What Is TP53 ?
TP53 Is A Tumor Suppressor Gene

<table>
<thead>
<tr>
<th>p53+/+</th>
<th>1% at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53+-/-</td>
<td>2% at 9 months</td>
</tr>
<tr>
<td>p53-/-</td>
<td>75% at 6 months</td>
</tr>
</tbody>
</table>

Donehower et al. 1992
TP53 is the Most Frequently Mutated Gene in a Majority of Cancers

From Bouaoun et al., 2016
In Specific Types Of Cancers Where TP53 Mutations Are Unfrequent p53 Protein May Be Inactivated By Protein Interactions

<table>
<thead>
<tr>
<th>Cancer</th>
<th>TP53 mutation frequency</th>
<th>Inactivating protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>&lt; 2%</td>
<td>Twist</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>&lt; 20%</td>
<td>Mdm2/Twist</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>&lt; 1%</td>
<td>Mdm4</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>&lt; 10%</td>
<td>E6 (HPV)</td>
</tr>
</tbody>
</table>
The **Li-Fraumeni syndrome** (LFS, OMIM# **151623**) is a rare autosomal disorder characterised by a familial clustering of early onset tumors (<45), with a predominance of sarcomas, breast cancers, brain tumors and adrenocortical carcinomas.

In 1990, Malkin et al. found that this syndrome may be caused by a germline mutation in the TP53 gene.
TP53 Encodes The p53 protein, A Transcription Factor

TP53 Encodes The p53 protein, A Transcription Factor

**Transactivation** (1-42; 43-62)

**Proline-rich** (63-97)

**DNA binding** (102-292)

**Oligomerisation** (323-356)

**Regulation** (363-393)
The p53 Pathway

From KEGG database
The p53 pathway: positive and negative feedback loops

From Harris & Levine, 2005
miRNA In The TP53 Pathway (1)
miRNA In The TP53 Pathway (2)

Hermeking, NatRevCancer, 2012
miRNA In The TP53 Pathway (3)

Hermeking, NatRevCancer, 2012
p53 and Ageing

Rufini et al., Oncogene, 2013
Regulation of energy metabolism by p53

Vousden, BBA, 2018
Several Post-Transcriptional Modifications On p53 Regulate p53 Activities

**Figure 1** Overview of p53 post-translational modifications. The major sites for p53 modifications (phosphorylation, ubiquitination, sumoylation, neddylation, acetylation, methylation, O-GlcNAcylation, ADP-ribosylation, hydroxylation, and β-hydroxybutyrylation) are plotted. Different colors are used to differentiate distinct modification types. Representative functions of some modifications are indicated. The figure is mainly revised from Dai and Gu (2010) and Gu and Zhu (2012) and not drawn to scale.

From Liu et al., 2019
p53 Activation: Breaking p53-mdm2 Association

Genotoxic stress

ATM/ATR 
Chk2 
CK2

p53

mdm2 

p53 ubiquitination and degradation 

Proteasome

mdm2 

Target gene
p53 Regulation by miRNA

Hermeking, NatRevCancer, 2012
TP53 Family Members: Similar Structure

Family of Transcription Factors

Transactivation domain  DNA-binding domain  Oligomerisation & Regulation domain

TP53  TP73  TP63
Sequence Identity Between p53, p63, p73 proteins

From Courtois et al., 2004
p63 & p73 Isoforms Are Generated By Alternative Splicing And Alternative Promoters
p53 locus and mRNA Isoforms

Joruiiz & Bourdon, CSHP, 2017
p53 Consensus Protein Isoforms In 2017

Joruis & Bourdon, CSHP, 2017
Role of p53 Splice Variants in Human Malignancy

Surget et al., OncoTargets and Therapy, 2013
The role of p53 in developmental syndromes

Figure 2 Proposed role for p53 in mouse models of human developmental syndromes. Mutations affecting a range of cellular processes trigger p53 activation. Once active, p53 is thought to drive developmental defects by inducing apoptosis, restraining proliferation, or modulating other developmental programs in specific cell compartments during embryonic or postnatal development. For each type of p53-driven developmental defect, an example of a mouse model exhibiting this defect is indicated.
TP53 Family Members: Different Functions

**TP53**
- 17p13(h)
- 23% female death by exencephaly
- High frequency of tumor development

**TP73**
- 1p36(h)
- Hydrocephalus,
- Chronic infections,
- Inflammation,
- Abnormalities in pheromone sensory pathways

**TP63**
- 3q27-28(h)
- Defects in the limb, craniofacial and epithelial development.
- No Skin!
TP53 Family Members: Mutations In Human Diseases

**TP53**
17p13(h)
- Somatic mutations frequent in almost all cancer types
- Germline mutations cause Li-Fraumeni syndrome

**TP73**
1p36(h)
- LOH or isoforms overexpression in some tumor types, but no somatic mutation
  
  No disease causing germline mutation

**TP63**
3q27-28(h)
- Isoforms overexpression in some tumor types, but no somatic mutation
  
  Germline mutations cause developmental disorders but not cancer
Figure 2. Scenario of the p53 family gene evolution. The earliest indication of p53 family genes dates back to invertebrates and unicellular choanoflagellae. Aside from independent gene duplications, such as in sea anemone or mosquitos, the earliest indication for mammalian gene splitting dates back to cartilaginous fishes, with tentative orthologs visible in elephant sharks, and all three mammalian paralogs appearing in bony fishes.
An Elephant in the Room!
Elephant cells have 40 copies of *TP53* gene

Compared with other mammalian species, elephants appeared to have a lower-than-expected rate of cancer.

Compared with human cells, elephant cells demonstrate increased apoptotic response following DNA damage.

Abegglen et al., JAMA, 2015
2009: 30 years of p53

1979: discovery
1983: defined as an oncogene
1985: cloning of the human gene
1989: the WT form is defined as a tumor suppressor
1989: LOH and first mutations identified in cancer
1990: TP53 is constitutively mutated in Li-Fraumeni syndrome
1990: p53 is a transcription factor
1991: participation of p53 in the cellular response to DNA damage
1991: p53 induces apoptosis
1991: selective G to T mutation of TP53 gene in HCC from Africa
1992: TP53-/- mice develop tumors spontaneously
1993: p53 induces G1 arrest via p21Waf1
1993: TP53 mutation is associated with poor prognosis in breast cancer
1994: crystal structure of p53 in complex with DNA
1996: p53 is induced by hypoxia
1997: role of mdm2 in the regulation of p53 stability demonstrated in mice
1997: TP73, first TP53 related gene discovered
1999: 10,000 human mutations described
1999: p53 plays a role in DNA repair
2002: constitutive expression of p53 accelerates ageing in mice
2002: discovery of a N-terminally truncated variant of p53
2003: p53 plays a role in global chromatin remodelling
2004: wt p53 and mutant p53 are targeted for cancer therapy
2005: description of nine p53 protein isoforms
2006: p53 plays a direct role in cellular metabolism
2007: p53 regulation of microRNAs, a new layer of complexity in the p53 network
2008: a dual role for p53 in autophagy is described
2009: p53 deficiency help cellular reprogramming and stem cells production
The most popular genes in the human genome

A tour through the most studied genes in biology reveals some surprises.

Elle Dolgin
The IARC TP53 Database
A Locus Specific Database To Study TP53 Gene Variations In Human Cancers

p53.iarc.fr/
Why Study TP53 Mutations?

TP53 somatic mutations are frequent in most types of **sporadic human cancers** (frequencies vary from 5% to 70% depending on cancer type and stage).

TP53 mutations may also be inherited in families with a predisposition to multiple cancers, as in the **Li-Fraumeni syndrome** (LFS).

In several cancers, the nature of TP53 mutations and their distribution along the coding sequence have allowed the identification of **tumor-specific mutation spectra**, revealing clues on the mechanisms that might have caused the mutation.

Different types of mutation have different phenotypes.

The presence of a TP53 mutation may be **predictive** of the tumor response to treatment and patient survival.
The IARC Database: Information System For TP53 Mutations

- Extract TP53 mutation data from publications
- Organize and annotate data into a format that allows easy retrieval and analysis
- Provide a web-based tool to analyse TP53 mutation patterns in cancers
Data Available

- Somatic mutations in human sporadic cancers
- Germline mutations and Li-Fraumeni syndrome
- Polymorphisms in human populations
- TP53 status of human cell-lines
- Functional assays of mutant proteins
- Structural properties of mutant proteins
- Mouse-models with engineered TP53 gene
- Experimentally-induced mutations
Criteria For Inclusion

- **TP53 somatic mutations** associated with human sporadic cancers that have been identified by sequencing and published in peer-reviewed literature. This includes mutations found in normal, pre-neoplastic and neoplastic tissues, including metastases, as well as in cell-lines derived from such tissues.

- Human TP53 **germline mutations** (identified by sequencing and published in peer-reviewed literature) in individuals affected or not by a cancer.

- p53 mutants that have been tested in human cells or yeast assay for **functional activities** such as specific DNA-binding, transcriptional activation, dominant-negative effects on the wild-type protein, gain of function...

- **Mouse-models** with engineered TP53 gene that are included in caMOD database or have been reported in peer-reviewed literature.

- **Experimentally-induced mutations** obtained in the Hupki mouse models or a yeast assay of mutagenesis.
Database Structure And Contents


**SOMATIC**
- Tumor pathology
- Molecular alterations
- Patient demographics
- Patients life-style
- Mutation prevalence
- Prognostic value

**CELL LINES**
- Tumor pathology
- Patient demographics
- ATCC link
- COSMIC link

**GERMLINE**
- Tumor pathology
- Individual demographics
- Family structure
- Mutation prevalence*

**EXPERIMENTALLY INDUCED***
- Cell model
- Mutagen tested

**POLYMORPHISMS**
- Validated SNP
- Link to dbSNP

**MOUSE MODELS**
- Affected tissues
- CaMOD link
- PubMed link

**TP53 GENE VARIATIONS**
- Genomic, coding and protein description
- Effect

**STRUCTURE/FUNCTION**
- Structural properties
- Functional assessment
- Predicted impact

* New in R17
Database Figures And Facts

- **Database contents:**
  - >29,000 somatic mutations
  - >1,500 germline mutations
  - >8,400 mutants with functional properties
  - >180 studies on TP53 mutation and clinical outcome
  - > Mouse models with engineered p53
  - > 900 experimentally-induced mutations linked to human exposures
  - Mutation occurrences in TCGA, ICGC and GENIE datasets

- **Database usage**
  - > 9,600 visits per month
  - > 700 downloads per month
  - > 6,300 citations in the scientific literature
  - Links with COSMIC, CLINVAR, dbSNP, gnomAD, ATCC, HGVS
IARC TP53 DATABASE: A Resource For Various Disciplines

- Molecular Epidemiology
- Molecular Pathology
- Medical Genetics
- Structure/Function Research

TP53 MUTATION DATABASE
- Molecular data
- Functional data
- Epi data
- Clinical data
- Recommendations and Guidelines
TP53 Mutations In Human Cancers
Types Of Genetic Alterations In Cancer

Somatic: Acquired during development and present only in cells undergoing clonal expansion

Inherited: present in the germline and detectable in both healthy and cancer cells

- Loss of parts or whole chromosomes
- Duplication of chromosomes
- Chromosome translocations
- Amplifications of chromosome fragments

- Intragenic deletions or insertions
- Recombination between adjacent genes
- Nonsense (Stop) mutations
- Missense mutations (substitutions)
- Methylation
TP53 Somatic Alterations in Human Cancers: data from genomic studies

cBioportal, July 2019
TP53 Germline Mutations Predispose To Several Types of Cancers

![Tumors Associated with TP53 germline mutations (N = 2591)](chart)

- **Breast**: 31.48% (815)
- **Soft Tissues**: 12.16% (315)
- **Brain**: 11.15% (289)
- **Adrenal Gland**: 9.53% (247)
- **Bones**: 9.3% (241)
- **Other**: 8.61% (223)
- **Hematological**: 4.17% (108)
- **Colorectum**: 2.82% (73)
- **Lung**: 2.78% (72)
- **Skin**: 2.32% (60)
- **Ovary**: 1.80% (49)
- **Stomach**: 1.16% (30)
- **Kidney**: 0.89% (23)
- **Prostate**: 0.46% (12)
- **Testis**: 0.30% (10)
- **Liver**: 0.31% (8)
- **Head & Neck**: 0.31% (8)
- **Esophagus**: 0.12% (3)
- **Larynx**: 0.12% (3)
- **Bladder**: 0.08% (2)

© IARC TP53 Database, R20.
p53 Protein is Targeted by Viruses

Polyomaviruses

- pRb
- p53
- Large T (708 aa)

Adenoviruses

- pRb
- p53
- E1A (283 aa)
- E1B (390 aa)

Papillomaviruses

- pRb
- E6-AP
- E7 (98 aa)
- E6 (158 aa)
The Majority Of TP53 Mutations Are Missense Mutations
Missense Mutations are Clustered in the DNA-binding Domain

![Graph showing mutations in different domains of p53]

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mut. frequency</th>
<th>Missense mut.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transactivation (1-42; 43-62)</td>
<td>1%</td>
<td>50.8%</td>
</tr>
<tr>
<td>Proline-rich (65-97)</td>
<td>2.3%</td>
<td>45.4%</td>
</tr>
<tr>
<td>DNA binding (102-292)</td>
<td>80%</td>
<td>82.1%</td>
</tr>
<tr>
<td>Oligomerisation (323-356)</td>
<td>3.4%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Regulation (363-393)</td>
<td>0.3%</td>
<td>72.7%</td>
</tr>
</tbody>
</table>
Post-Translational Modification Sites Are Rarely Mutated In Cancer

Number of missense mutations reported in sporadic cancers (IARC TP53 database, R12).
Most Frequent Mutations Are In The Loops That Make Contact With DNA

Codon: 175 > 248 > 273 > 282 > 249 > 245 > 220 > 176
# Effects Of The Most Frequent TP53 Mutations

Mutations that represent about 20% of all mutations

<table>
<thead>
<tr>
<th>Codon</th>
<th>Residue</th>
<th>Mutant</th>
<th>Effects on protein structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>Arg</td>
<td>His</td>
<td>Breaks crucial H-bond bridging loops L2 and L3</td>
</tr>
<tr>
<td>248</td>
<td>Arg</td>
<td>Gln</td>
<td>Breaks main contact with DNA in minor groove</td>
</tr>
<tr>
<td>273</td>
<td>Arg</td>
<td>His</td>
<td>Breaks main contact with DNA in major groove</td>
</tr>
<tr>
<td>248</td>
<td>Arg</td>
<td>Trp</td>
<td>Breaks main contact with DNA in minor groove</td>
</tr>
<tr>
<td>273</td>
<td>Arg</td>
<td>Cys</td>
<td>Breaks main contact with DNA in major groove</td>
</tr>
<tr>
<td>282</td>
<td>Arg</td>
<td>Trp</td>
<td>Destabilizes H2 helix and DNA binding in the major groove and breaks contacts on the β- hairpin</td>
</tr>
</tbody>
</table>
Biological Activities Of p53 Mutant Proteins

**WT p53**
- DNA-Binding
- Transactivation
- Growth suppression

**Dominant Negative**
- Loss Of Function
- Retained Function

**Mutant p53**
- Protein interactions
  - Transactivation, Repression, ….
- Gain Of Function
- Growth promotion

**Temperature Sensitivity**
Models of Mechanisms Through Which p53 Mutants Function

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mutant p53 interacts with DNA directly using mutant p53 binding elements or other regions on the DNA, including MARs, to regulate transcription. Transcriptional cofactors and other proteins can be involved.</td>
<td>PML, EGR1, TOP1, p300</td>
</tr>
<tr>
<td>2a</td>
<td>Mutant p53 enhances transcription by forming a complex with TFs that can include transcriptional cofactors and other proteins.</td>
<td>EGR1, TopBP1, PIN1, VDR, ETS1, NF-xB, p63, p73, SP1, SREBP, NF-Y, ETS2, E2F1, p300, HDAC, CBP</td>
</tr>
<tr>
<td>2b</td>
<td>In response to a stimulus, mutant p53 is recruited to a transcription regulatory complex that can include TFs, transcriptional cofactors and other proteins. This mostly results in activation of target gene expression.</td>
<td>VDR, PLK2, NF-Y, SP1, p300, stimulus: TPA, vitamin D, DNA damage</td>
</tr>
<tr>
<td>3</td>
<td>Mutant p53 decreases transcription by binding TFs and/or transcriptional cofactors and other proteins, sometimes preventing their binding to DNA. This activity can also involve aggregation of mutant p53 with other proteins.</td>
<td>TopBP1, ANKRD11, VDR, SMAD2, p63, p73, SP1, p300</td>
</tr>
<tr>
<td>4</td>
<td>Mutant p53 interacts with other proteins, not directly involved in transcriptional regulation, and enhances or blocks their function.</td>
<td>NRD1, EFEMP2, TOP1, BTG2, MRE11</td>
</tr>
</tbody>
</table>

Muller & Vousden, NatCellBiol, 2012
How to Interpret Mutation Patterns?

- **Nature of carcinogen**
- **Type of mutation**
  - Position and sequence context
  - Strand bias/asymmetry
- **Metabolization and intracellular processing**
- **ADAPTATION**
- **Cellular strategies to cope with the lesion:**
  - DNA repair
- **Effects of the mutation on cell behavior**
Sequence Context: CpG Mutations Are The Most Frequent Type Found In Human Cancers

C>T mutations occur frequently at CpG sites by endogenous mechanisms.

From Yang et al., 1995
There is a strand bias (or strand asymmetry) when a mutation event occurs preferentially on one strand of DNA.

**DNA**

5' AGT GT C 3' 3' TCA CAG 5'

**RNA**

5' AGU GUC 3' 3' AGU GUC 5'

**Coding strand or non-transcribed strand**

**Non-coding strand or transcribed strand**
Interplay Between Mutagenesis And Biological Selection

Most frequent mutations are those arising from mutation events with high dinucleotide substitution rates and that produce non-functional proteins.

*Substitution rates calculated according to dinucleotide substitution rates derived from human-mouse aligned sequences of chromosomes 21 and 10 (Lunter and Hein 2004) represent an estimate of the expected frequency of mutation events.
The Hupki Mouse And HUF Assay: New Tools To Investigate Human p53 Mutagenesis *In Vivo*

HUF is an embryonic fibroblast immortalization assay that uses cells from the Hupki mice, which can be used as an in vitro approximation of p53 gene mutagenesis in human cancer development.

Adapted from Hollstein
A Specific Mutation Pattern In Lung Cancer From Smokers

G:C>T:A

Smokers (N=419): 30%
Non-Smokers (N=153): 12%
Non-tobacco related, (N=4516): 9%

G>T mutations are more frequent in lung cancers from smokers than in non-tobacco related cancers.

Adapted from Pfeifer et al. Oncogene (2002)
Mutagenesis And Selection in Lung Cancer

- **C>T(CpG)**
- **G>T**
- **Other**

% of all mutations

**Lung cancers**

**G>T mutations at hotspot residues**

**Breast, Brain, CRC**

Adapted from Pfeifer et al. Oncogene (2002)
Tobacco carcinogens

Cigarettes contain many hazardous substances that damage the lungs when inhaled.

- 4-Aminobiphenyl
- 2-Naphthylamine
- Benzo(a)pyrene

Concentration/cigarette
- 15-40 mg
- 10-23 mg
- 100-600 mg
- 20-50 mg
- 0-200 ng
- 1.3-16 ng
- 20-70 ng
- 2.4-4.6 ng
- 1.7-22 ng

Source: IARC monograph vol 138
TP53 Mutations Hotspots In Lung Tumors Of Smokers Coincide With Experimentally Induced B(a)P Adducts

Benzo(a)pyrene

From Pfeifer et al.
TP53 Mutations Induced By B(a)P In the HUF assay Are Similar To The One Found In Lung Tumors Of Smokers

From Hollstein et al.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Base change*</th>
<th>Amino acid substitution</th>
<th>Lung cancer p53 mutation† (rank)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bap-treated²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-4</td>
<td>GCC to GGC (C to G)</td>
<td>A 138 G</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GTC to GTT (C to T)</td>
<td>V 157 V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CGC to CCC (G to C)</td>
<td>R 158 P</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-13</td>
<td>CGT to CAT (G to A)</td>
<td>R 273 H</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-14</td>
<td>GGG to TGG (G to T)</td>
<td>G 117 W</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-D14B</td>
<td>GTC to TTC (G to T)</td>
<td>V 157 F</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-15</td>
<td>g to t (G to T)</td>
<td>(intron 7)¹</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-16</td>
<td>GAG to GAA (G to A)</td>
<td>E 224E³</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-20</td>
<td>g to c (G to C)</td>
<td>(intron 5)¹</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-28</td>
<td>GTC to GTT (C to T)</td>
<td>V 157 V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CGC to CTC (G to T)</td>
<td>R 158 L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g to t (G to T)</td>
<td>(intron 5)¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g to t (G to T)</td>
<td>(intron 5)¹</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-48</td>
<td>AGA to GGA (A to G)</td>
<td>R 280 G</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-106</td>
<td>CCT to TCT (C to T)</td>
<td>P 278 S</td>
<td></td>
</tr>
<tr>
<td>HUF-BaP-116</td>
<td>GGG to TGG (G to T)</td>
<td>G 279 W</td>
<td></td>
</tr>
</tbody>
</table>
TP53 Mutations In Skin Cancer: Effect Of UV Exposure

**Repair defects:**

Skin SCC in XP patients

- CC > TT: 47%
- Insertion/deletion: 6%
- Other: 24%
- UV-induced mutations: 13%

**UV exposure:**

Sporadic Skin SCC

- CC > TT: 24%
- Insertion/deletion: 5%
- Other: 5%
- UV-induced mutations: 6%

CC > TT = UV-induced mutations
TP53 Mutations In Breast Cancer: Effect Of Genetic Background

All Breast

- A:T>C:G: 4%
- A:T>G:C: 15%
- A:T>T:A: 12%
- G:C>A:T: 21%
- G:C>C:G: 7%
- G:C>T:A: 10%
- del: 2%  
- ins: 3%
- other: 12%

24% AT

BRCA1/2 carriers

- A:T>C:G: 3%
- A:T>G:C: 10%
- A:T>T:A: 12%
- G:C>A:T: 12%
- G:C>C:G: 18%
- G:C>T:A: 8%
- del: 1%  
- ins: 3%
- other: 10%

36% AT
Mutations As “Carcinogen Fingerprints”

A mutation can be considered as a carcinogen fingerprint if there is:

- Evidence that a characteristic mutation pattern is found in exposed compared with non-exposed individuals. This pattern should be distinct by at least one of the following criterion: type of mutations, site of mutations, strand bias.

- Evidence that the suspected carcinogen induces similar mutations in experimental model systems.

- Evidence that mutations occur early in tumor development.
## Known TP53 Mutation Fingerprints

<table>
<thead>
<tr>
<th>Source</th>
<th>Mutagen</th>
<th>Adduct</th>
<th>TP53 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UV radiations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|                | ![UV Radiations](image) | ![Electromagnetic Spectrum](image) | **CC to TT**  
Various codons  
Skin cancer: 15%  
Other cancers: <1% |
| **Aflatoxins** | ![Aflatoxin](image) | ![Structure](image) | **G to T**  
Codon 249  
Liver cancer: >30%  
Other cancers: <1% |
| **Tobacco smoke** | ![Tobacco Smoke](image) | ![Benzo(a)pyrene](image) | **G to T**  
Codons 157, 158, 248, 273  
Lung cancer: 30%  
Other cancers: <10% |
| **Aristolochic acids** | ![Aristolochic Acids](image) | ![Structure](image) | **A to T**  
Codon 131  
Urothelial cancer |

### Source Mutagen Adduct TP53 mutations
- **UV radiations**
  - Mutagen: Various codons
  - Adduct: Ultraviolet Region of the Electromagnetic Spectrum
  - TP53 mutations: CC to TT  
Skin cancer: 15%  
Other cancers: <1%
- **Aflatoxins**
  - Mutagen: Codon 249
  - Adduct: Aflatoxin B1: C$_{17}$H$_{12}$O$_6$ PM: 312.3
  - TP53 mutations: G to T  
Liver cancer: >30%  
Other cancers: <1%
- **Tobacco smoke**
  - Mutagen: Codons 157, 158, 248, 273
  - Adduct: Benzo(a)pyrene
  - TP53 mutations: G to T  
Lung cancer: 30%  
Other cancers: <10%
- **Aristolochic acids**
  - Mutagen: Codon 131
  - Adduct: Aristolochic acids
  - TP53 mutations: A to T  
Urothelial cancer
Clinical Applications Of TP53 Mutations
From Early Detection To Gene Therapy

- Cancer diagnosis
  - Early detection of cancerous lesion
  - Identification of cancer type
  - Marker of clonality

- Cancer aetiology
  - Identification of cause/exposure

- Patient outcome
  - Predict patient survival
  - Surveillance of recurrence

- Cancer treatment
  - Prediction of treatment response, treatment selection
  - Gene therapy
  - Re-activating TP53 in mutated cells
# Prognostic Value Of TP53 Mutations

## Chapter 8: TP53 Somatic Mutations: Prognostic and Predictive Value in Human Cancers

<table>
<thead>
<tr>
<th>TUMOR SITE</th>
<th>Number of studies* reporting that TP53 mutations are:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Related to bad prognosis</td>
</tr>
<tr>
<td>Bladder</td>
<td>4</td>
</tr>
<tr>
<td>Bones</td>
<td>1</td>
</tr>
<tr>
<td>Brain</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>28</td>
</tr>
<tr>
<td>Colorectum</td>
<td>16</td>
</tr>
<tr>
<td>Esophagus</td>
<td>2</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>7</td>
</tr>
<tr>
<td>Hematol.</td>
<td>12</td>
</tr>
<tr>
<td>Larynx</td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>8</td>
</tr>
<tr>
<td>Ovary</td>
<td>7</td>
</tr>
<tr>
<td>Pancreas</td>
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</tr>
<tr>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>2</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
</tr>
<tr>
<td>Renal pelvis</td>
<td>1</td>
</tr>
</tbody>
</table>

* Only studies with > 50 cases were included

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Assessing p53 status: Protein Accumulation vs Mutation

- 90% are negative by IHC
- 95% are negative by IHC
- 90% are negative by IHC
- 96% are positive by IHC

- 23% of cases with mutations may stain negative
- Studies using IHC to investigate p53 prognostic value have yielded inconsistent results
- IHC alone is not suitable for assessing TP53 mutation status
TP53 Mutations Are Associated With Shorter Survival in Breast Cancer Independently Of Stage, Grade And Hormone Receptors Status

Tumor grade <3, tumor size <5 cm, node negative and ER or PR positive cases (204 patients)

No mutation

40% decrease in survival at 5 years

\[ p<0.0001 \]

Olivier et al., Clin Cancer Res, 2006
TP53 Missense Mutations Within The DNA-binding Loops And Non-Missense Mutations Are Associated With The Worst Prognosis In Breast Cancer

Olivier et al., Clin Cancer Res, 2006
TP53 Mutations Are Unevenly Distributed Across Molecular Subtypes

From Langerod et al., Breast Cancer Res, 2007 & Sorlie et al., PNAS, 2002
Gene Expression Signature Of TP53 Status

Langerod et al., Breast Cancer Res, 2007
Strategies for Efficient Cancer Therapy: Virus-based Therapies

- **ONYX-015**
  - Is an attenuated chimeric human group C adenovirus, that has been developed to preferentially replicates in and lyses tumor cells that are p53 negative (McCormick, Cancer Biol Ther. 2003).

- **Advexin (Ad5CMV-p53)**
  - Is a non-replicating, non-integrating adenoviral vector that carries the p53 gene (Gabrilovich, Expert Opin Biol Ther., 2006).
Strategies for Efficient Cancer Therapy: Small Molecules That Target p53

- **Inhibition of mdm2/p53 interaction** (*Nutlin-3, RITA*)
  - Kill cancer cells with WT p53

- **Reactivation of mutant p53** (*PRIMA-1, CP31398, WR1065, MIRA-1, STIMA-1, RETRA*)
  - Kill cancer cells with MUT p53
Further Information

Selected references and other resources links at: http://p53.iarc.fr/