

Review

Cyclin D1 and human neoplasia

R Donnellan, R Chetty

Abstract

Neoplasia is characterised by abnormal regulation of the cell cycle. Cyclin D1 is a protein derived from the PRAD1, CCND1 or bcl-1 gene on chromosome 11q13, which is involved in both normal regulation of the cell cycle and neoplasia. In the G₁ (resting) phase of the cell cycle, cyclin D1 together with its cyclin dependent kinase (cdk) partner, is responsible for transition to the S (DNA synthesis) phase by phosphorylating the product of the retinoblastoma gene (pRB), which then releases transcription factors important in the initiation of DNA replication. Amplification of the CCND1 gene or over-expression of the cyclin D1 protein releases a cell from its normal controls and causes transformation to a malignant phenotype. Analysis of these changes provides important diagnostic information in mantle cell (and related) lymphomas, and is of prognostic value in many cancers. Knowledge of cyclin D1's role in malignancy at the various sites, provides a basis on which future treatment directed against this molecule can proceed.

(J Clin Pathol: Mol Pathol 1998;51:1-7)

Keywords: neoplasia; cell cycle; cyclin D1

If way to the better there be, it exacts a full look at the worst—Thomas Hardy

This review provides a background to neoplasia and the important role of cell cycle regulators, especially the contributions of cyclin D1, in human neoplasms. In 1952 the eminent British oncologist Sir Rupert Willis¹ provided what for many years has been considered the most accurate definition of neoplasia when he described a neoplasm as “an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change.” Although this definition is relevant today, it may not do justice to the critical role played by the cell cycle in carcinogenesis. Many more recent investigators examining the uncoordinated growth and proliferation in neoplasms, have implicated proteins involved in regulation of the cell cycle; so much so that neoplasia is considered by some to be the result of dysregulation of the cell cycle machinery.²

Increased expression of one such cell cycle regulator, cyclin D1, is a feature of many different primary human tumours with current diagnostic and prognostic implications. The central part played by this molecule deserves more attention if many important questions regarding neoplasia are to be answered.

Normal cell cycle

At the centre of the cell cycle engine are a group of protein kinases, the cyclin dependent kinases (Cdks), which move cell proliferation forward by phosphorylating specific substrates in a cell cycle dependent fashion. To become active protein kinases, a Cdk subunit must associate with a cyclin subunit to form a heterodimeric molecule. Unique complexes of Cdks and cyclins with specific activities during each phase of the cell cycle ensure progression through various cell cycle transitions.³

Cyclins

Eight major classes of mammalian cyclins have been isolated, although within some classes a number of subclasses exist. There are at least 11 different mammalian cyclins termed A, B1, B2, C, D1, D2, D3, E, F, G, and H.⁴⁻⁵ The different cyclins attain peak activity during different phases of the cell cycle—for example, cyclins C, D1-3, and E reach their maximum activity during the G₁ phase, and apparently regulate transition from G₁ to S, whereas cyclins A and B1-2 are most active during the S and G₂ phases when they regulate transition to the mitotic phase of the cell cycle.⁶ However, it must be noted that the fluctuations in cyclin D1 are more subtle than those characteristic of the other cyclins, and may represent redistribution during the S phase rather than enhanced activity during the G₁ phase.⁷

Cyclin dependent kinases and their inhibitors

The activities of the seven different Cdks (Cdk 1-7) acting in concert with their cyclin partners also vary with successive phases of the cell cycle. Cdk1, also known as cell division control molecule 2 (cdc2) bound to cyclin B, has maximal activity at the G₂/M transition. Cdk2 is important before and during the S phase, binding to cyclins E and A. Cdk4 and cdk6 preferably associate with the D type cyclins during the G₁ phase.⁶ Also involved in cell cycle regulation is a recently discovered group

Department of Pathology, University of Natal Medical School, Private Bag 7, Congella 4013, Durban, South Africa
R Donnellan
R Chetty

Correspondence to:
Dr Donnellan.
email: donnellanr@med.und.ac.za

Accepted for publication
16 December 1997

of molecules, the cyclin dependent kinase inhibitors (CKIs).⁸ The CKIs fall into two classes—the Kip/Cip family comprising three structurally related proteins (p21, p27, and p57), and the INK4 proteins comprising four similar molecules (p15, p16, p18, and p19). In general, the amount of CKI present provides a threshold that the catalytically operative cyclin–Cdk must overcome to drive the cell cycle forward. However, the two classes of CKI appear to exert their inhibiting effects in different ways. The Kip/Cip family are capable of binding to and inhibiting most cyclin–Cdk complexes, whereas the INK4 molecules seem to be specific inhibitors of complexes containing cyclin D. It appears that the INK4 molecules compete with D-type cyclins for binding to their Cdk partners.³

Cell cycle in neoplasia

Predictably, proteins involved in driving the cell cycle, such as cyclins, are frequently overexpressed in primary tumours, whereas proteins that slow cell division, such as the CKIs, are often inactivated.⁹ Of the many cell cycle regulators implicated in the development of cancers, cyclin D1 is among the most prevalent. Overexpression of D-type cyclins has been shown to contract the G₁ phase, decrease cell size, and reduce the dependency of the cell on mitogens^{10–12} in animal models and cell lines.

A link between D-type cyclins and the retinoblastoma protein

The connection between D-type cyclins and tumorigenesis is bolstered further by compelling evidence that D-type cyclins are important in cell cycle regulation of the retinoblastoma tumour suppressor protein (pRB), an approximately 105 kDa nuclear phosphoprotein.^{13–15} The amount of pRB is not altered with progression of the cell cycle, however, the phosphorylation state of pRB is cell cycle dependent.^{16–18} pRB is hypophosphorylated throughout G₁ phase, phosphorylated just before S phase, and remains phosphorylated until late mitosis. Hypophosphorylated pRB arrests cells in G₁,¹⁹ an effect most likely mediated through complex formation with DNA binding proteins (including members of the E2F family)^{20–22} required for transcriptional activation of cellular genes. Phosphorylation of pRB during late G₁ phase reverses the growth suppressive effects of pRB, by untethering E2F from its inhibitory constraint and thereby allowing the activation of genes required for DNA replication.²³ Because D-type cyclins are able to bind to pRB through an N-terminal LXCXE motif,^{24–26} they are excellent candidates for G₁ phase pRB protein kinases as part of a complex with their specific Cdk partners. Interestingly, this LXCXE motif is common to the SV40 T antigen, adenovirus E1A, and human papillomavirus E7 proteins,²³ which may also bind to pRB and release E2F; a fact that in part explains the oncogenic potential of these viruses. Support for the idea that D-type cyclins can inactivate pRB comes from reports that increased amounts of D-type cyclins can reverse the pRB induced cell cycle arrest and

accelerate progression through G₁.^{12 25 27 28} In some mouse lymphoma cells overexpressing D cyclins, pRB is hyperphosphorylated compared with pRB in cells not overexpressing D cyclins.²

Cells that lack a functional pRB have significantly lower amounts of cyclin D1 and cyclin D1–CDK4 complexes,^{29–31} a result which has been interpreted to mean that hypophosphorylated pRB is involved in the stimulation of cyclin D1 transcription. The reported ability of exogenously expressed pRB to induce cyclin D1 is in accordance with this hypothesis.³¹ Thus, a negative feedback loop seems to exist in which cyclin D1 synthesis and activation lead to pRB phosphorylation, which in turn causes decreased cyclin D1 expression.³²

Cyclin D1 gene as the bcl-1 oncogene?

The cyclin D1 gene (CCND1), linked closely to the bcl-1 gene on chromosome 11q13, is sometimes referred to as the PRAD1 gene because of an initial finding of frequent rearrangement of this gene in benign parathyroid adenomas.³³ The important role of cyclin D1 in parathyroid neoplasia has subsequently been confirmed.³⁴ The bcl-1 locus, so called because of the involvement of this chromosomal region in translocations {(t11; 14) (q13, q32)} characteristic of certain B cell lymphomas (now called mantle cell lymphomas), was originally thought to be identical to the cyclin D1/PRAD1 gene, but it has been shown to reside 110–130 kb upstream or centromeric to the PRAD1 gene.³⁵ However, no transcriptional units have been identified in the immediate vicinity of the major translocation cluster (MTC)³⁶ of the bcl-1 breakpoint area or any of the breakpoints that have been found up to 63 kb telomeric to the MTC region.³⁷ The absence of CpG islands between the original bcl-1 locus and PRAD1's CpG island^{35 36 38} lends further support to the notion that no other gene lies within this interval. Thus, the probability remains that the cyclin D1/PRAD1 gene is the bcl-1 oncogene. Although bcl-1 often co-amplifies with other genes on 11q13 (such as EMS-1, FGF3, FGF4, int-2, and hst-1), cyclin D1 and EMS-1 are the only proteins, so far, overexpressed as a result.^{36 39 40}

Cyclin D1 expression in human cancers

In addition to parathyroid adenomas, increased cyclin D1 expression has been shown in a number of primary human tumours and cell lines. In general, primary tumours provide more reliable information as it is often difficult to determine when the amplification occurred during the development of the cell line. This is because other influences, which cause the cells to proliferate at faster rates, may upregulate cyclin D1 expression. It should be remembered that although increased cyclin D1 protein expression correlates in most instances with amplification of the CCND1 gene, this is not always the case. In some tumours there is an increased cyclin D1 RNA and/or protein without apparent gene amplification, suggesting that other cellular genes (such as the retinoblastoma gene) may impact on the protein expression of cyclin D1,⁴¹ although all the

mechanisms have not yet been satisfactorily elucidated. DNA amplification is the most frequent abnormality affecting the CCND1 gene. Furthermore, no major abnormality in the coding region of the cyclin D1 gene has been detected⁴²⁻⁴³ suggesting that it is the normal gene product that contributes to tumorigenesis.

MANTLE CELL LYMPHOMAS

All or almost all mantle cell (centrocytic) lymphomas in several studies^{35, 44-51} have raised activity of cyclin D1, even in cases in which no rearrangement at 11q13 was found.⁵² Generally, however, positive nuclear staining with monoclonal antibody to the cyclin D1 protein correlates with amplification of the CCND1 gene as well as mRNA.⁵³ It has been suggested that expression of cyclin D1 by lymphocytes in the mantle zone impairs the capacity of these cells to exit the cell cycle and to differentiate into mature plasma cells.⁵⁴ This pathogenetic theory is contradicted by a recent finding of cyclin D1 protein expression in 26% of plasma cell neoplasms, however, the same study⁵⁵ supports a relation between mantle cells, plasma cells, and their corresponding neoplasms. An international lymphoma consensus⁵⁶ acknowledged the importance of chromosome 11q13 translocation and increased cyclin D1 expression in mantle cell lymphomas; in the future it may be elevated to a defining characteristic, given the high sensitivity and relative specificity of this molecule in mantle cell lymphoma compared with other B cell neoplasms.⁴⁵⁻⁵⁷ Cyclin D1 protein expression and bcl-1 gene rearrangement has been identified as a key component in the diagnosis of the blastoid variant⁵⁸ of mantle cell lymphoma as well as in an entity closely related to mantle cell lymphoma—multiple lymphomatous polyposis.⁵⁹

BREAST CANCERS

About half of all invasive breast cancers⁶⁰⁻⁶³ have raised expression of cyclin D1 compared with normal epithelium, although the figure for gene amplification averages around 13%.⁴¹ Some earlier studies⁶⁴⁻⁶⁷ failed to find any significant association between 11q13 amplification and oestrogen receptor positive cancers, but a wealth of material⁶⁸⁻⁷⁷ has now accumulated supporting a correlation between cyclin D1 gene amplification and/or protein overexpression with oestrogen receptor positive tumours. Studies in mice⁷⁸⁻⁷⁹ and man⁸⁰ link cyclin D1 to steroid induced proliferation of mammary epithelial cells. In fact, cyclin D1 appears to be an independent activator of the oestrogen receptor.⁸¹ Despite the correlation with oestrogen receptor status, there is lack of agreement as to the prognostic significance of cyclin D1 in breast cancers in general. More work needs to be done to identify the subsets of patients in whom cyclin D1 may play a more prominent role. It seems that cyclin D1 is more important in node positive,⁷⁴ well differentiated, and particularly lobular, varieties than other types of invasive breast cancer.⁷⁵⁻⁷⁷ In a recent paper⁸² examining the role of cyclin D1 in ductal carcinoma in situ (DCIS), high grade

lesions (graded according to the Silverstein system⁸³) were more likely to show gene amplification but demonstrated lower percentages of nuclei expressing cyclin D1 protein than low grade lesions, which suggests that mechanisms other than gene amplification may be responsible for increased cyclin D1 protein. In this situation, assessment of cyclin D1 protein in combination with pRB may provide more useful information.⁸⁴⁻⁸⁶ The publication about cyclin D1 in DCIS followed a previous paper⁸⁷ by the same group in which overexpression of cyclin D mRNA, determined by in situ hybridisation, was able to distinguish DCIS from atypical ductal hyperplasia and other lesions associated with a low risk of progression to invasive carcinoma.

HEAD AND NECK SQUAMOUS CELL CARCINOMAS

A range of 35% to 64% of head and neck squamous carcinomas⁸⁸⁻⁹³ (squamous carcinomas in the oral cavity, nasopharynx, pharynx, hypopharynx, and larynx) show overexpression of cyclin D1 and/or CCND1 amplification. Overexpression of cyclin D1 in the initial surgical specimens corresponds not only with more frequent recurrence⁹¹ but also with more advanced disease, lymph node involvement, and reduced overall survival.^{89-92, 93} In one study of squamous carcinomas of the larynx, a correlation among cyclin D1 gene amplification, mRNA overexpression, and tumour progression, was shown in a cohort of 46 patients.⁸⁹ This and another study⁹² demonstrated a significant association between molecular abnormalities of the cyclin D1 gene and pathological measures of poor prognosis. Recently, overexpression of cyclin D1 protein in resection material from head and neck squamous carcinomas was found to be an independent prognostic factor⁹³ a finding that has been confirmed.⁹⁴ In Japanese hypopharyngeal squamous cell carcinomas, cyclin D1 gene amplification and protein overexpression correlated not only with prognosis but were also useful in identifying optimum treatment regimens.⁹⁵ Cyclin D1 negative tumours responded particularly well to multimodality treatment in these tumours.

OESOPHAGEAL CANCERS

In approximately 30% of oesophageal cancers, amplification⁹⁶ and overexpression⁹⁷⁻⁹⁹ of cyclin D1 have been demonstrated, with several studies showing an association with increased mortality.⁹⁹⁻¹⁰¹ Also, the ability of antisense to cyclin D1 to reverse the transformed phenotype of oesophageal cancer cells¹⁰² provides strong supporting evidence for the molecule's role in cancers at this site. Our group¹⁰³ has demonstrated recently an association between cyclin D1 protein and pRB expression, a finding that is in line with the results of another study in a similarly high incidence area.⁹⁸ Although our results supported an association between cyclin D1, pRB staining, and aggressive behaviour, the exact nature of this interaction will need to be clarified.

HEPATOCELLULAR CARCINOMAS

Amplification and raised protein concentrations have been observed in 10% of hepatocellular carcinomas.^{104 105} Among other hypotheses, it has been suggested that hepatitis B or C viral integration within the cyclin D1 gene or one of its adjacent regulator sequences may be a mechanism in malignant transformation.¹⁰⁶ In some reports^{107 108} the hepatitis B viral genome was detected on chromosome 13 at an upstream site close to the CCND1 gene. Another study¹⁰⁵ showed that cyclin D1 amplification was restricted to hepatocellular carcinomas that contained the hepatitis B or C virus. Although the evidence is scant, the possibility of an interaction between these viruses and cyclin D1 is an intriguing one.

COLORECTAL CANCERS

Despite an initial report¹⁰⁹ using cell lines that suggested that cyclin D1 was not an important factor in colorectal adenocarcinomas, recent work has enlightened this previously dark area. Not only does cyclin D1 overexpression occur as an early event in tumour progression, it may also be an independent prognostic factor.¹¹⁰ There is increased nuclear immunostaining in adenomatous polyps and adenocarcinomas, but not in adjacent normal, transitional or hyperplastic mucosa. These findings apply to both sporadic¹¹¹ and familial forms¹¹² of colon cancer. Furthermore, as has been demonstrated in the oesophagus, antisense to cyclin D1 inhibits the growth and tumorigenicity of colon cancer cells.¹¹³

GENITOURINARY CANCERS

Amplification of 11q13 has been demonstrated in between 6% and 21%¹¹⁴⁻¹¹⁶ of transitional cell cancers of the urinary bladder, although nuclear accumulation of the protein appears in a much greater percentage of cases. Alterations in cyclin D1 appear to be an early event in tumorigenesis of the urinary bladder, but the prognostic significance of amplification and overexpression remain to be determined. While one study observed a significant relation between cyclin D1 overexpression and low tumour grade as well as T classification,¹¹⁷ these findings were not duplicated in a similar study.¹¹⁸ Abnormalities of cyclin D1 are also common in both vulval and cervical squamous cell carcinomas.¹¹⁹ At these sites, cyclin D1 appears to inactivate pRB in a similar manner to oncogenic human papillomavirus genotypes. Thus, it seems that in vulval and cervical squamous carcinomas, human papillomavirus proteins can circumvent cellular requirements for cyclin D1¹²⁰ or vice versa.

In endometrial carcinomas, 11q13 amplification is exceedingly rare, but about 40% of cases show aberrant accumulation of cyclin D1.¹²¹ Again, the effect of other genes is the likely explanation for this phenomenon, although in this case the interaction of cyclin D1 with p53¹²² appears to be more important than with pRB. Because cyclin D1 can activate the oestrogen receptor independently,⁵¹ if this molecule were also overexpressed in endometrial hyperplasia it would provide a useful link with

known pathogenetic mechanisms. To the best of our knowledge, this has not yet been studied.

In epithelial ovarian cancers, abnormalities of cyclin D1 are early events in the progression to malignancy, and they may be associated with the degree of transformation.¹²³ There is a strong positive correlation between cyclin D1 and c-Ki-ras immunopositivity,¹²⁴ but no correlation with the c-erb-B2 oncogene.¹²⁵ The relation with the Ras proto-oncogene is important because it has been shown that inactivation of Ras in cycling cells causes a decline in cyclin D1 protein, accumulation of the hypophosphorylated, growth suppressive form of pRB, and G₁ arrest.^{126 127} Strangely, the relation between cyclin D1 amplification and oestrogen is not as clear cut as has been demonstrated in the breast.^{75 125}

LUNG CANCERS

Studies have shown a higher frequency of bcl-1 gene amplification in squamous cell carcinomas of the lung than in other types of non-small cell lung cancer,¹²⁸ and an association with poor grade and high Ki-67 labelling index.¹²⁹ However, current research is contradictory as to the prognostic usefulness of detecting cyclin D1 protein overexpression.¹³⁰⁻¹³² From studies of the resection margin epithelia of lung cancer patients, compared with non-smoking controls, it seems that genetic alteration of cyclin D1 is an early event in non-small cell lung cancer,¹³³ and therefore an attractive therapeutic target.

SKIN CANCERS

Compared to normal skin and benign lesions, cyclin D1 protein expression is significantly greater in various malignant skin tumours, including squamous cell carcinomas, melanomas, and malignant fibrous histiocytomas.¹³⁴ Studies of chemically induced squamous cell carcinomas in mice also implicate cyclin D1 (and other G₁ cyclins) in the process of carcinogenesis.¹³⁵

SARCOMAS

Amplification of the cyclin D1 gene has been detected in a small percentage of a variety of sarcomas,¹³⁶ but the increased cyclin D1 protein expression in at least some cases may be due to a mutant protein with greater stability.¹³⁷

OTHER SITES AND MALIGNANCIES

Central nervous system malignancies such as astrocytomas¹³⁸ and glioblastomas¹³⁹ are not exempt from cyclin D1 amplification or protein overexpression, nor are gastric adenocarcinomas,^{140 141} pancreatic adenocarcinomas (may be associated with a poor prognosis),¹⁴² or squamous carcinomas of the gall bladder.¹⁴³ Only a few human tumours are still holding out against the storm of cyclin D1 research. These include pituitary tumours,¹⁴⁴ renal cell tumours,¹⁴⁴ prostate carcinoma,¹⁴⁵ and many haemopoietic malignancies.⁵⁷ However, with some of these tumours there are possible links with cyclin D1. For example, the 11q13 region (although apparently not the CCND1 gene) is important in pituitary neoplasms of MEN-1,¹⁴⁶

and cyclins including cyclin D1 are important in renal development.¹⁴⁷ Such is the ubiquity of cyclin D1's involvement in neoplasia that some authors are touting this molecule as the next "molecule of the year".^{148 149}

Conclusion

The role of cyclin D1 in many human neoplasms supports the importance of cell cycle alterations in carcinogenesis. Cyclin D1 is not just a research tool. It is a useful aid in the diagnosis of mantle cell lymphoma. In other cancers, cyclin D1 may provide prognostic information important in the management of patients with these diseases. In the future, the cyclin D1 gene and/or protein may be a site for immunotherapy.^{113 150 151} Before such treatments are possible, the full significance of this molecule in neoplasia needs to be examined. In the words of Winston Churchill: "It is a mistake to look too far ahead. Only one link in the chain of destiny can be handled at a time."

- Willis RA. *The spread of tumors in the human body*. London: Butterworth and Co, 1952.
- Johnson DG, Richie E, Conti C. The cell cycle and cancer. *Cancer Bull* 1995;47:480-5.
- Clurman BE, Roberts JM. Cell cycle and cancer. *J Nat Cancer Inst* 1995;87:1499-501.
- Hunter T, Pines J. Cyclins and cancer 2: cyclin D and CDK inhibitors come of age. *Cell* 1994;79:573-82.
- Sherr CJ. G1 phase progression: cycling on cue. *Cell* 1994;79:551-5.
- Cordon-Cardo C. Mutations of cell cycle regulators: biological and clinical implications for human neoplasia. *Am J Pathol* 1995;147:545-60.
- Peters G. The D-type cyclins and their role in tumorigenesis. *J Cell Sci* 1994;18:89-96.
- Sherr CJ, Roberts JM. Inhibitors of mammalian G1 cyclin dependent kinases. *Genes Dev* 1995;9:1149-63.
- Hirama T, Koeffler HP. The role of the cyclin-dependent kinase inhibitors in the development of cancer. *Blood* 1995;86:841-54.
- Ohtsubo M, Roberts JM. Cyclin-dependent regulation of G1 in mammalian fibroblasts. *Science* 1993;259:1908-12.
- Quelle DE, Ashmun RA, Shurtleff SA. Overexpression of mouse D-type cyclins accelerates G1 phase in rodent fibroblasts. *Genes Dev* 1993;7:1559-71.
- Resnitzky D, Gossen M, Bujard H. Acceleration of the G1/S phase transition by expression of cyclins D1 and E with an inducible system. *Mol Cell Biol* 1994;14:1669-79.
- Friend SH, Horowitz JM, Gerber MR. Deletions of a DNA sequence in retinoblastomas and mesenchymal tumors: organisation of the sequence and its encoded protein. *Proc Natl Acad Sci USA* 1987;84:9059-63.
- Lee W-H, Shew J, Hong FD. The retinoblastoma susceptibility gene encodes a nuclear phosphoprotein associated with DNA binding activity. *Nature* 1987;329:642-5.
- Fung Y-K, Murphree A, T'Ang A. Structural evidence for the authenticity of the human retinoblastoma gene. *Science* 1987;236:1657-61.
- De Caprio JM, Ludlow J, Lynch D. The product of the retinoblastoma susceptibility gene has properties of a cell cycle regulatory element. *Cell* 1989;58:1085-95.
- Buchkovich K, Duffy L, Harlow E. The retinoblastoma protein is phosphorylated during specific phases of the cell cycle. *Cell* 1989;58:1097-105.
- Chen P, Scully P, Shew J-Y. Phosphorylation of the retinoblastoma gene product is modulated during the cell cycle and cellular differentiation. *Cell* 1989;58:1193-8.
- Hinds PW, Weinberg RA. Tumor suppressor genes. *Curr Opin Genet Dev* 1994;4:135-41.
- Kaelin WG, Pallas DC, De Caprio JA, et al. Identification of the cellular proteins that can react specifically with the E1A-binding region of the retinoblastoma gene product. *Cell* 1991;64:521-32.
- DeFeo-Jones D, Huang PS, Jones RE, et al. Cloning of cDNAs for cellular proteins that bind to the retinoblastoma gene product. *Nature* 1991;352:251-4.
- Chellappan SP, Hiebert S, Mudryj M, et al. The E2F transcription factor is a cellular target for the RB protein. *Cell* 1991;65:1053-61.
- Nevins JR. E2F: A link between the Rb tumor suppressor protein and viral oncoproteins. *Science* 1992;258:424-9.
- Dowdy SF, Hinds PW, Louie K, et al. Physical interaction of the retinoblastoma protein with human D cyclins. *Cell* 1993;73:499-511.
- Ewen ME, Sluss HK, Sherr CJ, et al. Functional interactions of the retinoblastoma protein with mammalian D-type cyclins. *Cell* 1993;73:487-97.
- Kato J, Matsushime H, Hiebert SW, et al. Direct binding of cyclin D to the retinoblastoma gene product (pRB) and pRB phosphorylation by the cyclin D-dependent Cdk4. *Genes Dev* 1993;7:331-42.
- Hinds PW, Mittnacht S, Dulic V, et al. Regulation of retinoblastoma protein functions by ectopic expression of human cyclins. *Cell* 1992;70:993-1006.
- Jiang W, Khan SM, Zhou P, et al. Overexpression of cyclin D1 in rat fibroblasts causes abnormalities in growth control, cell cycle progression and gene expression. *Oncogene* 1993;8:3447-57.
- Bates S, Parry D, Bonnetta L, et al. Absence of cyclin D/Cdk complexes in cells lacking functional retinoblastoma protein. *Oncogene* 1994;9:1633-40.
- Tam SW, Theodoras AM, Shay JW, et al. Differential expression and regulation of cyclin D1 protein in normal and tumor cells: association with Cdk4 is required for cyclin D1 function in G1 progression. *Oncogene* 1994;9:2663-74.
- Muller H, Lukas J, Schneider A, et al. Cyclin D1 expression is regulated by the retinoblastoma protein. *Proc Natl Acad Sci USA* 1994;91:2945-9.
- Lukas J, Muller H, Bartkova J, et al. DNA tumor virus oncoproteins and retinoblastoma gene mutations share the ability to relieve the cell's requirement for cyclin D1 function in G1. *J Cell Biol* 1994;125:625-38.
- Motokura T, Bloom T, Kim HG, et al. A novel cyclin encoded by a bcl-1 linked candidate oncogene. *Nature* 1991;350:512-15.
- Hsi ED, Zukerberg LR, Yang WI, et al. Cyclin D1/PRAD1 expression in parathyroid adenomas: an immunohistochemical study. *J Endocrinol Metabol* 1996;81:1736-9.
- Rosenberg CL, Wong E, Petty EM, et al. PRAD1, a candidate bcl1 oncogene: mapping and expression in centrocytic lymphoma. *Proc Natl Acad Sci USA* 1991;88:9638-42.
- Lammie GA, Fantl V, Smith R, et al. D11S287, a putative oncogene on chromosome 11q13, is amplified and expressed in squamous cell and mammary carcinomas and linked to BCL-1. *Oncogene* 1991;6:439-44.
- Meeker TC, Grimaldi JC, O'Rourke R, et al. An additional breakpoint in the bcl1 locus associated with the t(11;14)(q13;q32) translocation of a B-cell malignancy. *Blood* 1989;74:1801-6.
- Withers DA, Harvey RC, Faust JB, et al. Characterization of a candidate bcl-1 gene. *Mol Cell Biol* 1991;11:4846-53.
- Schuuring E, Verhoeven E, Mooi WJ, et al. Identification and cloning of two overexpressed genes, U21B31/PRAD1 and EMS1, within the amplified chromosome 11q13 region in human carcinomas. *Oncogene* 1992;7:355-61.
- Schuuring E. The involvement of the chromosome 11q13 region in human malignancies: cyclin D1 and EMS1 are two new candidate oncogenes—a review. *Gene* 1995;159:83-96.
- Hall M, Peters G. Genetic alterations of cyclins, cyclin-dependent kinases, and cdk inhibitors in human cancer. *Adv Cancer Res* 1996;68:67-108.
- Rosenberg CL, Motokura T, Kronenberg H, et al. Coding sequence of the overexpressed transcript of the putative oncogene Prad1/cyclin D1 in two primary human tumors. *Oncogene* 1993;8:519-21.
- Rimokh R, Berger F, Bastard C, et al. Rearrangement of CCND1 (BCL1/PRAD1) 3' untranslated region in mantle cell lymphomas and t(11q13)-associated leukaemias. *Blood* 1994;83:3689-6.
- Rimokh R, Berger F, Delsol G, et al. Rearrangements and overexpression of the bcl-1/PRAD-1 gene in intermediate lymphocytic lymphomas and in t(11q13)-bearing leukaemias. *Blood* 1993;81:3063-7.
- Bosch F, Jares P, Campo E, et al. PRAD-1/cyclin D1 gene overexpression in chronic lymphoproliferative disorders: a highly specific marker of mantle cell lymphoma. *Blood* 1994;84:2762-32.
- Hayashi T, Ohno H, Yamabe H, et al. Clinical aspects of B-cell malignancy involving the BCL-1/PRAD-1 locus. *Int J Hematol* 1994;59:281-96.
- de Boer CJ, Schuurung E, Dreef E, et al. Cyclin D1 protein analysis in the diagnosis of mantle cell lymphoma. *Blood* 1995;86:2715-23.
- de Boer CJ, van Krieken JH, Kluijn-Nelemans HC, et al. Cyclin D1 messenger RNA overexpression as a marker for mantle cell lymphoma. *Oncogene* 1995;10:1833-40.
- Banno S, Yoshikawa K, Nakamura S, et al. Monoclonal antibody against PRAD1/cyclin D1 stains nuclei of tumor cells with translocation or amplification at BCL-1 locus. *Jpn J Cancer Res* 1994;85:918-26.
- Oka K, Ohno T, Kita K, et al. PRAD1 gene over-expression in mantle cell lymphoma but not in other low-grade B-cell lymphomas including extranodal lymphoma. *Br J Haematol* 1994;86:786-91.
- Nakamura S, Seto M, Banno S, et al. Immunohistochemical analysis of cyclin D1 protein in hematopoietic neoplasms with special reference to mantle cell lymphomas. *Jpn J Cancer Res* 1994;85:1270-9.
- Swerdlow SH, Yang WL, Zukerberg LR, et al. Expression of cyclin D1 protein in centrocytic/mantle cell lymphomas with and without rearrangement of the BCL1/cyclin D1 gene. *Hum Pathol* 1995;26:999-1004.
- Kuroda H, Komatsu H, Nakamura S, et al. The positive nuclear staining observed with monoclonal antibody against PRAD1/cyclin D1 correlates with mRNA expression in mantle cell lymphoma. *Jpn J Cancer Res* 1995;86:890-8.
- Banks PM, Chan J, Cleary ML, et al. Mantle cell lymphoma: a proposal for unification of morphologic, immunologic and molecular data. *Am J Surg Pathol* 1992;16:637-40.

- 55 Vasef MA, Medeiros LJ, Yospur LS, *et al.* Cyclin D1 protein in multiple myeloma and plasmacytoma: an immunohistochemical study using fixed, paraffin-embedded tissue sections. *Mod Pathol* 1997;10:927-32.
- 56 Harris NL, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361-92.
- 57 Nakamura S, Yatabe Y, Kuroda H, *et al.* Immunostaining of PRAD1/cyclin D1 protein as a marker for the diagnosis of mantle cell lymphoma. *Leukemia* 1997;11:536-7.
- 58 Ott G, Kalla J, Ott MM, *et al.* Blastoid variants of mantle cell lymphoma: frequent bcl-1 rearrangements at the major translocation cluster region and tetraploid chromosome clones. *Blood* 1997;89:1421-9.
- 59 Kumar S, Krenacs L, Otsuki T, *et al.* bc1-1 rearrangement and cyclin D1 protein expression in multiple lymphomatous polyposis. *Am J Clin Pathol* 1996;105:737-43.
- 60 Gillet C, Fantl V, Smith R, *et al.* Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. *Cancer Res* 1994;54:1812-17.
- 61 Bartkova J, Lukas J, Muller H, *et al.* Cyclin D1 protein expression and function in human breast cancer. *Int J Cancer* 1994;57:353-61.
- 62 Buckley MF, Sweeney KJ, Hamilton JA, *et al.* Expression and amplification of cyclin genes in human breast cancer. *Oncogene* 1993;8:2127-33.
- 63 Zhang SY, Caamano J, Cooper F, *et al.* Immunohistochemistry of cyclin D1 in human breast cancer. *Am J Clin Pathol* 1994;102:695-8.
- 64 Adnane J, Gaudray P, Simon MP, *et al.* Proto-oncogene amplification and human breast tumor phenotype. *Oncogene* 1989;4:1389-95.
- 65 Tang RP, Kacinski B, Validire P, *et al.* Oncogene amplification correlates with dense lymphocyte infiltration in human breast cancers: a role for hematopoietic growth factor release by tumor cells? *J Cell Biochem* 1990;44:189-98.
- 66 Schuurin E, Verhoeven E, van Tinteren H, *et al.* Amplification of genes within the chromosome 11q13 region is indicative of poor prognosis in patients with operable breast cancer. *Cancer Res* 1992;52:5229-34.
- 67 Frierson HF Jr, Gaffey MJ, Zukerberg LR, *et al.* Immunohistochemical detection and gene amplification of cyclin D1 in mammary infiltrating ductal carcinoma. *Mod Pathol* 1996;9:725-30.
- 68 Fantl V, Richards MA, Smith R, *et al.* Gene amplification on chromosome band q13 and oestrogen receptor status in breast cancer. *Eur J Cancer* 1990;26:423-9.
- 69 Borg A, Sigurdsson H, Clark GM, *et al.* Association of INT2/HST1 coamplification in primary breast cancer with hormone-dependent phenotype and poor prognosis. *Br J Cancer* 1991;63:136-42.
- 70 Berns EM, Klijn JG, van Staveren IL, *et al.* Prevalence of amplification of the oncogenes c-myc, HER2/neu, and int-2 in one thousand human breast tumours: correlation with steroid receptors. *Eur J Cancer* 1992;28:697-700.
- 71 Michalides R, Hageman P, van Tinteren H, *et al.* A clinicopathological study on overexpression of cyclin D1 and of p53 in a series of 248 patients with operable breast cancer. *Br J Cancer* 1996;73:728-34.
- 72 Gillett C, Smith P, Gregory W, *et al.* Cyclin D1 and prognosis in human breast cancer. *Int J Cancer* 1996;69:92-9.
- 73 Nielsen NH, Emdin SO, Landberg G. Deregulation of G1 cyclins and pRB alterations in estrogen receptor negative breast cancer with poor prognosis. *Proc Am Assoc Cancer Res* 1996;37:28.
- 74 Pelosio P, Barbareschi M, Bonoldi E, *et al.* Clinical significance of cyclin D1 expression in patients with node-positive breast carcinoma treated with adjuvant therapy. *Ann Oncol* 1996;7:695-703.
- 75 Courjal F, Louason G, Speiser P, *et al.* Cyclin gene amplification and overexpression in breast and ovarian cancers: evidence for the selection of cyclin D1 in breast and cyclin E in ovarian tumors. *Int J Cancer* 1996;69:247-53.
- 76 Barbareschi M, Pelosio P, Caffo O, *et al.* Cyclin D1 gene amplification and expression in breast carcinoma: relation with clinicopathologic characteristics and with retinoblastoma gene product, p53 and p21 WAF1 immunohistochemical expression. *Int J Cancer* 1997;74:171-4.
- 77 van Dierst PJ, Michalides RJ, Jannink L, *et al.* Cyclin D1 expression in invasive breast cancer. Correlations and prognostic value. *Am J Pathol* 1997;150:705-11.
- 78 Fantl V, Stamp G, Andrews A, *et al.* Mice lacking cyclin D1 are small and show defects in eye and mammary gland development. *Genes Dev* 1995;9:2364-72.
- 79 Scinski P, Donaher JL, Parker SB. Cyclin D1 provides a link between development and oncogenesis in the retina and breast. *Cell* 1995;82:621-30.
- 80 Dees C, Foster JS, Ahamed S, *et al.* Dietary estrogens stimulate human breast cells to enter the cell cycle. *Environ Health Perspect* 1997;3:633-6.
- 81 Zwijsen RM, Wientjens E, Klompaker R, *et al.* CDK-independent activation of estrogen receptor by cyclin D1. *Cell* 1997;88:405-15.
- 82 Simpson JF, Quan DE, O'Malley F, *et al.* Amplification of CCND1 and expression of its protein product, cyclin D1, in ductal carcinoma in situ of the breast. *Am J Pathol* 1997;151:161-8.
- 83 Silverstein MJ, Poller DN, Waisman JR, *et al.* Prognostic classification of breast ductal carcinoma-in-situ. *Lancet* 1995;345:1154-7.
- 84 McIntosh GG, Anderson JJ, Milton I, *et al.* Determination of the prognostic value of cyclin D1 overexpression in breast cancer. *Oncogene* 1995;11:885-91.
- 85 Nielsen NH, Emdin SO, Cajander J, *et al.* Deregulation of cyclin E and D1 in breast cancer is associated with inactivation of the retinoblastoma protein. *Oncogene* 1997;14:295-304.
- 86 Wakasugi E, Kobayashi T, Tamaki Y, *et al.* Analysis of phosphorylation of pRB and its regulatory proteins in breast cancer. *J Clin Pathol* 1997;50:407-12.
- 87 Weinstat-Saslow D, Merino MJ, Manrow RE, *et al.* Overexpression of cyclin D mRNA distinguishes invasive and in situ breast carcinomas from non-malignant lesions [see comments]. *Nat Med* 1995;1:1257-60.
- 88 Callander T, El Naggat AK, Lee MS, *et al.* PRAD1 (CCND1/cyclin D1) oncogene amplification in primary head and neck squamous carcinoma. *Cancer* 1994;74:152-8.
- 89 Jones P, Fernandez P, Campo P. PRAD1/cyclin D1 gene amplification correlates with messenger RNA overexpression and tumor progression in human laryngeal carcinomas. *Cancer Res* 1994;54:4183-7.
- 90 Bartkova J, Lukas J, Muller H, *et al.* Abnormal patterns of D-type cyclin expression and G1 regulation in human head and neck cancer. *Cancer Res* 1995;55:949-56.
- 91 Michalides R, van Veelen N, Hart A, *et al.* Overexpression of cyclin D1 correlates with recurrence in a group of forty-seven operable squamous cell carcinomas of the head and neck. *Cancer Res* 1995;55:975-8.
- 92 Fracchiolla NS, Pruneri G, Pignataro L, *et al.* Molecular and immunohistochemical analysis of the bcl-1/cyclin D1 gene in laryngeal squamous cell carcinomas: correlation of protein expression with lymph node metastases and advanced clinical stage. *Cancer* 1997;79:1114-21.
- 93 Michalides RJ, van Veelen NM, Kristel PM, *et al.* Overexpression of cyclin D1 indicates a poor prognosis in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1997;123:497-502.
- 94 Akervall JA, Michalides RJ, Mineta H, *et al.* Amplification of cyclin D1 in squamous cell carcinoma of the head and neck and the prognostic value of chromosomal abnormalities and cyclin D1 overexpression. *Cancer* 1997;79:380-9.
- 95 Masuda M, Hirakawa N, Nakashima T, *et al.* Cyclin D1 overexpression in primary hypopharyngeal carcinomas. *Cancer* 1996;78:390-5.
- 96 Tsuda T, Tahara E, Kajiyama G, *et al.* High incidence of coamplification of hst-1 and int-2 genes in human esophageal carcinomas. *Cancer Res* 1989;49:5505-8.
- 97 Jiang W, Kahn SM, Tomita N, *et al.* Amplification and expression of the human cyclin D gene in esophageal cancer. *Cancer Res* 1992;52:2980-3.
- 98 Jiang W, Zhang YJ, Kahn SM, *et al.* Altered expression of the cyclin D1 and retinoblastoma genes in human esophageal cancer. *Proc Natl Acad Sci USA* 1993;90:9026-30.
- 99 Naitoh H, Shibata J, Kawaguchi A, *et al.* Overexpression and localization of cyclin D1 mRNA and antigen in esophageal cancer. *Am J Pathol* 1995;146:1161-9.
- 100 Kitagawa Y, Ueda M, Ando N, *et al.* Significance of int-2/hst-1 coamplification as a prognostic factor in patients with esophageal squamous carcinoma. *Cancer Res* 1991;51:1504-8.
- 101 Shinozaki H, Ozawa S, Ando N, *et al.* Cyclin D1 amplification as a new predictive classification for squamous cell carcinoma of the esophagus, adding new gene information. *Clin Cancer Res* 1995;2:1155-61.
- 102 Zhou P, Jiang W, Zhang YJ, *et al.* Antisense to cyclin D1 inhibits growth and reverses the transformed phenotype of human esophageal cancer cells. *Oncogene* 1995;11:571-80.
- 103 Chetty R, Chetty S. Cyclin D1 and retinoblastoma protein expression in oesophageal squamous cell carcinoma. *J Clin Pathol: Mol Pathol* 1997;50:257-60.
- 104 Zhang YJ, Jiang W, Chen CJ, *et al.* Amplification and overexpression of cyclin D1 in human hepatocellular carcinoma. *Biochem Biophys Res Commun* 1993;196:1010-16.
- 105 Nishida N, Fukuda Y, Kameda T, *et al.* Amplification and overexpression of the cyclin D1 gene in aggressive human hepatocellular carcinoma. *Cancer Res* 1994;54:3107-10.
- 106 Rogler CE. Cellular and molecular mechanisms of hepatocarcinogenesis associated with hepatitis B virus infection. *Curr Top Microbiol Immunol* 1991;168:103-40.
- 107 Hatada I, Tokino T, Ochiya T, *et al.* Co-amplification of integrated hepatitis B virus DNA and transforming gene hst-1 in a hepatocellular carcinoma. *Oncogene* 1988;3:537-40.
- 108 Nakamura T, Tokino T, Nagaya T, *et al.* Microdeletion associated with the integration process of hepatitis B virus DNA. *Nucleic Acids Res* 1988;16:4865-73.
- 109 Leach F, Elledge S, Sherr C, *et al.* Amplification of cyclin genes in colorectal carcinomas. *Cancer Res* 1993;53:1986-9.
- 110 Maeda K, Chung YS, Kang SM, *et al.* Overexpression of cyclin D1 and p53 associated with disease recurrence in colorectal adenocarcinoma. *Int J Cancer* 1997;74:310-15.
- 111 Arber N, Hibshoosh H, Moss SF, *et al.* Increased expression of cyclin D1 is an early event in multistage colorectal carcinogenesis. *Gastroenterology* 1996;110:669-74.
- 112 Zhang T, Nanney LB, Luongo C, *et al.* Concurrent overexpression of cyclin D1 and cyclin-dependent kinase 4 (Cdk4) in intestinal adenomas from multiple intestinal neoplasia (Min) mice and human familial adenomatous polyposis patients. *Cancer Res* 1997;57:169-75.

- 113 Arber N, Doki Y, Han EK, *et al.* Antisense to cyclin D1 inhibits the growth and tumorigenicity of human colon cancer cells. *Cancer Res* 1997;57:1569-74.
- 114 Tsutsumi M, Sakamoto H, Yoshida T, *et al.* Coamplification of the hst-1 and int-2 genes in human cancers. *Jpn J Cancer Res* 1988;79:428-32.
- 115 Theillet C, Le Roy X, De Lapeyriere O, *et al.* Amplification of FGF-related genes in human tumors: possible involvement of HST in breast carcinomas [erratum published in *Oncogene* 1989;4:1537]. *Oncogene* 1989;4:915-22.
- 116 Proctor AJ, Coombs LM, Cairns JP, *et al.* Amplification at chromosome q13 in transitional cell tumours of the bladder. *Oncogene* 1991;6:789-95.
- 117 Lee CC, Yamamoto S, Morimura K, *et al.* Significance of cyclin D1 overexpression in transitional cell carcinomas of the urinary bladder and its correlation with histopathologic features. *Cancer* 1997;79:780-9.
- 118 Shin KY, Kong G, Kim WS, *et al.* Overexpression of cyclin D1 correlates with early recurrence in superficial bladder cancers. *Br J Cancer* 1997;75:1788-92.
- 119 Kurzrock R, Ku S, Talpaz M. Abnormalities in the PRAD1 (CYCLIN D1/BCL-1) oncogene are frequent in cervical and vulvar squamous cell carcinoma cell lines. *Cancer* 1995;75:584-90.
- 120 Nichols GE, Williams ME, Gaffey MJ, *et al.* Cyclin D1 gene expression in human cervical neoplasia. *Mod Pathol* 1996;9:418-25.
- 121 Bartkova J, Lukas J, Strauss M, *et al.* Cyclin D1 oncoprotein aberrantly accumulates in malignancies of diverse histogenesis. *Oncogene* 1995;10:775-8.
- 122 Nikaido T, Li SF, Shiozawa T, *et al.* Coabnormal expression of cyclin D1 and p53 protein in human uterine endometrial carcinomas. *Cancer* 1996;78:1248-53.
- 123 Barbieri F, Cagnoli M, Ragni N, *et al.* Expression of cyclin D1 correlates with malignancy in human ovarian tumours. *Br J Cancer* 1997;75:1263-8.
- 124 Hung WC, Chai CY, Huang JS, *et al.* Expression of cyclin D1 and c-Ki-ras gene product in human epithelial ovarian tumors. *Hum Pathol* 1996;27:1324-8.
- 125 Worsley SD, Ponder BA, Davies BR. Overexpression of cyclin D1 in epithelial ovarian cancers [see comments]. *Gynecol Oncol* 1997;64:189-95.
- 126 Peepker DS, Upton TM, Ladha MH, *et al.* Ras signalling linked to the cell-cycle machinery by the retinoblastoma protein [erratum published in *Nature* 1997;386:521]. *Nature* 1997;386:177-81.
- 127 Downward J. Cell cycle: routine role for Ras. *Curr Biol* 1997;7:R258-60.
- 128 Berenson JR, Koga H, Yang J, *et al.* Frequent amplification of the bcl-1 locus in poorly differentiated squamous cell carcinoma of the lung. The Lung Cancer Study Group. *Oncogene* 1990;5:1343-8.
- 129 Mate JL, Ariza A, Aracil C, *et al.* Cyclin D1 overexpression in non-small cell lung carcinoma: correlation with Ki67 labelling index and poor cytoplasmic differentiation. *J Pathol* 1996;180:395-9.
- 130 Yang WI, Chung KY, Shin DH, *et al.* Cyclin D1 protein expression in lung cancer. *Yonsei Med J* 1996;37:142-50.
- 131 Betticher DC, Heighway J, Hasleton PS, *et al.* Prognostic significance of CCND1 (cyclin D1) overexpression in primary resected non-small-cell lung cancer. *Br J Cancer* 1996;73:294-300.
- 132 Kwa HB, Michalides RJ, Dijkman JH, *et al.* The prognostic value of NCAM, p53 and cyclin D1 in resected non-small cell lung cancer. *Lung Cancer* 1996;14:207-17.
- 133 Betticher DC, Heighway J, Thatcher N, *et al.* Abnormal expression of CCND1 and RB1 in resection margin epithelia of lung cancer patients. *Br J Cancer* 1997;75:1761-8.
- 134 Inohara S, Kitagawa K, Kitano Y. Expression of cyclin D1 and p53 protein in various malignant skin tumors. *Dermatology* 1996;192:94-8.
- 135 Zhang SY, Liu SC, Goodrow T, *et al.* Increased expression of G1 cyclins and cyclin-dependent kinases during tumor progression of chemically induced mouse skin neoplasms. *Mol Carcinog* 1997;18:142-52.
- 136 Maelandsmo GM, Berner JM, Florenes VA, *et al.* Homozygous deletion frequency and expression levels of the CDKN2 gene in human sarcomas—relationship to amplification and mRNA levels of CDK4 and CCND1. *Br J Cancer* 1995;72:393-8.
- 137 Welcker M, Lukas J, Strauss M, *et al.* Enhanced protein stability: a novel mechanism of D-type cyclin overabundance identified in human sarcoma cells. *Oncogene* 1996;13:419-25.
- 138 Dicks PB, Hubbard SL, Murakami M, *et al.* Cyclin and cyclin-dependent kinase expression in human astrocytoma cell lines. *J Neuropathol Exp Neurol* 1997;56:291-300.
- 139 He J, Allen JR, Collins VP, *et al.* CDK4 amplification is an alternative mechanism to p16 gene homozygous deletion in glioma cell lines. *Cancer Res* 1994;54:5804-7.
- 140 Wang LD, Shi ST, Zhou Q, *et al.* Changes in p53 and cyclin D1 protein levels and cell proliferation in different stages of human esophageal and gastric-cardia carcinogenesis. *Int J Cancer* 1994;59:514-19.
- 141 Nakagawa H, Wang TC, Zukerberg L, *et al.* The targeting of the cyclin D1 oncogene by an Epstein-Barr virus promoter in transgenic mice causes dysplasia in the tongue, esophagus and forestomach. *Oncogene* 1997;14:1185-90.
- 142 Gansauge S, Gansauge F, Ramadan M, *et al.* Overexpression of cyclin D1 in human pancreatic carcinoma is associated with poor prognosis. *Cancer Res* 1997;57:1634-7.
- 143 Tsuda T, Nakatani H, Tahara E, *et al.* HST1 and INT2 gene coamplification in a squamous cell carcinoma of the gallbladder. *Jpn J Clin Oncol* 1989;19:26-9.
- 144 Boggild MD, Jenkinson S, Pistorello M, *et al.* Molecular genetic studies of sporadic pituitary tumors. *J Clin Endocrinol Metabol* 1994;78:387-92.
- 145 Latil A, Baron JC, Cussenot O, *et al.* Oncogene amplifications in early-stage human prostate carcinomas. *Int J Cancer* 1994;59:637-8.
- 146 Clayton RN, Boggild M, Bates AS, *et al.* Tumour suppressor genes in the pathogenesis of human pituitary tumours. *Hormone Res* 1997;47:185-93.
- 147 Park SK, Kang SK, Lee DY, *et al.* Temporal expressions of cyclins and cyclin dependent kinases during renal development and compensatory growth. *Kidney Int* 1997;51:762-9.
- 148 Betticher DC. Cyclin D1, another molecule of the year? [editorial]. *Ann Oncol* 1996;7:223-5.
- 149 Barnes DM. Cyclin D1 in mammary carcinoma. *J Pathol* 1997;181:267-9.
- 150 Weinstein IB. Relevance of cyclin D1 and other molecular markers to cancer chemoprevention. *J Cell Biochem* 1996;25(suppl):23-8.
- 151 Ligueros M, Jeoung D, Tang B, *et al.* Gossypol inhibition of mitosis, cyclin D1 and Rb protein in human mammary cancer cells and cyclin-D1 transfected human fibrosarcoma cells. *Br J Cancer* 1997;76:21-8.



Cyclin D1 and human neoplasia.

R Donnellan and R Chetty

Mol Path 1998 51: 1-7

doi: 10.1136/mp.51.1.1

Updated information and services can be found at:

<http://mp.bmj.com/content/51/1/1>

References

These include:

Article cited in:

<http://mp.bmj.com/content/51/1/1#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>