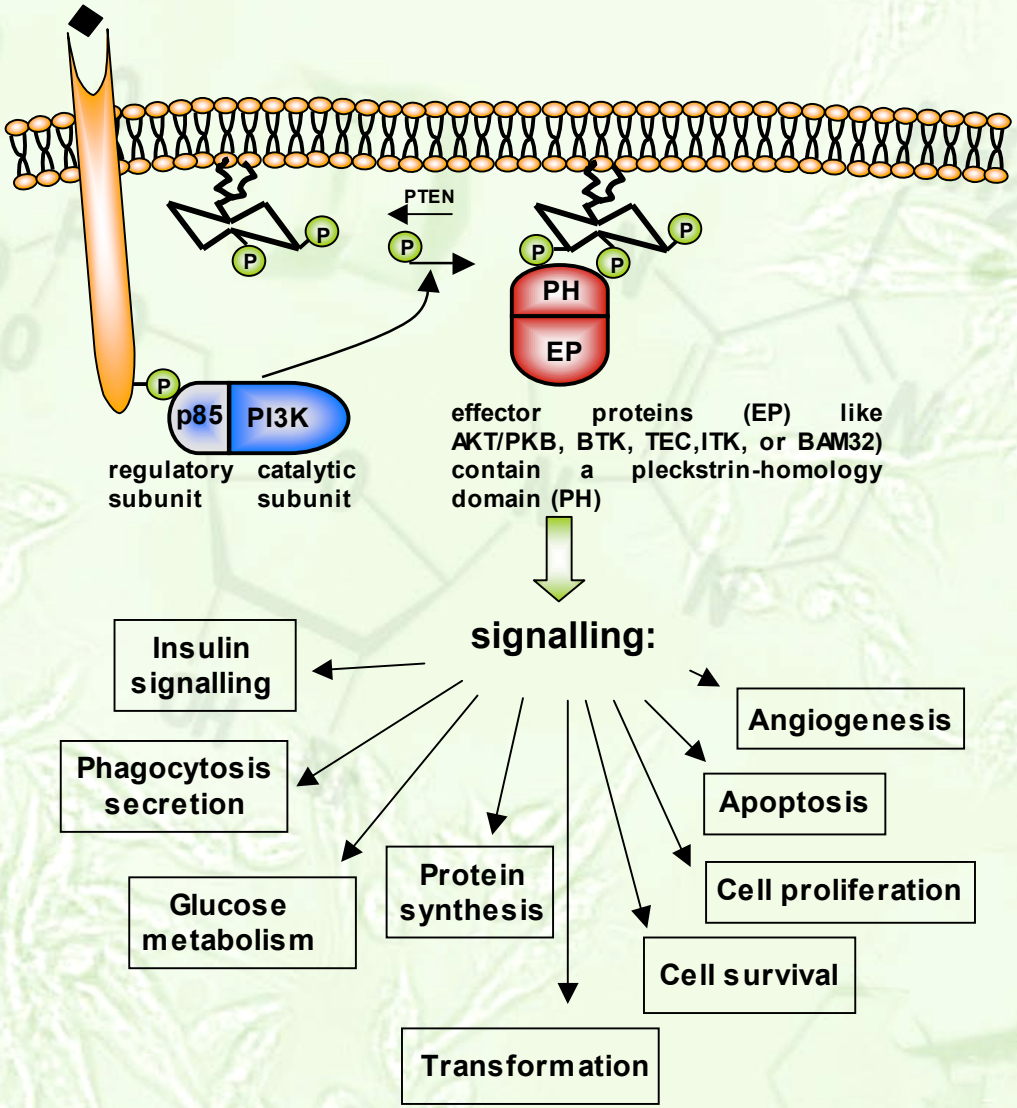
Phosphoinositide 3-kinases – a protein family of high medical relevance

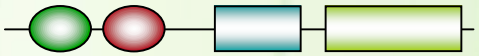
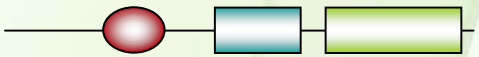
Phosphoinositide 3-kinases (PI3Ks):

- play a pivotal role in important cellular regulatory mechanisms such as cell growth, proliferation and survival/ apoptosis
- play key roles in cardiac growth (PI3Kα), cardiac contractability and the function of β-adrenergic receptors (PI3Kγ)
- are thus of outstanding medical interest
  - diabetes
  - various types of cancer
  - chronic inflammation
  - cardiovascular disease
- are targets for novel cancer therapeutics and/or immunosupressants



Phosphoinositide 3-kinases are divided into 3 classes

- Phosphoinositide 3-kinases are lipid kinases that catalyze the transfer of the γ- phosphate from ATP to the 3`-hydroxyl group of Phosphatidylinositol (PtdIns) and its derivatives (collectively called phosphoinositides)
- 8 isoforms of the PI3K family have been isolated from mammalian cells and grouped into *three classes* depending on their primary structure and substrate specificity

class	primary structure	subunits catalytic	subunits regulatory	regulated by	substrate *in vitro*	substrate *in vivo*
I A		p110α,β,δ	p85α,β p55γ	tyrosine kinases, Ras	PI PI4P	PI4,5P_2
I B		p110γ	p101	heterotrimeric G-proteins	PI4,5,P_2	
II		PI3K-C2α,β,γ	not known	clathrin, chemokines, integrins	PI PI4P	not known
III		Vps34p-Analoge	p150	constitutively active	PI	PI

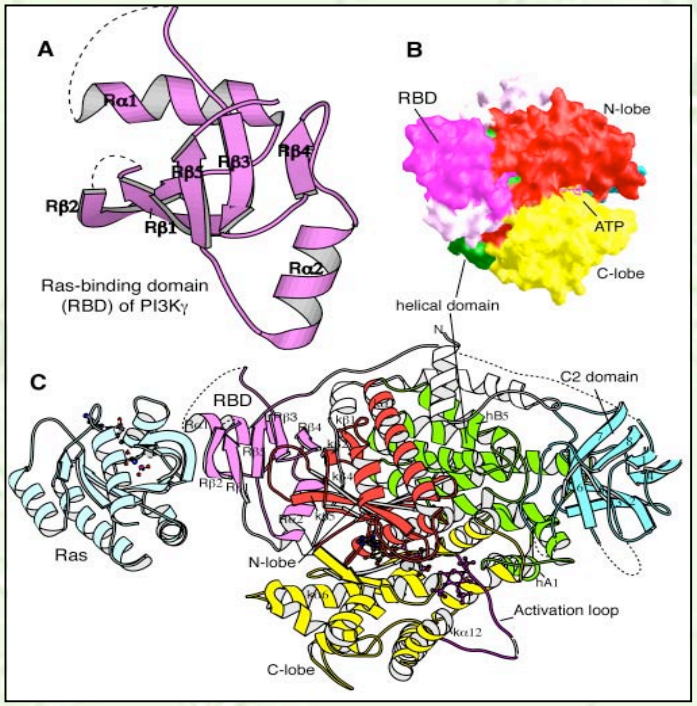
Adaptor-binding site · Ras-binding domain · PI3K accessory domain (PIK) · catalytic domain · C2-domain

Phosphoinositide 3-kinases now available from Jena Bioscience

- produced in insect cells
- native proteins, affinity-tagged variants and important mutants
- purity > 95 %
- quality monitored by SDS-Page and *in vitro* activity assays

Recombinant PI3-kinases are used for:

- screening strategies to identity PI3K inhibitors and activators
- target identification for cancer prevention and therapy
- interaction studies with PI3K signaling modulators
- phosphorylation assays (lipid and protein kinase assays)



taken from: Walker et al. (1999) Structural insights into phosphoinositide 3-kinase catalysis and signalling. Nature. **402**:313.