

Targeting the PI3K/AKT/mTOR pathway in cancer

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

PTEN

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Institute of Research in Oncology

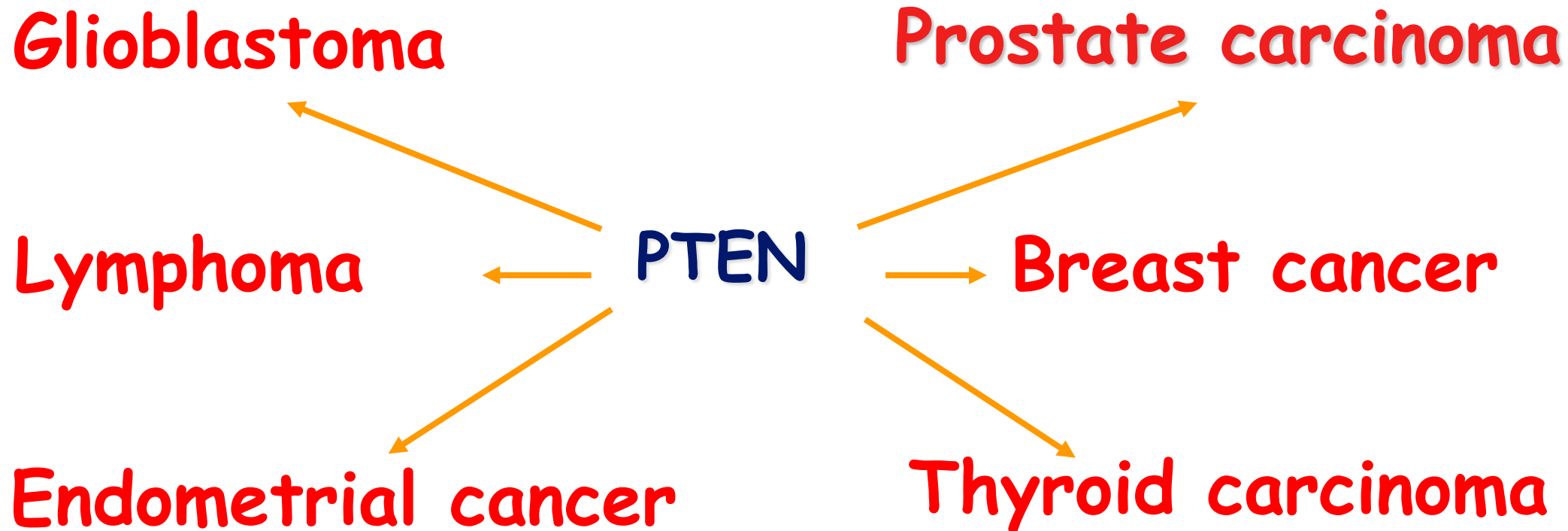
Oncology Institute of Southern

Switzerland

DISCLOSURE SLIDE

I do not have any conflict of interest

PTEN Alterations Are Extremely Common in Human Cancers



PTEN mutations are also observed in familial syndromes

- Cowden Syndrome

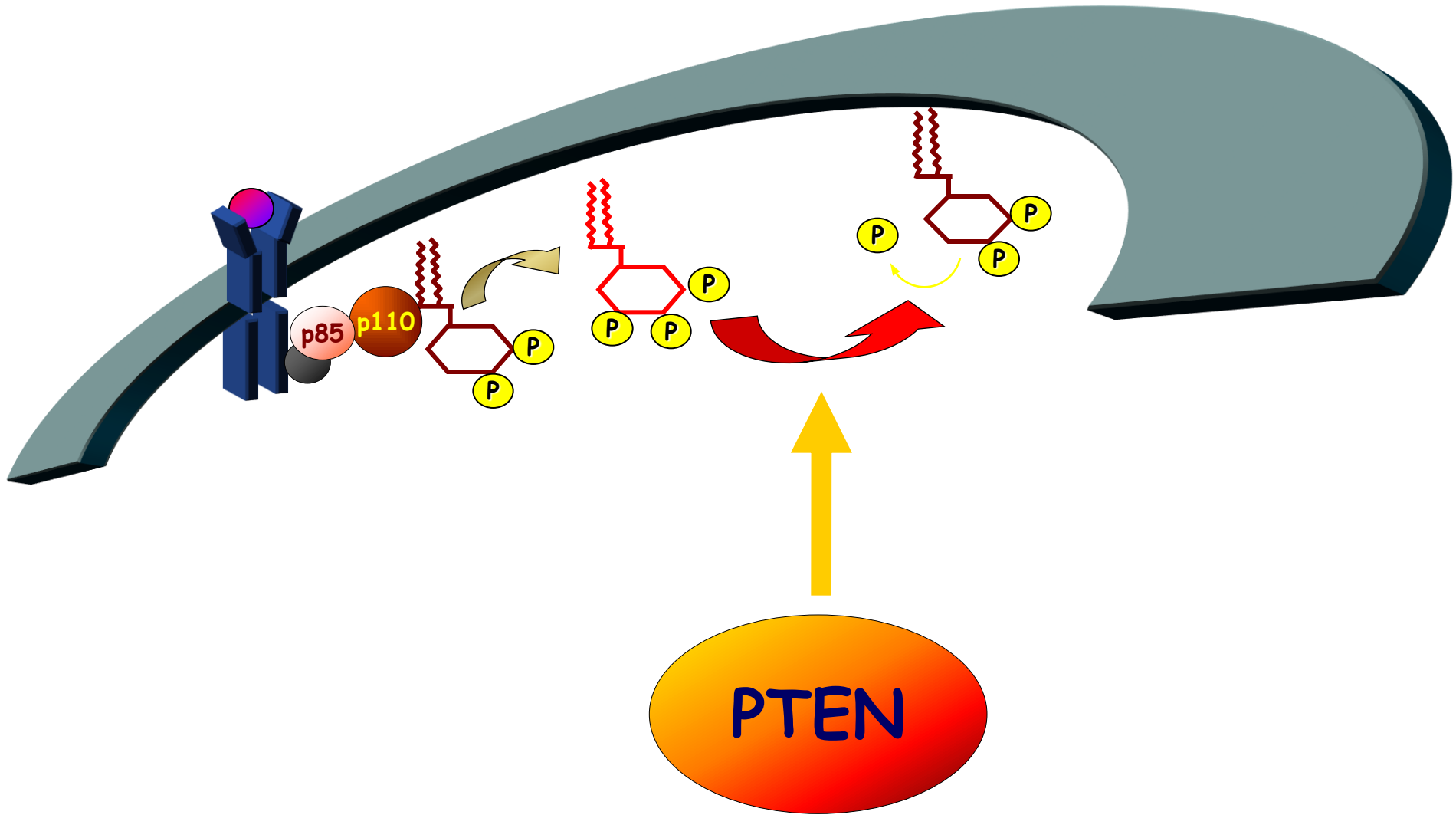
- 1) Hamartomas

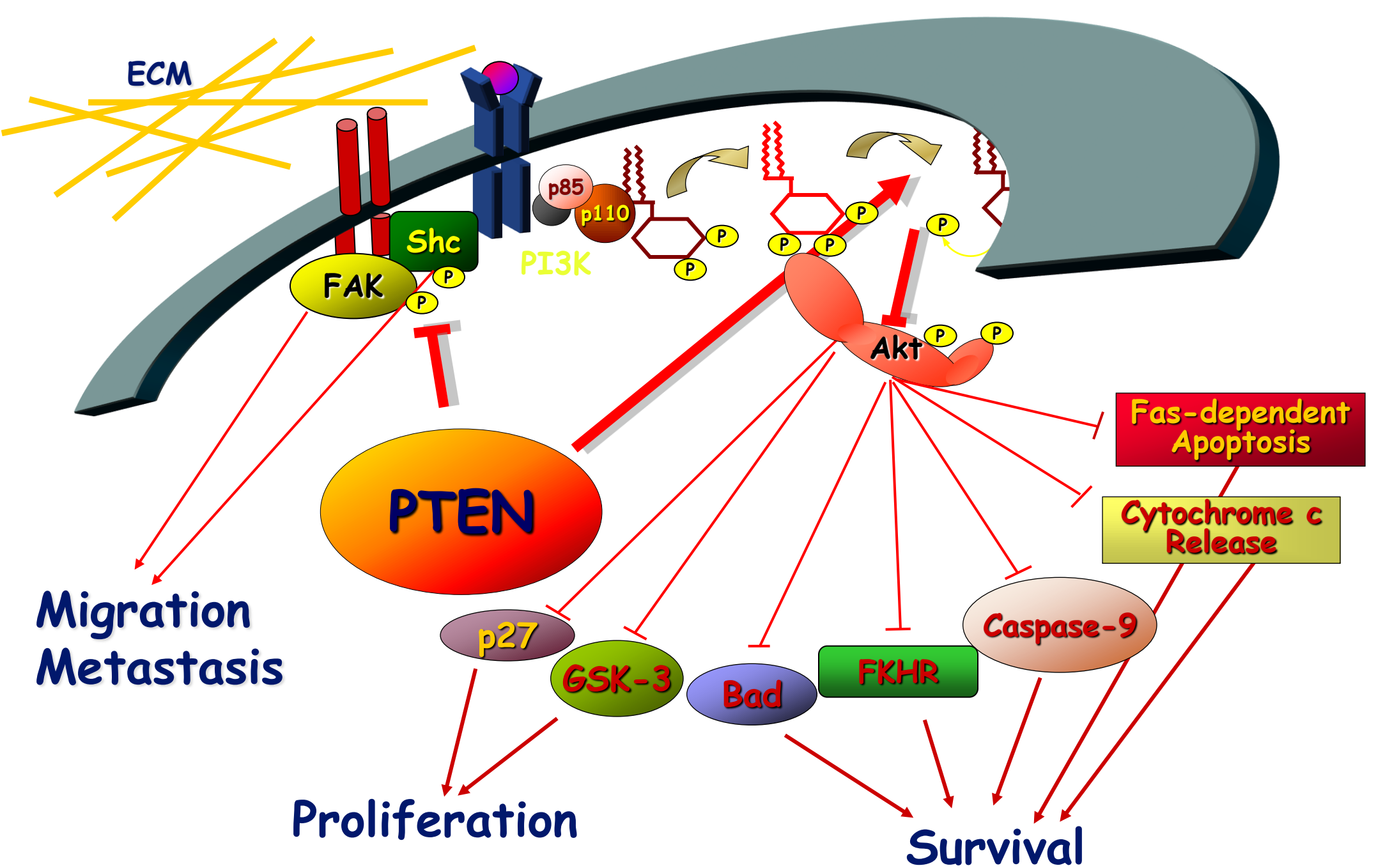
- 2) Cancer predisposition → Breast cancer

- 3) Macrocephaly and mental retardation

- Lhermitte Duclo and Bannayan-Riley Ruvalcaba

PTEN Dephosphorylates PIP-3

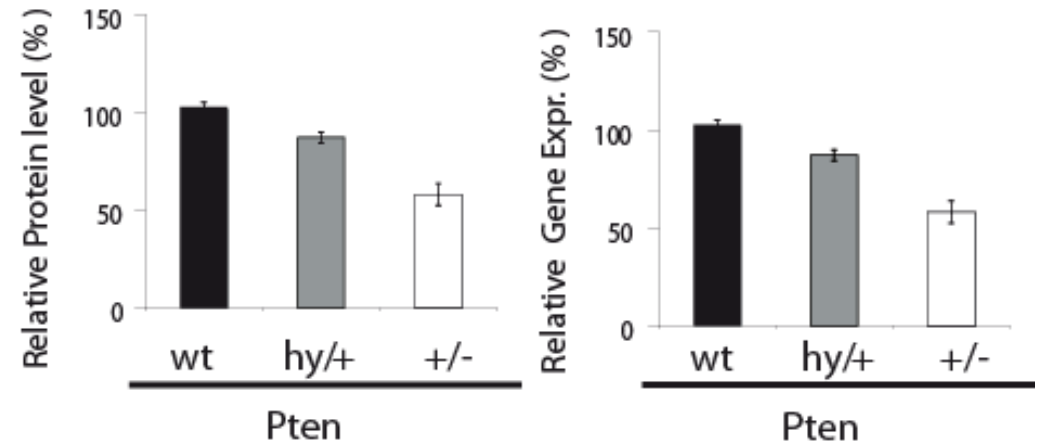
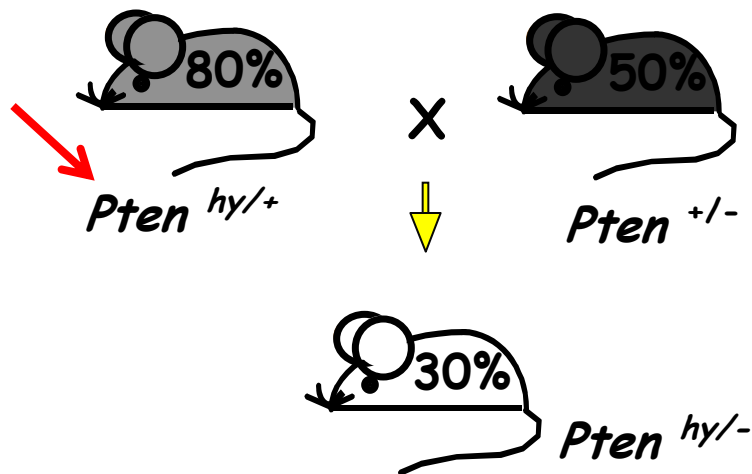
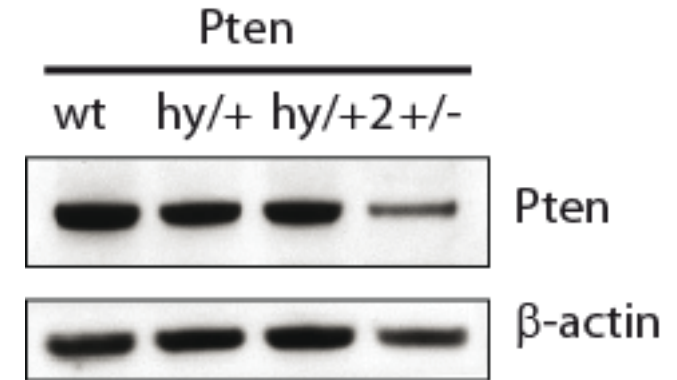
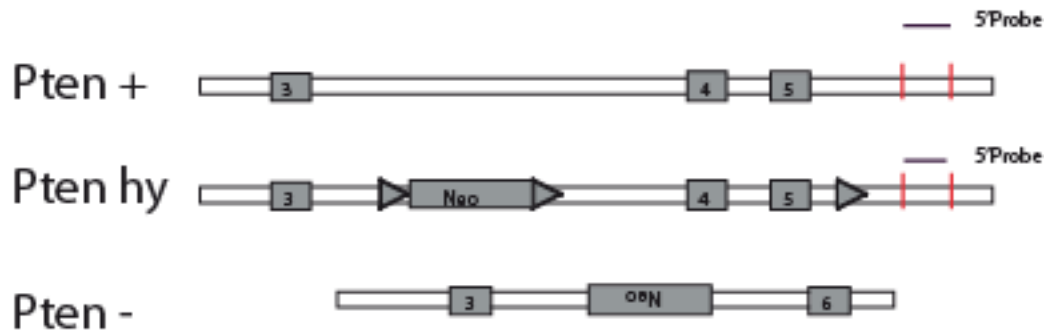




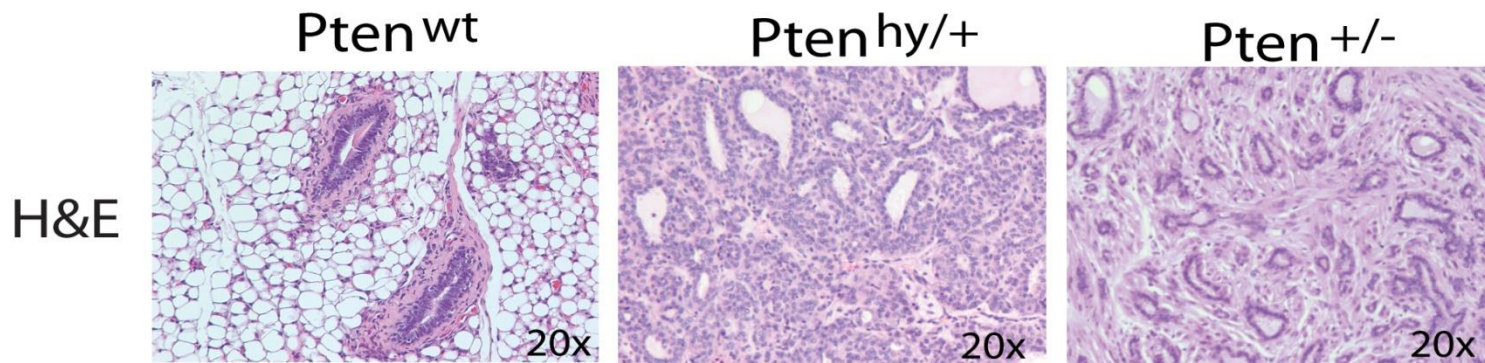
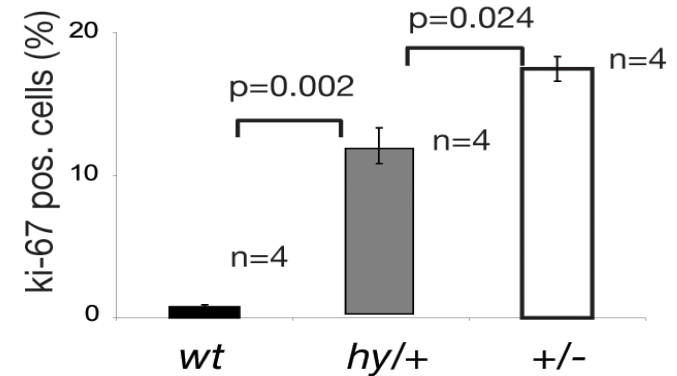
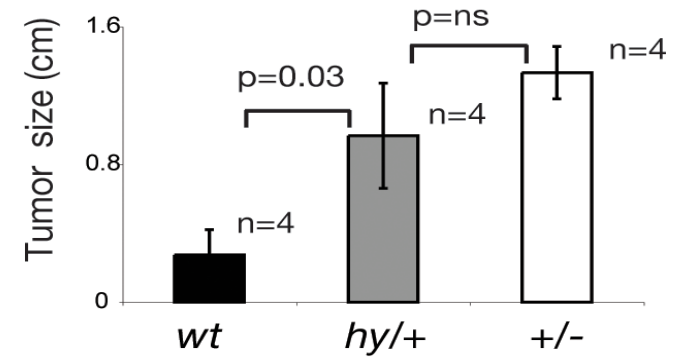
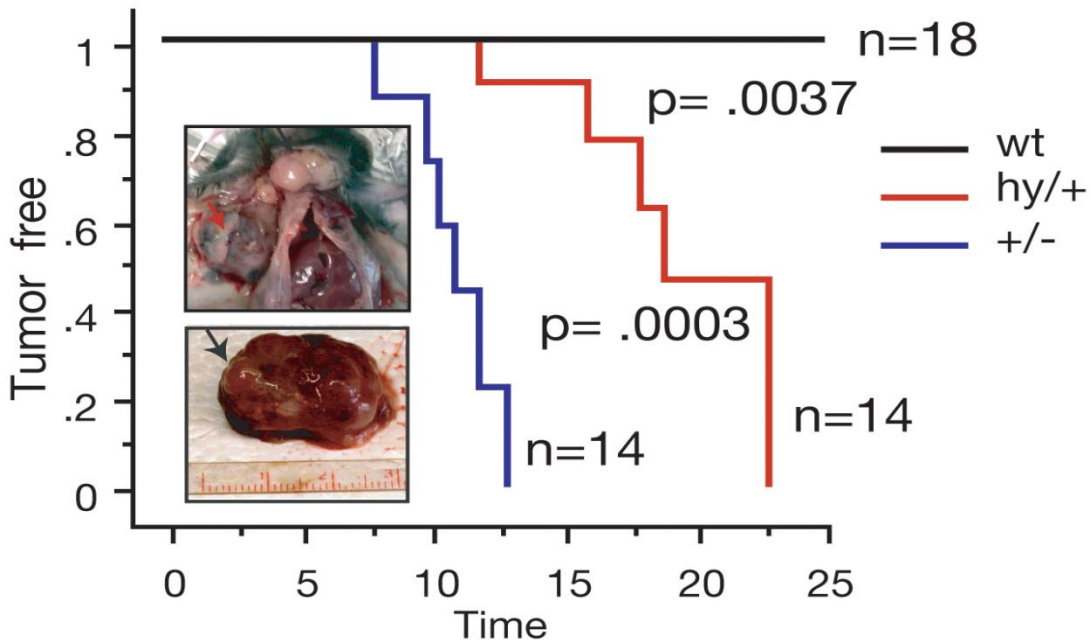
PTEN is a haploinsufficient tumor suppressor gene

In some tumors (e.g. breast cancer, colon cancer) documented coding mutations of PTEN or PTEN deletion are rare (<5%). However, in these tumors PTEN protein levels are significantly diminished

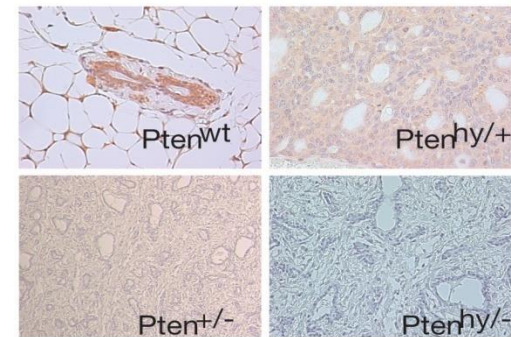
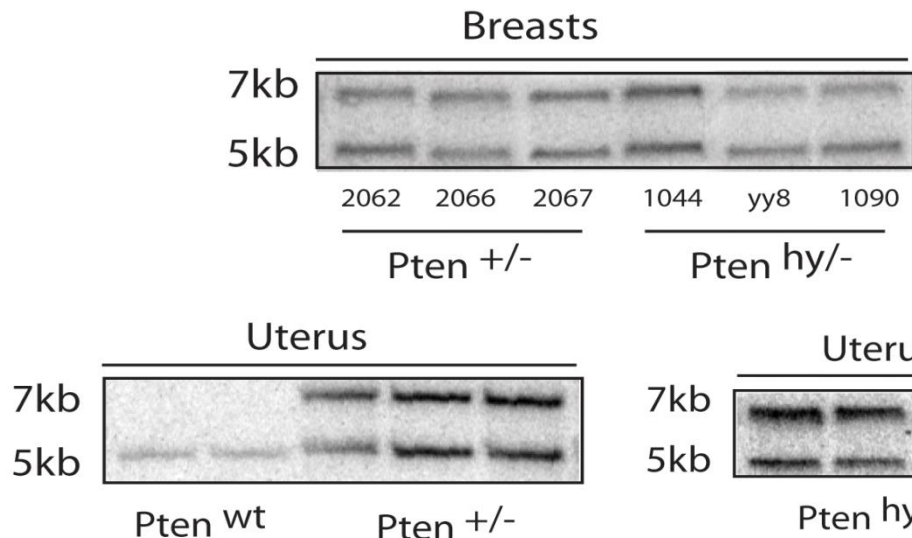
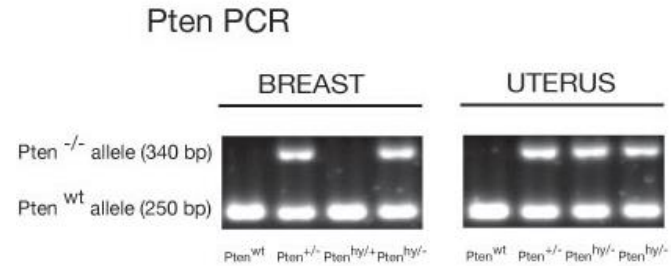
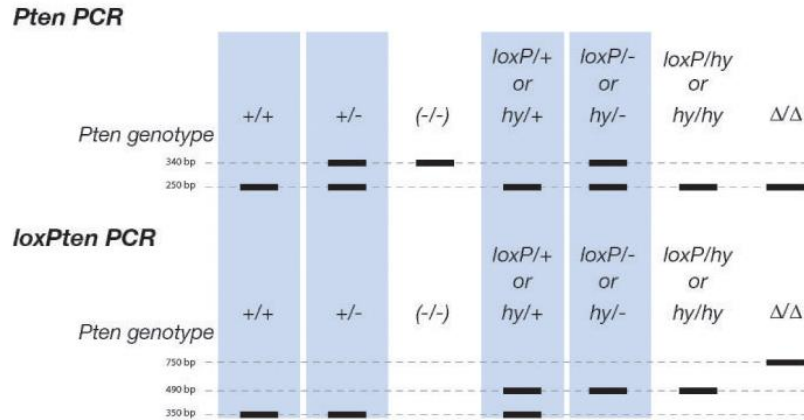
Transcriptional Interference Leads to *Pten* Hypomorphism



Pten "hyper" develop breast cancer

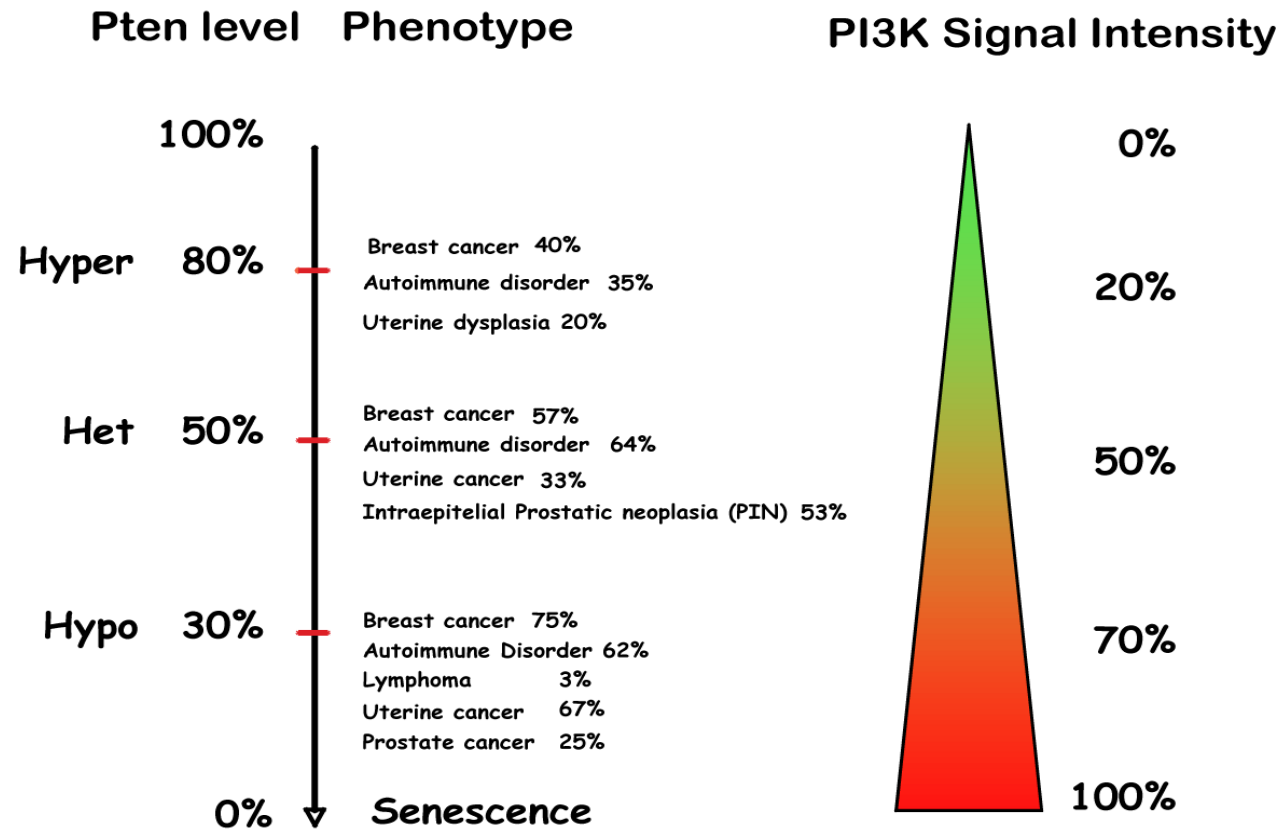


Pten hyper mutants develop tumors in absence of *Pten* LOH

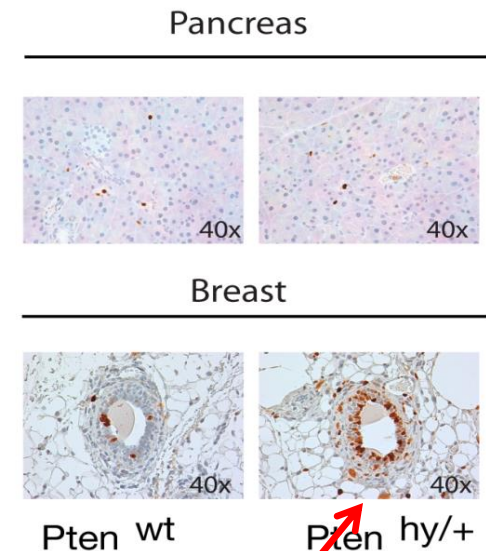
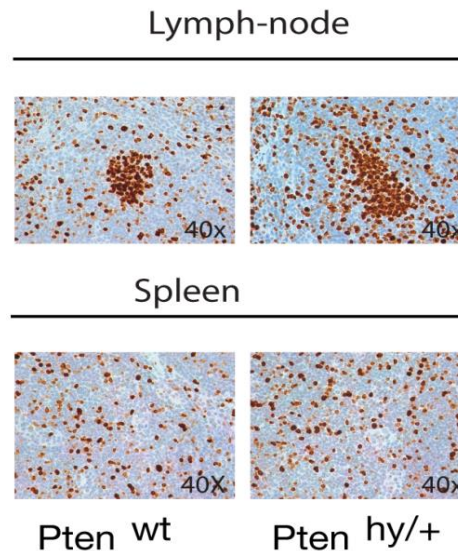
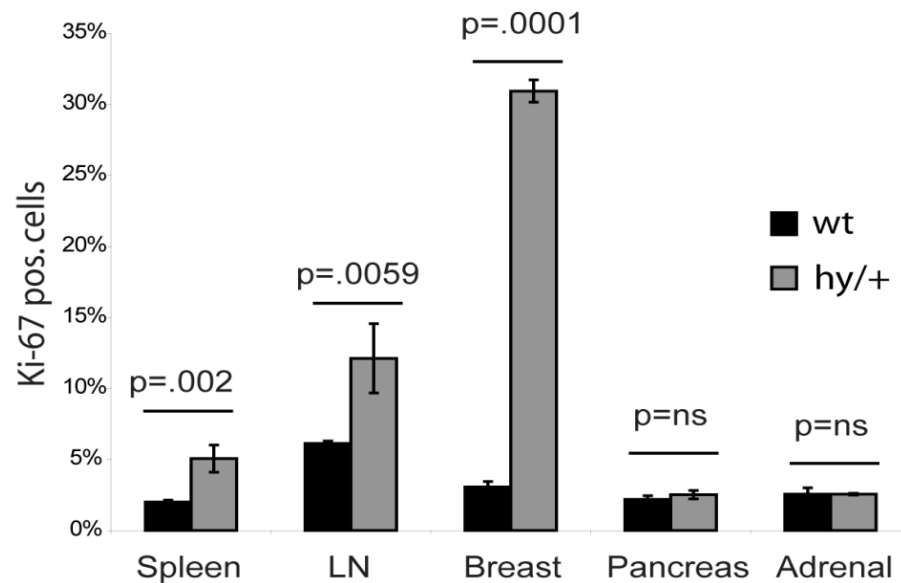


Breast tumors

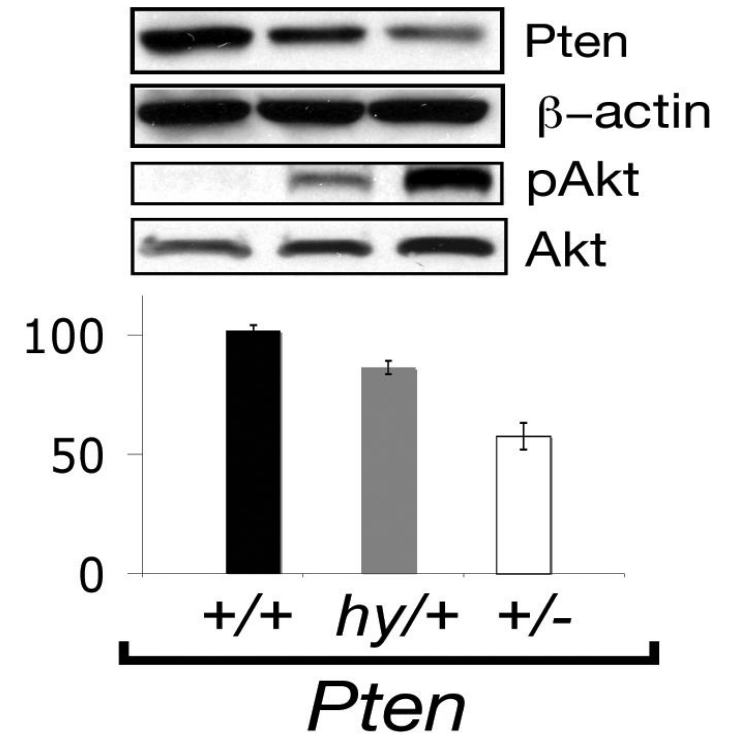
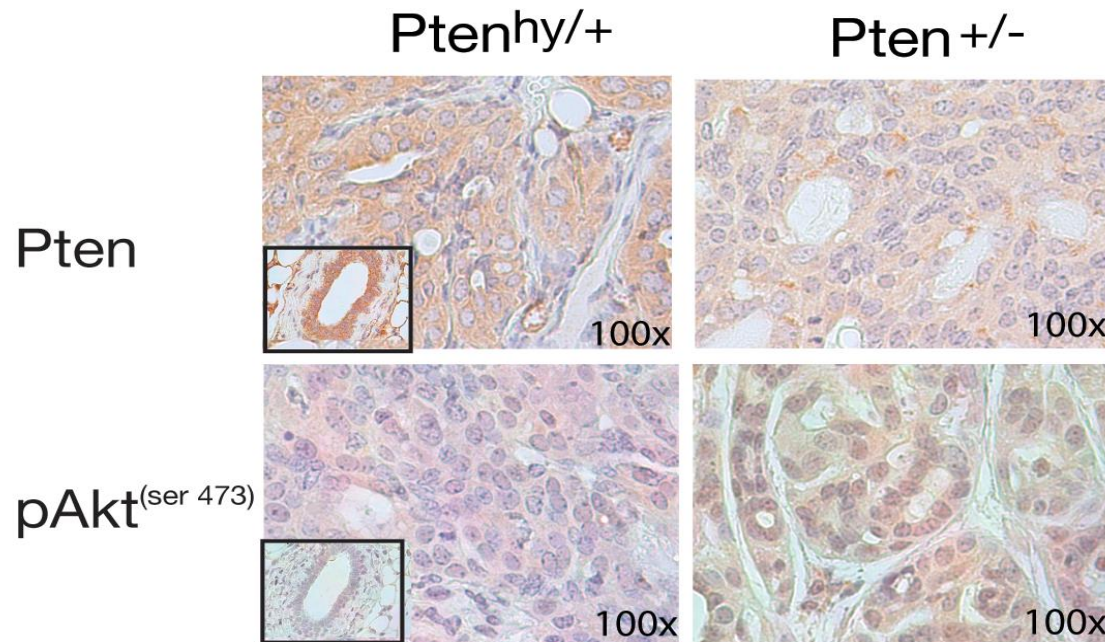
Consequence of Pten subtle protein variations are tissue specific



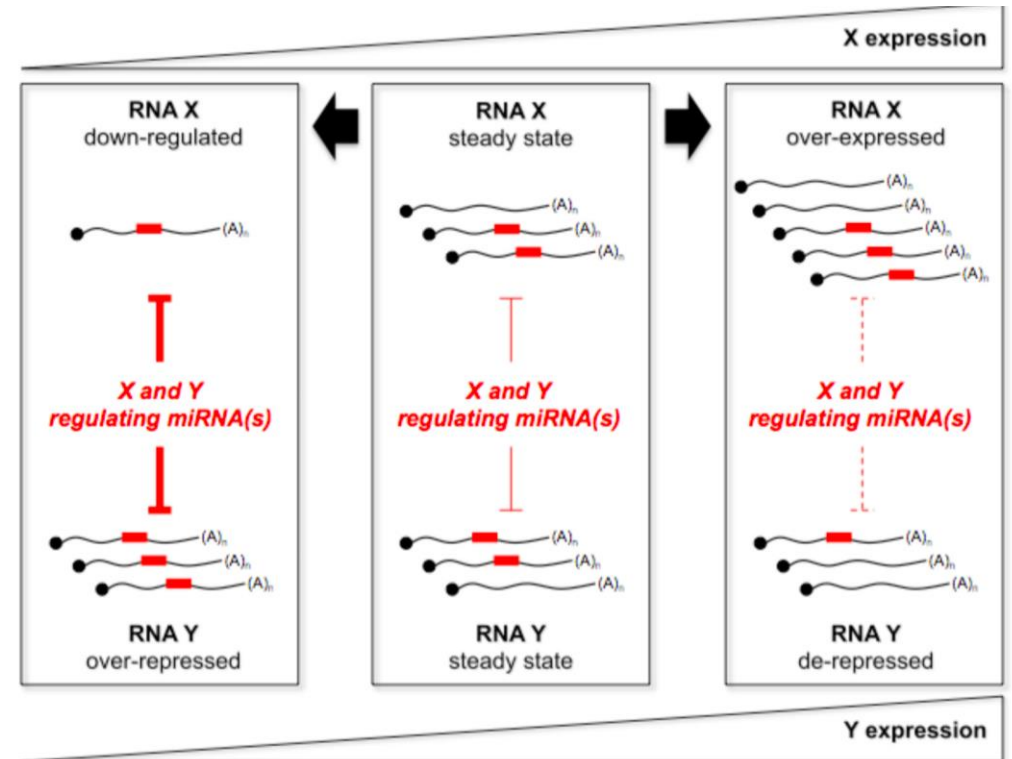
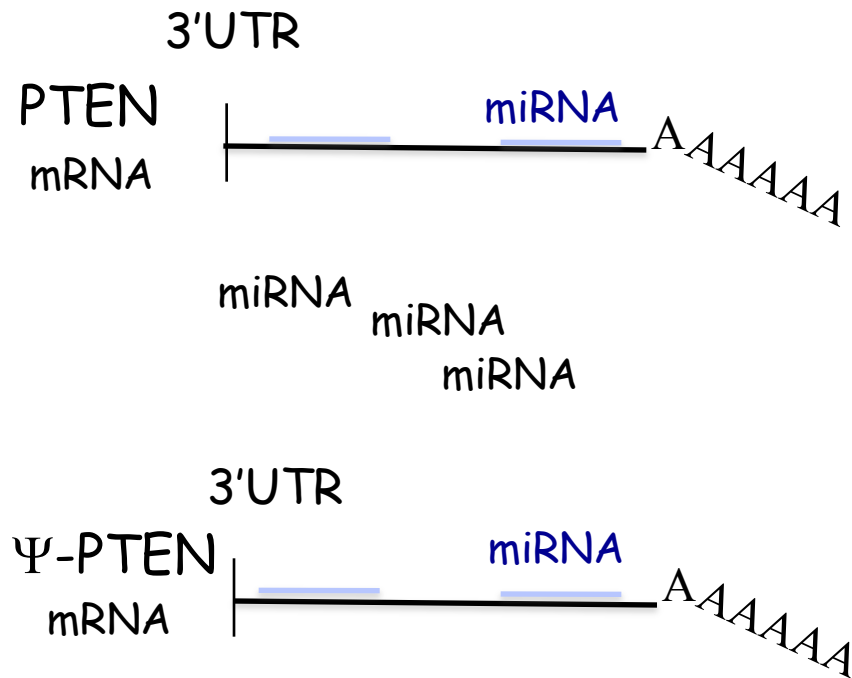
Consequence of Pten subtle protein variations are tissue specific



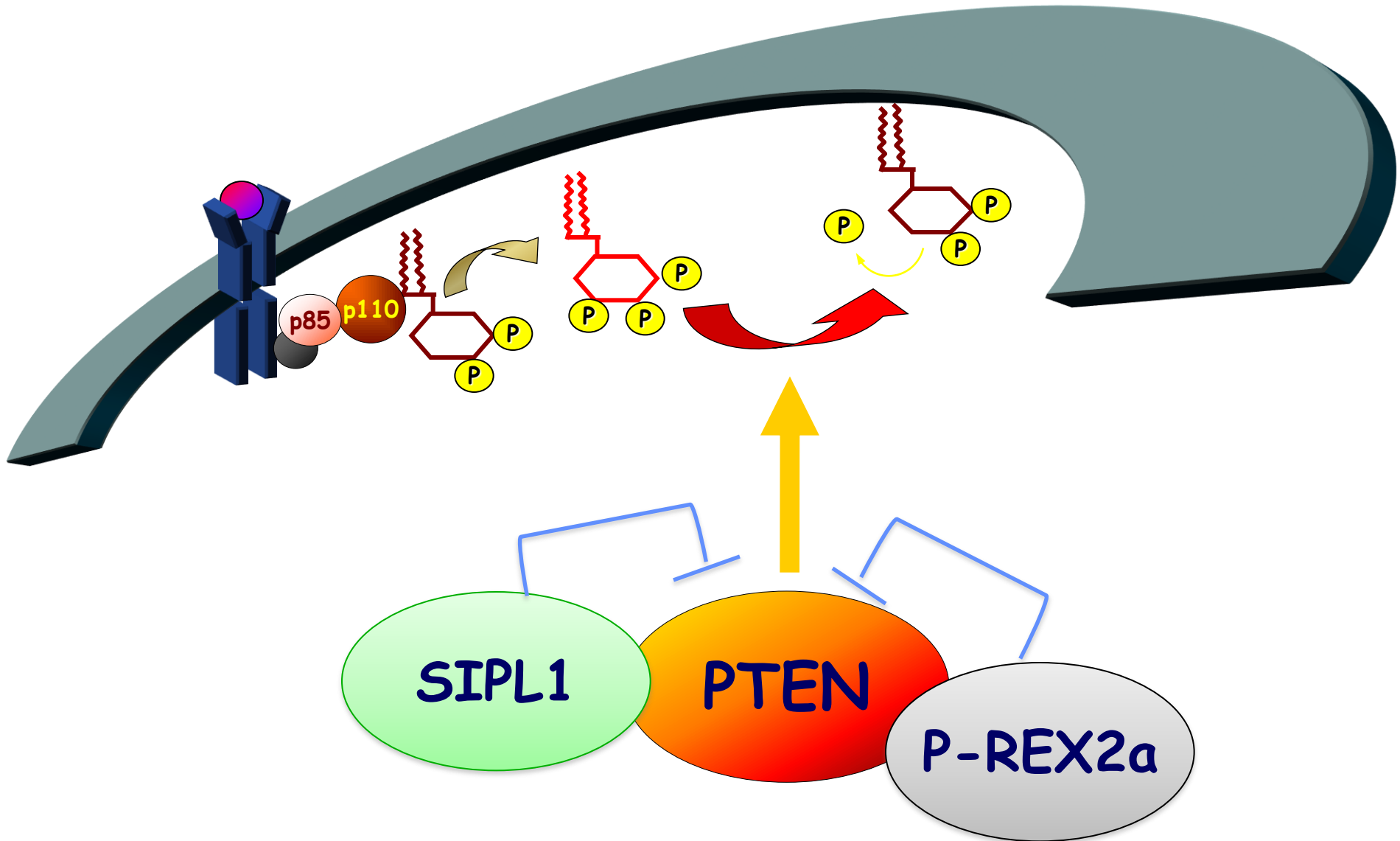
Progressive increase in Akt activation in breast cancers from *Pten* hyper and het mutants



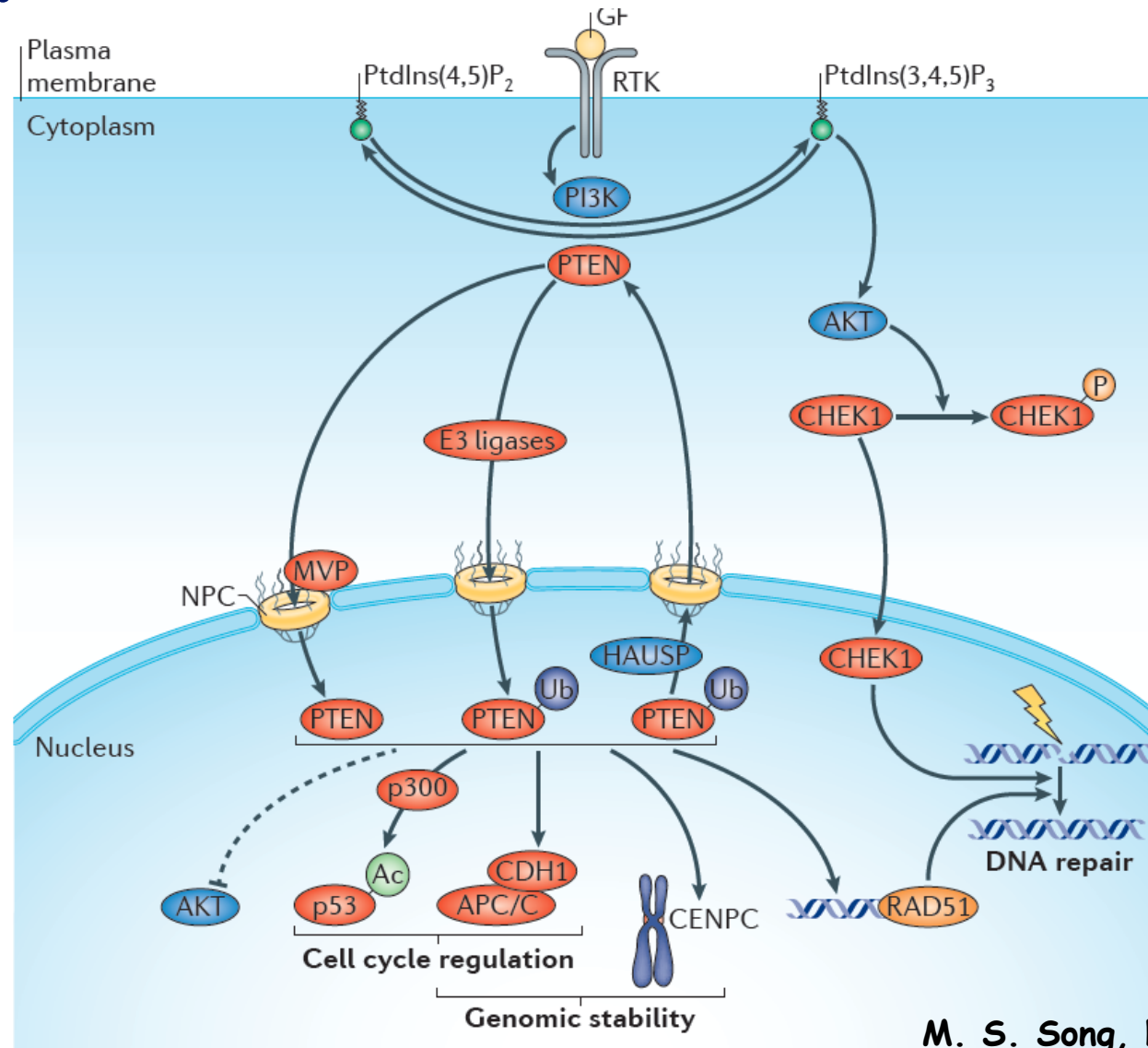
A coding-independent function of gene and pseudogene mRNAs regulates tumour biology



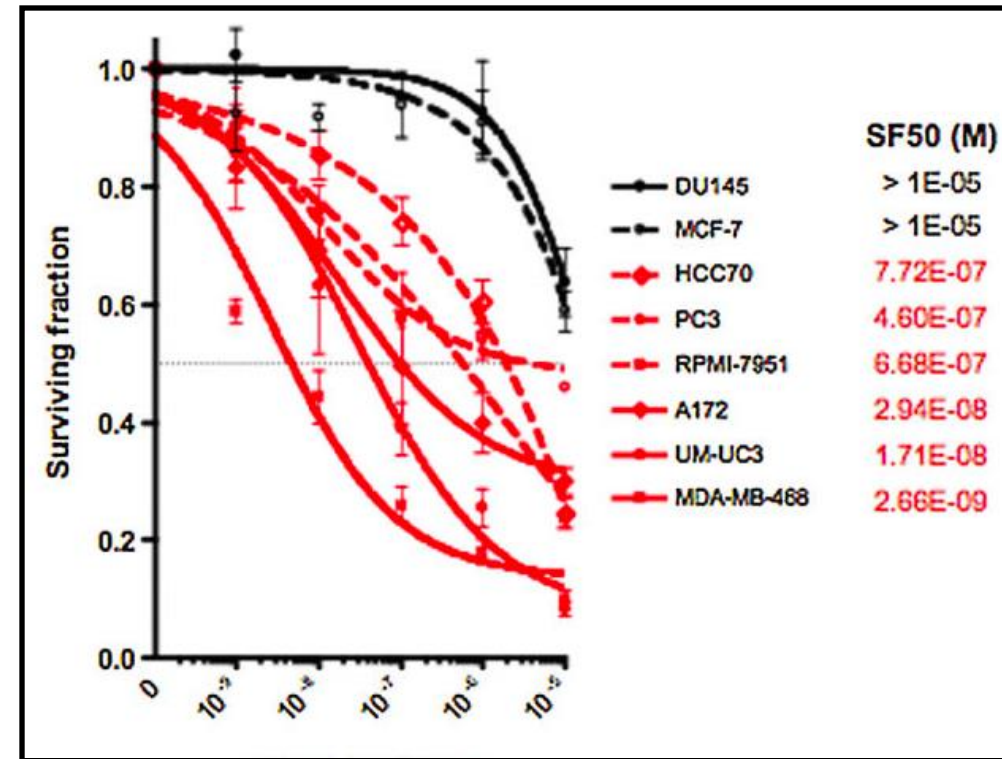
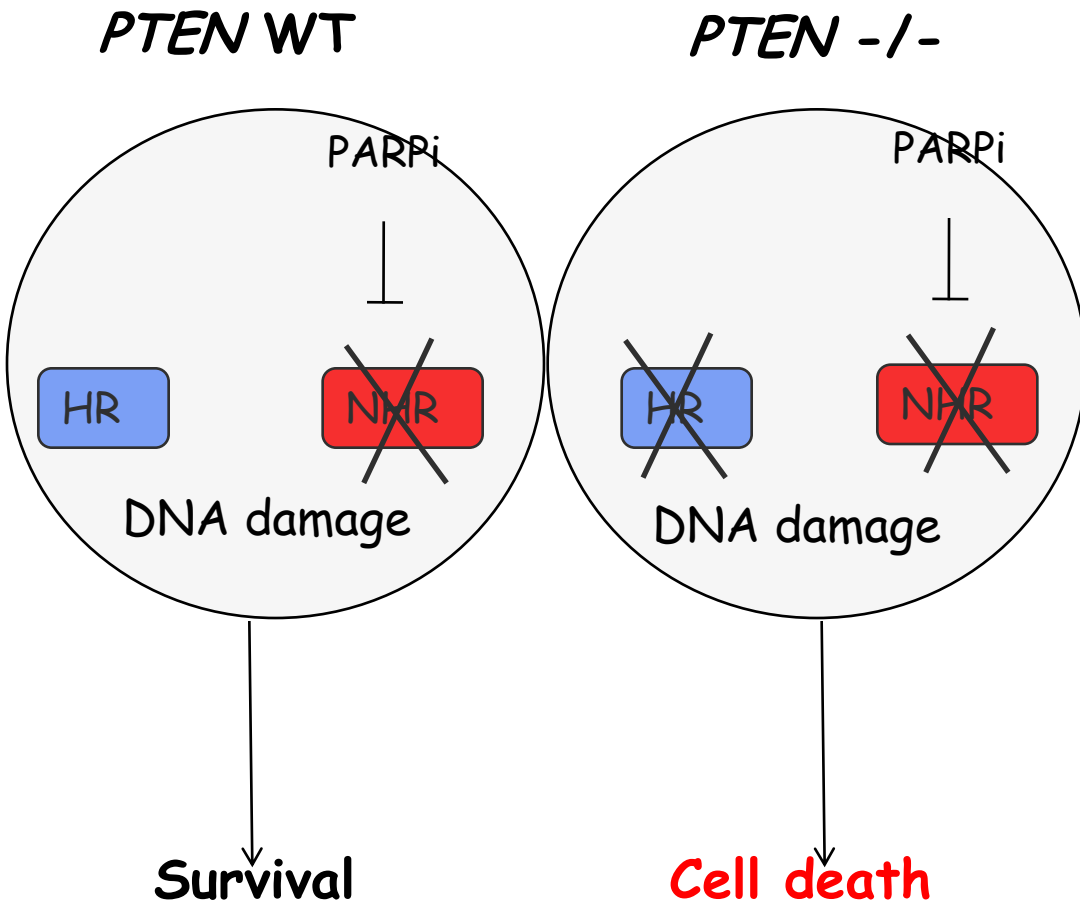
PTEN interactors and regulators



PTEN has a phosphatase independent, nuclear function

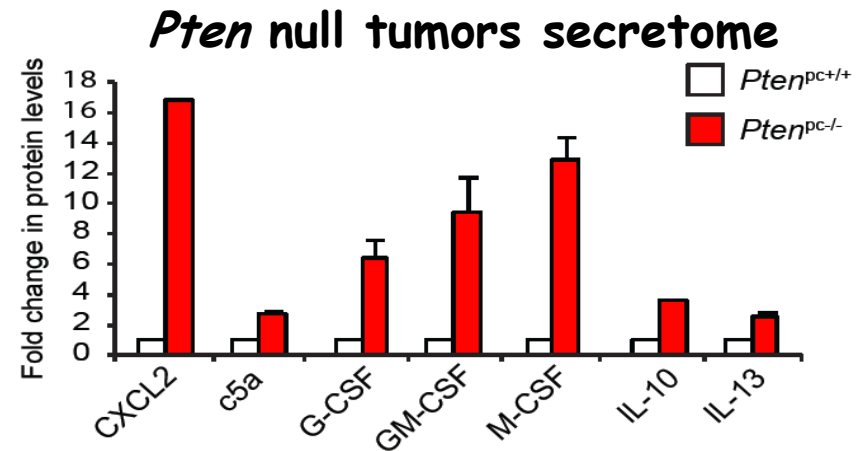
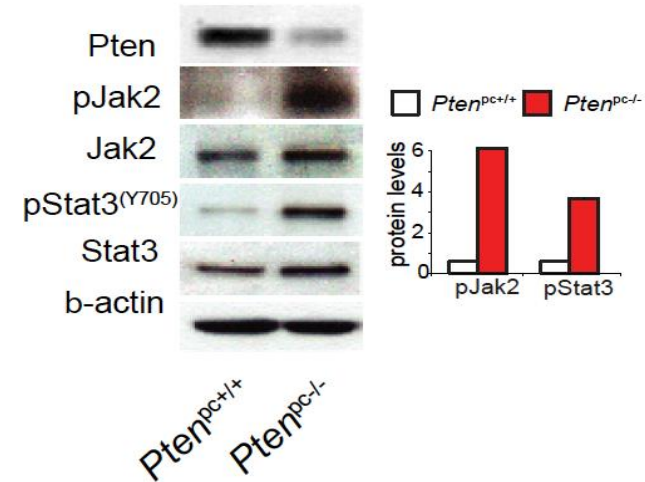
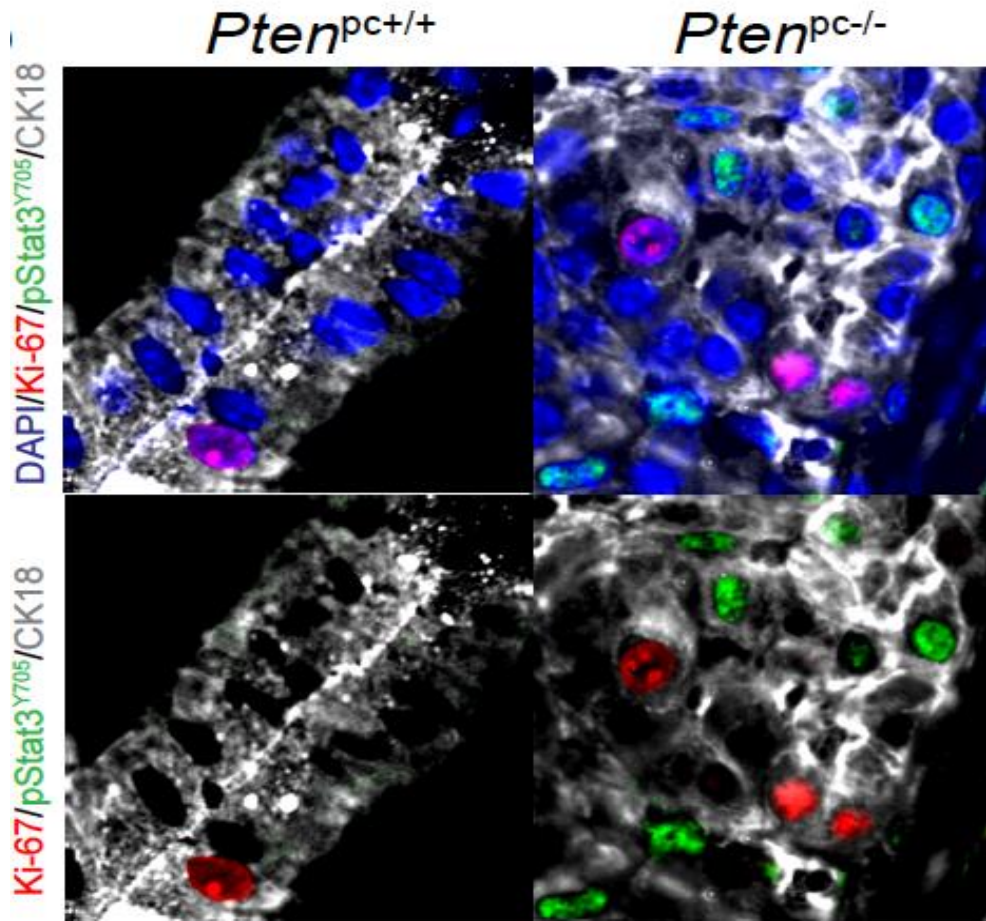


PTEN, genetic instability and synthetic lethality

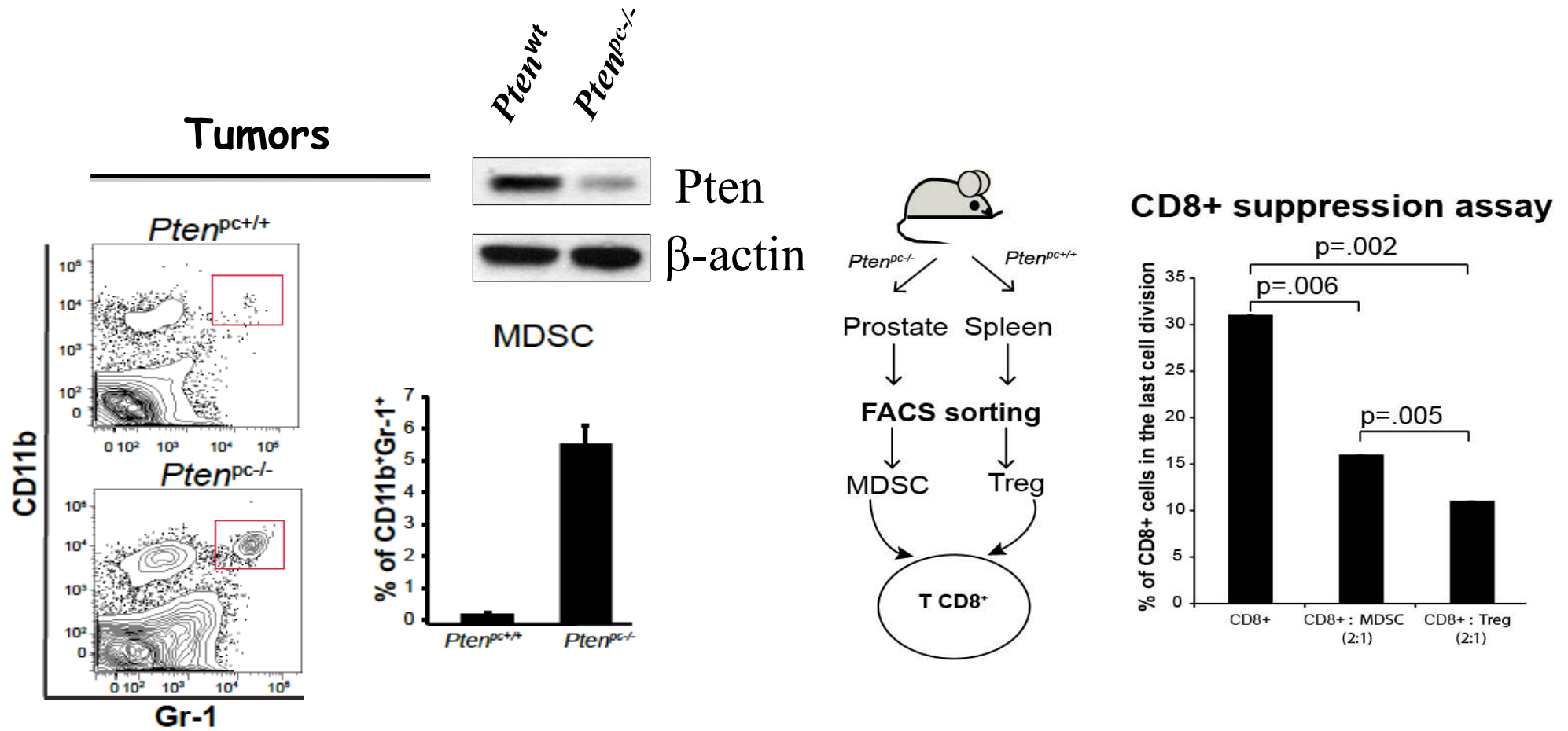


A Ashworth, EMBO 2009

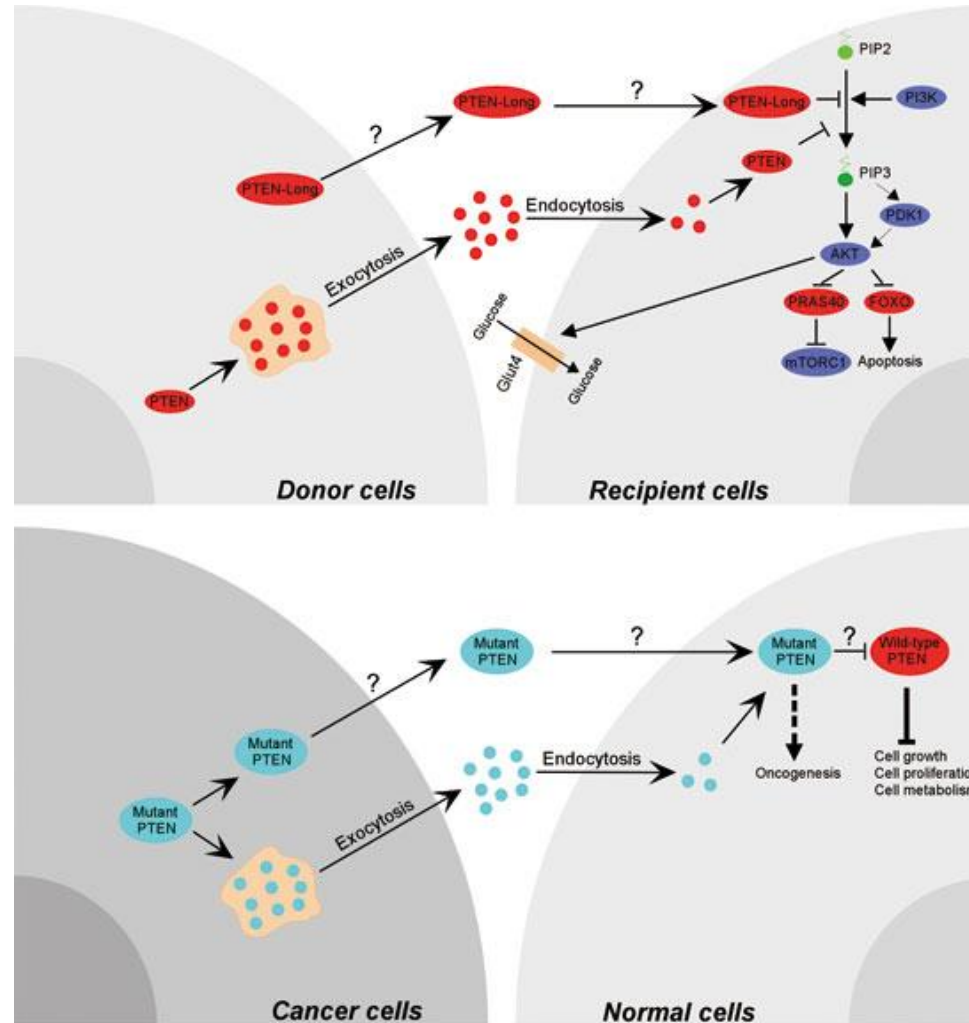
The Jak2/Stat3 pathway is up-regulated in *Pten*^{pc-/-} tumors



Immunophenotype of *Pten*^{pc-/-} tumors



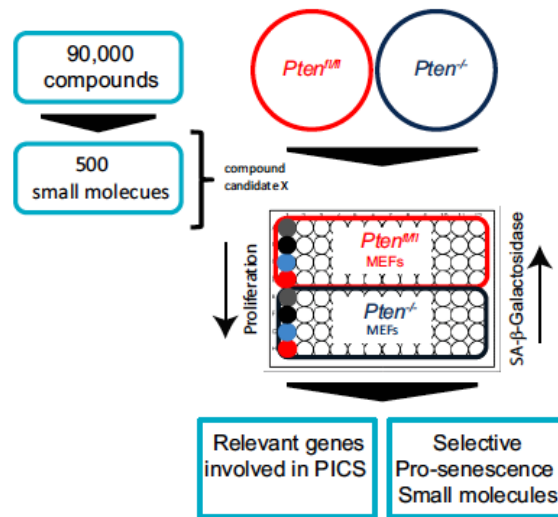
Secreted PTEN can control the tumor microenvironment, normal and recipient tumor cells



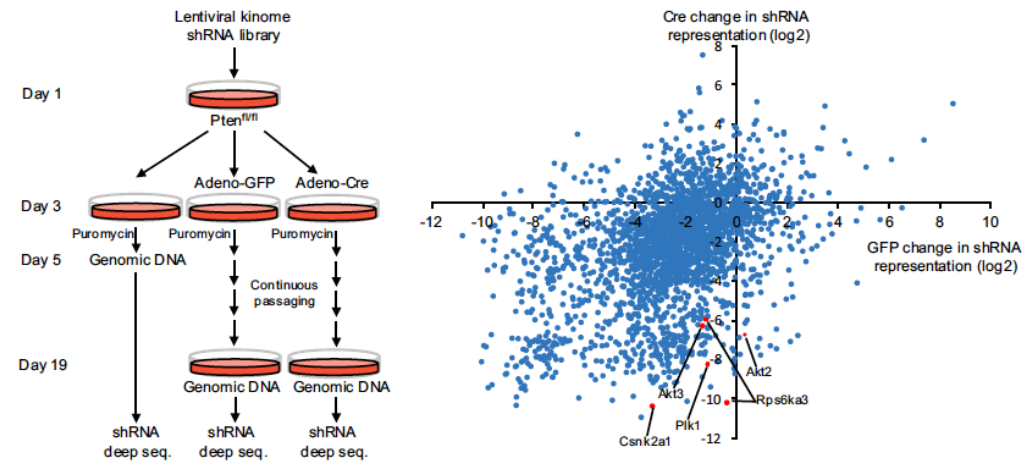
Targeting PTEN for cancer therapy: A feasible strategy???

A novel chemogenomic and sh-RNA screening platform identifies markers of drug sensitivity in PTEN null cells

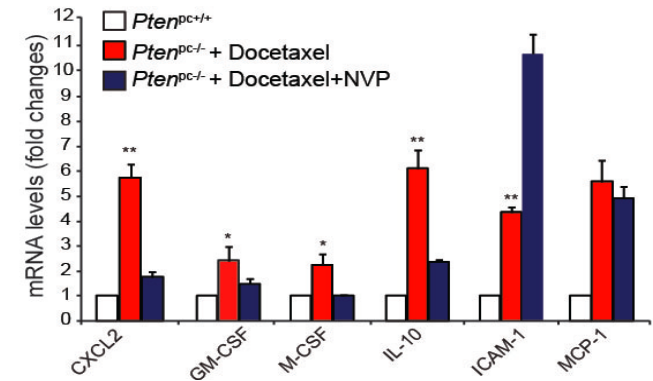
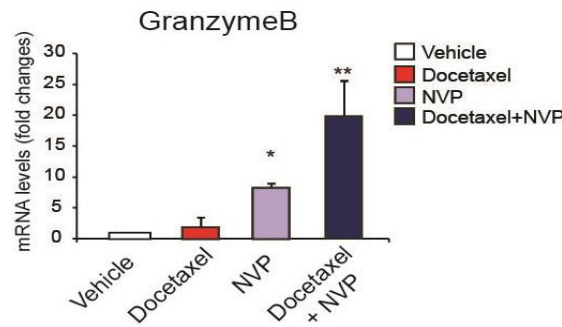
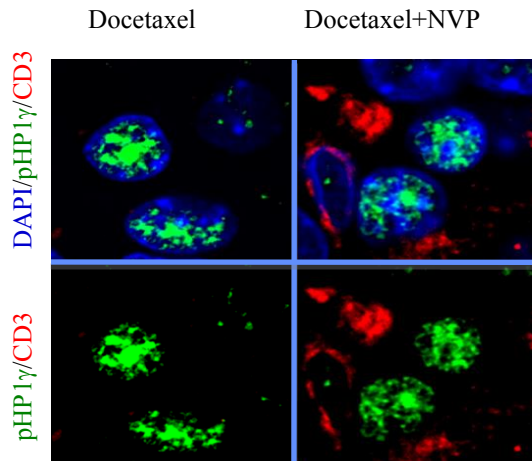
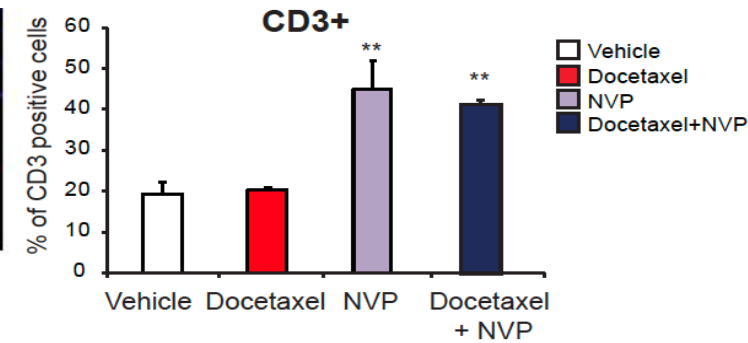
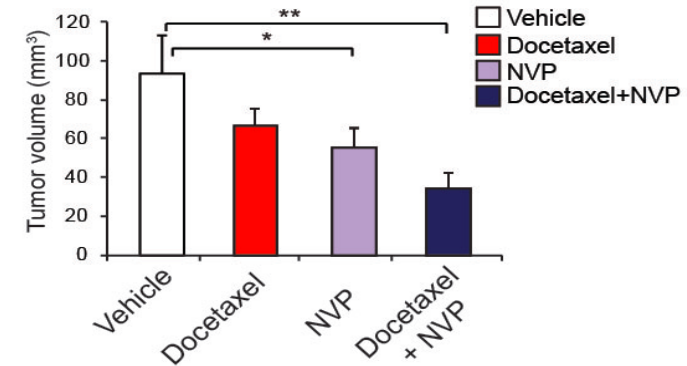
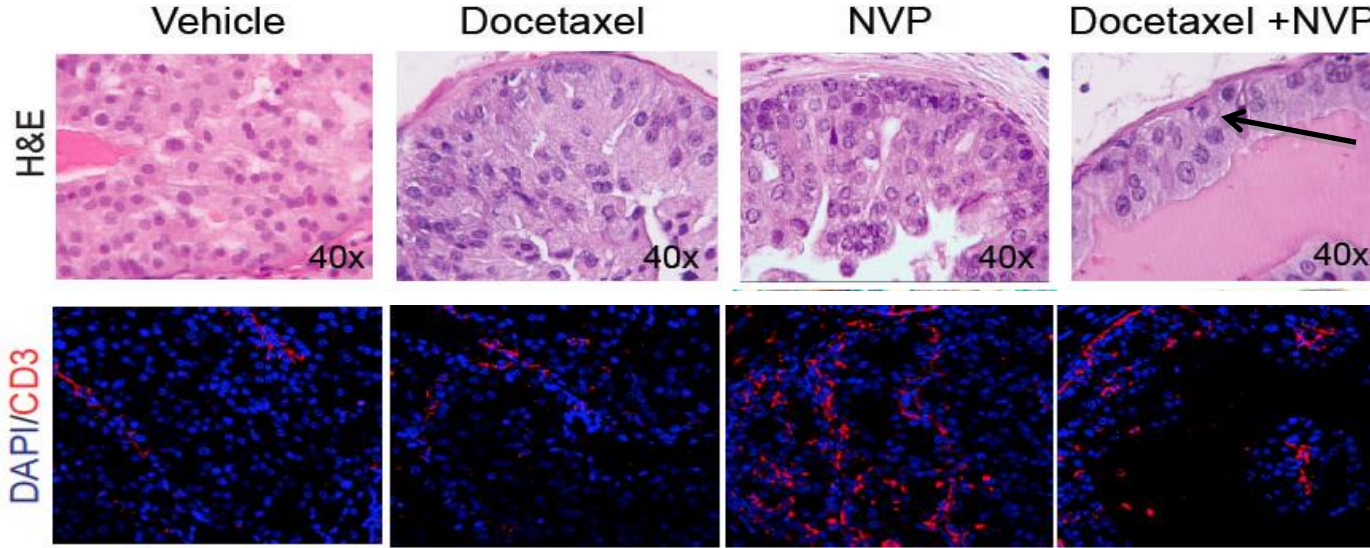
Chemogenomic screening platform



sh-RNA screening platform

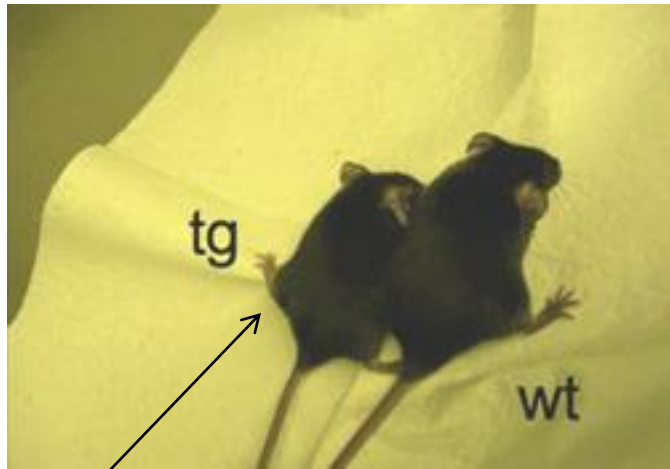


JAK2 inhibitors reprograms the Pten null "secretome" driving a strong anti-tumor immune response

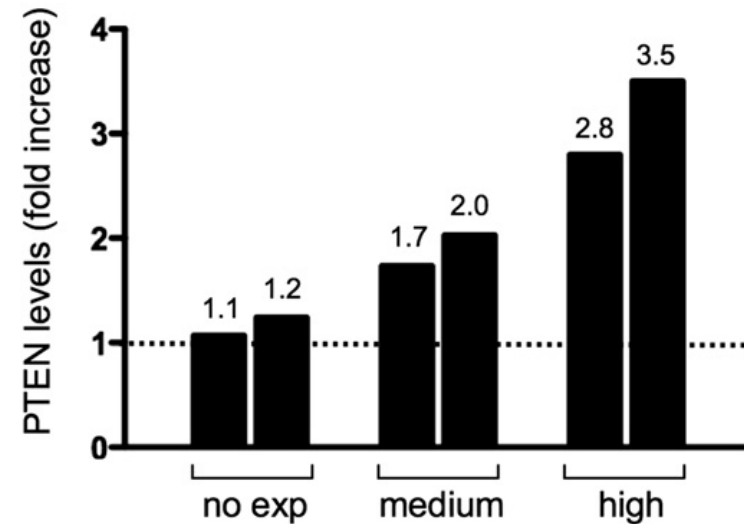


Identification of compounds that enhance the level of PTEN in tumors?

A Super-Pten State Is Compatible with Life



Super-Pten



I. Garcia Cao, Cell 2012

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Abdulla Alajati
Ilaria Guccini
Jinjing Chen
Ajinkia Revandkar
Madhuri Kalathur
Tiziano Bernasocchi
Enrica Mira Cato
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