

SIGNALLING PATHWAYS SYMPOSIUM

Targeting the PI3K/AKT/mTOR pathway in cancer

Sitges, Barcelona **28 February - 1 March 2014**

INTRODUCTION TO THE PI3K PATHWAY

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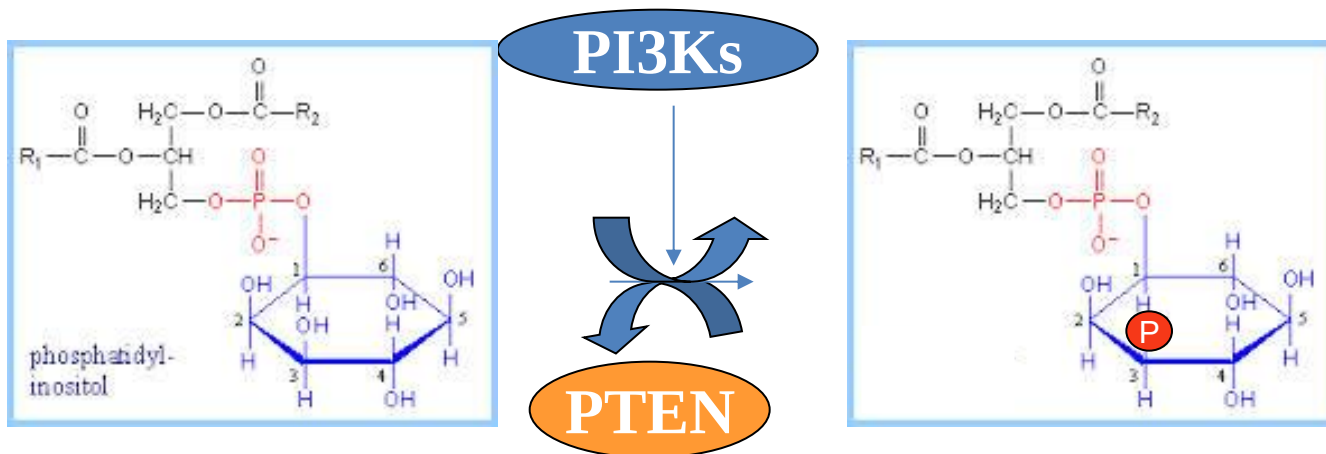
MILAN, ITALY

February 28, 2014

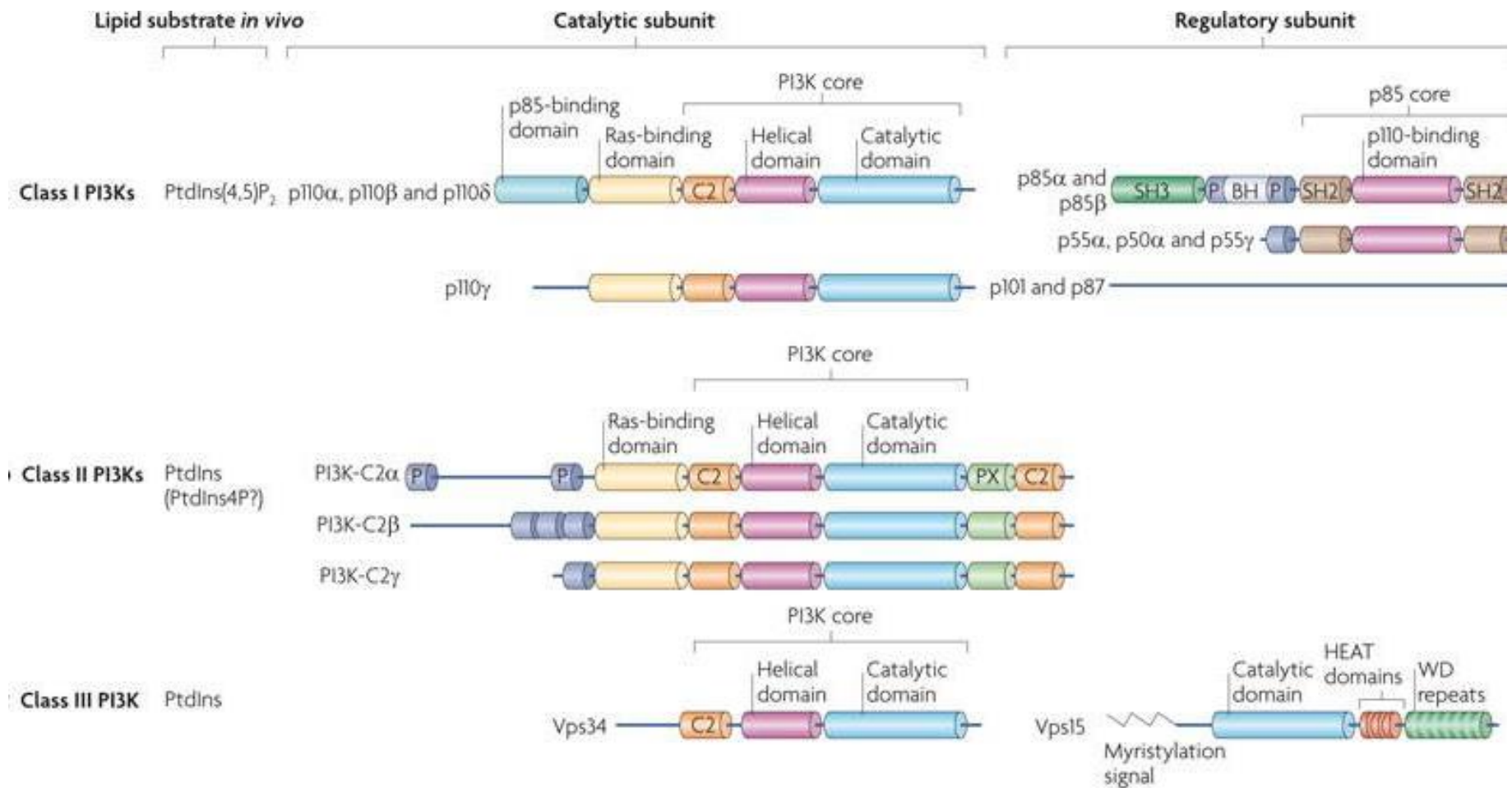
DISCLOSURE SLIDE

No conflicts of interest to declare

The PI3K/Akt pathway



The PI3K/Akt pathway



Nature Reviews | Molecular Cell Biolog

PI3K COMPLEXITY

CATALYTIC SUBUNIT

REGULATORY SUBUNIT

CLASS I

p110 α , PIK3CA
p110 β , PIK3CB
p110 δ , PIK3CD

p110 γ , PIK3CG

p85 α , PIK3R1
p85 β , PIK3R2

p87, PIK3R6
p101, PIK3R5

CLASS II

PI3K-C2 α , PIK3C2A
PI3K-C2 β , PIK3C2B
PI3K-C2 γ , PIK3C2G

CLASS III

VPS34, PIK3C3

VPS15

PI3K COMPLEXITY

CATALYTIC SUBUNIT

REGULATORY SUBUNIT

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CLASS II

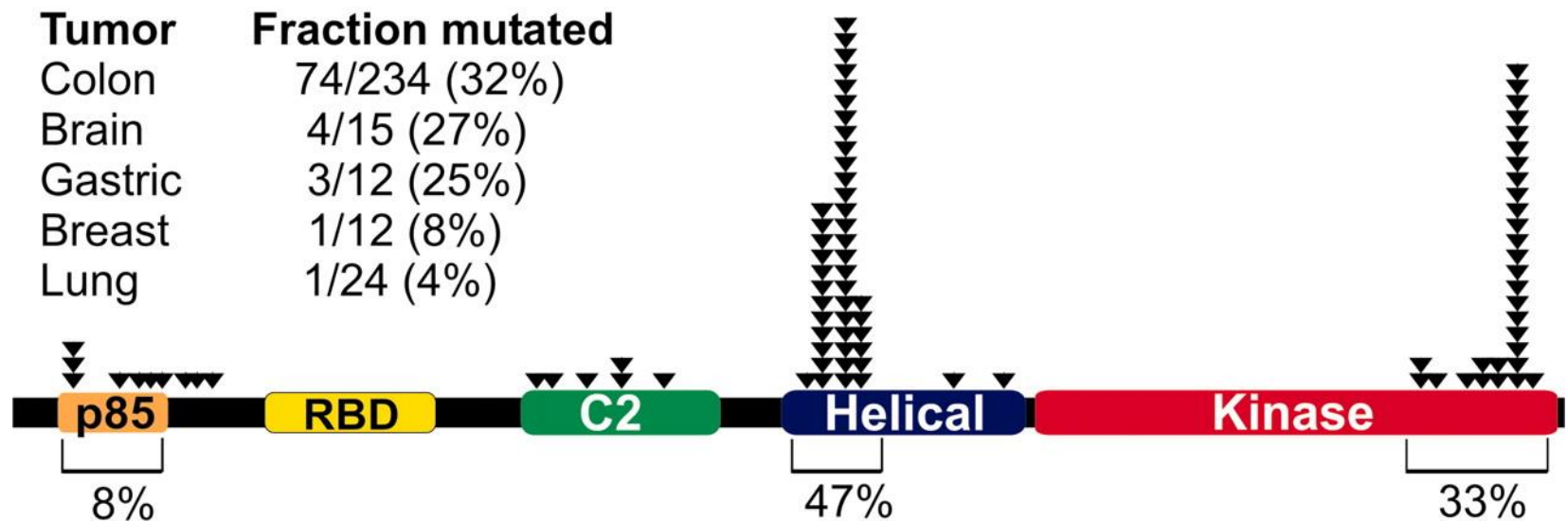
PI3K-C2 α , PIK3C2A
PI3K-C2 β , PIK3C2B
PI3K-C2 γ , PIK3C2G

CLASS III

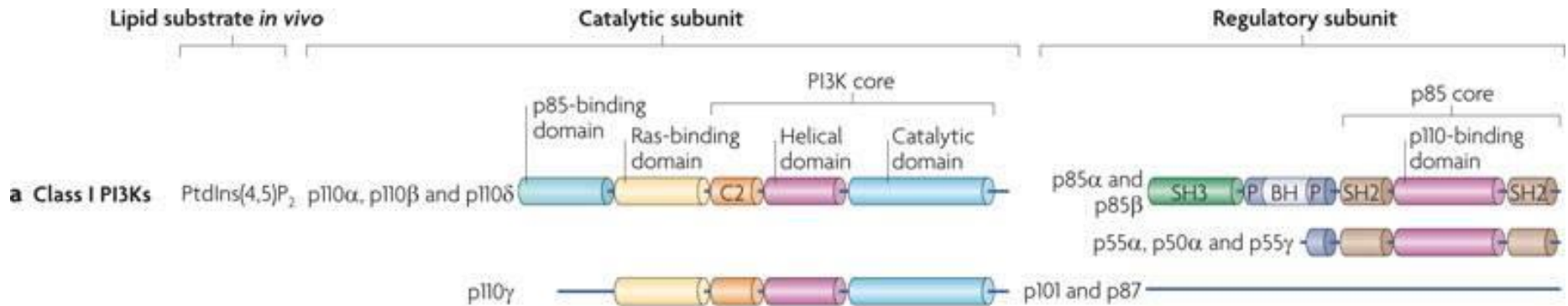
VPS34, PIK3C3

VPS15

The PI3K/Akt pathway



The PI3K/Akt pathway



PI3Ks AS MONOMERS ARE RAPIDLY DEGRADED

**BINDING OF THE CATALYTIC SUBUNIT TO
THE REGULATORY SUBUNIT STABILIZES PI3Ks**

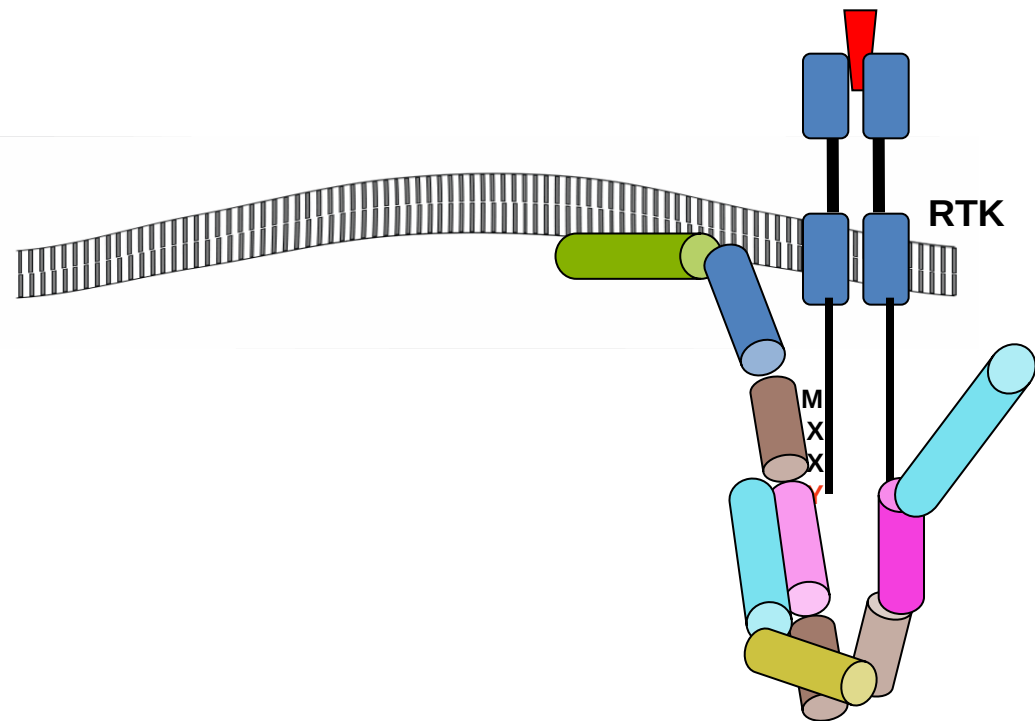
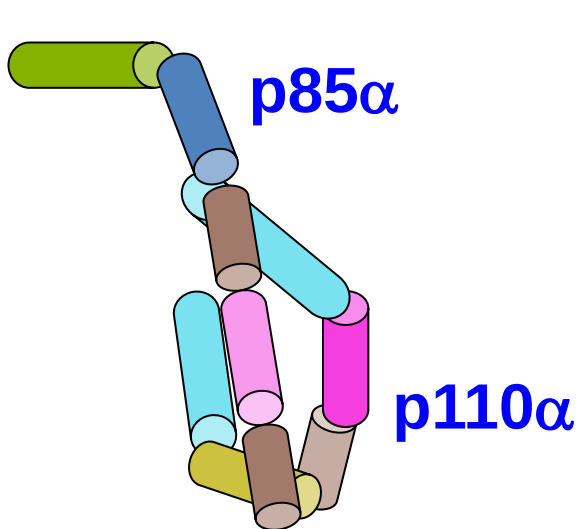
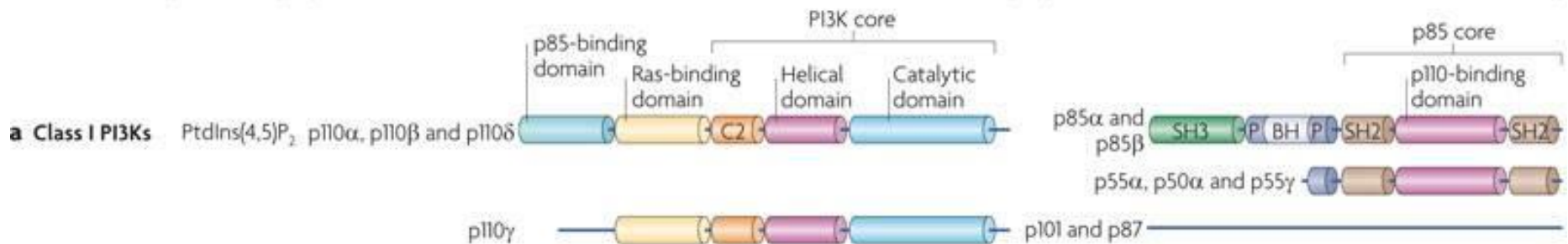
AT THE SAME TIME THE p85 BINDING INACTIVATES PI3Ks

The PI3K/Akt pathway

Lipid substrate *in vivo*

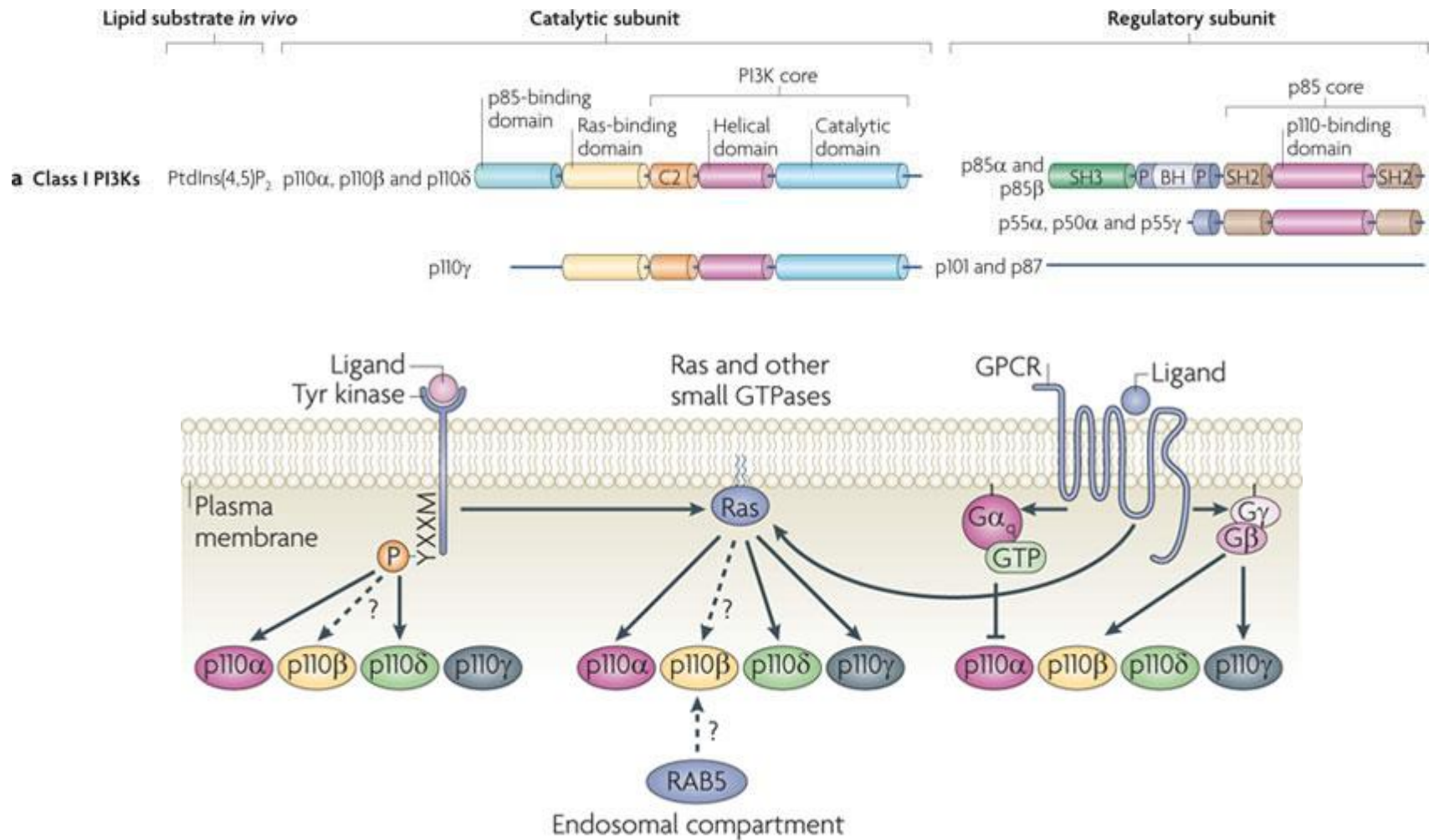
Catalytic subunit

Regulatory subunit



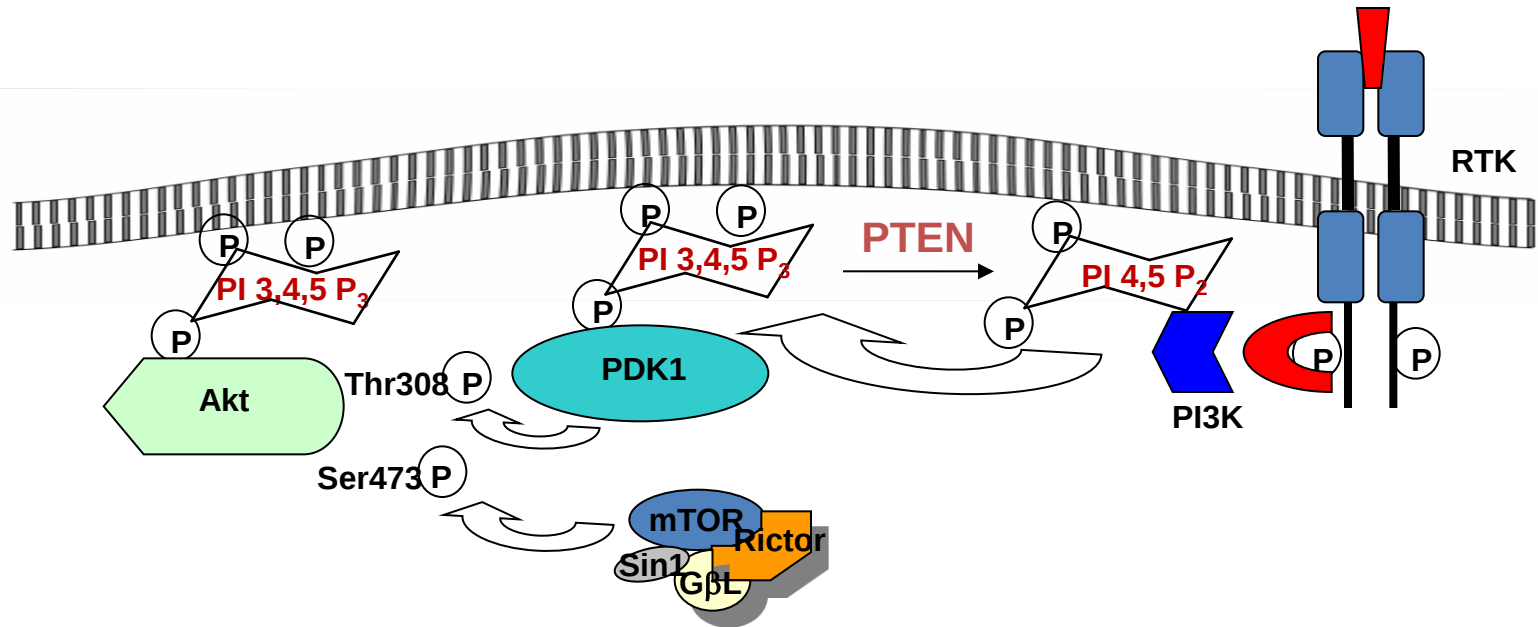
The PI3K/Akt pathway

SIGNALS ACTIVATING THE PATHWAY

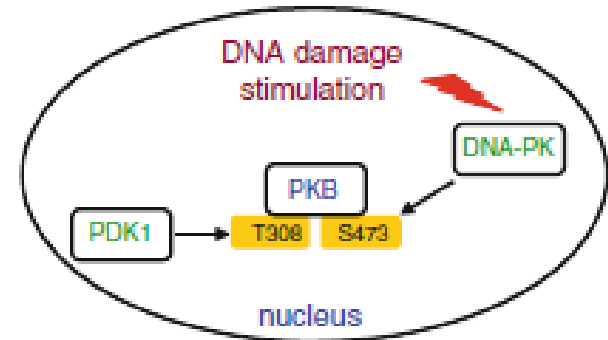


The PI3K/Akt pathway

SIGNALS ACTIVATING THE PATHWAY



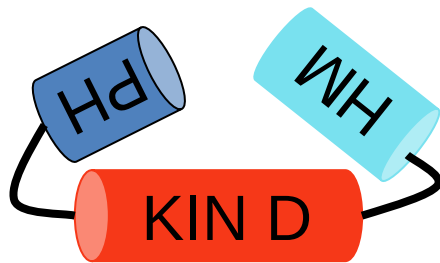
Proliferation
Survival
Angiogenesis
Migration



The PI3K/Akt pathway

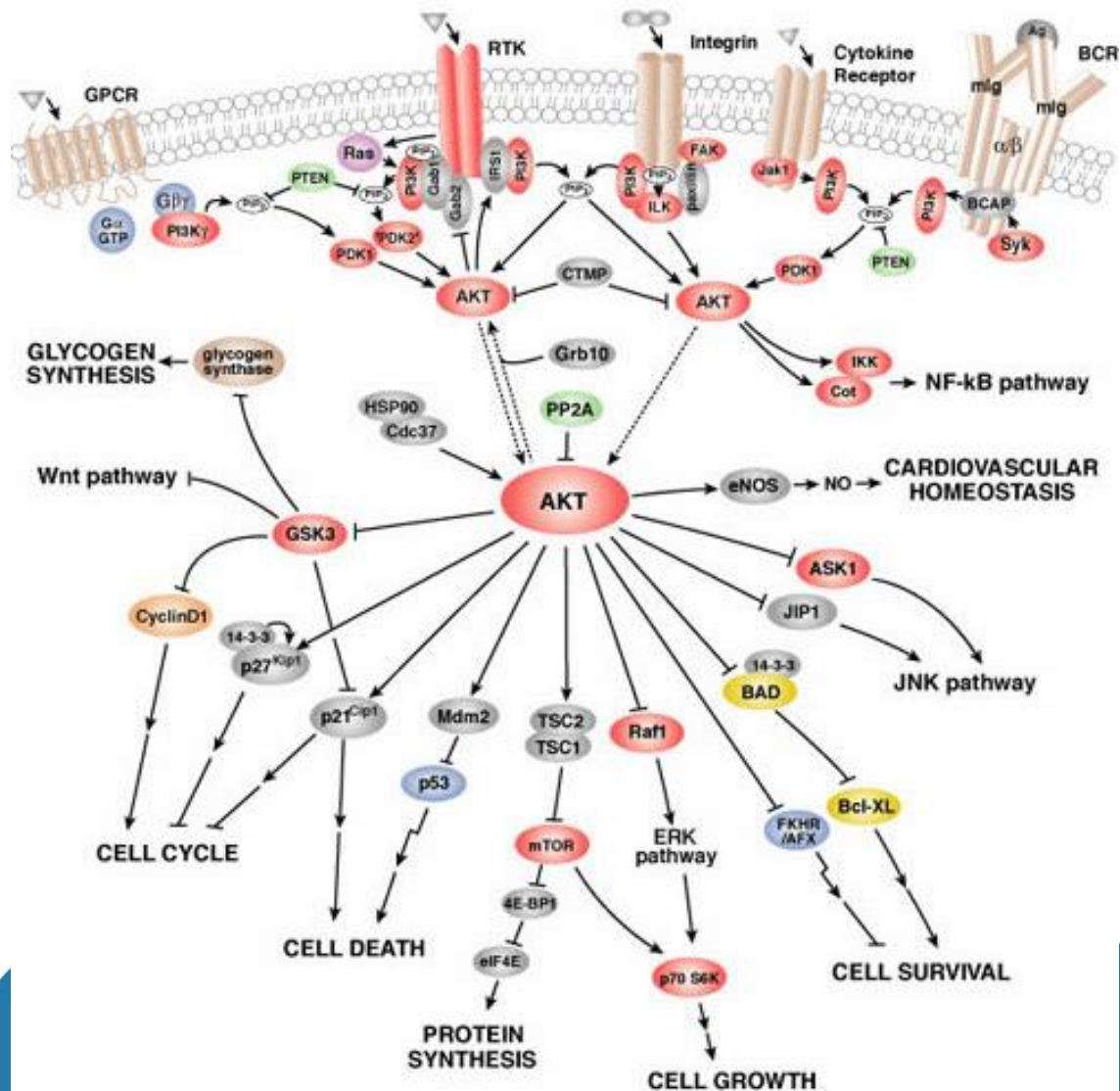
SIGNALS DOWNSTREAM THE PATHWAY

				Chr	EXPR	
AKT1	PH	KIN D	HM 480	14q32	UBIQUITOUS	RXRXX[S/T]B ↓ MORE THAN 50 SUBSTRATES
		T308	S473			
AKT2	PH	KIN D	HM 481	19q13	INSULIN SENS	
		T309	S474			
AKT3	PH	KIN D	HM 479	1q44	BRAIN TESTIS	
		T305	S472			



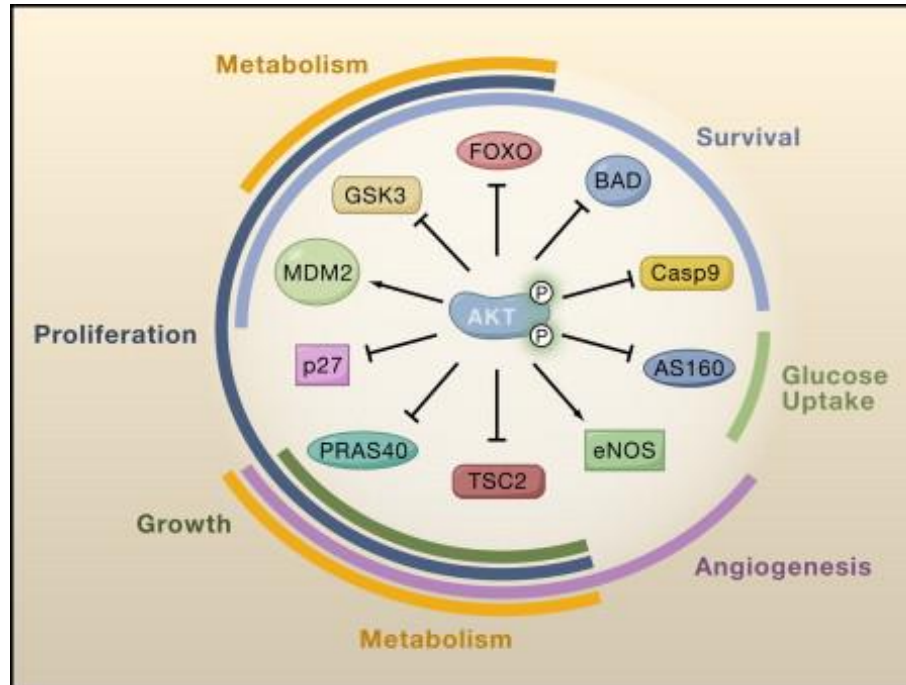
The PI3K/Akt pathway

SIGNALS DOWNSTREAM THE PATHWAY



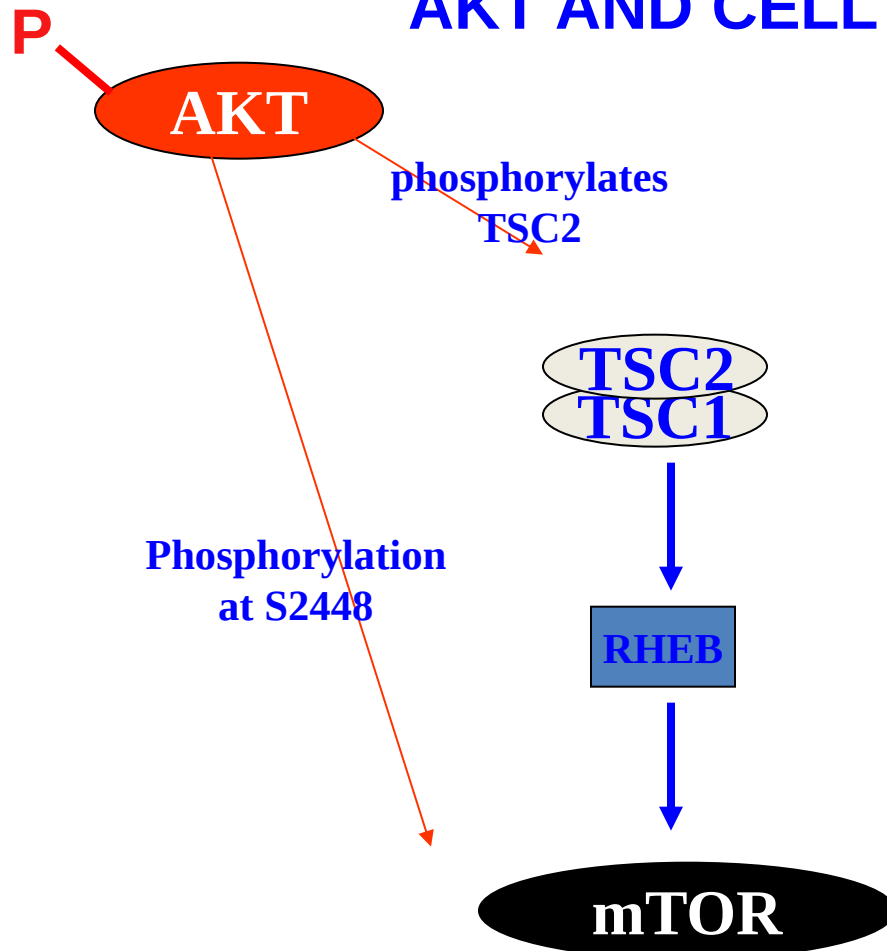
The PI3K/Akt pathway

SIGNALS DOWNSTREAM THE PATHWAY



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

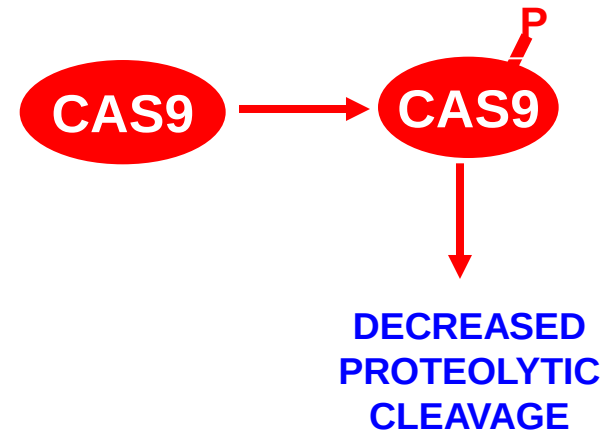
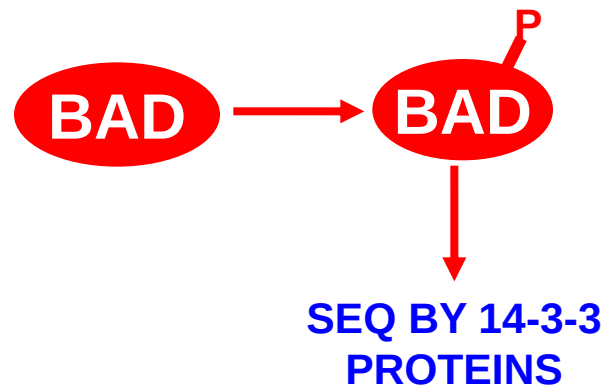
AKT AND CELL GROWTH



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

AKT AND SURVIVAL

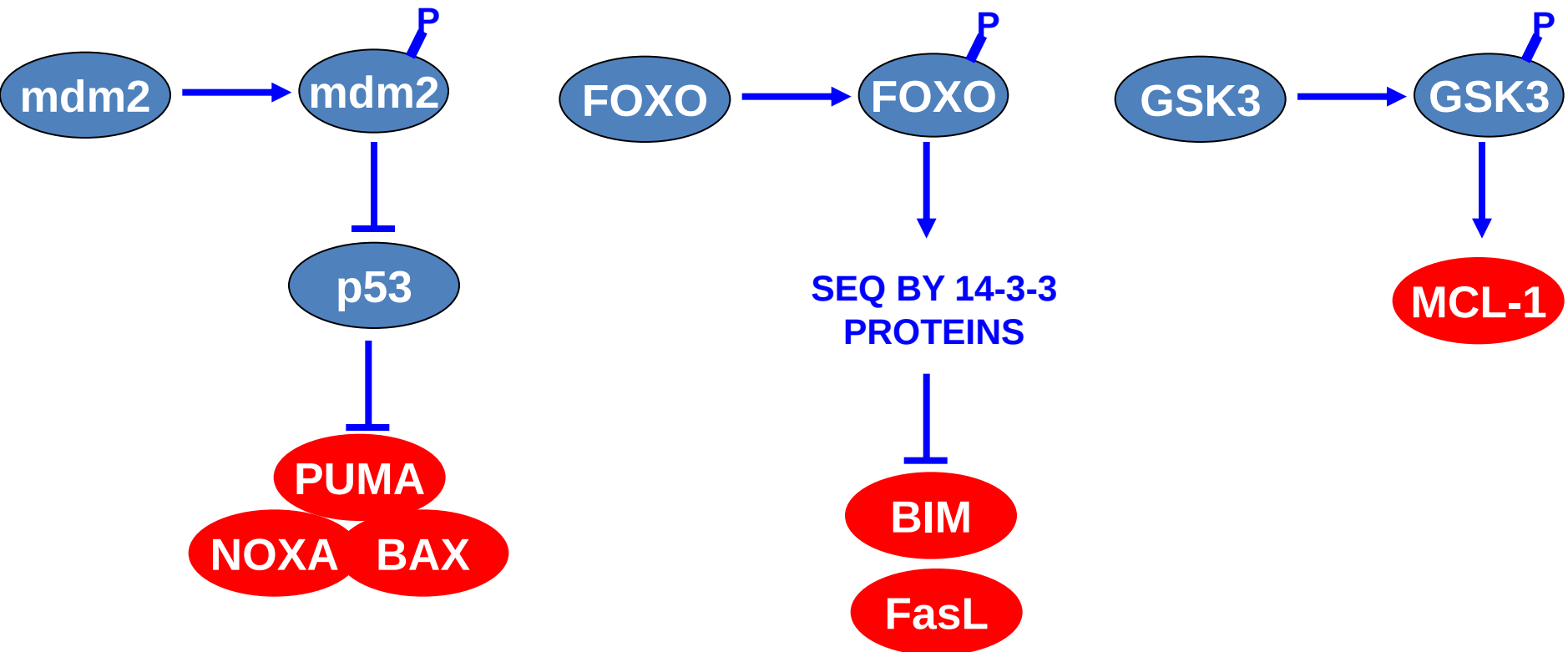
AKT $\longrightarrow$ **AKT-p**



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

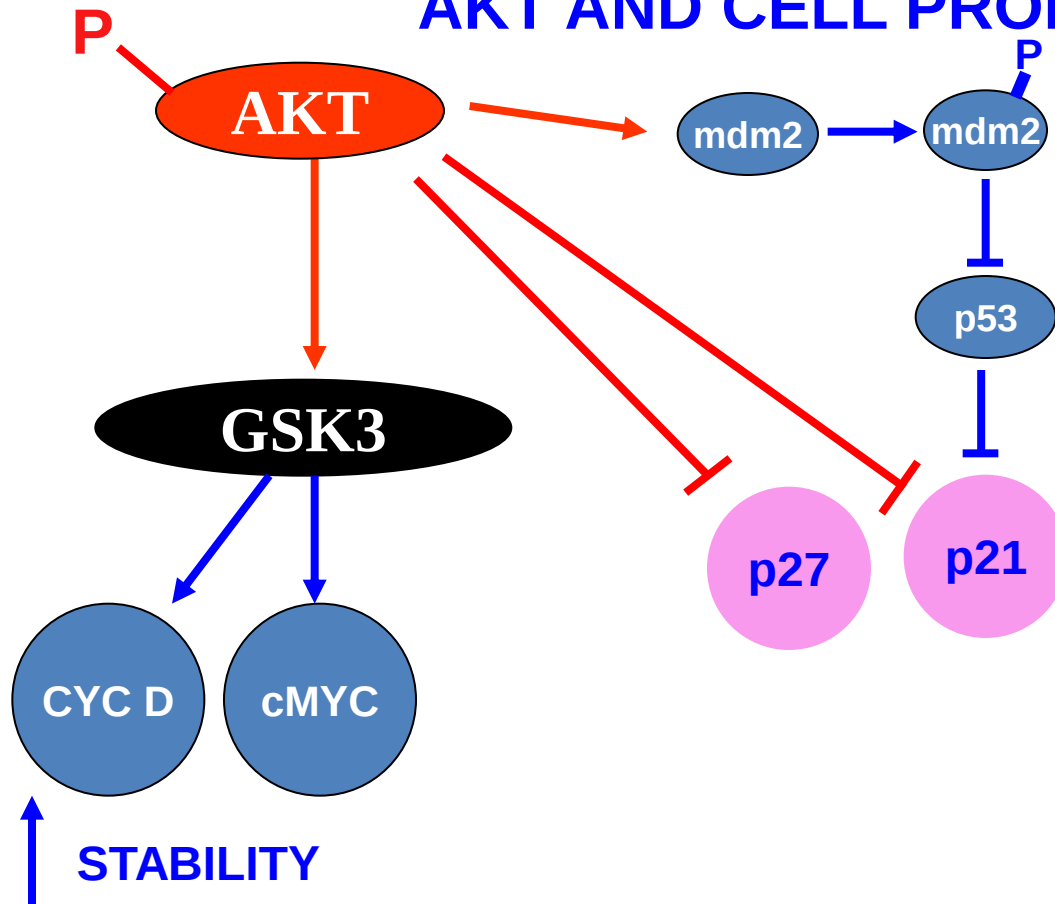
AKT AND SURVIVAL

AKT → **AKT-p**



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

AKT AND CELL PROLIFERATION



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

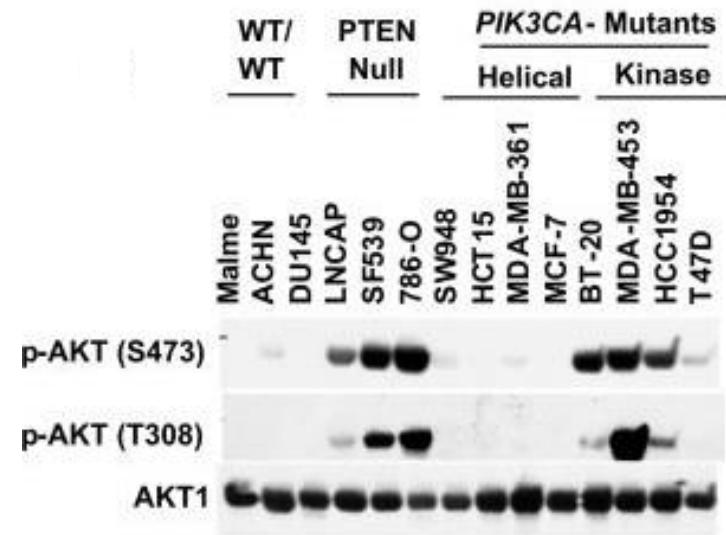
Akt-independent PI3K signaling

Evidence that an alternative PI3K-dependent, akt independent pathway contributes to malignant transformation.

While almost invariably PTEN null cancer cells present increased phospho akt levels, some cancer cell lines with activating mutations in PIK3CA gene have low levels of activated akt.

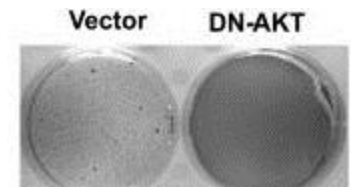
The PI3K/Akt pathway SIGNALS DOWNSTREAM THE PATHWAY

Akt-independent PI3K signaling

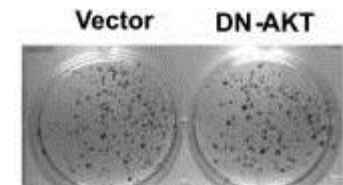


GSK3 α/β
FOXO

PTEN null



PIK3CA Hel

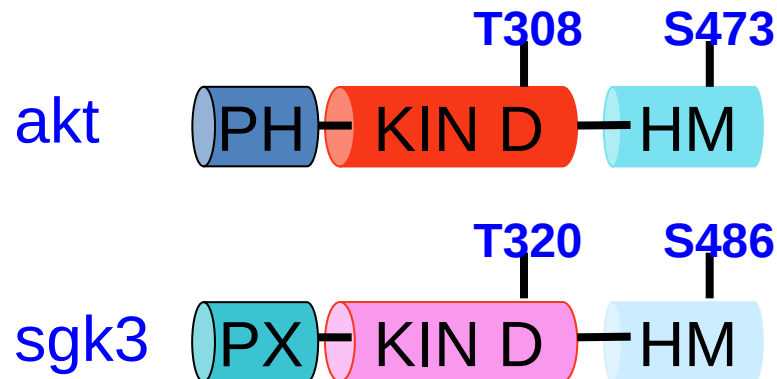


The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

Akt-independent PI3K signaling

SGK protein isoforms are candidates downstream effectors for PI3K signaling independent of akt.

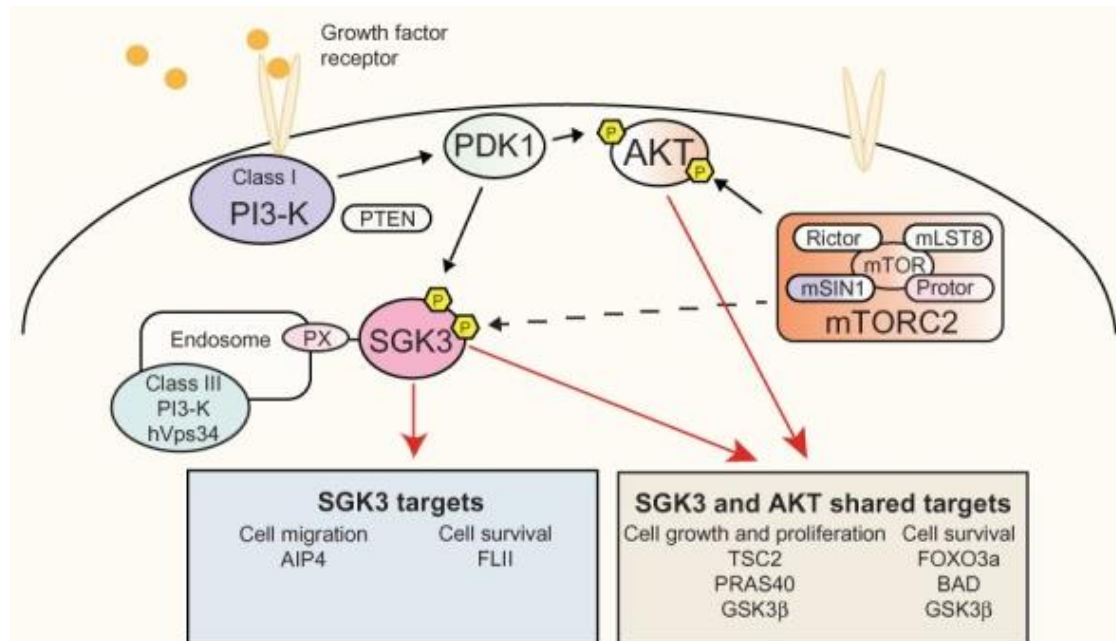
SGK3, in particular, shares homology with akt both at molecular level:



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

Akt-independent PI3K signaling

And at downstream activation level:



The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

THE SPECIFIC CASE OF p110 δ

- p110 δ and p110 γ are expressed primarily in cells of hematopoietic lineage, such as B and T cells, respectively.
- Mice KO for p110 δ exhibit a B-cell defect, decreased mature B cell numbers, and impaired antibody production. B cells from p110 δ ko mice also show less AKT phosphorylation.
- Isoform specific inhibitors?

GS-1101 (CAL-101)

CLASS I PI3K				CLASS II PI3K	CLASS III PI3K
p110 α	p110 β	p110 δ	p110 γ	C2 β	VPS34
820	595	2.5	89	>1000	970

The PI3K/Akt pathway
SIGNALS DOWNSTREAM THE PATHWAY

THE SPECIFIC CASE OF p110 δ

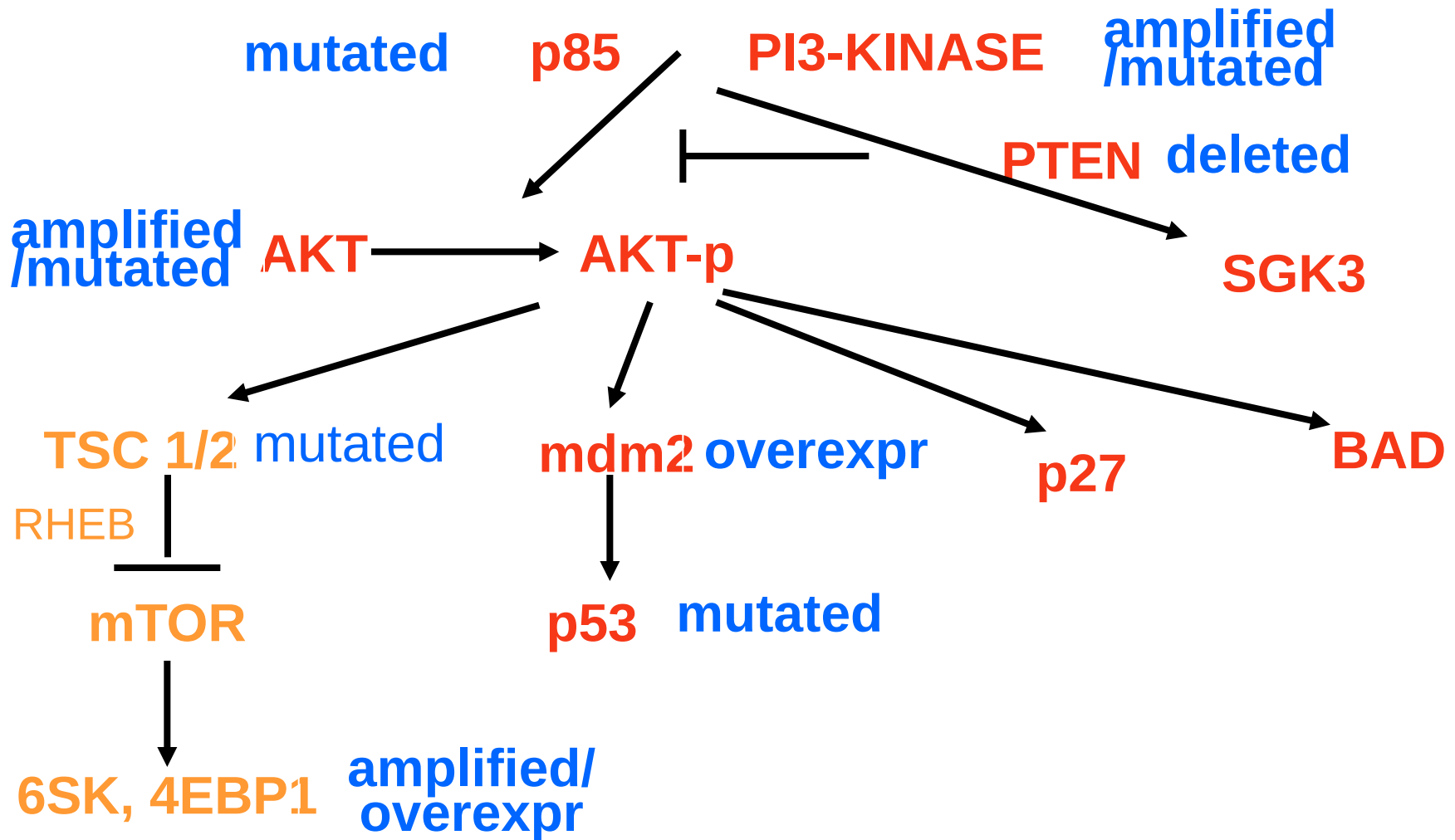
GS-1101 (CAL-101) idelalisib / BTK ibrutinib

Activity at preclinical level at low doses in CLL (11 out of 42 cell lines)

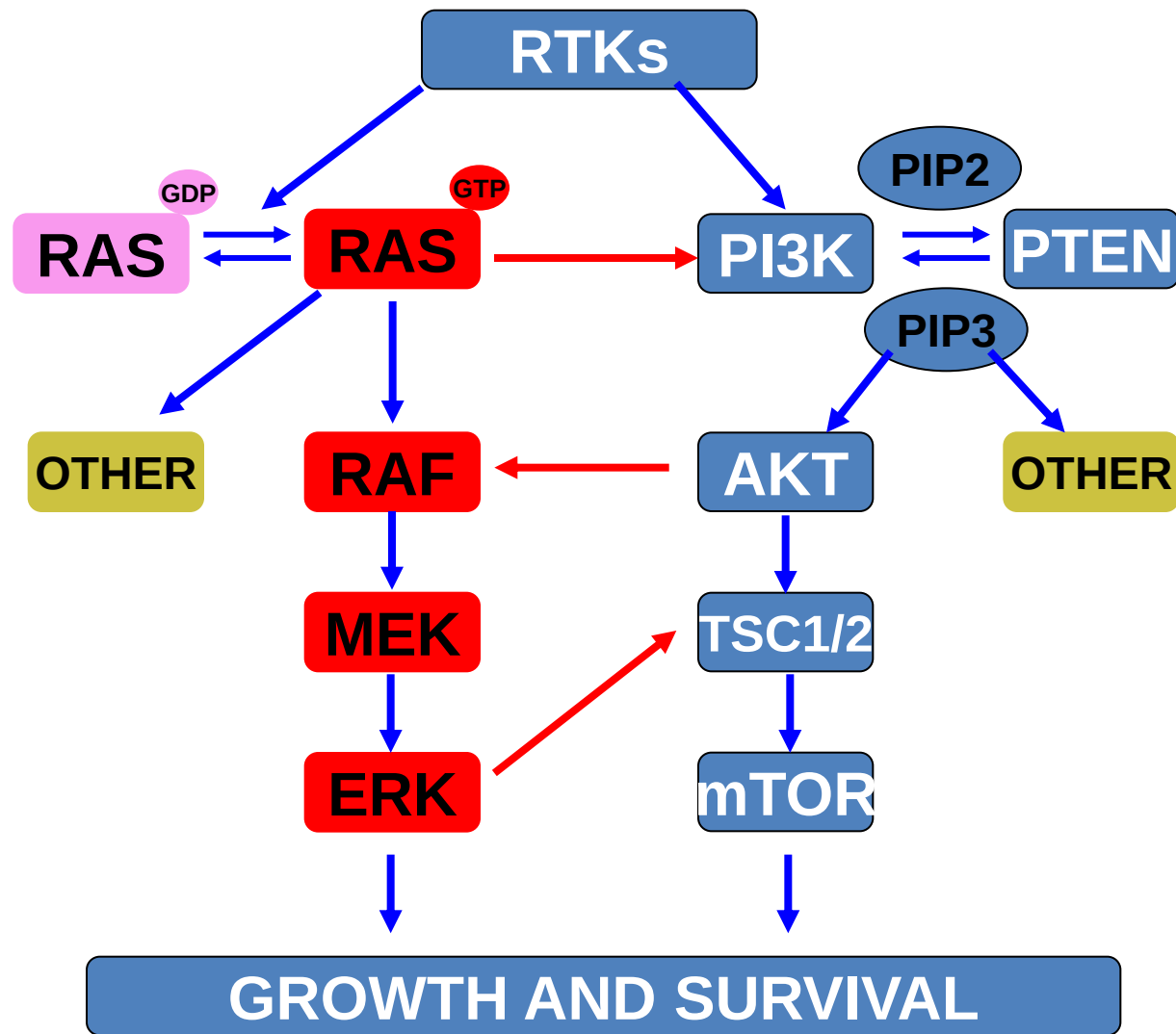
Induction of apoptosis - downregulation of p-akt - selectivity for CLL compared to normal B cells.

Unexpected (?) high clinical activity in CLL and other B-cell tumors

The PI3K/Akt pathway



The PI3K/Akt pathway



The PI3K/Akt pathway

- The PI3K pathway plays a central role in driving and sustaining cancer cell growth.
- Several activating mutations/deletions/amplifications converge to the activation of this pathway
- Several other pathways interact with the PI3K pathway posing for the design of rational combination strategies
- Advantages and disadvantages of pan versus selective inhibitors
- Selection of the best therapeutic strategy based on the molecular characteristics of the tumor?
- Availability of new inhibitors
- Extending the evidences to class II and III