Novel targets and approaches in advanced prostate cancer

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Purpose of review

The development of therapeutic resistance is the underlying cause for most cancer deaths. By understanding the molecular basis of resistance to androgen withdrawal and chemotherapy in prostate cancer, the rational design of targeted therapeutics is possible. We review new treatment options for men with advanced prostate cancer.

Recent findings

Although the taxanes currently represent the most active chemotherapeutic agents and standard of care for first-line treatment of metastatic hormone-refractory prostate cancer, most patients eventually progress because of intrinsic or acquired drug resistance. In recent years, increased knowledge of cancer progression and therapeutic resistance has identified many gene targets that regulate apoptosis, proliferation, and cell signalling. To date, numerous novel compounds have entered clinical trials as either single agents or in combination with cytotoxic chemotherapy.

Summary

Even though hormone-refractory prostate cancer is still incurable, it is not untreatable. As cancer cells are proficient at adapting to therapeutic stressors, a combination regimen with drugs that target crucial cellular networks like the apoptotic rheostat may be more promising than treatment with highly selective single-target agents. Recent findings are very hopeful, but challenges remain to demonstrate effective antitumour activity in phase III trials with survival as the principal endpoint.

Keywords

advanced prostate cancer, antisense oligonucleotides, novel agents, targeted therapy

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Abbreviations

ASO	antisense oligonucleotide
HRPC	hormone-refractory prostate cancer
HSP27	heat-shock protein 27
PSA	prostate-specific antigen

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Introduction

Treatment options for men with advanced prostate cancer have changed dramatically over the last decade. With a 9% response rate, chemotherapy was once thought to play a clinically insignificant role in metastatic hormone-refractory prostate cancer (HRPC) [1]. This led many clinicians at that time to treat patients with HRPC with a degree of therapeutic nihilism. More recently, however, a role has emerged for systemic chemotherapy after the demonstration of a small but significant survival benefit for taxane-based chemotherapy in the two landmark studies TAX327 and SWOG9916 [2,3]. Since median survival for patients with HRPC is still only around 18 months, current chemotherapy leaves plenty of room for further improvement.

There is a substantial number of novel agents that have been developed that show promise in the management of patients with advanced prostate cancer, both alone and especially in a combination regimen. Whereas hormonal therapy as well as conventional chemo- and immunotherapy are reviewed elsewhere in this issue, novel agents like nucleotide-based targeted therapies, small-molecule inhibitors, antiangiogenic agents, novel cytotoxic therapeutics, and calcitriol will be discussed here. Due to the rapid progress of this field it is beyond the scope of this review to cover all compounds under investigation. Therefore, we focus on several broad therapeutic categories and selected targets with significant biologic rationale and a reasonable likelihood of success.

Nucleotide-based targeted therapy

Therapeutic resistance results from multiple, stepwise changes in DNA structure and gene expression: a Darwinian interplay of genetic and epigenetic factors, ironically arising in part from selective pressures of treatment. This highly dynamic process cannot be attributed to singular events, involving instead cumulative genetic changes that facilitate escape from normal regulatory control of cell growth. In prostate cancer, changes in the hormonal environment precipitate a cascade of events in gene expression and signalling networks that provide a selective survival and growth advantage for subpopulations of tumour cells, thereby accelerating androgen-independent progression and rendering cells more resistant to chemotherapy [4,5]. Advances in tumour biology research have identified a plethora of attractive molecular targets for new drug discovery. The most promising candidates are those targets that become upregulated during and are causally related to cancer progression

and therapeutic resistance. Moreover, the targets should be selectively overexpressed in tumour cells to minimize the side effects of knockdown. Although potential gene-target libraries developed by microarray technology are valuable, their information must be balanced by the inherent limitations of gene-array analyses. These include the inability to examine translational and post-translational regulatory mechanisms that impact the activity of various cellular proteins.

Antisense oligonucleotides (ASOs) offer one approach to regulate genes involved in cancer progression, especially those that are not amenable to small-molecule or antibody inhibition [6]. ASOs are single-stranded, chemically modified DNA-like molecules that are 17–22 nucleotides in length. They are designed to be complementary to a selected gene's mRNA and thereby specifically inhibit expression of that gene. It is estimated that any sequence of at least 13 bases in RNA and 17 bases in DNA is represented only once within the human genome. Thus, the specificity implicit in the design of ASOs theoretically leads to decreased toxicity. ASO technology has quickly moved from preclinical models to testing in the clinic. Challenges remain to optimize tissue exposure, cellular uptake and demonstration of mechanism and antitumour activity. The lack of success of the first-generation ASOs G3139 and ISIS3521 in recent randomized phase III trials in lung cancer, leukaemia, myeloma, and melanoma has dampened enthusiasm for ASO therapeutics [7,8•,9,10,11•]. However, next-generation ASO chemistry holds significant potential advantages for patient-friendly dosing and routes of administration, enhanced activity, and improved toxicity profile. A survey of a number of ASO drugs in clinical development against HRPC is given in Table 1 and three compounds are discussed below.

The clusterin gene encodes a cytoprotective chaperone protein which has been implicated in a number of physiologic processes [12•]. During times of stress it is thought to act as a survival protein and stabilizes conformations of proteins, thereby inhibiting their precipitation and membrane damage [13]. In prostate cancer, increased clusterin levels are closely correlated with the Gleason score [14,15,16•]. Although clusterin expression is low in most untreated hormone-naïve tissues, levels increase significantly within weeks after neoadjuvant hormone therapy [17]. Preclinical studies have indicated that clusterin suppresses apoptotic cell death in response to androgen withdrawal, chemotherapy, and radiation [18–21]. OGX-011 (OncoGeneX Technologies, Vancouver, British Columbia, Canada) is a second-generation ASO against the human clusterin mRNA. OGX-011 incorporates *2′-O*-methoxyethyl modifications to the four bases on either end of the 21-mer phosphorothioate backbone [22]. Such 'gapmer' modifications maintain the improved tissue pharmacokinetic profile and relaxed dosing regimen of second-generation chemistry but preserve the high affinity for target mRNA and the recruitment of RNase H necessary for target degradation. Indeed, weekly OGX-011 was recently reported to potently suppress clusterin expression in prostate cancer tissues in combination with androgen-deprivation therapy [23]. This phase I trial had a unique design, where men with localized prostate cancer were administered OGX-011 prior to radical prostatectomy, allowing for dose-dependent correlations between clusterin expression and drug concentrations in tissues. Thus, in addition to the usual parameters of toxicity the presurgery study design allowed determination of an optimal biologically effective dose based on a >90% knockdown of clusterin. A second phase I trial combined increasing doses of OGX-011 with docetaxel in patients with metastatic breast cancer, nonsmall cell lung cancer, and HRPC and confirmed the phase II dose for OGX-011 of 640 mg for use in a combination regimen with docetaxel [24]. Two randomized phase II trials of OGX-011 in combination with both first- and second-line chemotherapy are now underway in HRPC patients (NCIC IND.165, CUOG P-06B). Moreover, a phase III registration trial of OGX-011 with mitoxantrone as second-line chemotherapy in men with docetaxel-resistant HRPC will begin by mid-2007.

Table 1 Antisense therapeutics targeting hormone-refractory prostate cancer in late-stage preclinical or clinical development

Target	Compound	Company	Phase of development
BCL2	G3139 (Oblimersen, Genasense)	Genta	II–III
PKCα	ISIS3521 (Affinitak, Aprinocarsen)	Lilly/Isis	II–III
Clusterin	OGX-011	OncoGeneX	II
RAF1	ISIS5132	Isis	II
PKA	GEM231	Hybridon/Idera	II
RNR (R1 and R2 component)	GTI-2501, GTI-2040	Lorus	I–II
Survivin	LY2181308, ISIS23722	Lilly/Isis	I
XIAP	AEG35156, GEM640	Aegera	I
HSP27	OGX-427	OncoGeneX	I
eIF4E	LY2275796	Lilly/Isis	Preclinical–phase I
IGFBPs 2 and 5	OGX-225	OncoGeneX	Preclinical

BCL2, B-cell lymphoma 2; eIF4E, eukaryotic translation-initiation factor 4E; HSP27, heat-shock protein 27; IGFBP, insulin-like growth factor-binding protein; PKA, protein kinase A; PKC, protein kinase C; RAF1, v-raf-1 murine leukaemia viral oncogene homologue 1; RNR, ribonucleotide reductase; XIAP, X-linked inhibitor of apoptosis protein.

The rationale behind the second-line approach is that OGX-011 has been shown to reverse docetaxel resistance and enhance the antitumour activity of mitoxantrone and docetaxel *in vitro* and *in vivo* (R.D. Sowery and M.E. Gleave, unpublished data).

Ribonucleotide reductase is an important enzyme for cell division and tumour growth that is required for the reductive conversion of ribonucleotides to deoxyribonucleotides, which is a crucial step in the synthesis and repair of DNA [25]. GTI-2040 (Lorus Therapeutics, Toronto, Ontario, Canada) is a first-generation phosphorothioate antisense molecule that inhibits the expression of the R2 subunit of ribonucleotide reductase [26]. In a dose-finding phase I study four out of 36 patients with advanced tumours had a stabilization of their disease [27]. Preliminary results of a following phase II trial of GTI-2040 in combination with docetaxel and prednisone in patients with chemotherapy-naïve HRPC have recently been reported, with nine patients out of 22 having a response in prostate-specific antigen (PSA) [28].

Heat-shock protein 27 (HSP27) is one of the most strongly induced chaperones at times of cellular stress. Similar to clusterin, HSP27 binds to a wide variety of client proteins and prevents the aggregation of damaged proteins [29]. HSP27 is abundantly expressed in malignant cells and participates in conferring chemoresistance [30,31]. Accumulating evidence links rising HSP27 levels with HRPC [32–36]. HSP27 may eventually serve as a therapeutic hyper-node, a target situated at the centre of many pathways involved in regulating the response of a cell to treatment-induced stress. Thus, HSP27 is a rational target for drug development as its inhibition would silence multiple survival pathways at once. Several phase I/II clinical trials using a second-generation ASO against HSP27 (OGX-427; OncoGeneX Technologies) are set to begin in 2007.

Small-molecule inhibitors

Small-molecule inhibitors herald considerable promise as they can specifically block cellular signalling pathways involved in growth and apoptosis. Endothelin-1 and its ET-A receptor have been demonstrated to generate multiple effects on cellular physiology and paracrine signalling in prostate cancer. Endothelin-1 is implicated in the regulation of cell growth and higher levels correlate with progressive disease [37]. Endothelin-1 has also been shown to be involved in osteoblastic activity and may influence the development of bony metastasis and bone-related pain in prostate cancer [38•]. Atrasentan (Xinlay, Abbott Labs, Abbott Park, Illinois, USA) is a selective ET-A receptor antagonist under investigation for use in HRPC. In a phase II trial, patients with metastatic HRPC treated with an oral 10 mg dose of atrasentan had a trend toward prolongation in median time to progression compared with placebo (183 compared with 137 days, $P = 0.13$) [39]. In addition, a statistically significant delay in median time to PSA progression was demonstrated (155 days for atrasentan compared with 71 days for placebo, $P = 0.002$). In the following phase III trial, 809 men with metastatic prostate cancer were randomized to atrasentan or placebo [40]. However, this study was closed early on review of the unexpectedly large number of early events that suggested the trial results would not be different from control outcomes. The significance of the radiographic markers of progression used in the study without clinical symptoms remains controversial. Although the primary endpoint, time to progression, was not statistically different from the placebo group, secondary endpoints demonstrated clinical activity. These included improvement in quality of life and pain scores, and reductions in the rise of laboratory markers, including alkaline phosphatase and PSA. A meta-analysis of pooled phase II and III data was able to show a significant increase in time to progression, as well as a prolongation in the pain-free duration by 3 months for patients taking atrasentan [41]. In all trials, atrasentan was well tolerated with mild adverse events such as headache, rhinitis, and peripheral oedema. These data suggest biological activity and identify the endothelin axis as a potential target in advanced prostate cancer. Atrasentan has not yet obtained US Food and Drug Administration approval because of a failure to demonstrate a perceived clinically relevant benefit. A phase III study of docetaxel and prednisone with or without atrasentan is currently recruiting HRPC patients with bone metastases (SWOG-S0421).

Imatinib (Gleevec; Novartis Pharmaceuticals, East Hanover, New Jersey, USA) is an agent that inhibits the tyrosine kinase activity of the platelet-derived growth factor receptor, which is abundant in metastatic prostate cancer and has therefore been evaluated in the treatment of patients with HRPC [42,43•]. A phase II trial in men with biochemical relapse of prostate cancer after definitive local therapy was recently conducted [44]. Unfortunately, a lack of effect on PSA-doubling time, and pronounced toxicity at the dose given in the trial (400 mg orally, twice daily) led to early closure of this trial. The role of imatinib in combination therapy, however, may be promising, and phase II clinical trials combining imatinib and docetaxel in the metastatic setting are underway (NCT00080678, NCT00251225).

Angiogenesis inhibitors

Angiogenesis is a complex and tightly regulated process that is necessary for tumour growth and metastasis [45]. Vascular endothelial growth factor is a key mediator in promoting tumour angiogenesis [46]. Bevacizumab (Avastin; Genentech, San Francisco, California, USA) is a humanized monoclonal antibody that neutralizes

activity of vascular endothelial growth factor and has shown promise in HRPC. The role of bevacizumab in combination with estramustine and docetaxel was investigated in the CALGB 90006 trial in 79 patients with metastatic HRPC [47]. Early results showed that 53% of patients had a partial response and 65% had a greater than 50% decrease in PSA. The regimen was fairly well tolerated, although there was some increase in thrombosis. When compared with another CALGB triplet trial in which carboplatin was added to estramustine and docetaxel (CALGB 99813) [48], the use of bevacizumab resulted in a posttherapy PSA decline in 81% of patients compared with 68% of the patients treated with the carboplatin regimen, and an overall median survival of 21 months compared with 19 months, respectively. These results are encouraging and safety would be enhanced with the elimination of estramustine, especially in light of the evolving data suggesting that estramustine adds little to the overall survival of patients. Another ongoing phase II trial as first-line treatment in combination with docetaxel, prednisone, and thalidomide in metastatic HRPC patients showed until now no thrombosis and a high durable 86% response in PSA (NCT00091364) [49]. A phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic HRPC is currently enrolling patients (CALGB 90401).

Thalidomide and its analogues are additional agents with antiangiogenic properties under investigation in HRPC. Thalidomide has multiple mechanisms of action including immunomodulatory effects on the tumour microenvironment [50]. As single agent thalidomide demonstrated a greater then 50% PSA response rate of only 18% of patients [51]. In combination with docetaxel however, the median time to progression of chemotherapy-naïve metastatic HRPC patients was delayed notably by adding thalidomide (5.9 compared with 3.7 months, $P = 0.32$) [52]. Moreover, as a second-line regimen a triplet combination of thalidomide, paclitaxel, and estramustine warrants further investigation, due to a recently reported PSA response rate of 76% [53••].

Novel cytotoxic therapeutics

Satraplatin (Spectrum Pharmaceuticals, Irvine, California, USA/GPC Biotech, Martinsried, Germany) is an orally bioavailable third-generation platinum-based compound [54]. A first phase III study of satraplatin with or without prednisone as first-line chemotherapy in HRPC patients was closed prematurely because of sponsorship difficulties. An ad-hoc analysis with only 50 of the anticipated 380 patients enrolled and randomized reported a statistically significant increase in progression-free survival with satraplatin and prednisone compared to prednisone alone (5.2 compared with 2.5 months, $P = 0.023$) [55]. Another phase III registration trial (SPARC; Satraplatin and Prednisone against Refractory Cancer) is now evaluating satraplatin plus prednisone as a second-line therapy in patients with HRPC [56]. At the time of submission of this review, GPC Biotech reported a significant improvement in median progression-free survival of these second-line patients (11 weeks in the satraplatin plus prednisone arm compared with 9.7 weeks in the placebo plus prednisone arm, $P < 0.00001$). Nonetheless, the more important survival data will not be available until late 2007.

Epothilones are a new class of tubulin-polymerizing agents that suppress microtubule dynamics similar to the taxanes, but are less susceptible to P-glycoprotein-induced drug efflux [57]. Phase II trials of BMS-247550 (Ixabepilone; Bristol-Myers Squibb, New York, USA) in chemotherapy-naïve HRPC have shown PSA responses in single-agent therapy (33–48%) and in combination with estramustine (69%) [58,59]. Since BMS-247550 showed potent cytotoxic effects in phase I studies on advanced tumours in patients previously treated with taxanes, there might be a possible role in second-line therapy [60]. To evaluate this hypothesis in HRPC there is currently a phase I/II combination trial with BMS-247550, mitoxantrone, and prednisone underway (NCT00331344). However, results of a second-line therapy study of taxane-resistant HRPC with BMS-247550 as a single agent showed only modest activity [61].

Calcitriol

Calcitriol, the principal active metabolite of vitamin D, has been shown to enhance many commonly used chemotherapeutic agents, producing antitumour activity in several prostate cancer models [62]. DN-101 (Asentar; Novacea, San Francisco, California, USA) is a proprietary high-dose formulation of calcitriol which has entered phase III trials. A previous phase II/III trial of 250 metastatic HRPC patients (ASCENT; Androgen independent prostate cancer Study of Calcitriol Enhancing Taxotere) showed a trend that favoured DN-101 over placebo when used in combination with docetaxel but did not reach statistical significance (63% compared with 52% PSA response rate, $P = 0.073$). The estimated survival for patients treated with DN-101 and docetaxel was 23.5 months compared with 16.4 months for patients treated with placebo and docetaxel [63]. Since this study was underpowered to detect a significant difference in survival, a second phase III study (ASCENT-2) investigating DN-101 in combination with docetaxel compared with docetaxel and prednisone is currently enrolling patients, with a target enrolment of 900 patients.

Conclusion

Currently, the combination of docetaxel every 3 weeks plus low-dose prednisone represents the standard of care for patients with metastatic HRPC. This chemotherapy

can provide durable palliation and a modest but real improvement in overall survival. Nonetheless, with a median survival of 18–20 months rationally designed therapeutic approaches continue to be needed urgently. The development of novel therapeutics, some of which were discussed in this review, is essential to provide clinicians multiple avenues through which prostate cancer can be treated more effectively. The biggest impact on mortality is likely to come from a multimodal combination regimen. To provide patients with the most appropriate treatment strategy, an integrated multidisciplinary approach with urologists and oncologists working closely together must be further encouraged. However, it is imperative that we as urologists are involved in the assessment and implementation of these novel therapeutics as we have a close interaction with the patient from early-stage, localized disease to HRPC. With several promising agents on the horizon, well-designed clinical trials are needed to establish the role of these agents in treatment regimens. The clinical experience to date should still be considered part of the beginning of the era of targeted treatment for prostate cancer.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 208–209).

1 Yagoda A, Petrylak D. Cytotoxic chemotherapy for advanced hormone-resistant prostate cancer. Cancer 1993; 71:1098–1109.

2 Tannock IF, de Wit R, Berry WR, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351:1502–1512.

3 Petrylak DP, Tangen CM, Hussain MH, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351:1513–1520.

4 Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005; 23:8253–8261.

5 So A, Gleave M, Hurtado-Col A, Nelson C. Mechanisms of the development of androgen independence in prostate cancer. World J Urol 2005; 23:1–9.

6 Gleave ME, Monia BP. Antisense therapy for cancer. Nat Rev Cancer 2005; 5:468–479.

7 Rai KR, Moore JO, Boyd TE, *et al.* Phase 3 randomized trial of fludarabine/cyclophosphamide chemotherapy with or without oblimersen sodium (Bcl-2 antisense; Genasense; G3139) for patients with relapsed or refractory chronic lymphocytic leukemia (CLL). ASH Annual Meeting Abstracts 2004; 104:338.

8 • Bedikian AY, Millward M, Pehamberger H, *et al.* Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. J Clin Oncol 2006; 24:4738–4745.
This paper, highlighting a lack of success for a first generation ASO in a phase III trial illustrates the early challenges facing antisense therapeutics.

9 Chanan-Khan AA, Niesvizky R, Hohl RJ, *et al.* Randomized multicenter phase 3 trial of high-dose dexamethasone (dex) with or without oblimersen sodium (G3139; Bcl-2 antisense; Genasense) for patients with advanced multiple myeloma (MM). ASH Annual Meeting Abstracts 2004; 104:1477.

10 Lynch TJ, Raju R, Lind M, *et al.* Randomized phase III trial of chemotherapy and antisense oligonucleotide LY900003 (ISIS 3521) in patients with advanced NSCLC: initial report. Proc Am Soc Clin Oncol 2003; 22: abstract 2504.

11 • Paz-Ares L, Douillard JY, Koralewski P, *et al.* Phase III study of gemcitabine and cisplatin with or without aprinocarsen, a protein kinase C-alpha antisense oligonucleotide, in patients with advanced-stage nonsmall-cell lung cancer. J Clin Oncol 2006; 24:1428–1434.
Aprinocarsen failed to enhance survival in the studied nonsmall-cell lung cancer patient population. However, it is unknown whether the target was actually relevant in the cohort and target knockdown was not assessed.

12 • Shannan B, Seifert M, Leskov K, *et al.* Challenge and promise: roles for clusterin in pathogenesis, progression and therapy of cancer. Cell Death Differ 2006; 13:12–19.
This is a recent overview of clusterin and its different isoforms.

13 Wilson MR, Easterbrook-Smith SB. Clusterin is a secreted mammalian chaperone. Trends Biochem Sci 2000; 25:95–98.

14 Steinberg J, Oyasu R, Lang S, *et al.* Intracellular levels of SGP-2 (Clusterin) correlate with tumor grade in prostate cancer. Clin Cancer Res 1997; 3:1707–1711.

15 Miyake H, Yamanaka K, Muramaki M, *et al.* Enhanced expression of the secreted form of clusterin following neoadjuvant hormonal therapy as a prognostic predictor in patients undergoing radical prostatectomy for prostate cancer. Oncol Rep 2005; 14:1371–1375.

16 • Miyake H, Muramaki M, Kurahashi T, *et al.* Expression of clusterin in prostate cancer correlates with Gleason score but not with prognosis in patients undergoing radical prostatectomy without neoadjuvant hormonal therapy. Urology 2006; 68:609–614.
This paper reports on a large pathologic study to evaluate clusterin expression as a prognostic marker without proapoptotic stimuli.

17 July LV, Akbari M, Zellweger T, *et al.* Clusterin expression is significantly enhanced in prostate cancer cells following androgen withdrawal therapy. Prostate 2002; 50:179–188.

18 Miyake H, Nelson C, Rennie PS, Gleave ME. Testosterone-repressed prostate message-2 is an antiapoptotic gene involved in progression to androgen independence in prostate cancer. Cancer Res 2000; 60:170–176.

19 Miyake H, Chi KN, Gleave ME. Antisense TRPM-2 oligodeoxynucleotides chemosensitize human androgen-independent PC-3 prostate cancer cells both in vitro and in vivo. Clin Cancer Res 2000; 6:1655–1663.

20 Zellweger T, Chi K, Miyake H, *et al.* Enhanced radiation sensitivity in prostate cancer by inhibition of the cell survival protein clusterin. Clin Cancer Res 2002; 8:3276–3284.

21 Trougakos IP, So A, Jansen B, *et al.* Silencing expression of the clusterin/apolipoprotein j gene in human cancer cells using small interfering RNA induces spontaneous apoptosis, reduced growth ability, and cell sensitization to genotoxic and oxidative stress. Cancer Res 2004; 64:1834–1842.

22 Zellweger T, Miyake H, Cooper S, *et al.* Antitumor activity of antisense clusterin oligonucleotides is improved in vitro and in vivo by incorporation of 2′-O-(2-methoxy)ethyl chemistry. J Pharmacol Exp Ther 2001; 298:934–940.

23 Chi KN, Eisenhauer E, Fazli L, *et al.* A phase I pharmacokinetic and pharmacodynamic study of OGX-011, a 2′-methoxyethyl antisense oligonucleotide to clusterin, in patients with localized prostate cancer. J Natl Cancer Inst 2005; 97:1287–1296.

24 Chi KN, Eisenhauer E, Siu L, *et al.* A phase I study of a second generation antisense oligonucleotide to clusterin (OGX-011) in combination with docetaxel: NCIC CTG IND.154. ASCO Meeting Abstracts 2005; 23:3085.

25 Fan H, Villegas C, Huang A, Wright JA. The mammalian ribonucleotide reductase R2 component cooperates with a variety of oncogenes in mechanisms of cellular transformation. Cancer Res 1998; 58:1650–1653.

26 Lee Y, Vassilakos A, Feng N, *et al.* GTI-2040, an antisense agent targeting the small subunit component (R2) of human ribonucleotide reductase, shows potent antitumor activity against a variety of tumors. Cancer Res 2003; 63:2802–2811.

27 Desai AA, Schilsky RL, Young A, *et al.* A phase I study of antisense oligonucleotide GTI-2040 given by continuous intravenous infusion in patients with advanced solid tumors. Ann Oncol 2005; 16:958–965.

28 Sridhar SS, Canil CM, Hotte SJ, *et al.* A phase II study of the antisense oligonucleotide GTI-2040 plus docetaxel and prednisone as first line treatment in hormone refractory prostate cancer (HRPC). ASCO Meeting Abstracts 2006; 24:13015.

29 Concannon CG, Gorman AM, Samali A. On the role of Hsp27 in regulating apoptosis. Apoptosis 2003; 8:61–70.

30 Garrido C, Schmitt E, Cande C, *et al.* HSP27 and HSP70: potentially oncogenic apoptosis inhibitors. Cell Cycle 2003; 2:579–584.

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