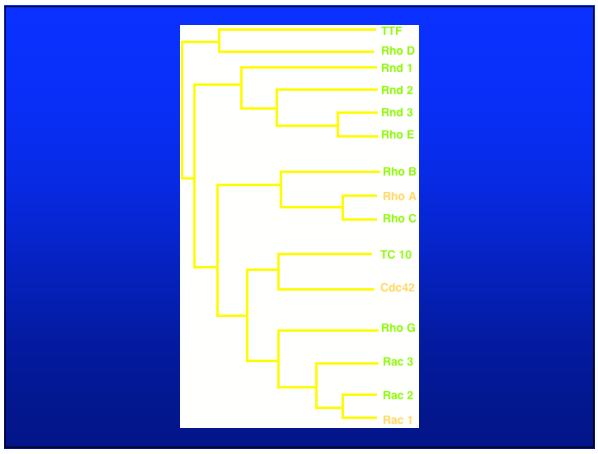

Exchange Factor
GTP
GDP
GTPase
GDP
GTPase
GTP
Mutations in codons
12, 13 or 61
GAP
EFFECTORS

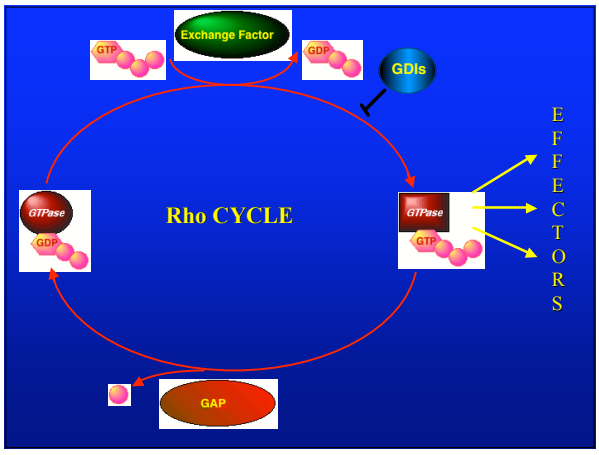

Ras-specific GAPs
PP
SH3
Calb
p120GAP
SH2
SH2
PH
GAP
GAP1m
C2A
C2B
GAP
PH
GAP3
C2A
C2B
GAP
PH
GAPIP4BP
C2A
C2B
GAP
PH
GAP1
GAP
PH
NF1
GAP
IRA1
GAP
IRA2
GAP

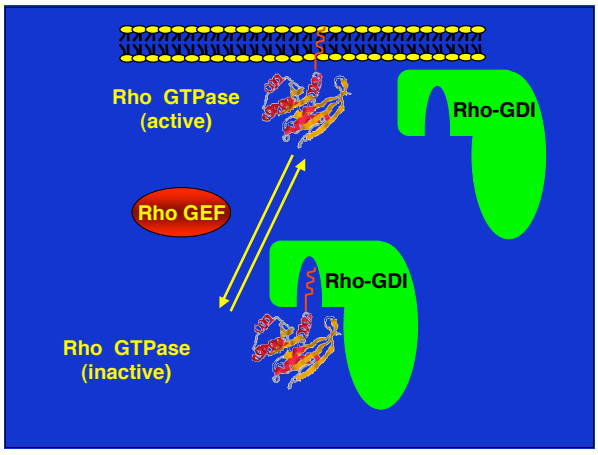

Overlay of Gα-GDP-AlF4- with
the Ras-GDP-AlF3-Gap complex
switch II
AlFx
GDP
Gln 61
Gln 204
Arg 178
Arg 789
switch I
finger loop
Cis-Arginine
Trans-Arginine

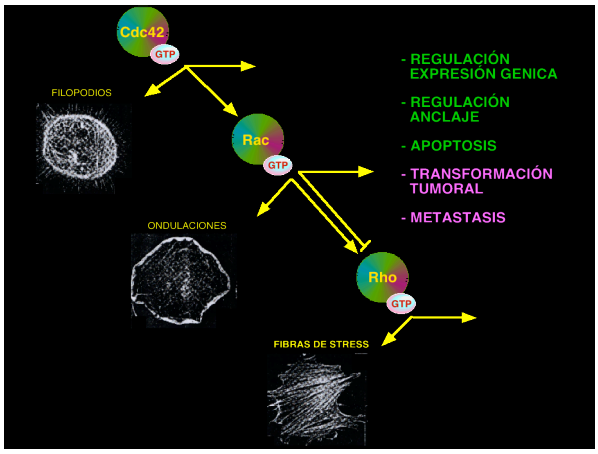

α1
Sw II
WAT
AlF3
3.09
3.97
Gly 12
GDP
Gln 61
3.63
3.15
Gly 13
3.80
Ala 790
Arg 789
Finger loop

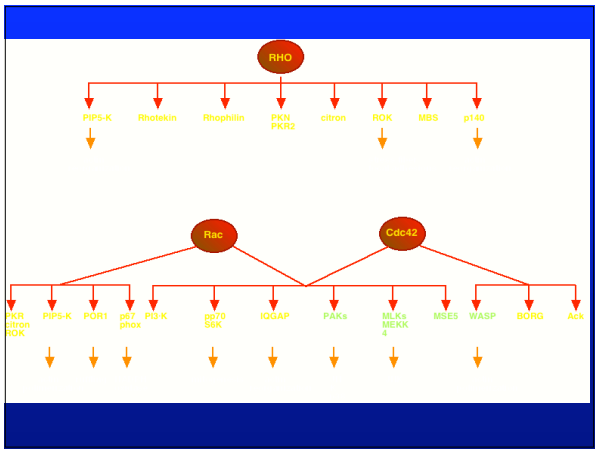

Rac
Rho
Cdc42
H, K, N - Ras
GTP

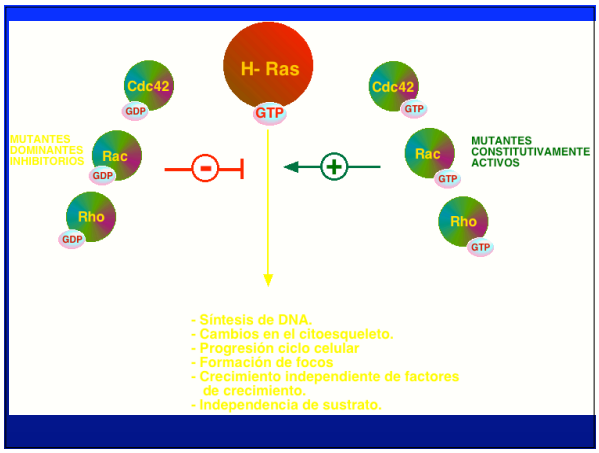

TTF
Rho D
Rnd 1
Rnd 2
Rnd 3
Rho E
Rho B
Rho A
Rho C
TC 10
Cdc42
Rho G
Rac 3
Rac 2
Rac 1

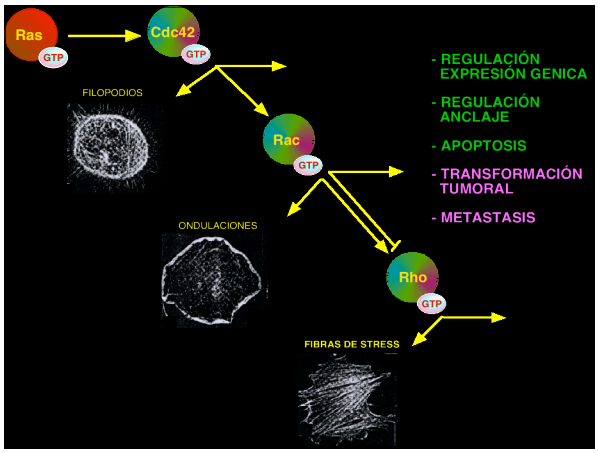

Exchange Factor
GTP
GDP
GDIs
GTPase
GDP
Rho CYCLE
GTPase
GTP
E
F
F
E
C
T
O
R
S
GAP

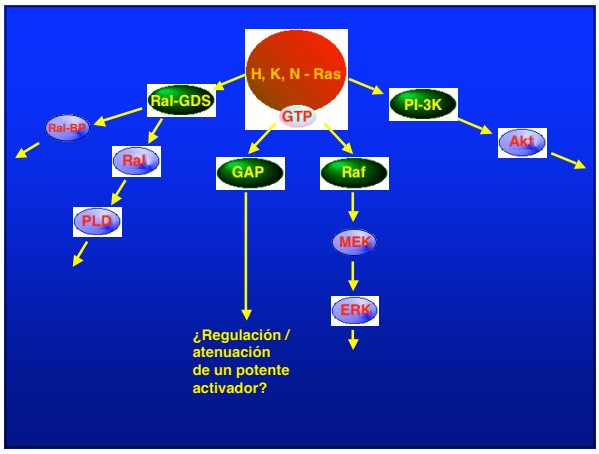

Rho GTPase
(active)
Rho-GDI
Rho GEF
Rho-GDI
Rho GTPase
(inactive)

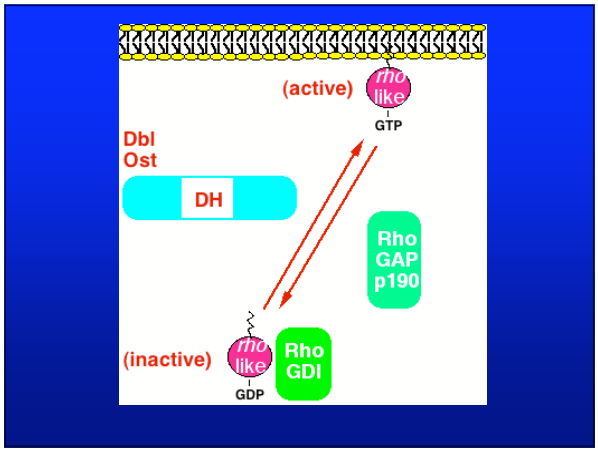

Cdc42
GTP
FILOPODIOS
Rac
GTP
ONDULACIONES
Rho
GTP
FIBRAS DE STRESS
- REGULACIÓN EXPRESIÓN GENICA
- REGULACIÓN ANCLAJE
- APOPTOSIS
- TRANSFORMACIÓN TUMORAL
- METASTASIS


RHO
PIP5-K
Rhotekin
Rhophilin
PKN
PKR2
citron
ROK
MBS
p140
Rac
Cdc42
PKR
citron
ROK
PIP5-K
POR1
p67
phox
PI3-K
p70
S6K
IQGAP
PAKs
MLKs
MEKK
4
MSE5
WASP
BORG
Act


H- Ras
GTP
Cdc42
GDP
Cdc42
GTP
MUTANTES DOMINANTES INHIBITORIOS
Rac
GDP
Rac
GTP
MUTANTES CONSTITUTIVAMENTE ACTIVOS
Rho
GDP
Rho
GTP
- Síntesis de DNA.
- Cambios en el citoesqueleto.
- Progresión ciclo celular
- Formación de focos
- Crecimiento independiente de factores de crecimiento.
- Independencia de sustrato.


Ras
GTP
Cdc42
GTP
FILOPODIOS
Rac
GTP
ONDULACIONES
Rho
GTP
FIBRAS DE STRESS
- REGULACIÓN EXPRESIÓN GENICA
- REGULACIÓN ANCLAJE
- APOPTOSIS
- TRANSFORMACIÓN TUMORAL
- METASTASIS





"La ciencia es aceptable siempre que no contradiga la fe".

"Todas las ciencias deben tender a la búsqueda de la verdad en su orden y su lícita autonomía metodológica, si bien sus conclusiones no pueden contradecir la fe, ya que tanto el mundo como el saber teológico tienen su origen en Dios".

Pío XII; encíclica Humani Generi, 1950

"Eeeeeeleeeeeeeee".
El Cordobés, Las Ventas 1970.