ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI

FONDAZIONE G. Pascale – NAPOLI
SC Biologia Cellulare e Bioterapie

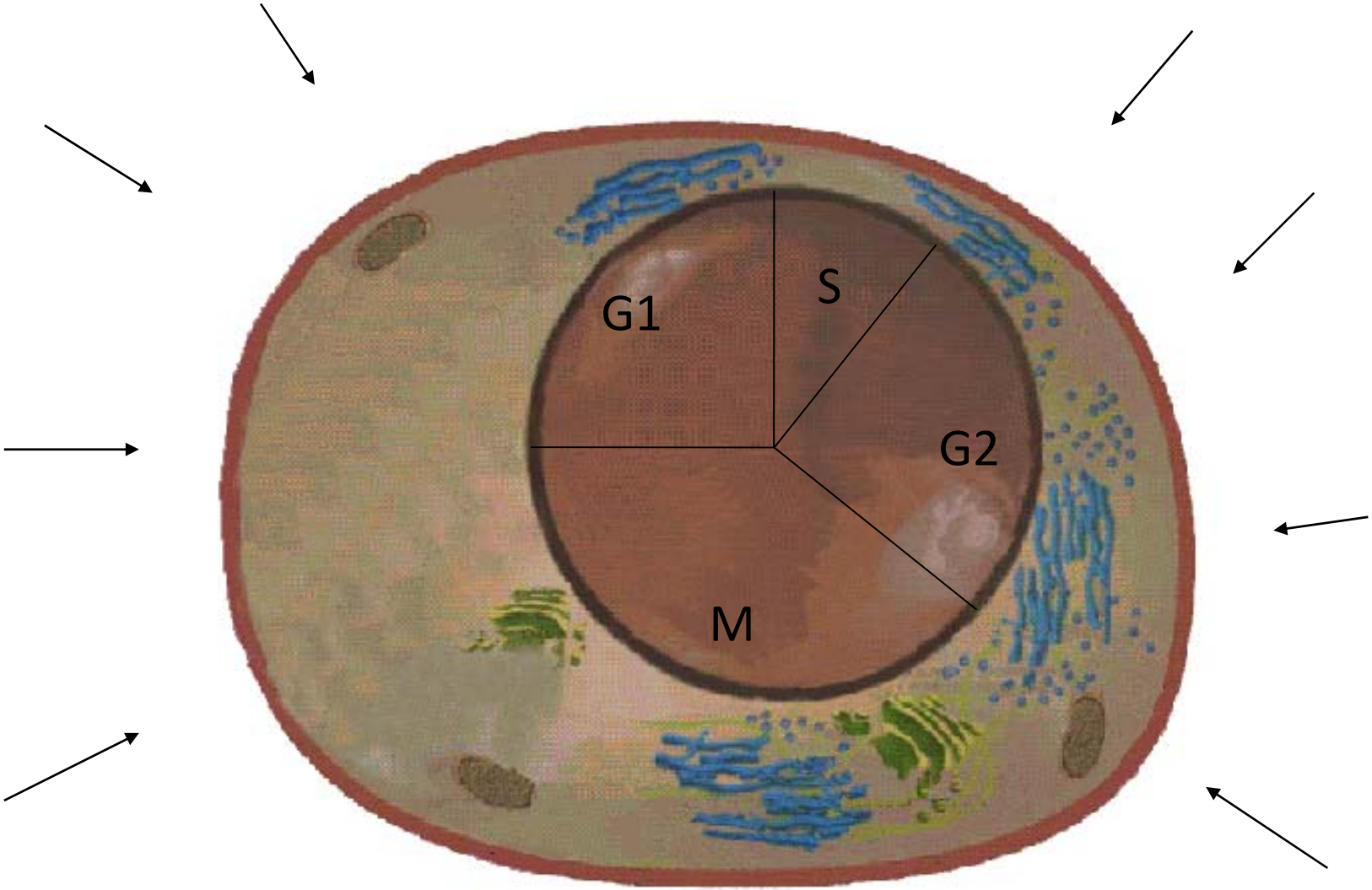
CENTRO RICERCHE ONCOLOGICHE MERCOGLIANO (AV)

Laboratorio di Farmacogenomica

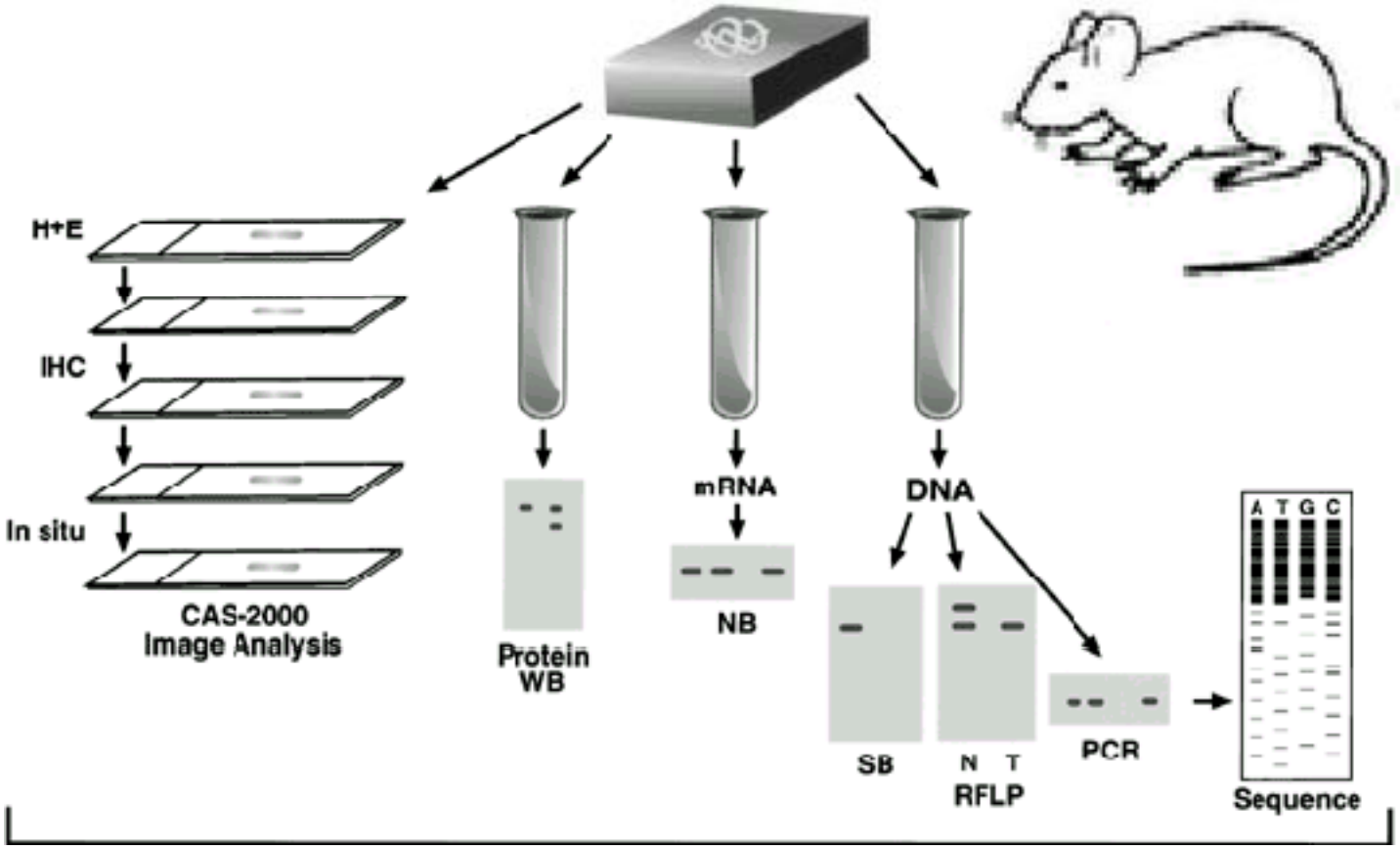
FARMACI "PERSONALIZZATI" PER SCONFIGGERE I TUMORI

Nicola Normanno

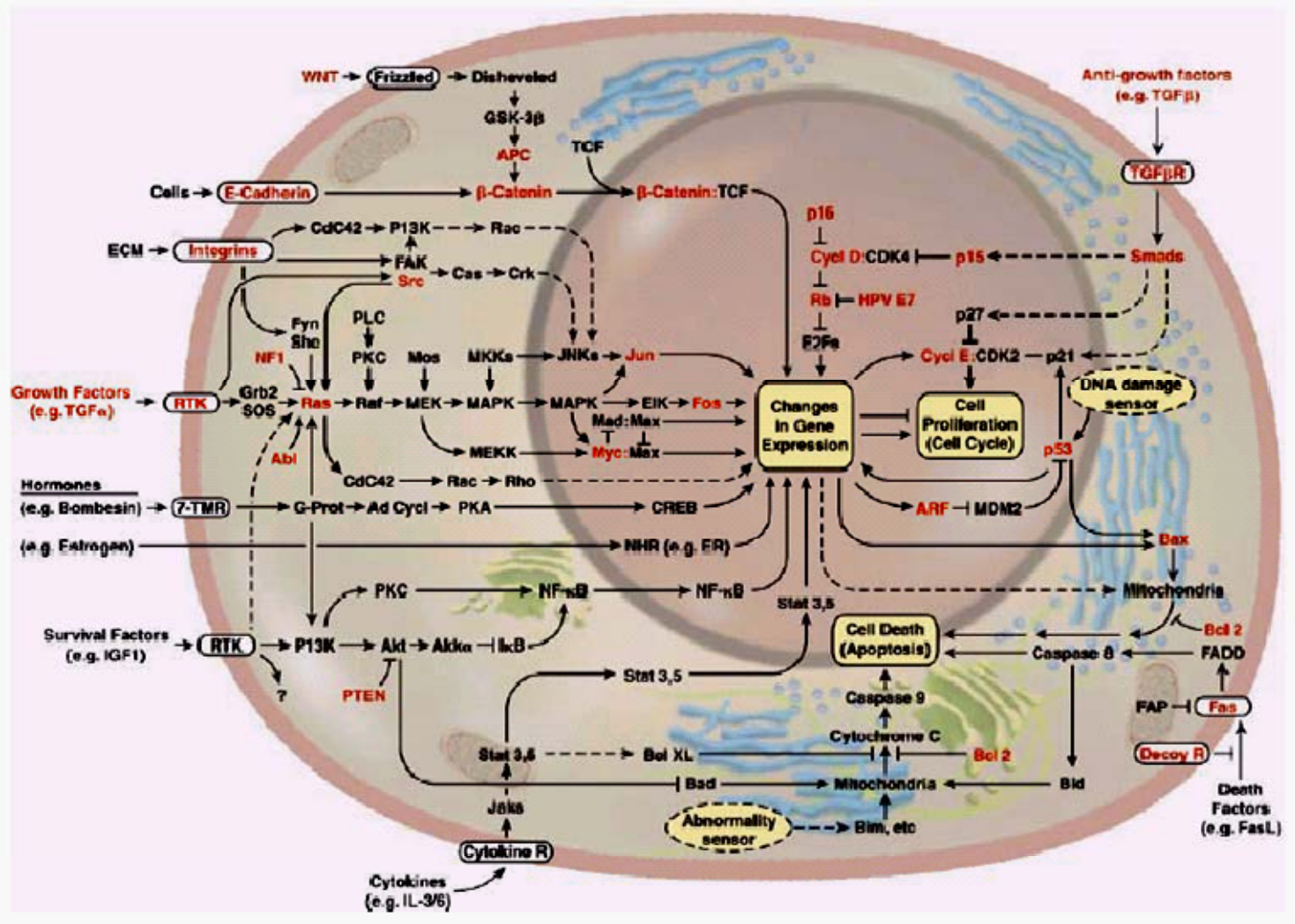
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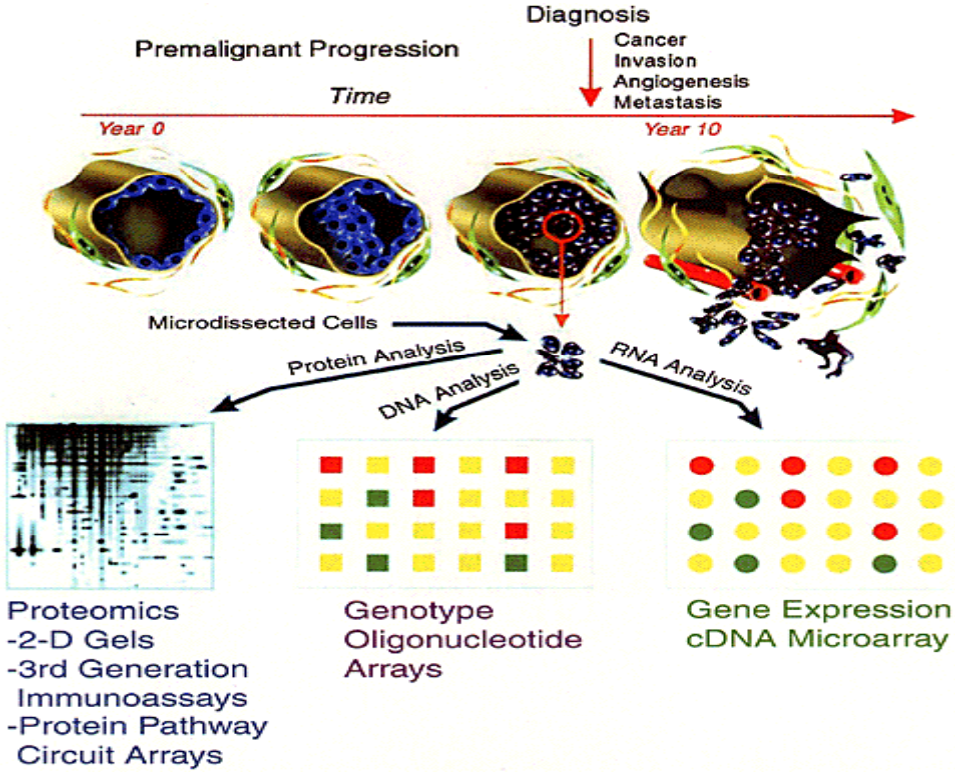
PRE –GENOME ERA



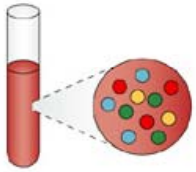
Signal transduction pathways involved in the proliferation and survival of cancer cells

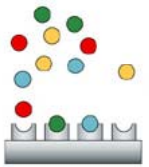


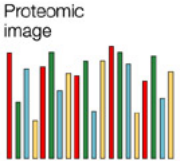
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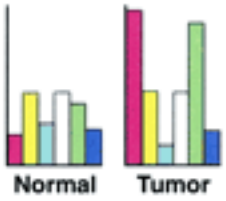


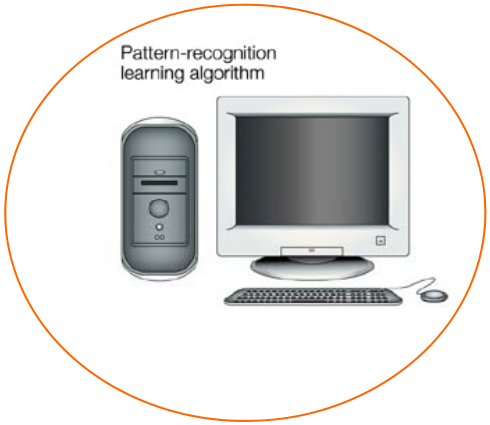


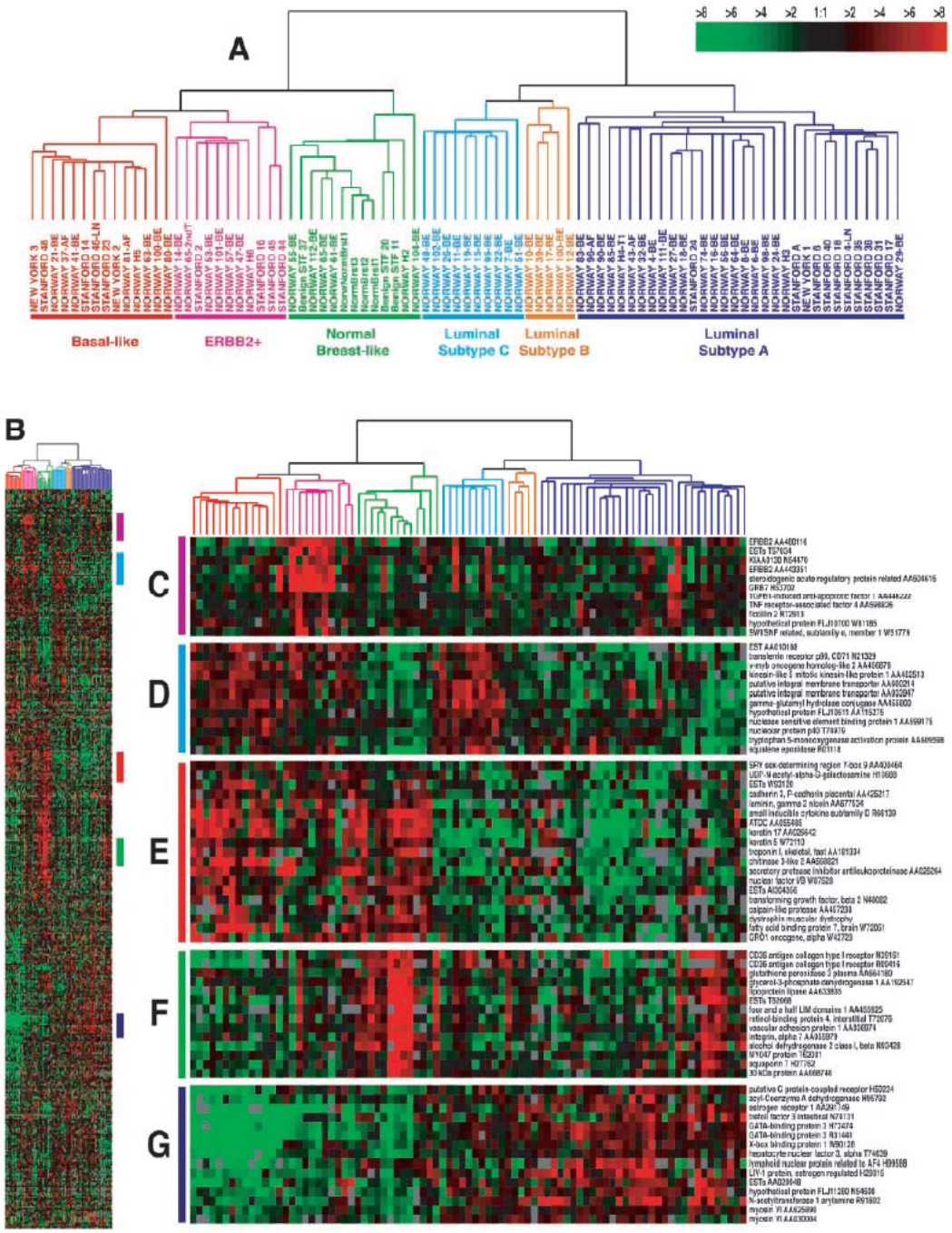


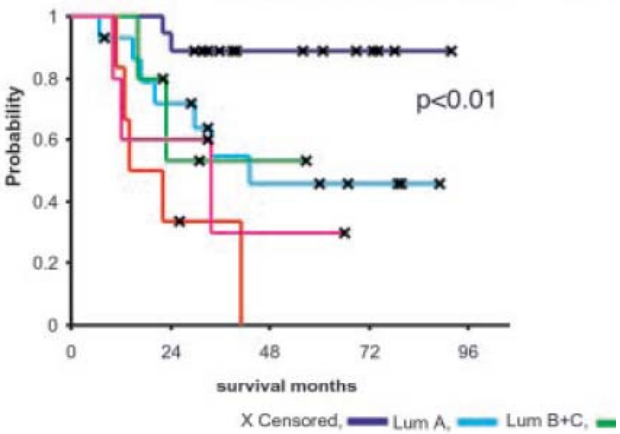


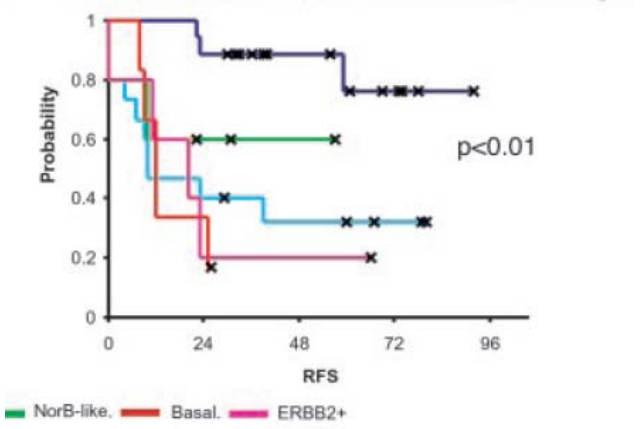






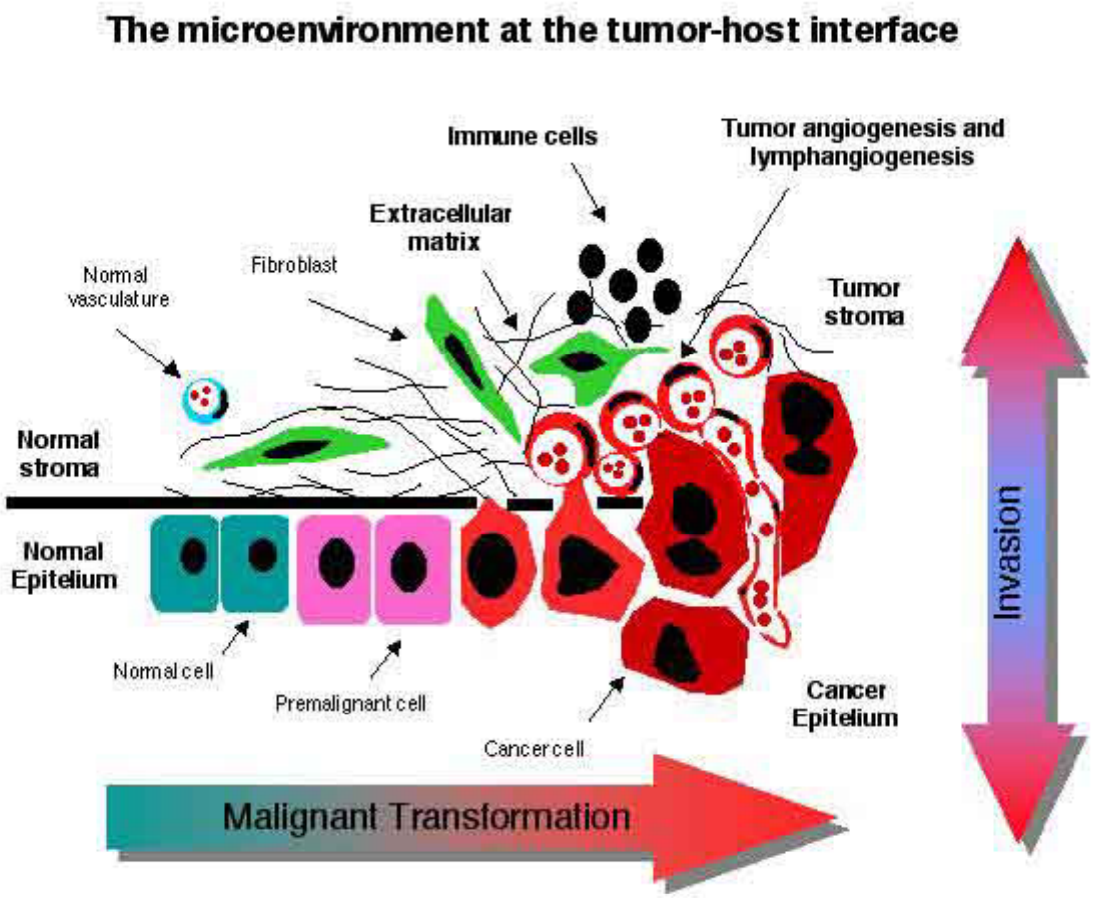




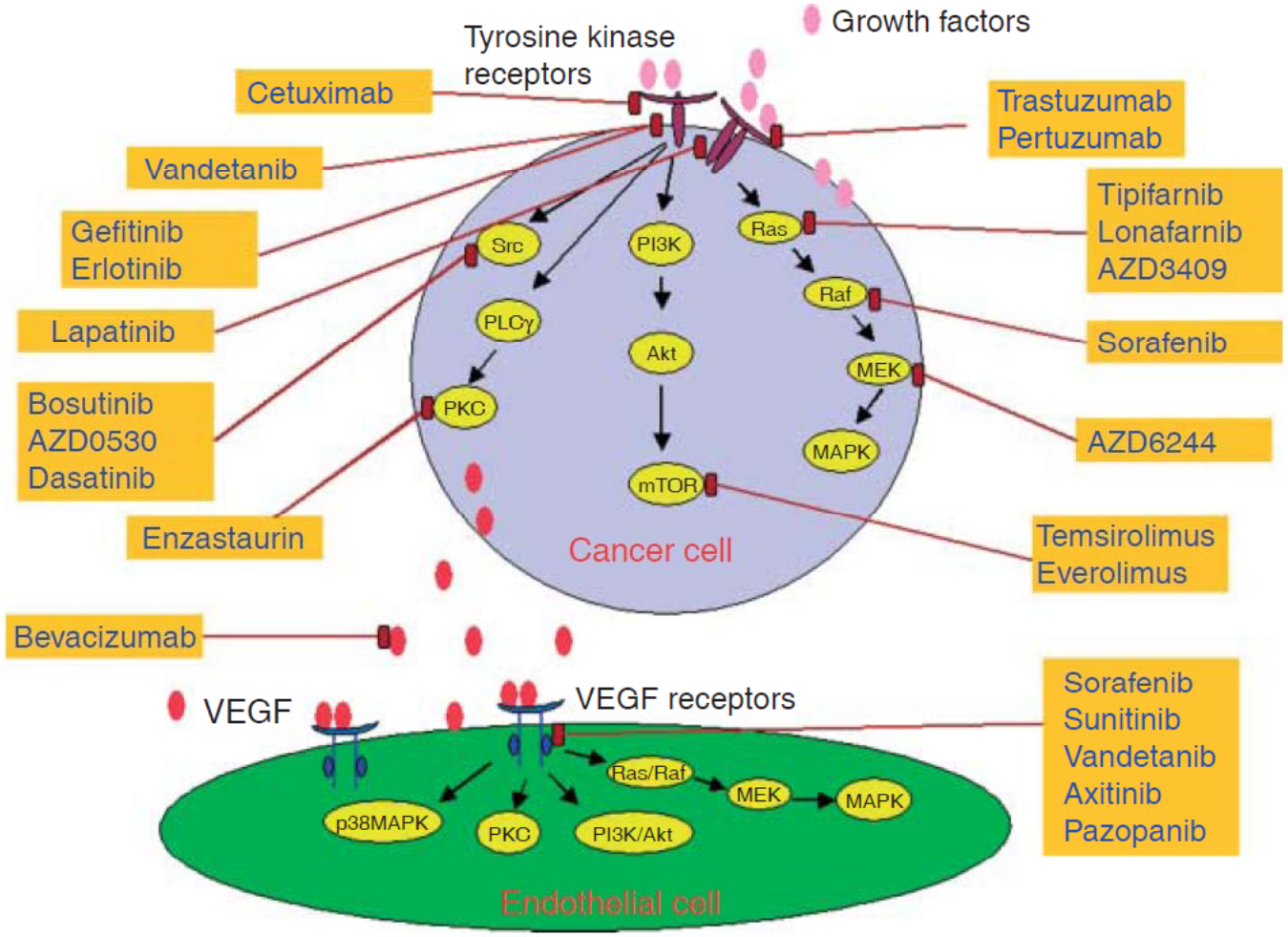


Sorlie PNAS 2001

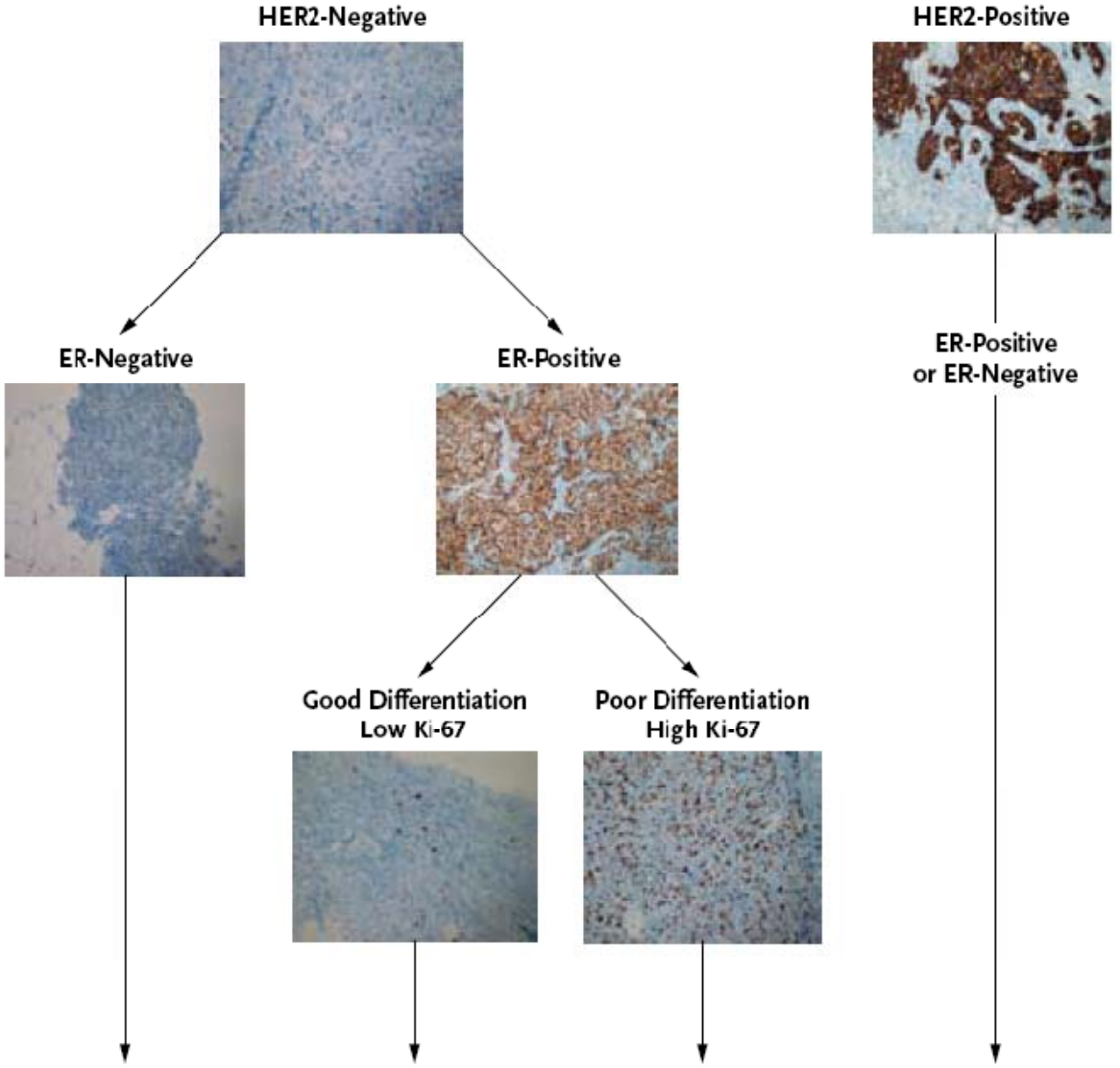
Tumor/Stroma interaction



Target-based agents in clinical development in breast cancer

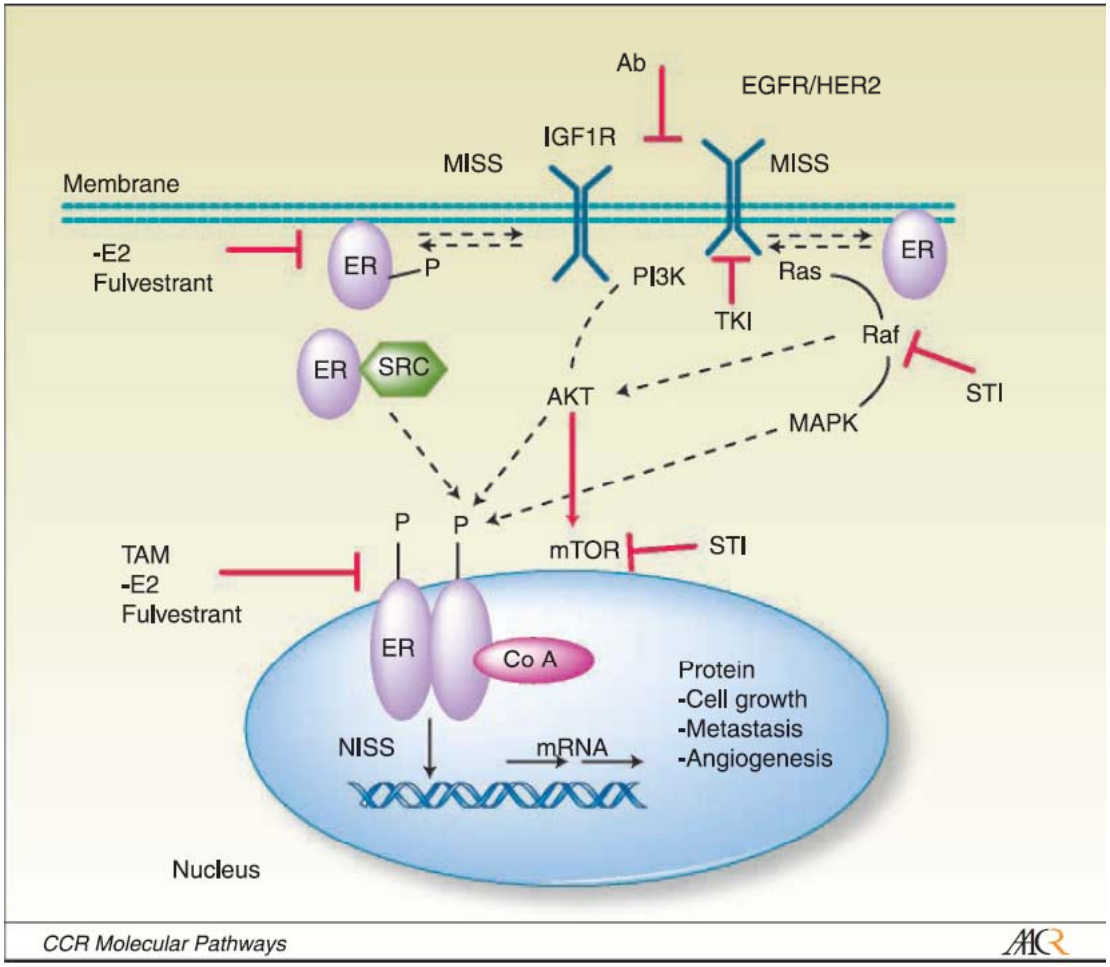


Normanno Endocr Relat Cancer 2009

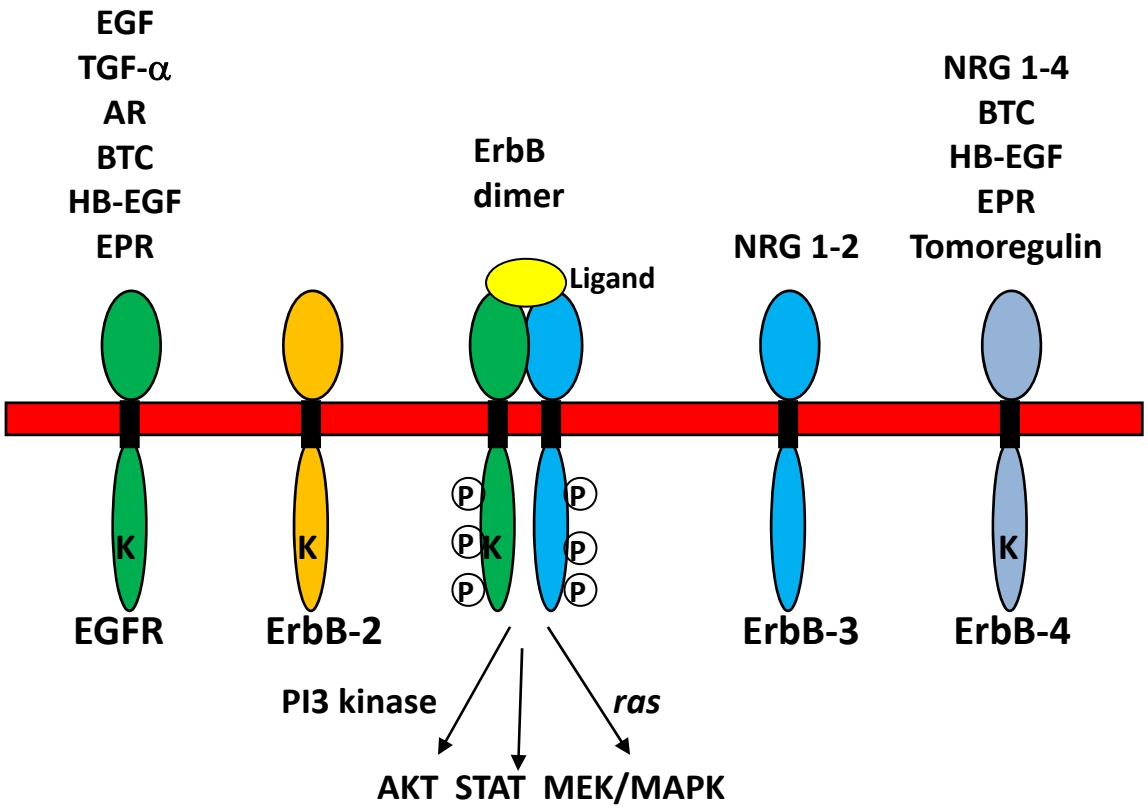


Pathological Variables	Basal-like (%)	Luminal A (%)	Luminal B (%)	HER2-like (%)
HER2-positive (IHC)	10	12	20	100
ER-positive (IHC)	12	96	97	46
Grade III	84	19	53	74
Tumor size >2 cm	75	53	69	74
Node-positive	40	52	65	66

Sotiriou & Pusztai
NEJM 2009

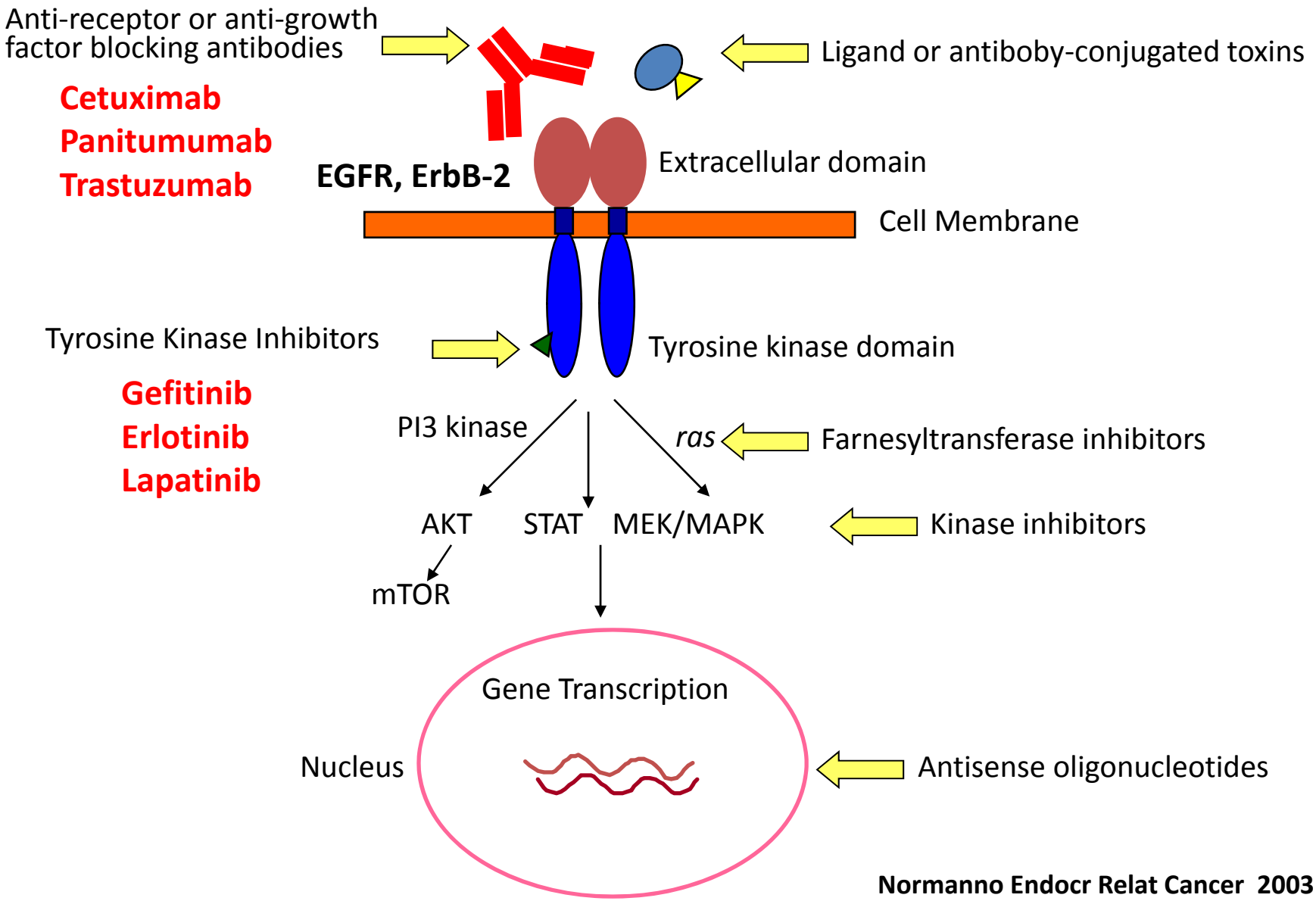

Ab
EGFR/HER2
IGF1R
MISS
MISS
Membrane
-E2
Fulvestrant
ER
P
PI3K
Ras
ER
TKI
Raf
ER
SRC
AKT
STI
MAPK
P
P
TAM
-E2
Fulvestrant
mTOR
STI
ER
Co A
Protein
-Cell growth
-Metastasis
-Angiogenesis
NISS
mRNA
Nucleus
CCR Molecular Pathways
AACR

The ErbB family of receptors and their cognate ligands



Normanno Curr Drug Targets 2005

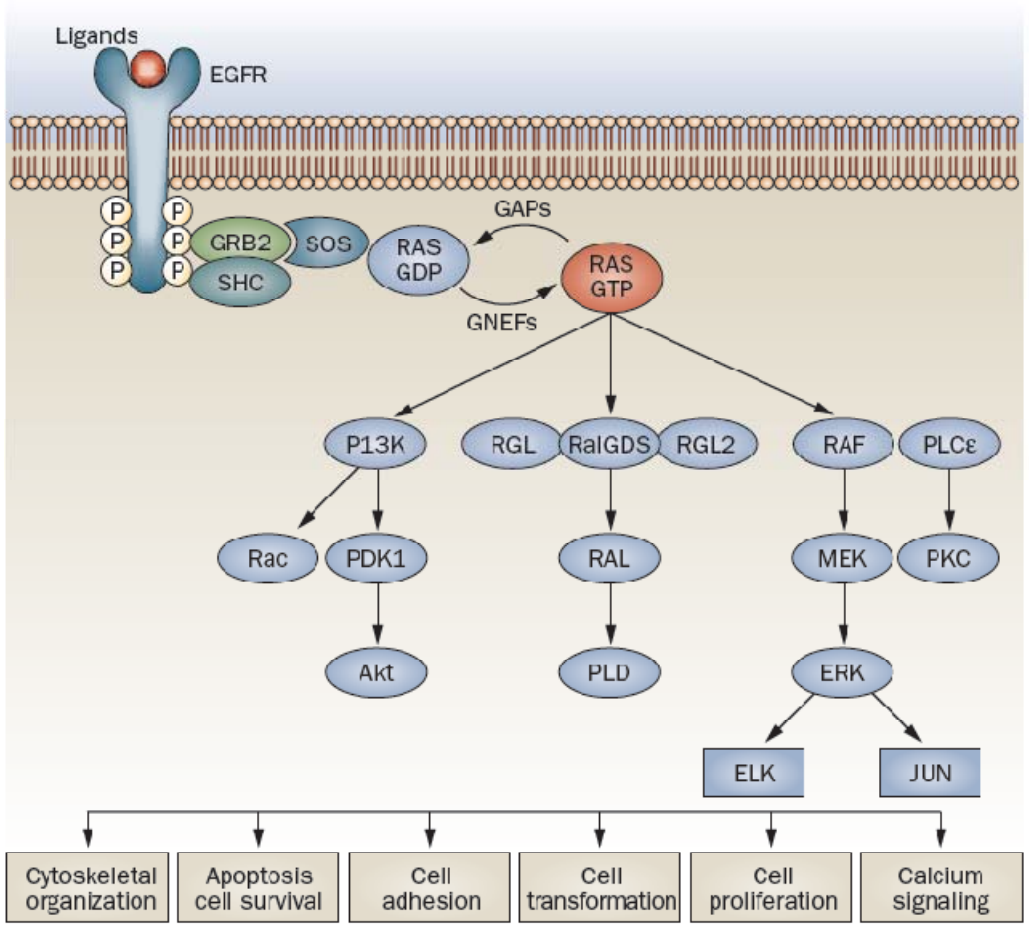
Potential sites for therapeutic intervention in growth factor-driven signal transduction pathways



Normanno Endocr Relat Cancer 2003

Farmaci anti-EGFR nel carcinoma del colon retto

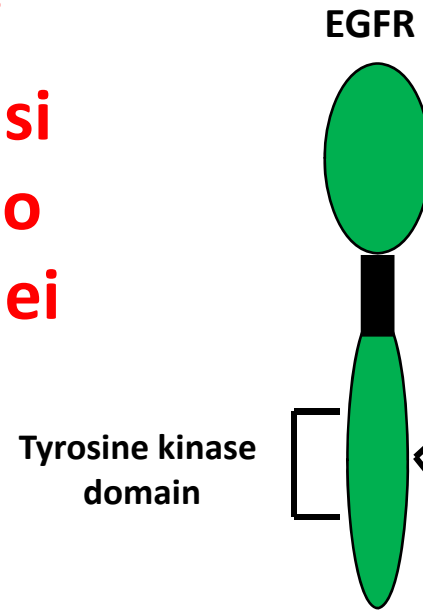
- **Gli anticorpi monoclonali anti-EGFR sono efficaci solo nei pazienti che non hanno mutazioni dell'oncogene KRAS**



Normanno Nat Rev Clin Oncol 2009

Mutazioni del gene EGFR nel carcinoma polmonare

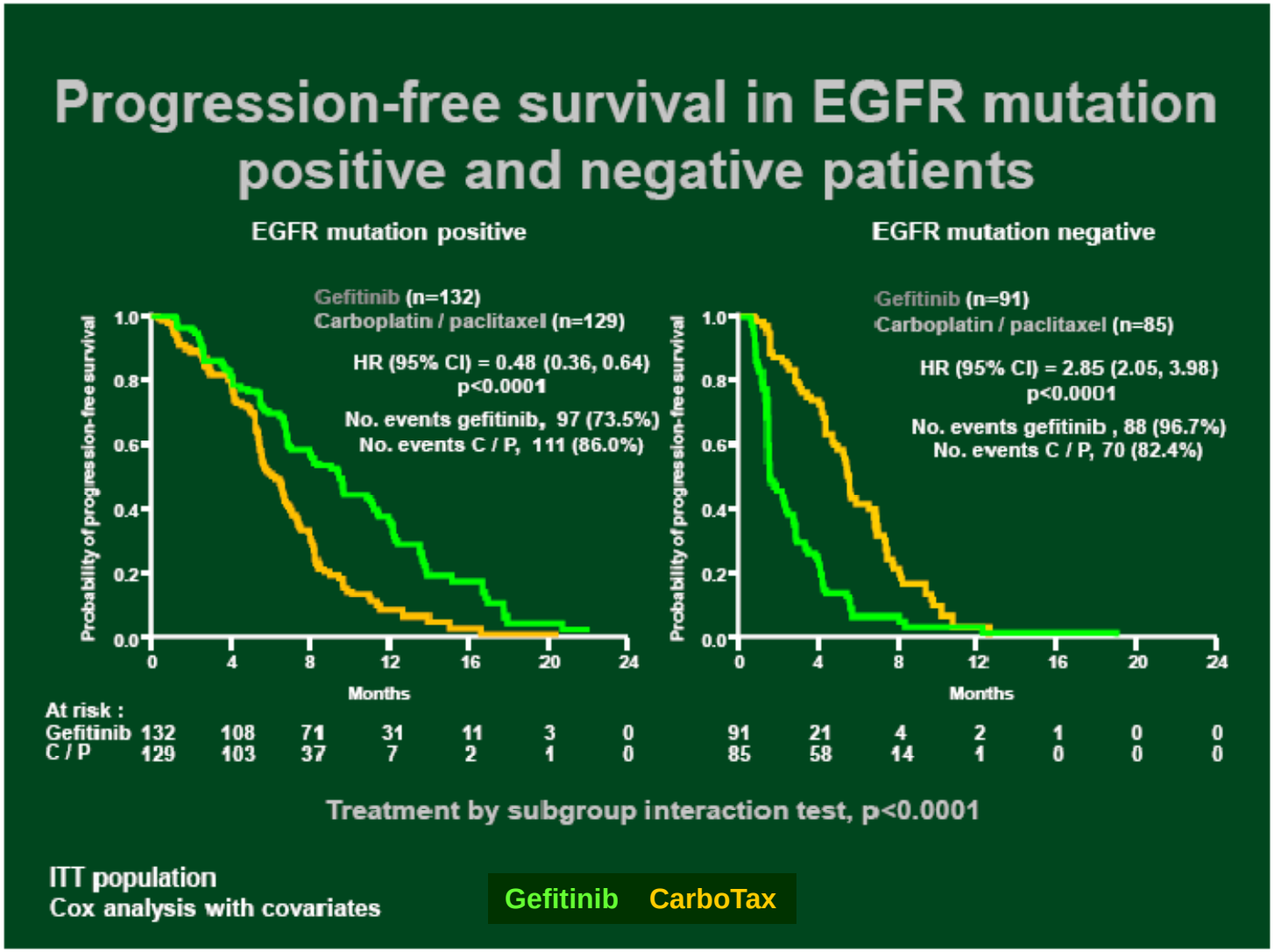
- **Gli inibitori di tirosino chinasi dell'EGFR sono efficaci solo nei pazienti che presentano mutazioni dell'EGFR**



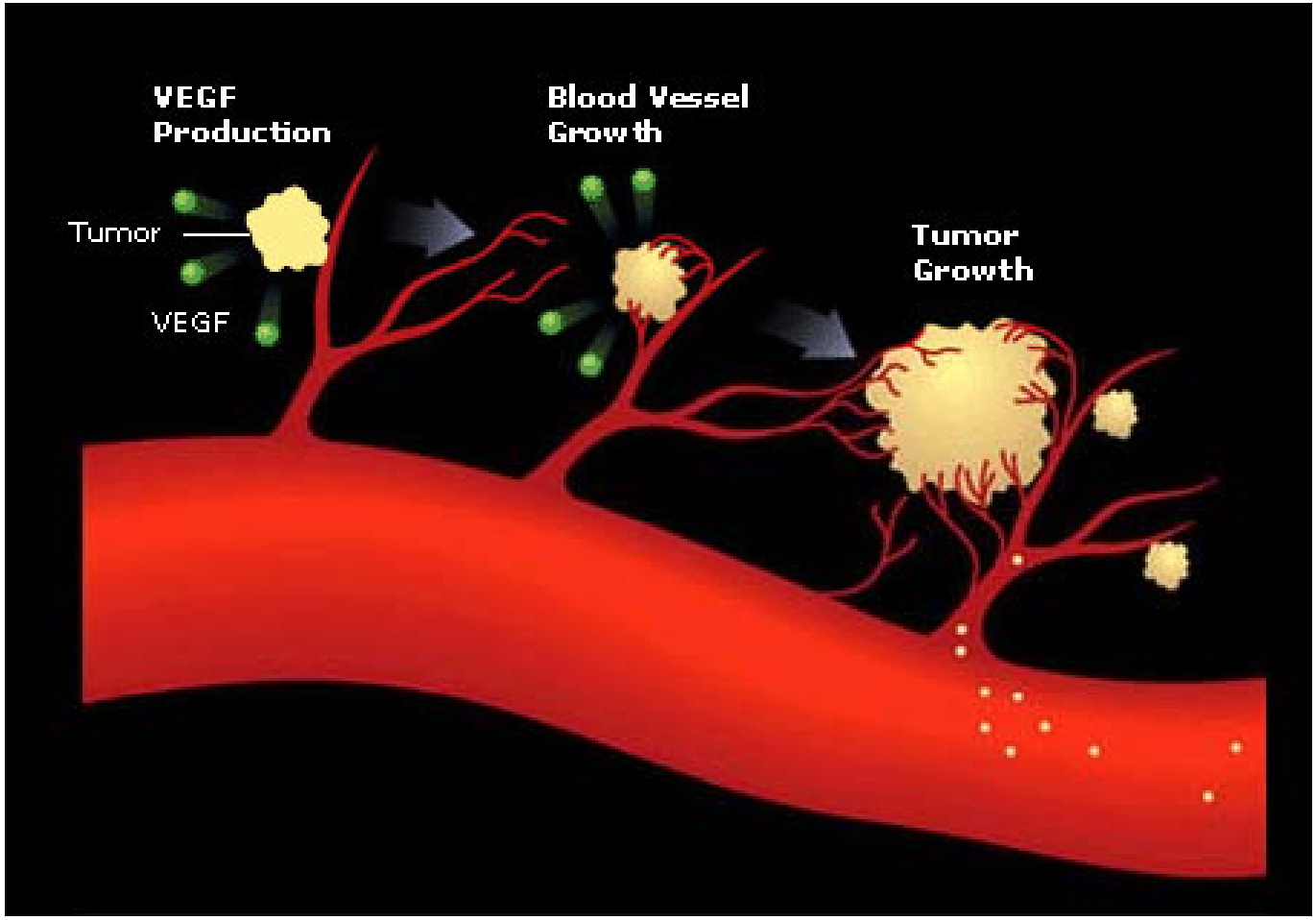
Mutations	*Frequency (%)*
Exon 19 deletions	46
L858R substitution	40
Exon 20 variants	9
Other variants	5

De Luca & Normanno Curr Drug Targets 2010

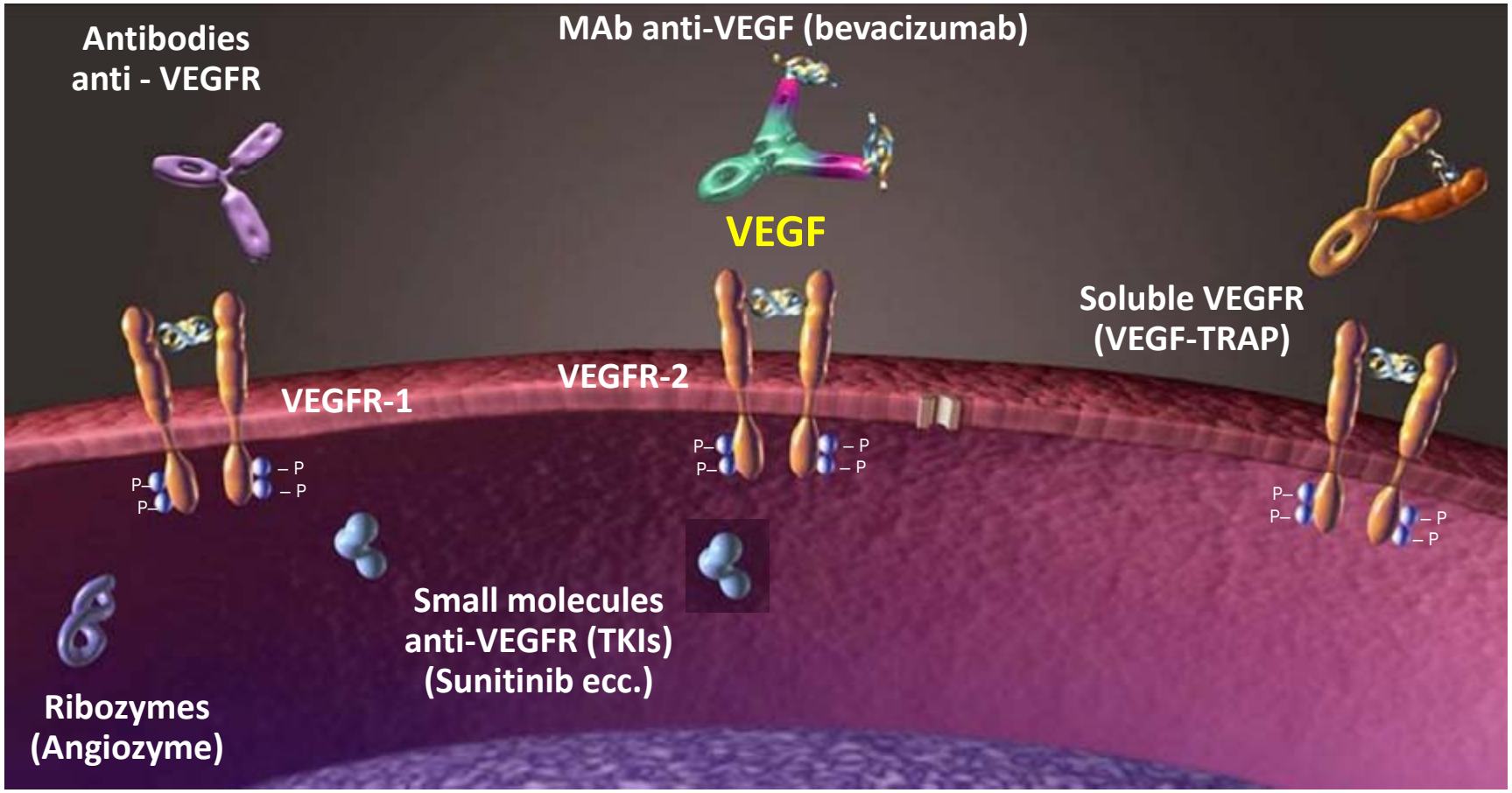
IPASS


Progression-free survival in EGFR mutation positive and negative patients
EGFR mutation positive
Gefitinib (n=132)
Carboplatin / paclitaxel (n=129)
HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001
No. events gefitinib, 97 (73.5%)
No. events C / P, 111 (86.0%)
Probability of progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 4 8 12 16 20 24
Months
EGFR mutation negative
Gefitinib (n=91)
Carboplatin / paclitaxel (n=85)
HR (95% CI) = 2.85 (2.05, 3.98)
p<0.0001
No. events gefitinib , 88 (96.7%)
No. events C / P, 70 (82.4%)
Probability of progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 4 8 12 16 20 24
Months
At risk :
Gefitinib 132 108 71 31 11 3 0
C / P 129 103 37 7 2 1 0
91 21 4 2 1 0 0
85 58 14 1 0 0 0
Treatment by subgroup interaction test, p<0.0001
ITT population
Cox analysis with covariates
Gefitinib CarboTax

Angiogenesis and Tumor Growth



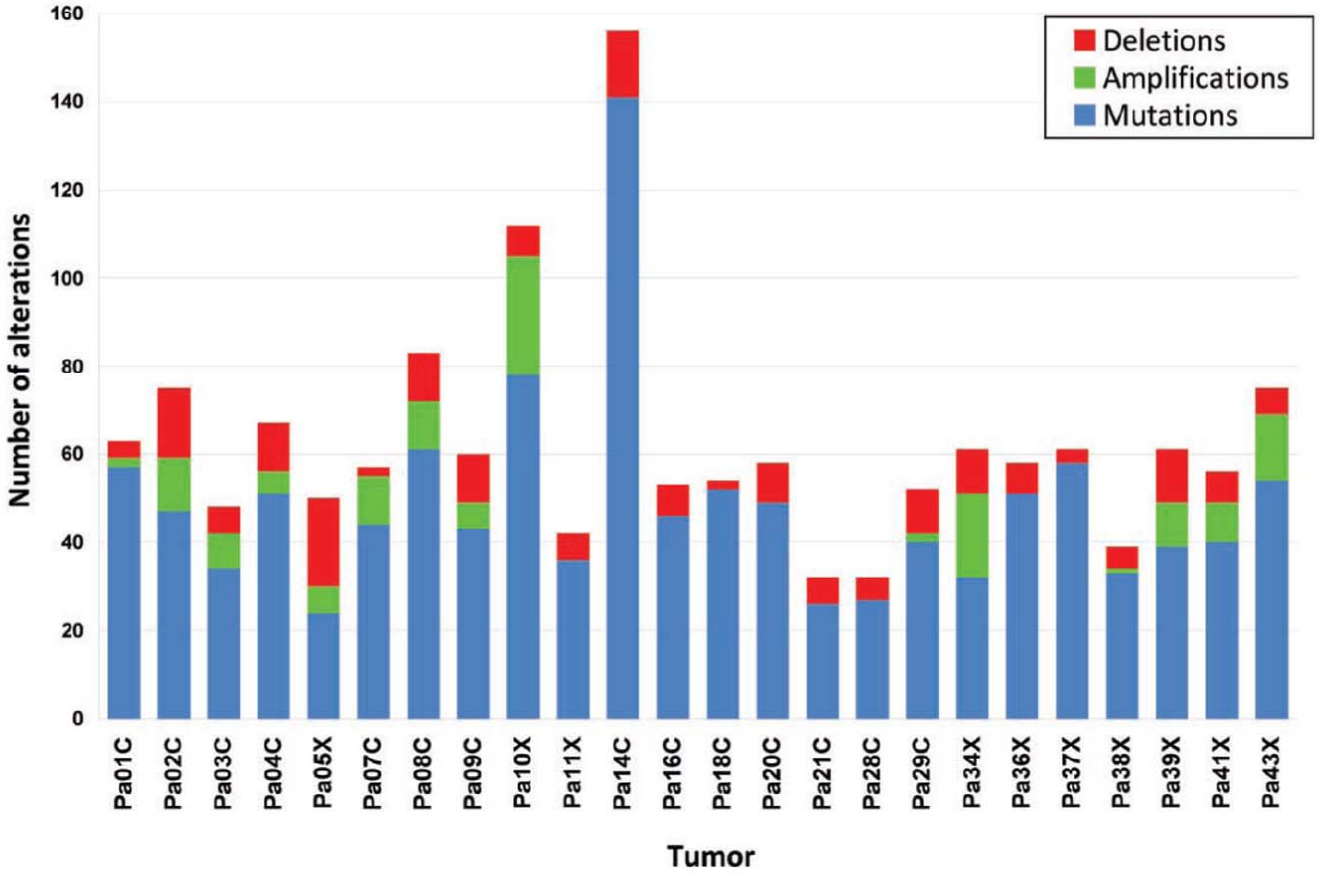
DRUGS INTERFERING WITH THE VEGF PATHWAY



Targeted Agents in Pancreatic cancer

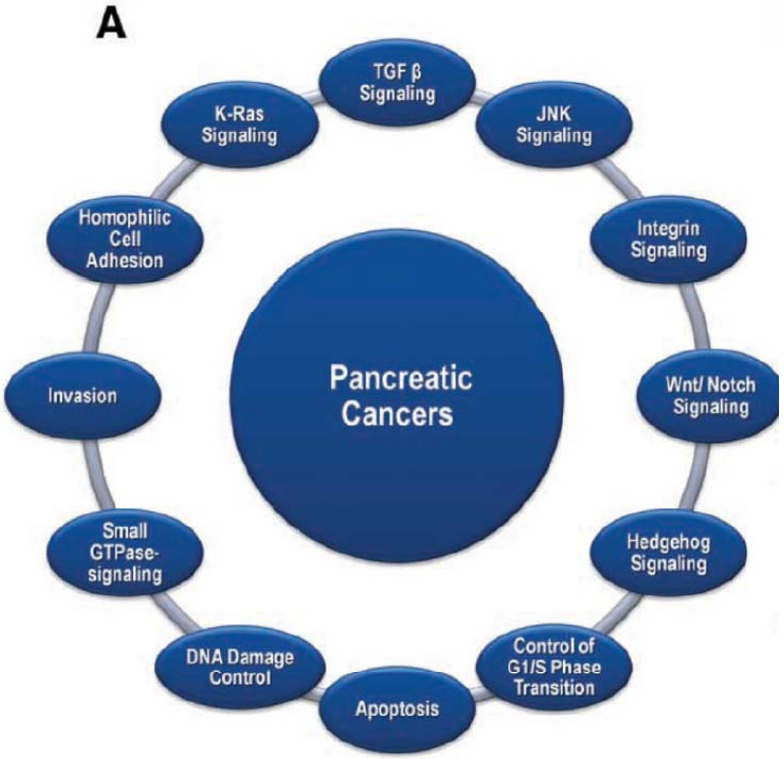
• Tipifarnib	Failed
• Marimastat	Failed
• Tanomastat (BAY 12-9566)	Failed
• Cetuximab	Failed
• Sorafenib	Failed
• Axitinib	Failed
• Lapatinib	Failed
• Tarceva	Approved (??!!)
• Bevacizumab	Failed

Molecular alterations in PCa



Jones Science 2008

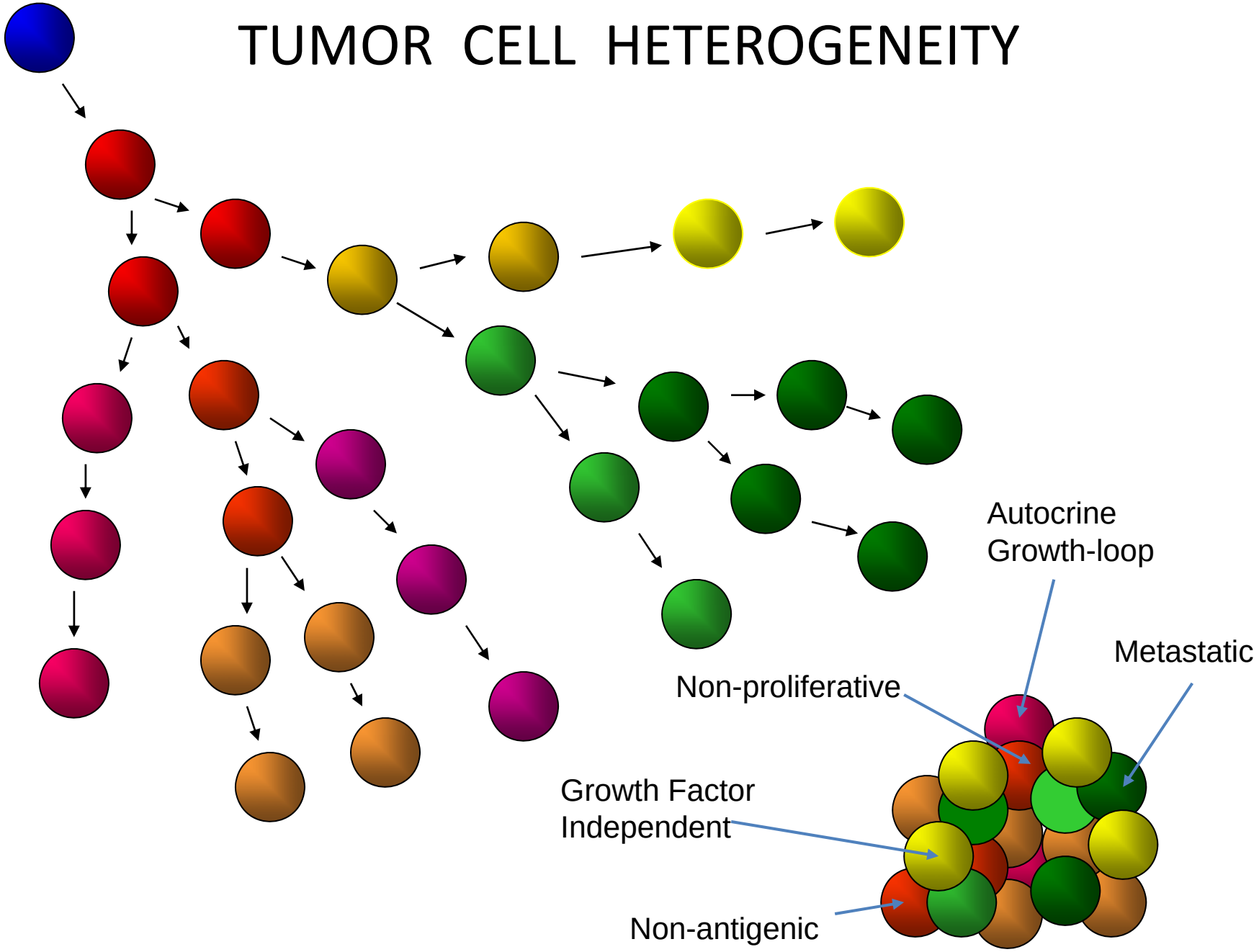
Molecular alterations in PCa



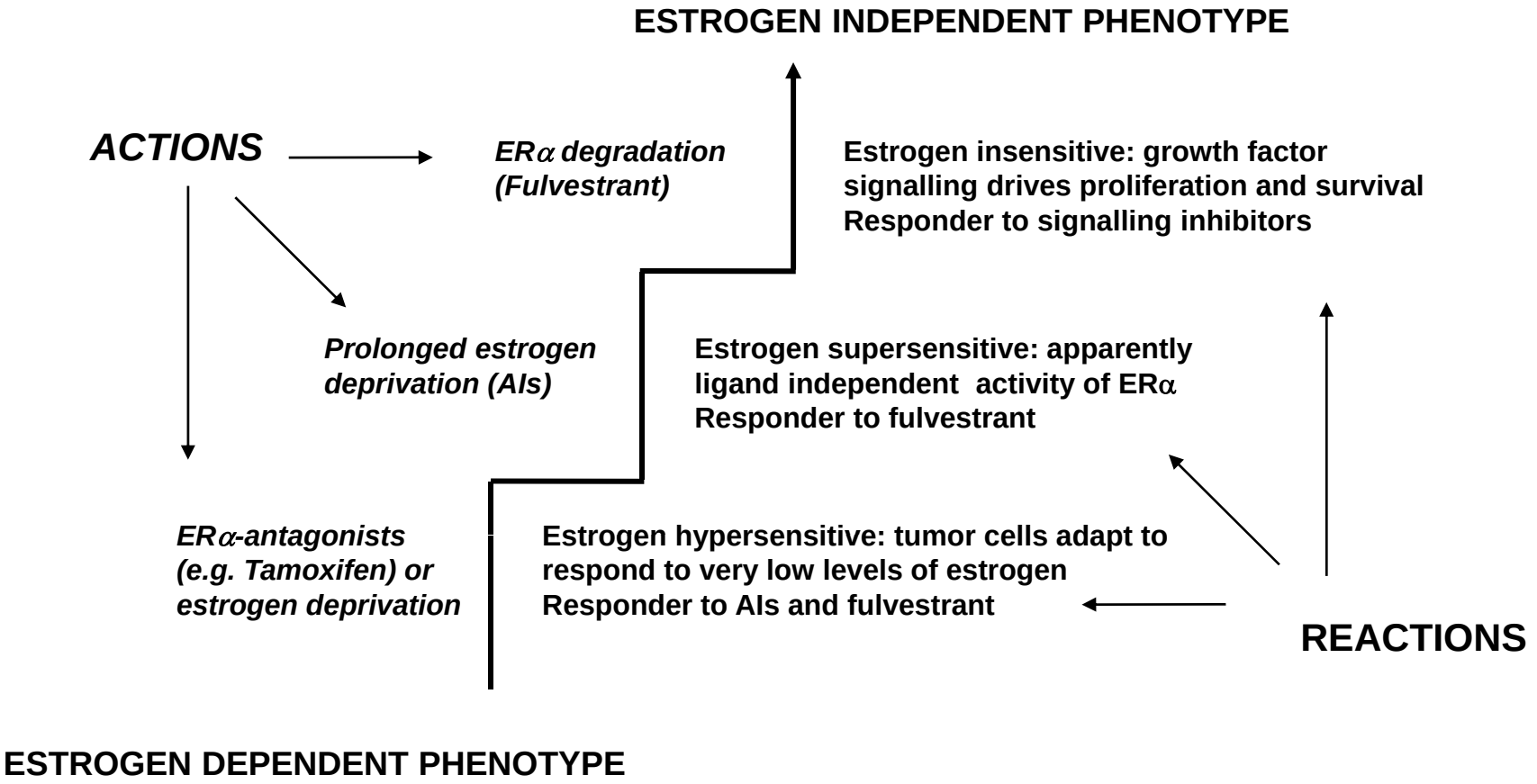
Regulatory process or pathway	Number of genetically altered genes detected	Fraction of tumors with genetic alteration of at least one of the genes	Representative altered genes
Apoptosis	9	100%	*CASP10, VCP, CAD, HIP1*
DNA damage control	9	83%	*ERCC4, ERCC6, EP300, RANBP2, TP53*
Regulation of G_1/S phase transition	19	100%	*CDKN2A, FBXW7, CHD1, APC2*
Hedgehog signaling	19	100%	*TBX5, SOX3, LRP2, GLI1, GLI3, BOC, BMPR2, CREBBP*
Homophilic cell adhesion	30	79%	*CDH1, CDH10, CDH2, CDH7, FAT, PCDH15, PCDH17, PCDH18, PCDH9, PCDHB16, PCDHB2, PCDHGA1, PCDHGA11, PCDHGC4*
Integrin signaling	24	67%	*ITGA4, ITGA9, ITGA11, LAMA1, LAMA4, LAMA5, FN1, ILK*
c-Jun N-terminal kinase signaling	9	96%	*MAP4K3, TNF, ATF2, NFATC3*
KRAS signaling	5	100%	*KRAS, MAP2K4, RASGRP3*
Regulation of invasion	46	92%	*ADAM11, ADAM12, ADAM19, ADAM5220, ADAMTS15, DPP6, MEP1A, PCSK6, APG4A, PRSS23*
Small GTPase–dependent signaling (other than KRAS)	33	79%	*AGHGEF7, ARHGEF9, CDC42BPA, DEPDC2, PLCB3, PLCB4, RP1, PLXNB1, PRKCG*
TGF-β signaling	37	100%	*TGFBR2, BMPR2, SMAD4, SMAD3*
Wnt/Notch signaling	29	100%	*MYC, PPP2R3A, WNT9A, MAP2, TSC2, GATA6, TCF4*

Jones Science 2008

TUMOR CELL HETEROGENEITY

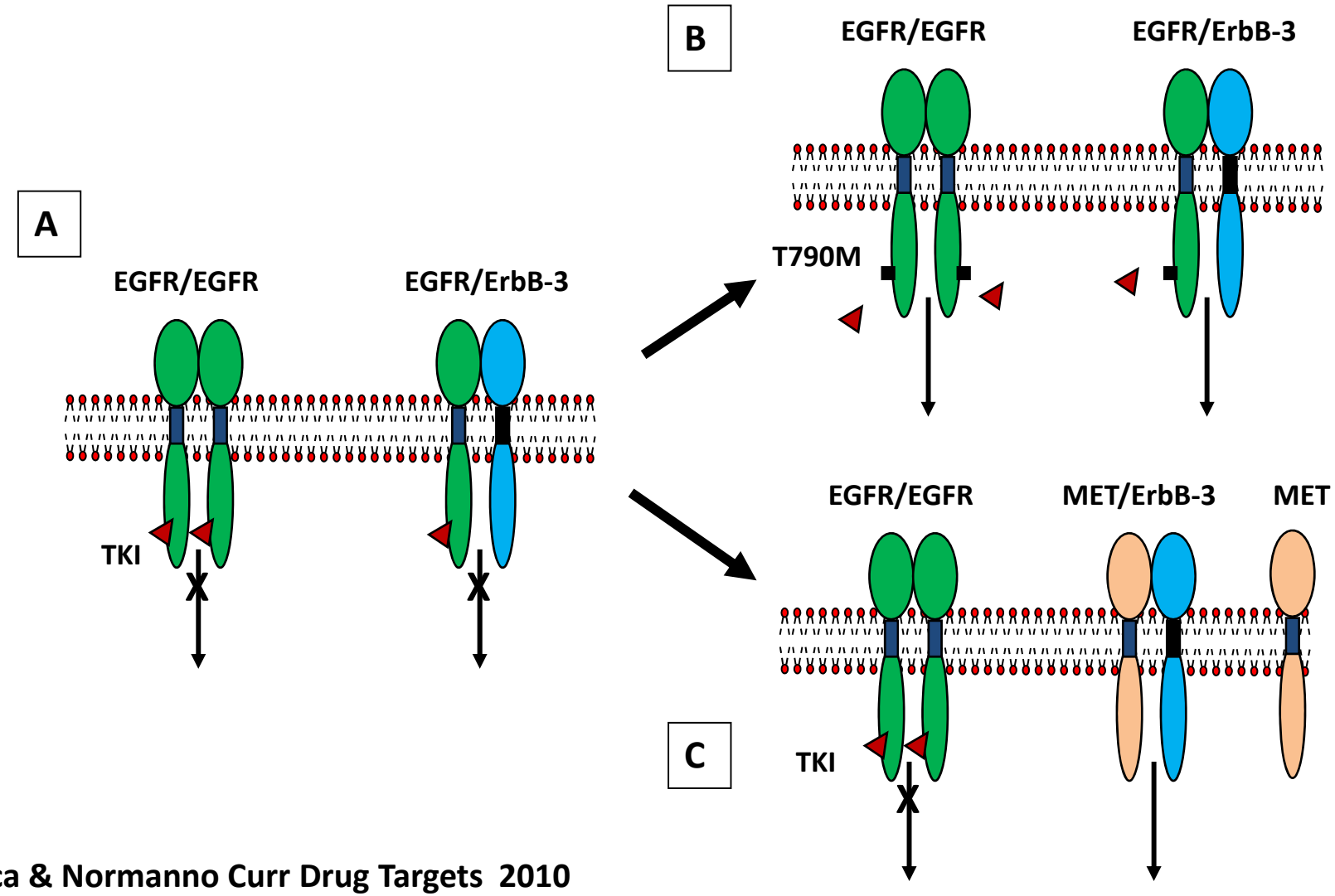


The action/reaction hypothesis

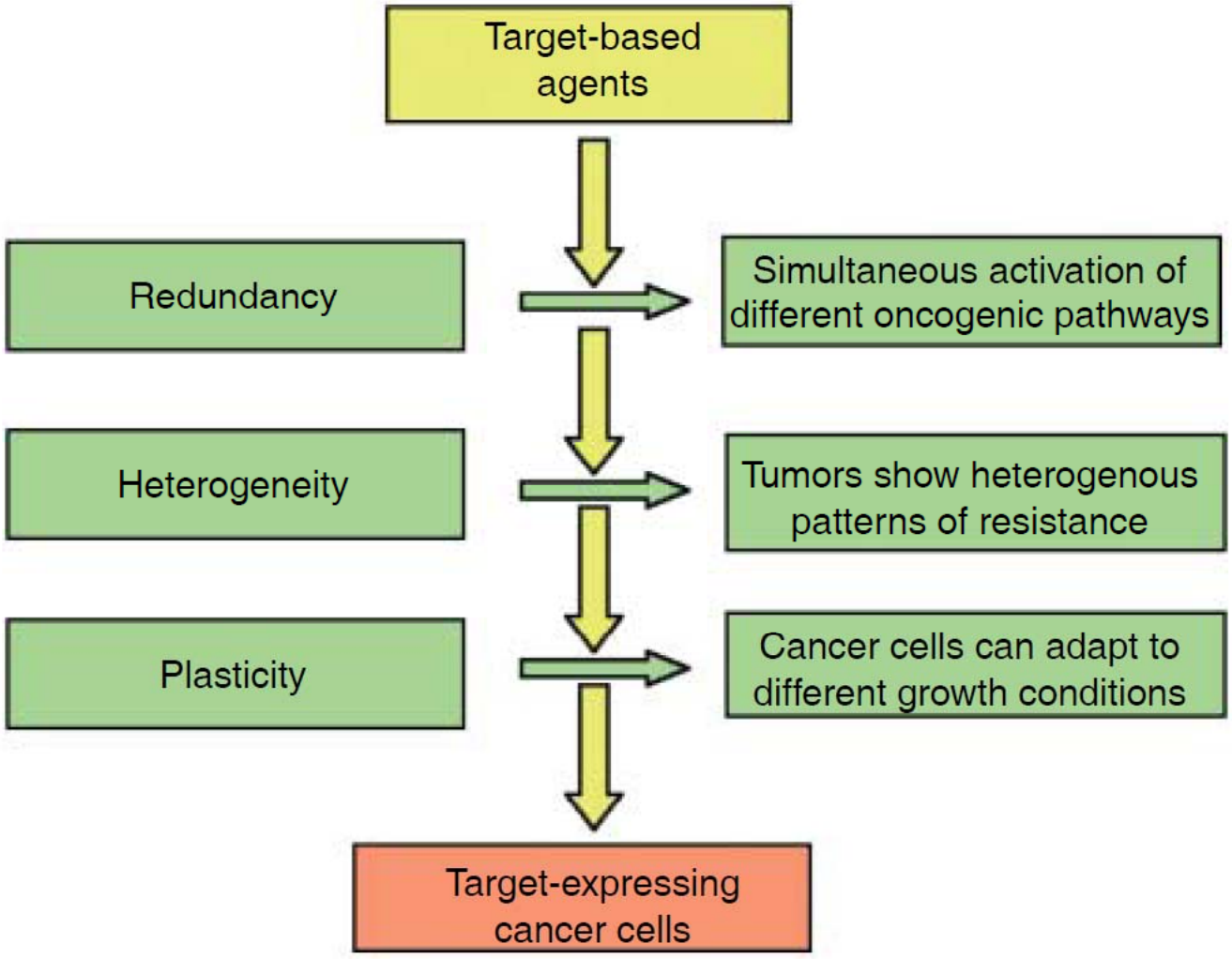


Normanno Endocr Relat Cancer 2005

Mechanisms of resistance to EGFR TKIs in NSCLC



De Luca & Normanno Curr Drug Targets 2010



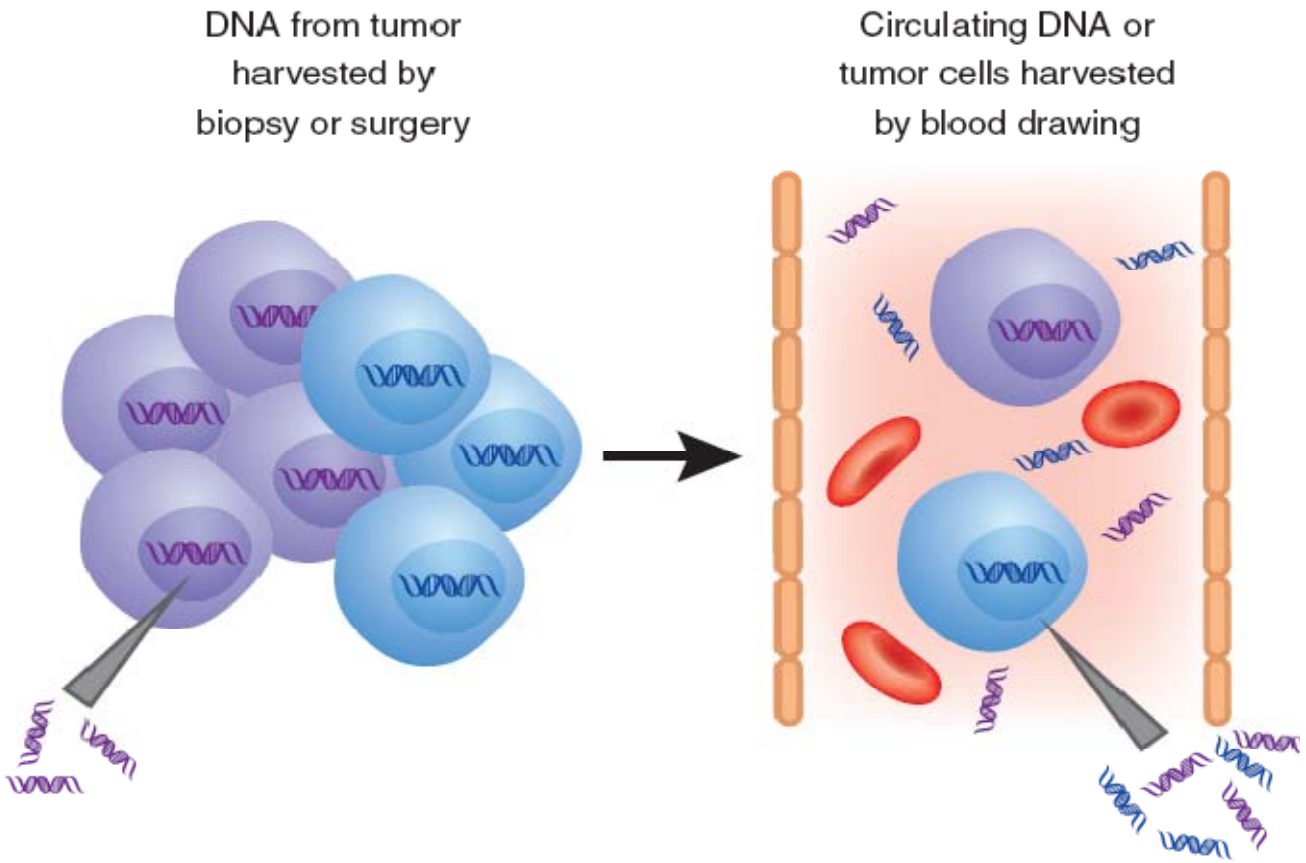
Normanno Endocr Relat Cancer 2009

Next Generation Sequencing Platforms

- Roche/454 FLX: 2004
- Illumina Solexa Genome Analyzer: 2006
- Applied Biosystems SOLiD™ System: 2007
- Helicos Heliscope™ : recently available
- Pacific Biosciencies SMRT: launching 2010



Different sources of tumor DNA



Fleischhacker & Schmidt Nat Med 2008

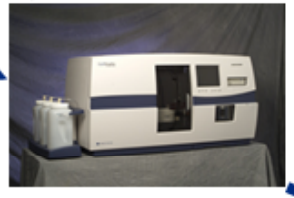
CellSearch System



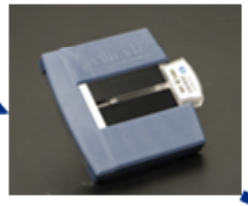
Sample Collection



Reagents:
CTC capture
& staining



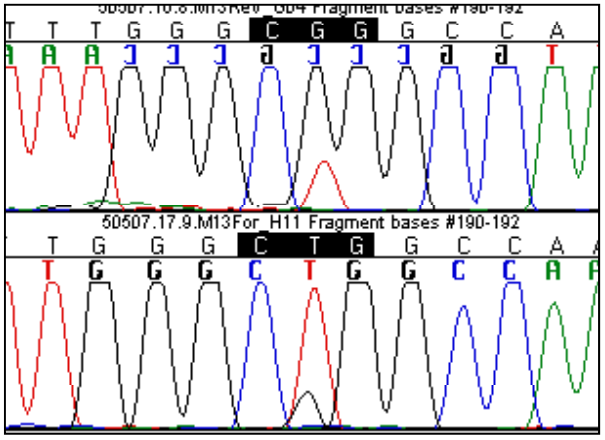
Sample
Processing

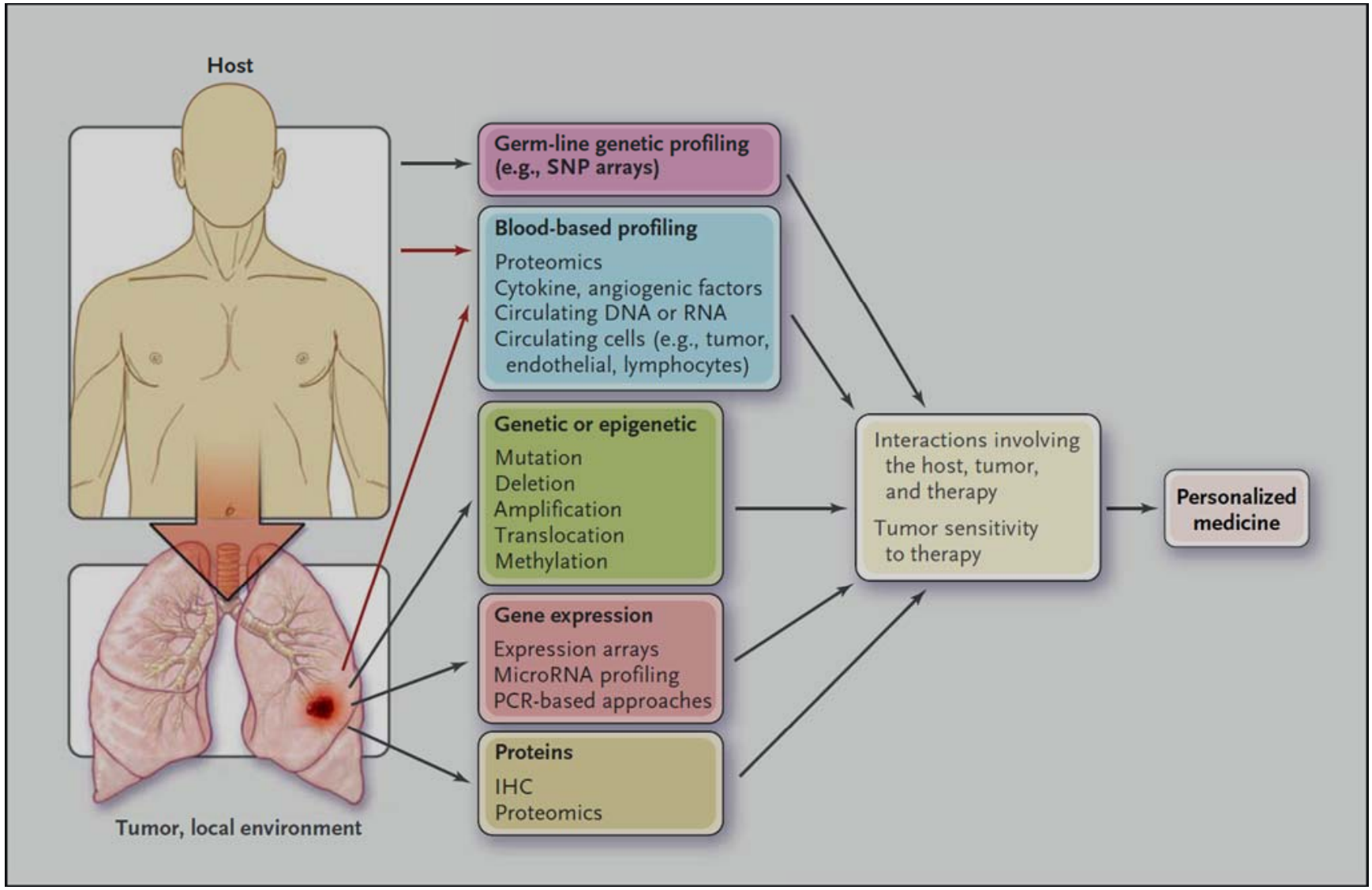


Sample
Presentation



Sample
Analysis





Herbst NEJM 2008