Alterations of p53 are common in early stage prostate cancer

Sean R. Downing, PhD,[1,2] Pamela J. Russell, PhD,[1,2] Paul Jackson, PhD[1,2]

[1]Oncology Research Centre, Prince of Wales Hospital, Randwick, NSW, 2031, Australia
[2]Faculty of Medicine, University of New South Wales, Kensington, NSW, 2033, Australia

DOWNING SR, RUSSELL PJ, JACKSON P. Alterations of p53 are common in early stage prostate cancer. The Canadian Journal of Urology. 2003;10(4):1924-1933.

Introduction: *Mutations in the p53 tumor suppressor gene are generally believed to be a late event in the progression of prostate cancer, and are associated with androgen-independence, increased angiogenesis, metastasis, recurrence, and a worse prognosis. In this review, we examine the current literature available on p53 mutations found in prostate cancer and focus on stages A (T1) and B (T2) of the disease. The alteration of genes involved in p53 regulation are also examined, as well as animal models that support an early role for p53 in the initiation and development of prostate cancer.*
Results: *We report here that p53 mutations occur in approximately one third of early stage prostate cancers and that expression of HPV E6 or over-expression of mdm2 contributes to loss of p53 function in an additional 25% of organ-confined disease. High levels of p53 mutation are found in normal prostate tissue of prostate cancer patients and in the precursor lesion, prostatic intraepithelial neoplasia, further implicating p53 mutation or loss as an early event in prostate tumorigenesis.*
Conclusions: *In contrast to popular opinion, p53 mutations are a common event in early stage, organ-confined prostate cancer and although more studies are needed, the loss of p53 function through expression of viral or cellular oncoproteins also appears quite common. Evidence from animal models of prostate cancer further supports the notion that loss of p53 function plays a critical role in the development of prostate cancer.*

Key Words: p53, prostate cancer, tumor progression, tumor suppressor

Accepted for publication February 2003

Acknowledgements
The authors would like to note a previously published manuscript on p53 mutations in early stage prostate cancer that discussed difficulties with current methodologies for the detection of p53 mutations, contained a more limited review of the available data (Urologic Oncology 2001; 6:103-110).

Address correspondence to Dr. Sean R. Downing, Dana-Farber Cancer Institute, Room D710B, 44 Binney Street, Boston, MA 02115, USA

Background

The importance of p53 as a tumor suppressor gene is highlighted by the observation that it is mutated in a large proportion of diverse cancers.[1] An enormous amount of investigation into the structure and function of p53 has been performed and reviewed extensively.[2-4] The main role of p53 appears to be mediation of the cellular response to agents that induce DNA damage, thereby preventing the replication and inheritance of mutations. In this

capacity, p53 has been termed "the guardian of the genome",[5] and it accomplishes this role through the regulation of transcription, initiation of cell death, induction of DNA repair, and maintenance of the diploid state, all of which can contribute to growth arrest via G_1 and G_2/M checkpoints, apoptosis, differentiation, or senescence of the cell.[6-8]

As with many other cancers, mutations in the p53 tumor suppressor gene are a frequent genetic event in prostate cancer (CaP), and can be detected in up to 94% of cases.[9] In cancer as a whole, six codons within p53 (codons 175, 245, 248, 249, 273, and 282) are more likely to be mutated than any other codon and are defined as "hotspots". Unlike other tumors, in which "hotspot" residues account for approximately one-half of the reported p53 mutations,[10] "hotspot" mutations account for less than twenty percent of p53 mutations in CaP and a prostate-specific mutation has not been identified Figure 1. A key question remaining is to address at what stage of CaP progression do p53 mutations occur? Are they an early event associated with indolent disease or localized tumors, or are they a much later event associated with more aggressive disease involving androgen-independence and metastasis? Given the role of p53 in protecting cells from DNA damage, the answer to this question has important implications for clinicians because the presence of either a functional or functionally defective p53 protein in CaP could have major consequences for a tumor's response to current modes of therapy, which involve treating prostate cancer cells with DNA damaging drugs or radiation.

In contrast to the prevailing view of recent years, in this review, we shall present evidence that p53 mutations are not restricted to being a late event in the progression of CaP. This conclusion is supported by several lines of evidence from both the analysis of tumor samples, as well as data from experimental systems including: the presence of p53 mutations in early stage disease (stages A/T1 and B/T2) and premalignant prostate; loss of heterozygosity of the p53 gene in CaP; studies reporting the presence of cellular and viral proteins in CaP that inhibit wild type p53 function; the generation of prostate cancer cell lines; and studies of animal models that mimic prostate cancer progression.

Results

Are p53 mutations a common event in early stage, organ-confined prostate cancer?

Until recently, conclusions based on immunohistochemical and molecular analysis indicated that mutations in p53 were a late event in the progression of prostate cancer and associated with metastasis and androgen-independence.[11-12] However, more recently, evidence has been accumulating which suggests that p53 mutations might be present at a much earlier stage of the disease. This subject was first addressed by Heidenberg et al, who reviewed p53 mutations in CaP, and demonstrated that for primary, organ-confined CaP, the incidence of p53 mutations reached 80% in some cases.[9] In this study, we have chosen to examine stages A (T1) and B (T2) of CaP, because these stages are defined by the tumor being localized to the prostate, with no sign of capsular invasion or metastasis.[13]

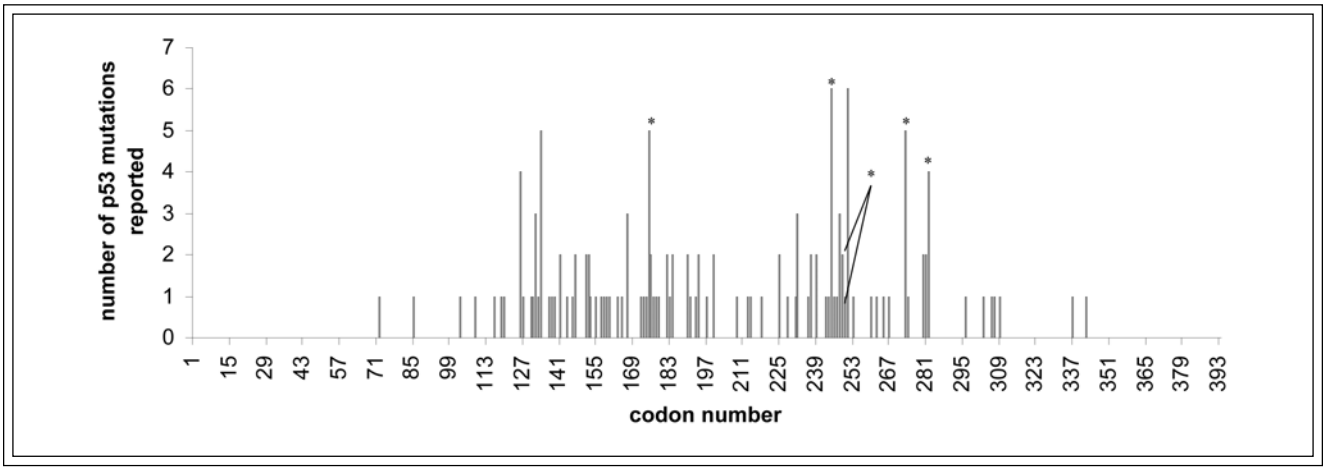

Figure 1. Spectrum of p53 gene mutations in carcinoma of the prostate. Data was compiled from papers reporting specific p53 mutations in prostate.[14,15,17,20,21,23-25,31,37,52,53,100,103,121-132] Care was taken to ensure that mutations from the same specimen reported in more than one article were only reported once in the figure. "Hotspot" mutations account for approximately 15% of the p53 mutations found in CaP.

Table 1 summarizes available data concerning the nature of p53 mutations in studies in which stages A and B CaP were clearly identified, together with the method used for analysis. Of a total of 32 studies, 29 found p53 mutations in the samples examined, with a range from 0% of cases [for example 14] to 100% of cases[15] and an overall incidence of approximately 30%. Interestingly, in contrast to the vast majority of reports, a study of Japanese prostate cancers by Wanatabe et al.[16] found no p53 mutations in stage A and only 4% in stage B tumors by single-strand conformation polymorphism (SSCP). Whilst these values are some of the lowest reported for early stage CaP, the authors found mutations in each of the coding exons (exons 2-11) and noted that in Japanese men, mutations were mostly transversions, unlike Western mutations that are mostly transitions.[17] This report highlights the need for examination of all coding exons of p53 (exons

TABLE 1. **Detection of p53 mutations in early prostate cancer**

Author (ref)	**Technique**	**Stage A or T1**	**Stage B or T2**	**Combined Stages (%)**
Fox 1993[19]	IHC (PAb240, PAb1801, CM-1 & DO-7)	6/45		6/45 (13)
Van Velduizen 1993[18]	IHC (PAb240 & PAb1801)	0/1	23/27	23/28 (82)
Navone 1993[20]	IHC (CM-1)			(0)
Uchida 1993[21]	SSCP (exons 5-8)		1/3	1/3 (33)
Chi 1994[17]	SSCP (exons 4-11)		8169	8/16 (50)
Ittmann 1994[22]	SSCP (exons 5-8), IHC (CM-1) & LOH			
Massenkeil 1994[23]	LOH (17p13.1)		1/5	
	SSCP (exons 5-8)		0/9	1/9 (11)
Eastham 1995[14]	IHC (DO-7 & CM-1)			0/18 (0)
Hall 1995[24]	IHC (PAb1801 & CM-1)			1/26 (4)
Konishi 1995[25]	LOH (codon 72) & IHC (BP53-12)		2/5	2/5 (40)
Bauer 1995[26]	IHC (Signet Labs)		28/57	28/57 (49)
Moyret-Lalle 1995[27]	IHC (PAb1801, CM-1 & DO-7) & SSCP (exons 2,4 & 5-9)		1/3	1/62/9 (22)
Zhang 1996[28]	IHC (DO-1)		0/1	0/1 (0)
Ittmann 1996[29]	LOH (17p)		2/26	2/26
Bauer 1996[30]	IHC (Signet Labs, Cat #8640)	10/25	103/149	113/174 (65)
Wertz 1996[31]	SSCP (exons 4-10)		4/7	
	IHC (PAb1801, CM-1, DO-7 & DO-1)		4/7	4/7 (57)
Yang 1996[32]	IHC (DO-7)			17/49 (35)
Moul 1996[33]	IHC (Signet Labs)	1/3	37/59	38/62 (61)
Stattin 1996[34]	IHC (DO-1)	4/32	6/57	10/89 (11)
Wanatabe 1997[16]	SSCP (exons 2-11)	0/5	1/25	1/30 (3)
Theodorescu 1997[35]	IHC (DO-1)	?/16	?/55	20/71 (28)
Schlechte 1997[36]	TGGE (exons 5-8)	0/3	1/4	1/7 (14)
Mottaz 1997[37]	IHC (DO-1 & PAb1801)			1/67
	SSCP (exons 5-8)			0/67 (1)
Gumerlock 1997[15]	SSCP (exons 4-10)		9/9	9/9 (100)
Byrne 1997[38]	IHC (DO-7)	2/10	3/5	5/15 (33)
Grignon 1997[39]	IHC (DO-7)		10/34	10/34 (29)
Ruijter 1998[40]	IHC (DO-1 & DO-7)		1/30	1/30 (3)
Osman 1999[41]	IHC (PAb1801)			3/51 (6)
Scherr 1999[42]	IHC (DO-7)			17/49 (35)
Brewster 1999[43]	IHC (DO-7)		40/62 (65)	
Stackhouse 1999[44]	IHC (PAb1801)			132/199 (66)
Leite 2001[45]	IHC (DO-7)		16/69	16/69 (23)
Average		**17%**	**36%**	**30%**

Abbreviations: %, percentage; SSCP, single strand conformation polymorphism; IHC, immunohistochemistry; LOH, loss of heterozygosity; TGGE, temperature gradient gel electrophoresis

2-11) for mutations, not just the conserved regions of exons 5-8, where most researchers have focused their attention. The values reported in the study by Wanatabe, although low, demonstrate that p53 mutations are more readily detected in stage B cancers than in stage A. As can be seen in Table 1, the levels of p53 mutations in CaP increase drastically from 17% in stage A to 36% in stage B. This may be due to better sampling of a larger tumor or an increase in the number of cells harboring a p53 mutation. This increase in p53 alteration across stages was best demonstrated by Van Velduizen et al, who found that 0% of stage A2 tumors (although they only examined 1 sample), 100% of stage B1, and 75% of stage B2 stained positive for p53.[18] Overall, they found that 83% of tumors with a Gleason score of less than 4 were positive for p53 immunostaining. Chi et al found that 50% of stage B cancers of Gleason Score 3-8 contained a p53 mutation by SSCP of exons 4-11.[17] They also found that 50% of normal prostatic tissue from patients with stage B cancer contained a p53 mutation and that this value was 43% for CaP patients over all stages of the disease. It would be beneficial to determine if the cancers in those patients, whose normal prostate tissue harbored a p53 mutation, carried the same mutation. This would allow for a determination of whether or not p53 mutation is a tumorigenic event in CaP development.

p53 mutations in "normal" prostate and PIN

Table 2 summarizes the occurrence of p53 mutations in normal prostatic tissue and prostatic intraepithelial neoplasia (PIN). Given its essential role in maintaining genomic integrity, alterations of p53 in non-malignant tissue would be rare, and few studies have directly examined "normal" prostate tissue. However, there are two reports in which normal prostate was examined in CaP patients. These studies indicated that nearly one third of CaP patients harbored a p53 mutation in their normal prostatic epithelium.[17,46] In addition, Stattin et al reported that 6% of T0 cases were also positive for p53 immunoreactivity.[34] These findings suggest that p53 mutations may be acquired early, before phenotypic malignant changes have occurred, at least in a subgroup of prostate cancers.

PIN is widely held to be a premalignant condition that can give rise to CaP, and genetic changes that occur within PIN have often been considered to be initiating events for the development of prostate cancer. Mutations in p53 have been reported in 5%-70% of PIN cases Table 2.[46-50] It was also found that PIN associated with stage C prostate cancer contained high levels of mutant p53.[51] Since mutations were found concomitantly in both CaP and PIN, it may be concluded that p53 mutations enhance the development of CaP from PIN. It would be of interest to determine if the PIN and CaP lesions contained an identical p53 mutation as it has been reported that metastatic deposits of CaP carry the same p53 mutations as the primary tumor and that cells containing the mutation are selected for in the metastases.[52,53]

Inactivation without mutation – other mechanisms involved in loss of p53 function

Thus far, the studies discussed have used mutation

TABLE 2. **Detection of p53 mutations in "normal" prostate and PIN**

Author (ref)	Technique	"Normal" (%)	PIN (%)
Chi 1994[17]	SSCP (exons 4-11)	5/10 (stage B) 1/4 (stage C) (43)	
Yaman 1997[48]	IHC (CM-1)		2/11 (CaP) (18)
Salem 1997[51]	IHC (PAb1801 & BP53-12)		6/6 (stage C) (100)
Cheng 1999[47]	IHC (DO-7)		19/28 (CaP) (68)
Tamboli 1998[46]	IHC (DO-7)	(CaP) (20)	(CaP) (56)
Johnson 1998[49]	IHC		(CaP) (5)
Yasunaga 1998[50]	SSCP		3/22 (CaP) (14)
Incognito 2000[54]	SSCP (exons 5-9)	0/5 (0)	
Average		**21%**	**44%**

All of the "normal" prostate and PIN specimens were from patients that also had CaP.
Abbreviations: %, percentage; PIN, prostatic intraepithelial neoplasia; SSCP, single strand conformation polymorphism; IHC, immunohistochemistry; CaP, carcinoma of the prostate (stage unknown); TGGE, temperature gradient gel electrophoresis

TABLE 3. **Abnormal expression of genes involved in p53 regulation during early stage CaP**

Author	Abnormality	Technique	Number of cases (%)
Ittman[22]	Mdm2 gene amplification	Southern blot	0/29 (0)
Moyret-Lalle1995[88]	HPV-16/18 E6	PCR & ISH	3/7 (43)
Suzuki 1996[87]	HPV-16 E6	PCR	5/29 (17)
Osman 1999[41]	Mdm2	IHC	11/51 (22)
Leite 2001[45]	Mdm2	IHC	23/69 (33)

Abbreviations: %, percentage; PCR, polymerase chain reaction; ISH, in situ hybridization; IHC, immunohistochemistry; HPV, human papilloma virus

as a marker for loss of p53 function in CaP, however, reports have shown that other modes of p53 loss exist in the development of tumors, for example: methylation of the p53 promoter, loss of $p19^{ARF}$ activity either through mutations or loss of expression (LOE), over-expression of the mdm-2 oncogene, and inhibition of p53 activity due to binding of viral oncogenes or exclusion from the nucleus.[55-61] Except for methylation of the p53 promoter, all of these modes of p53 loss have been examined in prostate cancer Table 3 and will be discussed.

Mdm-2 is a p53-responsive gene that serves as a negative feedback regulator of p53 activity.[56] The role of mdm-2 in this regulatory mechanism is to bind and inactivate p53 and to shuttle p53 out of the nucleus, where it is then ubiquitinated and degraded.[62-66] Once released from p53, mdm-2 relocates to the nucleus to continue cytoplasmic translocation of p53. Thus over-expression of mdm-2 by gene amplification can result in a loss of p53 function in the absence of mutations and this occurs in several cancers Figure 2a.[67-70] There does not appear to be any amplification of the mdm-2 gene itself in stage B CaP,[22] however, mdm-2 protein has been shown to be over-expressed, by IHC, in as many as 32.5% of radical prostatectomy specimens,[71] including one third of stage B tumors,[45] suggesting that there may be multiple pathways to CaP progression involving the loss of p53 function. Given that very few studies have examined the expression pattern of mdm-2 in the normal prostate and in CaP thus far, more research is required. The degradation of p53 by mdm2 is inhibited by $p19^{ARF}$ Figure 2b,[59,60] thus adding another regulatory level to the control of p53 activity within the cell, and loss of $p19^{ARF}$ may allow for improper degradation of p53 by mdm2. Two studies have examined alterations in the ARF gene in prostate cancer specimens. Park et al found no mutations in $p19^{ARF}$ [72] while Nguyen et al found hypermethylation in exon 2 in 73% of prostate cancers.[73] Individual stages of CaP could not be determined from the manuscripts, however, the findings support the notion of multiple pathways to loss of p53 function in prostate cancer.

Several viral proteins can inhibit the function of wild type p53 by a manner analogous to that used by mdm-2, for example, the E6 protein of the human papilloma virus (HPV).[74] Infection by HPV is a major factor in the development of cervical cancer,[75] and the presence of HPV in prostatic tissue has been examined to determine a possible link with the development of a subset of CaP, with the presence of HPV reported in

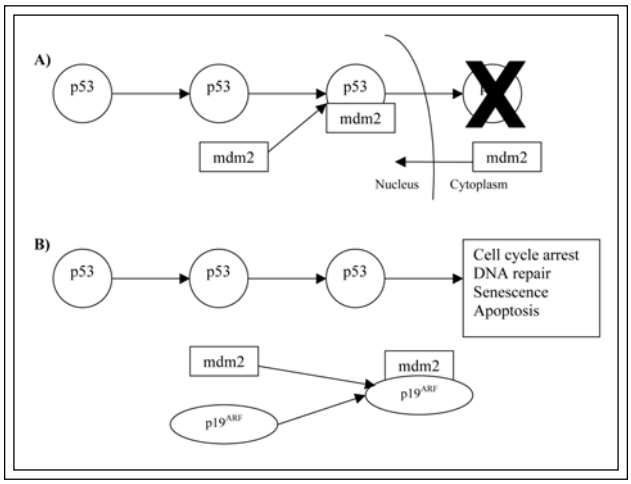

Figure 2. Regulation of p53 activity. Mdm2 binds to p53 resulting in nuclear export, ubiquitination, and eventual degradation of the p53 protein. Once released from p53, mdm2 is free to shuttle back into the nucleus to continue translocation of p53 into the cytoplasm (a). Viral oncoproteins, such as E6, act in a similar fashion to mdm2. The degradation of p53 by mdm2 can be inhibited by the $p19^{ARF}$ protein (b). This allows p53 to remain in the nucleus and accumulate. Over-expression of mdm2, or the loss of $p19^{ARF}$ expression, results in loss of p53 function due to reduced protein levels.

prostatic tissue ranging from 0%-100% of cases.[76-82] One suggested explanation for these varying levels of HPV has been proposed by Terris and Peehl, who found that the levels of detected HPV varied between 0%-14% in normal prostate tissue, 0%-25% in adenocarcinomas, and from 0%-18% in CaP when using different primer sets on the same tissue samples.[83] Although the levels of HPV reported in CaP vary greatly, the majority of reports place the levels at 10%-50%[84-86] with high levels being reported in both adenomas and stage B CaP,[87,88] and no mutations of p53 found in these cancers.[88] The absence of p53 mutations in these tumors suggests that p53 function may have been abrogated, and that there is no longer a selective pressure for the acquisition of p53 mutations. While some reports found high levels of HPV in CaP, there is still debate over the possibility that HPV directly contributes to CaP initiation and progression, or rather that the prostate merely serves as a reservoir for the sexual transmission of HPV.[89-91] However, the presence of HPV can result in an increased risk of developing CaP and may be able to predict the development of metastasis to bone.[92,93] Experimental evidence to support the notion that inhibition of p53 function by viral proteins can lead to the development of CaP has come from studies using prostate epithelial cells immortalised with HPV or SV40.[94-99]

Studies examining other modes of inhibiting p53 function, including LOH, and nuclear exclusion are very limited. Most, if not all, studies which examined p53 staining by IHC only counted cells as positive, if the nucleus stained positive or if the nucleus stained more intensely than the cytoplasm.[100] Nuclear localization is necessary for most p53 functions, thus if excluded from the nucleus, these functions cannot be performed.[101] It has also been suggested that prostate cells may inhibit p53 function by localizing p53 to the nucleolus.[102] Of several reports examining LOH of 17p or the p53 locus itself, LOH was found in 8%-11% of stage B CaP,[22,29] and 32% of biopsies and prostatectomy specimens.[103] LOH can result in the retention of one wild type allele, however, there does appear to be a gene dosage affect with p53, and simply reducing the level of wild type p53 within a cell can increase susceptibility to tumorigenesis.[104]

Lessons to be learned from animal models

Transgenic animals offer a unique opportunity for the study of prostate cancer. Models have been developed that mimic CaP progression in humans from PIN through to metastatic disease, and the advantages and disadvantages of each model have been reviewed extensively.[105-107] Animal models that do not address p53 will not be discussed here as they are beyond the scope of this review and to-date we know of no animal model that directly refutes the involvement of p53 mutations in the development of prostate cancer.

Several models indirectly support the hypothesis that p53 mutation, or inactivation, is an early and necessary event in the development and progression of CaP because they all use simian virus (SV) 40 large T antigen (TAg) under the control of a prostate specific promoter to inactivate p53 function in prostate cells,[108-114] and the transgenic mice generated develop CaP in the absence of functional p53. Several of these models appear to mimic the course of CaP in humans because the animals develop PIN and progress to CaP[109-111,115] with two of the models also developing metastatic disease.[109,110] As a side note, several of these models also strengthen the link between metastatic and androgen-independent disease, and p53 inactivation.[110-112,116,117]

SV40 large TAg can also inhibit the function of the retinoblastoma (Rb) protein,[114] so it is not clear if inactivation of both Rb and p53 is required for CaP development in the above transgenic models. However, other animal models specifically implicate loss of p53 function. The 'reconstitution model' involves introduction of oncogenic *ras* and *myc* into the developing urogenital sinus of p53 knockout animals.[118] All $p53^{-/-}$ mice developed CaP, and those $p53^{+/-}$ animals that did develop CaP had lost the remaining wild type p53 allele. The loss of the wild type p53 allele in the heterozygous animals is crucial because wild type p53 can suppress *ras* mediated transformation even in the presence of *myc*.[119,120] The absence of the p53 gene also allowed establishment of a prostate cancer cell line derived from a p53 knockout mouse.[87]

The above models provide strong evidence that a loss of normal p53 function through viral proteins or allelic loss can result in the initiation and progression of prostate cancer. Furthermore, these models also describe the development of metastasis and androgen independence in the absence of p53. The importance of these processes to the development of prostate cancer in humans remains to be clearly determined, however, it should be emphasized that LOH has been found in up to one third of CaP specimens,[103,121] and human papilloma virus (HPV) has been found in approximately one fifth of prostate cancer specimens.[84,87]

Conclusions

Mutations in the p53 tumor suppressor gene occur at a much higher frequency in early stage prostate cancer than previously thought. However, mutation is not the only route to loss of function, and altered expression of cellular or viral oncoproteins also contributes to the loss of p53 function in early CaP. Further evidence in support of an early loss of p53 in CaP comes from studies that show a high rate of p53 mutation in PIN and animal models that mimic the development of prostate cancer. While more studies are warranted to examine the specific role alterations in p53 may play in prostate cancer initiation and progression, it is clear that p53 mutations are associated with increased microvessel density, androgen-independence, and metastasis in CaP. This raises the possibility that tumorigenesis and acquisition of metastatic ability may occur simultaneously, and not sequentially, in CaP. At a clinical level, knowing if a particular patient harbored a p53 mutation in the early stages of CaP could allow for the application of more appropriate treatment strategies specifically designed to enhance a patient's chances of being more effectively treated. □

References

1. Greenblatt MS, Bennett WP, Hollstein M, Harris CC. Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis. *Cancer Res* 1994;54:4855-4878.
2. Bates S, Vousden KH. p53 in signaling checkpoint arrest or apoptosis. *Curr Opin Gen Dev* 1996;6:12-19.
3. Hansen R, Oren M. p53; from inductive signal to cellular effect. *Curr Opin Gen Dev* 1997;7:46-51.
4. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. *Nature* 2000;408:307-310.
5. Lane DP. p53, guardian of the genome. *Nature* 1992;358:15-16.
6. Ko L, Prives C. p53: puzzle and paradigm. *Genes Dev* 1996;10:1054-1072.
7. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell* 1997;88:323-331.
8. Somasundaram K, El-Deiry WS. Tumor suppressor p53: regulation and function. *Front Biosci* 2000;5:D424-D437.
9. Heidenberg HB, Bauer JJ, McLeod DG, Moul JW, Srivastava S. The role of the p53 tumor suppressor gene in prostate cancer: a possible biomarker? *Urology* 1996;48:971-979.
10. Roemark K. Mutant p53: gain-of-function oncoproteins and wild-type p53 inactivators. *Biol Chem* 1999;380:879-887.
11. Bostwick DG, Pacelli A, Lopez-Beltran A. Molecular biology of prostatic intraepithelial neoplasia. *Prostate* 1996;29:117-134.
12. Rinker-Schaeffer CW, Partin AW, Isaacs WB, Coffey DS, Isaacs JT. Molecular and cellular changes associated with the acquisition of metastatic ability by prostatic cancer cells. *Prostate* 1994;25:249-265.
13. Appendix: Clinical classification for prostate cancer. Textbook of Prostate Cancer, Kaisary AV, Murphy GP, Denis L, Griffiths K (eds). London: Martin Dunitz Ltd.;1999:357.
14. Eastham JA, Stapleton AMF, Gousse AE, Timme TL, Yang G, Slawin KM et al. Association of p53 mutations with metastatic prostate cancer. *Clin Can Res* 1995;1:1111-1118.
15. Gumerlock PH, Chi S-G, Shi X-B, Voeller HJ, Jacobson JW, Gelmann EP et al. p53 abnormalities in primary prostate cancer: single-strand conformation polymorphism analysis of complementary DNA in comparison with genomic DNA. *J Natl Cancer Inst* 1997;89:66-71.
16. Watanabe M, Fukutome K, Shiraishi T, Murata M, Kawamura J, Shimazaki J et al. Differences in the p53 gene mutational spectra of prostate cancers between Japan and western countries. *Carcinogenesis* 1997;18:1355-1358.
17. Chi S, deVere White RW, Meyers FJ, Siders DB, Lee F, Gumerlock PH. p53 in prostate cancer: frequent expressed transition mutations. *J Natl Cancer Inst* 1994;86:926-933.
18. Van Veldhuizen PJ, Sadasivan R, Garcia F, Austenfeld MS, Stephens RL. Mutant p53 expression in prostate carcinoma. *Prostate* 1993;22:23-30.
19. Fox SB, Persad RA, Royds J, Kore RN, Silcocks PB, Collins CC. p53 and c-myc expression in stage A1 prostatic adenocarcinoma: useful prognostic determinants? *J Urol* 1993;10:490-494.
20. Navone NM, Troncoso P, Pisters LL, Goodrow TL, Palmer JL, Nichols WW et al. p53 protein accumulation and gene mutation in the progression of human prostate carcinoma. *J Natl Cancer Inst* 1993;85:1657-1669.
21. Uchida T, Wada C, Shitara T, Egawa S, Koshiba K. Infrequent involvement of p53 gene mutations in the tumorigenesis of Japanese prostate cancer. *Br J Cancer* 1993; 68:751-755.
22. Ittmann M, Wieczorek R, Heller P, Dave A, Provet J, Krolewski J. Alterations in the p53 and MDM-2 genes are infrequent in clinically localised, stage B prostate adenocarcinomas. *Am J Pathol* 1994;145:287-293.
23. Massenkeil G, Oberhuber H, Hailemariam S, Sulser T, Diener PA, Bannwart F et al. p53 mutations and loss of heterozygosity on chromosomes 8p, 16q, 17p, and 18q are confined to advanced prostate cancer. *Anticancer Res* 1994;14:2789-2794.
24. Hall MC, Zagars GK, Navone NM, von Eschenbach AC, Troncoso P, Conti CJ et al. Frequency and characterisation of p53 mutations in clinically localised prostate cancer. *Urology* 1995;45:470-475.
25. Konishi N, Hiasa Y, Matsuda H, Tao M, Tsuzuki T, Hayashi I et al. Intratumor cellular heterogeneity and alterations in *ras* oncogene and p53 tumor suppressor gene in human prostate carcinoma. *Am J Pathol* 1995;147:1112-1122.
26. Bauer JJ, Sesterhenn IA, Mostofi KF, McLeod DG, Srivastava S, Moul JW. p53 nuclear protein expression is an independent prognostic marker in clinically localised prostate cancer patients undergoing radical prostatectomy. *Clin Can Res* 1995;1:1295-1300.
27. Moyret-Lalle C, Marcais C, Jacquemier J, Moles J, Daver A, Soret J et al. *ras*, *p53* and HPV status in benign and malignant prostate tumors. *Int J Cancer* 1995;64:124-129.
28. Zhang XH, Sakamoto H, Takenaka I. Accumulation of p53 and expression of CD44 in human prostatic cancer and benign prostatic hyperplasia - an immuno-histochemical study. *Br J Urol* 1996;77:441-444.
29. Ittmann MM. Loss of heterozygosity on chromosomes 10 and 17 in clinically localised prostate carcinoma. *Prostate* 1996;28:275-281.
30. Bauer JJ, Sesterhenn IA, Mostofi FK, McLeod DG, Srivastava S, Moul JW. Elevated levels of apoptosis regulator proteins p53 and bcl-2 are independent prognostic biomarkers in surgically treated clinically localised prostate cancer. *J Urol* 1996;156:1511-1516.
31. Wertz IE, Deitch AD, Gumerlock PH, Gandour-Edwards R, Chi S, de Vere White RW. Correlation of genetic and immunodetection of tp53 mutations in malignant and benign

prostate tissues. *Hum Pathol* 1996;27:573-580.
32. Yang G, Stapleton AMF, Wheeler TM, Truong LD, Timme TL, Scardino PT et al. Clustered p53 immunostaining - a novel pattern associated with prostate cancer progression. *Clin Can Res* 1996;2:399-401.
33. Moul JW, Bettencourt MC, Sesterhenn IA, Mostofi FK, McLeod DG, Srivastava S et al. Protein expression of p53, bcl-2 and Ki-67 (MIB-1) as prognostic biomarkers in patients with surgically treated clinically localised prostate cancer. *Surgery* 1996;120:159-167.
34. Stattin P, Bergh A, Karlberg L, Nordgren H, Damber JE. p53 immunoreactivity as prognostic marker for cancer-specific survival in prostate cancer. *Europ Urol* 1996;30:65-72.
35. Theodorescu D, Broder SR, Boyd JC, Mills SE, Frierson Jr HF. p53, bcl-2 and retinoblastoma proteins as long-term prognostic markers in localised carcinoma of the prostate. *J Urol* 1997;158:131-137.
36. Schlechte HH, Schnorr D, Loning T, Rudolph BD, Pohrt UM, Loening SA. Mutation of the tumor suppressor gene p53 in human prostate and bladder cancers - investigation by temperature gradient gel electrophoresis (TGGE). *J Urol* 1997;157:1049-1053.
37. Mottaz AE, Markwalder R, Fey MF, Klima I, Merz VW, Thalmann GN et al. Abnormal p53 expression is rare in clinically localised human prostate cancer: comparison between immunohistochemical and molecular detection of p53 mutations. *Prostate* 1997;31:209-215.
38. Byrne RL, Horne CHW, Robinson MC, Autzen P, Apakama I, Bishop RI et al. The expression of waf-1, p53 and bcl-2 in prostatic adenocarcinoma. *Br J Urol* 1997;79:190-195.
39. Gignon DJ, Caplan R, Sarkar FH, Lawton CA, Hammond EH, Pilepich MV et al. p53 status and prognosis of locally advanced prostatic adenocarcinoma - a study based on RTOG 8610. *J Natl Cancer Inst* 1997;89:158-165.
40. Ruijter E, van de Kaa C, Aalders T, Ruiter D, Miller G, Debruyne F et al. Heterogeneous expression of E-cadherin and p53 in prostate cancer: clinical implications. *Mod Pathol* 1998;11:276-281.
41. Osman I, Drobnjak M, Fazzari M, Ferrara J, Scher HI, Cordon-Cardo C. Inactivation of the p53 pathway in prostate cancer: Impact on tumor progression. *Clin Cancer Res* 1999;5:2082-2088.
42. Sherr DS, Vaughan D, Wei J, Chung M, Felsen D, Allbright R et al. Bcl-2 and p53 expression in clinically localised prostate cancer predicts response to external beam radiotherapy. *J Urol* 1999;162:12-16.
43. Brewster SF, Oxley JD, Trivella M, Abbott CD, Gillatt DA. Preoperative p53,bcl-2,CD44 and E-cadherin immunohistochemistry as predictors of biochemical relapse after radical prostatectomy. *J Urol* 1999;161:1238-1243.
44. Stackhouse GB, Sesterhenn IA, Bauer JJ, Mostofi FK, Connelly RR, Srivastava SK et al. p53 and bcl-2 immunohistochemistry in pretreatment prostate needle biopsies to predict recurrence of prostate cancer after radical prostatectomy. *J Urol* 1999;162:2040-2045.
45. Leite KRM, Franco MF, Srougi M, Nesrallah LJ, Nesrallah A, Bevilacqua RG et al. Abnormal expression of MDM2 in prostate carcinoma. *Mod Pathol* 2001 14:428-436.
46. Tamboli P, Amin MB, Xu HJ, Linden MD. Immunohistochemical expression of retinoblastoma and p53 tumor suppressor genes in prostatic intraepithelial neoplasia - comparison with prostatic adenocarcinoma and benign prostate. *Mod Pathol* 1998;11:247-252.
47. Cheng L, Sebo TJ, Cheville JC, Pisansky TM, Slezak J, Bergstralh EJ et al. p53 protein overexpression is associated with increased proliferation in patients with locally recurrent prostate carcinoma after radiation therapy. *Cancer* 1999;85:1293-1299.
48. Yaman O, Ozdiler E, Orhan D, Sak SD, Baltaci S, Tulunay O *et al*. Immuno-histochemical determination of p53 protein in prostatic cancer and prostatic intraepithelial neoplasms. *Urol Internat* 1997;58:199-202.
49. Johnson MI, Robinson MC, Marsh C, Robson CN, Neal DE, Hamdy FC. Expression of bcl-2, bax, and p53 in high-grade prostatic intraepithelial neoplasia and localised prostate cancer - relationship with apoptosis and proliferation. *Prostate* 1998;37:223-229.
50. Yasunaga Y, Shin M, Fujita MQ, Nonomura N, Miki T, Okuyama A, Aozasa K. Different patterns of p53 mutations in prostatic intraepithelial neoplasia and concurrent carcinoma – analysis of microdissected specimens. *Lab Invest* 1998;78:1275-1279.
51. Salem CE, Tomasic NA, Elmajian DA, Esrig D, Nichols PW, Taylor CR et al. p53 protein and gene alterations in pathological stage C prostate carcinoma. *J Urol* 1997;158:510-514.
52. Meyers FJ, Gumerlock PH, Chi SG, Borchers H, Deitch AD, deVere White RW. Very frequent p53 mutations in metastatic prostate carcinoma and in matched primary tumors. *Cancer* 1998;83:2534-2539.
53. Stapleton AMF, Timme TL, Gousse AE, Li Q, Tobon AA, Kattan MW et al. Primary human prostate cancer cells harboring p53 mutations are clonally expanded in metastases. *Clin Can Res* 1997;3:1389-1397.
54. Incognito LS, Cazares LH, Schellhammer PF, Kuban DA, Van Dyk EO, Moriarty RP et al. Overexpression of p53 in prostate carcinoma is associated with improved overall survival but not predictive of response to radiotherapy. *Int J Oncol* 2000;17:761-769.
55. Kang JH, Kim SJ, Noh D, Park IA, Choe KJ, Yoo OJ, Kang H. Methylation in the p53 promoter is a supplementary route to breast carcinogenesis: correlation between CpG methylation in the p53 promoter and the mutation in the p53 gene in the progression from ductal carcinoma *in situ* to invasive ductal carcinoma. *Lab Invest* 2001;81:573-579.
56. Piette J, Neel H, Marechal V. Mdm2: keeping p53 under control. *Oncogene* 1997;15:1001-1010.
57. Gao X, Porter AT, Honn KV. Involvement of the multiple tumor suppressor genes and 12-lipoxygenase in human prostate cancer. Therapeutic implications. *Adv Exp Med Biol* 1997;407:41-53.
58. Dong J, Isaacs WB, Isaacs JT. Molecular advances in prostate cancer. *Curr Opin Oncol* 1997;9:101-107.
59. Tao WK, Levine AJ. p19(ARF) stabilises p53 by blocking nucleo-cytoplasmic shuttling of Mdm2. *Proc Natl Acad Sci USA* 1999;96:6937-6941.
60. Honda R, Yasuda H. Association of p19(ARF) with mdm2 inhibits ubiquitin ligase activity of mdm2 for tumor suppressor p53. *EMBO J* 1999;18:22-27.
61. Robertson KD, Jones PA. The human ARF cell cycle regulatory gene promoter is a CpG island which can be silenced by DNA methylation and down-regulated by wild-type p53. *Mol Cell Biol* 1998;18:6457-6473.
62. Kubbutat MHG, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. *Nature* 1997;387:299-303.
63. Haupt Y, Maya R, Kazaz A, Oren M. Mdm2 promotes the rapid degradation of p53. *Nature* 1997;387:296-299.
64. Roth J, Dobbelstein M, Freedman DA, Shenk T, Levine AJ. Nucleo-cytoplasmic shuttling of the hdm2 oncoprotein regulates the levels of the p53 protein via a pathway used by the human immunodeficiency virus rev protein. *EMBO J* 1998;17:554-564.
65. Fuchs SY, Adler V, Buschmann T, Wu X, Ronai Z. Mdm2 association with p53 targets its ubiquitination. *Oncogene* 1998;17:2543-2547.
66. Tao WK, Levine AJ. Nucleocytoplasmic shuttling of oncoprotein Hdm2 is required for Hdm2-mediated degradation of p53. *Proc Natl Acad Sci USA* 1999;96:3077-3080.

67. Momand J, Jung D, Wilczynski S, Niland J. The mdm2 gene amplification database. *Nucleic Acids Res* 1998;26:3453-3459.
68. Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. Amplification of a gene encoding a p53-associated protein in human sarcomas. *Nature* 1992; 38:80-83.
69. Sigalas I, Calvert AH, Anderson JJ, Neal DE, Lunec J. Alternatively spliced mdm2 transcripts with loss of p53 binding domain sequences: transforming ability and frequent detection in human cancer. *Nature Medicine* 1996;2:912-917.
70. Wiethege T, Voss B, Muller KM. Detection of mdm2-proto-oncogene in paraffin embedded human bronchial epithelium. *J Cancer Res, Clin Oncol* 1994;120:252-255.
71. Osman I, Drobnjak M, Fazzari M, Ferrara J, Scher HI, Cordon-Cardo C. Inactivation of the p53 pathway in prostate cancer: impact on tumor progression. *Clin Can Res* 1999;5:2082-2088.
72. Park DJ, Wilczynski SP, Pham EY, Miller CW, Koeffler HP. Molecular analysis of the INK4 family of genes in prostate carcinomas. *J Urol* 1997;157:1995-1999.
73. Nguyen TT, Nguyen CT, Gonzales FA, Nichols PW, Yu MC, Jones PA. Analysis of cyclin-dependent kinase inhibitor expression and methylation patterns in human prostate cancers. *Prostate* 2000;43:233-242.
74. Tommasino M, Crawford L. Human papillomavirus E6 and E7: proteins which deregulate the cell cycle. *Bioessays* 1995;17:509-518.
75. zur Hausen. Papillomavirus infections—a major cause of human cancers. *Biochim Biophys Acta* 1996;1288:F55-78.
76. Anderson M, Handley J, Hopwood L, Murant S, Stower M, Maitland NJ. Analysis of prostate tissue DNA for the presence of human papillomavirus by polymerase chain reaction, cloning, and automated sequencing. *J Med Virol* 1997;52:8-13.
77. Strickler HD, Burk R, Shah K, Viscidi R, Jackson A, Pizza G et al. A multifaceted study of human papillomavirus and prostate carcinoma. *Cancer* 1998;82:1118-1125.
78. Noda T, Sasagawa T, Dong Y, Fuse H, Namiki M, Inoue M. Detection of human papillomavirus (HPV) DNA in archival specimens of benign prostatic hyperplasia and prostatic cancer using a highly sensitive nested PCR method. *Urol Res* 1998;26:165-169.
79. Serfling U, Ciancio G, Zhu WY, Leonardi C, Penneys NS. Human papilloma-virus and herpes virus DNA are not detected in benign and malignant prostatic tissue using the polymerase chain reaction. *J Urol* 1992;148:192-194.
80. Effert PJ, Frye RA, Neubauer A, Liu ET, Walther PJ. Human papillomavirus types 16 and 18 are not involved in human prostate carcinogenesis: analysis of archival human prostate cancer specimens by differential polymerase chain reaction. *J Urol* 1992;147:192-196.
81. McNicol PJ, Dodd JG. Detection of human papillomavirus DNA in prostate gland tissue by using the polymerase chain reaction amplification assay. *J Clin Microbiol* 1990;28:409-412.
82. Tu H, Jacobs SC, Mergner WJ, Kyprianou N. Rare incidence of human papillomavirus types 16 and 18 in primary and metastatic human prostate cancer. *Urology* 1994;44:726-731.
83. Terris MK, Peehl DM. Human papillomavirus detection by polymerase chain reaction ion benign and malignant prostate tissue is dependent on the primer set utilized. *Urology* 1997;50:150-156.
84. Serth J, Panitz F, Paeslack U, Kuczyk MA, Jonas U. Increased levels of human papillomavirus type 16 DNA in a subset of prostate cancers. *Cancer Res* 1999;59:823-825.
85. Wideroff L, Schottenfeld D, Carey TE, Beals T, Fu G, Sakr W et al. Human papillomavirus DNA in malignant and hyperplastic prostate tissue of black and white males. *Prostate* 1996;28:117-123.
86. Sarkar FH, Sakr WA, Li YW, Sreepathi P, Crissman JD. Detection of human papillomavirus (HPV) DNA in human prostatic tissues by polymerase chain reaction (PCR). *Prostate* 1993;22:171-180.
87. Suzuki H, Komiya A, Aida S, Ito H, Yatani R, Shimazaki J. Detection of human papillomavirus DNA and p53 gene mutations in human prostate cancer. *Prostate* 1996;28:318-324.
88. Moyret-Lalle C, Marcais C, Jacquemier J, Moles JP, Daver A, Soret JY *et al*. *ras*, *p53* and HPV status in benign and malignant prostate tumors. *Int J Cancer* 1995;64:124-129.
89. Dodd JG, Paraskevas M, McNicol PJ. Detection of human papillomavirus 16 transcription in human prostate tissue. *J Urol* 1993;149:400-402.
90. Rotola A, Monini P, DiLuca D, Savioli A, Simone R, Secchiero P et al. Presence and physical state of HPV DNA in prostate and urinary-tract tissues. *Int J Cancer* 1992;52:359-365.
91. McNicol PJ, Dodd JG. High prevalence of human papillomavirus in prostate tissues. *J Urol* 1991;145:850-853.
92. Dillner J, Knekt P, Boman J, Lehtinen M, Af Geijersstam V, Sapp M et al. Sero-epidemiological association between human-papillomavirus infection and risk of prostate cancer. *Int J Cancer* 1998;75:564-567.
93. Anwar K, Nakakuki K, Shiraishi T, Naiki H, Yatani R, Inuzuka M. Presence of ras oncogene mutations and human papillomavirus DNA in human prostate carcinomas. *Cancer Res* 1992;52:5991-5996.
94. Burger AM, Fiebig HH, Kuettel MR, Lautenberger JA, Kung HF, Rhim JS. Effect of oncogene expression on telomerase activation and telomere length in human endothelial, fibroblast and prostate epithelial cells. *Int J Oncol* 1998;13:1043-1048.
95. Bello D, Webber MM, Kleinman HK, Wartinger DD, Rhim JS. Androgen responsive adult human prostatic epithelial cell lines immortalised by human papillomavirus 18. *Carcinogenesis* 1997;18:1215-1223.
96. Bright RK, Vocke CD, Emmert-Buck MR, Duray PH, Solomon D, Fetsch P et al. Generation and genetic characterisation of immortal human prostate epithelial cell lines derived from primary cancer specimens. *Cancer Res* 1997;57:995-1002.
97. Choo CK, Ling MT, Chan KW, Tsao SW, Zheng Z, Zhang D et al. Immortalisation of human prostate epithelial cells by HPV 16 E6/E7 open reading frames. *Prostate* 1999;40:150-158.
98. Wang M, Liu A, Garcia FU, Rhim JS, Stearns ME. Growth of HPV-18 immortalised human prostatic intraepithelial neoplasia cell lines. Influence of IL-10, follistatin, activin-A, and DHT. *Int J Oncol* 1999;14:1185-1195.
99. Degeorges A, Hoffschir F, Cussenot P, Gauville C, Le Duc A, Dutrillaux B et al. Recurrent cytogenetic alterations of prostate carcinoma and amplification of c-myc or epidermal growth factor receptor in subclones of immortalised PNT1 human prostate epithelial cell line. *Int J Cancer* 1995;62:724-731.
100. Heidenberg HB, Sesterhenn IA, Gaddipati JP, Weghorst CM, Buzard GS, Moul J et al. Alteration of the tumor suppressor gene p53 in a high fraction of hormone refractory prostate cancer. *J Urol* 1995;154:414-421.
101. Shaulsky G, Goldfinger N, Tosky MS, Levine AJ, Rotter V. Nuclear localisation is essential for the activity of p53 protein. *Oncogene* 1991;6:2055-2065.
102. Burk U, Selter H, Zwergel T, Wullich B, Montenarh M, Unteregger G. Different subnuclear localisation of wild-type and mutant p53 in human prostate cancer cells. *Int J Oncol* 1995;7:1355-1360.
103. Macera MJ, Godec CJ, Sharma N, Verma RS. Loss of heterozygosity of the TP53 tumor suppressor gene and detection of point mutations by the non-isotopic RNAse cleavage assay in prostate cancer. *Cancer Genet Cytogenet* 1999;108:42-47.
104. Venkatachalam S, Shi Y-P, Jones SN, Vogel H, Bradley A, Pinkel D et al. Retention of wild-type p53 in tumors from p53 heterozygous mice: reduction of p53 dosage can promote cancer formation. *EMBO J* 1998;17:4657-4667.
105. Russell PJ, Voeks D, Martiniello-Wilks R. Preclinical models of prostate cancer. Prostate cancer: biology, diagnosis and

management. Syringos KN, editor. Oxford: Oxford Medical Publications; 2001:pp84-103.
106. Green JE, Greenberg NM, Ashendel CL, Barrett JC, Boone C, Getzenberg RH et al. Workgroup 3: Transgenic and reconstitution models of prostate cancer. *Prostate* 1998;36:59-63.
107. Sharma P, Schreider-Agus N. Mouse models of prostate cancer. *Oncogene* 1999;18:5349-5355.
108. Maroulakou IG, Anver M, Garrett L, Green JE. Prostate and mammary adeno-carcinoma in transgenic mice carrying a rat C3(1) simian virus 40 large tumor antigen fusion gene. *Proc Natl Acad Sci USA* 1994;91:11236-11240.
109. Greenberg NM, DeMayo F, Finegold MJ, Medina D, Tilley WD, Aspinall JO *et al*. Prostate cancer in a transgenic mouse. *Proc Natl Acad Sci USA* 1995;92:3439-3443.
110. Perez-Stable C, Altman NH, Mehta PP, Deftos LJ, Roos BA. Prostate cancer progression, metastasis, and gene expression in transgenic mice. *Cancer Res* 1997;57:900-906.
111. Kasper S, Sheppard PC, Yan Y, Pettigrew N, Borowsky AD, Prins GS et al. Development, progression, and androgen-dependence of prostate tumors in probasin-large T antigen transgenic mice: a model for prostate cancer. *Lab Invest* 1998;78:i-xv.
112. Garabedian EM, Humphrey PA, Gordon JI. A transgenic mouse model of metastatic prostate cancer originating from neuroendocrine cells. *Proc Natl Acad Sci USA* 1998;95:15382-15387.
113. Levine AJ, Momand J, Finlay C. The p53 tumor suppressor gene. *Nature* 1991;351:453-456.
114. Vousden KH. Regulation of the cell cycle by viral oncoproteins. *Semin Cancer Biol* 1995;6:109-116.
115. Shibata M, Ward JM, Devor DE, Liu M, Green JE. Progression of prostatic intraepithelial neoplasia to invasive carcinoma in C3(1)/SV40 large T antigen transgenic mice: histopathologial and molecular biological alterations. *Cancer Res* 1996;56:4894-4903.
116. Gingrich JR, Barrios RJ, Morton RA, Boyce BF, DeMayo FJ, Finegold MJ et al. Metastatic prostate cancer in a transgenic mouse. *Cancer Res* 1996;56:4096-4102.
117. Gingrich JR, Barrios RJ, Kattan MW, Nahm HS, Finegold MJ, Greenberg NM. Androgen-independent prostate cancer progression in the TRAMP model. *Cancer Res* 1997;57:4687-4691.
118. Thompson TC, Park SH, Timme TL, Ren C, Eastham JA, Donehower LA et al. Loss of p53 function leads to metastasis in ras + myc- initiated mouse prostate cancer. *Oncogene* 1995;10:869-879.
119. Eliyahu D, Michalovitz D, Eliyahu S, Pinhasi-Kimhi O, Oren M. Wild-type p53 can inhibit oncogene-mediated focus formation. *Proc Natl Acad Sci USA* 1989;86:8763-8767.
120. Hinds P, Finlay C, Levine AJ. Mutation is required to activate the p53 gene for cooperation with the ras oncogene and transformation. *J Virol* 1989;63:739-746.
121. Hugel A, Wernert N. Loss of heterozygosity (LOH), malignancy grade and clonality in microdissected prostate cancer. *Br J Cancer* 1999;79:551-557.
122. Mirchandani D, Zheng J, Miller GJ, Ghosh AK, Shibata DK, Cote RJ *et al*. Heterogeneity in intratumor distribution of p53 mutations in human prostate cancer. *Am J Pathol* 1995;147:92-101.
123. Voeller HJ, Sugars LY, Pretlow T, Gelmann EP. p53 oncogene mutations in human prostate cancer specimens. *J Urol* 1994;151:492-495.
124. Dahiya R, Deng G, Chen KM-K, Chui RM, Haughney PC, Narayan P. p53 tumor-suppressor gene mutations are mainly localised on exon 7 in human primary metastatic prostate cancer. *Br J Cancer* 1996;74:264-268.
125. Effert PJ, McCoy RH, Walther PJ, Liu ET. p53 gene alterations in human prostate carcinoma. *J Urol* 1993;150:257-261.
126. Rakozy C, Grignon DJ, Li YW, Gheiler E, Gururajanna B, Pontes JE et al. p53 gene alterations in prostate cancer after radiation failure and their association with clinical outcome: a molecular and immunohistochemical analysis. *Pathol Res Pract* 1993;95:129-135.
127. Shi X, Bodner SM, deVere White RW, Gumerlock PH. Identification of p53 mutations in archival prostate tumors. *Diagn Mol Pathol* 1996;5:271-278.
128. Bookstein R, MacGrogan D, Hilsenbeck SG, Sharkey F, Allred DC. p53 is mutated in a subset of advanced-stage prostate cancers. *Cancer Res* 1993;53:3369-3373.
129. Brooks JD, Bova GS, Ewing CM, Piantadosi S, Carter BS, Robinson JC et al. An uncertain role for p53 gene alterations in human prostate cancers. *Cancer Res* 1996;56:3814-3822.
130. Navone NM, Labate ME, Troncoso P, Pisters LL, Conti CJ, von Eschenbach AC et al. p53 mutations in prostate cancer bone metastases suggest that selected p53 mutants in the primary site define foci with metastatic potential. *J Urol* 1999;161:304-308.
131. Isaacs WB, Carter BS, Ewing CM. Wild-type p53 suppresses growth of human prostate cancer cells containing mutant p53 alleles. *Cancer Res* 1991;51:4716-4720.
132. Dinjens WNM, Van Der Weiden MM, Schroeder FH, Bosman FT, Trapman J. Frequency and characterisation of p53 mutations in primary and metastatic human prostate cancer. *Int J Cancer* 1994;56:630-633.