IMIBIC INSTITUTO MAIMÓNIDES DE INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

II JORNADAS DE JÓVENES INVESTIGADORES EN BIOMEDICINA

DE LA ONCOLOGÍA MOLECULAR A LAS TERAPIAS INDIVIDUALIZADAS: IMPACTO EN LA PRÁCTICA CLÍNICA

MARIANO BARBACID

DIRECTOR
CENTRO NACIONAL DE INVESTIGACIONES ONCOLÓGICAS

Introducción

- Durante las últimas tres décadas hemos sido testigos de la época mas productiva de toda nuestra historia en el campo de la investigación oncológica.

- Durante este periodo se han establecido, de forma inequívoca, las bases moleculares del cáncer.

- Sin embargo, y hasta hace muy poco tiempo, estos conocimientos han tenido una repercusión muy limitada en la diagnosis y tratamiento del cáncer.

- Por ejemplo, los protocolos de quimioterapia se establecían de forma empírica sin conocer porqué los agentes citotóxicos poseen esa "ventana terapéutica" que permite su aplicación clínica y menos aún porqué ciertos citotóxicos son mas activos en unos tipos de tumores que en otros.

- Además en los últimos años, el "pipeline" de agentes citotóxicos se ha reducido muy significativamente. En los últimos cinco años, la FDA no ha aprobado ningún citotóxico con un mecanismo de acción nuevo.

Introducción

- Yondelis, un inhibidor que se une al surco pequeño del DNA, ha sido aprobado por la EMEA pero no por la FDA.

- Este panorama, un tanto desalentador, ha empezado a cambiar hace ahora 10 años con una nueva generación de fármacos dirigidos contra **dianas moleculares**, tanto de origen biológico (Herceptina/Transtuzumab) para cáncer de mama aprobado en 1998, como quimiotipos o moléculas de bajo peso molecular (Gleevec/Imatinib) para leucemia mieloide crónica y sarcomas blandos (GIST) aprobado en 2001.

- Hoy en día, los increíbles avances en las técnicas de ultrasecuenciación están permitiendo secuenciar los genomas, o al menos los exomas, de un gran numero de tumores lo que nos esta permitiendo conocer **TODOS** los errores genéticos existentes en un determinado tumor

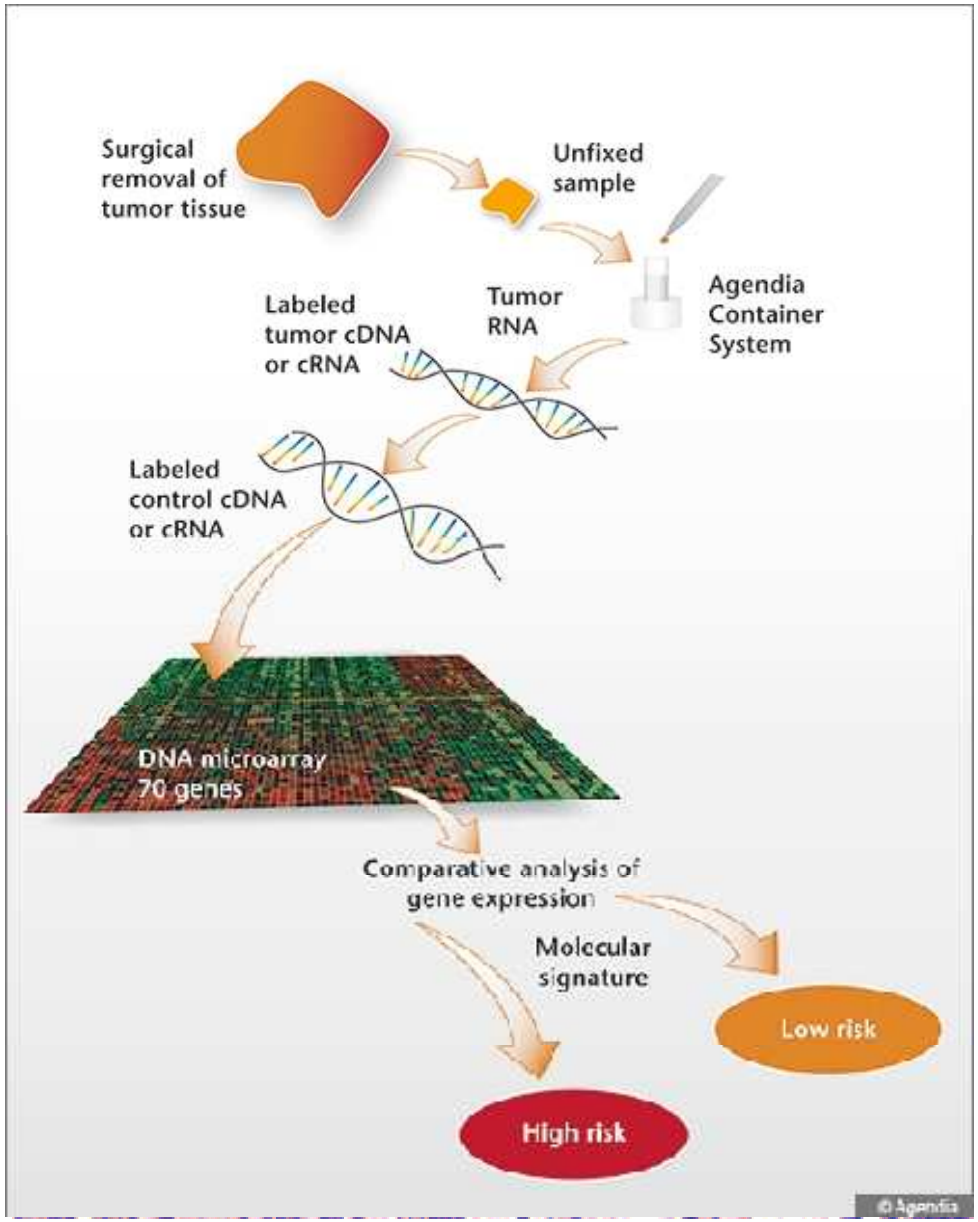
- Ahora el reto está en como procesar toda esta información de forma rápida y efectiva para que pueda tener una incidencia directa en la diagnosis y el tratamiento del paciente de cáncer

A personal view

The future of cancer treatment will depend on improvements in four basic areas:

- **Molecular classification of tumors & Biomarkers:** Cancers will no longer be classified just based on pathology. Although the routine use of exonic analysis is still far in the future, limited sequencing of tumors may replace current "signature profiling".

Classification of Tumors

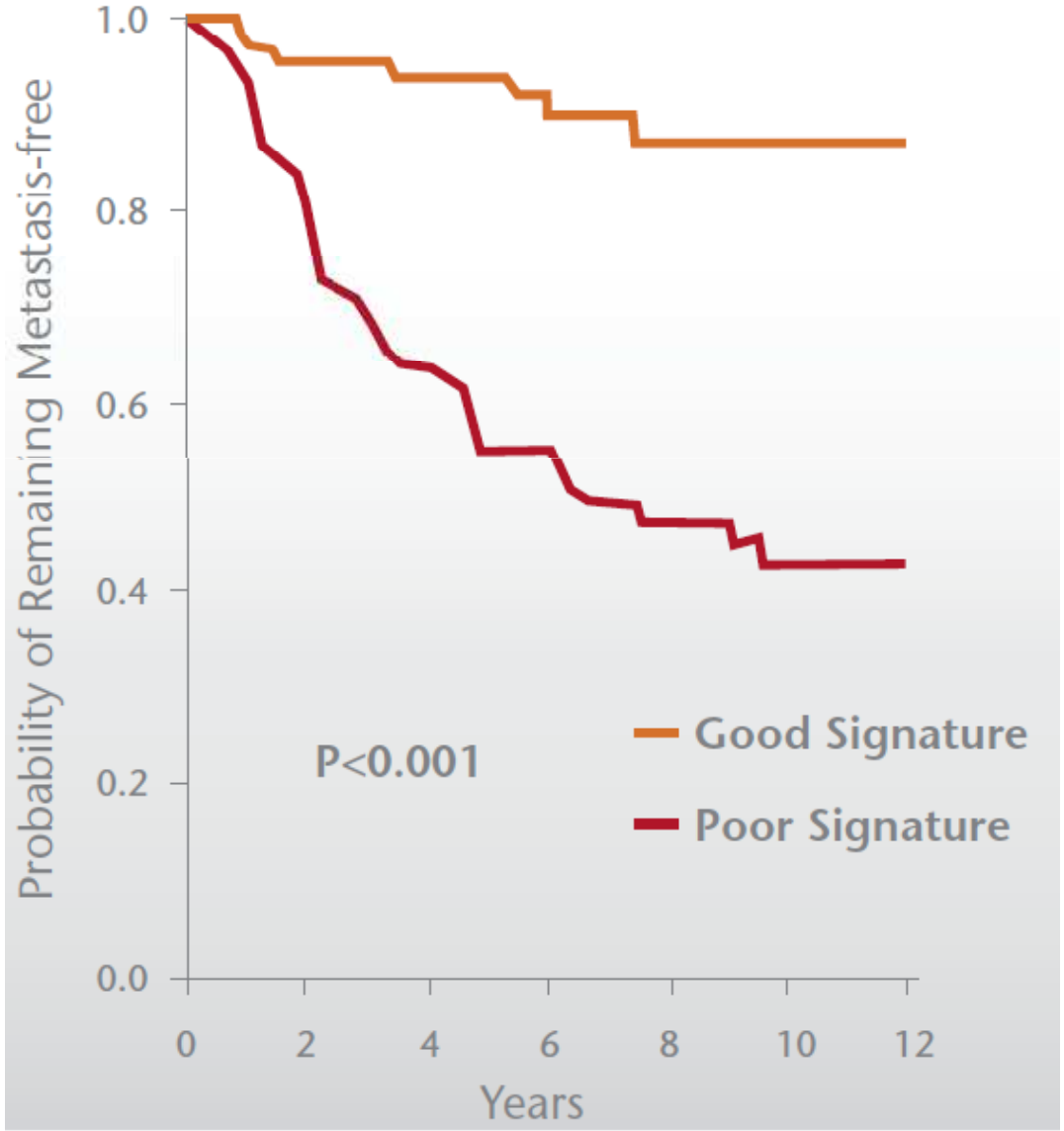


Classical Pathology

Molecular Profiling

Predictive Signatures

Classification of Tumors



Classification of Tumors

Other Platforms

Gene-expression signatures	Biological hypothesis	Microarray platform	Number of genes in the signature	Independent validation	Prospective clinical validation
Amsterdam signature	Clinical outcome	Agilent (oligonucleotides)	70	Yes	Yes (MINDACT trial)
Rotterdam signature	Clinical outcome	Affymetrix (oligonucleotides)	76	Yes	No
Reccurence score	Clinical outcome	RT-PCR	21	Yes	Yes (TAILORX trial)
Wound-response signature	Wound healing and tumour progression	cDNA (custom made)	512	Yes	No
Genomic grade	Histologic grade and tumour progression	Affymetrix (oligonucleotides)	97	Yes	No
p53 signature	Functional status of p53	Affymetrix (oligonucleotides)	32	Yes	No
Death-from-cancer signature	BMI1 oncogenic pathway self renewal	Affymetrix (oligonucleotides)	11	Yes	No
Invasiveness gene signature	Tumorigenic cancer cells $CD44^{+}$:$CD24^{-/low}$	Affymetrix (oligonucleotides)	186	Yes	No

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2008 VOL. 359 NO. 17

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

CONCLUSIONS

Patients with a colorectal tumor bearing mutated *K-ras* did not benefit from cetuximab, whereas patients with a tumor bearing wild-type *K-ras* did benefit from cetuximab. The mutation status of the *K-ras* gene had no influence on survival among patients treated with best supportive care alone. (ClinicalTrials.gov number, NCT00079066.)

Molecular Biomarkers & Clinical Practice

Tumour type	Biomarker	Potential clinical use
Breast	Steroid hormone receptors	Select hormone therapy
Breast	HER2	Select trastuzumab use
Breast	Oncotype Dx gene profile	Assess prognosis; select chemotherapy
Colon	KRAS mutation status	Guide EGFR-specific antibody use
Colon	Microsatellite instability	Assess prognosis or utility of 5-fluoruracil adjuvant treatment
Non-small cell lung	EGFR mutation	Guide selection or use of EGFR tyrosine kinase inhibitors
Non-small cell lung	ERCC1	Select platinum-based chemotherapy
Glioblastoma	MGMT methylation	Guide temozolomide use
Melanoma	BRAF V600E mutation	Select therapy

EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; HER2, also known as ERBB2; MGMT, methyl guanine methyltransferase.

Cancer Genomes: The ICGC

Table 1. *ICGC cancer genome projects, committed or active, including 37 projects in 12 countries and two European consortia as of January 2011*

Lead jurisdiction	Organ sites	Tumor subtypes
Australia	Ovary	Serous cystadenocarcinoma
	Pancreas	Pancreatic ductal adenocarcinoma
Canada	Pancreas	Pancreatic ductal adenocarcinoma
	Prostate	Prostate adenocarcinoma
China	Stomach	Intestinal- and diffuse-type gastric cancer
European Union/France	Kidney	Renal cell carcinoma
European Union/United Kingdom	Breast	ER-positive, HER2-negative breast cancer
France	Breast	HER2-amplified breast cancer
	Liver	Hepatocellular carcinoma secondary to alcohol and adiposity
	Prostate	Prostate adenocarcinoma
Germany	Blood	Germinal center B-cell-derived lymphoma
	Brain	Medulloblastoma and pediatric pilocytic astrocytoma
	Prostate	Early onset prostate cancer
India	Oral cavity	Gingivobuccal carcinoma
Italy	Pancreas	Rare pancreatic subtypes, including enteropancreatic endocrine tumors and exocrine tumors
Japan	Liver	Virus-associated hepatocellular carcinoma
Mexico	Multiple	Common tumor types in Mexico
Spain	Hematopoietic	Chronic lymphocytic leukemia with mutated and unmutated IgVH
United Kingdom	Bone	Osteosarcoma/chondrosarcoma/rare bone cancers
	Breast	Triple negative/lobular/other breast cancers
	Hematopoietic	Chronic myeloid disorders, including myelodysplastic syndrome, myeloproliferative neoplasms, and other chronic myeloid malignancies
United States (TCGA)	Brain	GBM and low-grade gliomas
	Breast	Ductal and lobular breast adenocarcinomas
	Stomach	Intestinal-type gastric adenocarcinoma
	Liver	Hepatocellular carcinoma
	Intestine	Colon and rectal adenocarcinomas
	Gynecologic	Serous ovarian adenocarcinoma; endometrial carcinoma; cervical adenocarcinoma; and squamous carcinomas
	Prostate	Prostate adenocarcinoma
	Bladder	Nonpapillary bladder cancer
	Head and neck	Head and neck squamous cell and thyroid papillary carcinomas
	Hematopoietic	Acute myeloid leukemia
	Skin	Metastatic cutaneous melanoma
	Lung	Non-small-cell lung cancer, adenocarcinoma, and squamous subtypes
	Kidney	Renal clear cell and renal papillary carcinomas
	Pancreas	Pancreatic adenocarcinoma

For updated information, see http://www.icgc.org and http://cancergenome.nih.gov.

Cancer Genomes: "Early Studies"

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Nature, September 4th, on line publication

Sciencexpress Research Article

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

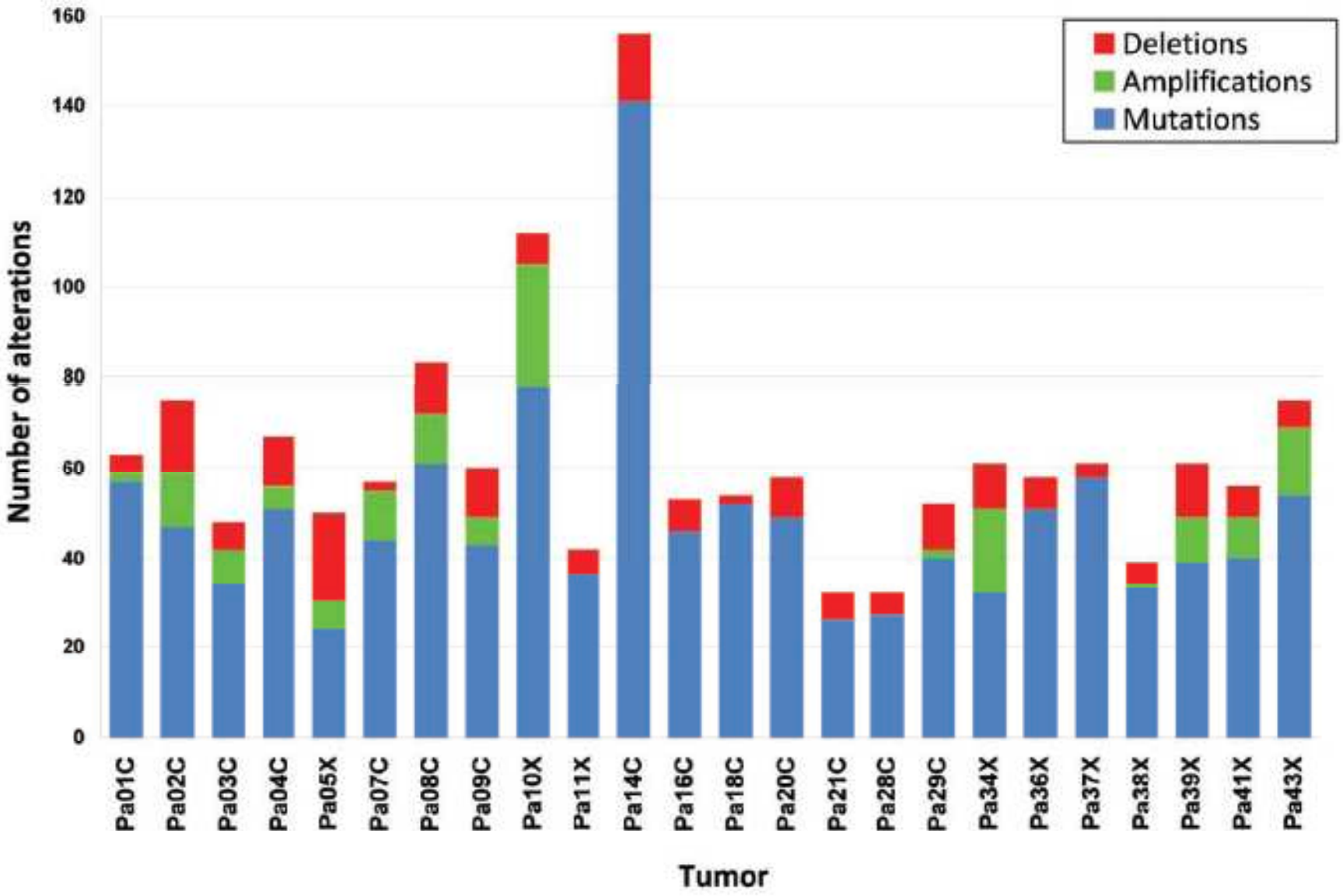
Science, September 4th, on line publication

Sciencexpress Research Article

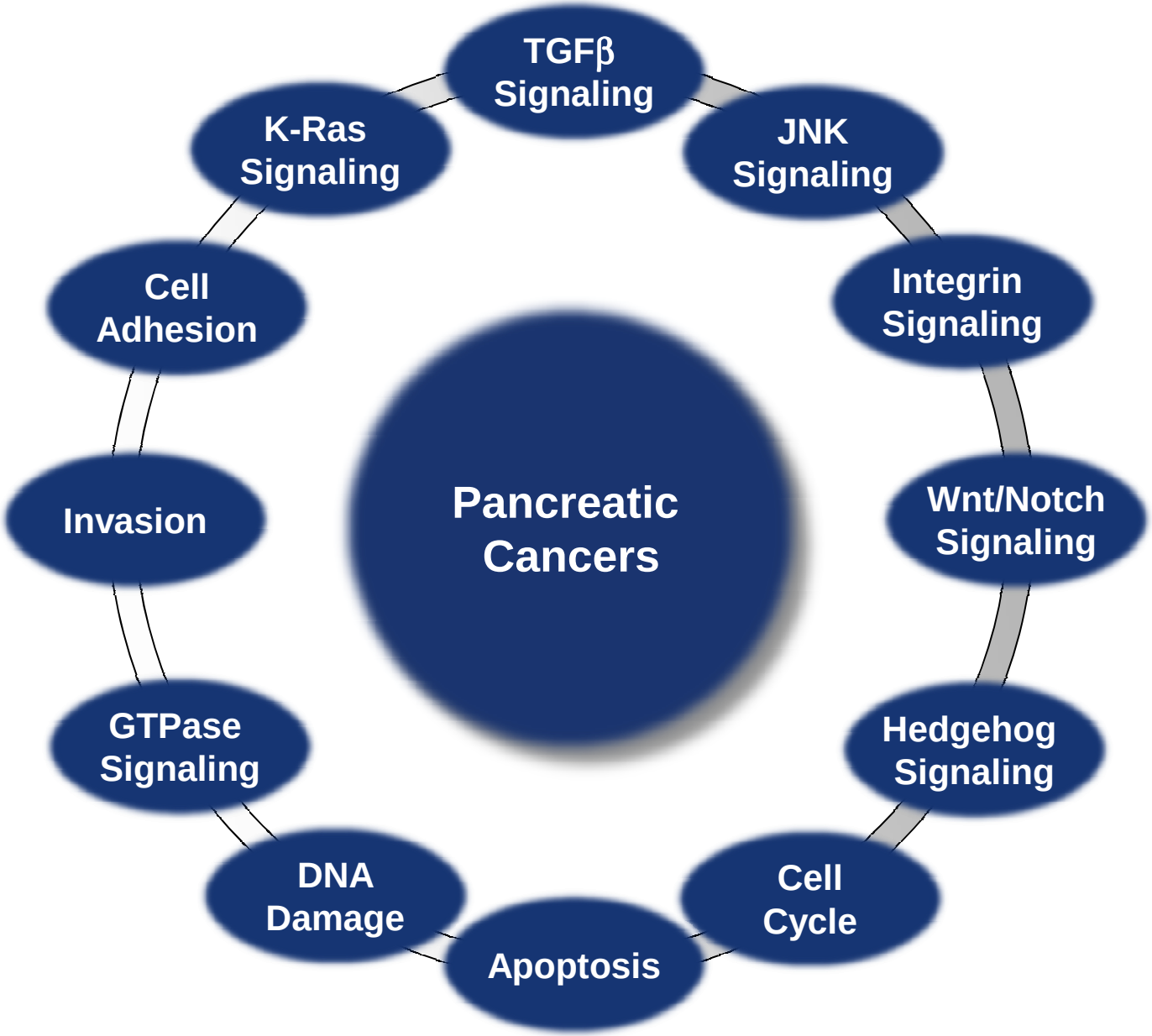
Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses

Science, September 4th, on line publication

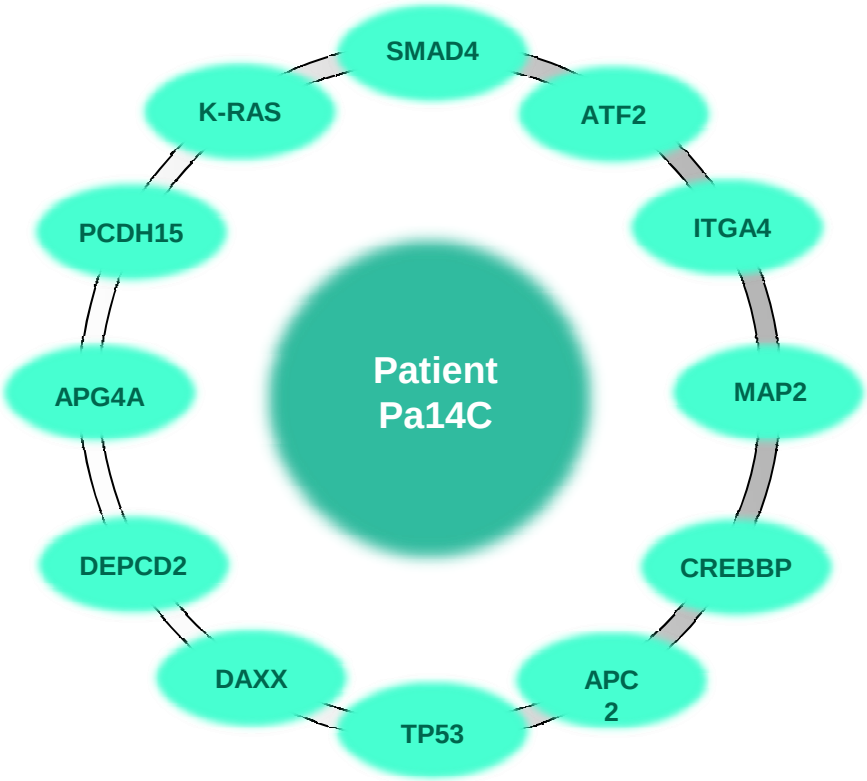
PDAC Genomes

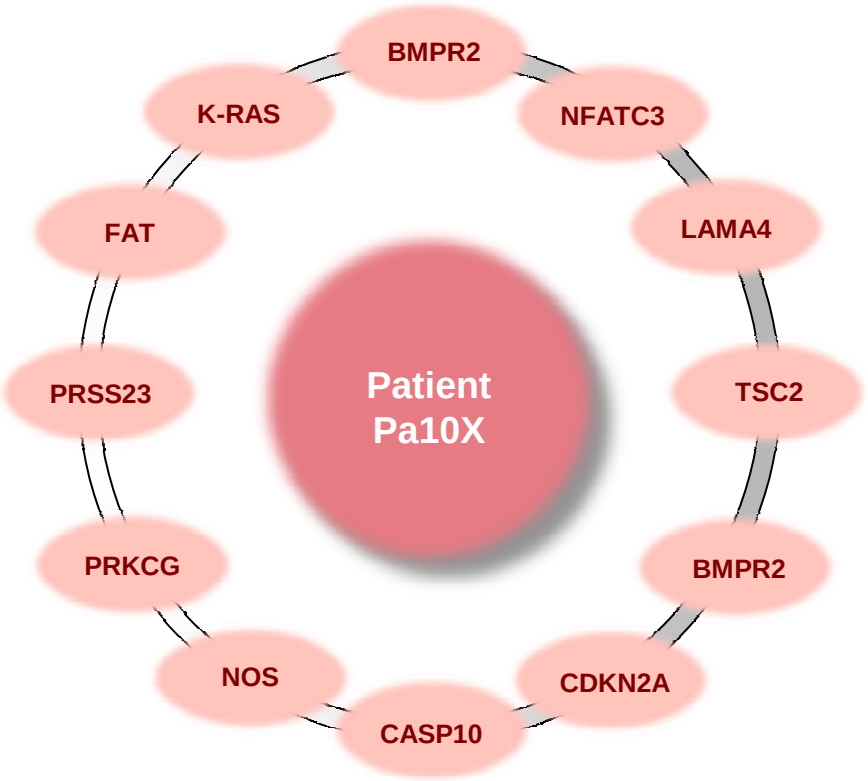


PDAC Genomes

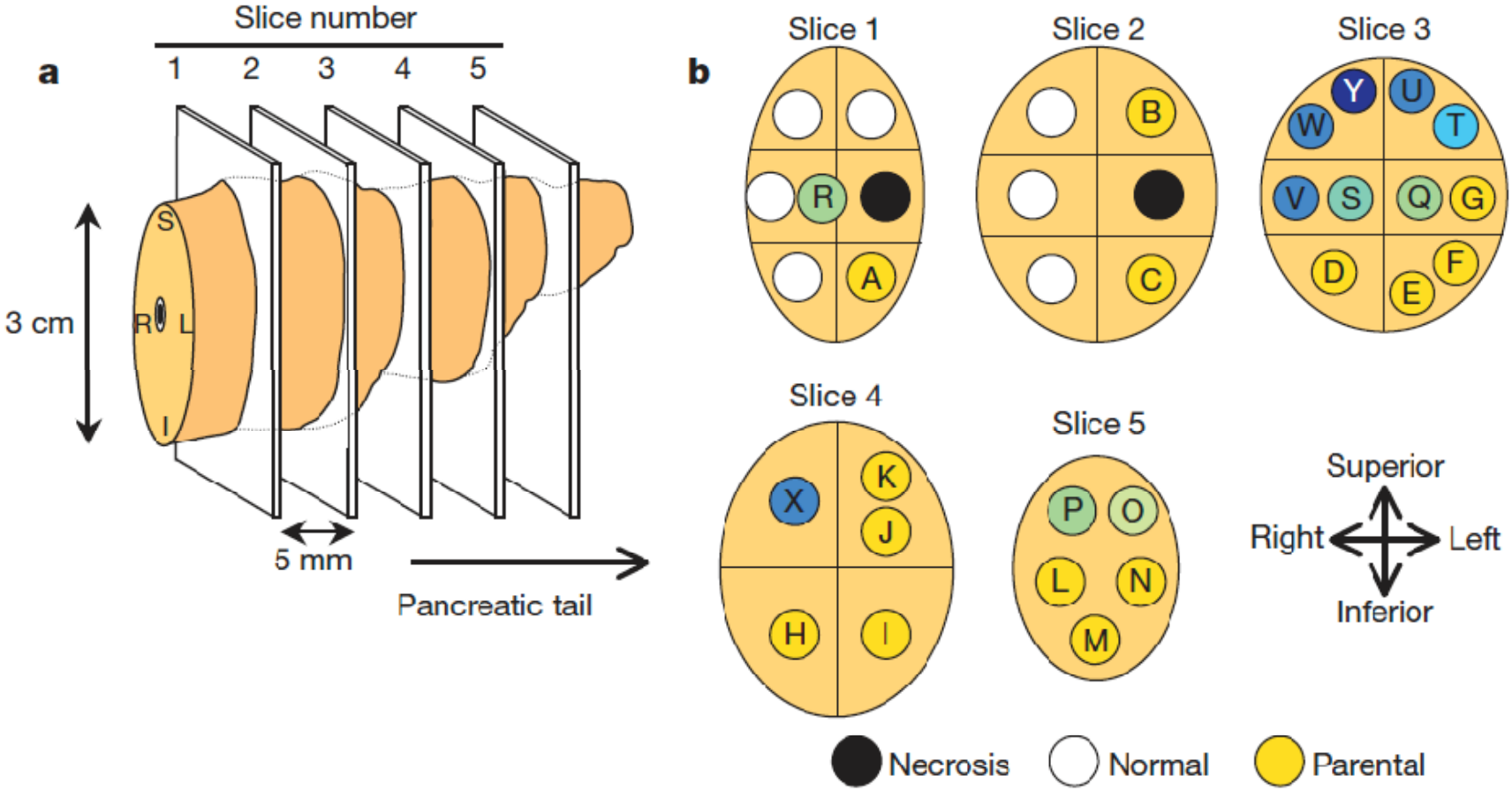


PDAC Genomes

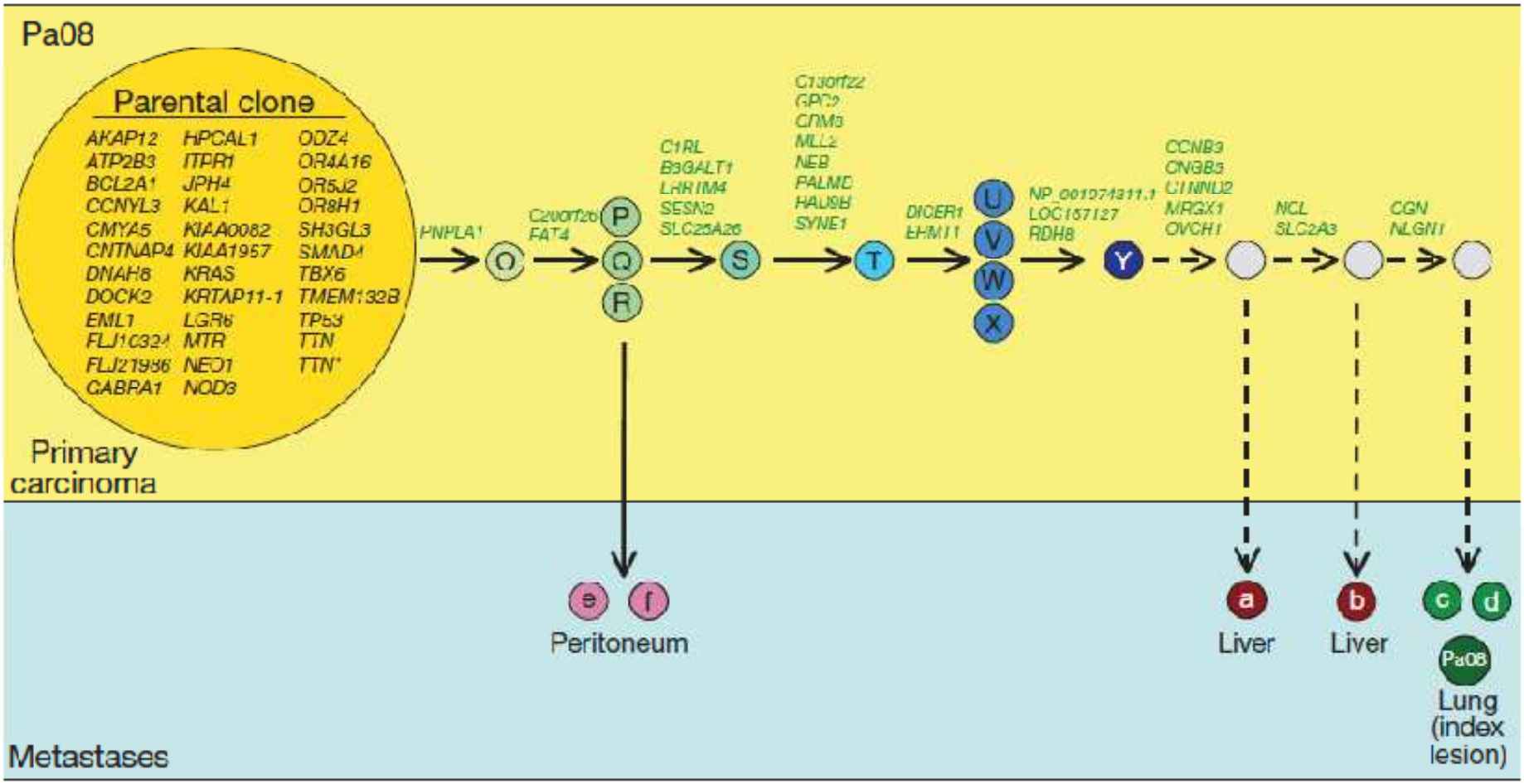




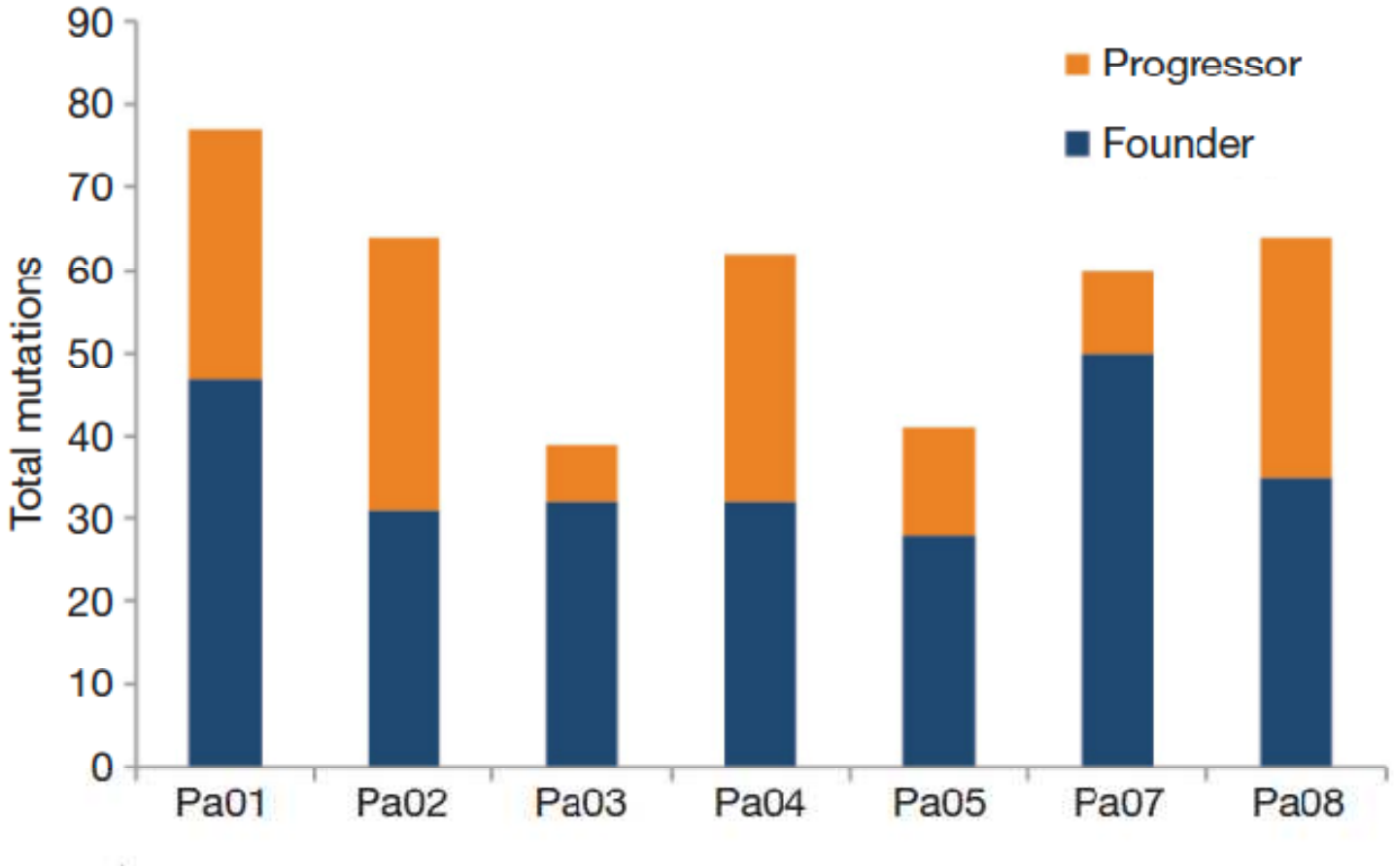
PDAC Genomes



Metastatic PDAC: Genomic Analysis

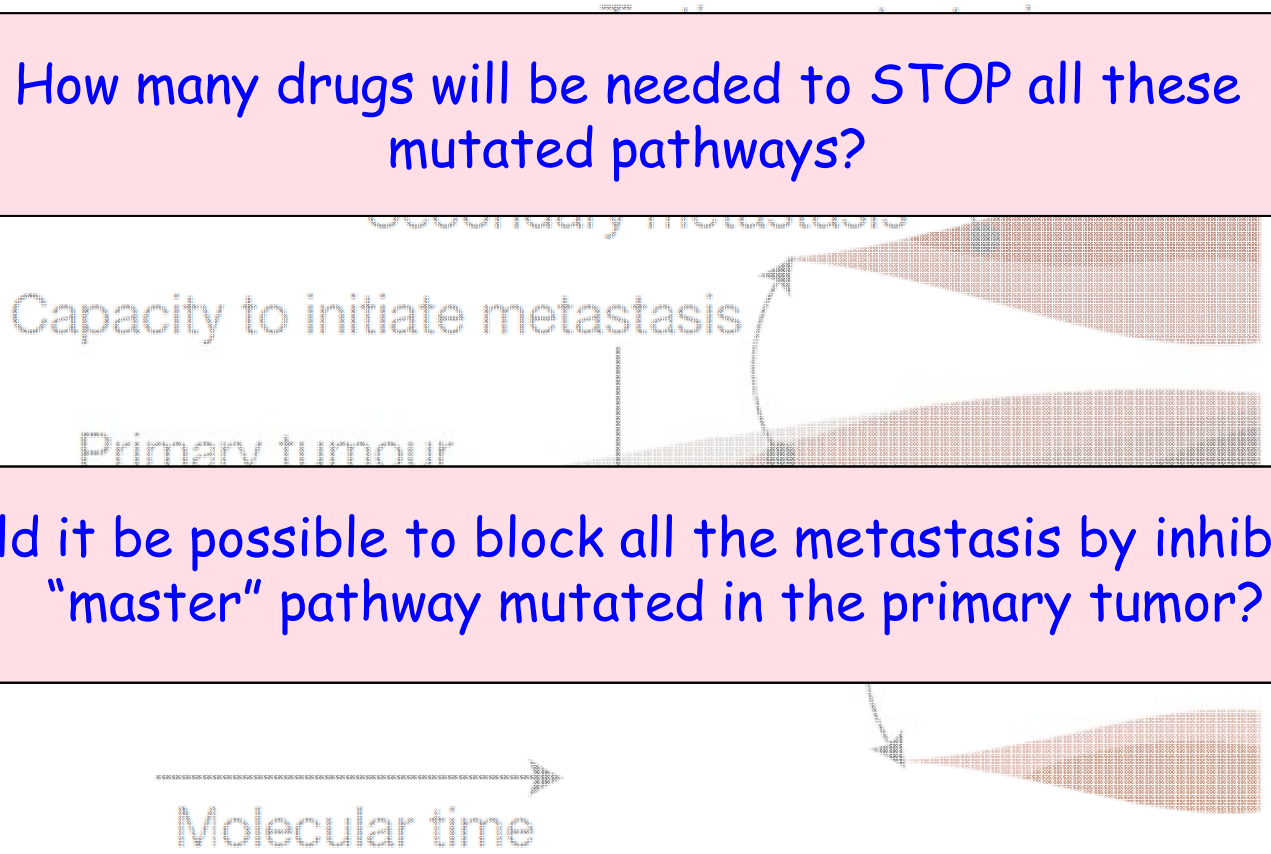


Metastatic PDAC: Genomic Analysis



Metastatic PDAC: Genomic Analysis

How many drugs will be needed to STOP all these mutated pathways?



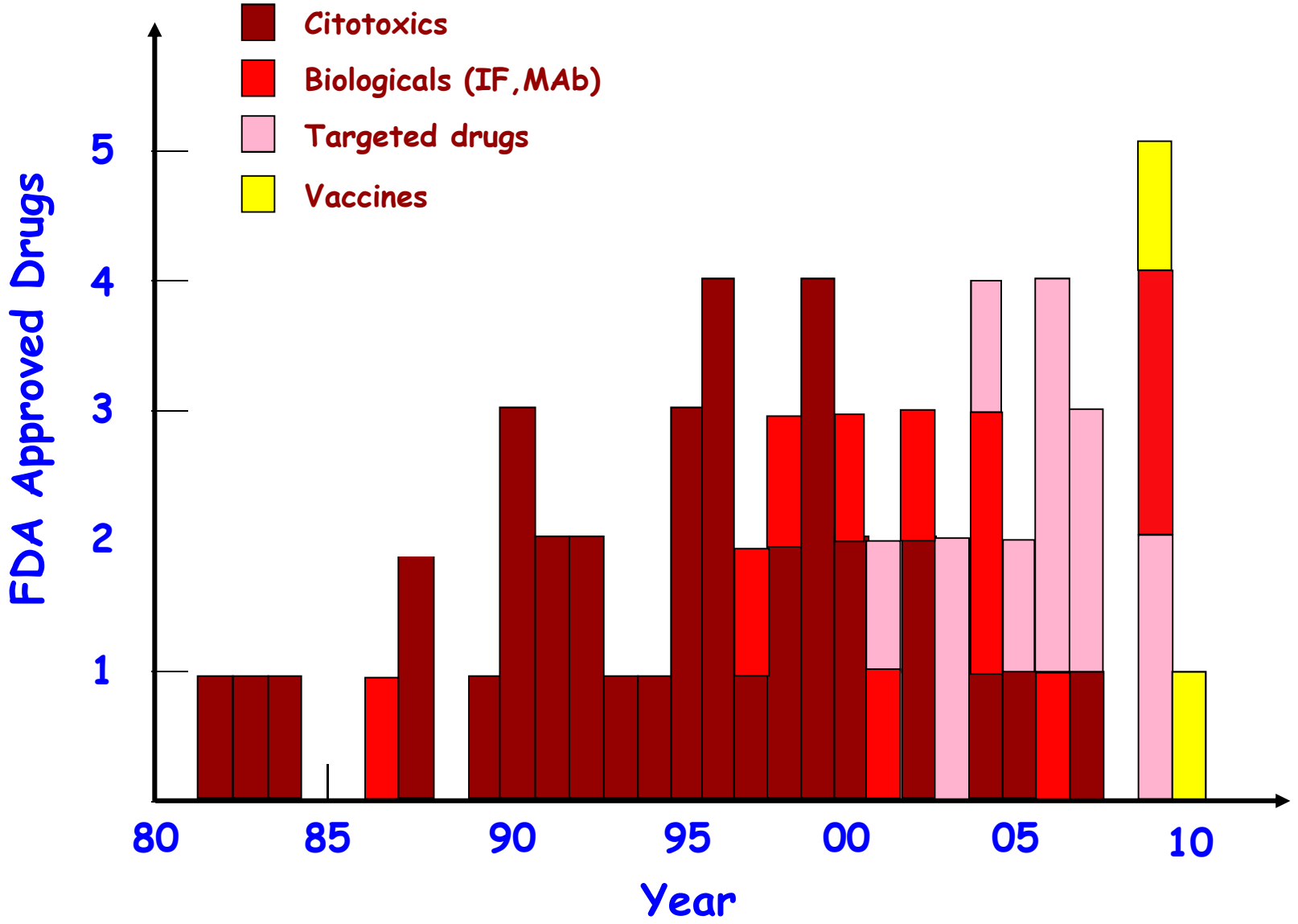
Would it be possible to block all the metastasis by inhibiting a "master" pathway mutated in the primary tumor?

A personal view

The future of cancer treatment will depend on improvements in four basic areas:

- **Targeted Therapies**: This is the future. Yet, we still need to select targets based on more solid information regarding their role in tumor development. Targeted therapies will only thrive when we will be able to translate genomic information into functional information. Unfortunately, understanding the precise function of each target in each tumor type cannot be done through "omic" approaches. Hence, this process will have to be done "*one gene at a time*" or at best "*one pathway at a time*".

Approved Oncology Drugs (novel mechanism of action)



Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

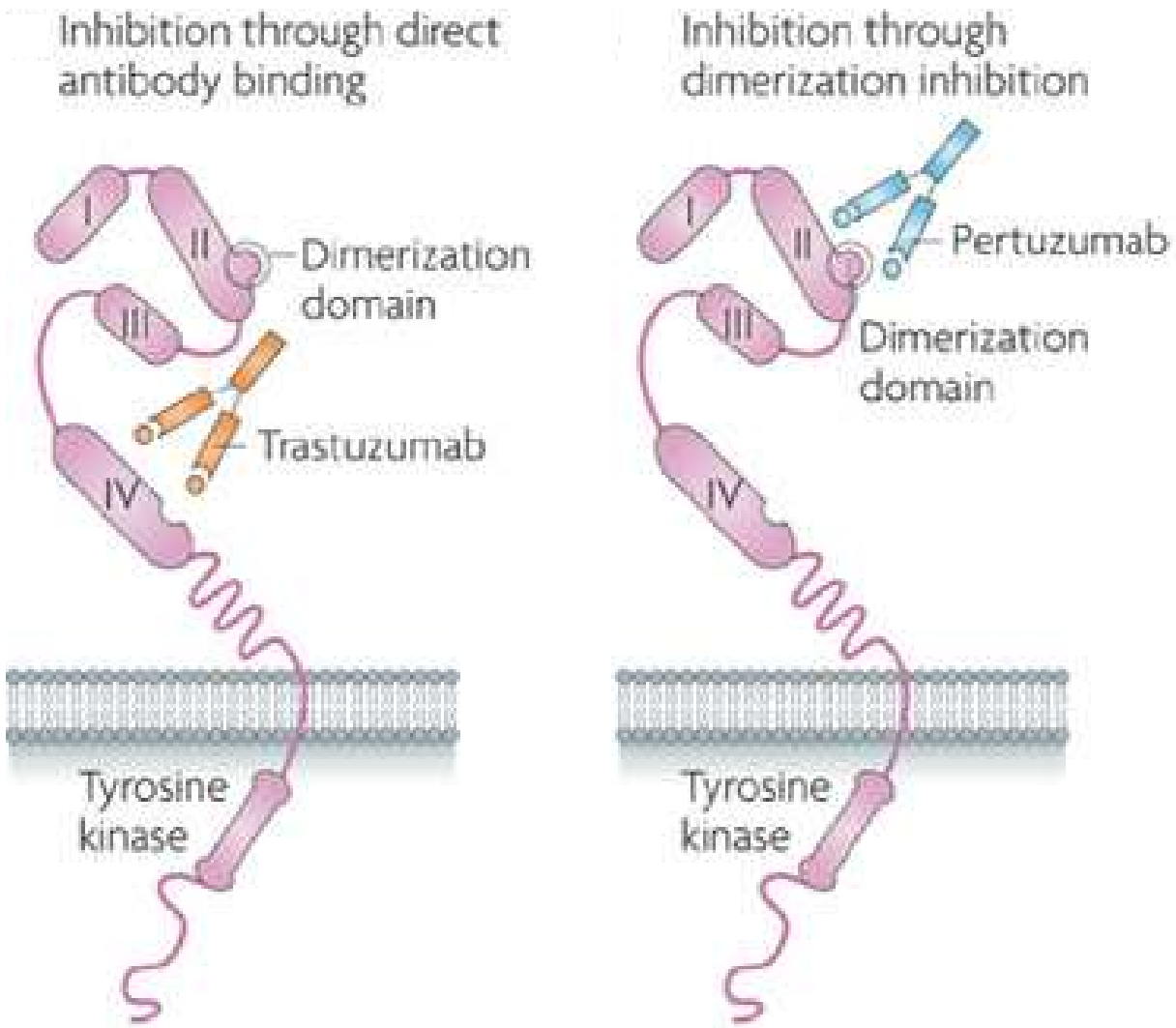
DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, WILLIAM L. MCGUIRE

SCIENCE, VOL. 235

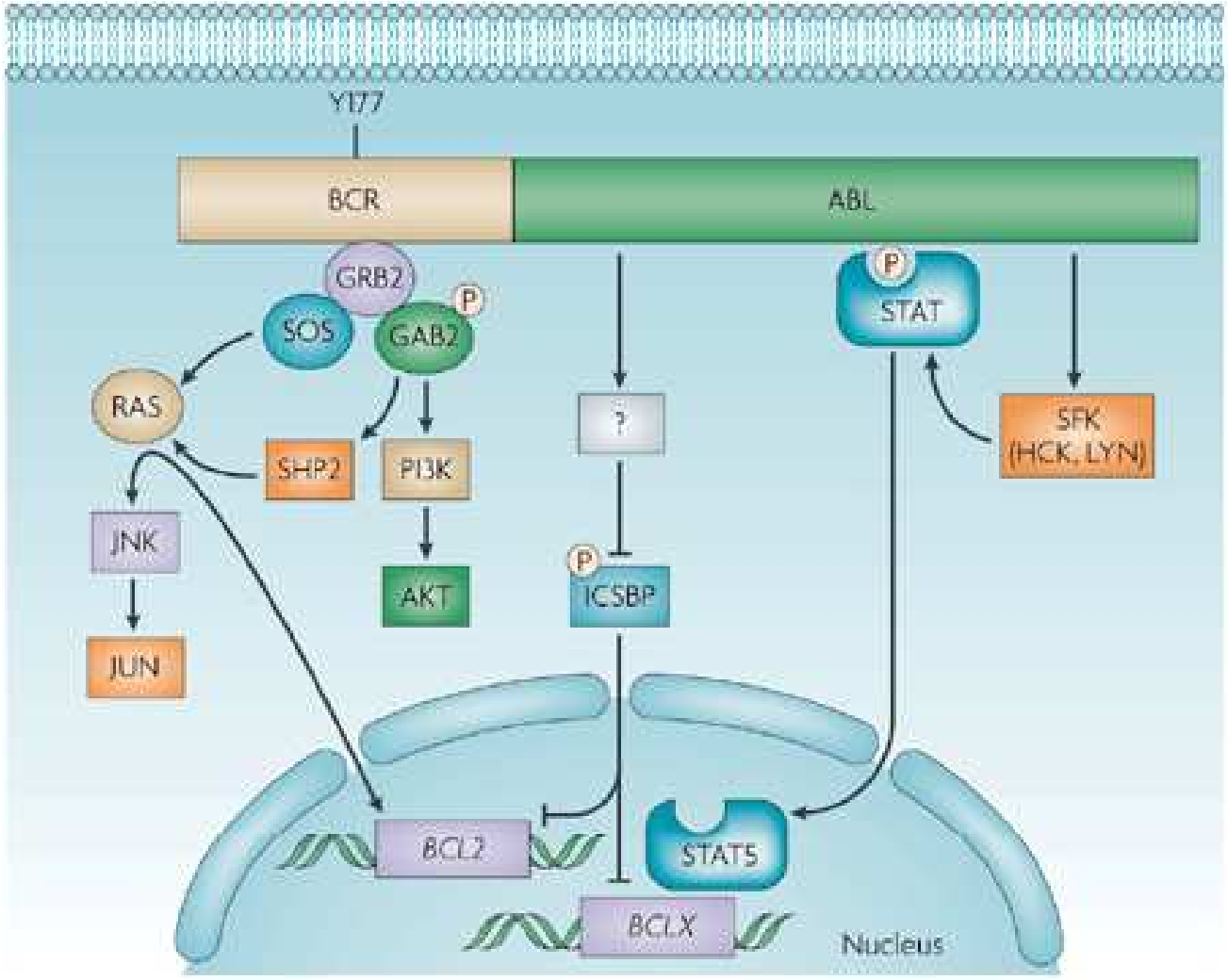
9 JANUARY 1987

The HER-2/*neu* oncogene is a member of the *erb*B–like oncogene family, and is related to, but distinct from, the epidermal growth factor receptor. This gene has been shown to be amplified in human breast cancer cell lines. In the current study, alterations of the gene in 189 primary human breast cancers were investigated. HER-2/*neu* was found to be amplified from 2- to greater than 20-fold in 30% of the tumors. Correlation of gene amplification with several disease parameters was evaluated. Amplification of the HER-2/*neu* gene was a significant predictor of both overall survival and time to relapse in patients with breast cancer. It retained its significance even when adjustments were made for other known prognostic factors. Moreover, HER-2/*neu* amplification had greater prognostic value than most currently used prognostic factors, including hormonal-receptor status, in lymph node–positive disease. These data indicate that this gene may play a role in the biologic behavior and/or pathogenesis of human breast cancer.

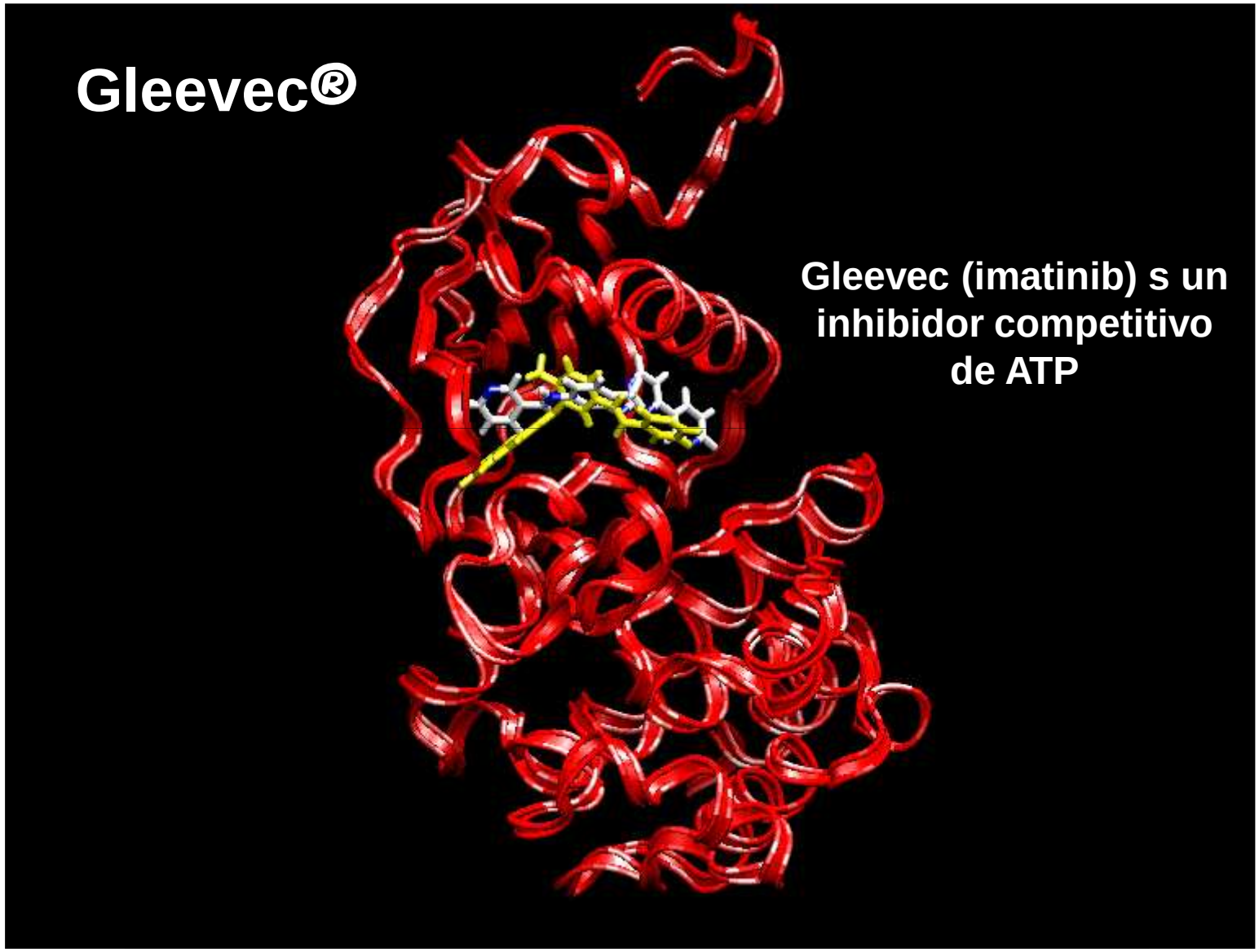
Dianas Moleculares: HER2



CML, BCR-ABL y Gleevec®

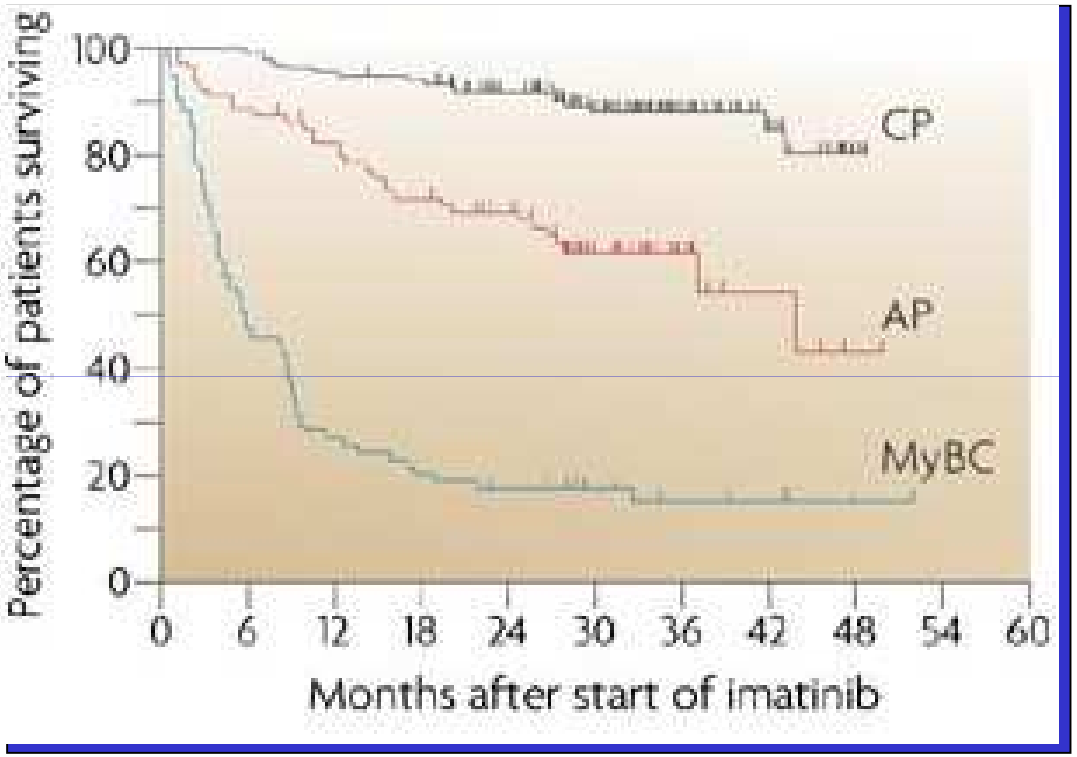


CML, BCR-ABL and Gleevec®



CML, BCR-ABL y Gleevec®

Terapias Moleculares: El caso de Gleevec

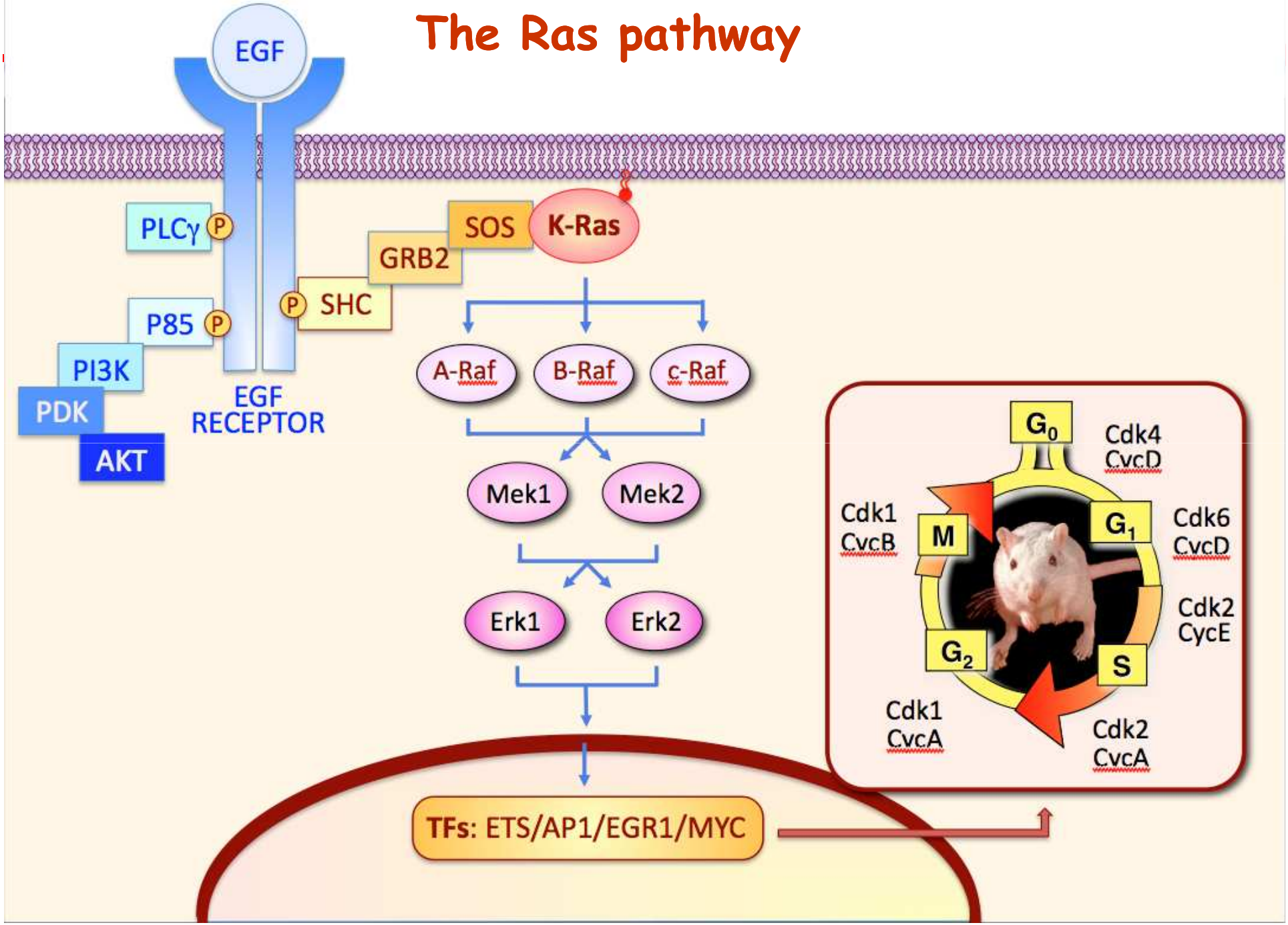


CP: Chronic phase
AP: Accelerated phase
BC: Blast Crisis

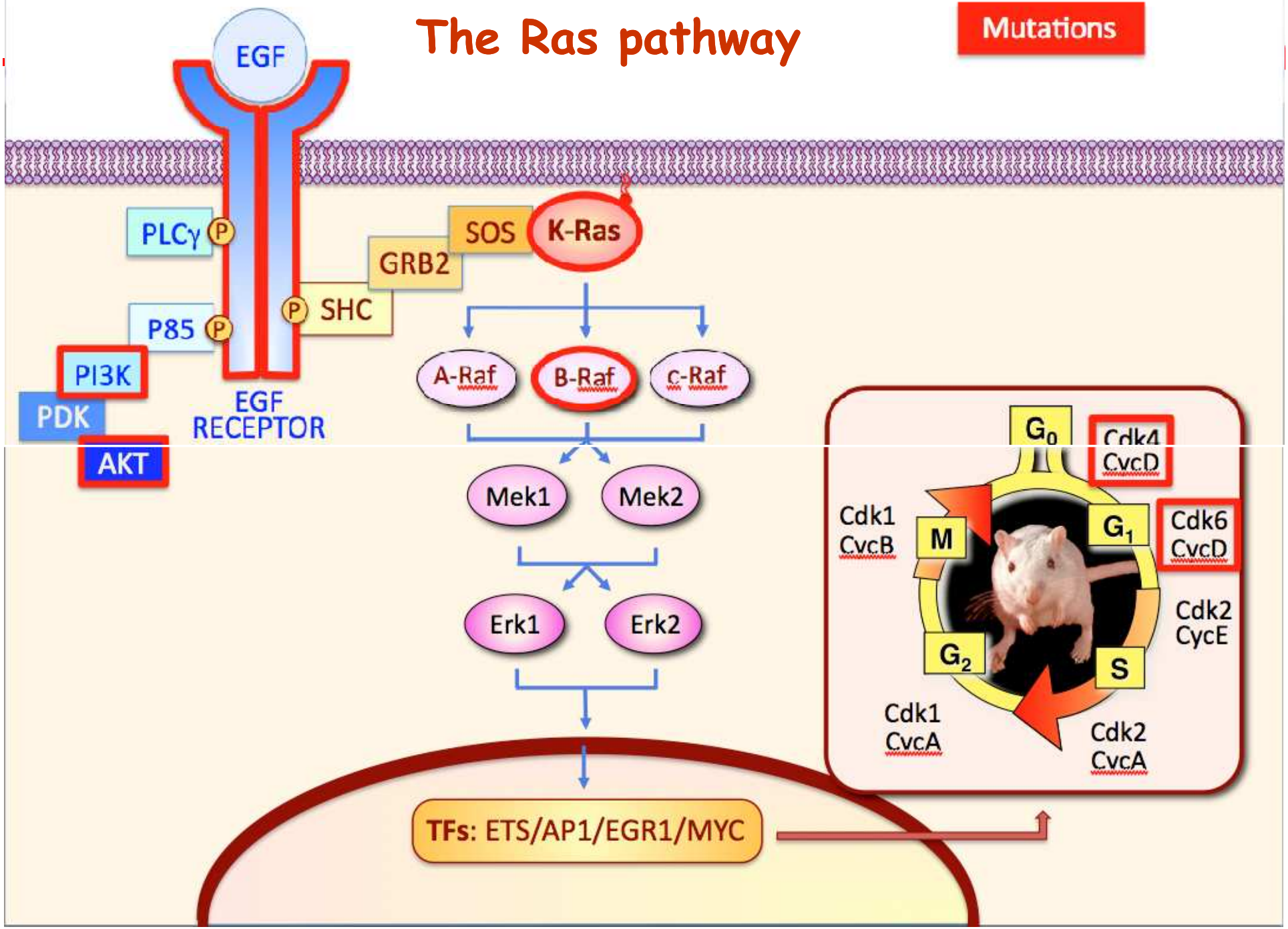
Nuevas Terapias: Quimiotipos I

- Los inhibidores selectivos contra dianas moleculares aprobados hasta la fecha incluyen :
  - 2001 Imatinib (Gleevec) contra leucemia mieloide crónica y GIST. Es un inhibidor de las tirosina quinasas como Bcr-Abl, Kit y PDGFR.
  - 2003 Bortezomib (Velcade) contra mieloma múltiple. Es un inhibidor del proteosoma
  - 2004 Erlotinib (Tarceva) contra carcinoma de pulmón no microcitico metastásico. Es un inhibidor del receptor tirosina quinasa del EGF.
  - 2005 Sorafenib (Nexabar) contra carcinoma renal avanzado. Es un inhibidor no muy selectivo de quinasas.
  - 2006 Sunitinib (Sutent) contra sarcoma de tejidos blando y carcinoma renal avanzado. Es un inhibidor múltiple de tirosina quinasas, principalmente PDGF y VEGF.
  - 2006 Vorinostat (Zolinza) contra linfomas cutáneos de linfocitos T. Es un inhibidor genérico de deacetilasas de histonas (HDAC inhibitors).
  - 2007 Lapatinib (Tykerb) contra cáncer de mama metastásico. Es un inhibidor dual de los receptroes HER1 and HER2.
  - 2007 Temsirolimus (Torisel) carcinoma renal avanzado. En un inhibidor de mTOR, una quinasa de la ruta de PI3K y Akt.

The Ras pathway



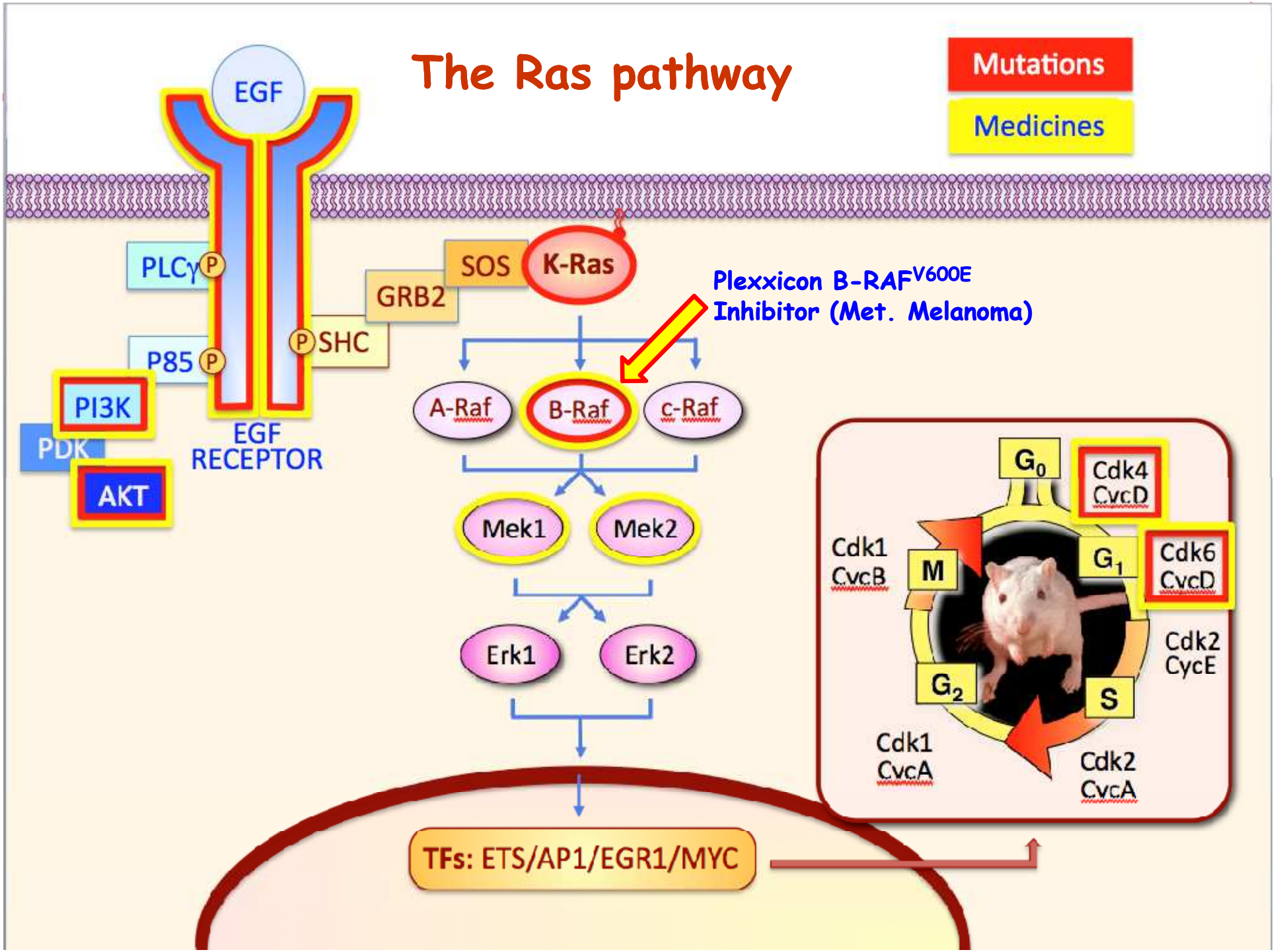
The Ras pathway



The Ras pathway

Mutations

Medicines



Diagnóstico Molecular: Biomarcadores

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

CONCLUSIONS

Sin embargo PLX-4032 parece no tener efecto en pacientes con carcinoma de colon portadores de la misma mutación B-RAF^{V600E} presente en melanomas

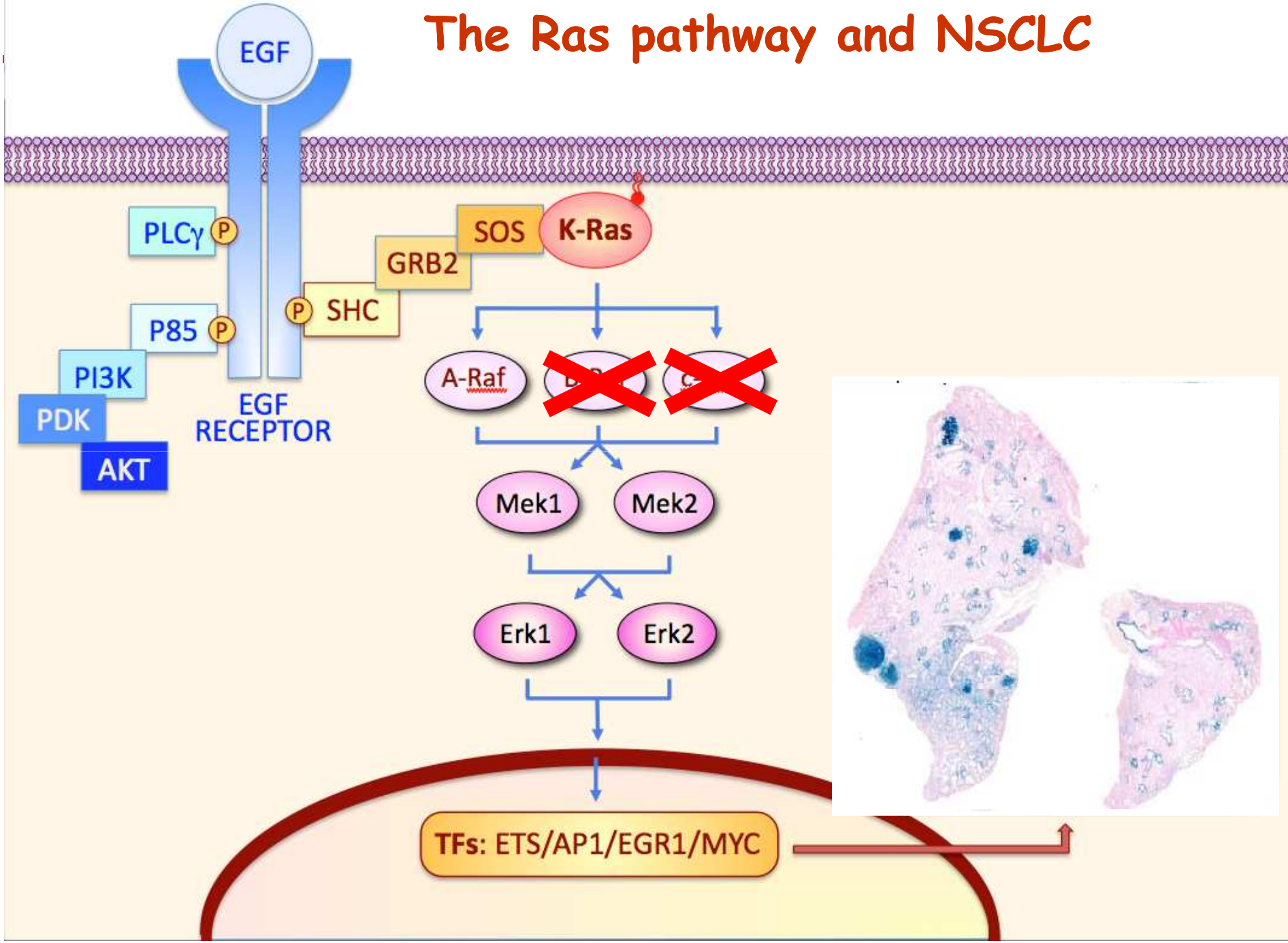
doi:10.1038/nature09454 nature

LETTERS

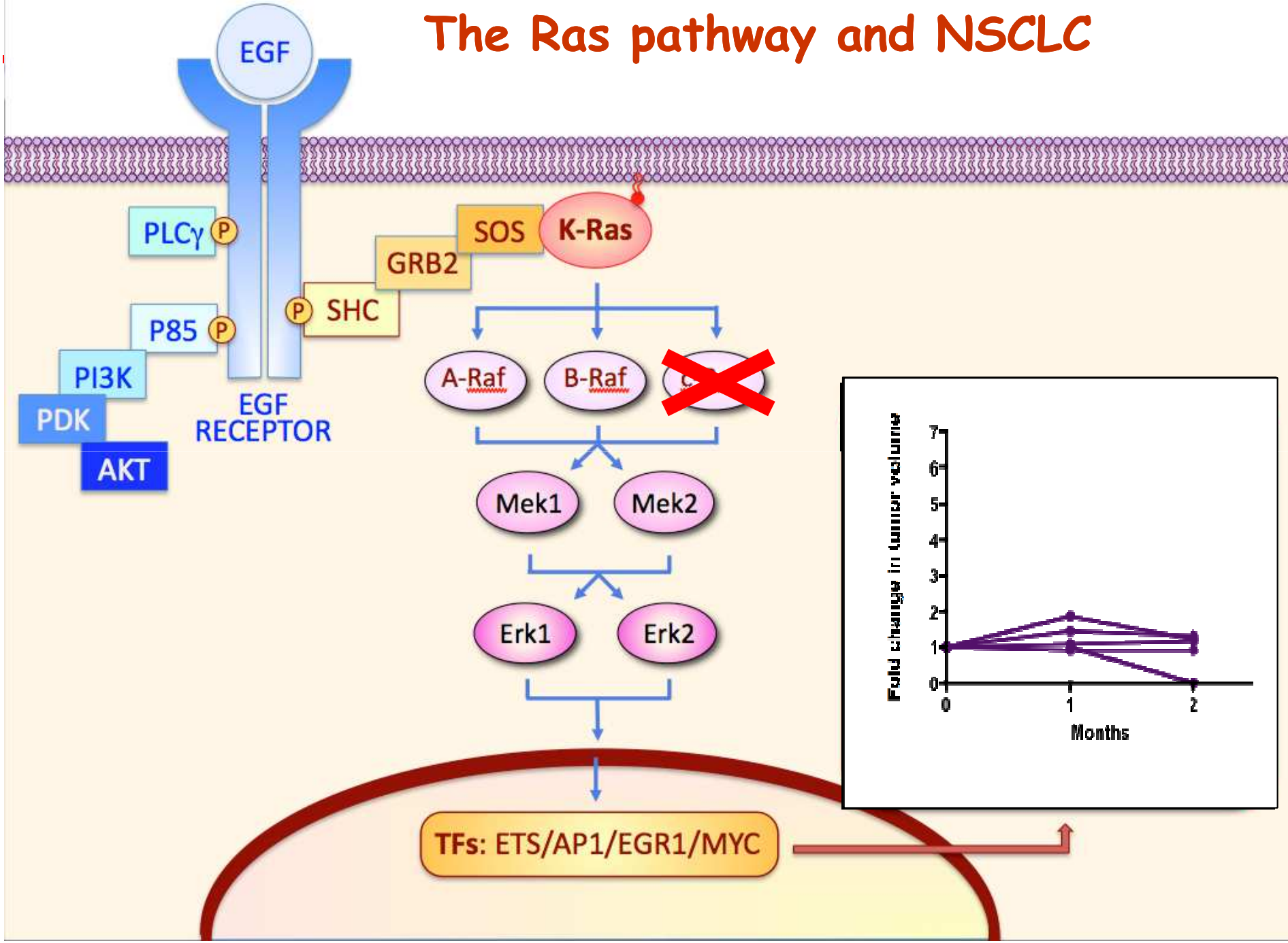
Clinical efficacy of a RAF inhibitor needs broad target blockade in *BRAF*-mutant melanoma

Gideon Bollag[1], Peter Hirth[1], James Tsai[1], Jiazhong Zhang[1], Prabha N. Ibrahim[1], Hanna Cho[1], Wayne Spevak[1], Chao Zhang[1], Ying Zhang[1], Gaston Habets[1], Elizabeth A. Burton[1], Bernice Wong[1], Garson Tsang[1], Brian L. West[1], Ben Powell[1], Rafe Shellooe[1], Adhirai Marimuthu[1], Hoa Nguyen[1], Kam Y. J. Zhang[1], Dean R. Artis[1], Joseph Schlessinger[2], Fei Su[3], Brian Higgins[3], Raman Iyer[3], Kurt D'Andrea[4], Astrid Koehler[3], Michael Stumm[3], Paul S. Lin[1], Richard J. Lee[3], Joseph Grippo[3], Igor Puzanov[5], Kevin B. Kim[6], Antoni Ribas[7], Grant A. McArthur[8], Jeffrey A. Sosman[5], Paul B. Chapman[9], Keith T. Flaherty[4], Xiaowei Xu[4], Katherine L. Nathanson[4] & Keith Nolop[1]

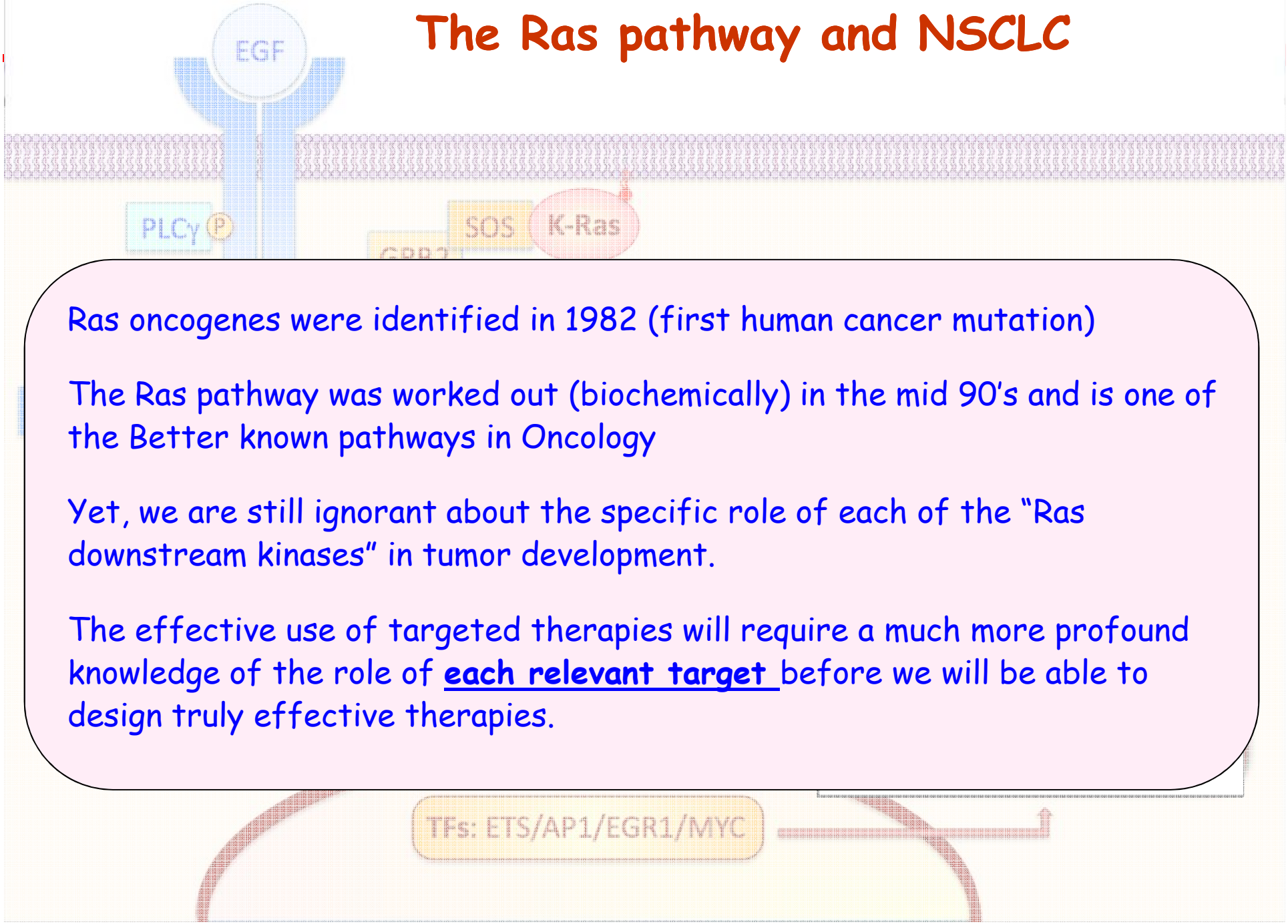
The Ras pathway and NSCLC



The Ras pathway and NSCLC



The Ras pathway and NSCLC



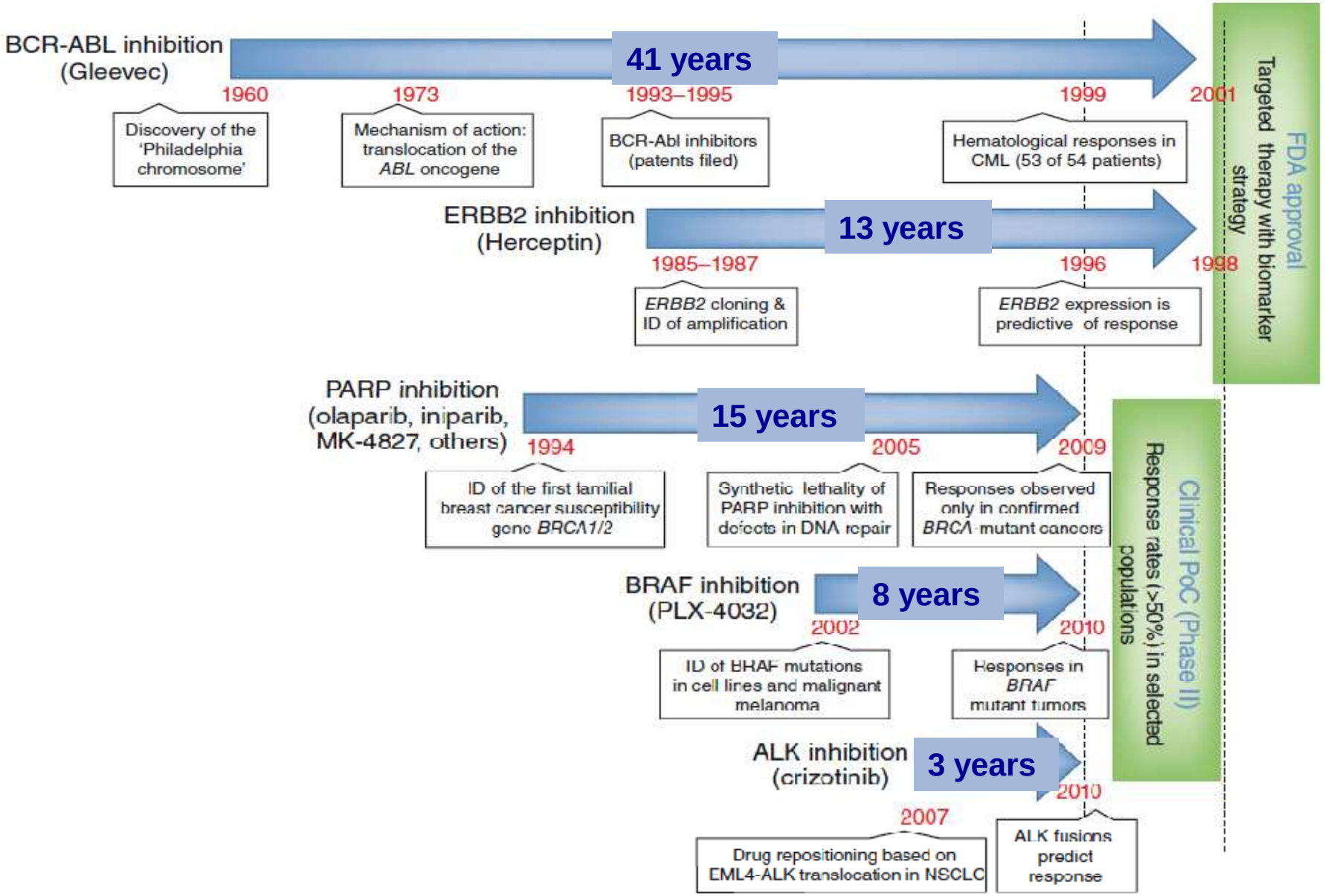
Ras oncogenes were identified in 1982 (first human cancer mutation)

The Ras pathway was worked out (biochemically) in the mid 90's and is one of the Better known pathways in Oncology

Yet, we are still ignorant about the specific role of each of the "Ras downstream kinases" in tumor development.

The effective use of targeted therapies will require a much more profound knowledge of the role of **each relevant target** before we will be able to design truly effective therapies.

Molecular Therapies




CMO