The p53 tumor suppressor protein

p53 is a major tumor suppressor

1. Nearly all human cancers have either mutated p53 or altered p53 pathway genes

2. Cancer-prone Li-Fraumeni families harbor germ line mutant p53 alleles

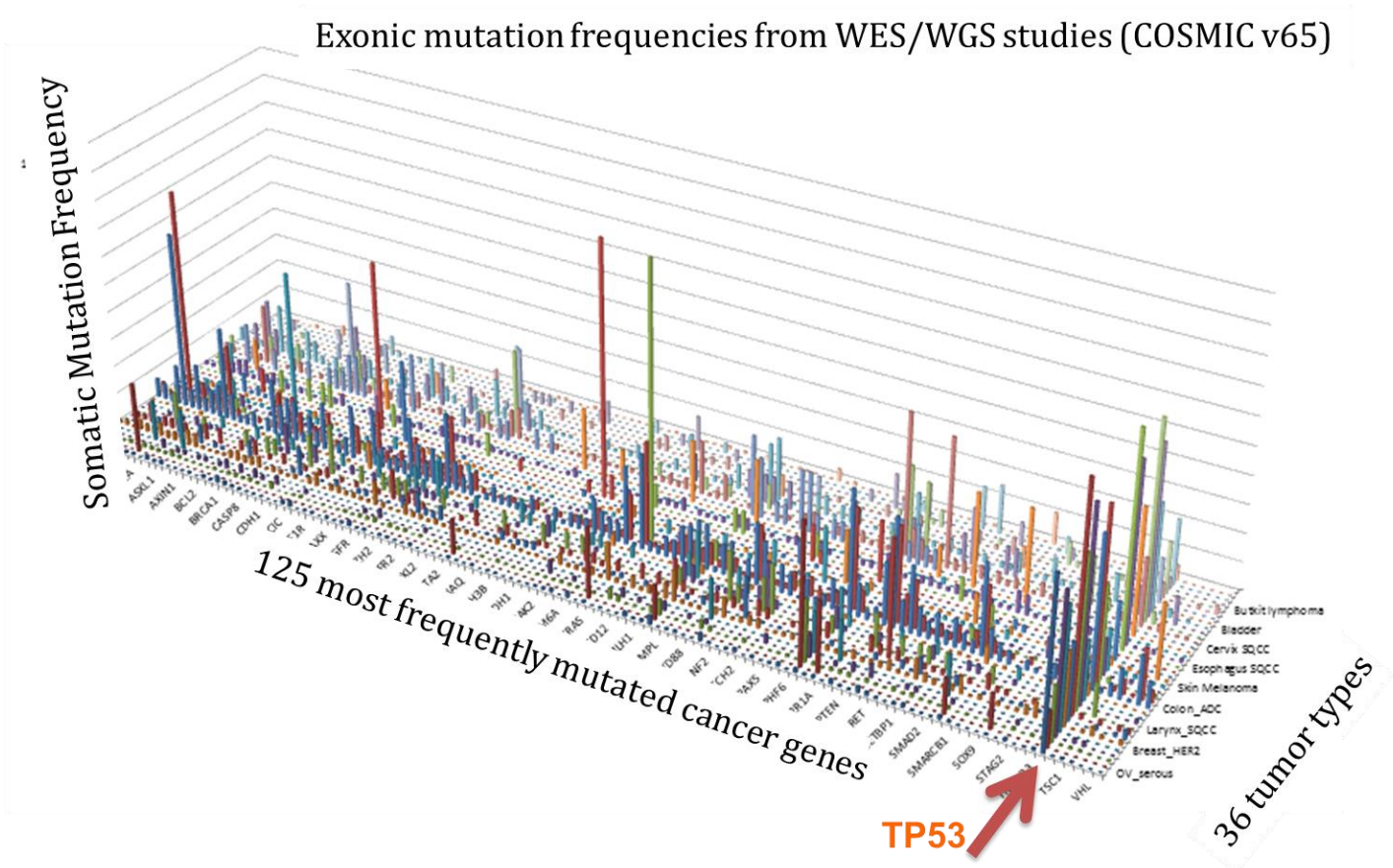
3. p53-null mice develop tumors with 100% frequency

4. Wild-type p53 can suppress the ability of oncogenes to transform cells

5. Several cancer-causing viruses have evolved mechanisms to functionally counteract p53

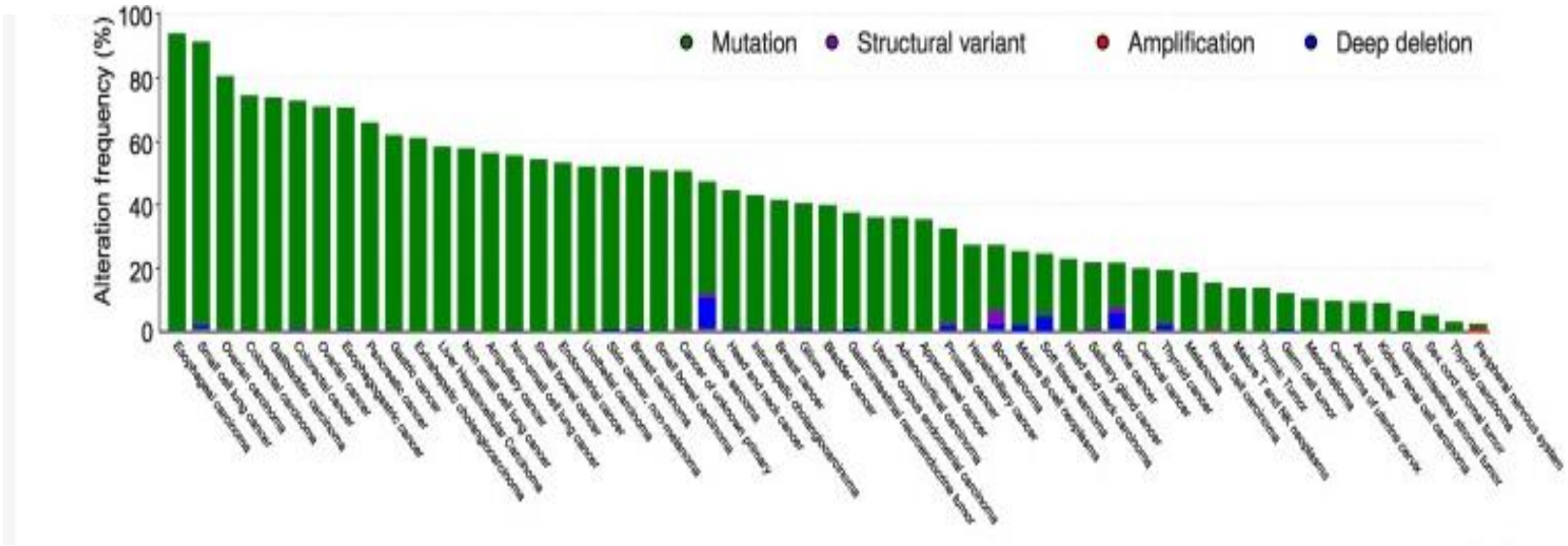
1. Nearly all human cancers have either mutated p53 or have altered p53 pathway genes

TP53 Somatic Mutations in the Genome Era

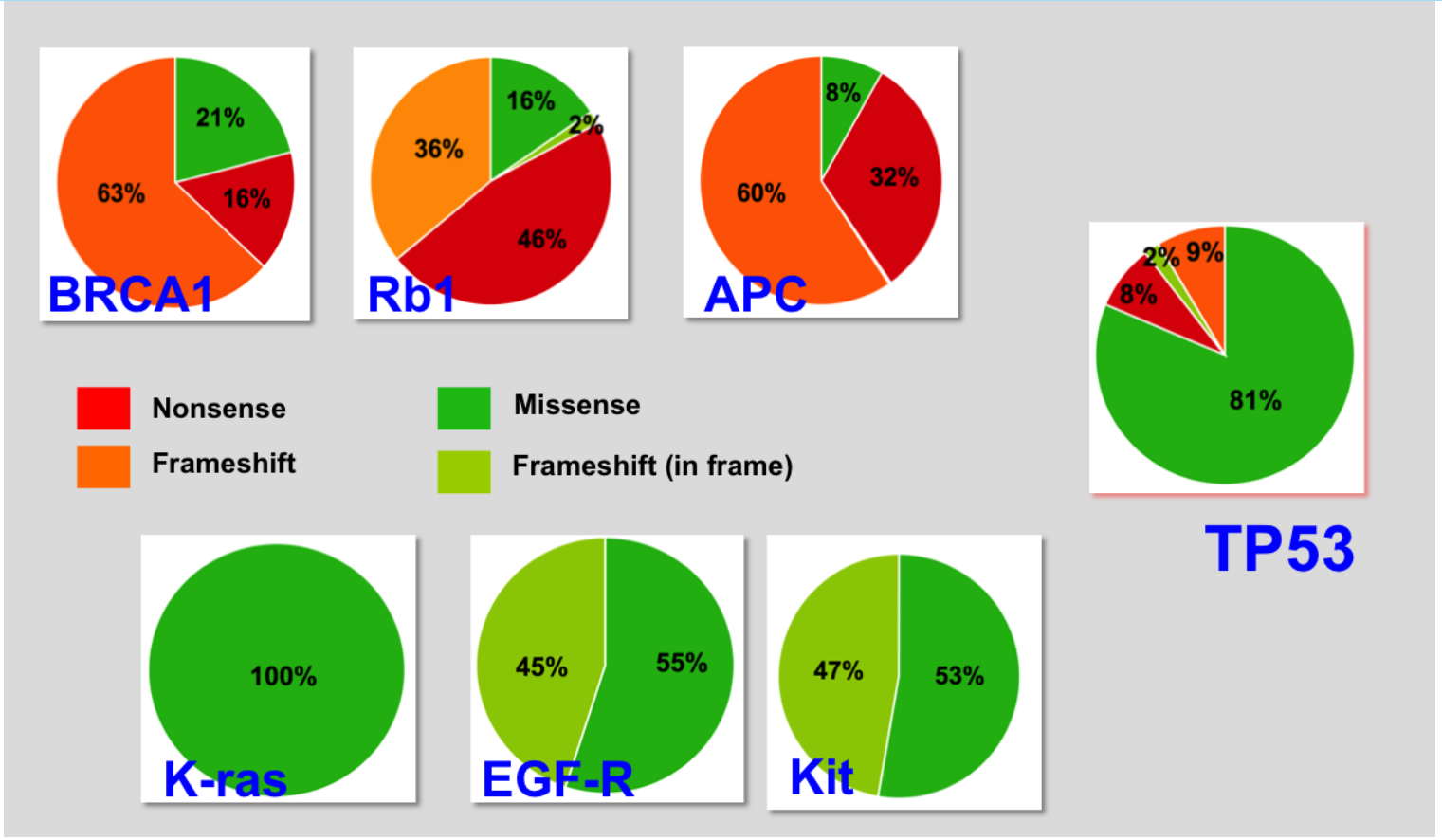


Courtesy Magali Olivier (IARC Lyon) **http://p53.iarc.fr**

p53 mutation frequency varies with tumor type

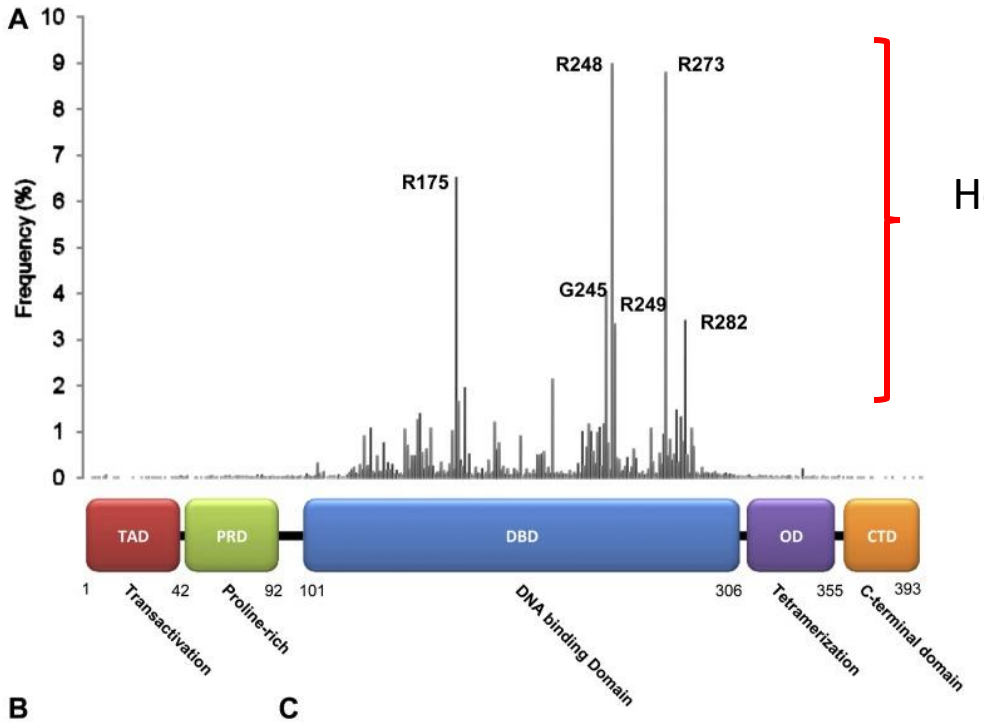


p53 mutations are different from those of other tumor suppressors



https://p53.fr/tp53-information/historical-aspects/14-informations/story/38-mutant-tp53-an-oncogene

p53 protein domains and tumor-derived missense mutations



Hotspot mutations

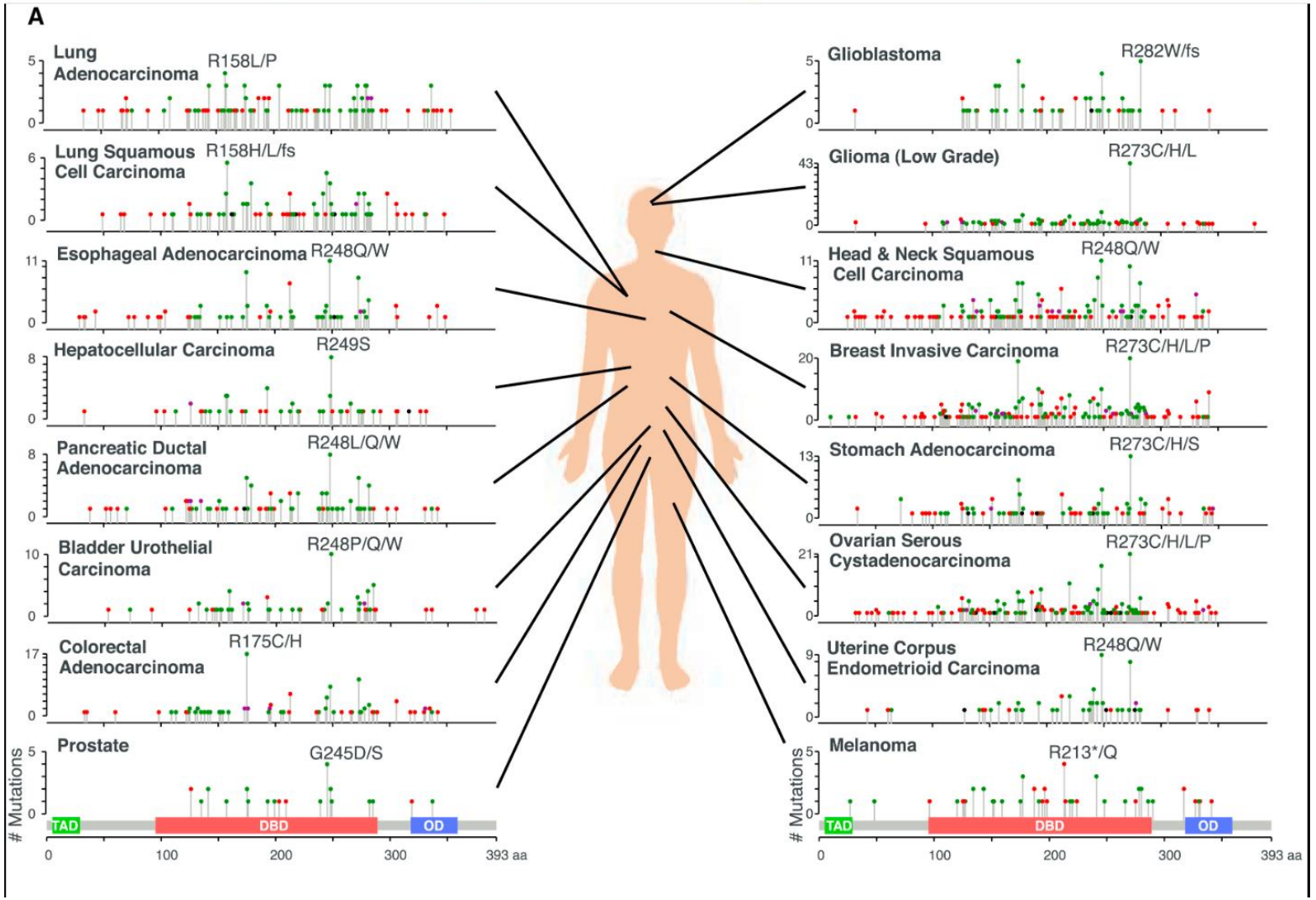
B

Amino Acid Residue	Frequency of Alteration
248	7.0%
273	6.7%
175	5.1%
245	3.3%
249	2.9%
282	2.9%

C

Mutation	Overall Frequency	Wild-Type Codon	Mutant Codon	CpG	Class
R175H	4.6%	CGC	CAC	Yes	Conformation
R248Q	3.5%	CGG	CAG/CAA	Yes	DNA Contact
R273H	3.1%	CGT	CAT	Yes	DNA Contact
R248W	2.8%	CGG	TGG	Yes	DNA Contact
G245S	2.8%	GGC	AGC	Yes	Conformation
R273C	2.7%	CGT	TGT	Yes	DNA Contact
R282W	2.4%	CGG	TGG	Yes	DNA Contact
R249S	1.8%	AGG	AGT	No	Conformation
G245D	0.68%	GGC	GAC	No	Conformation

TP53 mutation distribution for 16 cancer types



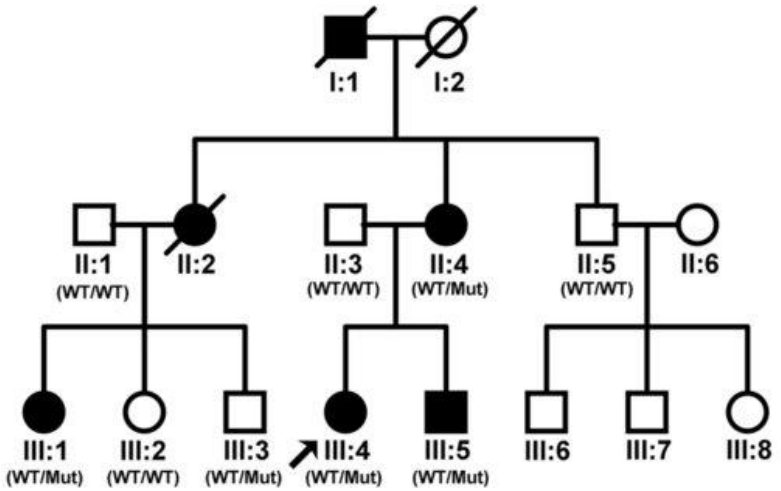
Kastenhuber and Lowe Cell 2017

2. Cancer-prone Li-Fraumeni Syndrome (LFS) families harbor germ line mutant pa53 alleles

Li-Fraumeni Syndrome: deadly inheritance of mutant p53 alleles

Frederick Li and Joseph Fraumeni, 1991.

A



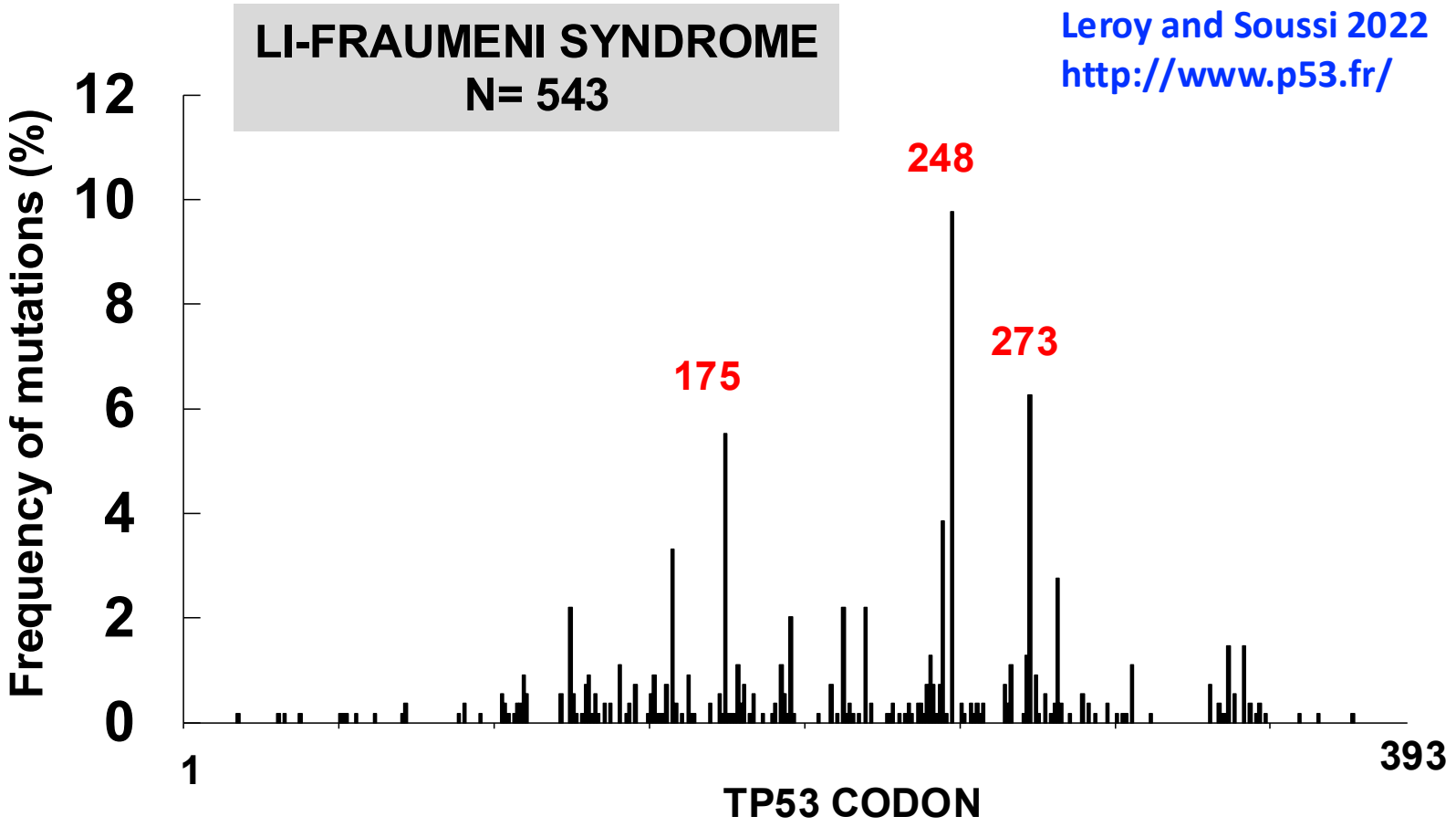
B

ID	Age in 2014	Tumors
I:1	Deceased	Liver mass at 46 y
II:1	40 y	None
II:2	Deceased	Breast cancer at 32 y
II:3	35 y	None
II:4	35 y	Breast cancer at 34 y
II:5	30 y	None
III:1	13 y	Adrenal pheochromocytoma at 3 y, and kidney cyst at 12 y
III:2	10 y	None
III:3	6 y	No
III:4	5 y	Medulloblastoma at 5 y
III:5	3 y	Choroid plexus papilloma at 3 y

1969: Li and Fraumeni report the existence of a familial cancer predisposition syndrome
1990: Germ-line mutations in p53 discovered in LFS patients (Malkin et al., Science, 1990; Srivastava et al Nature 1990)

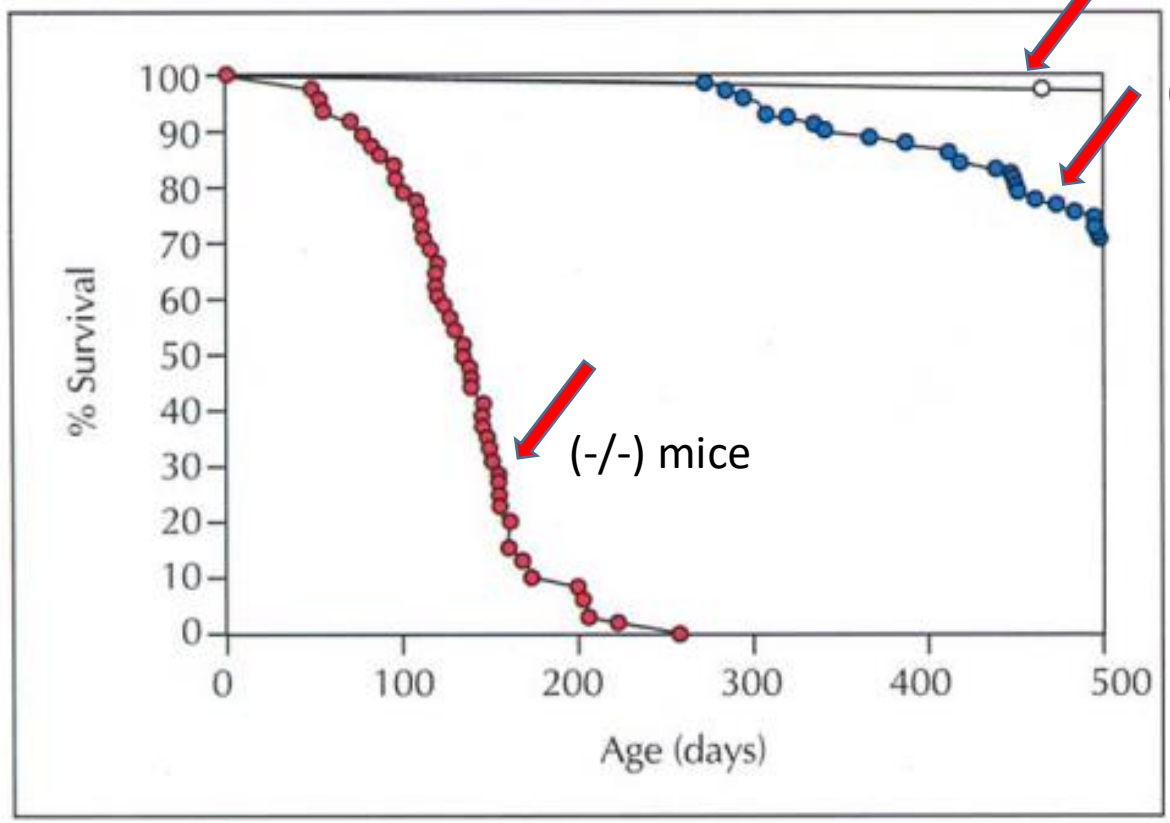
The mutational spectrum of p53 missense mutations in LFS patients is roughly similar to that in sporadic cancer cases

The UMD TP53 database
Leroy and Soussi 2022
http://www.p53.fr/



3. p53-null mice develop tumors with 100% frequency

Loss of p53 predisposes mice to cancer (~75% lymphomas and 25% sarcomas)



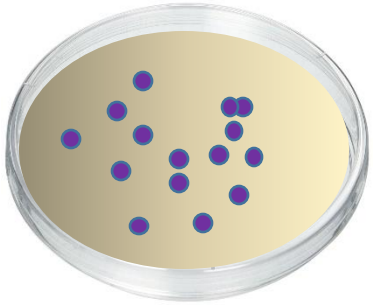
Jacks T et al., Curr. Biol. 1994

4. Wild-type p53 can suppress the ability of oncogenes to transform normal cells

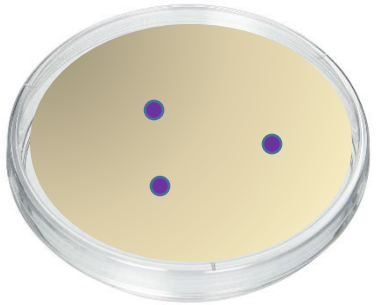
5. Wild-type p53 can suppress the ability of oncogenes to transform normal cells

Control (empty vector)
or
WT p53

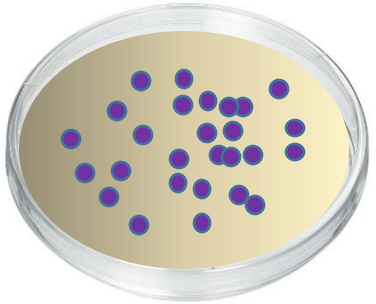
Ras + Myc
or
E1a + Ras



Ras + Myc + WT p53
or
E1a + Ras + WT p53



Ras + Myc + mutant p53
or
E1a + Ras + mutant p53

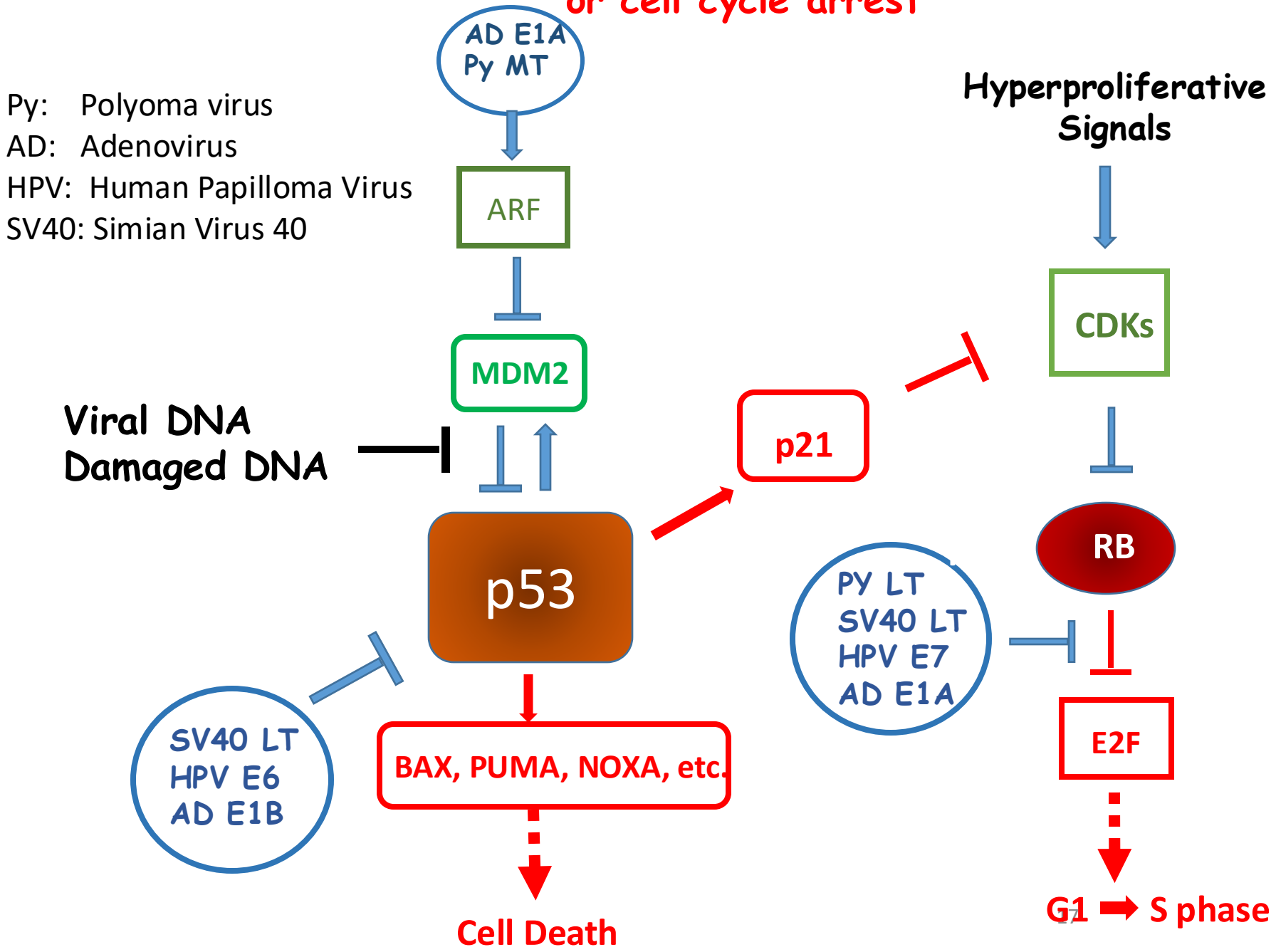


Finlay et al., Cell 1989
Eliyahu et al., PNAS 1989

5. Several cancer-causing viruses have evolved mechanisms to functionally counteract p53

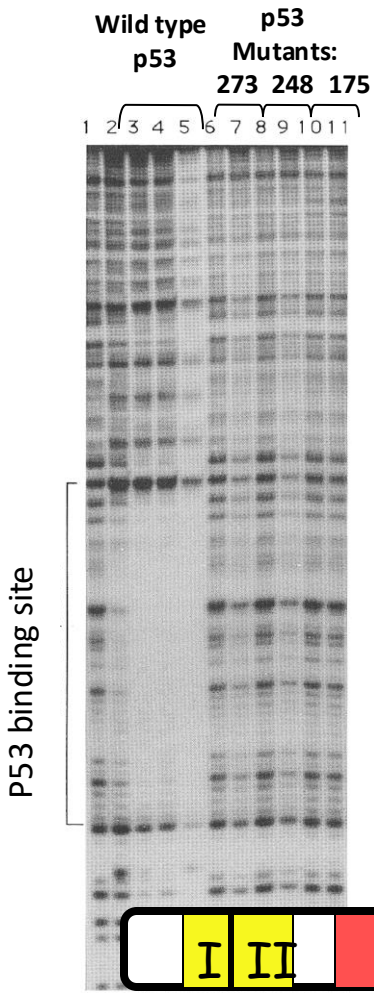
DNA Viruses prevent p53 and RB from producing cell death or cell cycle arrest

Py: Polyoma virus
AD: Adenovirus
HPV: Human Papilloma Virus
SV40: Simian Virus 40

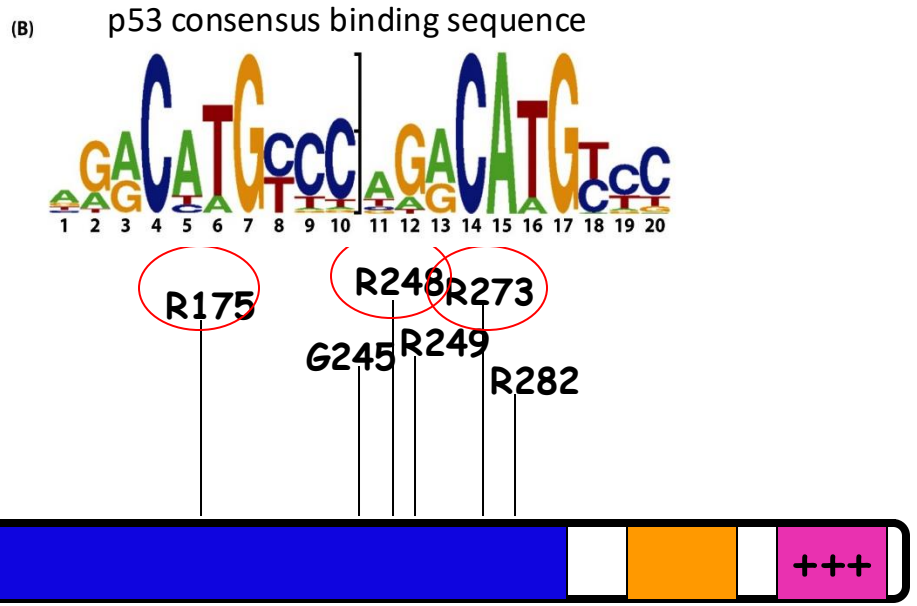


How does p53 work?

DNase I footprint:

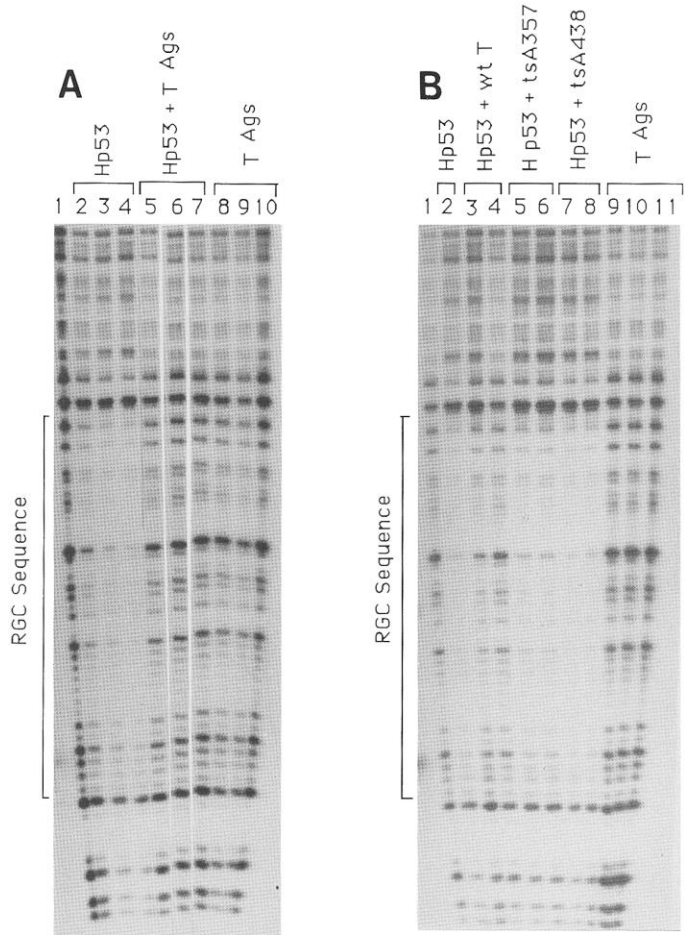


Wild-type but not tumor-derived mutant forms of p53 bind specifically to DNA



Wild-type but not conditionally transformation defective SV40 T antigen prevents p53 from binding specifically to DNA

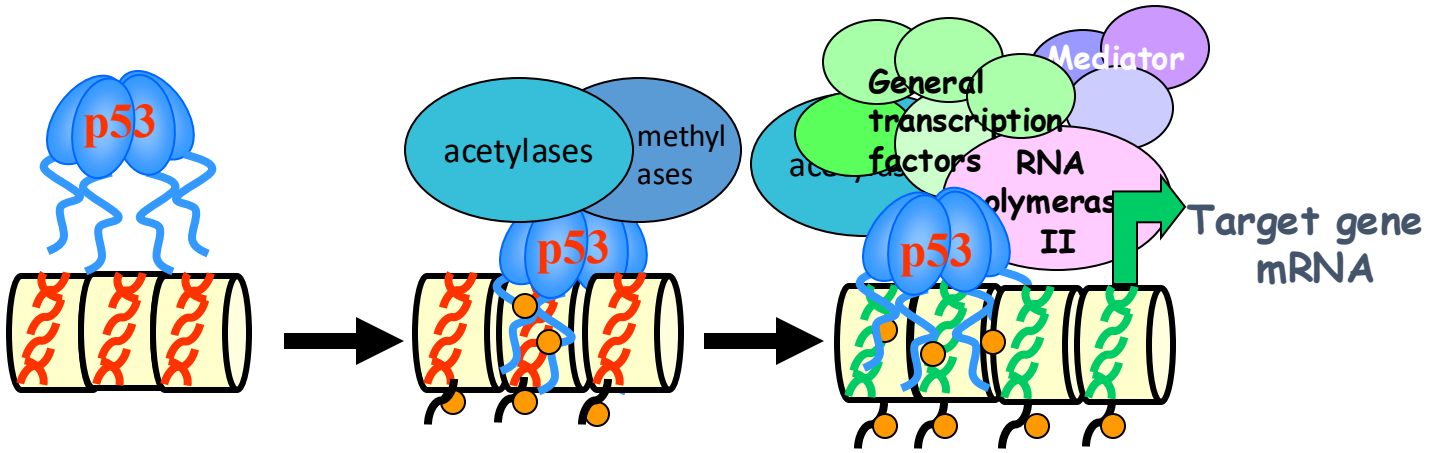
DNase I footprints:



33°C 41°C

Bargonetti, Reynisdottir et al., Genes Dev 1992

Stepwise activation of p53 target genes

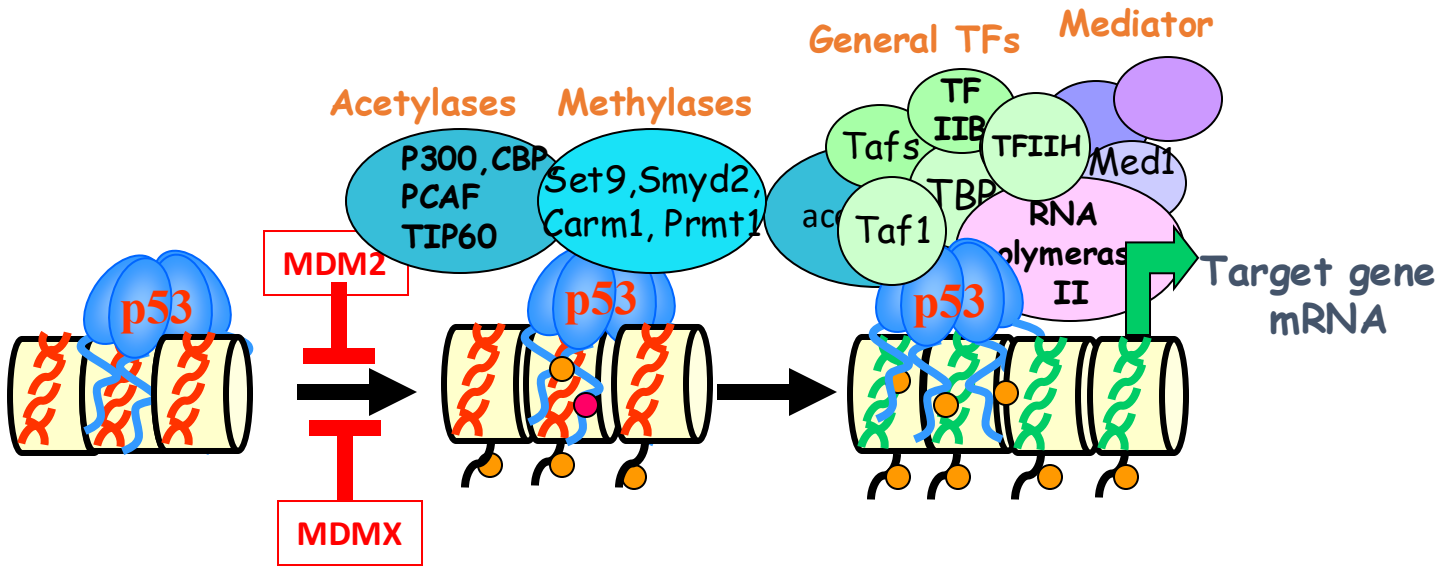


Location and binding to cognate sites

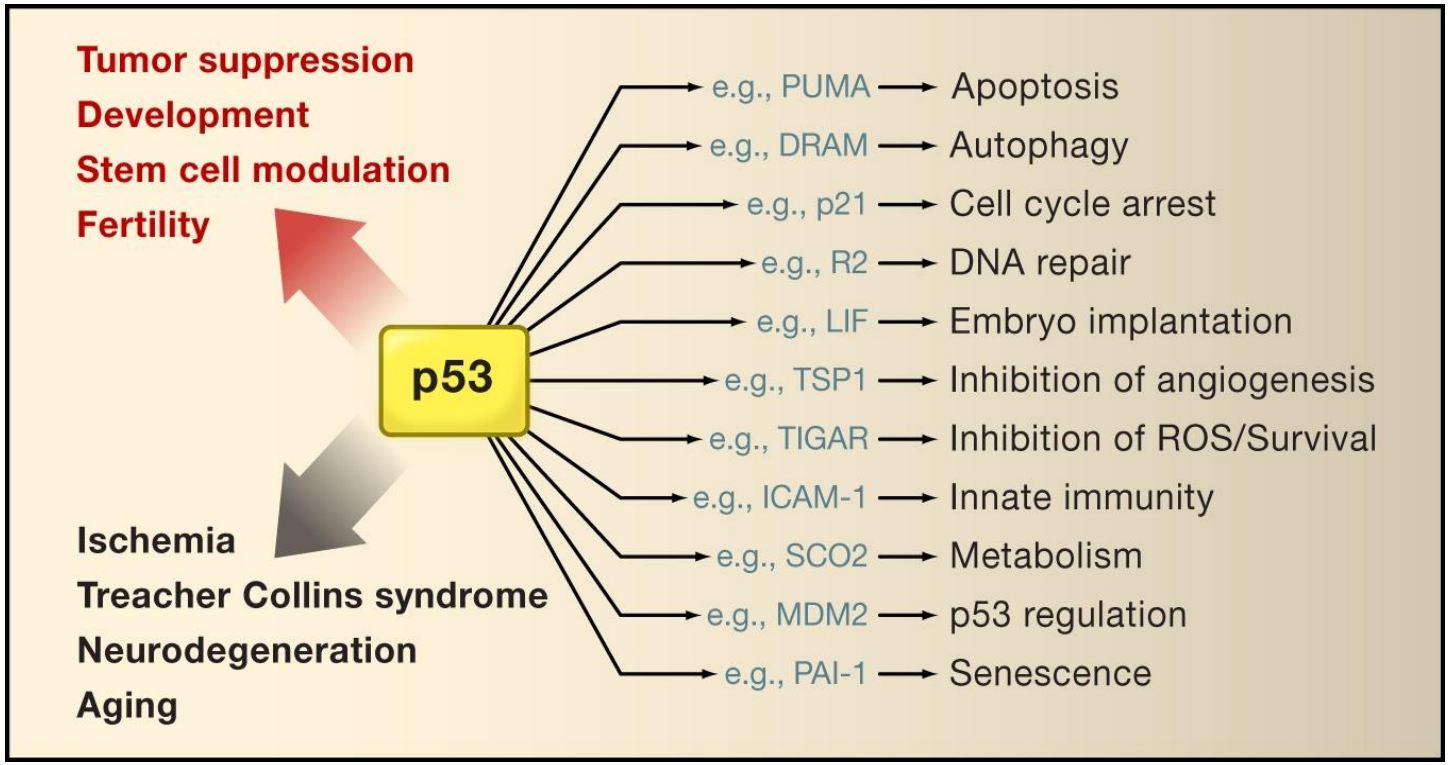
Recruitment of histone and p53 modifying enzymes

Recruitment of General Transcription Factors, Mediator, and RNA Pol II

p53 recruits many factors involved in chromatin and transcriptional regulation



p53 regulates multiple cellular processes: too little vs. too much

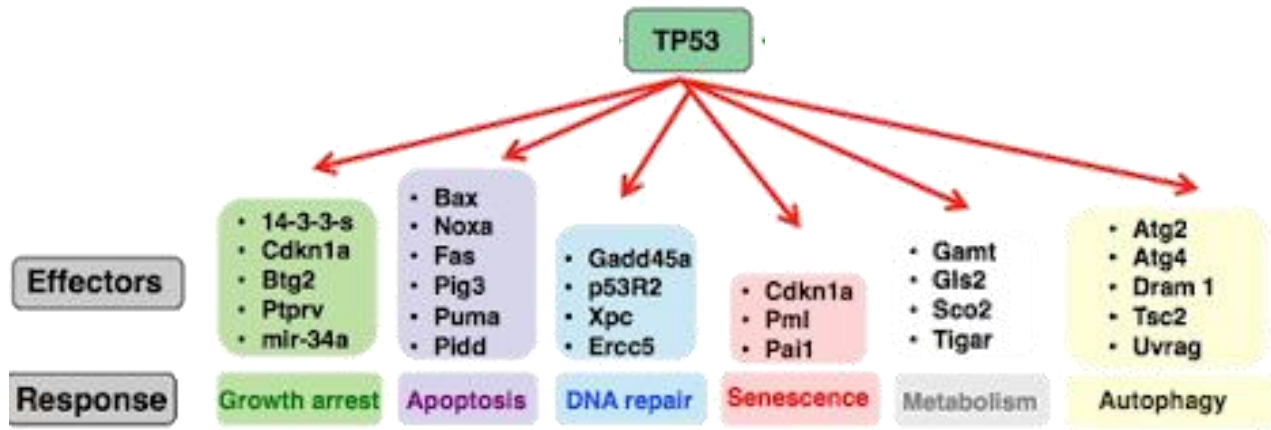


Vousden and Prives, Cell 2008

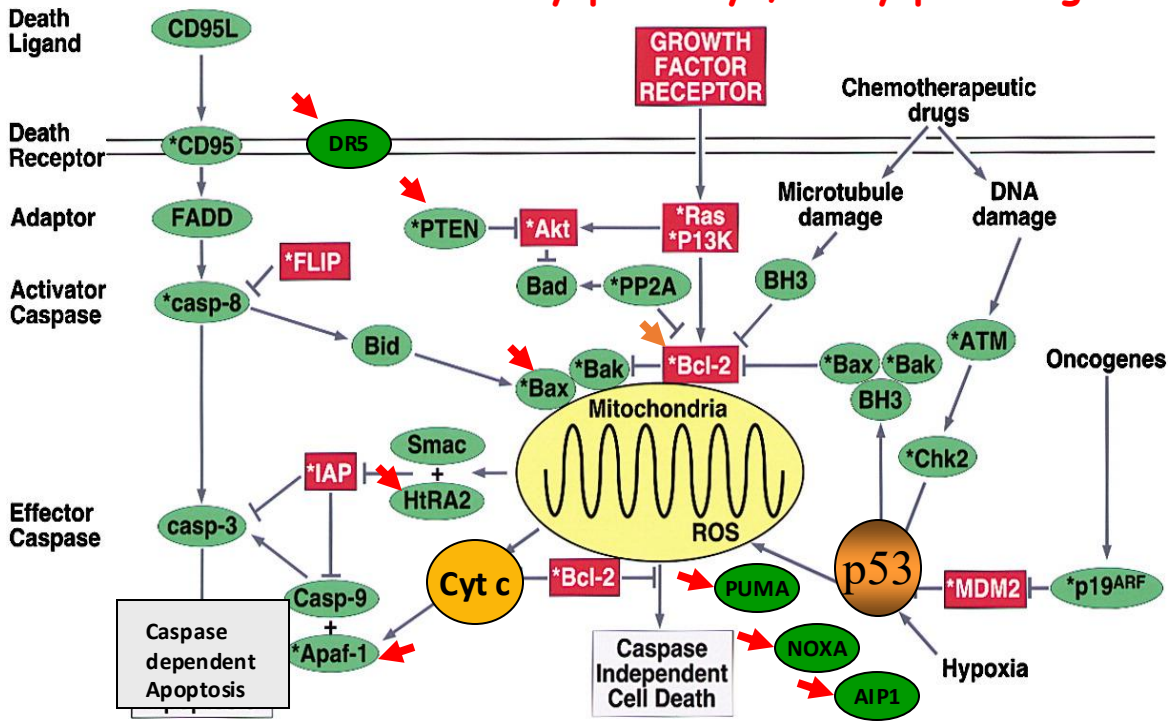
P53 target genes reveal many possible modes of tumor suppression

Table 9.2 Examples of p53 target genes according to function The expression of genes in this table is induced by p53 unless otherwise indicated.

Class of genes	Name of gene	Function of gene product
p53 antagonist	*MDM2/HDM2*	induces p53 ubiquitylation
Growth arrest genes	*$p21^{Cip1}$*	inhibitor of CDKs, DNA polymerase
	Siah-1	aids β-catenin degradation
	14-3-3σ	sequesters cyclin B–CDC2 in cytoplasm
	Reprimo	G_2 arrest
DNA repair genes	*p53R2*	ribonucleotide reductase—biosynthesis of DNA precursors
	XPE/DDB2	global NER
	XPC	global NER
	XPG	global NER, TCR
	GADD45	global NER ?
	DNA pol κ	error-prone DNA polymerase
Regulators of apoptosis	*BAX*	mitochondrial pore protein
	PUMA	BH3-only mitochondrial pore protein
	NOXA	BH3-only mitochondrial pore protein
	p53AIP1	dissipates mitochondrial membrane potential
	Killer/DR5	cell surface death receptor
	PIDD	death domain protein
	PERP	pro-apoptotic transmembrane protein
	APAF1	activator of caspase-9
	NF-κB	transcription factor, mediator of TNF signaling
	Fas/APO1	death receptor
	PIG3	mitochondrial oxidation/reduction control
	PTEN	reduces levels of the anti-apoptotic PIP_3
	Bcl-2	(repression of) its expression
	IGF-1R	(repression of) its expression
	IGFBP-3	IGF-1–sequestering protein
Anti-angiogenic proteins	*TSP-1* (thrombospondin)	antagonist of angiogenesis


TP53
Effectors
Response
• 14-3-3-s
• Cdkn1a
• Btg2
• Ptprv
• mir-34a
• Bax
• Noxa
• Fas
• Pig3
• Puma
• Pidd
• Gadd45a
• p53R2
• Xpc
• Ercc5
• Cdkn1a
• Pml
• Pai1
• Gamt
• Gls2
• Sco2
• Tigar
• Atg2
• Atg4
• Dram 1
• Tsc2
• Uvrag
Growth arrest
Apoptosis
DNA repair
Senescence
Metabolism
Autophagy

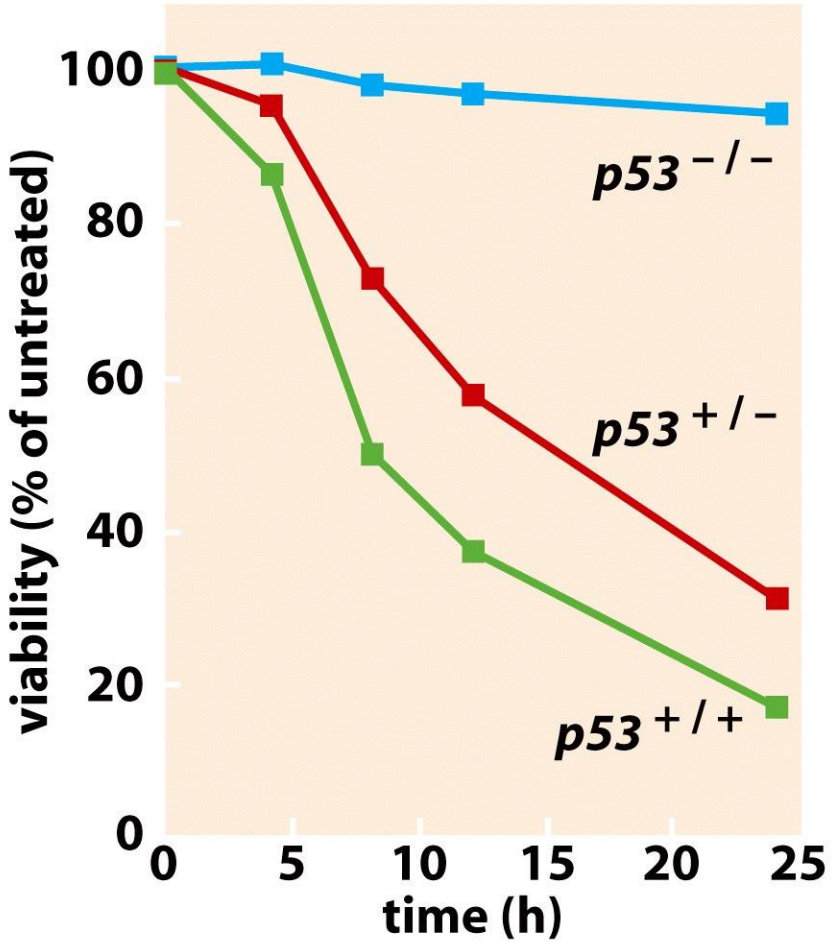
APOPTOSIS: Many pathways, many p53 targets



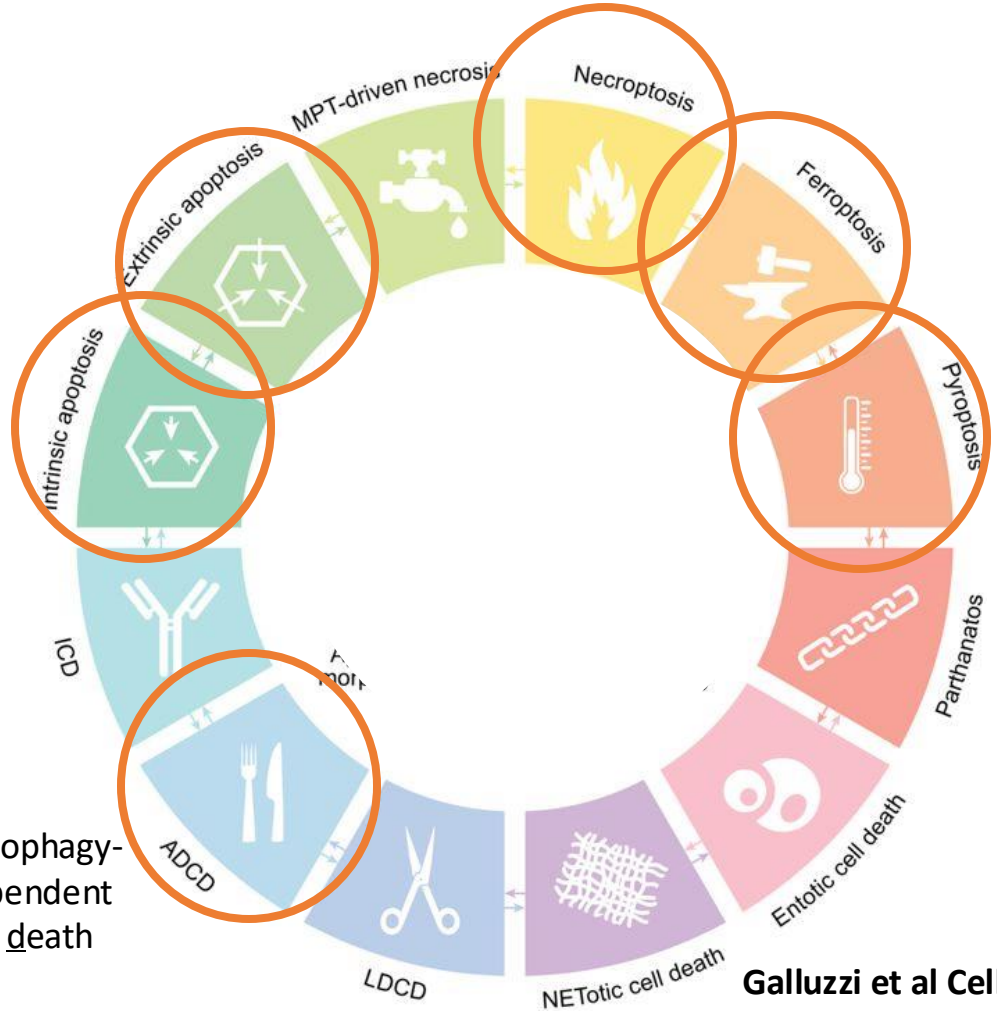
A schematic diagram showing some of the known components of the intrinsic and death receptor apoptotic programs that may modulate tumor development and therapy. An asterisk denotes components that are frequently mutated or aberrantly expressed in human cancers. Components in red inhibit apoptosis while those in green promote apoptosis. Abbreviations used: casp, caspase; cyt, cytochrome. Red arrows indicate genes activated by p53; blue arrow indicates gene repressed by p53

Modified from: Johnstone, Ruefli, and Lowe Cell vol 108, 2002

Cells from p53 null mice are resistant to apoptosis



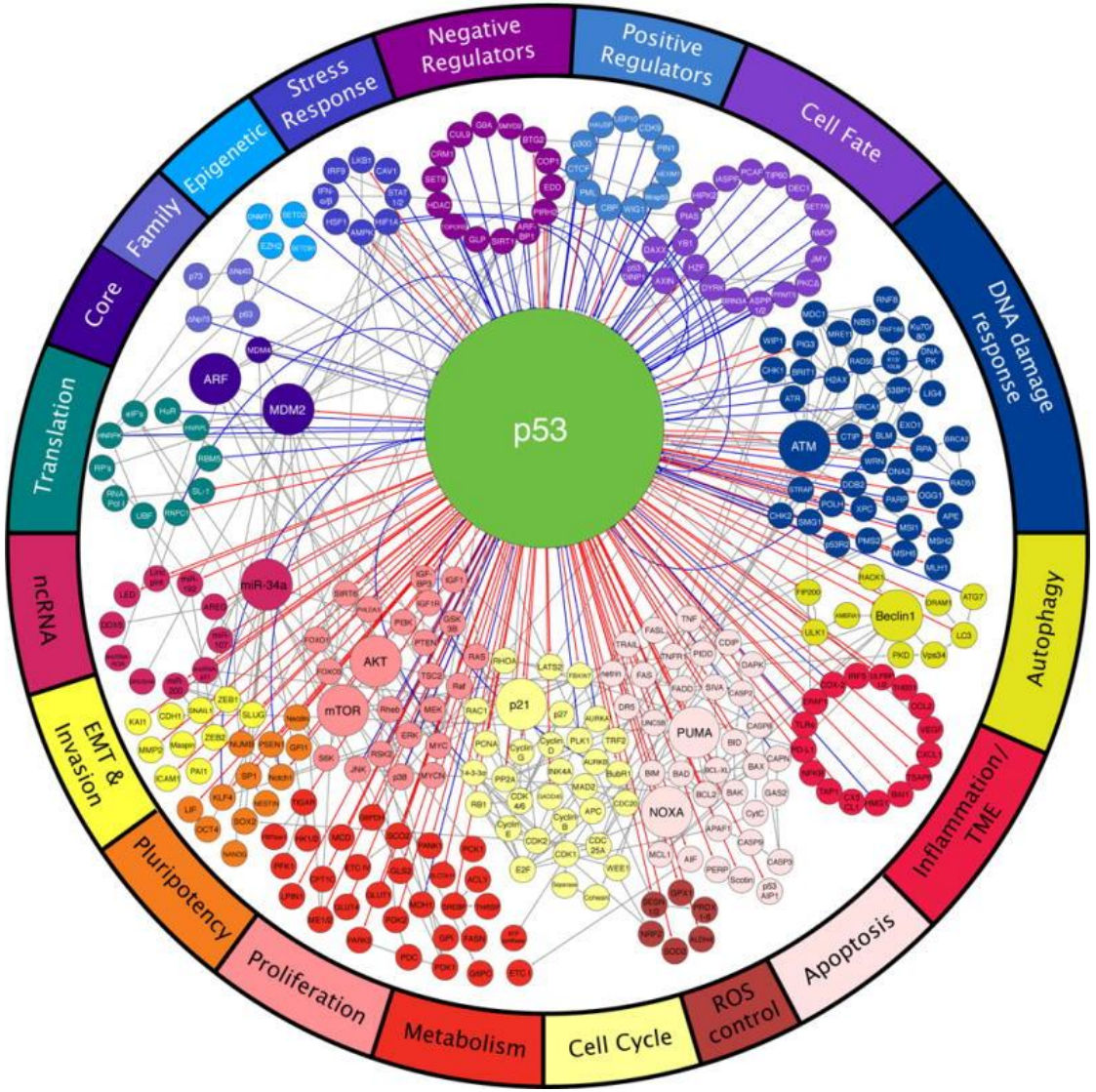
Many forms of cell death are regulated by p53



Autophagy-dependent cell death

Galluzzi et al Cell Death Diff 2018

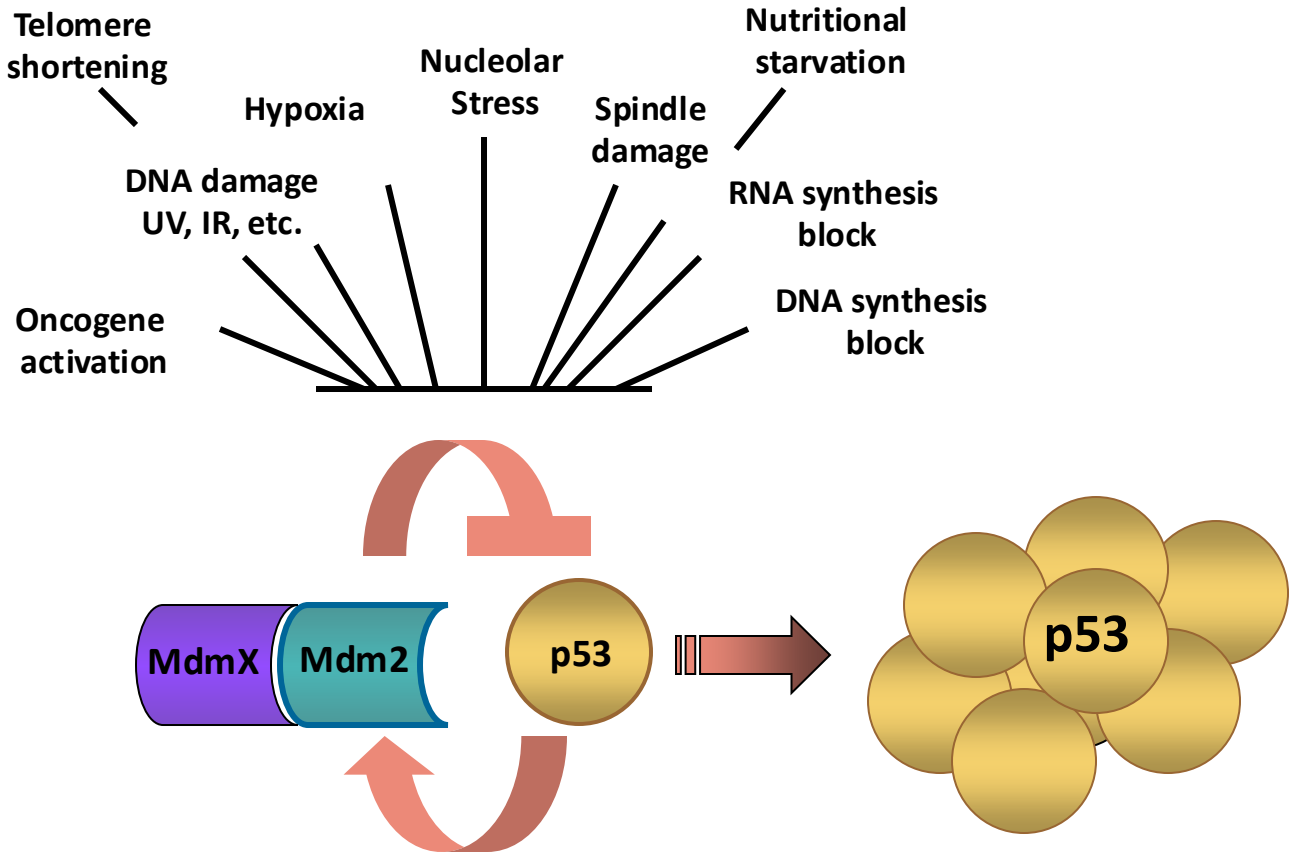
The p53 Network



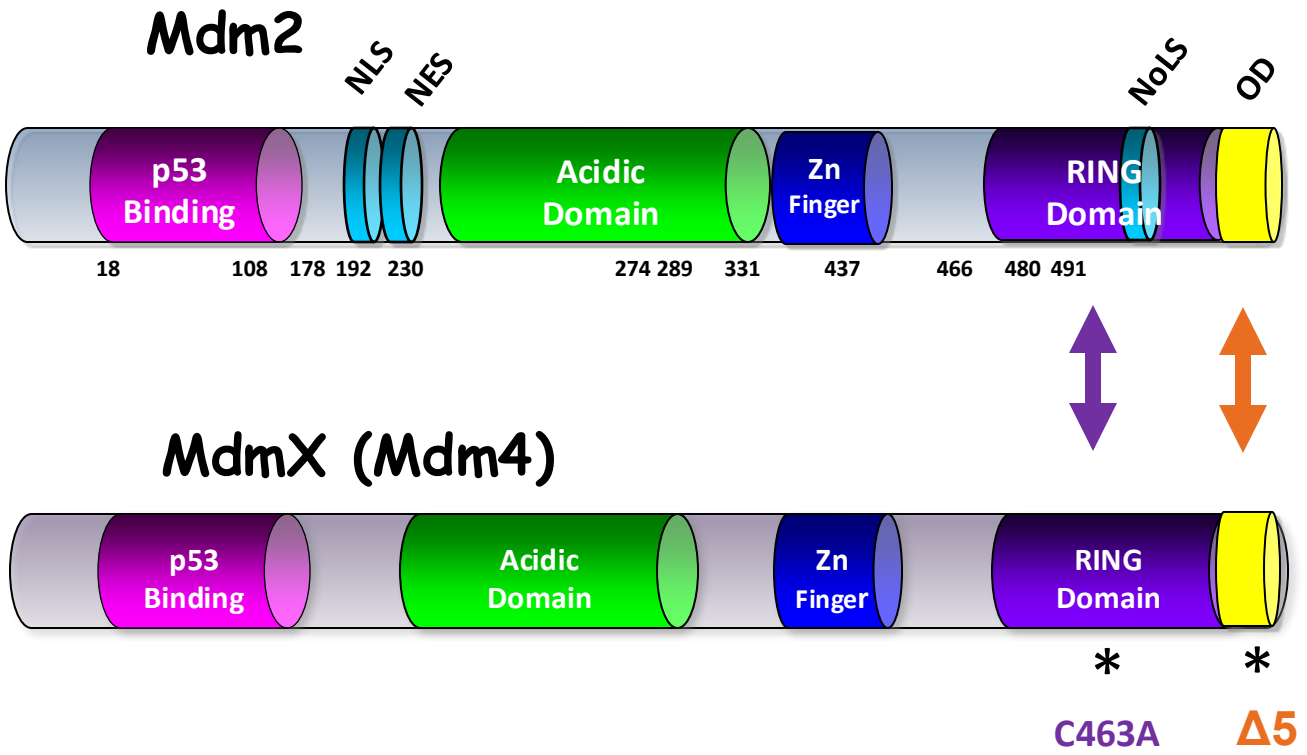
Kastenhuber and Lowe Cell 2017

Each node represents a gene and each line represents an interaction.
Direct p53 inputs are indicated as blue lines and direct p53 outputs are indicated as red lines.

How is p53 regulated?

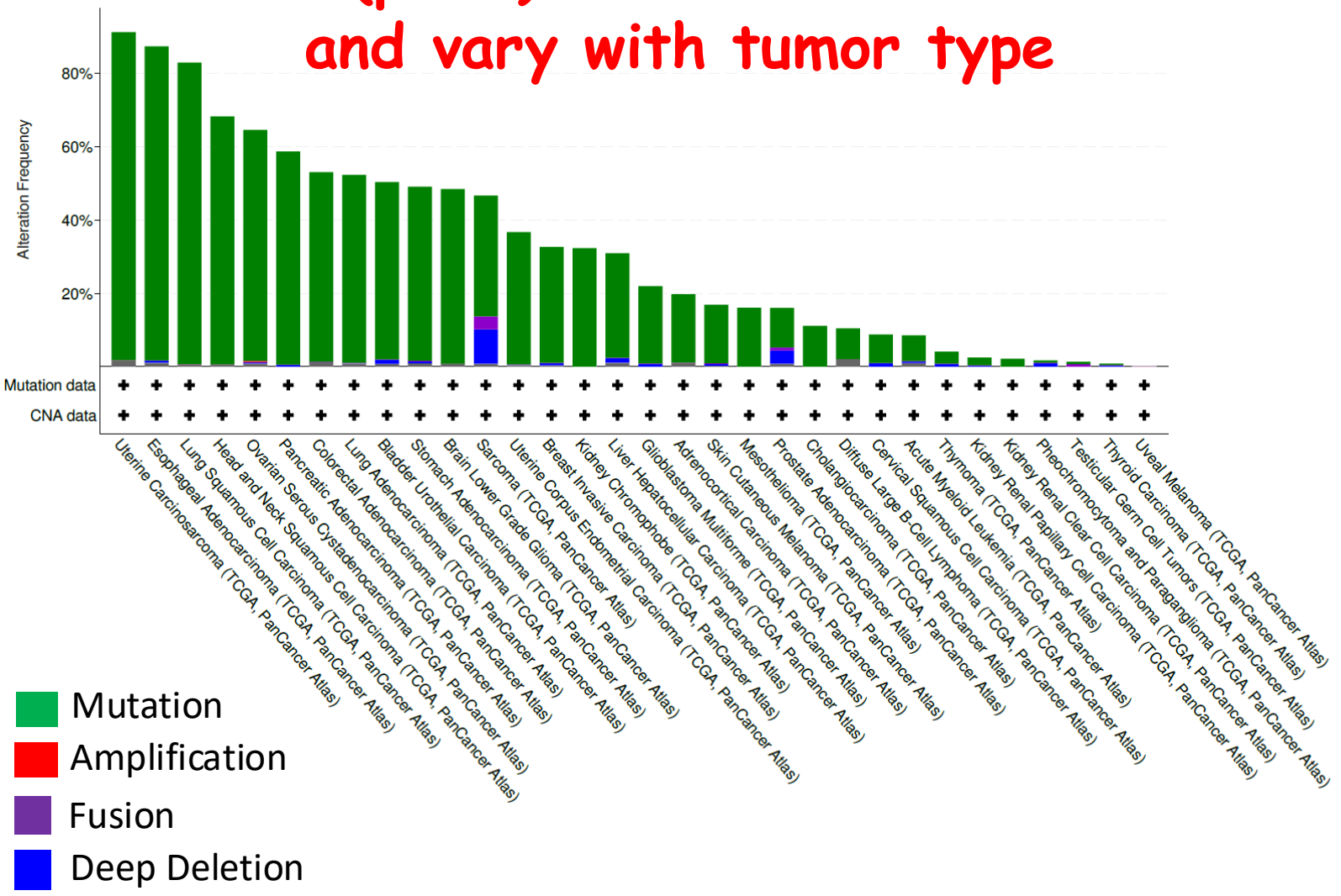

Telomere shortening
Hypoxia
Nucleolar Stress
Spindle damage
Nutritional starvation
DNA damage UV, IR, etc.
RNA synthesis block
Oncogene activation
DNA synthesis block
MdmX
Mdm2
p53
p53

MDM2 and MDMX: key regulators of p53



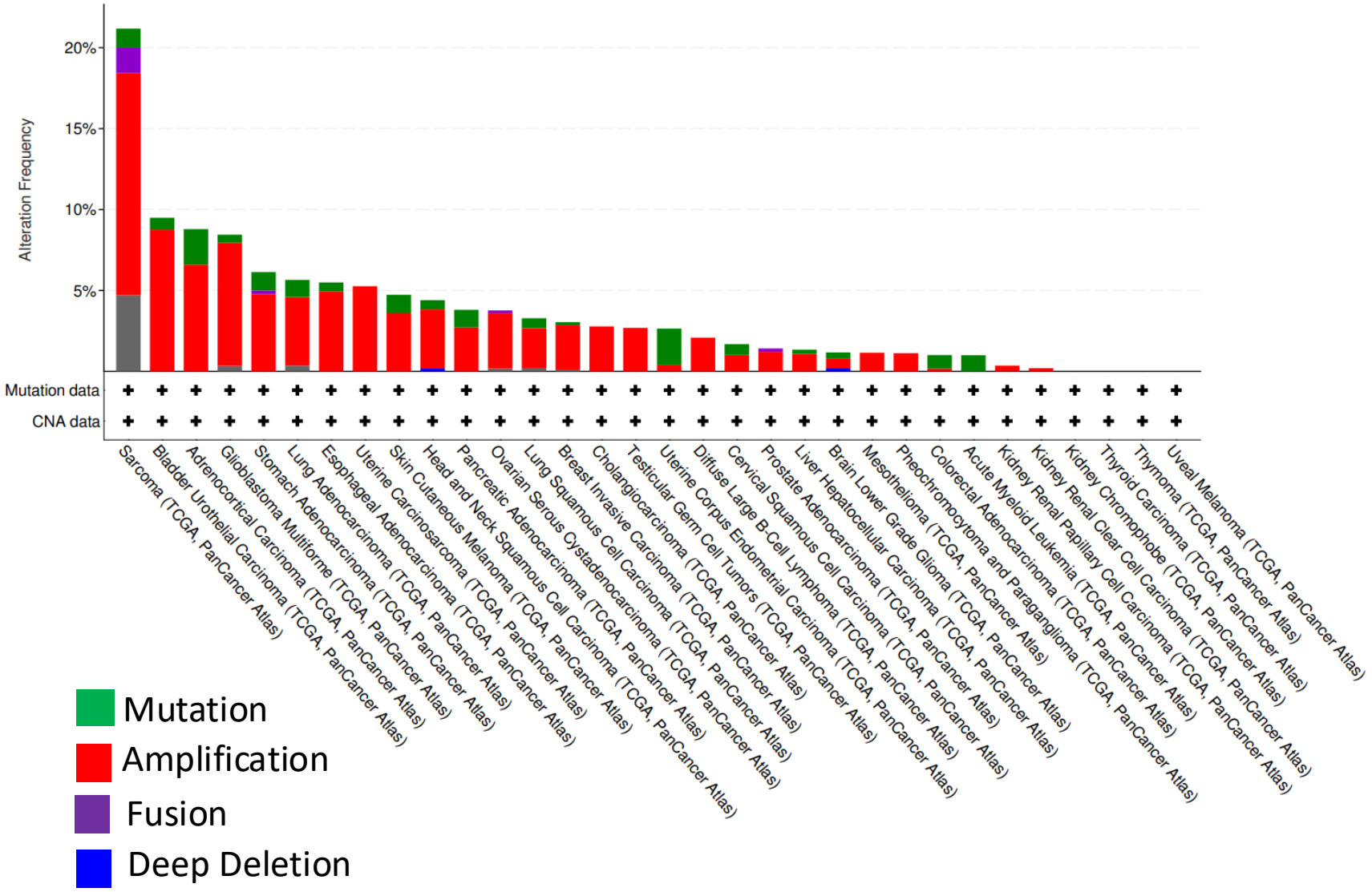
OD: oligomerization domain

Tumor derived p53 variants are largely fine (point) missense mutations and vary with tumor type



Data taken from cBioPortal

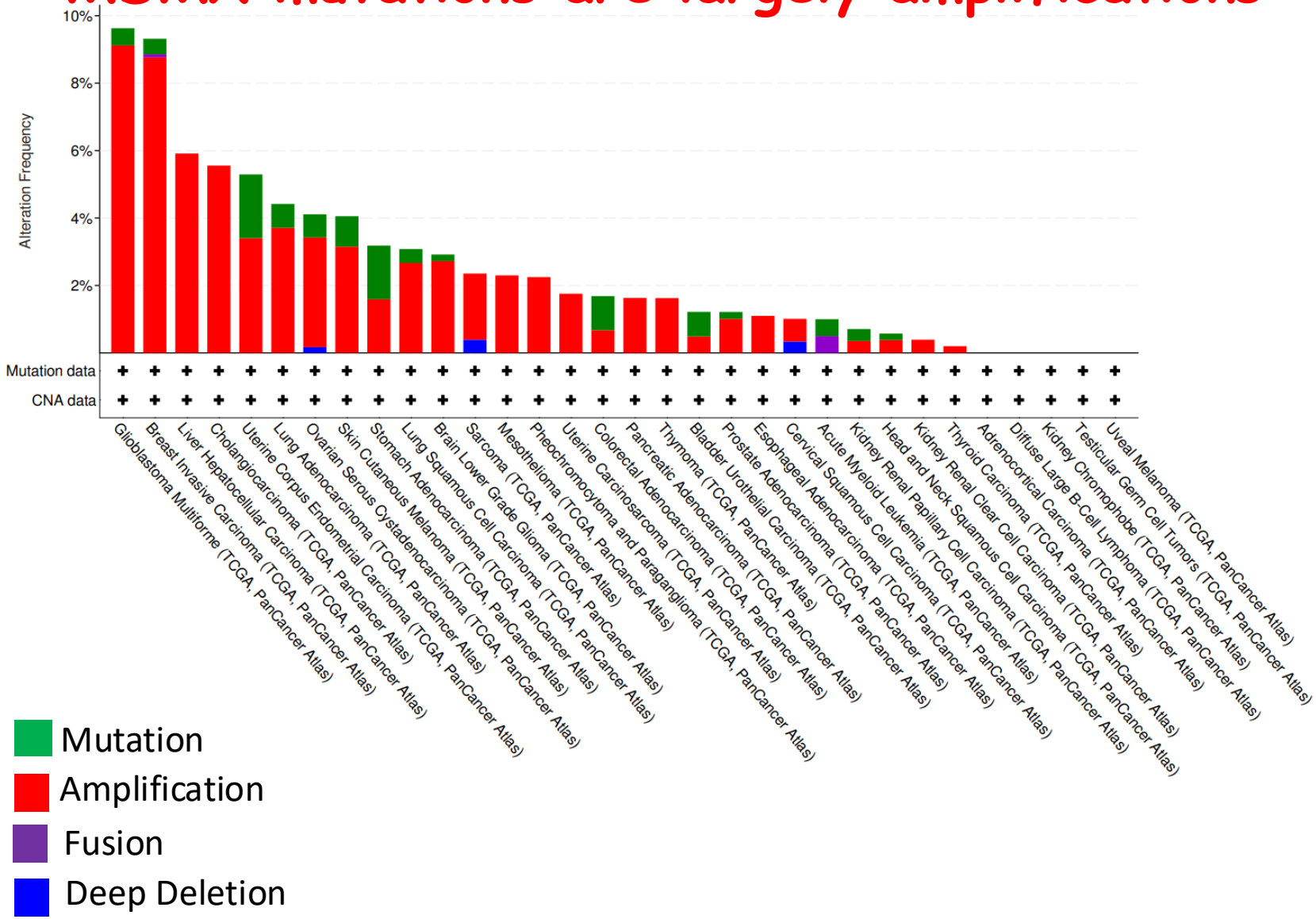
MDM2 mutations are largely amplfications*



*Mdm2 amplifications are almost always associated with wild-type p53

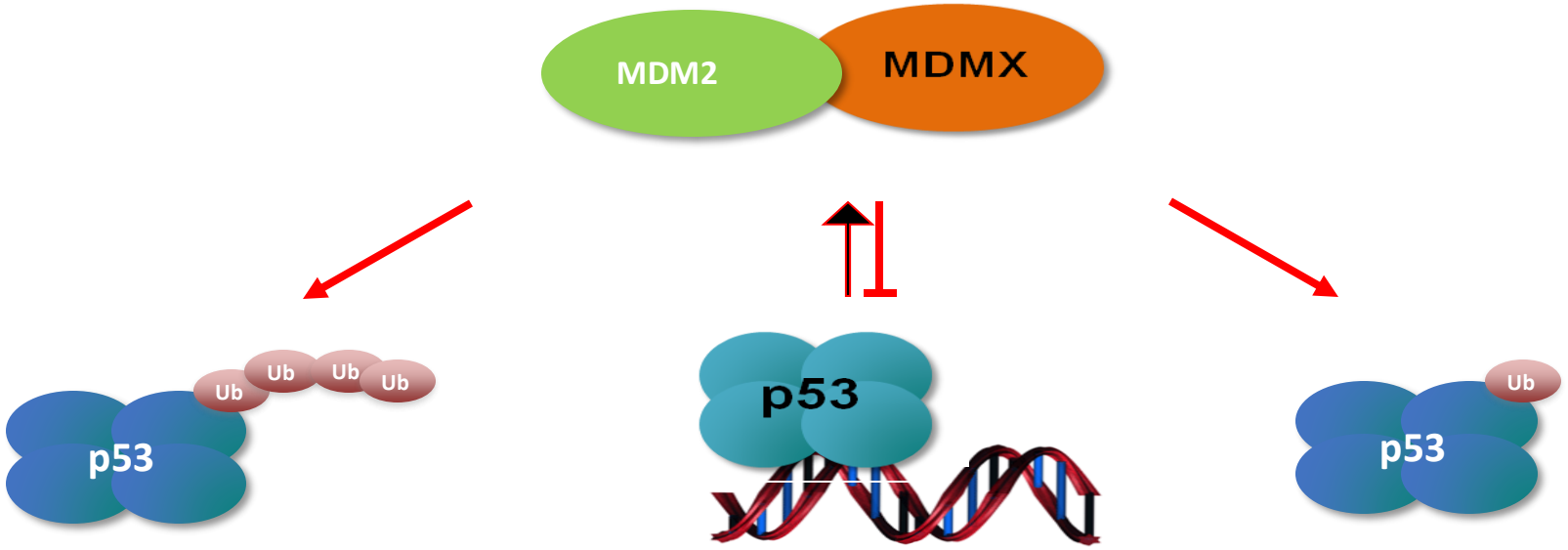
Data taken from cBioPortal

MDMX mutations are largely amplifications



Data taken from cBioPortal

Regulation of p53 by MDM2 and MDMX



Proteasome degradation

Transactivation inhibition

Nuclear export

Reduction of p53 levels

Inhibition of p53 activity

The p53 protein is extensively modified

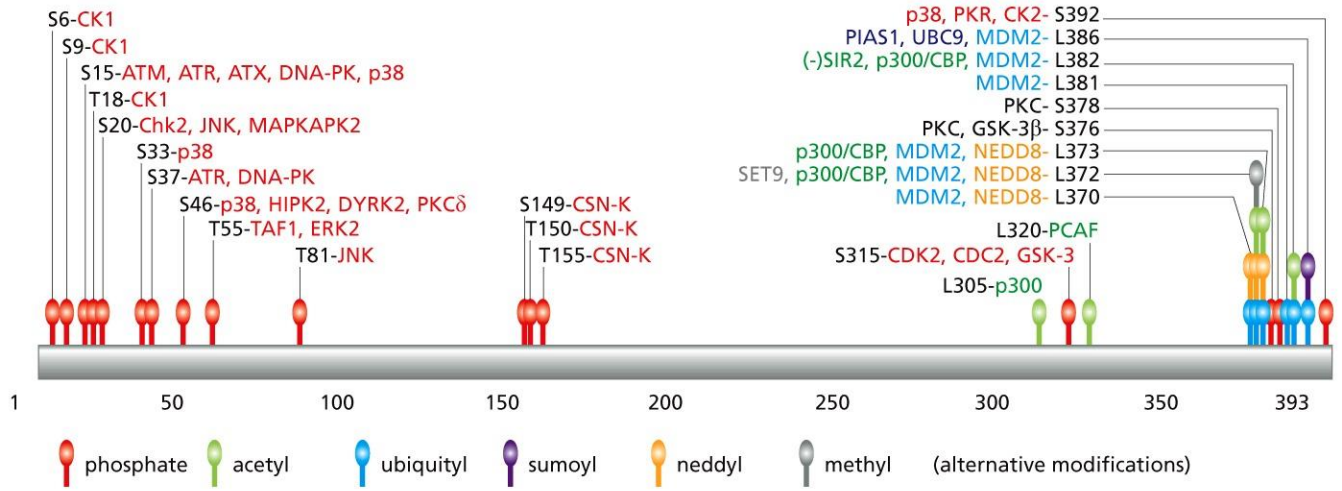


Figure 9.39 The Biology of Cancer (© Garland Science 2014)

Regulation of p53 and Mdm2 by DNA damage-induced phosphorylation

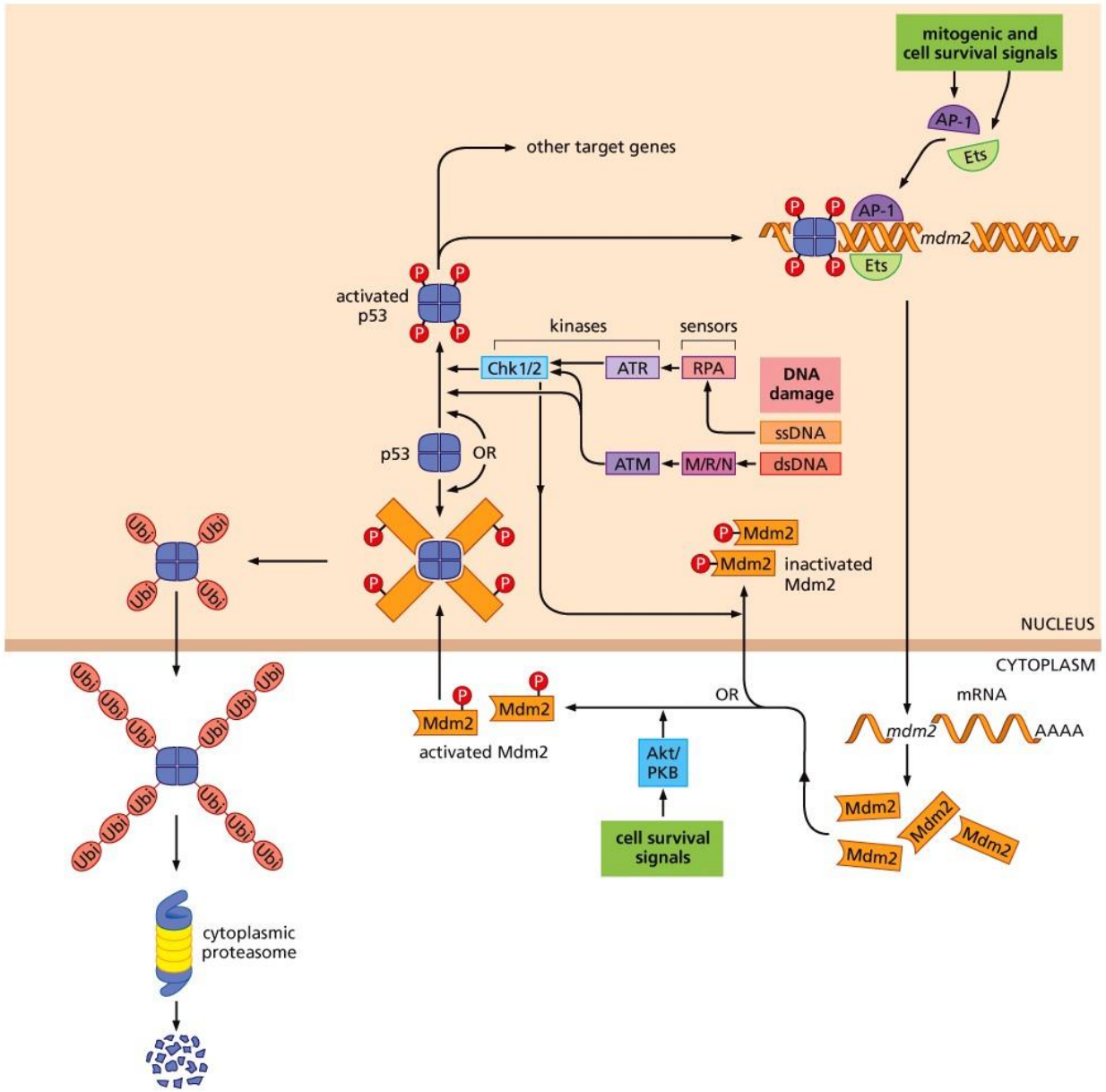


Figure 9.13a The Biology of Cancer (© Garland Science 2014)

The INK4a locus utilizes 2 reading frames to encode p16 and ARF

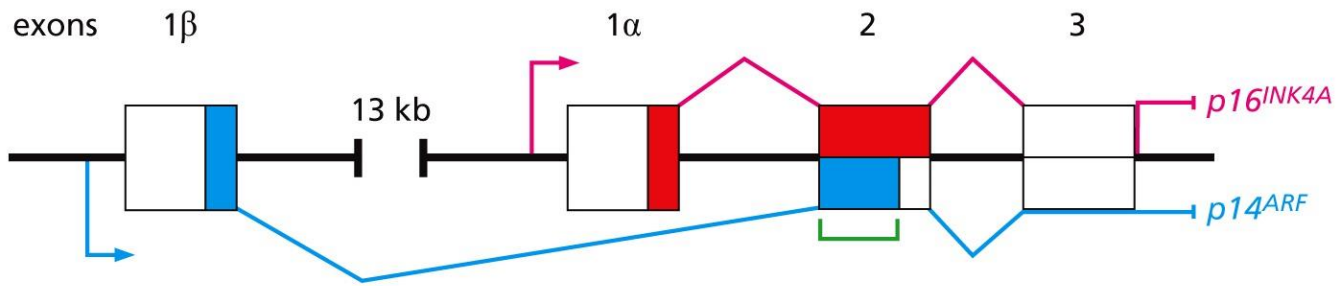


Figure 9.14 The Biology of Cancer (© Garland Science 2014)

Unscheduled proliferation activates p53 via ARF

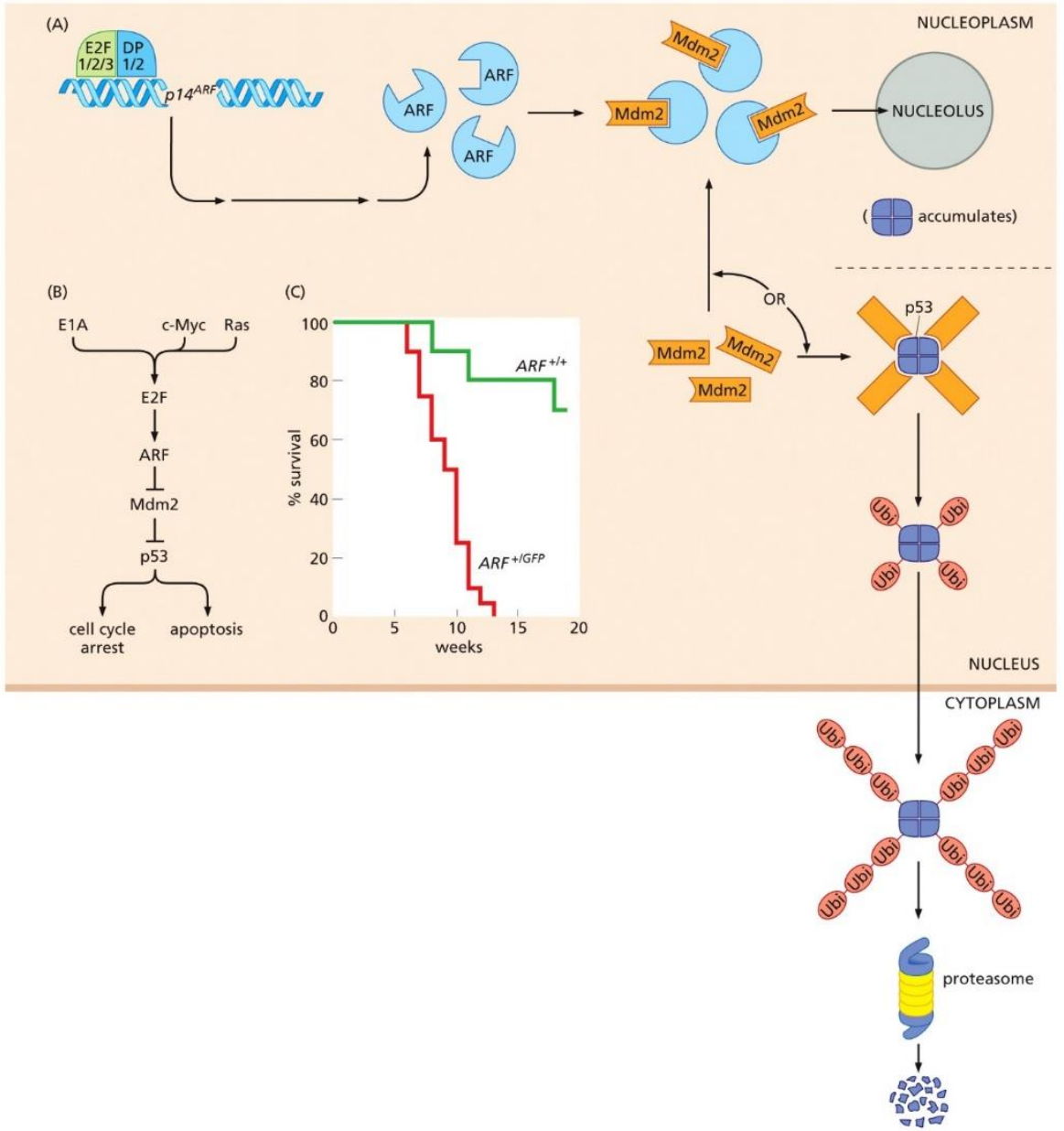


Figure 9.15 The Biology of Cancer (© Garland Science 2014)

Tumor-derived mutant forms of p53 are oncogenic

Mouse models provide genetic proof of oncogenic *gain of function* of mutant p53 proteins

Knock-out mutations

Tumor types:
T cell lymphomas
Sarcomas

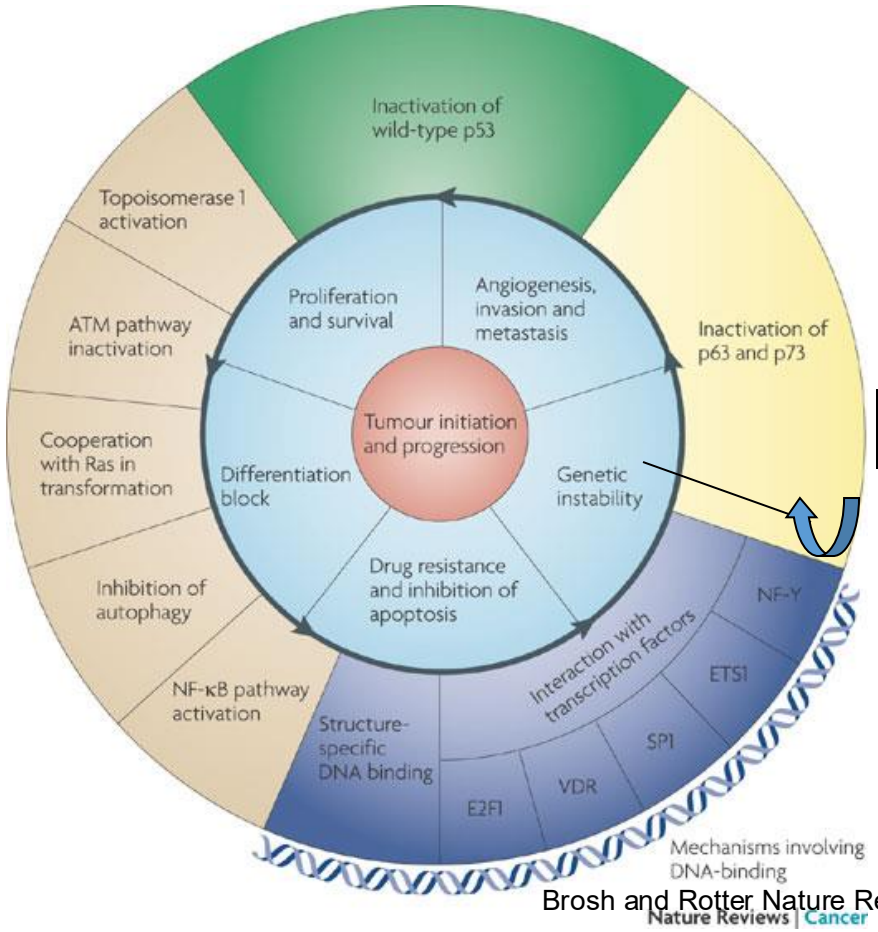
Tumor characteristics:
Survival: (1/2 gone at ~200 days)
No metastatic lesions identified

Knock-in mutations (R172H; R270H; R248Q)

Tumor types
T cell lymphomas
Sarcomas
Carcinomas

Tumor characteristics:
R248Q mice: (1/2 gone at ~150 days)
Metastatic lesions identified
Expanded hematopoetic and stem cells

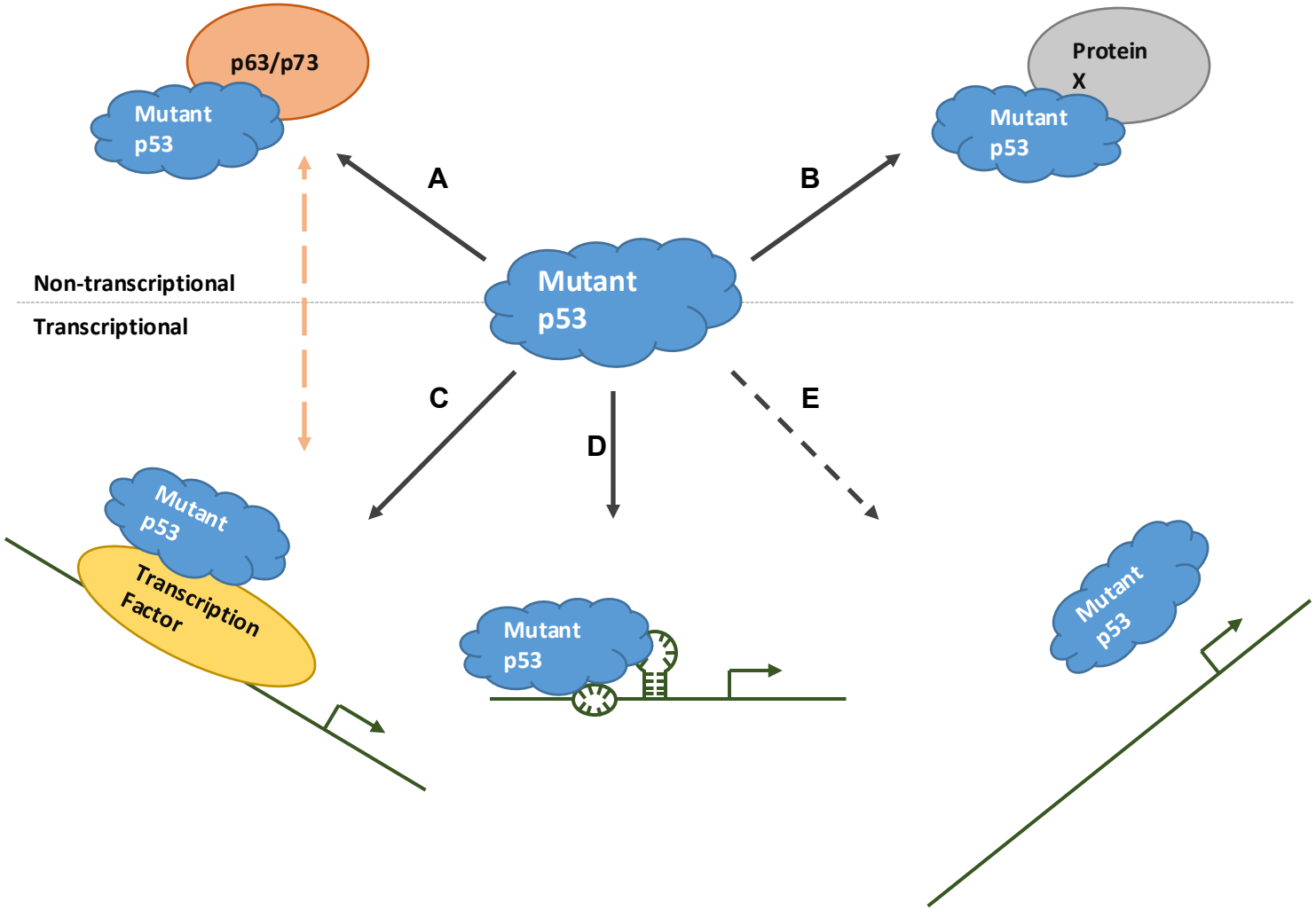
Mutant p53 activities, targets and interacting proteins



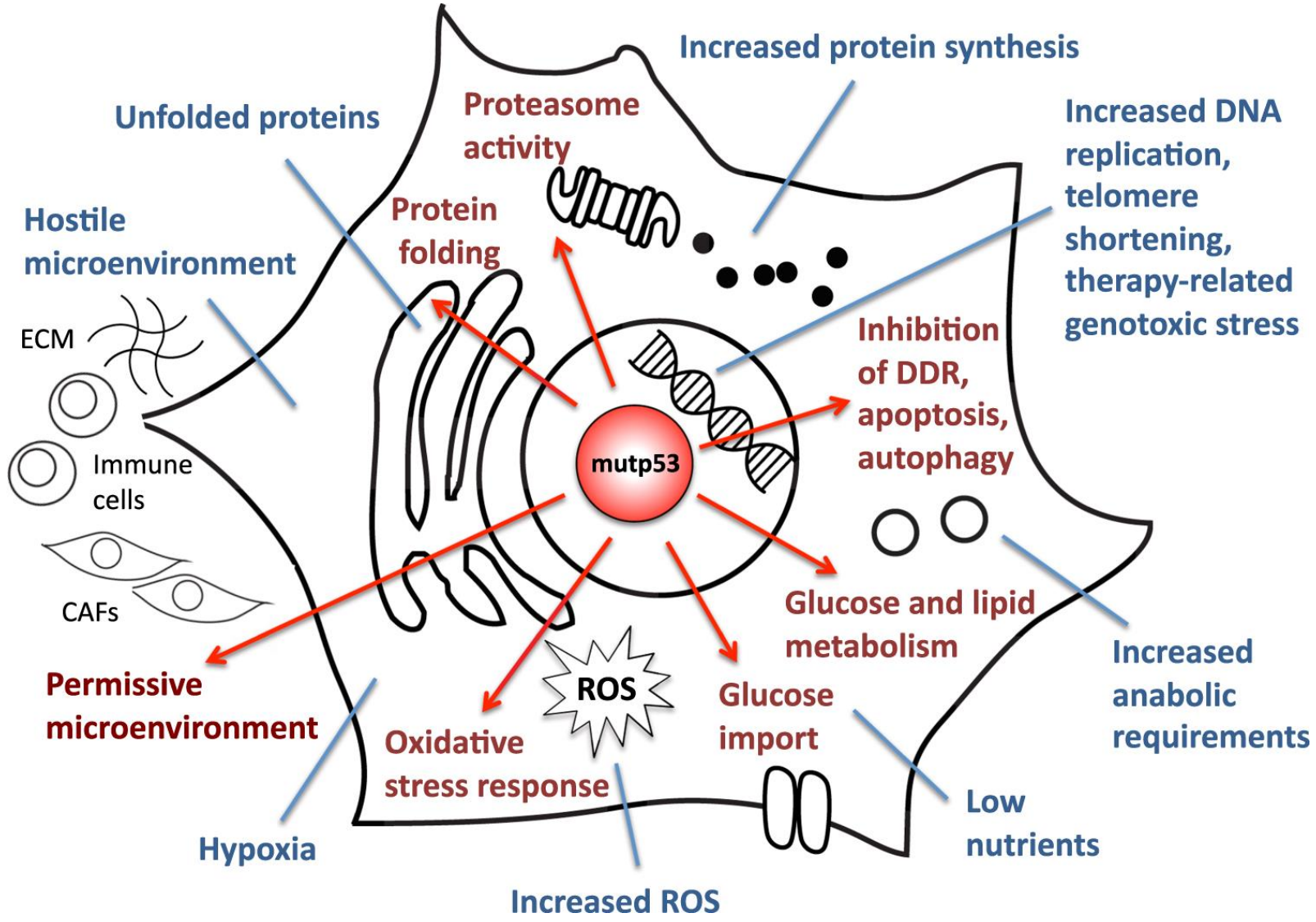
New: Srebp2, TopBP1, Pin1, Mre11, PML,

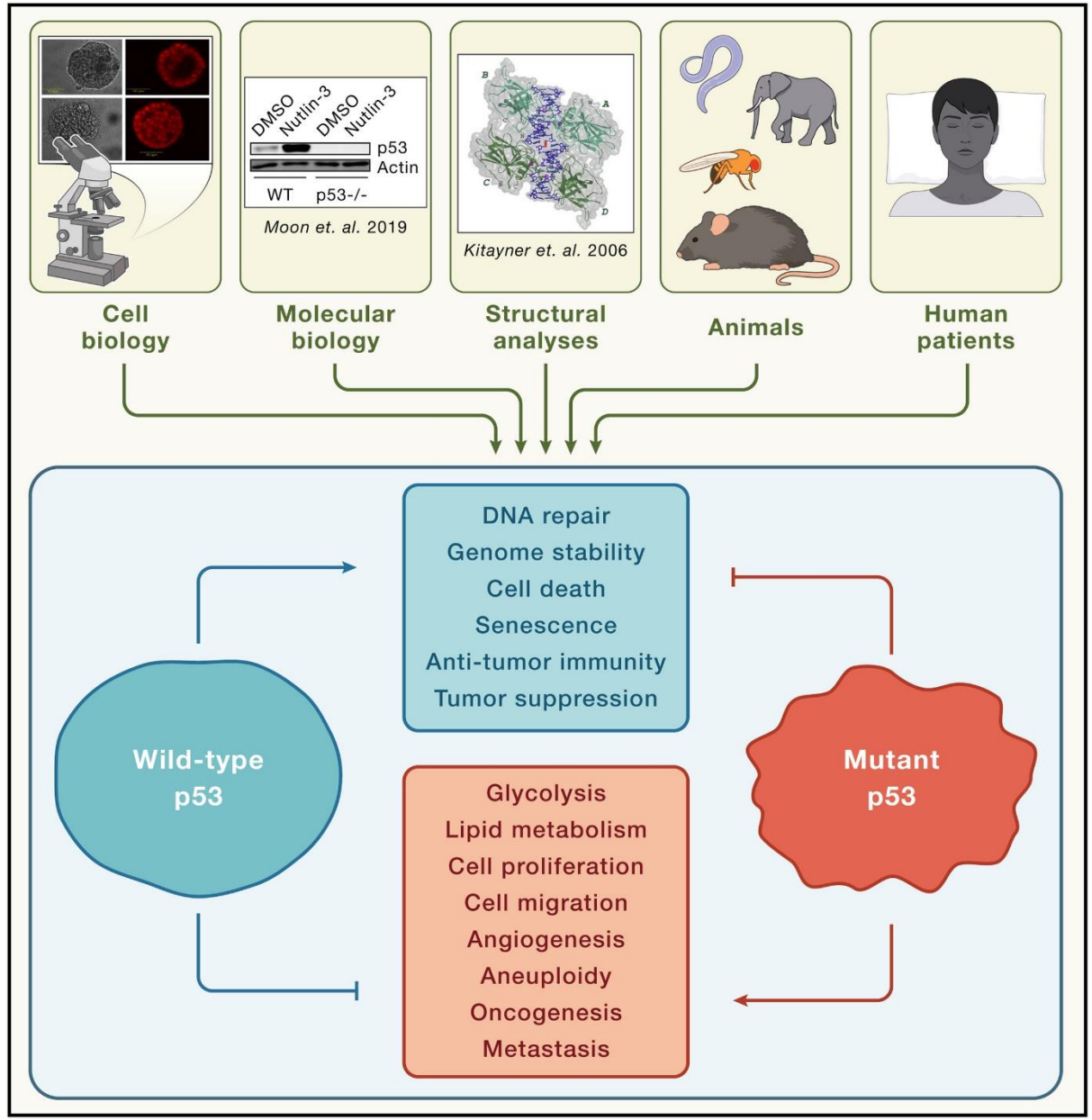
Brosh and Rotter Nature Reviews Cancer 2009

Mechanisms of Mutant p53 Gain-of-Function



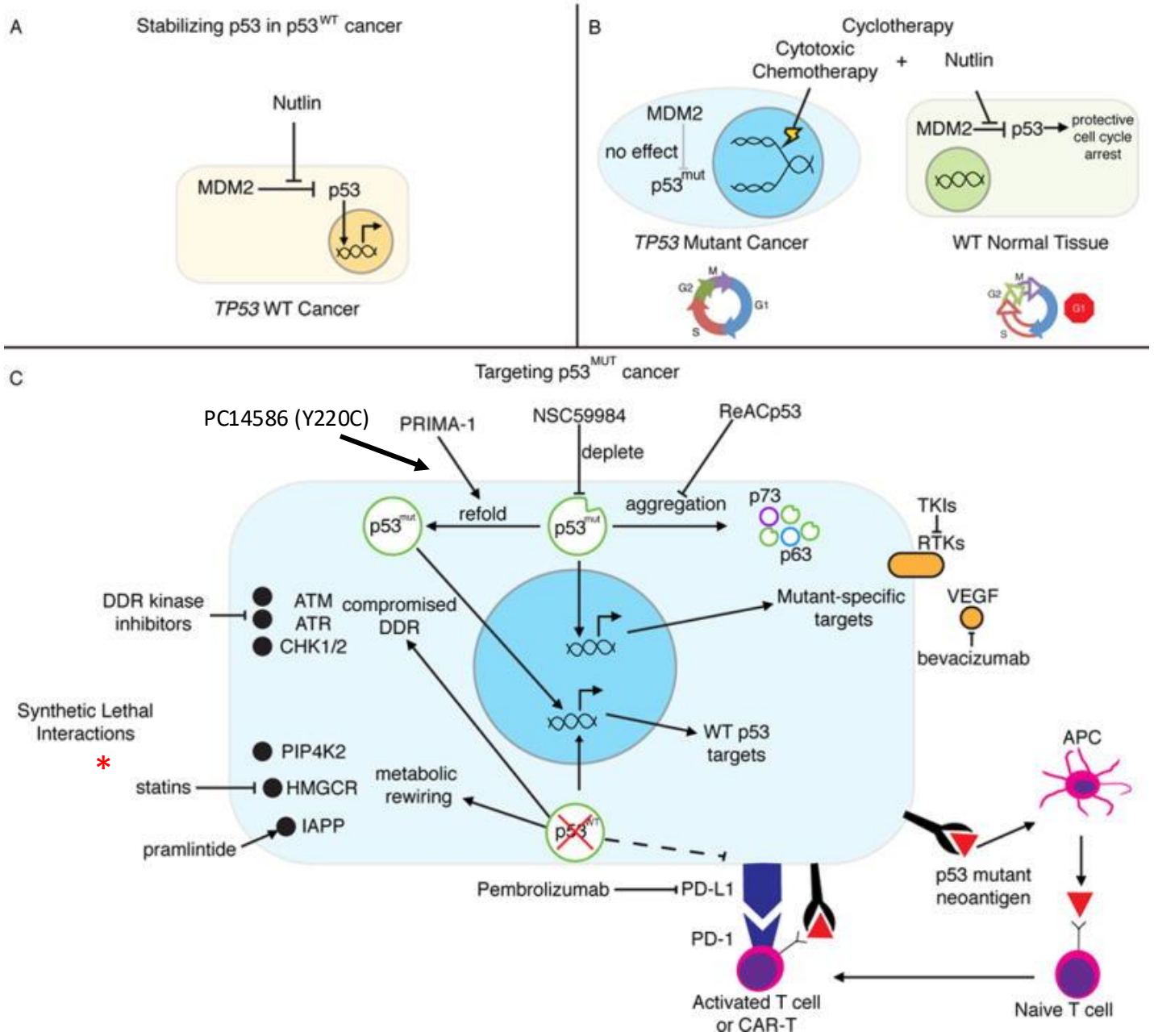
Mutant p53 proteins regulate several aspects of cellular functions and growth



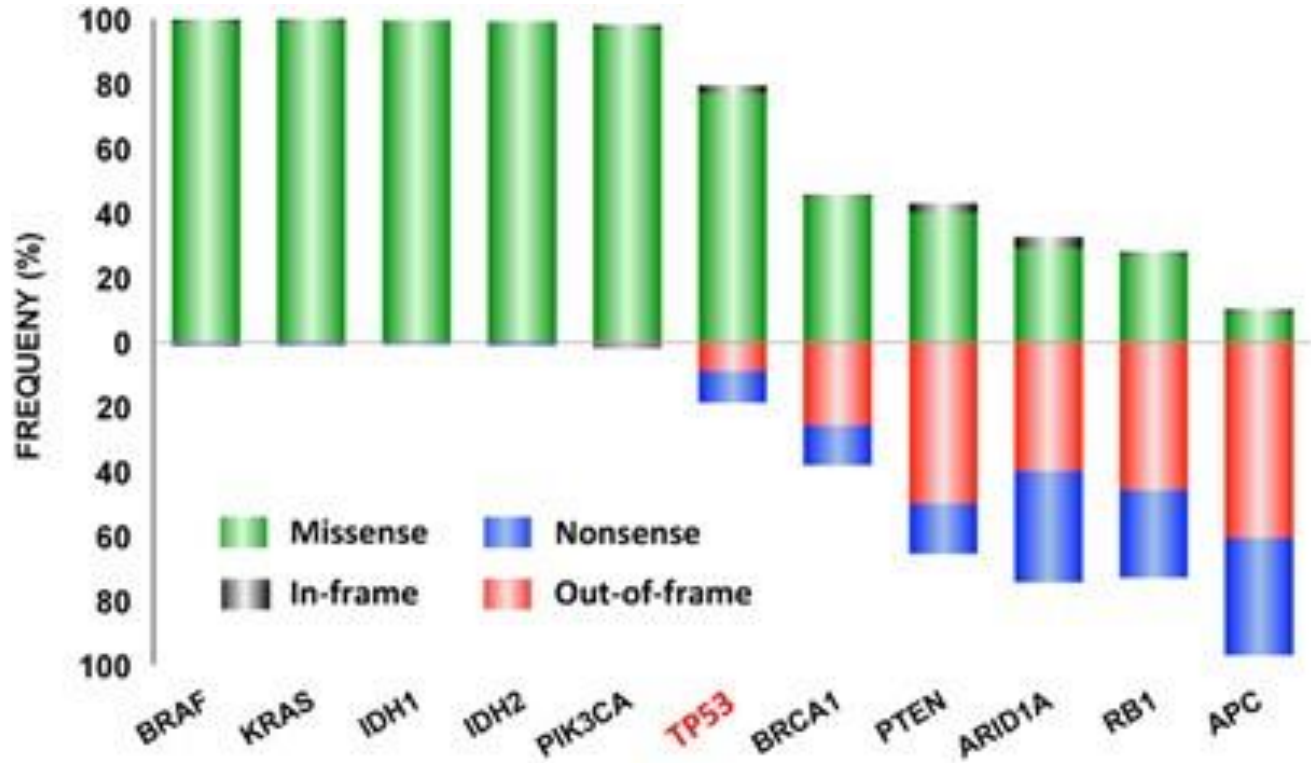


Oren and Prives Cell 2024

Harnessing knowledge about p53 and Mdm2 for eventual therapeutic benefit



Thank you!



Soussi and Wiman Cell Death and Differentiation 2015