



北京大学
PEKING UNIVERSITY

Why tumor hates PTEN 肿瘤为什么如此憎恨PTEN

22-1-2015

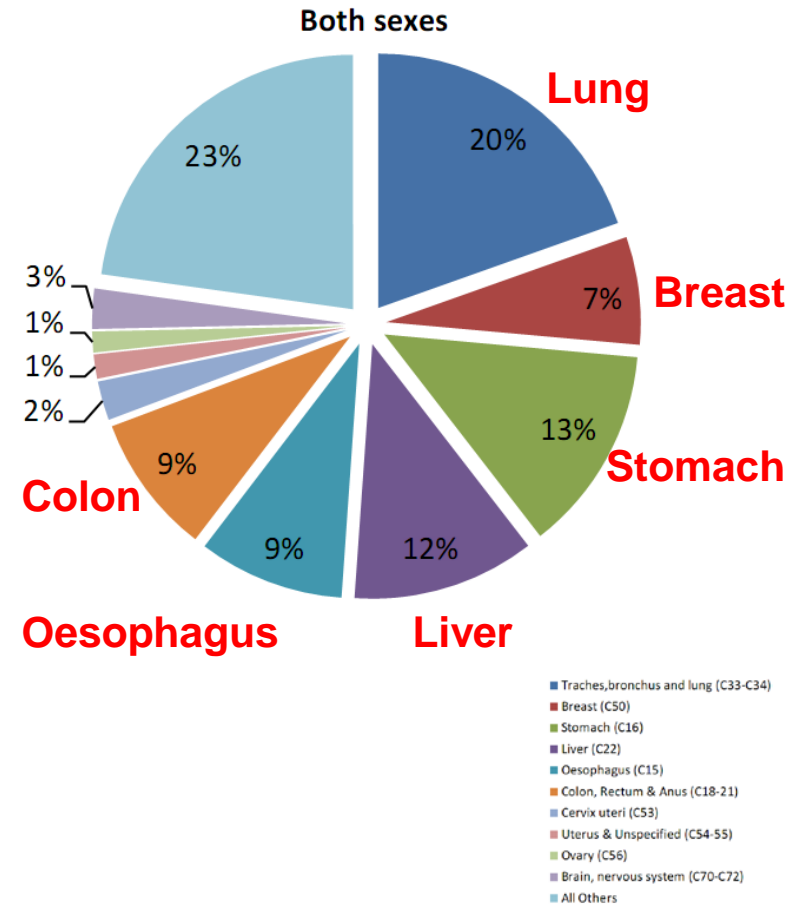
pku14f-g13

Cancer Incidence and Death Rate

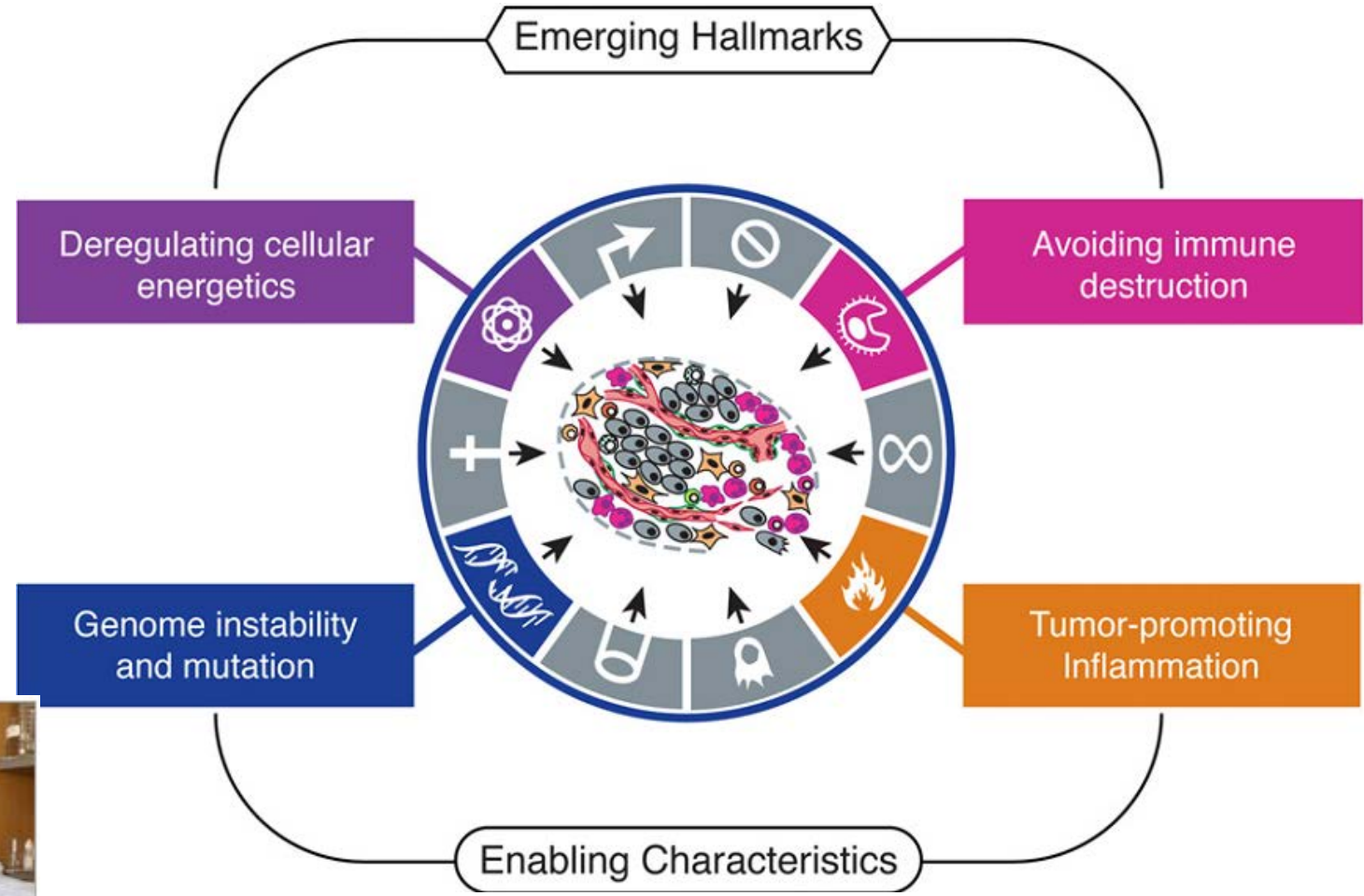
Geographic variation in cancer incidence and death rates

Countries showing highest and lowest incidence of specific types of cancer ^a			
Cancer site	Country of highest risk	Country of lowest risk	Relative risk H/L ^b
Skin (melanoma)	Australia (Queensland)	Japan	155
Lip	Canada (Newfoundland)	Japan	151
Nasopharynx	Hong Kong	United Kingdom	100
Prostate	U.S. (African American)	China	70
Liver	China (Shanghai)	Canada (Nova Scotia)	49
Penis	Brazil	Israel (Ashkenazic)	42
Cervix (uterus)	Brazil	Israel (non-Jews)	28
Stomach	Japan	Kuwait	22
Lung	U.S. (Louisiana, African American)	India (Madras)	19
Pancreas	U.S. (Los Angeles, Korean American)	India	11
Ovary	New Zealand (Polynesian)	Kuwait	8

Geographic areas showing highest and lowest death rates from specific types of cancer ^c			
Cancer site	Area of highest risk	Area of lowest risk	Relative risk H/L ^b
Lung, male	Eastern Europe	West Africa	33
Esophagus	Southern Africa	West Africa	16
Colon, male	Australia, New Zealand	Middle Africa	15
Breast, female	Northern Europe	China	6



Hallmarks of cancer



Robert A. Weinberg

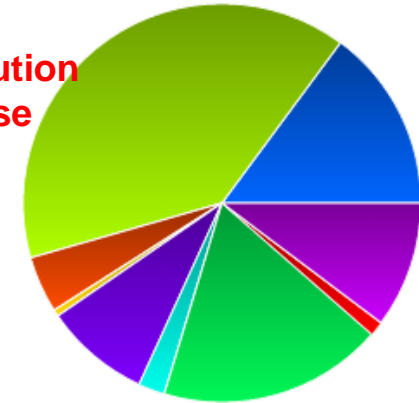
PTEN mutations in cancer

Cosmic

Catalogue of somatic mutations in cancer, Sanger Institute, U.K.

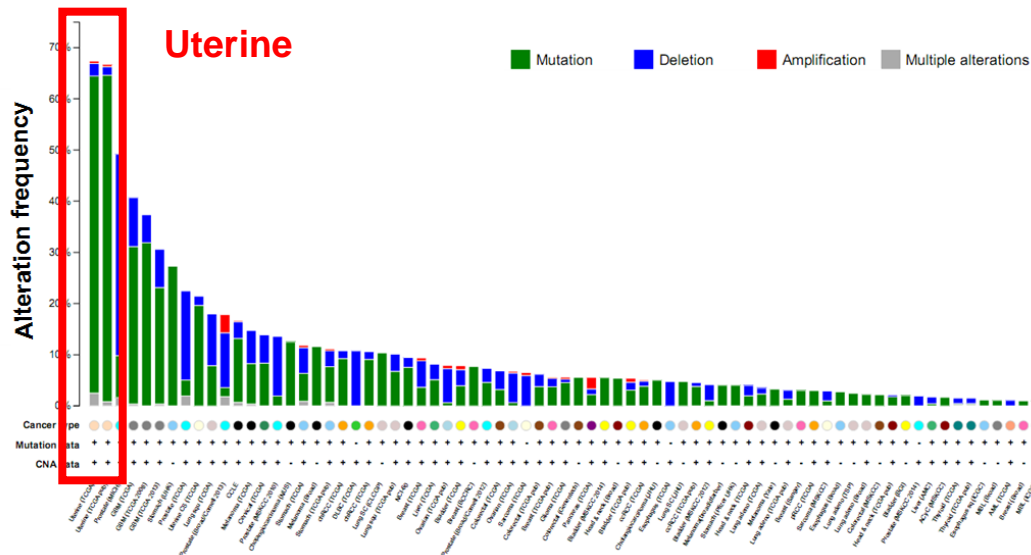
Color	Mutation Type	Mutant samples	Percentage
Blue	Substitution nonsense	491	15.68
Light Green	Substitution missense	1308	41.76
Orange	Substitution synonymous	152	4.85
Brown	Insertion inframe	18	0.57
Purple	Insertion frameshift	284	9.07
Teal	Deletion inframe	71	2.27
Bright Green	Deletion frameshift	603	19.25
Red	Complex	39	1.25
Magenta	Other	339	10.82
	Total	3132	100

Substitution missense



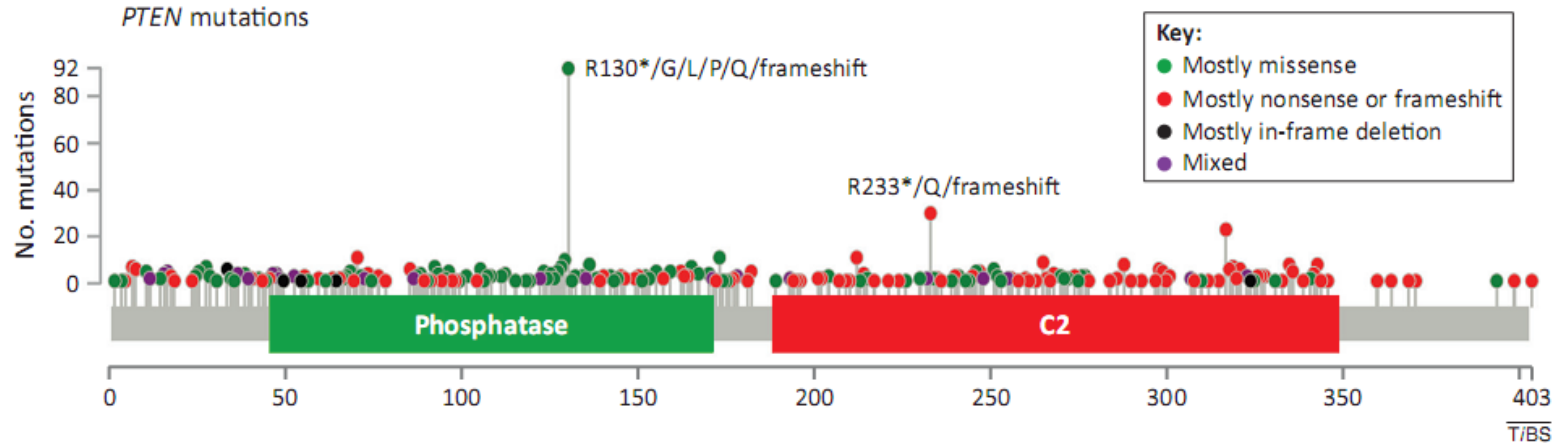
TCGA

The Cancer Genome Atlas (TCGA), National Cancer Institute, U.S.



PTEN mutations in cancer

TCGA

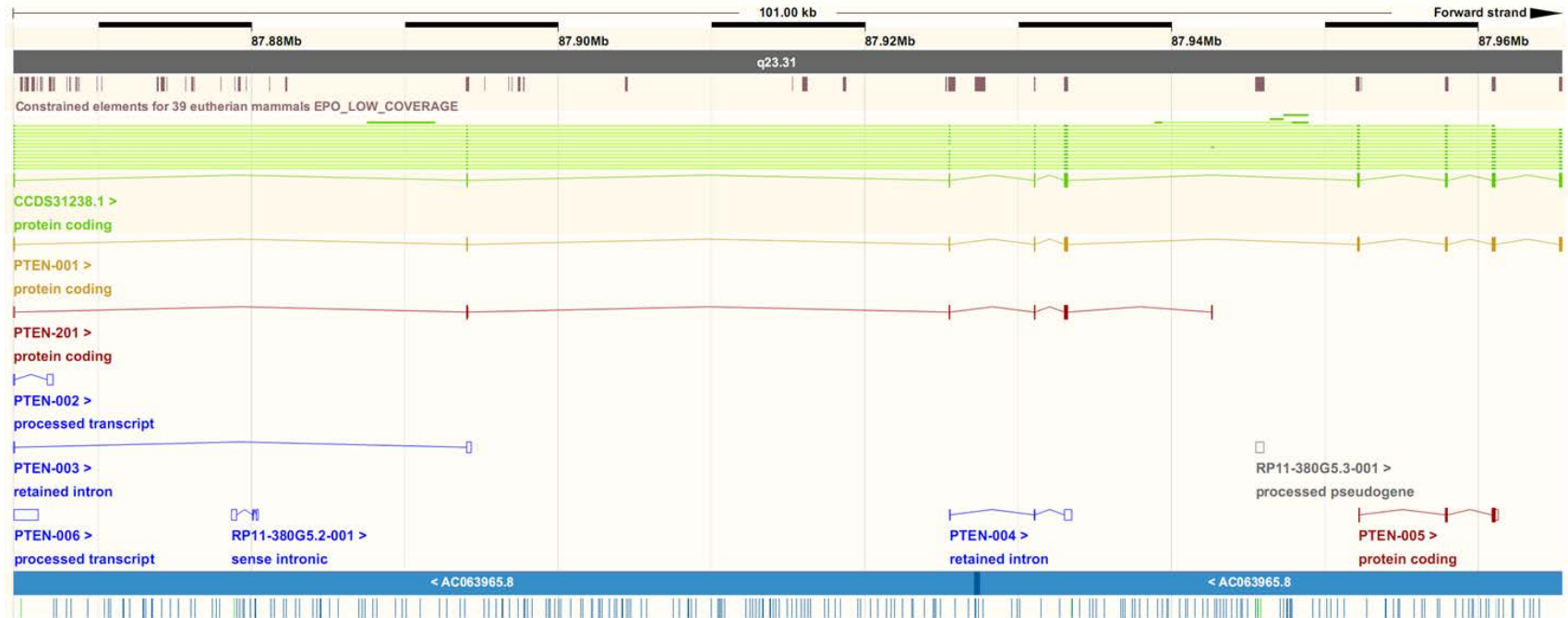


ICGC

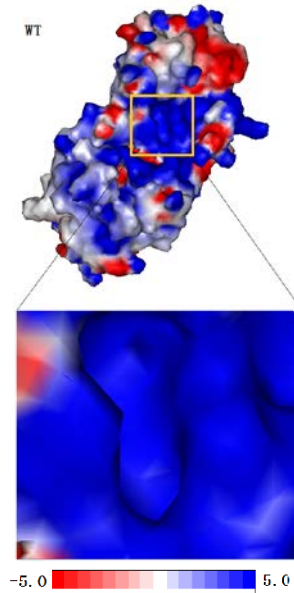
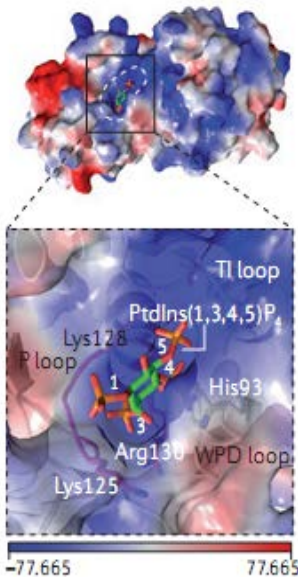
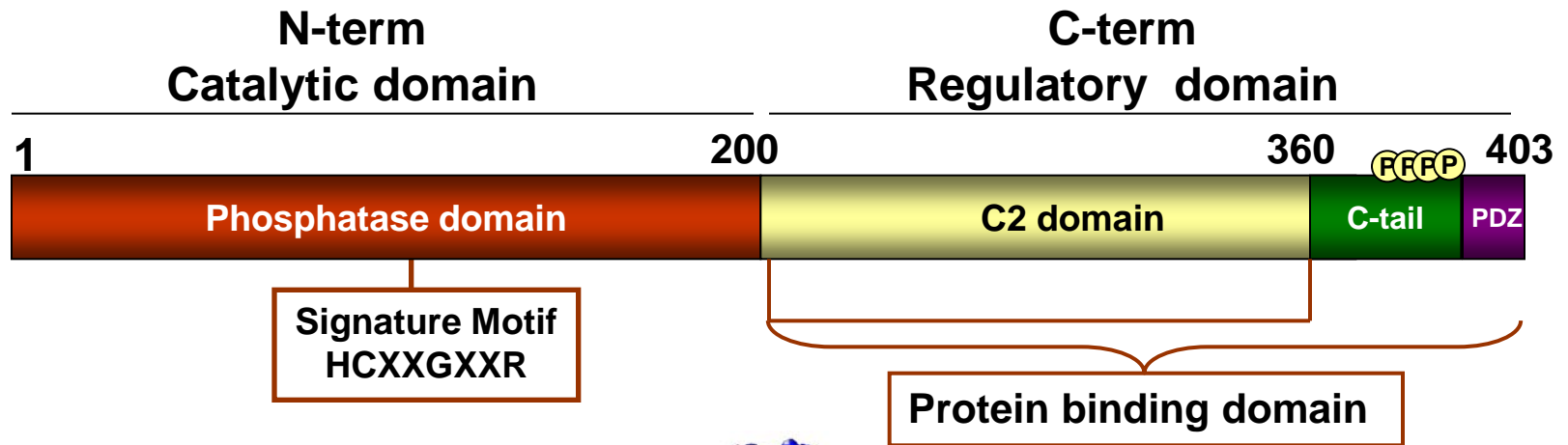
international cancer genome consortium



PTEN gene



PTEN protein

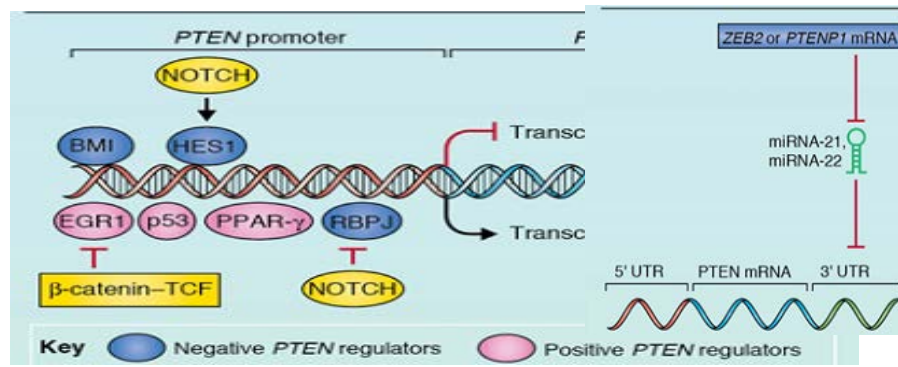


Discovery studio

Regulation of mRNA level

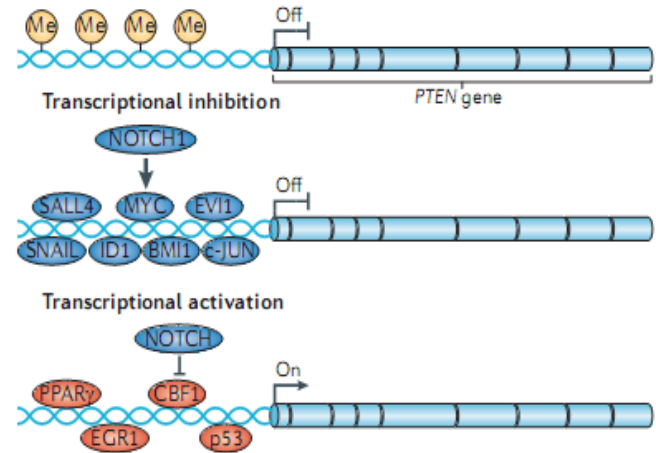
Transcription, miRNA, epigenetic regulation

Transcriptional regulation



miRNA regulation

Epigenetic regulation



MatInspector

Common TFs

MatBase (TF database)

Regulatory Pattern Definition & Search (GEMS Launcher) >>>

Overrepresented TFBS

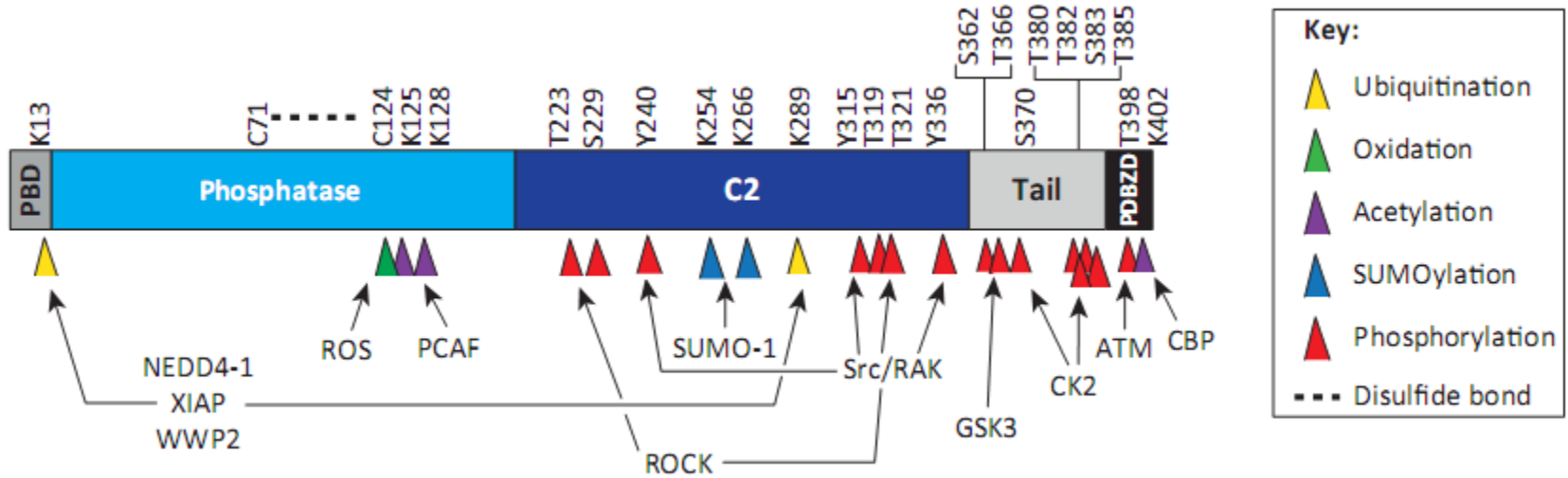


microRNA.org - Targets and Expression

[RNAdb 2.0](http://RNAdb.org) - A database of mammalian noncoding RNAs

Hopkins BD et al. *Trends Biochem Sci.* 2014
Song MS et al. *Nat Rev Mol Cell Biol.* 2012
Shi Y. et al. *J Cell Sci.* 2012

Post-translational modification of PTEN

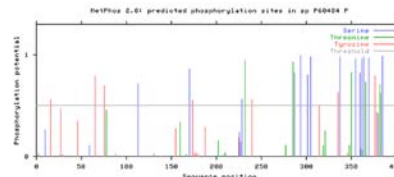
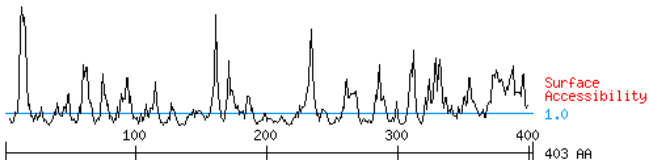


T/BS

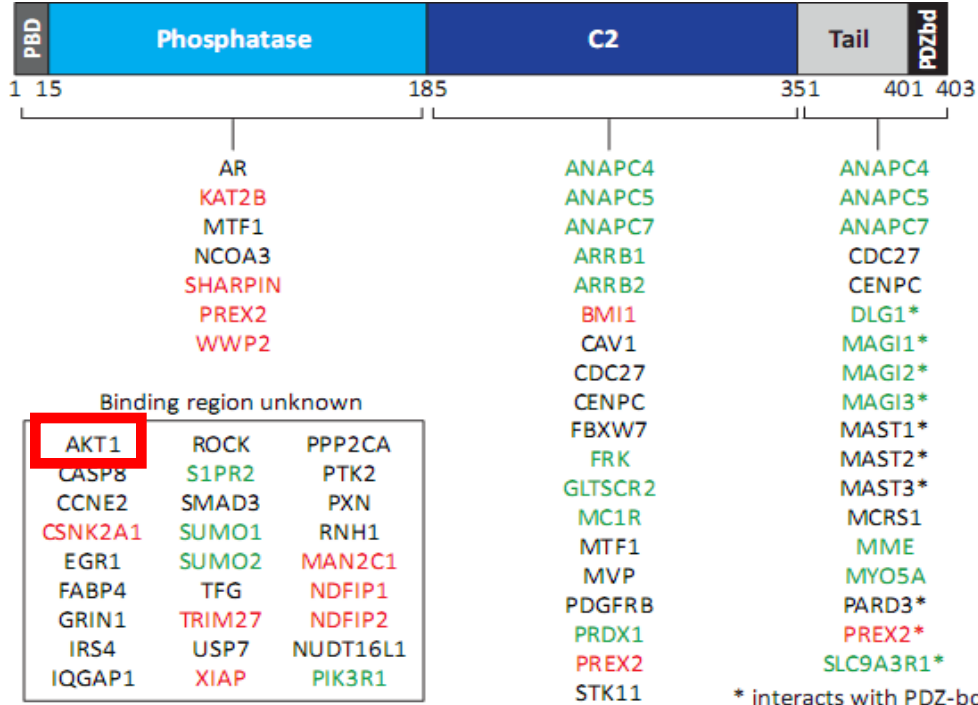
Center for Biological Sequence Analysis(CBS), Technical University of Denmark
Phospho.ELM, European Commission Community Research

Phosphorylation: NetPhos 2.0 Server, Motif Scan

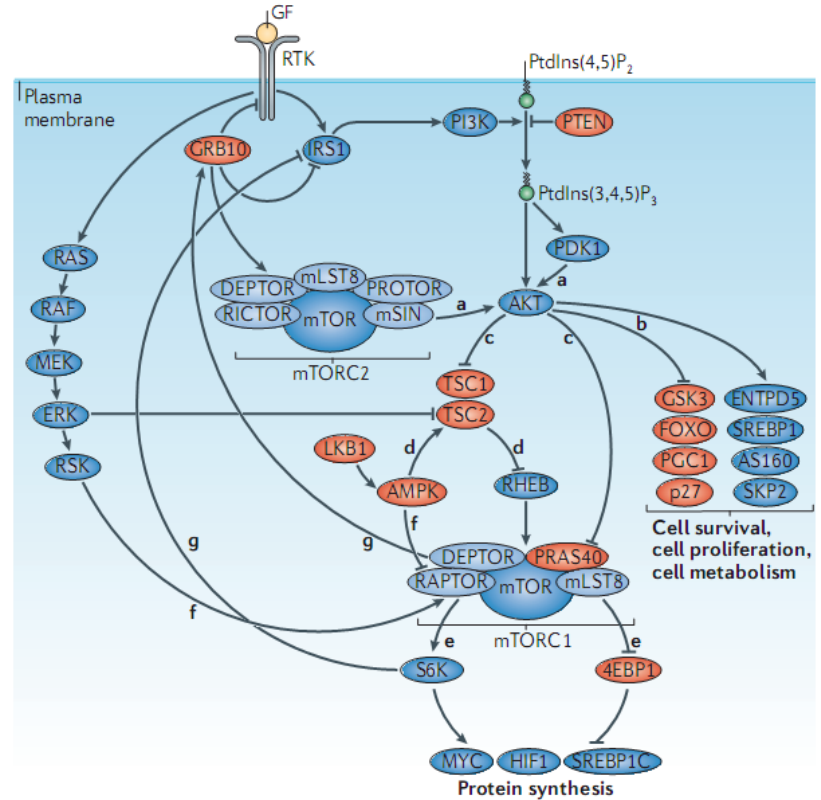
Methylation: Methylation Modification Prediction Server (2.0), BPB-PPMS



Reactome pathways



Interaction increases PTEN function (green)
Interaction decreases PTEN function (red)

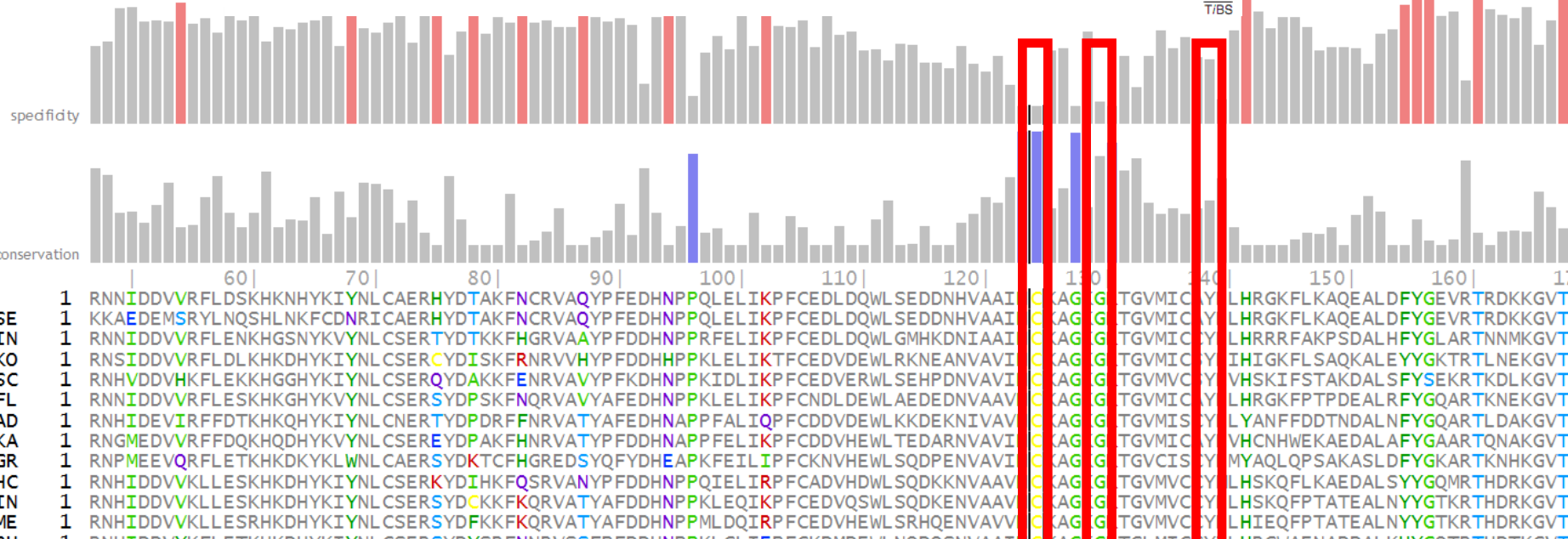
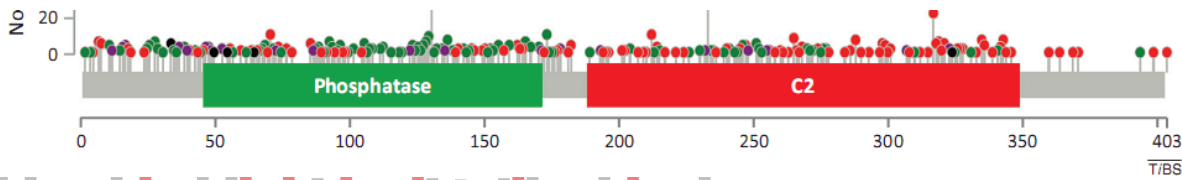


PTEN phosphatase activity deletion

Activity	Lipid	Protein
PTEN wt	+	+
PTEN C124S	-	-
PTEN G129E	-	+
PTEN Y138L	+	-

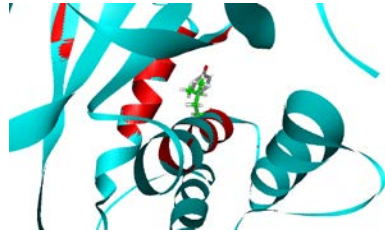
AA variant	Gene	MSA	PDB	Func. Impact
C124S	PTEN	msa	pdb	high
G129E	PTEN	msa	pdb	high
Y138C	PTEN	msa	pdb	medium

TCGA

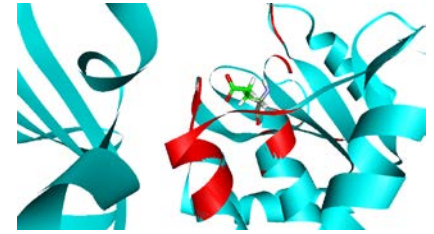


PTEN phosphatase activity mutation in cancer

Activity	Lipid	Protein
PTEN wt	+	+
PTEN Y138L	+	-

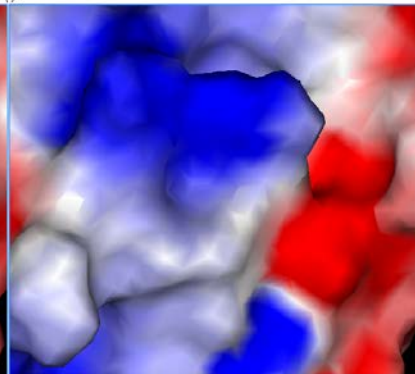
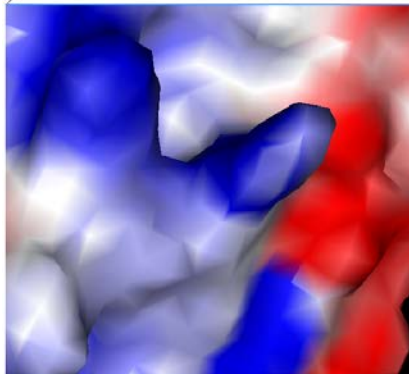
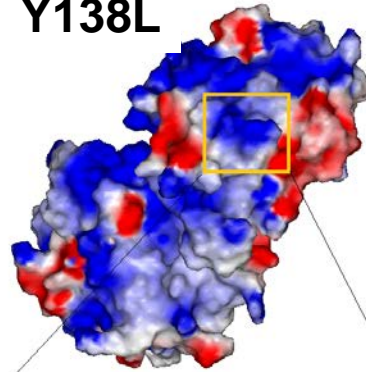
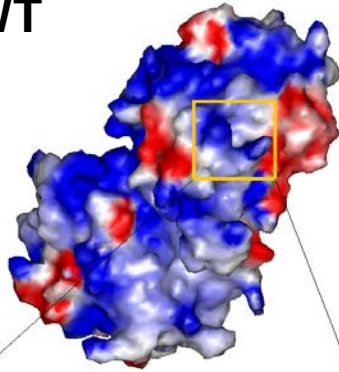


Activity	Lipid	Protein
PTEN wt	+	+
PTEN G129E	-	+



WT

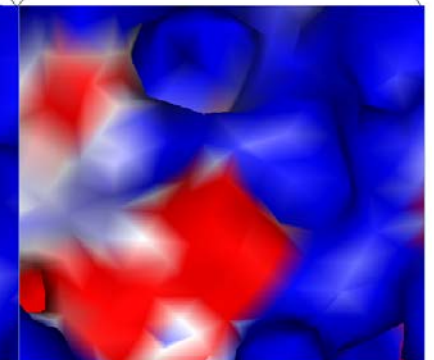
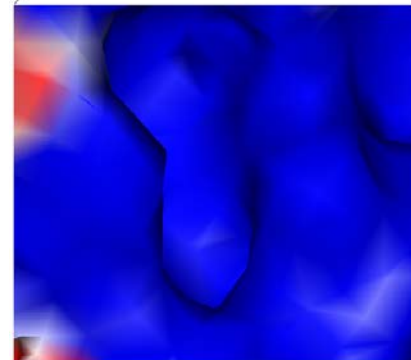
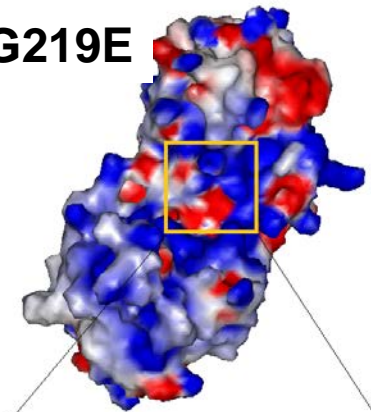
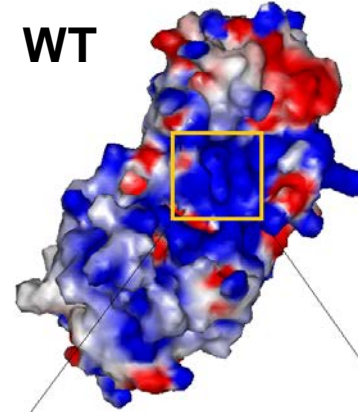
Y138L



-5.0 5.0

WT

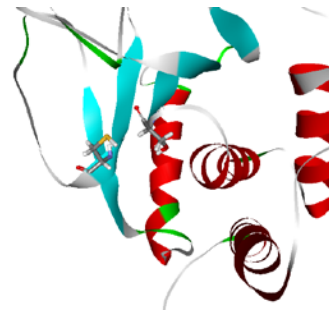
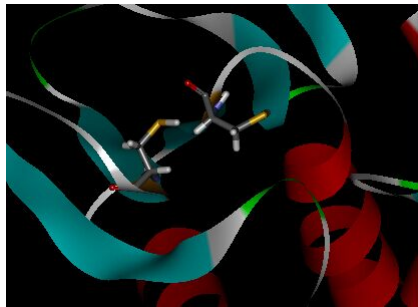
G219E



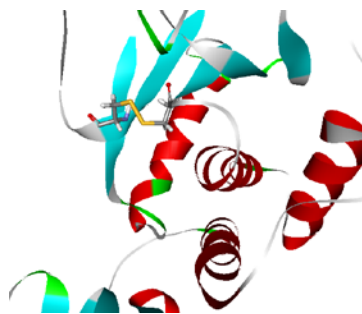
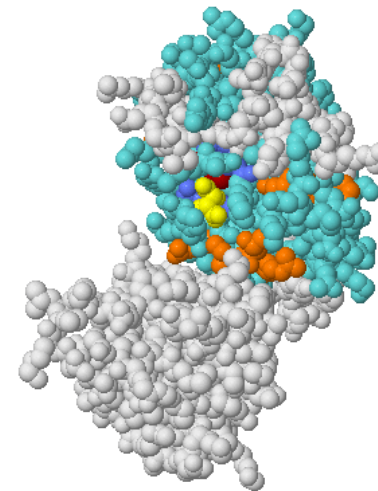
-5.0 5.0

How can C124S make PTEN catalytically inactive

PTEN_HUMAN/47-175 : RNNIDDVVRFLD**S**HKNH^vYKIYNLCAERHYDTAKFNCRVAQYPPFEDHNPPQLELIKPF
 midline : RNNIDDVVRFLD**S**HKNH^vYKIYNLCAERHYDTAKFNCRVAQYPPFEDHNPPQLELIKPF
 1d5r:A/34-162 : RNNIDDVVRFLD**S**HKNH^vYKIYNLCAERHYDTAKFNCRVAQYPPFEDHNPPQLELIKPF



specificity ■
 conserved ■
 neutral ■
 unmapped ■
 hetero ■
 variant ■



6.073A

Serine predictions				
Name	Pos	Context	Score	Pred
sp_P60484_P	10	KEIVSRNKR	0.263	.
sp_P60484_P	59	RFLDSKHKV	0.109	.
sp_P60484_P	113	DQWLSEDDN	0.720	*S*
sp_P60484_P	124	AAIHSKAGK	0.007	.

Acknowledgements

Dr. Jingchu Luo 罗静初教授

Project collaborations

Jie Cheng 程洁

Hong Chen 陈虹

Wei Wu 吴蔚

Ying Liu 刘莹

