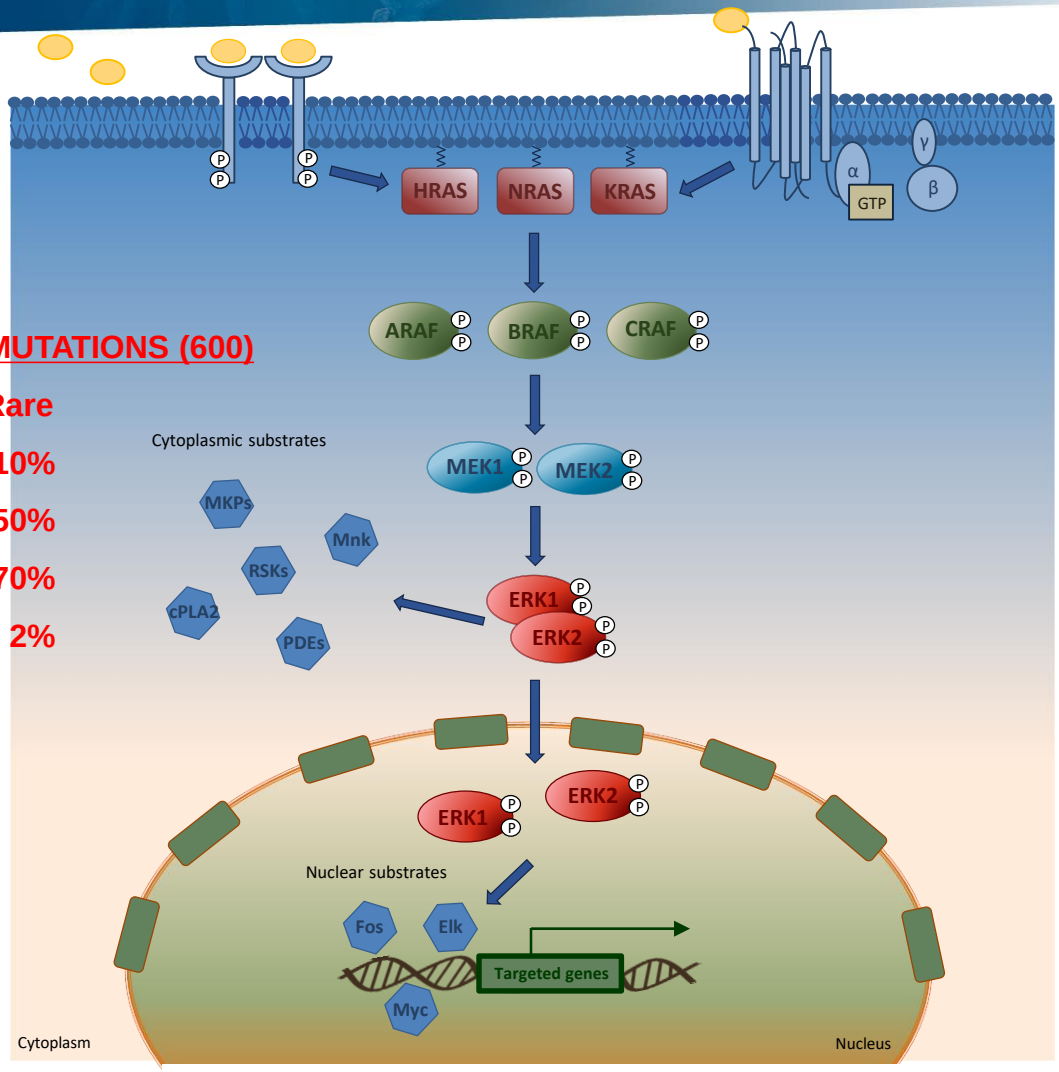
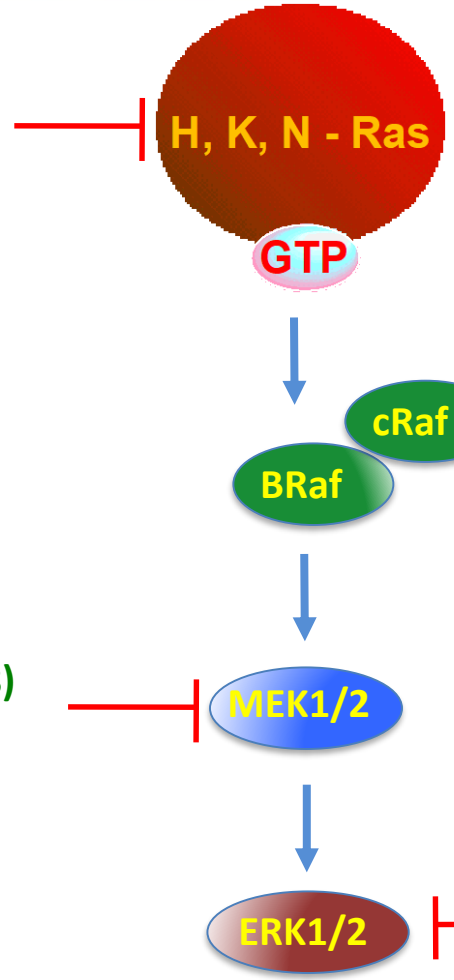
≈ 50% OF HUMAN CANCERS HARBOR MUTATIONS IN THE RAS-ERK PATHWAY

RAS MUTATIONS (12,13,61)		BRaf MUTATIONS (600)
- Pancreas (KRas)	90%	Rare
- Colorectal (KRas)	50%	10%
- Thyroid (KRas)	50%	50%
- Melanoma (NRas)	20%	70%
- Lung (KRas)	30%	2%



aseica
Asociación Española de Investigación sobre el Cáncer



FTIs
ISIS 2503
Salirasib

Failed compounds
Under clinical evaluation
FDA / EMA approved

Sorafenib (BAY 43-9006)

Raf265
Vemurafenib (PLX4032)
XL241
Dabrafenib (GSK2118436
RO 5126766
ISIS 5132

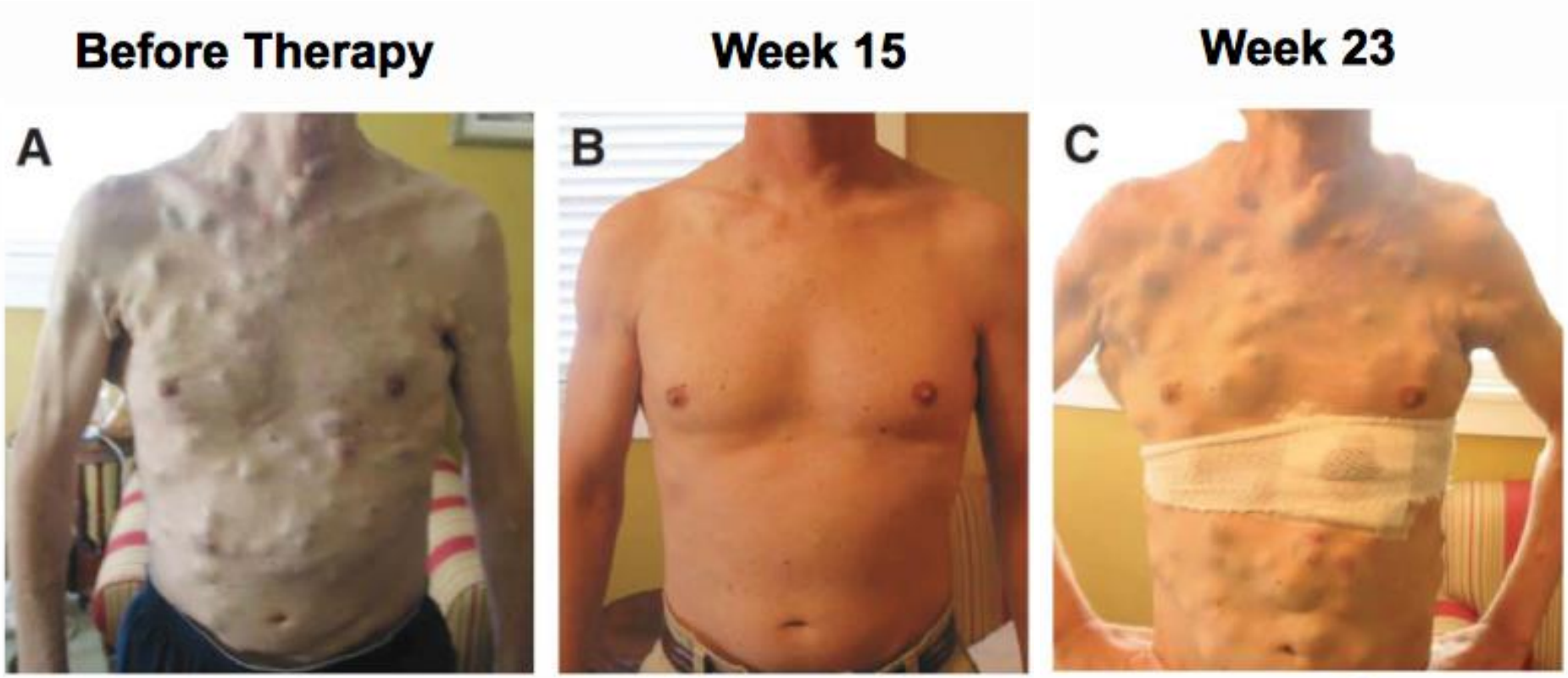
CI-1040
PD325901
Selumetinib (AZD6244)
Cobimetinib (GDC 0973/XL518)
Trametinib (GSK1120012)
Binimetinib (MEK 162)
ARRY -162, -300
BAY869766

SCH772984
FR 180204
VTX-11e
Ulixertinib (BVD-523)

"CLASSICAL" ANTI-TUMOR TARGETING IN THE RAS –ERK PATHWAY

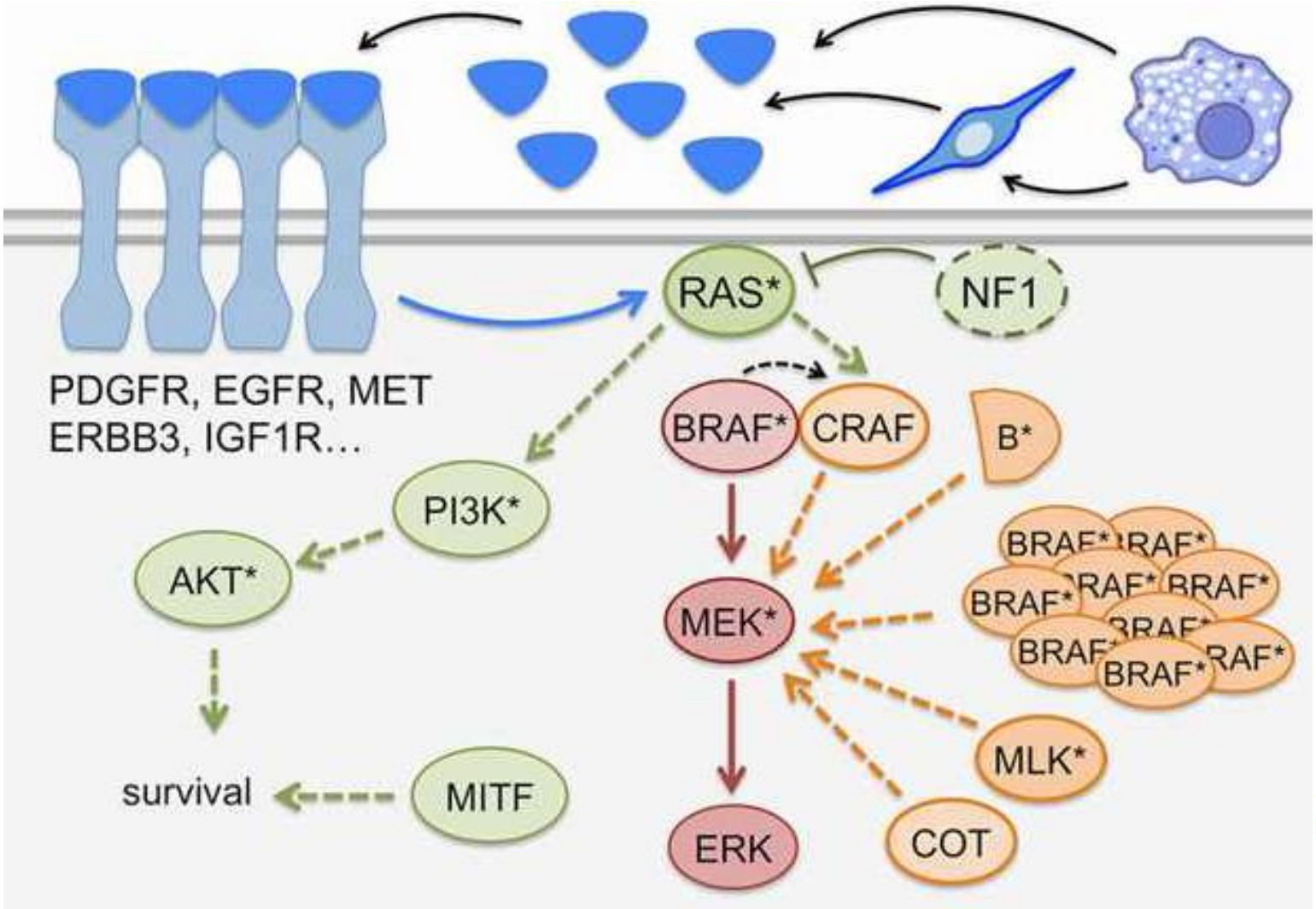
aseica Asociación Española de Investigación sobre el Cáncer

VEMURAFENIB (PLX 4032) IN METASTATIC MELANOMA

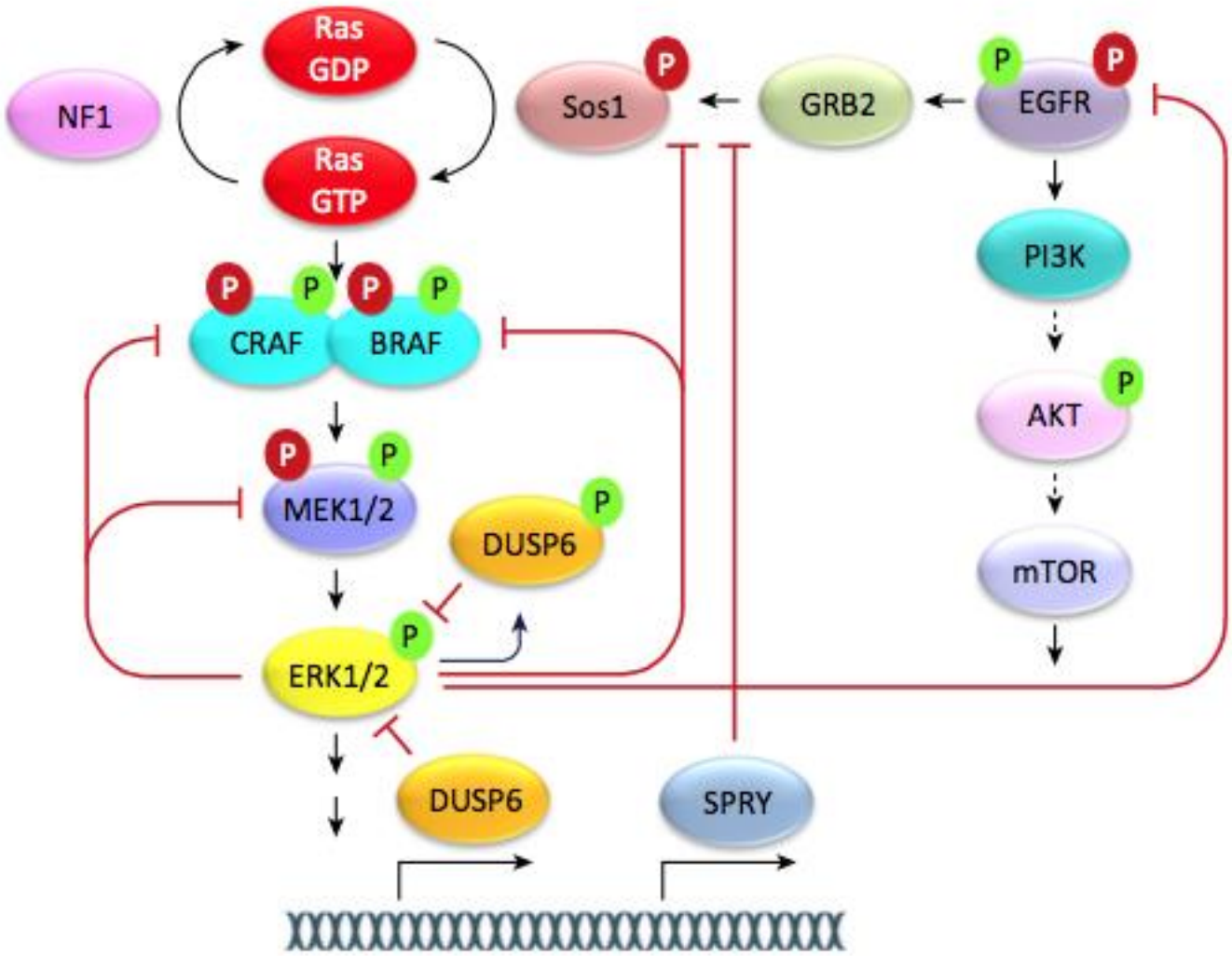


IN 70% OF THE CASES, RESISTANCE TO RAS-ERK PATHWAY INHIBITORS ENTAILS RE-INSTATEMENT OF ERK ACTIVATION

ACQUIRED RESISTANCE MECHANISMS



ADAPTIVE MECHANISMS



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma

G.V. Long, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. de Braud, J. Larkin, C. Garbe, T. Jouary, A. Hauschild, J.J. Grob, V. Chiarion Sileni, C. Lebbe, M. Mandalà, M. Millward, A. Arance, I. Bondarenko, J.B.A.G. Haanen, J. Hansson, J. Utikal, V. Ferraresi, N. Kovalenko, P. Mohr, V. Probachai, D. Schadendorf, P. Nathan, C. Robert, A. Ribas, D.J. DeMarini, J.G. Irani, M. Casey, D. Ouellet, A.-M. Martin, N. Le, K. Patel, and K. Flaherty

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

Caroline Robert, M.D., Ph.D., Boguslawa Karaszewska, M.D., Jacob Schachter, M.D., Piotr Rutkowski, M.D., Ph.D., Andrzej Mackiewicz, M.D., Ph.D.,

nature COMMUNICATIONS

ARTICLE

Received 9 Jul 2014 | Accepted 29 Oct 2014 | Published 2 Dec 2014

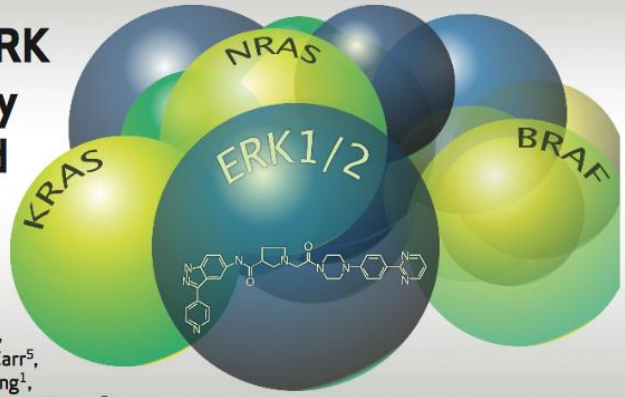
DOI: 10.1038/ncomms6694

Increased MAPK reactivation in early resistance to dabrafenib/trametinib combination therapy of BRAF-mutant metastatic melanoma

Georgina V. Long[1,2,3], Carina Fung[4,5], Alexander M. Menzies[1,2,6], Gulietta M. Pupo[5], Matteo S. Carlino[1,5,6], Jessica Hyman[1,7], Hamideh Shahheydari[4,5], Varsha Tembe[5], John F. Thompson[1,8,9], Robyn P. Saw[1,8,9], Julie Howle[1,8,10], Nicholas K. Hayward[11], Peter Johansson[11], Richard A. Scolyer[1,7,12], Richard F. Kefford[1,2,4,5] & Helen Rizos[4,5]

RESEARCH BRIEF

Discovery of a Novel ERK Inhibitor with Activity in Models of Acquired Resistance to BRAF and MEK Inhibitors



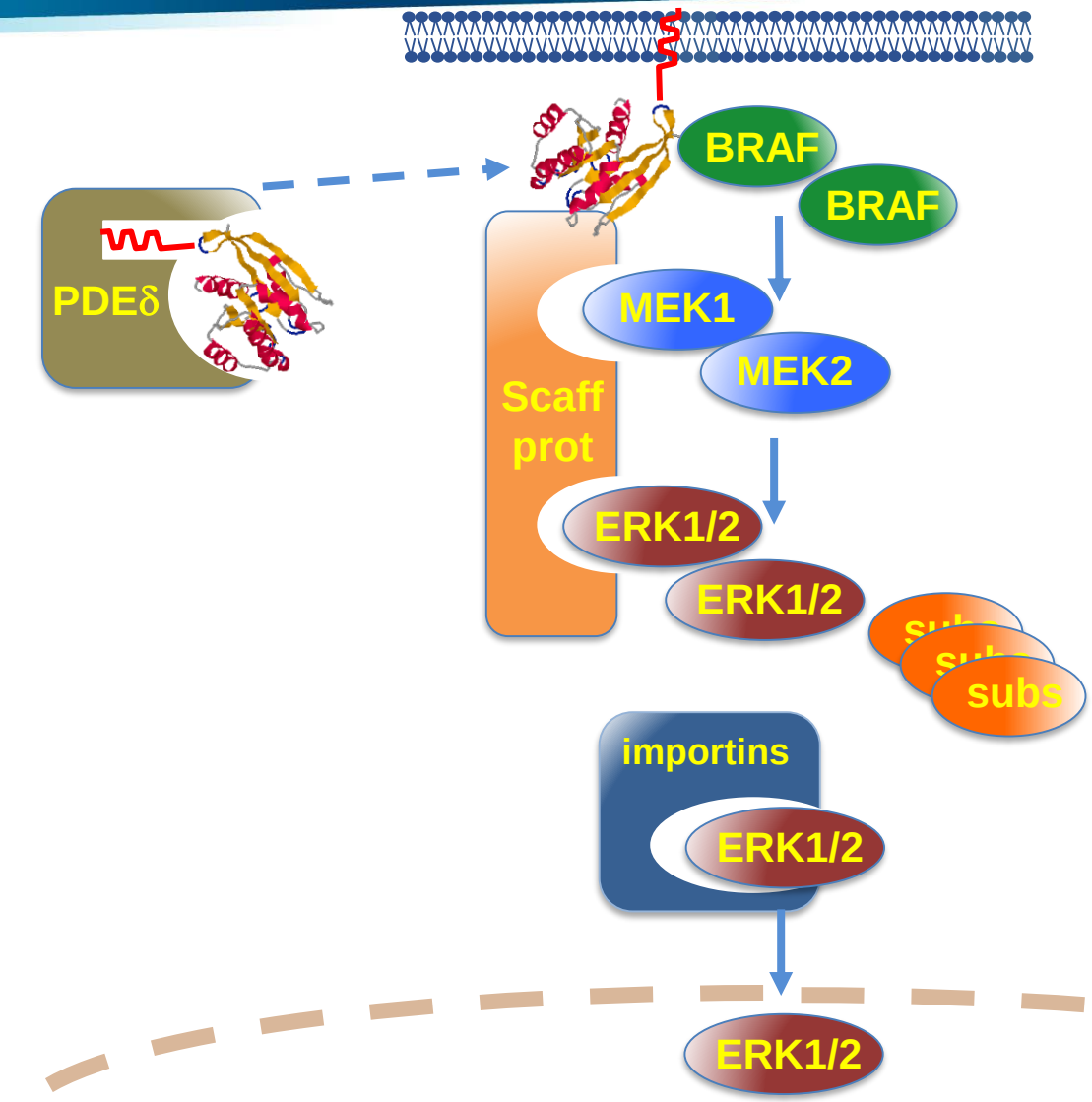
Erick J. Morris[1], Sharda Jha[1], Clifford R. Restaino[1], Priya Dayananth[5], Hugh Zhu[6], Alan Cooper[6], Donna Carr[5], Yongi Deng[2], Weihong Jin[5], Stuart Black[5], Brian Long[1], Jenny Liu[5], Edward DiNunzio[5], William Windsor[5], Rumin Zhang[5], Shuxia Zhao[1], Minilik H. Angagaw[1], Elaine M. Pinheiro[1], Jagdish Desai[6], Li Xiao[6], Gerald Shipps[2], Alan Hruza[5], James Wang[6], Joe Kelly[6], Sunil Paliwal[6], Xiaolei Gao[6], Boga Sobhana Babu[6], Liang Zhu[2], Pierre Daublain[3], Ling Zhang[4], Bart A. Lutterbach[1], Marc R. Pelletier[1], Ulrike Philippar[1], Phieng Siliphaivanh[2], David Witter[2], Paul Kirschmeier[5], W. Robert Bishop[5], Daniel Hicklin[5], D. Gary Gilliland[1], Lata Jayaraman[1], Leigh Zawel[1], Stephen Fawell[1], and Ahmed A. Samatar[1]

Molecular Cancer Therapeutics

Preclinical Development

ERK Inhibition Overcomes Acquired Resistance to MEK Inhibitors

Georgia Hatzivassiliou, Bonnie Liu, Carol O'Brien, Jill M. Spoerke, Klaus P. Hoeflich, Peter M. Haverty, Robert Soriano, William F. Forrest, Sherry Heldens, Huifen Chen, Karen Toy, Connie Ha, Wei Zhou, Kyung Song, Lori S. Friedman, Lukas C. Amler, Garret M. Hampton, John Moffat, Marcia Belvin, and Mark R. Lackner


BRAF
BRAF
PDEδ
MEK1
MEK2
Scaff
prot
ERK1/2
ERK1/2
subs
importins
ERK1/2
ERK1/2

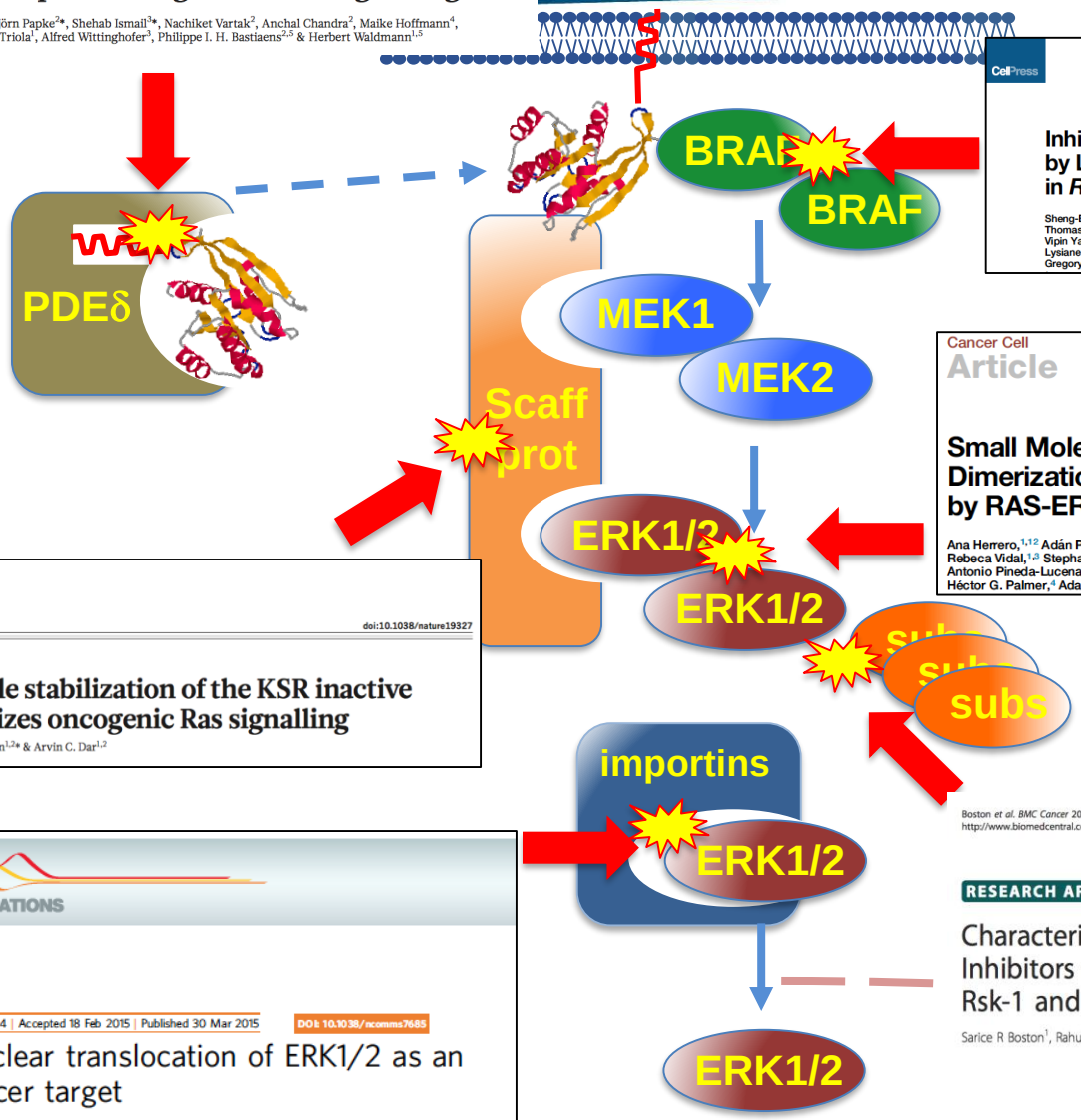
16th ASEICA

LETTER

doi:10.1038/nature12205

Small molecule inhibition of the KRAS–PDEδ interaction impairs oncogenic KRAS signalling

Gunther Zimmermann[1]*, Björn Papke[2]*, Shehab Ismail[3]*, Nachiket Vartak[2], Anchal Chandra[2], Maike Hoffmann[4], Stephan A. Hahn[4], Gemma Triola[1], Alfred Wittinghofer[3], Philippe I. H. Bastiaens[2,5] & Herbert Waldmann[1,5]



Cancer Cell
Article

Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in *RAS* or *BRAF* Mutant Cancers

Sheng-Bin Peng,[1,*] James R. Henry,[1] Michael D. Kaufman,[2] Wei-Ping Lu,[2] Bryan D. Smith,[2] Subha Vogeti,[2] Thomas J. Rutkoski,[2] Scott Wise,[2] Lawrence Chun,[1] Youyan Zhang,[1] Robert D. Van Horn,[1] Tinggui Yin,[1] Xiaoyi Zhang,[1] Vipin Yadav,[1] Shih-Hsun Chen,[1] Xueqian Gong,[1] Xiwen Ma,[1] Yue Webster,[1] Sean Buchanan,[1] Igor Mochalkin,[1] Lysiane Huber,[1] Lisa Kays,[1] Gregory P. Donoho,[1] Jennie Walgren,[1] Denis McCann,[1] Phenil Patel,[1] Ilaria Conti,[1] Gregory D. Plowman,[1] James J. Starling,[1] and Daniel L. Flynn[2]

Cancer Cell
Article

Small Molecule Inhibition of ERK Dimerization Prevents Tumorigenesis by RAS-ERK Pathway Oncogenes

Ana Herrero,[1,12] Adán Pinto,[1,12] Paula Colón-Bolea,[1,12] Berta Casar,[1,12] Mary Jones,[2] Lorena Agudo-Ibáñez,[1] Rebeca Vidal,[1,3] Stephan P. Tenbaum,[4] Paolo Nuciforo,[4] Elsa M. Valdizán,[1,3] Zoltan Horvath,[6] Laszlo Orfi,[5,6] Antonio Pineda-Lucena,[7] Emilie Bony,[8] Gyorgy Keri,[5,9] Germán Rivas,[10] Angel Pazos,[1,3] Rafael Gozalbes,[11] Héctor G. Palmer,[4] Adam Hurlstone,[3] and Piero Crespo[1,*]

LETTER

doi:10.1038/nature19327

Small molecule stabilization of the KSR inactive state antagonizes oncogenic Ras signalling

Neil S. Dhawan[1,2*], Alex P. Scopton[1,2*] & Arvin C. Dar[1,2]

nature COMMUNICATIONS

ARTICLE

Received 19 Oct 2014 | Accepted 18 Feb 2015 | Published 30 Mar 2015 DOI: 10.1038/ncomms7685

The nuclear translocation of ERK1/2 as an anticancer target

Alexander Plotnikov[1,*], Karen Flores[1,*], Galia Maik-Rachline[1,*], Eldar Zehorai[1], Einat Kapri-Pardes[1], Denise A. Berti[1], Tamar Hanoch[1], Michal J. Besser[2] & Rony Seger[1]

Boston *et al. BMC Cancer* 2011, **11**:7
http://www.biomedcentral.com/1471-2407/11/7

BMC Cancer

RESEARCH ARTICLE Open Access

Characterization of ERK Docking Domain Inhibitors that Induce Apoptosis by Targeting Rsk-1 and Caspase-9

Sarice R Boston[1], Rahul Deshmukh[1], Scott Strome[2], U Deva Priyakumar[1], Alexander D MacKerell Jr[1], Paul Shapiro[1*]

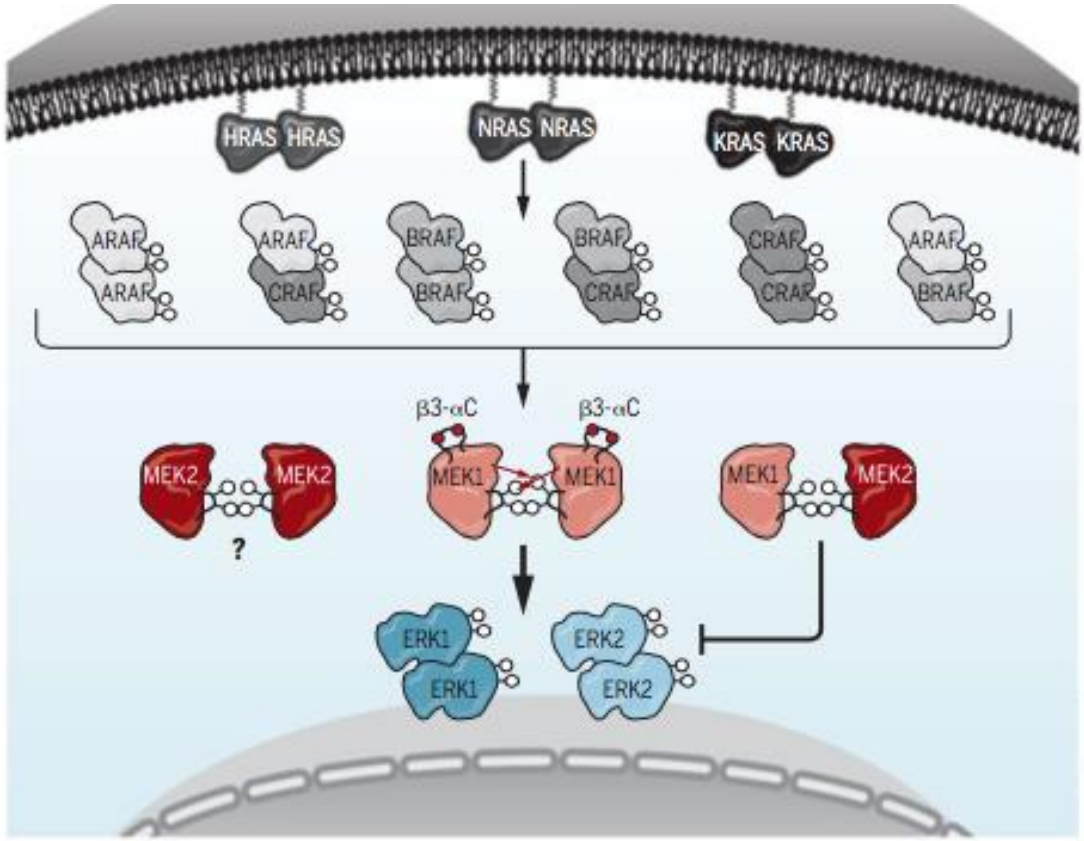
aeica Asociación Española de Investigación sobre el Cáncer

SCIENCE SIGNALING | FOCUS

BIOCHEMISTRY

The RAS-ERK pathway: A route for couples

Eugenio Santos[1,2] and Piero Crespo[1,3]*



"IMPORTANT BIOLOGICAL OBJECTS COME IN PAIRS"

James Watson, *The double helix*

Article

Cell

KRAS Dimerization Impacts MEK Inhibitor Sensitivity and Oncogenic Activity of Mutant KRAS

Chiara Ambrogio,[1,9,*] Jens Köhler,[1,8] Zhi-Wei Zhou,[2,8] Haiyun Wang,[3] Raymond Paranal,[1] Jiaqi Li,[1] Marzia Capelletti,[1] Cristina Caffarra,[1] Shuai Li,[1] Qi Lv,[3] Sudershan Gondi,[2] John C. Hunter,[2] Jia Lu,[2] Roberto Chiarle,[4,5] David Santamaría,[6,9] Kenneth D. Westover,[2,9,*] and Pasi A. Jänne[1,7,9,10,*]

RAS: The elephant in the room?

16th ASEICA
INTERNATIONAL CONGRESS
Valencia, 6th - 7th - 8th November 2018

RESEARCH ARTICLE

Oncogenic and Wild-type Ras Play Divergent Roles in the Regulation of Mitogen-Activated Protein Kinase Signaling

Amy Young[1,2], David Lou[1,3], and Frank McCormick[1]

nature COMMUNICATIONS

ARTICLE

Received 27 Jul 2012 | Accepted 27 Sep 2012 | Published 6 Nov 2012 DOI: 10.1038/ncomms2173

Sos-mediated cross-activation of wild-type Ras by oncogenic Ras is essential for tumorigenesis

Hao-Hsuan Jeng[1,2], Laura J. Taylor[1] & Dafna Bar-Sagi[1]

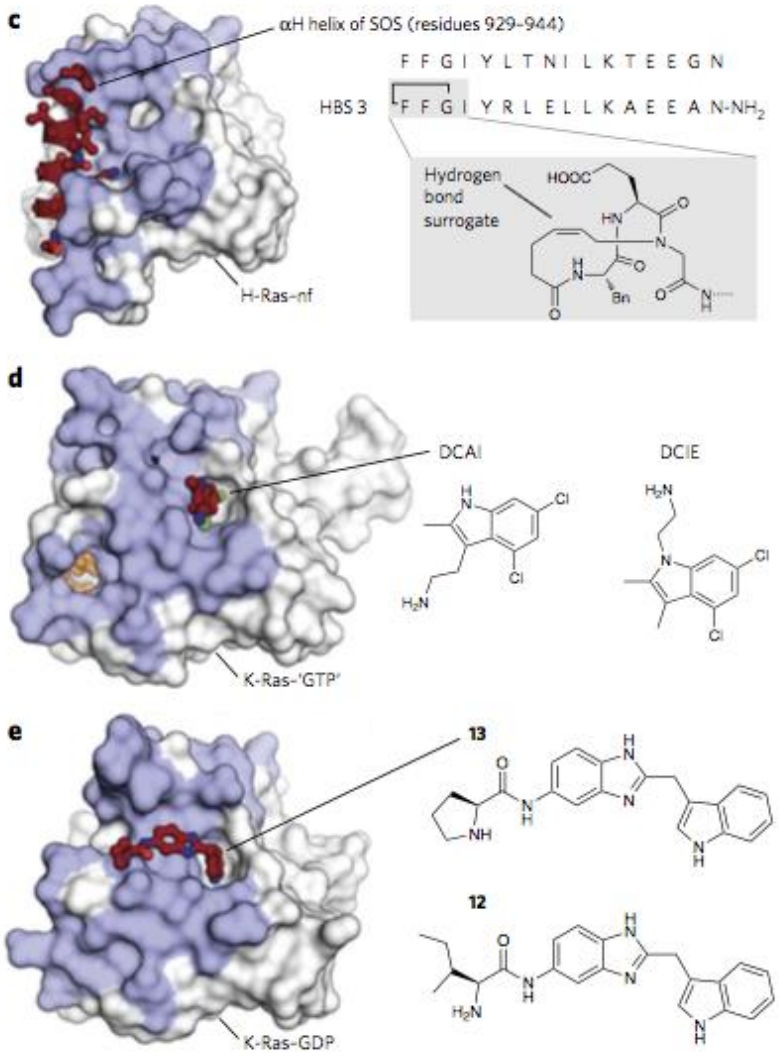
Cancer Cell
Article

Cell PRESS

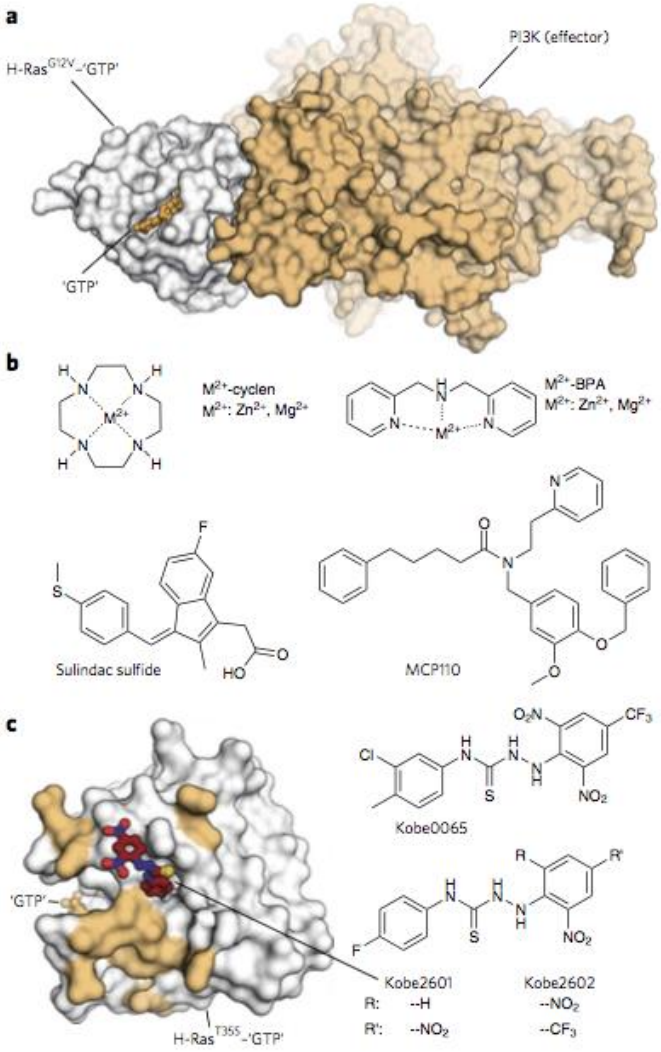
Wild-Type H- and N-Ras Promote Mutant K-Ras-Driven Tumorigenesis by Modulating the DNA Damage Response

Elda Grabocka,[1] Yuliya Pylayeva-Gupta,[1] Mathew J.K. Jones,[2] Veronica Lubkov,[1] Eyoel Yemanaberhan,[1] Laura Taylor,[1] Hao Hsuan Jeng,[1] and Dafna Bar-Sagi[1,*]

aseica
Asociación Española de Investigación sobre el Cáncer


c
αH helix of SOS (residues 929–944)
F F G I Y L T N I L K T E E G N
HBS 3
F F G I Y R L E L L K A E E A N-NH2
Hydrogen bond surrogate
HOOC
H-Ras-nf
d
DCAI
DCIE
K-Ras-'GTP'
e
13
12
K-Ras-GDP

Aiming at RAS-effector interactions



LETTER

doi:10.1038/nature12796

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem[1]*, Ulf Peters[1]*, Martin L. Sos[1], James A. Wells[2] & Kevan M. Shokat[1]

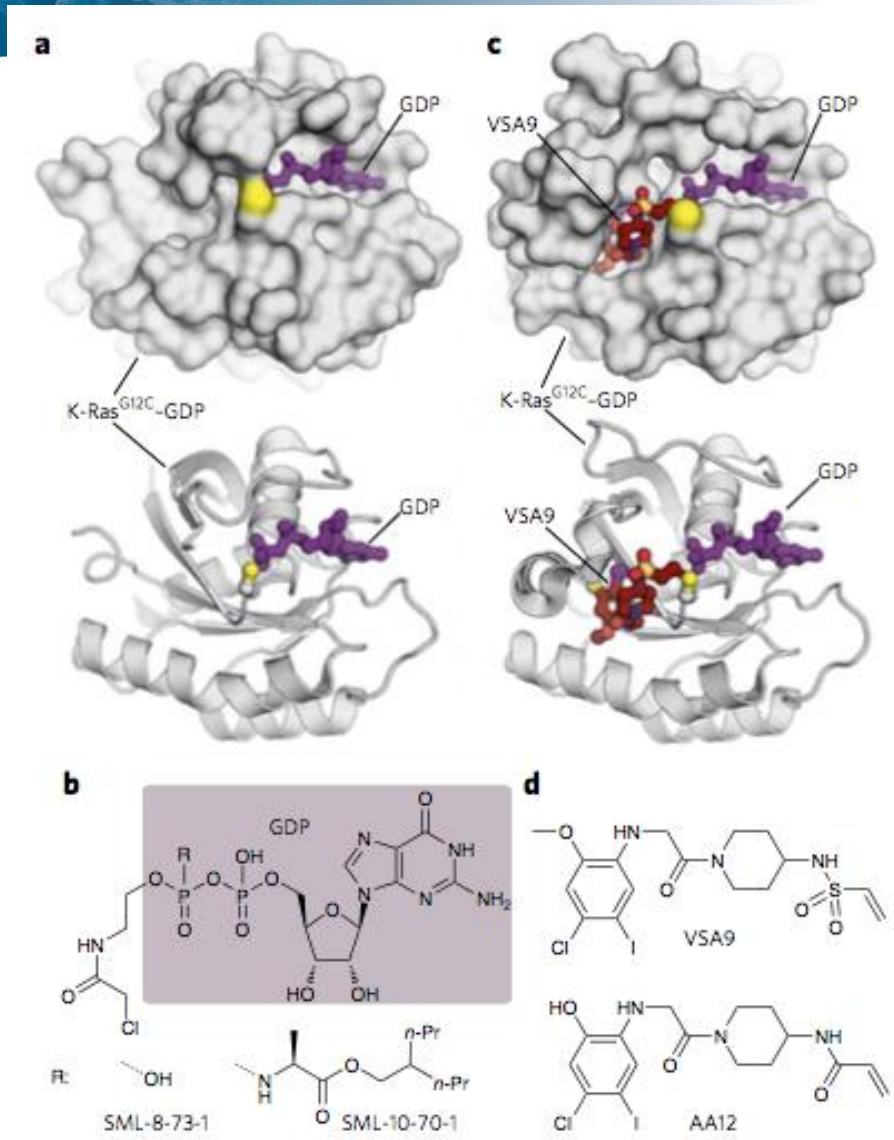
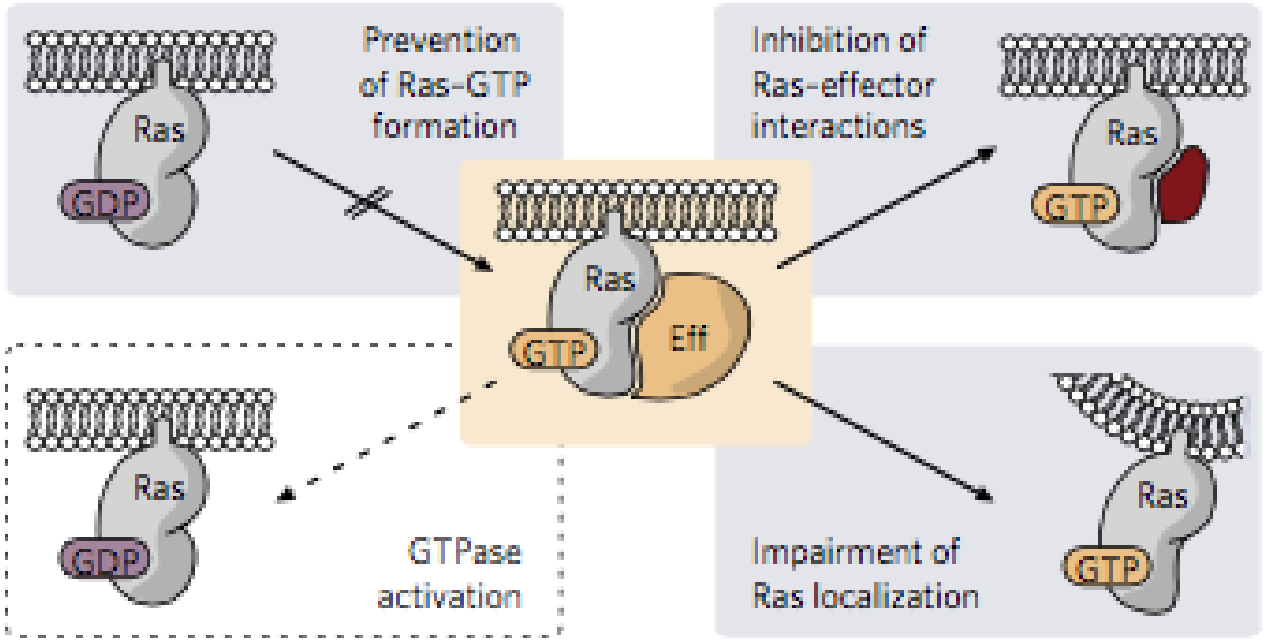
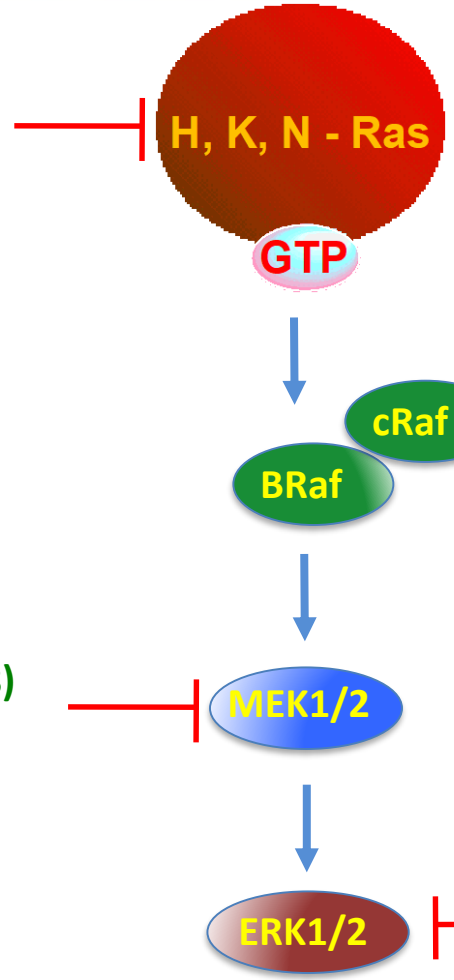


Figure 4 | Covalent inhibitors targeting Cys12 of mutated K-Ras^{G12C}.


Prevention of Ras-GTP formation
Ras
GDP
Inhibition of Ras-effector interactions
Ras
GTP
Ras
GTP
Eff
Ras
GDP
GTPase activation
Impairment of Ras localization
Ras
GTP



FTIs
ISIS 2503
Salirasib

Failed compounds
Under clinical evaluation
FDA / EMA approved

Sorafenib (BAY 43-9006)

Raf265
Vemurafenib (PLX4032)
XL241
Dabrafenib (GSK2118436
RO 5126766
ISIS 5132

CI-1040
PD325901
Selumetinib (AZD6244)
Cobimetinib (GDC 0973/XL518)
Trametinib (GSK1120012)
Binimetinib (MEK 162)
ARRY -162, -300
BAY869766

SCH772984
FR 180204
VTX-11e
Ulixertinib (BVD-523)

"CLASSICAL" ANTI-TUMOR TARGETING IN THE RAS –ERK PATHWAY

aseica Asociación Española de Investigación sobre el Cáncer