The Chinese University of Hong Kong
Joint Graduate Seminar
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p53 - The Demons of the Guardian of the Genome

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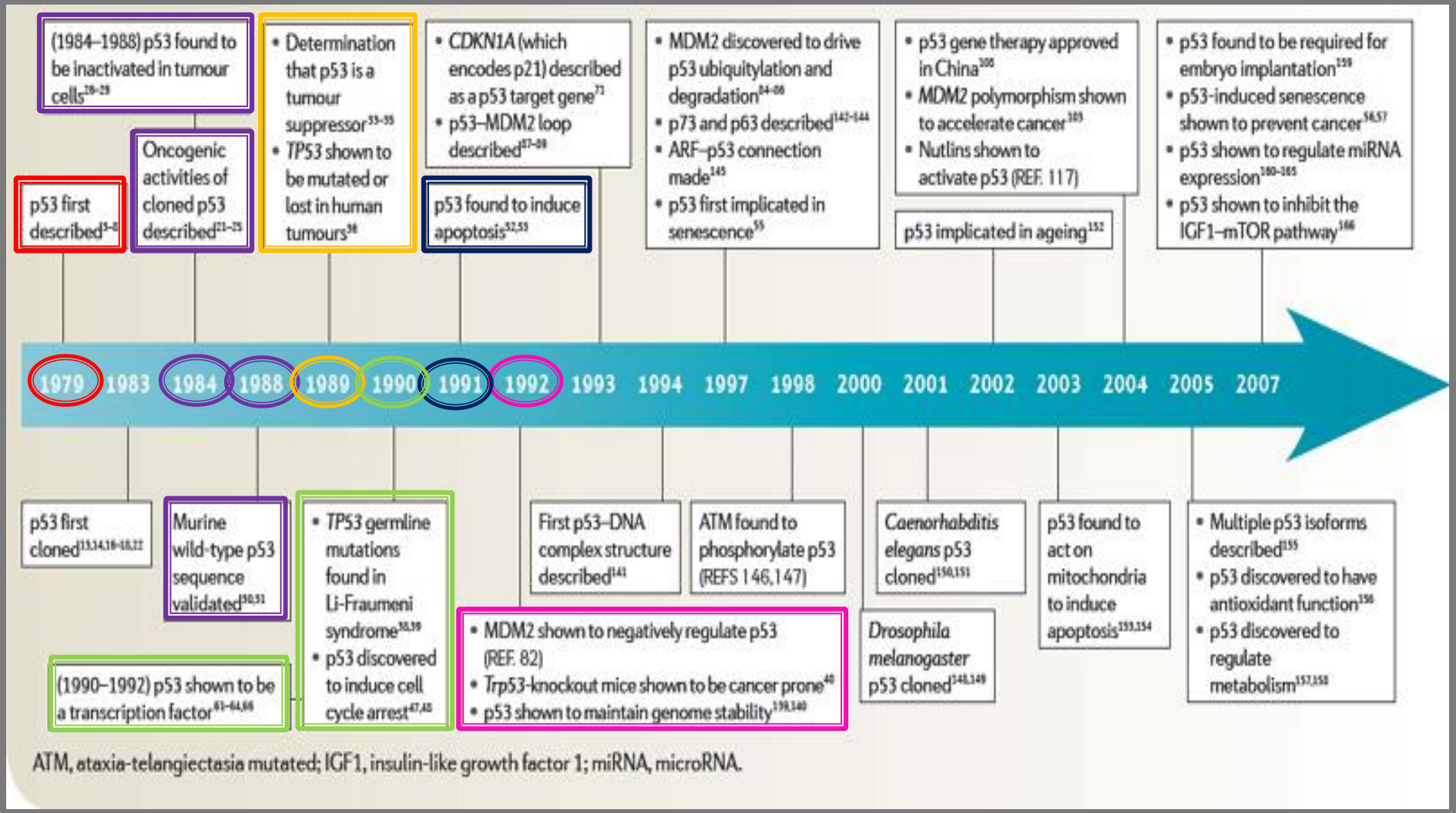
What is p53 ?

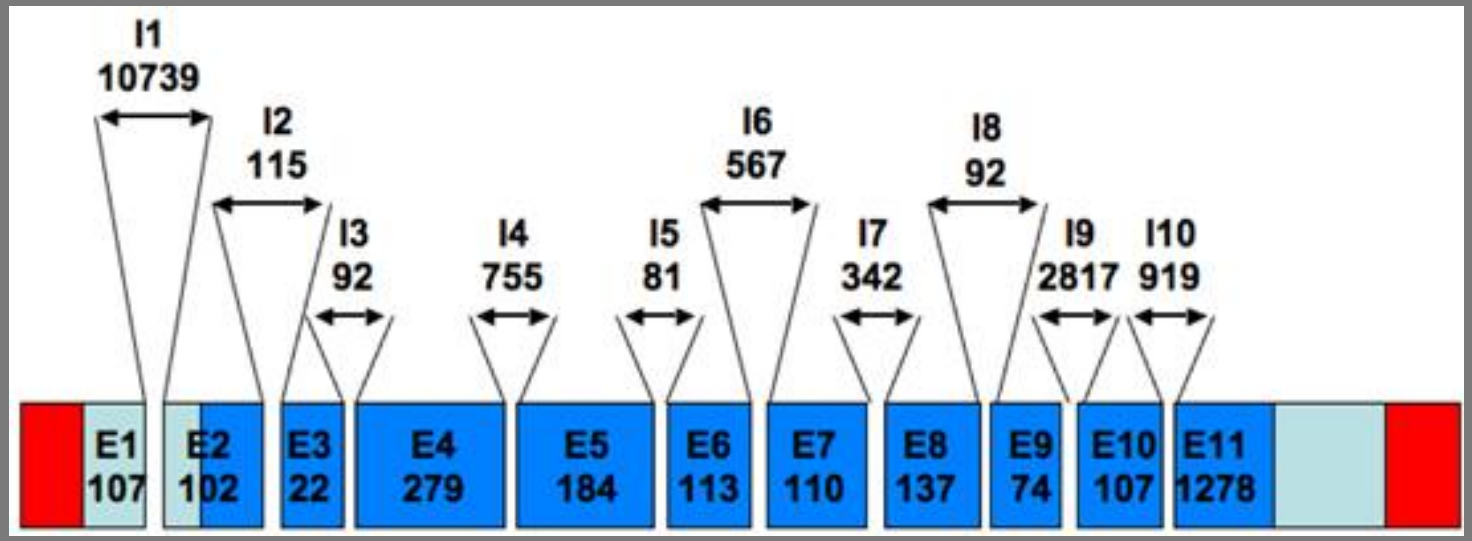
- **“Protein” 53 kilodaltons (a measure of protein size)**
- **Tumour suppressor protein**
- p53 is a **transcription factor** and **DNA binding protein** that plays a critical role in the network of signals that **control the fate of a cell**
- major p53 dependent responses; **DNA repair, cell cycle arrest, and programmed cell death or apoptosis**
- it is the **most commonly mutated tumor suppressor in** human cancers

History of p53



ATM, ataxia-telangiectasia mutated; IGF1, insulin-like growth factor 1; miRNA, microRNA.

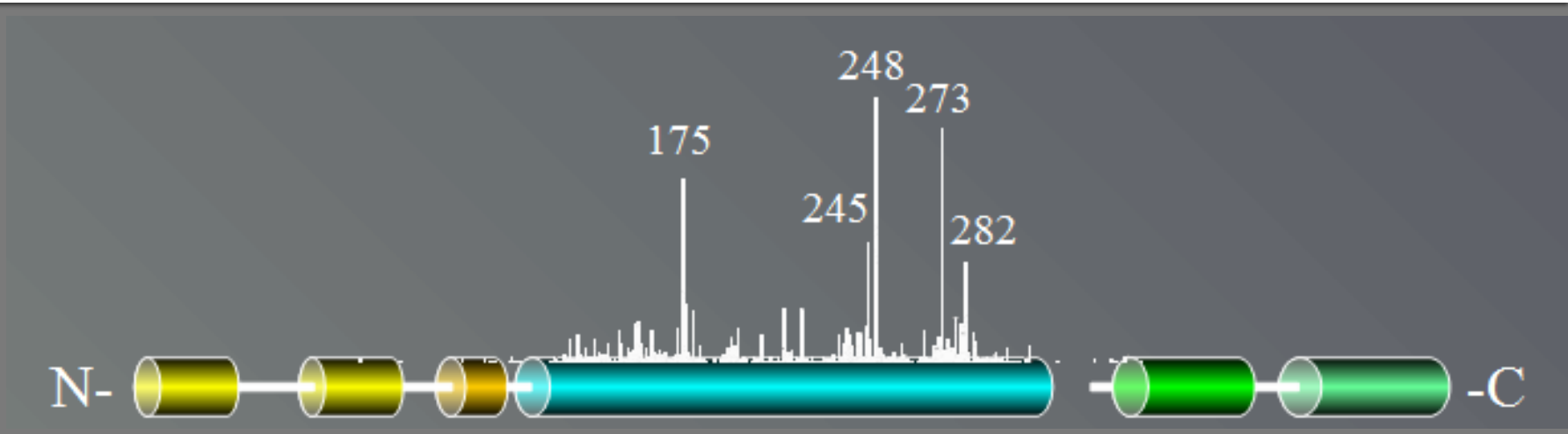
Organization of the Human TP53 Gene



- Located on chromosome 17
- 11 exons (blue), UTR (red)
- Spans 16-20 kb DNA
- Coding for an mRNA 2.2kb in length
- 393 amino acids

Adapted from: http://p53.free.fr/p53_info/p53_gene.html

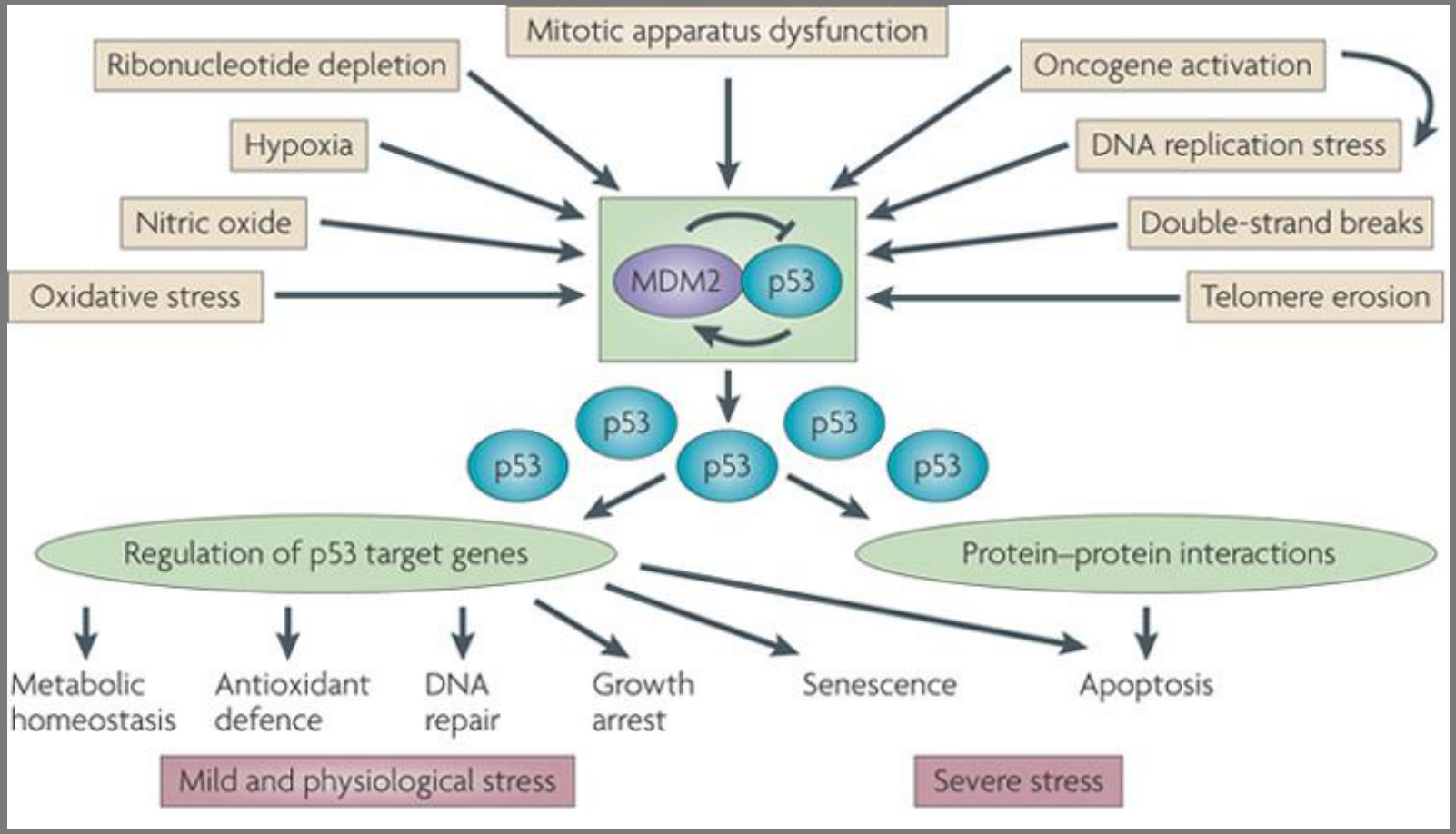
Missense Mutations are Clustered in the DBD



	Transactivation (1-42; 43-62)	Proline-rich (65-97)	DNA binding (102-292)	Oligomerisation (323-356)	Regulation (363-393)
Mutation frequency	1%	2.3%	80%	3.4%	0.3%
Missense mutations	50.8%	45.4%	82.1%	36.4%	72.7%

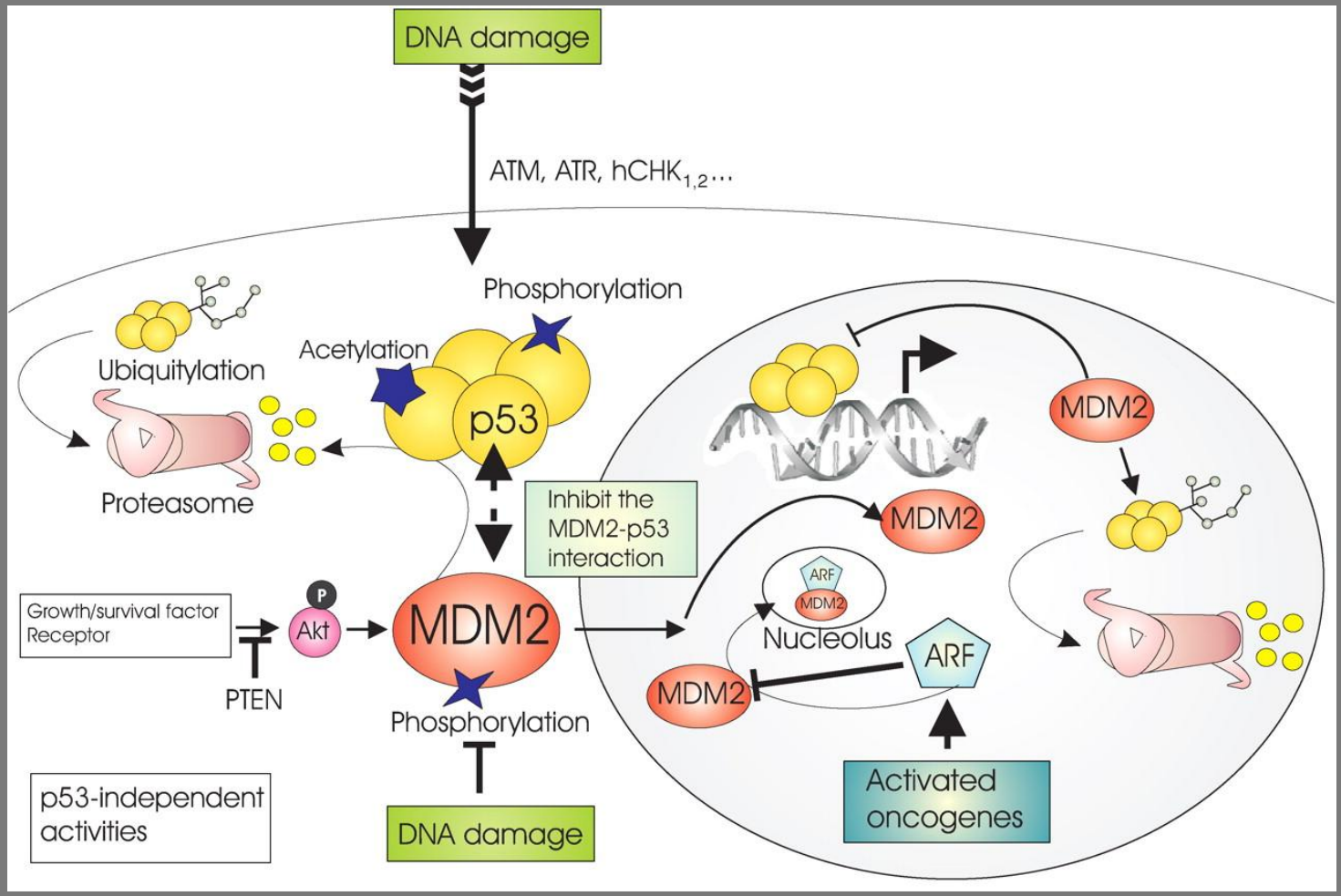
Adapted from: http://www-p53.iarc.fr/SlideShow2009_fichiers/texto.html

The p53 Pathway



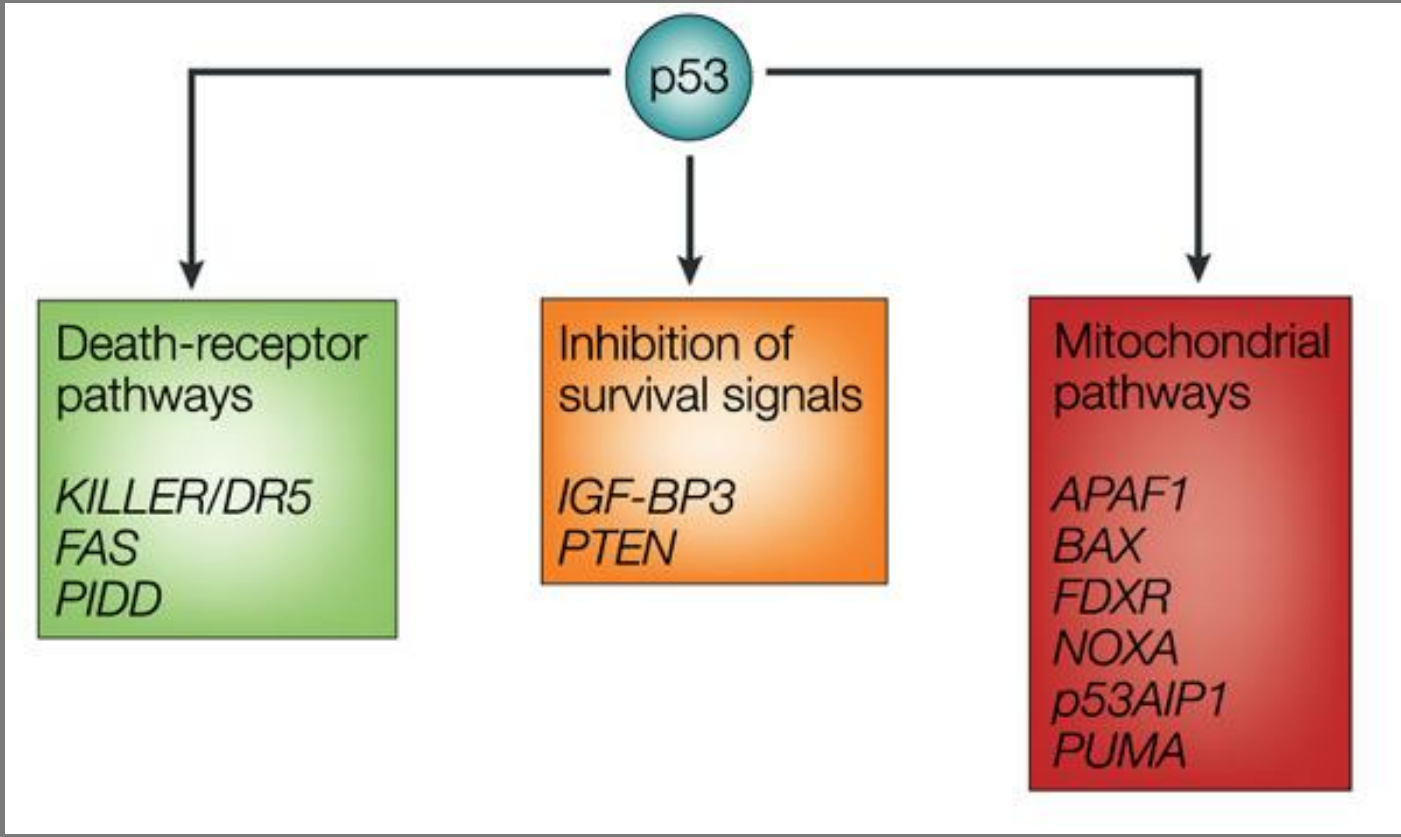
Adapted from Levine A et al., Nature Reviews Cancer **9,** 749-758 (October 2009)

Regulation of p53 by MDM2



Moll UT et al.,Mol Cancer Res. 2003 Dec;1(14):1001-8

Apoptotic Pathways Activated by p53



Vousden K et al., Nature Reviews Cancer **2**,594-604 (August 2002)

Examples of p53 Target Genes

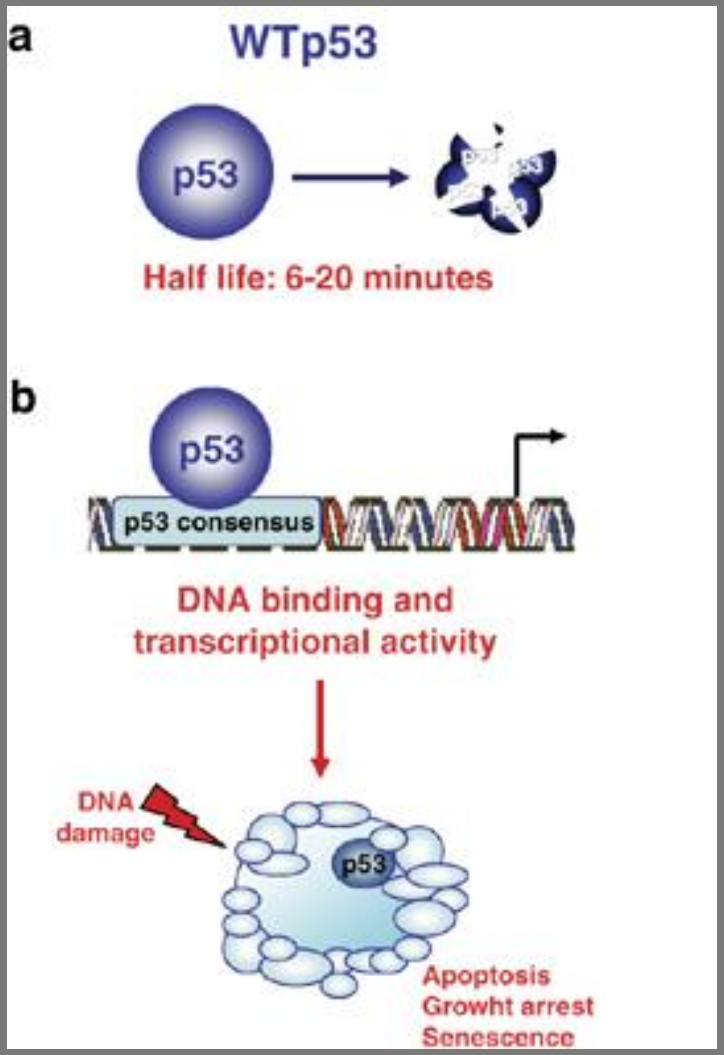
Gene name
Apoptosis and survival
APAF1
BAX
FAS
FDXR
IGF-BP3
KILLER/DR5
NOXA
p53AIP1
p53DINP1
PERP
PIDD
PIG3
PIG8/ei24
PTEN
PUMA
WIP1

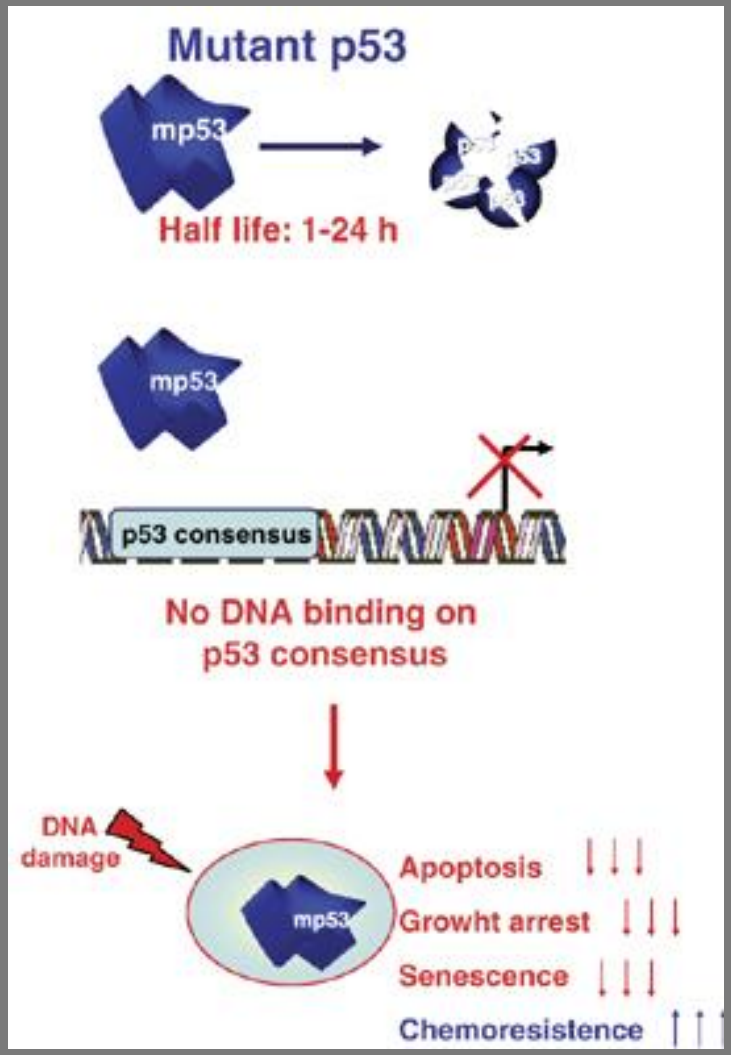
Cell-cycle arrest and DNA repair
BTG2
CDKN1A
14-3-3-σ
GADD45
p53R2

Angiogenesis and invasion
TSP1 (thrombospondin)
GD-AIF
BAI1
MMP2
MASPIN
KAI1

Autoregulation
MDM2
TP73
CCNG1

wt-p53 versus mutant p53: two sides of the same coin





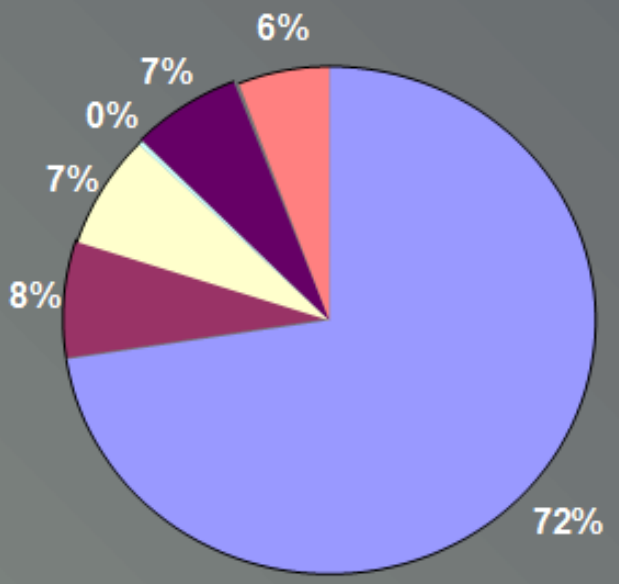
Strano S et al.,Oncogene (2007) **26,** 2212–2219.

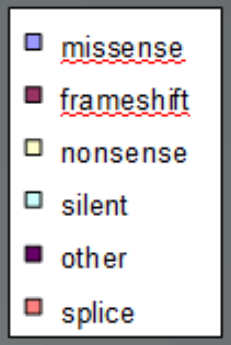
Majority of TP53 Mutations are Missense

Inherited: present in the germ line and detectable in both healthy and cancer cells

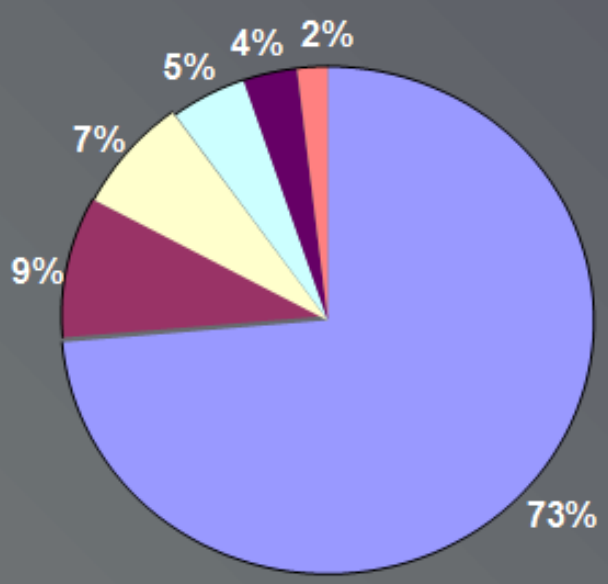
Somatic: acquired during development and present only cells undergoing clonal expansion

Germline





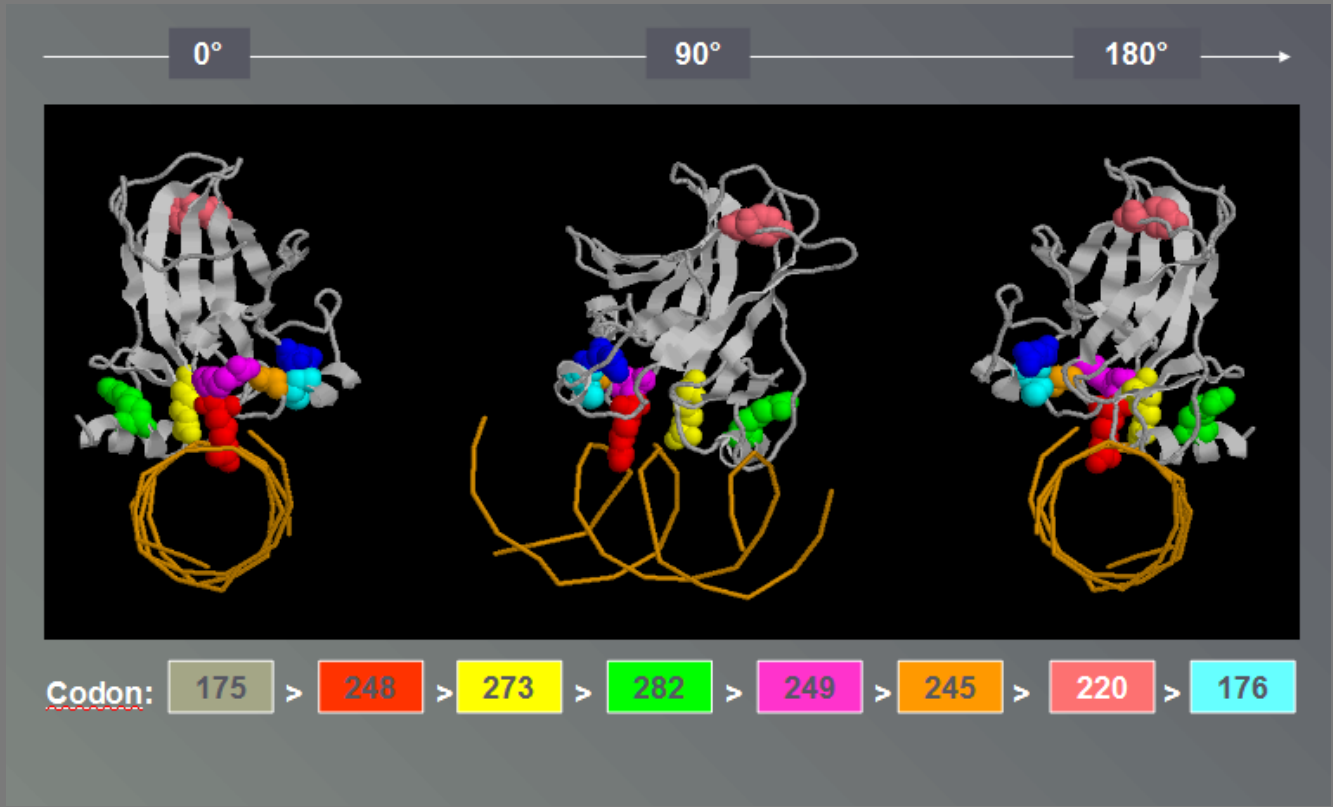
Somatic



Frequent p53 Mutations

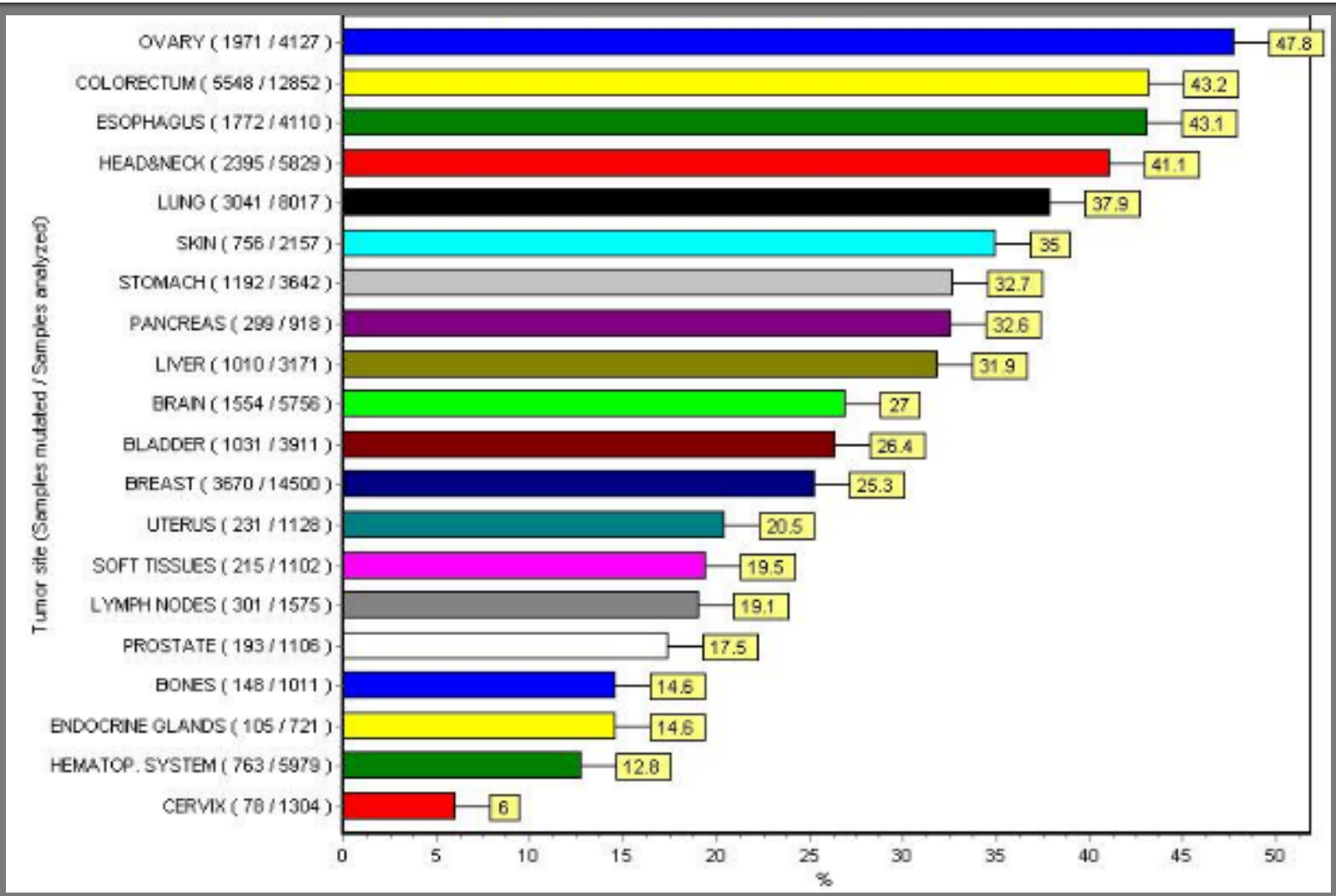
Codon
175*
245*
248#
249*
273#
282*

Most frequent mutations are within the loops that make contact with the DNA



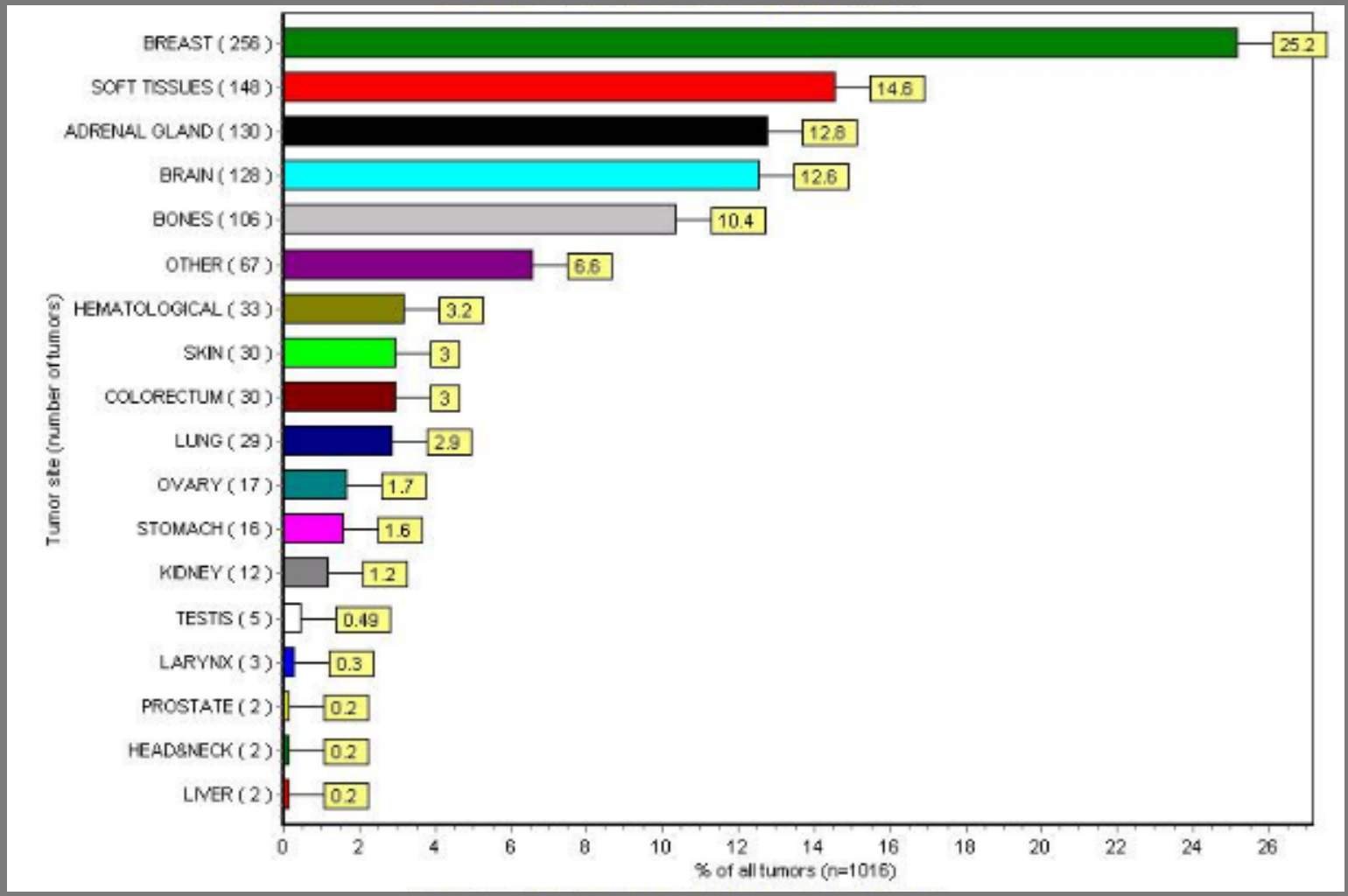
* Structural, # Contact

p53 Somatic Mutation are Frequent in Human Cancers



http://cshperspectives.cshlp.org/content/2/1/a001008.full.html#ref-list-1

p53 Germline Mutations Predispose to Several Types of Cancers



http://cshperspectives.cshlp.org/content/2/1/a001008.full.html#ref-list-1

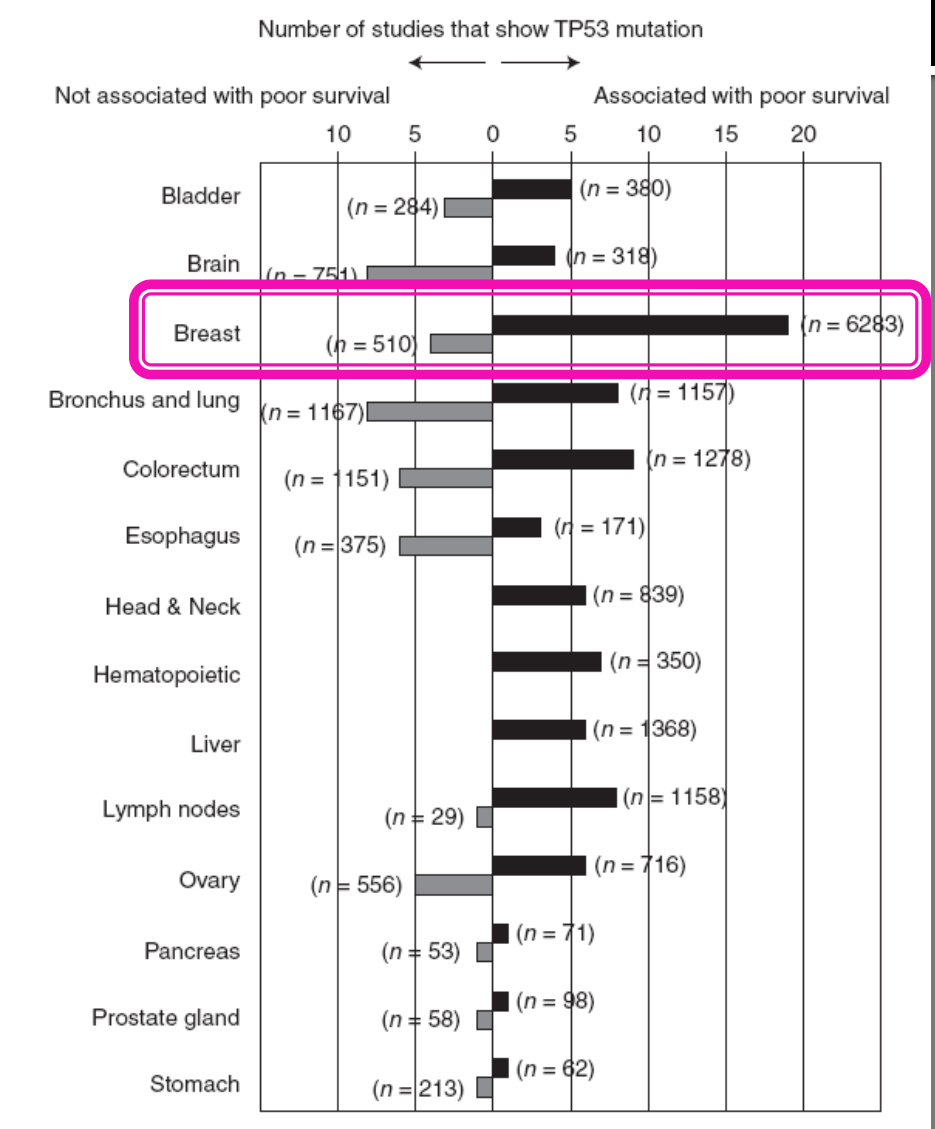
Breast Cancer Incidence

- **Most Common Cancer in Women Worldwide**

- Estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers)
- Ranks 2nd overall (10.9% of all cancers) (GloboScan 2008)
- Ranks 5th in among female cancer deaths worldwide

- In **Hong Kong** 2007, ranks 1st in most common cancer
- Ranks 3rd among female cancer deaths (Hong Kong Cancer Registry)

Number of studies that have shown an Association or Lack of Association of p53 mutation with poor survival

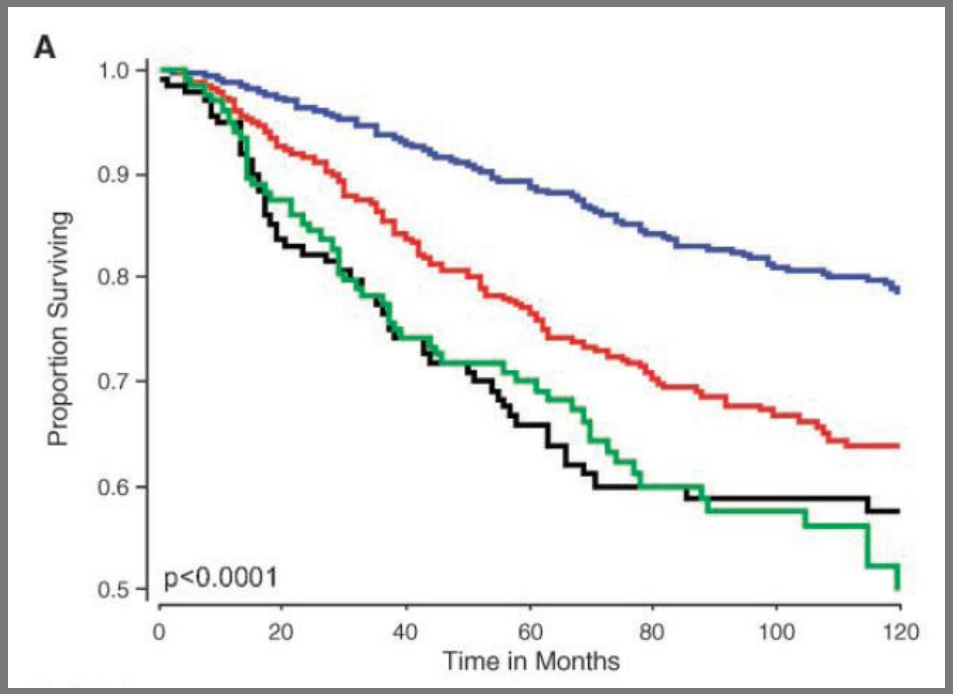


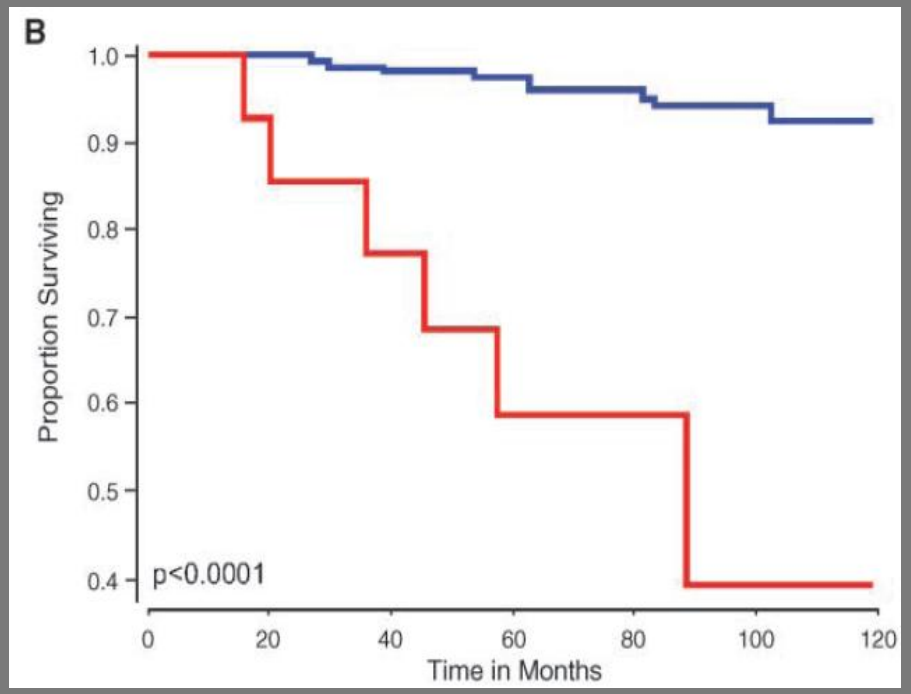
n = The cumulative number of patients in all cohorts reported in those studies for each cancer type

Robles Al et al., Cold Spring Harb Perspect Biol. 2010 Mar;2(3):a001016

Kaplan-Meier Survival Curves with Breast Cancer

- Stratified by p53 gene mutation status





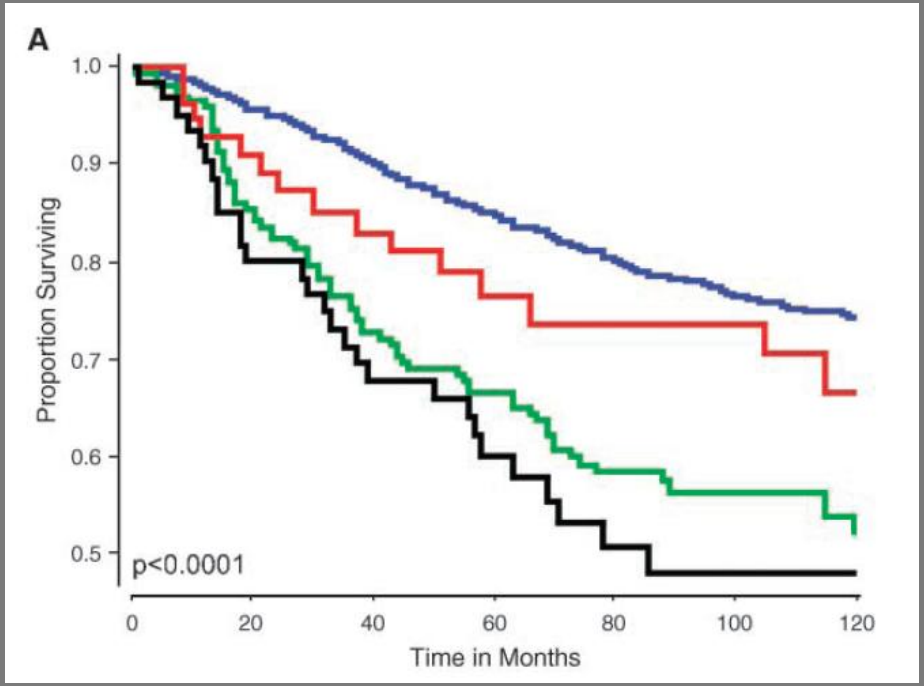
Blue =without mutation, PR +ve
Red = without mutation, PR –ve
Green= with mutation, PR +ve
Black = with mutation, PR-ve

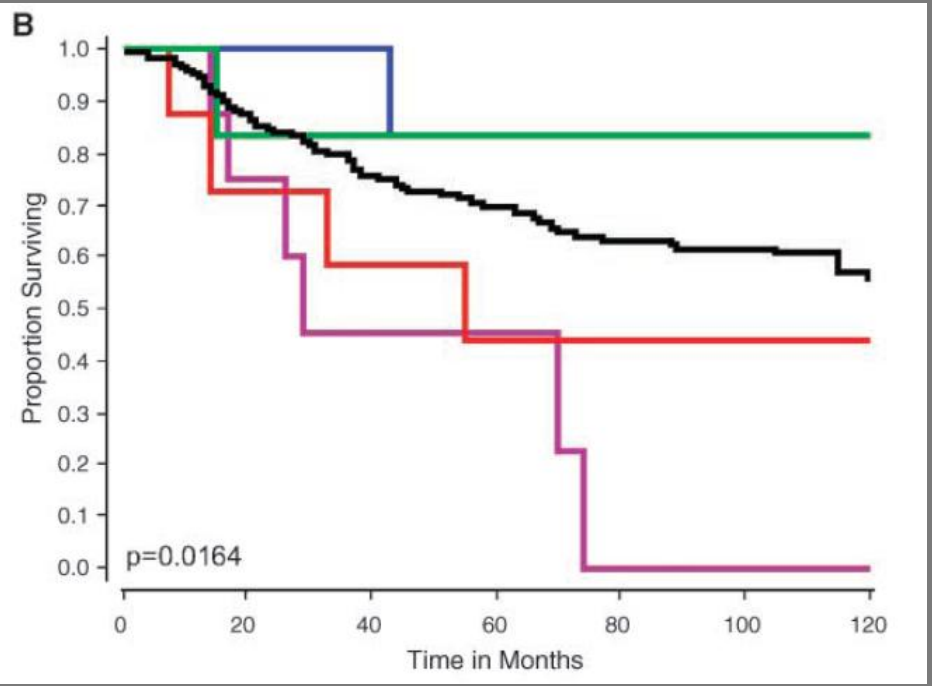
Favourable outcome, TG<3, TS<5, node –ve, ER/PR +ve
Blue =without mutation
Red = with mutation

Olivier M et al., Clin Can Res 2006; 12 (4) 1157-1167

Kaplan-Meier Survival Curves with Breast Cancer

- Stratified by the type of p53 gene mutation





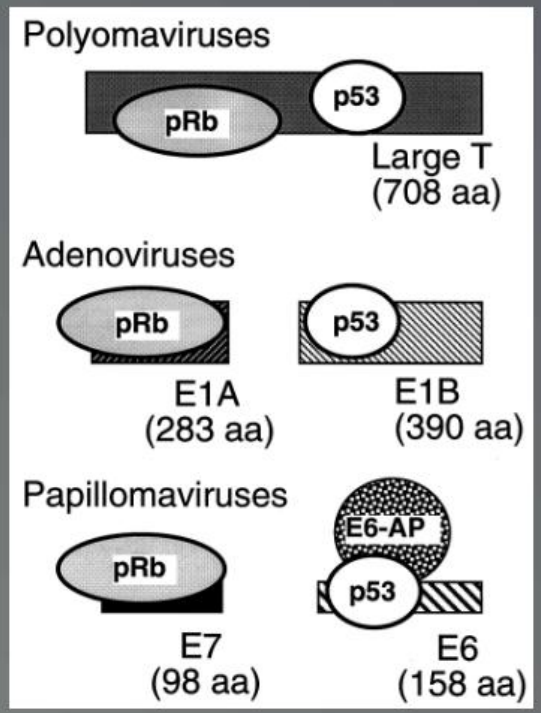
Blue =without mutation, or with silent mutation
Red = with missense mutation, outside DBS
Green= with missense mutation, in DBS
Black = with mutation, other than missense

Blue = with Y220C mutation
Green= with G245S
Black = with any other missense mutations
Red = with R248W
Purple = with any missense mutation at 179

Olivier M et al., Clin Can Res 2006; 12 (4) 1157-1167

In some Cancers, p53 is Targeted for Degradation

p53 Protein is Targetted by Viruses



p53 Protein Is Inactivated In Specific Types Of Cancers Where TP53 Mutations Are Unfrequent

Cancer	TP53 mutation frequency	Inactivating protein
Neuroblastoma	< 2%	Twist
Sarcomas	< 20%	Mdm2
Retinoblastoma	< 1%	Mdm4
Cervical cancer	< 10%	E6 (HPV)

To summarize…

- p53 plays a critical role in controlling signalling pathways and keep improper cell proliferation and tumour formation in check
- p53 and it's downstream genes consist of a complicated gene network
- functional inactivation seriously compromises the cellular processes resulting in decreased apoptosis and loss of cell cycle control
  → tumourogenesis

To summarize…

- Mutant p53 proteins not only represent a mere **LOSS** of wt-p53 function
- But **GAIN** additional oncogenic functions to promote to the development, maintenance and spreading and resistance to anti-cancer treatment of a tumour
- Increasing the understanding of p53 mediated pathways will provide intervention and therapeutic agents to awaken the sleeping guardian and may hold the key to more successful therapy for many cancers

The End