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STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER AND MEETING COVERAGE

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This article has been prepared based on the August 1998 version of the NEW MEDICINE Oncology KnowledgeBASE (nm|OK) and also incorporates information presented at the September 1997 meeting of the Association for the Cure of Cancer of the Prostate (CaP CURE97), Lake Tahoe, NV; the March 1998 meeting of the American Association for Cancer Research (AACR98), New Orleans, LA; and the May 1998 meeting of the American Society of Clinical Oncology (ASCO98), Los Angeles, CA. For additional information on prostate cancer, see FO, pp 790-7, 762-9, 730-1, 392-401 and 302-28.

The major challenge in management of prostate cancer is treatment of advanced and metastatic disease. Once tumor spreads beyond the gland, there is a good chance it will recur after first-line therapy and metastasize to distant sites, mostly bone. Hormonal therapies provide some control that may last for several years but eventually they also fail. When this occurs there is little more that can be done, other than bone pain palliation, because metastatic prostate cancer responds poorly to chemotherapy. Exhibit 1 lists over 150 agents in development to treat all stages of prostate cancer.

MECHANISMS IN PROSTATE CANCER

Although the process via which prostate cancer arises, spreads regionally through the gland, and metastasizes to distant sites has not been elucidated, various theories are being put forth. Also, numerous molecular markers that may serve as therapeutic targets, have been linked to every stage of prostate cancer.

Androgen and its Receptor

Androgen levels and androgen metabolism are considered important in prostate cancer and androgen deprivation is the mainstay treatment of advanced prostate cancer (see FO, pp 303 and 306).

PSA levels are upregulated in response to testosterone, or its more active metabolite dihydrotestosterone (DHT), that bind the androgen receptor (AR) which, in turn, becomes activated and goes on to bind DNA and to upregulate a family of genes that lead to prostate growth. It has been shown that human prostate cancer progresses in the presence of AR protein. It is currently believed that prostate cancer becomes non-responsive to hormonal treatment (androgen resistant) because of transcriptional inactivation of the AR gene catalyzed by cytosine DNA methyltransferase (CMT). However, even when prostate cancer evolves into a form independent of testosterone, it continues to grow uncontrollably because AR mutations enable this receptor to bind and become activated by other steroid molecules such as estrogens that are present in high levels in the body.

Despite the role of the AR in prostate cancer, none of the currently available antiandrogen therapies lead to inhibition of AR expression. One way to downregulate AR expression is by using antisense. Researchers at the University of Innsbruck in Austria, in collaboration with Schering AG, employed antisense phosphorothioate oligodeoxynucleotides directed against the poly Gln- and the poly Gly-region of the AR to specifically downregulate the AR in LNCaP cells *in vitro*. Using electroporation to ensure uptake, downregulation of AR to less than 10% of an untreated control 24 hours after electroporation was achieved which persisted for up to 120 hours. Treated cells, when stimulated with synthetic androgen, showed a

reduced proliferative response and PSA secretion (Eder IE, etal, AACR98, Abs. 87:13).

Another novel approach, being pursued by Calydon (Sunnyvale, CA) is aimed at a target downstream of the defective AR, i.e. the binding of the activated AR complex to DNA. Calydon's proprietary gene, the prostate specific enhancer (PSE), is the only known human piece of DNA that is activated by the AR exclusively in prostate cells. Calydon has developed an assay targeting the PSE and the associated AR complex, and is working to identify and develop a new class of oral drugs that will act at an early, critical stage, to block the growth of prostate cancer.

Some antiandrogens may also act as androgen receptor (AR) agonists. Promotion of agonist activity of antiandrogens by the androgen receptor coactivator, ARA70, was demonstrated in human DU145 prostate cancer cells. The molecular mechanism of this agonist response, however, remains unclear. Using mammalian two-hybrid assay, investigators at the University of Rochester Medical Center (Rochester, NY) found that such antiandrogens as hydroxyflutamide, bicalutamide (Casodex; Zeneca), cyproterone acetate (Androcur, Cyprostat; Schering AG), and RU-58841, and other compounds such as genistein, found in soybeans and related products, and the antiprogestin mifepristone (RU-486; Hoechst Marion Roussel) can promote the interaction between AR and its coactivator, ARA70, in a dose-dependent manner. In DU145 cells, these compounds significantly enhance the transcriptional activity of the AR by cotransfection of AR and ARA70 in a 1:3 ratio. These findings may provide a good model to develop better antiandrogens without agonist activity (Miyamoto H, etal, PNAS USA 23 Jun 1998, 95(13):7379-84).

Apoptosis

Upon androgen withdrawal, androgen-dependent cells undergo rapid apoptosis. However, because most prostate cancers contain androgen-dependent and androgen-independent cells, androgen deprivation usually leads to the expansion of androgen-independent clones and disease recurrence. Also, genetic alterations such as bcl-2 amplification, create apoptosis-resistant clones. Although androgen-independent prostate cancer cells do not undergo apoptosis upon androgen withdrawal, they still incorporate the appropriate molecular machinery of apoptosis, which may be induced using conventional chemotherapy drugs.

FGN-1 (Exisulind) and its analog, CP248, are sulfone metabolites of the NSAID sulindac under development by Cell Pathways (Horsham, PA). FGN-1 acts through a novel mechanism to selectively induce apoptosis in precancerous and cancerous cells without affecting normal cells. FGN-1 stimulates apoptosis independently of p53 induction and cell cycle arrest (Piazza, etal, Cancer Res 57:2452, 1997). Treatment of LNCaP and PC3 prostate cancer cell lines with FGN-1 or CP248, resulted in significant growth inhibition (Lim1 JTE, etal, AACR98, Abs. 3993:587). FGN-1 is being clinically investigated in a randomized, double blind, placebo-controlled, multicenter, phase II clinical trial (protocol IDs: UCLA-HSPC-971104401, NCI-V98-1405, CELLPATH-012) for the prevention of prostate cancer recurrence. The trial, sponsored by the NCI and being conducted at the Jonsson Comprehensive Cancer Center at UCLA under PI Diane Prager, MD, is to enroll 90 patients with rising PSA levels after undergoing prostatectomy. Patients are randomized either to oral FGN-1, administered twice daily for up to 12 months, or placebo.

Growth Factors

In addition to hormones, many polypeptide growth factors may be potent mitogens of cell proliferation and may facilitate the progression of prostate cancer as autocrine and/or paracrine factors, influencing cellular interactions between stroma and epithelium that are important in the growth and proliferation of this malignancy.

The fibroblast growth factor (FGF) family, which incorporates at least 9 closely related members, is essential for both normal and abnormal proliferation of prostate cells. Also, there are four transmembrane receptors of mammalian FGFs, FGFr1 (Flg), FGFr2 (Bek), FGFr3 and FGFr4 which exhibit intrinsic protein tyrosine kinase (PTK) activity. Inappropriate activation of FGF receptors may be involved in tumor angiogenesis.

One member of the FGF family, FGF2, also known as basic FGF (bFGF), is a potent mitogen for fibroblasts derived from normal prostate and, to a lesser extent, for prostatic epithelial cells. Its the normal prostate, its physiological role seems to be limited to stromal cells, whereas in prostate cancer, FGF2 may also have an autocrine/paracrine effect on epithelial cells (Ropiquet F, etal, Int'l J Cancer, 1997 Jul 29, 72(3):543-7).

In an example of highly regulated alternative splicing, exons IIIb and IIIc of FGFr2 are used in a mutually exclusive manner in different cell types. Deregulation of FGFr2 splicing is associated with progression of prostate cancer. In the rat, loss of expression of isoform FGFr2 (IIIb) accompanies the transition of a well-differentiated, androgen-dependent prostate cancer cell line, DT3, to the more aggressive, androgen-independent AT3 cell line. Investigators postulate that a cis-acting element (intronic splicing activator and repressor, or ISAR) located in the intron between alternative exons IIIb and IIIc, mediates activation of splicing using the upstream IIIb exon and repression of the downstream IIIc exon in DT3 cells. Factors which bind ISAR are required for maintenance of expression of the FGFr2 (IIIb) isoform (Carstens RP, etal, Molecular and Cellular Biology, 1998 Apr, 18(4):2205-17).

In a model of human prostate cancer, it was shown that progression of prostate cancer from androgen sensitive to androgen insensitive is accompanied by a change in alternative splicing of fibroblast growth factor receptor 2 (FGFr2). This change results in loss of the FGFr2(IIIb) isoform and predominant expression of the FGFr2(IIIc) isoform (Carstens RP, etal, Oncogene, 1997 Dec 18, 15(25):3059-65).

The level of FGFr2 gene expression was reduced and lost altogether in over 30% of cancer cells, whereas all malignant cells abnormally express FGFr1, which is normally confined to stromal cells (Feng S, etal, Cancer Research, 57:5369-5378, 1997). Other investigators report that FGFr1 is present in primary tumors but is frequently lost during androgen-independent metastasis (Huss WJ and Greenberg NM, AACR98, Abs. 291:43). Progressive loss of the FGFr2(IIIb) isoform accompanies progression of premalignant androgen-responsive prostate tumor epithelial cells to the malignant phenotype. The FGFr1(IIIb) isoform was expressed in all cases of prostate cancer (n=17), but FGFr1(IIIc) mRNA was not detected. FGFr2(IIIb) expression was detected in 5/6 cases of BPH and 12/17 (71%) cases of prostate cancer. FGFr2(IIIc) expression was present in 11/17 tumors but was absent in all six cases of BPH (Leung HY, etal, Oncogene, 1997 Aug 28, 15(9):1115-20). However, although the FGFr2 kinase can mediate positive mitogenic effects, it mediates a net restriction on the growth of prostate tumor epithelial cells relative to FGFR1. Highly malignant prostate tumor cells, which have lost the FGFr2 tyrosine kinase, retain the cellular response mechanisms to it. Restoration of the FGFr2 kinase to malignant tumors that are refractory to treatment may present a new avenue for gene therapy (Matsubara A, etal, Cancer Research, 1998 Apr 1, 58(7):1509-14).

FGF7 or keratinocyte growth factor (KGF), also has a differentiative and proliferative effect on the epithelium of the developing rat prostate. KGF expression was not detected in benign prostatic hyperplasia (BPH) while 65% (11/17) cases of prostate cancer expressed KGF mRNA. Upregulation of KGF expression was related to hormone-insensitive tumors but not to tumor grade and stage. In a proliferation assay, recombinant KGF demonstrated a mitogenic effect of up to 100% on cultured prostatic epithelial cells (Leung HY, etal, Oncogene, 1997 Aug 28, 15(9):1115-20).

FGF8, also known as androgen-induced growth factor, was shown to be mitogenic to the androgen-sensitive LNCaP cell line. FGF8 was frequently expressed in human prostate cancer, being detected in 40 of 43 cases (93%), but was undetectable in both BPH specimens and normal prostate tissues. In contrast, FGF was detected in normal ductal and lobular epithelial cells in breast tissues. Androgen receptors were also immunohistochemically detected in 40/40 (100%) FGF8-positive prostate cancers. An anti-FGF8 antibody blocked androgen- and FGF8-stimulated growth in prostate cancer cells *in vitro,* but not bFGF-stimulated growth (Tanaka A, etal, Cancer Research, 1998 May 15, 58(10):2053-6).

Insulin-like growth factors-I and II (IGF-I and IGF-II, also IGF-1 and IGF-2), are tightly bound, both in the circulation and in tissues, to the IGF-binding proteins (IGFBPs). IGFs and their receptors appear to promote prostate cell growth while IGFBPs inhibit it. In a study conducted in Sweden, IGF-I levels were significantly higher (158.4 ng/ml) in 210 newly-diagnosed prostate cancer cases compared to 224 frequency-matched controls (147.4 ng/ml), but corresponding IGFBP-3 levels were similar. There was a statistically-significant positive association between serum levels of IGF-I and risk of prostate cancer that was particularly strong in those <70 years-of-age (Wolk A, etal, JNCI, 17 Jun 1998, 90(12):911-915).

IGF-I is elevated in both BPH and prostate cancer. It has been suggested that IGF-I, produced by stromal cells in prostatic hyperplasia, exerts its effects on IGF-I receptor (IGF-Ir)-positive epithelial cells through a paracrine mode. In adenocarcinoma, production of IGF-I appears to switch to epithelial cells, through which it regulates tumor cell growth via an autocrine mode by binding to IGF-Ir of malignant cells.

Because levels of serum IGF-I are regulated by growth hormone, the role of IGF-I in prostate cancer becomes germane in those treated chronically with growth hormone, particularly young patients. Nevertheless, the relationship between IGF and prostate cancer has not been established. Therefore, although IGF-I was found to be elevated in prostate cancer, using this marker as an prognostic indicator or a screening approach is unwarranted. If therapeutic strategies targeting IGF-I, such as somatostatin analogs and growth factor antagonists, prove successful, then screening for IGF-I in prostate cancer will become routine. However, it has yet to be shown that reducing IGF-I levels in prostate cancer will arrest tumor growth.

Vascular endothelial growth factor (VEGF) is overexpressed in hyperplastic/dysplastic and carcinoma cells and is also detected in endothelial cells. Results suggest that overexpression of VEGF in deranged epithelia and arterial muscle cells may exert its influence on stromal angiogenesis and abnormal growth of the prostate gland (Wang YZ and Wong YC, Prostate, 1998 May 15, 35(3):165-77). Detection of VEGF and mRNA for VEGF receptors flt and KDR in prostate tumors suggests possible involvement of VEGF in the growth and/or progression of prostate cancer (Jackson MW, etal, AACR98, Abs. 272:40). In addition VEGFr2 (Flk-1), and VEGFr3 (Flt-4) may also play a role in such progression through angiogenesis mechanisms. However, using the transgenic adenocarcinoma of the mouse prostate (TRAMP) model that closely mimics the progression and metastasis of human disease, researchers at Baylor College of Medicine (Houston, TX) found that neither VEGF nor FGF-2 (bFGF) appear to be upregulated with tumor progression, suggesting that neovascularization is regulated by other ligands or receptors (Huss WJ and Greenberg NM, *ibid*).

Cephalon (West Chester, PA) has identified a new class of molecules which may block the growth of solid tumors by preventing angiogenesis through the VEGF cascade.

Epidermal growth factor (EGF) family of tyrosine kinase receptors (TKr) is also a target in therapeutic strategies in prostate cancer. EGF and EGF receptor (EGFr) levels are regulated by androgens in human prostate cancer cell lines. In hormone-independent prostate cancer cell

lines, levels of EGFr are increased. A MAb blocking EGFr inhibited the growth of human prostate cancer cells *in vitro* (Peng D, etal, AACR96, Abs. 1664:243). Several MAb-based prostate cancer therapeutics target EGFr, such as the bispecific MDX-447, under development by Medarex (Annandale, NJ) and C225, a chimeric MAb against EGFr, under development by ImClone Systems (New York, NY).

HER2/neu, a 185 kDa protein human EGF-like receptor (HER), encoded by a human proto-oncogene belonging to the EGF TKr family, is also overexpressed in numerous tumors, as well as metastatic prostate cancer.

Metastasis, Angiogenesis and Cell Adhesion

Understanding the process of metastatic progression is critical in developing therapeutic and preventative interventions (see FO, p 815-821). It currently appears that, in prostate cancer, the metastatic process involves both a physiological and a molecular component. Tumor spread may be aided by an alteration of the physical environment of the tumor as well as by signaling. Prostate cancer preferentially metastasizes to the bone.

According to Kenneth Pienta, MD, of the University of Michigan Comprehensive Cancer Center (Ann Arbor, MI), speaking at CaP CURE97, cells from primary prostate tumors cross the blood vessel lumen by intravasation and travel in the bloodstream. Therefore, the first step in the metastatic process is contact with the endothelium. There appears to be a preferential binding of prostate cancer cells to bone marrow endothelium which was shown to be magnesium-dependent. Blocking galactose-binding lectin (galectin) 3, which is upregulated on the surface of PC-3 prostate cells, completely abrogates this binding. Investigators are attempting to identify a ligand for galactin 3. Another blocking agent is modified citrus pectin, a dietary fiber. An IND was filed in mid 1997 to begin clinical trials of this substance as an anti-adhesive therapy.

Another player in the process of metastasis is endothelin-1 (ET-1), a newly discovered vasoconstrictor peptide, that has been implicated in angiogenesis by stimulating growth of vascular endothelial cells and functioning as an autocrine/paracrine growth factor for human cancers. ET-1 has been implicated in cardiovascular disorders such as stroke and myocardial ischemia. It is not clear why overexpression of a vasoconstrictor enhances the metastatic potential of tumors and why endothelin overexpressing tumors paradoxically become more ischemic when treated with ET_Ar antagonists.

There are two ET-1 receptors, ET_Ar and ET_Br. Investigators at the Regina Elena Cancer Institute (Rome, Italy) have demonstrated that expression of ET-1 and its receptor, ET_Ar, correlates with vascularity in human ovarian carcinomas (Bagnato A, etal, AACR98, Abs. 1014:149). In prostate cancer, ET_Br, the predominant endothelin receptor expressed by normal prostate epithelium, is not expressed by any of the established human prostate cancer cell lines, while ET_Ar is widely expressed in prostate cancer that has metastacized to the bone. Also, ET_Br binding is decreased on prostate cancer tissues. The ET_Br gene EDNRB resides on chromosome 13q22 where allelic loss is common, and its underexpression in prostate cancer may be the result of such loss or mutation. Therefore, therapeutic strategies based on endothelin may involve activation of ET_Br or blocking of ET_Ar.

Somatic hypermethylation of the 5` CpG island sequences in EDNRB occurs in 70% of prostate cancer samples studied. Mutations often occur in this gene. A frameshift mutation (loss of thymidine at nucleotide 873) was detected in exon 4 of EDNRB in the human prostate cancer cell line LNCaP. A missense mutation has been identified in the same exon and transmembrane domain (W276C) in multigenic Hirschsprung's disease. As the receptor of ligand clearance and inhibition of ET-1 secretion, ET_B can also uniquely mediate the function of ET-1. Loss of this regulatory function may contribute to the progression and morbidity of prostate cancer (Nelson JB, etal, AACR98, Abs. #4224:623).

Adhesion signaling pathways are also involved in metastasis and are potential targets for novel therapeutics. According to J. Thomas Parsons, PhD, of the University of Virginia (Charlottsville, VA), speaking at CaP CURE97, cells need to adhere to the extracellular matrix (ECM) in order to divide and survive and ECM adhesion regulates cell motility. Progression of tumorigenesis in prostate cancer is mediated by the synergistic actions of a variety of growth factor receptors and the ECM. Also, intracellular signaling via signal transduction pathways, mediated by integrin receptors, is required for cell survival and growth factor receptor efficacy.

Neovascularization and angiogenesis has also been shown to play an important role in prostate cancer as they do in many other cancers. Angiogenesis inhibitors, being evaluated in prostate as well as other cancers, were discussed in FO, pp 815-21.

Thalidomide, is one of several angiogenesis inhibitors in clinical development. This drug, under development by EntreMed (Rockville, MD), is being evaluated in a randomized phase II clinical trial of refractory, androgen-independent prostate cancer. This trial is assessing two daily dosage levels (200 and 1,200 mg) of thalidomide administered orally to 14 patients in each arm to be expanded to 30 patients in each arm if >4 months of stable disease or PR is observed. Monitoring includes a biopsy at onset and at 6 months, CT, bone scan and nerve conduction/EMG every 2 months, and monthly PSA measurements. Molecular endpoints include microvessel count, mRNA of VEGF, bFGF and FGF β, and serum VEGF, bFGF and FGF β. There were no responders. Toxicity was mild, mostly Grade 1 or 2.

SU5416, a small molecule drug targeting the VEGF-mediated Flk-l TK pathway under development by Sugen (Redwood City, CA) also entered into two new clinical studies in the USA and Europe, in June 17, 1998. A phase I/II study, to be conducted by Ian Judson, MD, at the Cancer

Research Campaign (CRC) Center for Cancer Therapeutics at the Institute for Cancer Research (ICR) and the Royal Marsden Hospital (London, UK), will enroll up to 24 patients to assess leakiness of tumor blood vessels as a biological marker for the angiogenic process in addition to monitoring safety and pharmacokinetic parameters for SU5416. By using imaging methods to measure any changes in tumor blood vessel leakiness researchers hope to obtain a very early indication of SU5416's effective at blocking the unwanted signals in human cancers which lead to angiogenesis that is needed to support their continued growth.

In phase I clinical trials, being conducted at UCLA School of Medicine and Jonsson Comprehensive Cancer Center, 12 patients with colon (n=4), breast (n=3), lung (n=2), prostate (n=2) and Kaposi's sarcoma (n=1) were treated at four dose levels (4.4 mg/m^2 to 15 mg/m^2). Grade 1 toxicities included fatigue, change in voice, pain at the infusion site and one allergic reaction. Dose escalation continues with three additional patients being accrued every three weeks (Rosen LS, ASCO98, Abs. 843:218a). Another phase I clinical trial to be conducted at the Arizona Cancer Center (Tucson, AZ) by Alison Stopeck, MD, will assess alternative dose regimens of SU5416 in up to 30 patients with advanced malignancies.

Neovastat, a liquid extract derived from cartilage, under development by Æterna Laboratories (Ste-Foy, Quebec, Canada), has shown both antiangiogenic and antigelatinolytic activities. In a Lewis lung carcinoma model in mice, oral administration of Neovastat resulted in approximately 70% reduction in the number of lung surface metastases when compared to controls. The combination of oral Neovastat with intraperitoneal cisplatin resulted in an 85% decrease in metastases, without signs of toxicity, compared to a 54% decrease in metastases when cisplatin, at a higher dose, was administered alone. Neovastat is currently in phase I/II clinical trials in Canada and in the USA for the treatment of lung, prostate and breast cancer. An additional trial is also ongoing in Canada to evaluate long-term survival/quality of life (QoL) in patients with refractory solid tumors (Rivière M, etal, AACR98, Abs. 317:46). The NCI is planning to initiate pivotal phase III clinical trials of Neovastat in early 1999, including a double-blind placebo-controlled trial in which Neovastat will be administered to several hundred cancer patients in several hospitals and institutions in the USA and Canada.

AG3340, a matrix metalloproteinase inhibitor (MMPI) under development by Agouron Pharmaceuticals (see FO, p 815), is being evaluated in a multicenter randomized, double blind, placebo-controlled, phase III clinical trial (protocol ID: AG-3340-009) in combination with mitoxantrone (Novantrone; Immunex) and prednisone, in patients with HRPC. The regimen consists either of oral AG3340 administered at one of two dosages, twice daily, beginning on day one, in combination with IV mitoxantrone on day one and oral prednisone twice daily beginning on day 1, or with the two latter agents alone. The treatment course is repeated every 3 weeks in the absence of unacceptable toxicity. Mitoxantrone and/or prednisone may be discontinued or switched at the investigator's discretion. The primary objective of this study is to compare time to symptomatic progression of disease among patients treated with one of two doses of AG3340 or placebo, initially in combination with mitoxantrone and prednisone with provision for subsequent change in therapy. Secondary endpoints include response rates, survival, and QoL measurements. The study will enroll 525 patients in 50 centers.

Neutral endopeptidase 24.11 (NEP), a cell-surface peptidase, inactivates neuropeptides such as bombesin and ET-1, and blocks androgen-independent prostate cancer cell migration by inhibition of focal adhesion kinase (FAK) phosphorylation. Researchers at Memorial Sloan-Kettering Cancer Center (New York, NY) found that NEP is expressed by androgen-dependent LNCaP but not androgen-independent prostate cancer cells. Low levels of phosphorylated FAK in LNCaP cells compared to high levels detected in androgen-independent Tsu-Pr1 cells, suggest that cell-surface NEP on LNCaP cells inhibits neuropeptide-mediated FAK phosphorylation. Incubation of Tsu-Pr1 cells in recombinant NEP or stable overexpression of cell-surface NEP using a tetracycline-inducible vector system (Tsu-Pr1-NEP cells), resulted in no detectable phosphorylation of FAK on tyrosine. Examination of prostate cancer cell migration revealed that NEP-expressing LNCaP cells migrate 10-fold less than Tsu-Pr1 cells. Furthermore, induced overexpression of NEP in Tsu-Pr1-NEP cells resulted in >60% inhibition in migration compared to uninduced Tsu-Pr1-NEP cells or Tsu-Pr1 cells containing a neomycin control vector. These data indicate that exogenous recombinant NEP or overexpression of cell-surface NEP, results in inhibition of FAK phosphorylation in androgen-independent prostate cancer cells, and inhibition of FAK phosphorylation by NEP leads to decreased migratory capability of prostate cancer cells (Papandreou CN, etal, AACR98, Abs. 2025:296-97).

Interferon β (IFN-β), a tissue-factor, is also being used as an antiangiogenic treatment in prostate cancer. According to Isaiah J. Fidler, DVM, PhD, of the M.D. Anderson Cancer Center (Houston, TX) speaking at CaP CURE97, IFN-β is a multifunctional cytokine that:

- induces differentiation
- exhibits antiproliferative effects
- inhibits motility
- downregulates the message for MKP-2 and 9
- downregulates the message for bFGF
- activates host effector cells such as macrophages and turns on inducible nitric oxide synthase that produces nitric oxide

Negative angiogenic factors are dominant in normal tissue in sharp contrast to tumors. For instance, prostate

cancer does not expresses IFN-β. When highly metastatic prostate cancer cells, transfected with the IFN-β gene, were implanted into nude mice, no tumors or metastasis were formed. Although the degree of suppression of tumorigenicity is related to the amount of IFN-β produced by the transfected cells, there is also a strong bystander effect causing lysis of non-transfected cells. This kill is not accomplished directly but via the recruitment of activated killer cells. Because transfection of human prostate cells with the IFN-β gene suppresses tumorigenicity and abrogates metastasis, a reasonable antimetastasis strategy would involve introduction of the gene for IFN-β that generates production of this cytokine in non-producing cells. Intraprostatic injection of adenoviral vectors carrying the IFN-β gene may provide a highly localized effect similar to prostatectomy. A clinical trial of this gene therapy approach is in the planning stages. In the meantime, investigators have been treating patients with daily low-dose IFN-β or pegylated IFN-β. Interestingly, administration of high-dose IFN-β, usually at MDT, is not effective as an antiangiogenesis agent, probably because of the creation of a feedback loop.

ABT-627 (A127722), an ET_Ar antagonist, is under development by Abbott Laboratories. According to Joel B. Nelson, MD, speaking at CaP CURE97, investigators at the Johns Hopkins University School of Medicine, Brady Urological Institute (Baltimore, MD), are experimenting with ETAr antagonists to treat prostate cancer that has metastasized to the bone. Endothelin activates osteoblasts and inhibits osteoclasts, a combination in keeping with the pattern of prostate cancer metastasis in the bone. Use of the orally available potent ETAr antagonist ABT-627, blocks this process. Given its pharmacokinetics, it appears that ABT-627 can be administered once-a-day. In an ongoing phase I clinical trial, being conducted at Johns Hopkins by PI Michael A. Carducci, MD, ABT-627 was well-tolerated and appears to produce subjective and objective responses. Also, ready availability of ETAr antagonists, currently under active development for cardiovascular applications, may provide additional candidates for oncologic applications.

D2A21, a peptidyl membrane interactive molecule (MIM), under development by Demeter BioTechnologies (Durham, NC), was effective in reducing primary prostate tumors and metastases in animal models of prostate cancer. D2A21 is a unique peptide molecule having a structure based on principles discovered in naturally occurring peptides, but with greater potency and reduced toxicity. Generally, it is thought that peptidyl MIMs act by initial cell membrane disruption with subsequent cell lysis and death. However, additional factors may also come into play in the *in vivo* situation. For instance, D2A21 may also have antiangiogenic properties. Analysis of the structures of MIM peptides indicates a commonality with certain parts of and other angiogenesis inhibitors.

In preclinical experiments conducted at the University of Pittsburgh Cancer Institute, under the direction of Dr. Robert Getzenberg, rats treated with D2A21 achieved a 60% reduction in the growth of primary tumors and a significant reduction in the number of lung metastases. When D2A21 was administered intravenously at a low dose, it was effective without being toxic to the animals. Importantly, the survival rate increased from 25% for controls to 75% for D2A21-treated animals. In separate experiments, D2A21 was proven effective against prostate cancer in animals when administered either intraperitoneally or subcutaneously.

Antigen Expression

In addition to PSA, identification of tumor-associated antigens (TAA) on primary and metastatic prostate cancer and definition of their expression may provide novel immunotherapy targets. Putative carbohydrate and protein TAAs in prostate cancer include those detected in most (89%-100%) cases of metastatic prostate cancer such as GM2, KSA, MUC2; those less frequently (66.7%) detected in such cancers, such as MUC1; those strongly expressed (>72.7%) in primary prostate cancer, such as Thompson-Friedenreich (TF), sTn and hCG β chain; Tn and PSMA that are expressed frequently in both primary (>72.7%) and metastatic (66.7%) prostate cancer; and Globo H expressed in about 33% of metastatic prostate cancer (Zhang S, Clin Cancer Res, 1998 Feb, 4(2):295-302).

PMSA is recognized by MAb 7E11.C5 which is also the MAb used in ProstaScint developed by Cytogen (Princeton, NJ) as an *in vivo* imaging approach to identify micrometastases in prostate cancer. MAb 7E11.C5 targets an intracellular epitope that is not accessible to the antibody in intact viable cells. ProstaScint may, therefore, image dying cells within tumors (Troyer JK, etal, Prostate 1997, 30:322-342 and Urol Oncol 1995, 1:29-37). PMSA incorporates various peptides that bind HLA-A2. Sources of PMSA include:

- affinity purified from seminal plasma
- recombinant protein expressed in baculovirus and yeast systems
- synthetic peptides with specific binding motifs for HLA molecules

Other Molecular Markers

Numerous markers have been identified and more are being discovered at an accelerated rate with implications in prostate cancer as diagnostic, screening and/or prognostic approaches, or therapeutic targets. Newly reported findings include:

- p27KIP1 gene, a potential tumor suppressor gene that is a negative regulator of the cell cycle and may be used to predict recurrence and survival in localized prostate cancer (Cote RJ, etal, JNCI, 17 Jun 1998, 90(12):916-920 and Cordon-Cardo C, etal, JNCI, 2 Sept 1998, 90(17):1284-1291)
- RET proto-oncogene, overexpressed in high-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer, that may play a role in the growth of both

benign and neoplastic prostate epithelial cells (Dawson DM, etal, JNCI, 1 Apr 1998, 90(7):519-522).

- prostate tumor-inducing gene 1 (PTI-1) is a differentially expressed oncogene in human prostate as well as breast, colon, and small cell lung cancer, identified by researchers at Columbia University; antisense blocking of PTI-1 expression in athymic nude mice results in reversion of transformed PTI-1-expressing cells to a more normal cellular morphology, with suppression of both anchorage-independent growth and tumorigenic potential (Su Z-z, etal, PNAS USA, 17 Feb 1998, 95(4):1764-9)
- prostate stem cell antigen (PSCA), a cell membrane-associated antigen, encoded by a gene that maps on chromosome 8q24, also appears to be relative prostate cancer-specific [there was moderate to strong PSCA expression in 111 of 126 (88%) prostate cancer specimens examined by *in situ* analysis, including high-grade PIN and androgen-dependent and androgen-independent tumors] and may be used in diagnosis and immunotherapy of prostate cancer (Reiter RE, etal, PNAS USA, 17 Feb 1998, 95(4):1735-40)

Gene Logic (Gaithersburg, MD), a fully integrated molecular bioinformatics company is using its Restriction Enzyme Analysis of Differentially-expressed Sequences (READS) technology to identify genes differentially expressed in prostate cancer. READS, which is capable of capturing and analyzing the overall gene expression profile of any given cell in a single assay, is being applied both in the discovery of genomic targets for drug development, and for screening libraries of compounds for drug leads that can modulate gene expression in normal or diseased tissues. In September 1998, Gene Logic acquired Oncormed (Gaithersburg, MD).

GenQuest (New York, NY), using an immunological subtraction approach, surface-epitope masking (SEM), generated the Pro series of MAbs that detect a surface antigen of about 35 to 42 kDa, expressed on human prostate carcinoma cell lines and patient-derived carcinomas, but not on normal prostate or BPH tissue. Expression cloning using the Pro 1.5 MAb, identified a novel gene, PCTA-1, that is a new member of the galectin gene family. PCTA-1 expression is detected in human prostate carcinomas, but not in normal prostate, PIN or BPH tissue (Su, Z-z, etal, AACR98, Abs. 2818:414).

GenQuest, a wholly-owned subsidiary of Corixa (Seattle, WA) focused on functional genomics for cancer, is collaborating with researchers at Columbia University (New York, NY). In August 1997, GenQuest, also established a collaboration with ArQule (Medford, MA) to identify and develop novel drug candidates for the treatment of melanoma, and prostate and breast cancer. Under terms of the agreement, ArQule will provide GenQuest with access to its proprietary Mapping Array program to screen against GenQuest's proprietary cancer assays. Any leads will then be optimized through ArQule's Directed Array program. The Mapping Array program is comprised of libraries of novel, diverse, small organic, pure compounds used for screening against biological targets and generates a chemical information database of structural activity relationships from biased compound sets of novel, diverse and pure small organic compounds. The Directed Array program is an iterative parallel process to select a desired compound as a drug candidate. GenQuest and ArQule will share ownership rights and revenues upon commercialization of any active compounds resulting from the collaboration.

Reprogen (Irvine, CA) is using its lead discovery platform, the HIDDEN proprietary functional genomics technology, for the rapid identification of genes specifically regulated by hormones in reproductive disease progression. The company identified a 56 kDa nuclear matrix protein (PC-1) present only in human prostate cancer but absent in benign prostatic hyperplasia (BPH) or normal prostate tissue and raised MAb PRO:4-216 to PC-1 that may aid in distinguishing normal prostate and BPH from malignant tissue (Partin AW, etal, Urology, 1997 Nov, 50(5):800-8).

HORMONE THERAPIES

Standard treatment of advanced prostate cancer involves long-term administration of leutenizing hormone releasing hormone (LH-RH) agonists alone or in combination with antiandrogens (see FO, pp 303-306). Because, however, eventually most patients relapse, other potential combination therapies with LH-RH are being evaluated, including combination therapies with somatostatin analogs, bombesin antagonists, growth hormone-releasing hormone (GH-RH) antagonists, or LH-RH antagonists.

Abarelix

Abarelix, an LH-RH antagonist under development by Praecis Pharmaceuticals (Cambridge, MA), is in phase II clinical trials in advanced prostate cancer. A phase III clinical trial, to start in 1998, will compare the ability of abarelix to achieve androgen ablation rapidly, avoid the androgen surge common with LH-RH agonists, and maintain the effect of therapy over a period of several months as compared to leuprolide (Lupron; TAP Pharmaceuticals), in patients with large prostate glands.

A 240-patient phase II clinical trial evaluated the sustained-release formulation of abarelix, administered intramuscularly once-a-month. Trial enrollment involved three arms, those treated with abarelix, those eligible for abarelix but treated with leuprolide or goserelin (Zoladex; Zeneca) and those on placebo.

In a phase I/II clinical trial, testosterone serum levels of 26 enrollees treated with abarelix declined rapidly (within 24 to 72 hours). In another phase I/II clinical trial prostate gland volume declined 20% to 50% of baseline within the first 8 weeks. Patients could be treated by radiation within 1-3 months after treatment initiation with abarelix.

Hoffmann-La Roche has licensed marketing rights for abarelix in North America, Australia, Japan, and the rest of Asia. The agreement involves milestone payments and royalties. Synthelabo has licensed marketing rights for Europe, Latin America, the Middle East and Africa. Praecis has retained all manufacturing rights worldwide.

17-Azolyl Steroids

Investigators at the University of Maryland School of Medicine (Baltimore, MD) have identified 17-azolyl compounds that are novel inhibitors of the androgen synthesis pathway. When these compounds were evaluated *in vitro* and *in vivo*, three (I, II and III) showed potent non-competitive inhibition of human testicular microsomal 17[α]-hydroxylase$_{17,20}$-lyase with IC_{50} values of 8, 13 and 7 nM, respectively. III, but not I and II, also showed moderate inhibition of 5[α]-reductase in human prostatic microsomes with an IC_{50} of 142 nM. When male rats were treated with I, II or III, the wet weight of the prostate, testis, seminal vesicles and epididymis were significantly reduced by I and III but not by II. Furthermore, testosterone levels in the plasma and testis were lower by 83-92% in rats treated with I, II or III than in controls. Testosterone levels in the prostate declined by 62.1%, 66.5% and 69.6%, respectively, and plasma dihydrotestosterone (DHT) levels were reduced by 44%, 68.1% and 39.3%, respectively, in rats treated with I, II or III compared to controls, and concentrations of DHT in the prostate were also reduced by 60-80% in treated rats. These findings suggest that these novel inhibitors of 17[α]-hydroxylase$_{17,20}$-lyase and/or 5[α]-reductase may be suitable for further development as therapeutic agents for the treatment of prostatic cancer (Nnane IP, etal, AACR98, Abs. 2614).

Cetrorelix

Cetrorelix, being developed by Asta Medica (Frankfust am Main, Germany) under a license from Tulane University (New Orleans, LA), is also an LH-RH antagonist being evaluated in prostate cancer, as well as in BPH, endometriosis and ovarian cancer (see FO, p 306). Treatment of prostate cancer with cetrorelix is not associated with the flare-up seen with LH-RH agonists. Also, administration of cetrorelix in androgen-independent prostate cancer in animals caused tumors to shrink, probably by the downregulation of EGF and its receptor. Cetrorelix is in a phase II clinical trial in Germany.

Gonadimmune

Aphton (Woodland, CA) is developing Gonadimmure, a vaccine-like process to harness and direct the body's immune system to generate a controlled antibody response against administered immunogens. Gonadimmure neutralizes or blocks hormones which play a critical role in diseases of the reproductive system.

Gonadimmure is an oil-based vehicle incorporating a synthetic peptide identical to a portion of gonadotropin-releasing hormone (GnRH), bound chemically to a carrier (diphtheria toxoid), and an adjuvant, in a liquid solution. Gonadimmune induces host antibodies that neutralize GnRH, blocking production of testosterone, estrogen and progesterone. Aphton has demonstrated in animals that Gonadimmune blocks, or inhibits production of testosterone in prostate cancer.

Using Aphton's technology it is possible to specifically target a small sequence within the hormone to be neutralized in order to achieve a specific desired biological and physiological response. This approach directs all of the immunogen-induced antibodies to the targeted hormone sequence, and at the same time minimizes the possibility of undesired physiological consequences through cross-reactivity of the immunogen with any self molecule or portion thereof, other than the specifically-targeted hormone sequence. Aphton's vaccines may be administered in much smaller doses and less frequently, typically twice a year, which virtually eliminates the problem of patient compliance.

In June, 1998, Aphton signed a collaboration and license agreement with SmithKline Beecham for a worldwide strategic alliance involving Gonadimmune. The agreement covers the diagnosis, treatment and prevention of GnRH-related cancers and other diseases in humans including prostate, breast, ovarian and endometrial cancer, as well as endometriosis, polycystic ovaries, uterine fibroids, contraception, infertility and precocious puberty. Under terms of the agreement, SKB obtained exclusive rights worldwide to Aphton's related patents and proprietary technology. Aphton and SKB are planning to conduct clinical trials jointly, directed by a joint steering committee. SKB is responsible for funding product development, clinical trials and approvals for worldwide marketing and distribution. The agreement uses a royalty mechanism, based on worldwide product sales, to determine Aphton's revenues. Aphton elected to forego significant upfront and milestone payments in favor of a larger further royalty income under the agreed mechanism. As part of the agreement, SKB made an equity investment of $5 million for 237,867 shares of newly-issued Aphton common stock, purchased at a premium. In addition, SKB granted Aphton an irrevocable two-year option to sell to SKB additional shares of newly-issued Aphton common stock worth $5 million at the then current market price. If and when Aphton exercises that option, SKB has the right for 90 days to purchase a number of additional shares of newly-issued Aphton common stock for $5 million at the then current market price. An aggressive, combined safety and dose ranging phase I/II clinical trial is being planned in the UK, in prostate cancer patients.

MZ471

MZ471 is a GH-RH antagonist under development at Tulane University (New Orleans, LA) as reported by Andrew Schally, MD, PhD, at CaP CURE97. GH-RH antagonists interfere with secretion of IGF-I from the liver and IGF-I and IGF-II from prostate tumors. Treatment with MZ471 *in vitro* resulted in the inhibition of human DU 145 cancer cells.

PC-SPES

PC-SPES is a herbal preparation consisting of eight herbs that is commercially available as a nonestrogenic treatment for prostate cancer. However, it was shown that PC-SPES possesses potent estrogenic activity. Therefore, although it may indeed be useful in the treatment of prostate cancer, it also shares the potentially toxic effects of estrogen therapy and could confound results of other therapies (DiPaola RS, etal, NEJM, 17 Sept 1998, 339(12):785-791).

Vapreotide

Vapreotide, a somatostatin analog, is under development by Debiopharm (Lausanne, Switzerland). In a multicenter phase II clinical trial, conducted in France, 20 patients with hormone-refractory prostate cancer (HRPC) were treated with continuous subcutaneous perfusion of RC160 (3 mg), daily, for 3 months. Treatment response was evaluated on CT-scan, bone scintigraphy and centrally performed serial serum PSA. All patients were assessable and/or evaluable for response. Results included 1 PR and disease stabilized in 2, sustained after 6 months of treatment, with significant improvement in general condition and well-being. Disease progressed in 17 patients, in 13 before 3 months and in 4 before 6 months (Di Palma M, etal, AACR98, Abs. 3431:504). Vapreotide is well tolerated but has limited single agent activity in advanced metastatic HRPC (Chahine A, etal, ASCO98, Abs. 1263:328a).

YM116

YM116, a novel selective non-steroidal inhibitor of cytochrome P_{450} 17(α) (17[α]-hydroxylase/C_{17-20} lyase) under development by Yamanouchi Pharmaceutical (Ibaraki, Japan), decreased prostatic weights by reducing androgen production in the testes and adrenal glands and serum concentrations of testosterone and adrenal androgens in rats. YM116 was about 21-24 times more potent than other $C_{17,20}$-lyase inhibitors such as the antifungal ketoconazole and liarozole, and was twice as potent as Boehringer Ingelheim's abiraterone (CB7630) which in phase II clinical trials in hormone-dependent prostate cancer (see FO, pp 306-307).

In rats, YM116 was almost comparable to bilateral orchiectomy with respect to the time course and magnitude of the reduction in prostatic weight. Contrarily, leuprolide, a GnRH agonist, transiently increased prostatic weight and then decreased it. YM116 (100 mg/kg) had no effect on the serum cortisol level in guinea pigs, and slightly decreased serum aldosterone level in rats. These results indicate that YM116 may be a useful agent in the treatment of prostate cancer (Ideyama Y, etal, AACR98, Abs. 2613:384).

COMBINATION THERAPIES

LH-RH Agonists and Antiandrogens

In July 1998, Zeneca Pharmaceuticals received FDA approval of its supplemental NDA to market Zoladex as a combination treatment with the antiandrogen flutamide (Eulexin; Schering-Plough) prior to and during radiation therapy for the management of early-stage (Stages B2-C disease locally confined to the gland) prostate cancer. Zoladex, an LH-RH analog, also known as a GnRH agonist, is the first and only LH-RH agonist to be approved for combination treatment for this indication. Approval includes both the 3.6 mg monthly depot and 10.8 mg three-month depot formulations.

Zoladex in combination with flutamide plus radiation therapy was studied in a 466-patient multicenter, controlled clinical trial, conducted by the Radiation Therapy Oncology Group, in which 231 patients (Group 1) were treated with a combination of Zoladex, flutamide and radiation and 235 (Group 2) were treated with radiation alone. Results showed that disease-free survival (DFS) was significantly increased in Group 1 compared to Group 2 (4.4 versus 2.6 years). Inclusion of normal PSA level as a criterion to measure DFS, resulted in significantly increased DFS in patients undergoing combination therapy (2.7 versus 1.5 years). At four years, patients in Group 1 experienced a lower rate of local failure compared to Group 2 (16% versus 33%). Combination therapy also resulted in a trend toward reduction in distant spread of disease (27% versus 36% at 4 years).

Combination Therapies of Approved Chemotherapeutics

According to Christopher Logothetis of M.D. Anderson Cancer Center, speaking at CaP CURE97, combination of chemotherapeutics with different modes of action have increased response rate to about 70% and MST to about 2 years in advanced HRPC and, it is unlikely that any additional refinements in chemotherapeutic regimens with what is available today, will have a significant impact on these statistics. Best results have been achieved with an alternating regimen of ketoconazole and doxorubicin plus estramustine and vinblastine as a six-week cycle, repeated after 2 weeks rest. A 70% PR was achieved with this regimen with a MST of 20 months. Also, strontium 89 was added to the regimen in responders to palliate pain from bone metastases.

Combination Therapies using Drug Resistance Modulators

Among 17 antitumor agents tested for synergism or antagonism in combination studies in DU145, PC-3 and LNCaP cell lines, estramustine exhibited strong synergism in all three cell lines with hydroxyflutamide, the non-immunosuppressive cyclosporin analog PSC 833 (Novartis), and liarozole. In the hormone-sensitive cell line LNCaP alone, synergism was also observed with vinblastine, paclitaxel, docetaxel, bicalutamide, ketoconazole and all-trans-retinoic acid (ATRA). Based on these findings, new combinations, shown below may be more effective (Kreis W, etal, British J Urology, Feb1997, 79(2):196-202).

Two-agent Synergism	Three-agent Synergism
Liarozole plus docetaxel in LNCaP	Estramustine plus PSC 833 and liarozole
PSC 833 plus bicalutamide in DU145 and PC-3	Schedule-dependent combinations of estramustine, PSC 833, and ATRA
Dexamethasone plus docetaxel in LNCaP	Finasteride (Proscar; Merck) plus hydroxyflutamide in LNCaP

In a phase II clinical trial in HRPC, patients were administered 70 mg/m^2 of paclitaxel (Taxol; Bristol-Myers Squibb) as a 1-hour IV infusion on day 1 with etoposide (140 mg) PO *tid* on days 1-7. Prophylactic subcutaneous granulocyte colony-stimulating factor(G-CSF) was administered rou-tinely at daily doses of 300-600 µg, for 4 to 7 days, after paclitaxel. All patients were premedicated with dexamethasone (8 mg) PO *bid* for 3 days (d-1 to d1) and treatment cycles were repeated every 21 days. Criteria for response was a 50% PSA decline from baseline or a 50% decline in measurable lesions, with either maintained for at least 4 weeks. Among 5 patients with Stage D2 disease, treated for a mean of 4.4 cycles, there were 4 PR lasting 2, 3+, 5+ and 5+ months, and disease stabilized in one patient for 3+ months. In one patient a complete resolution of periaortic and paracaval adenopathy was confirmed on abdominal CAT scan. A major improvement involving numerous metastatic bone lesions was noted on bone scan in another patient, with only a few faint foci remaining. Two other patients with pre-existing bone pain requiring Vicodin were able to discontinue analgesics. The most common side effect associated with this treatment was major fatigue, experienced in 4/5 patients, and nausea and emesis that was more severe than typically seen with etoposide in other combination regimens. G-CSF effectively prevented granulocytopenia (Scholz M, etal, ASCO98, Abs. 1319:342a).

Biricodar dicitrate (VX-710, Incel) under development by Vertex Pharmaceuticals (Cambridge, MA) entered, in June 1998, an open-label, multicenter phase II clinical trial, in combination with mitoxantrone and prednisone, for the treatment of advanced HRPC. The trial will enroll up to 59 subjects and will measure reduction in PSA, tumor reduction, and additional clinical outcome parameters. Incel blocks activity of the MDR-1 protein and multidrug resistance-associated protein to combat multidrug resistance by resensitizing cancer cells to chemotherapy.

NOVEL CHEMOTHERAPEUTICS

One of the reasons for the chemotherapy-refractory nature of advanced HRPC, is the fact that although, as most tumors, prostate cancer is also vulnerable to conventional cytotoxics, prostate cancer cells are not killed as effectively as other tumor cells because they are slow-growing. Cytotoxics work best in rapidly proliferating cancer cells. This attribute of prostate cancer has given rise to the need for novel approaches targeted at destroying nonproliferating cancer cells.

Biochanin A

Investigators at the NCI have shown that modulation of testosterone by biochanin A reduces levels of oxygen radicals in LNCaP prostate cancer cells. Biochanin A, a dietary flavonoid, is a potent inducer of glucuronosyl transferase (GT) activity and mRNA levels. Induction of GT augments inactivation of testosterone in intact cells. Biochanin A inactivates testosterone and reduces testosterone-induced oxygen species in prostate cancer cells (Sun XY, etal, AACR98, Abs. 1968:288).

Diphenylureas

When compared to suramin, diphenylureas are less bound to plasma proteins, much less toxic, with a shorter half-life, and a molecular weight about half that of suramin, but are up to 30-fold more potent than suramin as inhibitors of angiogenesis in the chick chorioallantoic membrane assay and 100-fold more active as inhibitors of human microvascular endothelial cell growth, migration and *in vitro* (Matrigel) tube formation. When the MTT assay was used to examine the effects of selected diphenylureas on cell proliferation in renal carcinoma (A-498) and primary renal adenocarcinoma (786-0) cell lines, the three most active diphenylureas had 50% inhibitory concentrations (IC_{50}) equal to or less than suramin. For the most active diphenylurea (NF681), the IC_{50} was 16 and 32 µM in the A-498 and 786-0 cells, respectively, compared to >500 µM for suramin. Similar results were found for several other diphenylureas. The 786-0 cells also expressed metalloproteinase activity (MMP-2) in a serum-free culture medium, an activity that was stimulated by addition of EGF and inhibited, in a dose-related manner, on addition of the diphenylureas. These diphenylureas are potent inhibitors of renal carcinoma cell growth and metalloproteinase activity in vitro and may have therapeutic potential (Gagliardi ART, etal, ASCO98, Abs. 925:241a).

Diphenylureas are also potent inhibitors of gelatinase B (MMP-9) activity in PC-3 cells and gelatinase A (MMP-2) and B activity in DU145 cells. Results indicates potential application of diphenylureas for prostate cancer by inhibiting tumor growth, matrix metalloproteinase activity and angiogenesis (Gagliardi ART, etal, AACR98, Abs. 4386:644).

DPPE

DPPE, developed at the University of Manitoba in Canada and licensed to Bristol-Myers Squibb, is a novel antihistamine with potent affinity for growth-regulatory intracellular receptors. In preclinical tests conducted at that Manitoba Cancer Treatment and Research Foundation (MCTRF), DPPE increased the antitumor activity of several classes of chemotherapeutic drugs with no additive unwanted side effects.

A randomized phase II clinical trial (protocol IDs: BMS-CA151-003, NCI-V98-1410) to enroll a maximum of 90

evaluable patients (45 per arm) in 12 to 18 months, is investigating DPPE in combination with cyclophosphamide versus cyclophosphamide alone, in patients with metastatic hormone-resistant prostate cancer. In arm I patients are treated by IV cyclophosphamide plus DPPE weekly for 4 weeks followed by 1 week of rest. Thereafter, treatment is administered for 2 weeks, followed by one week of rest and continues for 2 weeks on, 1 week off, until disease progression. In arm II, patients are treated by IV cyclophosphamide alone over 20 minutes following the same treatment course schedule as in arm I.

Flavopiridol

Flavopiridol (L86-8275, NSC 649890), an N-methylpiperidinyl, chlorophenyl flavone, is a potent cdk1 inhibitor that arrests cell cycle progression in either G_1 or G_2. The drug was originally identified through the NCI screening program and is currently in development by Hoechst Marion Roussel under an NCI CRADA (see FO, pp 597-98). As of June 1998, a multicenter phase II clinical trial (protocol IDs: WCCC-CO-9781, NCI-T97-0038), sponsored by the NCI, was ongoing at the University of Wisconsin Comprehensive Cancer Center under PI George Wilding, MD. The trial is to accrue a maximum of 40 chemotherapy-naive patients with metastatic androgen-independent prostate cancer. Patients are treated with IV flavopiridol over 72 hours, every 2 weeks, for at least 4 courses. After 2 courses of treatment, the flavopiridol dose may be escalated in those not experiencing unacceptable toxic effects. In a phase I clinical trial involving a 72-hour infusion of flavopiridol every other week, the principal side effects we gastrointestinal and manageable.

A phase I open label trial (MSKCC-9677A, NCI-T96-001) is also being conducted at Memorial Sloan-Kettering Cancer Center that is to enroll up to 60 patients to evaluate combination of flavopiridol and paclitaxel. The protocol involves 24-hour central access infusion of paclitaxel on day one, followed by a 24-hour infusion of escalating doses of flavopiridol, also over 24 hours on day two, repeated every 21 days in responders and escalated until MDT is reached.

Among 15 patients entered in the study, neutropenia was the DLT with paclitaxel at 135 mg/m^2 and flavopiridol at 10 mg/m^2 and with paclitaxel at 100 mg/m^2 and flavopiridol at 20 mg/m^2. The degree of neutropenia observed was unrelated to prior therapy, was greater than that observed with paclitaxel alone, and did not correlate with paclitaxel or flavopiridol pharmacokinetics. One patient with esophageal cancer experienced a pathological CR of an intraluminal recurrence, and radiographic resolution of mediastinal nodes. One patient with prostate cancer who had failed prior treatment with paclitaxel at 135 mg/m^2 by a 24-hour infusion, experienced improvement in bone lesions on PET scan when treated with paclitaxel at 100 mg/m^2 by a 24-hour infusion and flavopiridol at 20 mg/m^2. When duration of paclitaxel was reduced to a 3-hour infusion at 100 mg/m^2, there was no DLT and flavopiridol dose escalations above 20 mg/m^2 were possible (Schwartz GK, etal, ASCO98, Abs. 725:188a).

Two phase I clinical trials of flavopiridol have been completed in solid tumors. MTD was established at 40 mg/m^2 every 24 hours in 21 patients treated by a 72-hour continuous infusion of flavopiridol, administered every two weeks at doses of 8, 16, 26.6, 40, and 56 mg/m^2 every 24 hours, at the University of Wisconsin Comprehensive Cancer Center (Madison, WI). Toxicity has been primarily gastrointestinal, with diarrhea being the predominant symptom; symptomatic orthostatic hypotension was also observed in several patients (Cleary TJ, etal, AACR97, Abs 1496:222). By the time this phase I clinical trial was completed, a total of 37 patients were treated. In addition to side effects mentioned above several patients experienced tumor-specific pain during their infusions. A patient with metastatic gastric cancer experienced CR at MDT and remained disease free for at least 8 months after completing therapy (Thomas J, etal, ASCO98, Abs. 804:209a). Activity was also observed in prostate cancer, based on sustained PSA declines, and in renal cancer.

Another phase I clinical trial, also using a 72-hour infusion protocol to treat 63 patients with advanced refractory neoplasms, encountered similar toxicities at an initial dose of 4 mg/m^2/day. MDT was 50 mg/m^2/day. Administration of anti-diarrhea prophylaxis with loperamide or cholestyramine made it possible to raise MDT to 98 mg/m^2/day (Senderowicz AM, ASCO97, Abs. 793:226a).

JM-216

JM-216 (BMS-182751), a bis-aceto-ammine-dichloro-cyclohexyl-amine platinum(IV), is an oral platinum-based drug in development by Bristol-Myers Squibb, under a licensing agreement from AnorMED (Langley, BC, Canada) that obtained the agent from Johnson Matthey (Wayne, PA), its original developer. AnorMED is a pharmaceutical company specializing in metal and metal-binding compounds for treatment of various diseases such as cancer and AIDS. The company is minority-owned (40%) by Johnson Matthey. In return for this shareholding, Johnson Matthey contributed a series of medium to longer term research projects, currently under way at its own research facilities, including JM-216. The rest of the shares in AnorMED are owned by a number of institutional and private investors (55%) and management (5%) who together invested about $14 million in the venture.

JM-216 is being evaluated in a variety of malignancies, including HRPC. Accrual has been completed in a multicenter 39-patient phase II clinical trial of JM-216 in HRPC, being conducted at the Cleveland Clinic Foundation (Cleveland, OH), the University Hospitals of Cleveland (Cleveland, OH), the University of Michigan and the University of Pennsylvania (Philadelphia, PA). Antiandrogens, if used by the enrollees, were withdrawn before entry. Patients with progressive HRPC were treated with JM-216 (120 mg/m^2) daily for five days, every 28 days, together with prophylactic oral ondansetron (Zofran; Glaxo Wellcome).

Twenty-two patients were evaluable for response. Among 9 with measurable disease, there was 1 (11%) PR and disease stabilized in 6 (66%). PSA declined >50% for >28 days in 7 patients (32%), 2 of whom having remained on the study for more than 12 months; 6 (27%) experienced PSA reductions >80%. A transient increase in PSA associated with a "flare" in the bone scan after 2 cycles occurred in 2 patients who eventually responded. The drug was generally well tolerated. Among 28 patients evaluable for toxicity, Grade 3 and 4 hematologic toxicities included neutropenia (8 each) with 1 patient admitted for febrile neutropenia, thrombocytopenia (G3=10 and G4=5) and anemia (G3=5 and G4=0). Several patients experienced a second neutrophil nadir on days 32-42. Grade 3 and 4 nonhematologic toxicities included transient elevation of AST (G3=3) and bilirubin (G4=2), diarrhea (G3=5 and G4=3), nausea (G3=2 and G4=1), and vomiting (G3=1 and G4=1). A phase III study of JM-216 + prednisone versus prednisone alone is in planning (Peereboom D, etal, ASCO98, Abs. 1210:314a).

A phase III randomized multicenter, open label clinical trial is ongoing in Europe by the EORTC Genito-Urinary Tract Cancer Cooperative Group (protocol ID: EORTC-30972), that is to enroll 380 patients in 3 years. The study objective is to compare overall survival and time to pain progression, pain response rates, safety, time to overall progression, and QoL of chemotherapy-naive HRPC patients treated either with oral prednisone alone, administered twice-a-day for 35 days, or in combination with BMS-182751, administered orally, once-daily, for 5 days. Courses repeat every 35 days. Patients may continue BMS-182751 monotherapy for a maximum of 8 courses or with prednisone, continuously, in the absence of toxicity and disease progression. Patients are followed every 3 months until death.

Liarozole

Liarozole (R75251, Liazal; Johnson & Johnson), an aromatase inhibitor, is a benzimidazole derivative that mediates an antitumor effect partly by disrupting retinoic acid metabolism; it promotes differentiation of cancer cells by increasing the intratumoral levels of retinoic acid. Liarozole is the first retinoic acid metabolism-blocking agent (RAMBA) to be developed as differentiation therapy for human solid tumors.

In a phase III, multicenter, randomized, controlled clinical trial, the efficacy of oral liarozole was compared with that of cyproterone acetate (CPA) for the treatment of metastatic prostate cancer. A total of 321 patients with metastatic prostate cancer, in relapse after first-line endocrine therapy, were enrolled between February 1992 and August 1994, and randomized either to liarozole (300 mg), twice daily, or CPA (100 mg) twice daily. There was a 26% lower risk of death with liarozole than CPA. Crude MST was the same in both groups (10.3 months). More patients experienced at least 50% reduction in PSA from baseline when treated with liarozole (20%) than with CPA (4%). PSA responders had a median survival benefit of 10 months over nonresponders, irrespective of treatment. PSA response was apparent within 3 months in approximately 90% of responders. Pain improved more in the liarozole group than in the CPA group. PSA responders had lower median pain scores than nonresponders (1.7 versus 2.5) and better QoL at treatment discontinuation, as well as throughout the treatment period. Among the most frequently occurring adverse events in the liarozole group that were mild to moderate in severity, included dry skin (51% of patients), pruritus (25%), rash (16%), nail disorders (16%), and hair loss (15%). In this clinical trial, liarozole was found to be superior to CPA in terms of PSA response, PSA progression, and survival, and QoL and, therefore, is a possible treatment option after first-line endocrine therapy fails [Debruyne FJ, etal, (Liarozole Study Group), Urology, 1998 Jul, 52(1):72-81)].

Molecular Motor Proteins

Cytoskeletal chemotherapeutics such as vinka alkaloids and taxanes kill proliferating cells by interfering with microtubles. However, because these structures are present in most normal cells, these agents are very toxic, causing serious neurotoxicity and myelosuppression. Microtubules do not only serve as structural elements to support chromosome division in proliferating cells, but also serve as tracks along which various intracellular substances are transported by molecular motor proteins. These proteins are ATP dependant (use up ATP as they progress along the microtubules), are diverse in structure and function, and carry various payloads. Different motor proteins are present in different cells. For instance two kinesins, chromo and cenp-E, are not expressed in normal prostate cancer cells but are found in cells from primary and metastatic prostate cancer. Therefore, it appears that targeting such proteins may provide a selective approach to chemotherapy sparing normal cells.

According to Lawrence Goldstein, PhD, speaking at CaP CURE97, he and colleagues at the University of California, San Diego, screened 259 extracts from different species of South Pacific sponges, provided by the Scripps Institute of Oceanography (La Jolla, CA), to identify small molecule inhibitors of kinesin. One such species (CH2) gave rise to 3 related compounds that appear to be relatively specific to motor proteins. They inhibit microtubule motility, microtubule-activated ATPase and microtubule binding of kinesin. They also activate ATPase of kinesin in the absence of microtubules, but do not compete with microtubules, or inhibit actin-activated ATPase of myosin or ATPase apyrase. These agents are currently being evaluated *in vitro* in prostate cancer.

Perillyl Alcohol

Perillyl alcohol (NSC 641066), under development by Wisconsin Genetics (WGI; Lake Bluff, IL), a joint venture of Endorex (Lake Bluff, IL) and the University of Wisconsin (Madison, WI), is in phase II clinical trials which began in March 1998. Phase I clinical trials began in 1995 and were

completed in 1997. Monoterpenes selectively inhibit cell growth and also act to induce apoptosis. They also act as farnesyl transferase inhibitors, activating a tumor suppressor gene encoding the receptor for mannose 6-phosphorate/insulin-like growth factor-II (M6P/IGF-II) which inactivates IGF-II and activates transforming growth factor-β that in turn prevents cancer cell proliferation.

In a phase I clinical trial, conducted by the University of Wisconsin Comprehensive Cancer Center (Madison, WI), perillyl alcohol was administered four times-a-day, based on previous pharmacokinetic and toxicity data with a 3 times-a-day schedule that indicated that a more frequent dosing schedule would be more optimal. Among 15 evaluable patients, treated for 57 courses at 800 mg/m^2/dose, or 1200 mg/m^2/dose, or 1600 mg/m^2/dose, evidence of antitumor activity was seen in one patient with metastatic colorectal cancer whose pulmonary nodules resolved completely. Disease stabilized in 2 patients with metastatic HRPC for 9 and 13 months, respectively. Predominant toxicities were gastrointestinal (nausea, vomiting, satiety, eructation and bad taste in the mouth) which were dose-limiting. MDT, based on continuous *qid* dosing, was 1200 mg/m^2/dose (Ripple G, etal, ASCO98, Abs. 885:231a). A phase II clinical trial (protocol IDs: WCCC-CO-9685, NCI-T97-0067), sponsored by the NCI and being conducted by the University of Wisconsin Comprehensive Cancer Center, began in March 1998. In this trial, scheduled to accrue 20-40 patients in two years, the agent is being administered PO, 4 times a day, for 4 weeks, and treatment continues in the absence of severe toxicity and disease progression.

Phenylbutyrate

Phenylbutyrate (EL532), a prodrug of phenylacetate, is under development by Targon, a wholly-owned subsidiary of Elan (Gainesville, GA). In an ongoing phase I clinical trial at the Johns Hopkins Oncology Center phenylbutyrate is administered orally, thrice daily, to 16 patients (advanced prostate cancer=9, renal cell cancer=3, breast cancer=2, thyroid cancer=1 and colon cancer=1). Dose escalation continues up to 36 g/day with patients ingesting 16-32 375 mg tablets 3 times a day. Toxicity has been mild with fatigue and lethargy as the most frequently cited most adverse effects. No measurable responses have been noted to date but disease stabilized in 3 patients for 6 months. PSA declined by >50% in 1 patient at 36 g/day, and PSA stabilized in 4 patients for over 2-6 months. Overall, oral phenylbutyrate is well-tolerated, with *in vitro* bioactive concentrations being consistently achieved *in vivo* (Carducci M, etal, ASCO98, Abs. 831:215a).

Roquinimex

Roquinimex (Linomide; Pharmacia & Upjohn), a quinoline-3-carboxamide (N-phenylmethyl-1,2-dihydro-4-hydroxyl-1-methyl-2-oxoquinoline-3-carboxamide), possesses immunomodulatory properties, is an angiogenesis inhibitor, and exerts apoptosis-inducing effects on prostate cancer cells in a proliferation-independent manner. Roquinimex inhibited growth in Dunning R-3327 rat prostatic cancers *in vivo* (Ichikawa, etal, Cancer Res 1992; 52:3022-3028). Also, daily treatment inhibits angiogenic responses in nontumor-bearing rats and reduces tumor blood flow in tumor-bearing rats (Vukanovic, etal, Cancer Res 1993; 53:1833). Linomide, when administered the day after castration, inhibited regrowth of Dunning R-3327 PAP tumors, and when administered after tumor regrowth (week 10 after castration) inhibited further tumor growth. In rats with Dunning G tumors, tumor blood vessel density was decreased either after castration (40%) or Linomide (32%) treatment alone. A combination of castration and Linomide demonstrated a 60% decrease in blood vessel density (Hartley-Asp B, etal, J Urol 1997 Sep 158:3 Pt 1, 902-7).

Suramin

Suramin (Metaret), a hexasulphonated naphylurea, is under development by Parke-Davis, in collaboration with the NCI, in the treatment of HRPC. In December 1997, Parke-Davis filed an NDA for suramin for this indication. One of suramin's putative mechanisms of action includes inhibition of angiogenesis. Also, it has been shown that suramin and related polysulfonated compounds, inhibit cleavage of pro-HGF/SF. Hepatocyte growth factor (HGF) or scattering factor (SF), is the ligand for the TKr encoded by the c-Met proto-oncogene. HGF/SF is involved in tumor establishment, progression and metastasis. Originally, HGF/SF is synthesized as a 90 kDa single chain precursor polypeptide (pro-HGF/SF) devoid of biological activity. Subsequently, it can be activated through a critical step involving proteolytic cleavage, generating an αβ heterodimer in which an α chain of 60 kDa and a β chain of 32-36 kDa are bound together by a disulfide bridge. The cleavage/activation of pro-HGF/SF represents the initial stage of HGF/SF-met activation and provides a possible point for interference by potential inhibitors. Investigators at the NCI have developed an efficient assay for finding inhibitors of HGF/SF activation and have identified suramin-like compounds that can be used to inhibit HGF/SF activation with less toxicity than comparable molecules. More information, about these compounds may be obtained from the NIH Office of Technology Transfer (301 496-7057 x 284).

Initial clinical trials with suramin that demonstrated antitumor activity in HRPC, have used an intermittent IV dosing schedule after a 5-day loading period. This regimen is rather cumbersome. For example, in a multicenter SWOG-sponsored phase I clinical trial, 59 hormone therapy-naive patients with Stage D2 prostate cancer were treated with total androgen blockade and a fixed bolus dose schedule of suramin at 1100 mg/m^2 on day 1, 400 mg/m^2 on day 2, 300 mg/m^2 on day 3, 250 mg/m^2 on day 4, 200 mg/m2 on day 5, and then weekly at 275 mg/m^2, starting on day 8, for 11 weeks. Cycles were repeated every 6 months, with the dose on day 1 reduced to 750 mg/m^2. This fixed bolus schedule achieved and maintained targeted suramin levels (Petrylak DP, etal, ASCO98, Abs. 1310:340a).

Other trials are evaluating slightly different regimens. Based on a previous phase I/II clinical trial (Kobayashi, etal, JCO, 1995, 13:2196), 3 different dose levels were found to be safe and potentially effective in metastatic HRPC, currently being evaluated in a 378-patient multicenter phase III trial (CALGB 9480) in the USA which was initiated in February 1996. As of late 1997, 248 patients were randomized to one of 3 fixed dose regimens. Successively lower doses of suramin are administered on days 1, 2, 8 and 9 of a 28-day cycle, for 3 cycles, with total doses of 3.19 g/m^2, 5.32 g/m^2, or 7.66 g/m^2. Grade 3 and 4 adverse events were seen in 76% of patients, and Grade 1, 2 adverse events in 95%. There were no treatment related deaths (Vogelzang NJ, etal, ASCO98, Abs. 1339:347a).

Feasibility of a less cumbersome regimen was also evaluated in a multicenter clinical trial involving 33 HRPC patients who were treated with a pharmacokinetically-derived 5-day schedule of suramin, administered monthly, every 28 days. Three cohorts were treated based on estimated peak plasma concentrations (C_{max}) of suramin (300 µg/ml, 350 µg/ml and 400 µg/ml). PR was seen in 2/12 patients with measurable disease, PSA declined >50% in 11/32 patients, and 12/19 patients with significant pain experienced notable improvement. Median time-to-progression was 5 months and overall MST was 17.6 months. This less cumbersome schedule was active and well tolerated and should facilitate development of combination regimens with suramin and make outpatient use possible (Sinibaldi VJ, etal, ASCO98, Abs. 841:218a).

In a multicenter phase III clinical trial, the combination of suramin and hydrocortisone that had shown efficacy in patients with HRPC (Reyno, etal, J Clin Oncol 13:2187, 1995), was investigated in 458 patients requiring narcotic analgesics for bone pain related to HRPC and with evidence of progression after antiandrogen withdrawal. Patients were randomized to be treated either by suramin and hydrocortisone or the latter and placebo. Those progressing on placebo (n=164) crossed over to suramin. Within a median follow-up of 21 months, disease stabilized in 48% of those treated with suramin compared to 27% of those on placebo. Survival was similar on both arms. Adverse events were generally mild in both groups but those on suramin experienced a significantly longer duration of pain response (240 days versus 69 days). It appears that the addition of suramin to hydrocortisone delays disease progression (Small EJ, etal, ASCO98, Abs. 1187:308a).

Suramin may play a more significant role as part of a combination regimen. In a multicenter phase I clinical trial in patients with HRPC, suramin was investigated in combination with topotecan because these two agents do not exhibit overlapping toxicities and preclinical studies have demonstrated synergistic activity. Patients were treated with a pharmacologically-derived 5-day fixed schedule of suramin (target C_{max} 300 µg/ml) IV, followed by topotecan (0.5 mg/m^2) IV, daily, for 5 days, every 28 days, for 3 courses. Topotecan was escalated (0.65, 0.85, 1.25 mg/m^2) in cohorts of at least 6 new patients. Among patients evaluable for response, 14/20 experienced less pain and 11/30 had ≥50% fall in PSA ≥4 weeks. Median time to progression was 150 days and 6 month survival rate was 89%. To date, no significant interactions have been observed between suramin and topotecan. Accrual continues to define a phase II dose for suramin, with topotecan at 1.25 mg/m^2 (Long GS, etal, ASCO98, Abs. 948:247a).

Tributyrin

Butyric acid produces cytodifferentiation in a wide variety of neoplastic cells *in vitro.* However, because its clinical application is limited by its rapid metabolism, compounds structurally related to butyrate have been identified with longer biological half lives. Tributyrin (NSC-661583), a butyrate prodrug, was shown to retain the effectiveness of butyrate in inducing growth inhibition and expression of morphologic and immunophenotypic properties in human neuroblastoma cell lines. Treatment with tributyrin resulted in a strong inhibition of cell proliferation and in induction of extensive differentiation (Rocchi P, Anticancer Research, 1998 Mar-Apr, 18(2A):1099-103). In a phase I clinical trial (protocol IDs: UMCC-9421, NCI-T94-0181O) sponsored by the NCI and being conducted at the Marlene & Stewart Greenebaum Cancer Center at the University of Maryland under PI David A. Van Echo, Tributyrin, is administered orally to approximately 24 in patients with HRPC (Stage D2) and other solid tumors. The drug is being administered for at least 3 weeks. The objectives of the study are to determine optimal dosing, check safety and establish MDT.

Vitamin D Analogs

High levels of vitamin D binding protein may be a risk factor for prostate cancer. Such risk decreases with increased serum levels of calcitriol ($1,25(OH)_2D_3$ or $1,25D_3$).

Researchers at the University of Pittsburgh Cancer Institute (Pittsburgh, PA) have shown that $1,25D_3$ alone has significant antitumor activity *in vitro* and *in vivo* in PC-3 and MLL cells and xenografts. In MLL cells, $1,25D_3$ treatment causes significant G_0/G_1 arrest, modulates expression of the cdk inhibitors p27 and p21, is implicated in cell cycle arrest, and induces apoptosis. Pretreatment with $1,25D_3$ also significantly enhances cisplatin- or carboplatin-mediated antitumor activity *in vitro* and *in vivo* in an SCC model. Pretreatment with $1,25D_3$ *in vitro* significantly enhanced paclitaxel clonogenic tumor cell kill. Treatment of established PC-3 and MLL tumors with $1,25D_3$ prior to paclitaxel, administered on the third day, resulted in significant inhibition of tumor growth. At day 30 post-implant, tumors from PC-3 animals treated with $1,25D_3$ and paclitaxel on day 8, remained 64% smaller than in controls, or in animals treated either with $1,25D_3$ or paclitaxel alone. Effects were maximal when $1,25D_3$ was administered 48 hours *in vitro* or 3 days *in vivo* prior to paclitaxel. Therefore, it appears that $1,25D_3$ exhibits a sequence and time-dependent enhancement of paclitaxel-

mediated antitumor activity in prostate models. In addition, paclitaxel prevented development of hypercalcemia associated with 1,25D3 administration in MLL rats (Johnson CS, etal, ASCO98, Abs. 830:215a).

Currently, investigators are looking for vitamin D analogs with less calcemic activity than calcitriol but with similar antiproliferative activity.

1-α-OH-D₂ (1-α-hydroxyvitamin-D_2), being developed by Bone Care International (Madison, WI) under a license obtained from the Wisconsin Alumni Research Foundation (WARF) in 1987, is a vitamin D analog with less calcemic but similar antiproliferative activity as calcitriol. In an ongoing phase I dose-escalation clinical trial of 1α-OH-D_2, among 14 evaluable patients with metastatic HRPC, the drug has generally been well tolerated with two cases of hypercalcemia noted, one Grade 1 that resolved without dose modification and one Grade 3, accompanied with Grade 2 renal dysfunction, requiring discontinuation of drug. Mild hyperphosphatemia was noted in 5 patients. Evidence of tumor response was seen in two patients who showed decreases in the size of soft tissue disease, and disease stabilized in 3 others for ≥6 months (Wilding G, etal, ASCO98, Abs. 829:215a). A second-generation product, LR-103, under development by Bone Care, is also being investigated for breast and prostate cancer (see FO, p 447).

IMMUNOTHERAPY/VACCINES

Currently, there is tremendous interest in immunotherapy of prostate cancer, an approach ignored in the past because it was believed that prostate cancer was not immunogenic, a view that was proven wrong. Immunotherapy is considered a particularly attractive alternative for the treatment of advanced prostate cancer and for prevention of recurrence by eliminating metastases because:

- prostate cancer is immunogenic
- advanced prostate cancer is a slow-growing malignacy and, therefore, is not effectively treated with high-intensity cytotoxic chemotherapy
- numerous antigens linked to prostate cancer have been identified that may serve as immunotherapy targets

Numerous approaches are being evaluated in the development of prostate cancer immunotherapies (see Exhibit 1) based on a variety of methodologies to elicit both humoral and cellular immunity. Immunotherapy may assume many forms, including:

- systemic administration of cytokines (IL-2, IL-4, GM-CSF)
- transfection of cytokine genes into tumors
- transfection of B7 or MHC genes into tumors
- targeting of T cells using bispecific antibodies
- antigen-based vaccines (monovalent and polyvalent)
- complement-induced inflammation and cytotoxicity
- use of conventional adjuvants such as BCG
- use of autologous cells, particularly dendritic cells, activated *ex vivo*

Prostate cancer antigens that may be used in immunotherapy include:

- lysates of prostate cancer cell lines (LNCaP, PC-3, DU145)
- purified prostate cancer-specific antigens such as PSA, PMSA
- lysates of autologous prostate cancer cells

Cancer Cells as Antigen Presenting Cells

The players involved in a cellular immune response include:

- the specific antigen produced by the cancer cell
- the antigen presenting cells (APC) of the MHC Class I system; dendritic cells (DC) are the most potent natural APC for stimulating immune responses
- B7, a costimulatory molecule required to present the antigen to the immune system
- The pre-cytotoxic T cell (CTL) that incorporates CD28, a receptor for B7, and CTLA4 which although has a higher affinity for B7, appears to down stimulating the activity of the pre-CTL
- CTL

According to Norman N. Greenberg, PhD, speaking at CaP CURE97, investigators at Baylor University have formed a consortium to devise and test an approach to bypass the traditional antigen presenting cells and use the cancer cell itself as the antigen presenting entity by directly attaching B7 onto the cancer cell and by inactivating CTLA4 via the use of MAbs. In order to test this manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer *in vivo*, investigators used a murine model, the transgenic adenocarcinoma mouse-prostate (TRAMP) model that posesses an intact immune system and also used cell lines TRAMP-C1, from this model. In order to test the hypothesis that expression of B7 costimulatory molecules on tumor cells will make it possible to bypass the APC system, as seen by the activation of tumor-specific CD8+ T cells, TRAMP-C1 cells were transfected by murine B7.1 gene (CD80) and B7.2 (CD86) using a retroviral vector. While cells with the empty vector were very tumorigenic when grafted into syngeneic mice, all such mice exposed to the transfected cells were cured while all nude mice that lacked an immune system rapidly developed tumors with either construct.

It was also hypothesized that use of an antibody against CTLA4 may augment the antitumor response observed with the B7-transfected cells. The strong influence of CTLA4 in regulating the immune response was confirmed when syngeneic mice grafted with TRAMP-C1 cells were-treated with 3 intraperitoneal injections of anti-CTLA4

Exhibit 1
Agents in Development for the Treatment of Prostate Cancer

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Development Status ❑ Indication(s)
Abbott Laboratories	ABT-627	Endothelin antagonist	Phase I/II➢USA
Æterna Laboratories	AE-941 ❑ Neovastat	Shark cartilage liquid extract ❑ PO	Phase I (b11/96, c/98), phase III (b99)➢USA and Canada ❑ advanced HRPC
Aeson Therapeutics (ATI) ❑ Research Corporation Technologies (RCT), Temple U Fels Institute for Cancer Research and Molecular Biology	Fluasterone	Synthetic version of the steroid dehydroepiandrosterone (DHEA)	Phase I (b1/97, c3/98)➢Switzerland
Agouron Pharmaceuticals ❑ Hoffmann-La Roche (terminated)	AG3340 (see FO, p 815)	Synthetic selective inhibitor of certain matrix metalloprotease (MMP) enzymes such as gelatinase A and B, stromelysin-1 and collagenase-3; angiogenesis inhibitor ❑ PO	Phase III (b5/98)➢USA ❑ advanced HRPC
Alanex	Pharma 5141	GnRH antagonist	Preclin (98)➢USA
AltaRex ❑ U Alberta	ProstaRex	Murine MAb binds to tumor associated antigen and elicits an immune response; anti-idiotype induction therapy (AIT)	Preclin (8/98)➢Canada
Alza ❑ Crescendo Pharmaceuticals	Leuprolide ❑ DUROS-leuprolide	Titanium implant containing leuprolide sufficient for one year, implanted subcutaneously under the arm	Phase III (b10/97, o6/98) ➢USA ❑ advanced prostate cancer
AntiCancer ❑ Shionogi	Recombinant methioninase (rMETase) ❑ AC9501 ❑ ONCase	Water soluble enzyme that breaks down methionine in blood; homote trameric pyridoxal 5'-phosphate enzyme derived from *Pseudomonas putida* and cloned in *E. coli*	Phase I (4/97)➢Japan ❑ solid tumor
Aphton ❑ SmithKline Beecham Biologicals	Gonadotropin-releasing hormone (GnRH) immunogen ❑ Gonadimmune	An oil-based vehicle incorporating a synthetic peptide identical to a portion of hormone GnRH, bound chemically to a carrier (diphtheria toxoid), and an adjuvant, in a liquid solution; induces antibodies in the patient which neutralize (or block) GnRH ❑ injection	Phase I/II (planned for 1998)➢UK
Argonex ❑ U Virginia	Direct Identification of Relevant Epitopes for Clinical Therapeutics (DIRECT)	A technology platform that employs mass spectrometry to identify antigens that trigger a human CTL; these functional antigens may then be combined with a broad range of vaccine delivery systems	Research (o6/98)➢USA ❑ solid tumor
Asta Medica ❑ Tulane U, Nippon Kayaku	Cetrorelix ❑ SB-75, SB-075	LH-RH antagonist; synthetic decapeptide which is structurally related to GnRH ❑ subcutaneous	Phase II (10/97)➢Germany ❑ hormone-dependent prostate cancer
Atrix Laboratories ❑ Gensia Sicor (terminated 11/97)	ATRIGEL System	Sustained release delivery of leuprolide acetate ❑ intratumoral	Preclin (98)➢USA
Avant (Virus Research Institute) ❑ Harvard University	Therapore	A delivery approach that uses two bacterial proteins to transport certain therapeutic polypepetides into cells to induce CTL and alter the amounts of cellular cytokines produced	Research (8/98)➢USA
Avigen ❑ Research Corporation Technologies, (terminated 3/97) U Manitoba, Baylor College of Medicine		Adeno-associated virus (AAV) vector system that uses a prostate-specific promoter ❑ intratumoral	Preclin (3/97)➢USA ❑ early-stage prostate cancer
Axis Genetics ❑ U College, London, Oxford U (terminated), John Innes Centre, Purdue U	See FO, p 393	Epicoat chimeric virus particle (CVP) technology; derived from genetically engineered plant viruses ❑ PO, nasal	Research (10/97)➢UK
Biomide Laboratoties	BMD188	Synthetic cyclic hydroxamic acid compound; induces apoptosis ❑ IV	Preclin (o5/98)➢USA ❑ androgen-independent prostate cancer

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BioNumerik Pharmaceuticals	Karenitecins ❑ BNP 1100 and 1350 ❑ Karenitecan	Highly lipophilic semi-synthetic camptothecin derivatives ❑ PO, parenteral	Preclin (98)➢USA ❑ solid tumors
BioStratum (BST)	BST-1003 ❑ Collamer	Peptides from collagenous domains of type IV collagen which have antimetastatic properties	Preclin (5/98)➢USA
Biovation ❑ New York Hospital-Cornell Medical Center, Ludwig Institute for Cancer Research		MAb J591, directed against the extracellular domain of PSMA, humanized using DeImmunisation technology	Research (7/98)➢USA, UK
Boehringer Ingelheim ❑ British Technology Group (BTG), CRC Centre for Cancer Therapeutics at the Institute of Cancer Research (IRC)	Abiraterone acetate ❑ CB7630 (see FO, pp 306-7)	Potent steroidal inhibitor of the key enzyme cytochrome $P_{450}(17)\ \alpha$, involved in androgen biosynthesis ❑ injection	Phase II (o98)➢USA ❑ hormone-dependent prostate cancer
Bone Care International ❑ Wisconsin Alumni Research Foundation	1α-OH-D_2	Synthetic vitamin D prohormone which is metabolized primarily to 1α-OH-D_2; has lower toxicity than calcitriol ❑ PO	Phase I/II (b11/96, o3/98)➢USA ❑ HRPC
Bone Care International	LR-103	Second-generation vitamin D compound characterized by equivalent activities and lower toxicity than 1α-OH-D_2; may substantially reduce calcemic activity ❑ PO	Preclin (7/98)➢USA
Boston Life Sciences	Troponin I	Inhibitory subunit of a protein complex involved in calcium-mediated prevention of actomyosin binding and ATPase activity during skeletal muscle contraction ❑ subcutaneous	Preclin (6/98)➢USA ❑ solid tumors
Bristol-Myers Squibb ❑ AnorMED	JM-216, BMS182751	Novel oral platinum analog ❑ PO	Phase II (c98)➢USA, phase III (o6/98)➢Europe ❑ HPRC
Bristol-Myers Squibb ❑ U Manitoba	DPPE ❑ BMS217830	DPPE, a novel antihistamine with potent affinity for growth-regulatory intracellular receptors, enhances cytotoxic effects of chemotherapy with no additive unwanted side effects ❑ IV	Phase II, in combination with cyclophosphamide (o98)➢Canada ❑ advanced HRPC
Bristol-Myers Squibb ❑ CRC Technology, NCI	Bryostatin-1 ❑ NSC-339555	Natural macrocyclic lactone that is a ligand and inhibitor of protein kinase C (PKC), derived from the marine bryozoan *Bugula neritina* ❑ IV	Preclin (5/98)➢USA ❑ drug-resistant prostate cancer
British Biotech ❑ Tanabe Seiyaku	Marimastat ❑ BB-25166 (see FO, pp 745 & 815)	MMPI ❑ PO	Phase I (o5/98)➢USA ❑ solid tumors
BZL Biologics ❑ Cornell U	J591	MAbs to extracellular PSMA	Phase I (b9/98)➢USA
Calydon		Discovery of novel small molecule pharmaceuticals using screening assays based on a proprietary prostate-specific regulatory gene which acts as a master controlling gene to regulate expression of other genes which code for proteins or other structural genes, uniquely expressed in prostate epithelial cells	Research (5/98)➢USA ❑ metastatic prostate cancer
Calydon ❑ Johns Hopkins U	CN706	Attenuated replication competent adenovirus (ARCA) containing a prostate tissue specific enhancer (PSE) gene; only infects and grows on the subtype of prostate cells that express PSA ❑ IV	Phase I (b7/98)➢USA
CarboMed ❑ NCI, Zeneca, Vanderbilt U	GBS toxin ❑ CM101, ZD0101 (Zeneca)	300 MW polysaccharide exotoxin produced by Group B Streptococcus ❑ infusion	Phase II (b12/97)➢USA ❑ solid tumors
Carrington Laboratories	Acemannan ❑ CarraVex	Complex carbohydrate aloe extract ❑ injection	Phase I (b95, c97)(USA ❑ solid tumors
Cascade Oncogenics ❑ NCI		p53-regulated genes related to DNA repair and the cell cycle	Research (2/97)➢USA ❑ solid tumors
CEL-SCI ❑ Cell-Med, NCI	LEAPS (Ligand Epitope Antigen Presentation System)	Heteroconjugate vaccine technology that selectively stimulates the immune system	Preclin (12/97)➢USA ❑
CEL-SCI ❑ Sittona, American Red Cross	Leukocyte interleukin injection ❑ Multikine	Combination of natural human IL-2 and certain lymphokines and cytokines	Phase I (b5/96, c9/97)➢USA ❑ HRPC

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Cell Genesys ❑ Ludwig Institute for Cancer Research, Sloan-Kettering Institute for Cancer Research, NCI, Dana-Farber Cancer Institute, Arizona Cancer Center at U Arizona		Genetically-engineered T cells based on antibody gene CC49 *ex vivo*	Phase I/II (8/97)➢USA ❑ colon cancer (may be applicable to prostate cancer)
Cell Pathways	Exisulind ❑ FGN-1	Sulfone metabolite of sulindac, an NSAID; induces apoptosis ❑ PO	Phase II/III (o6/98)➢USA ❑ prevention of prostate cancer recurrence
Cell Pathways	CP248	Novel drugs related to FGN-1 ❑ PO	Preclin (o6/98)➢USA ❑ solid tumors
Cell Therapeutics (CTI) ❑ BioChem Pharma	CT-2584	Low molecular weight phospholipid signaling inhibitors that alter production of the intracellular second messenger, phosphatidic acid (PS), which is involved in a variety of agonist-stimulated cell growth and activation responses ❑ infusion	Phase I (b5/96, o3/98)➢UK, USA ❑ HRPC
Cellcor (Cytogen)	Autolymphocyte therapy (ALT)	Polyclonal (non-specific) activation of cytotoxic and helper T cells which when returned to the patient, search out foreign targets (cancer or virus) ❑ *ex vivo*	Phase I (c6/95; discontinued 3/98)➢USA
Centocor ❑ National Institute of Environmental Health Sciences	See FO, p 285	Antibodies to a 267 amino acid glycoprotein belonging to the TM4 family of cell proteins, produced by KAI1 (a cloned prostate-specific metastasis suppressor gene on human chromosome 11p11.2)	Preclin (7/96)➢USA
Cephalon ❑ Kyowa Hakko Kogyo, TAP Holdings	CEP-2563, KT-8391 (see FO, p 325)	Ester of CEP-751; indolocarbazole; receptor tyrosine kinase (rTK) inhibitor ❑ IV	Phase I (b96, o6/98)➢USA ❑ advanced solid tumors
Cephalon ❑ Kyowa Hakko Kogyo, TAP Holdings	CEP-701	Small molecule TK inhibitor ❑ PO	Phase I (b3/98)➢USA
Cephalon		New class of molecules which may block the growth of solid tumors by preventing angiogenesis through the VEGF cascade	Preclin (9/98)➢USA
CliniChem Development (Biochem Pharma)	B-L-Dioxolane cytidine ❑ BCH 4556	An L-nucleoside analog with potent antitumor activity against both leukemia and solid tumors ❑ IV, PO	Phase I (c3/98)➢Canada ❑ solid tumors
CollaGenex Pharmaceuticals ❑ Boehringer Mannheim, NCI, U Miami, State U of New York at Stony Brook	Metastat	Chemically-modified, non-antimicrobial tetracycline; matrix metalloproteinase inhibitor (MMPI)	IND (f12/97), Phase I (b1/98)➢USA ❑ solid tumors
Corixa ❑ SmithKline Beecham		Vaccine based on a proprietary antigen	Research (8/98)➢USA
Cytogen	Prostatec	Second generation version of Cytogen's ProstaScint prostate cancer imaging agent using technetium-99 as the imaging radio-isotope instead of indium-111 ❑ IV	Phase II (12/97)➢USA
Debiopharm	Vapreotide ❑ RC-160	Somatostatin analog	Phase II (c97)➢France ❑ HRPC
Demeter BioTechnologies	D2A21	Peptidyl membrane interactive molecule (MIM); acts by cell membrane disruption causing cell lysis and death; may be antiangio-genic ❑ IV	Preclin (9/98)➢USA
Dendreon ❑ Immune Response, Mayo Clinic	APC8015	Dendritic cell therapy involving harvested autologous dendritic cells that are activated *ex vivo* with prostate tumor antigens, and returned to the patient ❑ IV	Phase I/II (o10/97)➢USA ❑ advanced HRPC
DiagnoCure ❑ MerckFrosst Canada		MAb that reacts exclusively with an antigen found on bladder, prostate, cervical and breast tumor cells, linked to a radioisotope	Research (3/98)➢Canada ❑ metastatic solid tumors

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Diatide	Sn-117m DTPA	Non-peptide radiotherapeutic consisting of tin radioisotope Sn-117m, which has an affinity for bone, combined with DTPA, a common chelating agent, for the palliation of cancer-related bone pain ❑ injection	Phase II (b12/97)➢USA (DIATIDE-117-30, UCMC-97012201)
DuPont Merck	Losoxantrone	Anthrapyrazole DNA complexing agent resembling doxorubicin and mitoxantrone ❑ IV	Phase III (97)➢USA ❑ solid tumors
Endorex	GMDP-GDP ❑ ImmTher	Lipophilic disaccharide peptides related to muramyl dipeptide (the minimum unit of the mycobacterial cell wall that is immunologically active) that act as a systemic macrophage activator ❑ IV	Phase II (o3/98)➢USA ❑ metastatic solid tumors
EntreMed ❑ Children's Hospital at Harvard Medical School, NCI	Thalidomide (see FO, pp 746)	Antiangiogenic compound; may block certain growth factors such as bFGF and VEGF ❑ PO	Phase II (6/97)➢USA ❑ androgen-independent, metastatic prostate cancer
EntreMed ❑ Children's Hospital at Harvard Medical School, Bristol-Myers Squibb	Thalidomide analogs	Antiangiogenesis compounds ❑ PO	Preclin (1/98)➢USA ❑ solid tumors
Enzon	PEG-[γ]-camptothecin ❑ Prothecan	Polyethylene glycol-conjugated camptothecin-20-alanate, a water soluble prodrug of camptothecin ❑ IV	Preclin (6/98)➢USA
EnzyMed		Synthesis and identification of natural product derivatives with improved inhibitory activity against protein kinase	Research (98)➢USA
Epimmune		Small antigenic peptides that are segments of foreign proteins; induce cellular immune response	Research (8/98)➢USA
Genentech	RhuMAB VEGF	Antagonist of VEGF ❑ IV	Phase II (b2/98)➢USA ❑ prostate cancer (in planning)
Genetronics ❑ Abbott Laboratories	Electroporation therapy (EPT) ❑ MedPulser	Electric field generator; induces pore formation on cell membranes to increase permeability for delivery of chemotherapeutics	Preclin (98)➢USA
Genos Biosciences		Gene discovery	Research (4/98)➢USA ❑ solid tumors
GenQuest (Corixa) ❑ ArQule		Gene discovery based on changes in phenotype in proprietary cell lines	Research (8/97)➢USA
Genset ❑ Synthelabo, Centre de Recherche pour les Pathologies Prostatiques (CEREPP)	See FO, p 312	Identification of chromosome regions, such as those on chromosome 1, that contain prostate-related cancer genes	Research (98)➢France
Genta ❑ Johns Hopkins U, NCI CRADA	G3139 ❑ Anticode (see FO, p 394)	Phosphorothioate-backbone antisense oligonucleotide targeting apoptosis gene bcl-2 ❑ IV	Phase I/IIa (b12/97 and 7/98) ❑ hormone-independent, metastatic prostate cancer
Glaxo Wellcome	3622W94	Humanized MAb that binds to EPG40 antigen (17-1A antigen) prevalent on most adenocarcinomas ❑ injection	Phase II (o3/98)➢USA
Glaxo Wellcome	GI198745	5-alpha reductase inhibitor	Phase II (5/97)➢USA
Glycosyn Pharmaceuticals		7-(hydroxymethyl) camptothecin analogs (HAR)	Preclin (2/97)➢USA
Hoechst Marion Roussel ❑ NCI	Flavopiridol ❑ NSC 649890, L86-8275	Synthetic derivative of a tree bark compound that is a potent cdk1 inhibitor; arrests cell cycle progression in either G_1 or G_2	Phase II (o6/98)➢USA ❑ androgen-independent, metastatic prostate cancer; phase I (o6/98)➢USA (in combination with paclitaxel) ❑ solid tumors
Hoechst Marion Roussel ❑ Matrix Pharmaceutical, Kyowa Hakko (Japan)	FMdC ❑ MDL-101731, KW-2331	Nucleoside analog; ribonucleotide reductase inhibitor; antimetabolite ❑ IV, PO	Phase I (b1/95)➢Japan (PO) ❑ solid tumors

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Hoffmann-La Roche	Ganirelix ❑ RS-26306	GnRH antagonist ❑ intranasal	Phase II (98)➢USA
IDEC Pharmaceuticals ❑ Pharmacia & Upjohn, NCI	9-aminocamptothecin (9-AC) ❑ NSC 603071	Water soluble camptothecin analog; small molecule ❑ IV, PO	Phase II (98)➢USA ❑ metastatic (Stage D2) androgen-independent prostate cancer
Idun Pharmaceuticals		Antagonists of the Bcl-2 family of apoptosis inhibitors	Preclin (98)➢USA ❑ solid tumors
Ilex Oncology ❑ Hoechst Marion Roussel	Alpha difluoromethylornithine HCl (DFMO) ❑ Ornidyl (see FO, p 326)	Antiparasitic ❑ injection, PO	Phase II (1/96)➢USA ❑ solid tumors
ImClone Systems ❑ U California, San Diego, Rhône-Poulenc Rorer	Anti-EGFr chimeric MAb ❑ C225 (see FO, p 326)	Chimeric MAb against EGFr overexpressed in certain solid tumors; inhibit uncontrolled cancer cell growth	Phase Ib/IIa (b1/96)➢USA ❑ androgen-independent prostate cancer
Immune Response ❑ Sidney Kimmel Cancer Center		Prostate cancer cell lines genetically modified to to express IL-2 and inhibit production of transforming growth factor β (TGF-β) ❑ injection	Preclin (3/97)➢USA
Immunex ❑ Wyeth-Ayerst Research, ImClone	Flt-3 ligand (Flt-3L)	Flt-3 ligand, a stem cell growth factor that consists of cloned cDNAs encoding a ligand for the Flt-3 receptor ❑ injection	Phase II (b6/97)➢USA
ImmunoTherapy (AVI BioPharma) ❑ Ohio State U	CTP- 37 ❑ Avicine	Synthetic peptide conjugate vaccine designed to elicit an anti-human chorionic gonadotropin (hCG) immune response; targets hCG-producing cancer cells ❑ injection	Phase II (b7/98)➢USA ❑ metastatic prostate cancer
Ingenex ❑ Baylor College of Medicine	RB-94 (was SG-94) (see FO, p 394)	Gene therapy product based on a truncated variant (p94) of tumor suppressor Rb gene and a viral vector ❑ Intratumoral	Preclin (12/96)➢USA
Introgen Therapeutics	Ad-C-CAM ❑ INGN 231 (see FO, p 394)	C-CAM tumor suppressor gene delivered by an adenoviral vector ❑ percutaneous	Preclin (4/98)➢USA
Introgen Therapeutics ❑ RPR Gencell, NCI, U Texas M. D. Anderson Cancer Center, Sidney Kimmel Cancer Center	AD-p53 ❑ INGN-201	Adenoviral p53 gene therapy ❑ intraperitoneal, intralesional, intratumoral	Phase I (b1/98)➢USA
Isis Pharmaceuticals ❑ Novartis	ISIS 3521/CGP 64128A	20-base antisense phosphorothioate oligonucleotide inhibitor of PKC-α expression ❑ IV	Phase II (b8/97 & 12/97)➢Canada, USA, Europe ❑ HRPC
Isis Pharmaceuticals ❑ Novartis	ISIS 5132/CGP 69846A	Antisense inhibitor of C-raf kinase ❑ IV	Phase II (b8/97 & 12/97)➢Canada, USA, Europe ❑ HRPC
Jenner Biotherapies ❑ Research Corporation Technologies, Walter Reed Army Institute of Research	OncoVax-Pr (see FO, p 323)	Liposome-encapsulated formulation of baculovirus-derived recombinant PSA (100 mg/ml) and lipid A (200 mg/ml), administered with or without AdjuVax-100a, a proprietary emulsion formulation ❑ intramuscular, IV, subcutaneous, intradermal	Phase II (b7/98)➢USA; phase I/II (b10/97)➢USA (with AdjuVax-100a) ❑ advanced prostate cancer
Johnson & Johnson (J&J)	Liarozole fumarate ❑ Liazal	Benzimidazole derivative; mediates an antitumor effect partly by disturbing retinoic acid metabolism ❑ PO	NDA (f97), phase III (o7/97)➢USA ❑ HRPC
Johnson & Johnson (J&J)	Fenretinide	Retinoid derivative with antineoplastic activity in various tumor types ❑ PO	Phase II (o98)➢Europe ❑ prostate cancer prevention
JW Nowicky Pharmaceuticals ❑ Ukrainian Anti-Cancer Institute	NSC 631570 ❑ Ukrain	Prepared from the plant *Chelidonium majus L.*, Ukrain exerts direct cytotoxic activity only against malignant cells, mediates cytotoxic actvity, is immunostimulating and immunomodulating, and shows antiviral activity	Phase II (o3/98)➢Ukraine ❑ solid tumors
Kyowa Hakko Kogyo ❑ NCI	UCN-01	Staurosporine analog ❑ continuous IV	Phase I (o8/97)➢USA, Japan ❑ solid tumors, lymphoma

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Ligand Pharmaceuticals	LGD 1069 ❑ Targretin	Retinoid X receptor ligand ❑ PO, topical	Phase IIb (oral; 9/96)➢USA
Ligand Pharmaceuticals	LG2293 series	Androgen antagonists	Research (2/97)➢USA
Ligand Pharmaceuticals ❑ NCI	9-cis retinoic acid (9cRA) ❑ LGD 1057 (formerly ALRT 1057) ❑ Panretin	Derivative of vitamin A; non-peptide regulatory hormone which influences cell growth, differentiation, apoptosis and embryonic development; pan-agonist that binds all six known retinoid receptors with high affinity; a natural hormone ligand for the retinoid acid receptor (RAR) and retinoid X receptor (RXR) subfamilies of retinoid receptors ❑ PO, topical	Phase IIb (oral) (2/97)➢USA, international
LXR Biotechnology ❑ Dana-Farber Cancer Institute, Boehringer Mannheim	LXR023 ❑ Maspin (see FO pp 312 and 319)	Serine protease inhibitor (serpin) with tumor-suppressing function in the mammary gland ❑ PO, injection	Preclin (8/98)➢USA
Matrix Pharmaceutical	Cisplatin/epinephrine ❑ IntraDose-CDDP Injectable Gel (see FO, pp 326-327	Biodegradable injectable collagen-based gel-like matrix of cisplatin/epinephrine ❑ intratumoral	Phase II (b3/95)➢USA
Matrix Pharmaceutical ❑ NCI	Azatoxins	Camptothecin formulation delivered in ADV technology	Preclin (3/97)➢USA
Matrix Pharmaceutical ❑ NCI		ADV formulation of paclitaxel	Research (4/96)➢USA
Maxia Pharmaceuticals ❑ Sidney Kimmel Cancer Center, Galderma	MX-3350-1	Retinoid-related molecules (RRM) ❑ PO	Preclin (97)➢USA
Maxim Pharmaceuticals ❑ Estero Anstalt, Amgen	Maxamine (formerly EpiLeukin)	A histamine type-2 receptor agonist (H2ra) based on the body's natural histamine molecule; inhibits production and release of free oxygen radicals thereby protecting NK-cells and T-cells and allowing for more effective activation by cytokines ❑ subcutaneous	Phase III (o6/96)➢USA ❑ solid tumors
Medarex ❑ Dartmouth Medical, NCI	CC49xH22, MDX-220	Bispecific therapeutic consisting of a Trigger component and a humanized CC-49 antibody targeting TAG-72+ tumors ❑ injection	Phase I/II (b6/98)➢USA
Medarex ❑ Dartmouth Medical, Novartis, Chiron	Bispecific antibody 520C9xH22, MDX-210 (see FO, p 322)	Bispecific therapeutic consisting of a Trigger antibody fragment and a targeting antibody fragment specific for the HER2 antigen; Fab' x Fab' bispecific antibody (BsAb) constructed by crosslinking mAb 520C9 (anti-HER2) and mAb H22 ❑ IV	Phase II (b10/96, o3/98)➢USA, UK ❑ HRPC
Medarex ❑ Merck KGaA, Dartmouth Medical	MDX-447	Bispecific MAb therapeutic consisting of a Trigger antibody fragment and an EGFr targeting component; constructed by cross-linking F(ab') ragments of MAb H22 to FcgRI fand MAb H425 to the EGFr ❑ IV	Phase I/II (b9/95; c7/97)➢USA ❑solid tumors overexpressing EGFr
Memorial Sloan-Kettering Cancer Center ❑ NCI	Globo H-KLH conjugate with QS21 adjuvant	Prostate cancer-associated hexasaccharide, originally detected by MAb MBr1, and now chemically synthesized; it is expressed on the surface of cells as a glycolipid O-linked to mucins or N-linked to other proteins; conjugated to keyhole limpet hemocyanin (KLH) with the immunologic adjuvant QS21 ❑ subcutaneous	Phase I/II (o3/98)➢USA ❑ advanced prostate cancer
Memorial Sloan-Kettering Cancer Center	MUC1-KLH	MUC1-KLH plus QS21 ❑ subcutaneous	Phase I (5/97)➢USA
metaGen ❑ Incyte Pharmaceuticals		Identification of genes involved in spontaneous forms of cancer	Research (3/98)➢Germany ❑ solid tumors
Memorial Sloan-Kettering Cancer Center	MUC2-KLH	MUC2-KLH plus QS21 ❑ subcutaneous	Phase II (o6/98)➢USA
Memorial Sloan-Kettering Cancer Center	Tn(c)-KLH	Tn(c)-KLH plus QS21 ❑ subcutaneous	Phase II (o6/98)➢USA
Metastatin Pharmaceuticals ❑ George Washington U		Therapeutics based on uteroglobin, a human protein that may play a role in prevention of metastasis	Research (4/98)➢USA

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MGI Pharma ❑ Ilex Oncology	Dihydro-5-azacytidine (DHAC)	Cytosine DNA methyltransferase (CMT) inhibitor	Preclin (6/98)➢USA ❑ HRPC
MGI Pharma ❑ Dainippon Pharmaceutical, U California, NCI	Acylfulvenes (6-HMAF) ❑ MGI 114, NSC 683863	Semisynthetic analog of illudin S, a sesquiterpene isolated from the Jack o' lantern mushroom, *Omphalotus illudens*; DNA synthesis inhibitor, apoptosis enhancer ❑ IV	Phase I (b12/95, o6/98), phase II (b7/98)➢USA
Milkhaus Laboratory	Chorionic gonadotrophin (CG) ❑ LDI-200	Formulation of chorionic gonadotropin	Phase II (8/97)➢USA
Miravant Medical Technologies ❑ Pharmacia & Upjohn, U Toledo, Medical College of Ohio, St. Vincent Medical Center, Medicis Pharmaceutical	SnET2 ❑ Purlytin (PhotoPoint)	Tin ethyl etiopurpurin (SnET2), when exposed to appropriate light wavelength, acts as a catalyst to generate a highly reactive form of oxygen which destroys the membrane of the cells containing the drug ❑ IV	Phase I (a9/98)➢USA ❑ localized prostate cancer
National Cancer Institute (NCI)		Immortal human prostate epithelial cell cultures derived from the prostate tumor cell line (E-053-96/0) that may be useful as an *in vitro* model of human prostate cancer	Research (4/97)➢USA
National Cancer Institute (NCI)		Oliogopeptide; PSA oligo-epitope peptide (PSA-OP) comprised of the sequence for PSA peptides PS1 and PS3 that are antigenic epitopes of PSA and are joined by a peptide linker sequence to form PSA-OP	Preclin (98)➢USA
National Cancer Institute (NCI)	Geldanamycin ❑ NSC-330507D	Member of the family of benzoquinoid ansamycin tyrosine kinase inhibitors; destabilizes oncogene and proto-oncogene products	Preclin (97)➢USA
National Cancer Institute (NCI)	Carboxyamidotriazole (CAI) ❑ NSC-609974 (see FO, p 746)	Synthetic signal transduction inhibitor that modulates non-voltage-gated calcium influx-regulated (non-excitable) signal pathways; metastasis inhibitor that targets a pertussin toxin-sensitive G protein; reversibly inhibits angiogenesis, tumor cell proliferation, and metastatic potential ❑ PO	Phase II (b12/97)➢USA ❑ androgren-independent prostate cancer
National Cancer Institute (NCI)	Biochanin A	Dietary flavonoid that is a potent inducer of glucuronosyl transferase (GT) activity and mRNA levels; modulation of testosterone by biochanin A reduces levels of oxygen radicals in LNCaP prostate cancer cells	Research (o3/98)➢USA
NeoPharm	Doxorubicin	Liposome encapsulated doxorubicin (LED)	Phase I (c6/98), phase II (b6/98)➢USA ❑ late stage HRPC
NeoRx ❑ Janssen Pharmaceutica, NSC Technologies	Avicidin	Murine or humanized antibody (NR-LU-13) that binds to most tumor cells, linked to yttrium-90; uses Pretarget technology ❑ IV	Phase II (b3/98); phase I/II (o8/97)➢USA
New York Medical College, Albert Einstein College of Medicine		Recombinant, BCG-based immunotherapeutic vaccine expressing PSA and prostate specific membrane antigen (PSMA)	Preclin (4/97)➢USA
New York U-Cornell Medical Center	MAb Prost 3 linked to ^{131}I	Radioimmunotherapy ❑ IV	Phase I (discontinued 98) ➢USA
NeXstar Pharmaceuticals	DaunoXome	Liposomal formulation of daunorubicin	Phase II (o3/98)➢USA
Northwest Biotherapeutics ❑ Pacific Northwest Cancer Foundation at Northwest Hospital, Cytogen, Prostagen		Dendritic cells pulsed with PSMA-derived peptides (PSM-P1 and PSM-P2) ❑ infusion	Phase II (b1/97)➢USA
Novopharm Biotech	NOVOMAb-G2	Pancarcinoma specific human MAb that recognizes an antigen widely present on 11 of 12 common tumor types ❑ infusion	Phase I (b6/96)➢USA ❑ solid tumors
Novopharm Biotech	NOVOMAab-G2 immunotoxin	NOVOMAb-G2 linked to a toxin	Preclin (10/97)➢Canada
Novopharm Biotech	NOVOMAab-G2 imaging	NOVOMAb-G2 linked to a radioisotope	Preclin (10/97)➢Canada

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OncoAntigenics ❑ Fordham U, Mount Sinai School of Medicine, Perseptive BioSystems	gp96 vaccine ❑ HSPPC-96	Heat shock protein (hsp) vaccines; hsp-peptide complexes that elicit an immune response without requiring adjuvants ❑ IV	Phase I (b5/96, c97)➢Germany ❑ solid tumors
Oxford BioMedica	ProCaStat	Combination of various technologies (gene transfer, macrophage targeting, etc.) for the treatment of solid tumors	Research (6/98)➢UK
OXiGENE ❑ Bioniche	Neu - Sensamide	A neutralized formulation of metoclopramide causes tumor toxicity by apoptosis; radiosensitizer ❑ intramuscular	Phase III (o98)➢Europe ❑ nsclc (clinical evaluation was also performed in prostate cancer)
Pacific Pharmaceuticals ❑ Wound Healing of Oklahoma		Glycated polysaccharide that acts as an immune system stimulant, used in combination with photodynamic therapy ❑ intratumoral	Preclin (1/98)➢USA ❑ metastatic solid tumors
Paracelsian	PN 27,1 ❑ AndroCar (see FO, p 325)	Active anticancer compounds isolated from the traditional Chinese medicinal herb *Andrographis paniculata*	Research (98)➢USA ❑ solid tumors
Paracelsian ❑ Southern Research Institute		Testing of a series of traditional Chinese medicine herbal extracts for antitumor activity	Research (8/98)➢USA
Parke-Davis ❑ NCI	CI-958, NSC-635371	Benzothiopyranoindazole DNA intercalator ❑ IV	Phase II (b96, o98)➢USA ❑ advanced HRPC
Parke-Davis	Mivobulin isethionate ❑ CI-980, NSC 370147	Synthetic mitotic inhibitor that binds to the colchinine-binding site on tubulin which is distinct from the binding site of the vinca alkaloids and inhibits polymerization of tubulin ❑ IV	Phase II (o6/98)➢USA ❑ hormone-refractory Stage D2 prostate cancer
Parke-Davis ❑ U Texas MD Anderson Cancer Center, NIH	Suramin (SUR) ❑ CI-1003, NSC-34936 ❑ Metaret	Polysulfonated naphthathylamine derivative; inhibits angiogenesis and enhances apoptosis; antiparasitic agent ❑ bolus, continuous IV	NDA (f12/97), phase III (b2/94)➢USA ❑ metastatic HRPC
Pharmacia & Upjohn	Turosteride ❑ FCE 26073	Testosterone 5 alpha-reductase inhibitor	Preclin (97)➢USA
Pharmactinium ❑ Mermorial-Sloan Kettering Cancer Center, Cornell U	^{213}Bi-J591	J591 MAb to PSMA linked to the alpha particle emitter bismuth-123 ❑ IV	Preclin (8/98)➢USA
Pharmacyclics ❑ NCI, U Texas, Hoechst Celanese	Gadolinium texaphyrin (Gd-Tex)	Selectively accumulates in cancer cells sensitizing them to radiation ❑ IV	Phase I (c97)➢USA ❑ solid tumors
PharmaMar	Ecteinascidin 743 ❑ ET-743	Tetrahydroisoquinolone alkaloid, a novel marine compound derived from the tunicate Ecteinascidia turbinata ❑ continuous IV	Phase I (b10/96, c97)➢USA, Scotland, the Netherlands, and France ❑ advanced, refractory solid tumors
PharmaMar	Thiocoraline ❑ PM 93135	Thiodepsipeptide compound isolated from the actinomycete, *Micromonospora marina*, originally found in the Mozambique Strait; inhibits growth in several tumor cell lines	Research (10/96)➢Spain
PharmaMar	Kahalalide F ❑ PM 92102	Small depsipeptide isolated from the mollusc, *Elysia rubefescens* from Oahu island with antitumor and antiviral properties; inhibits growth in several tumor cell lines	Research (10/96)➢Spain
PharmaMar	Dehydrodidemnin-B (DDB) ❑ Aplidine	Active didemnin isolated from the Carribean tunicate *Aplidium albicans*; dehydroderivative of didemnin-B	Preclin (3/98)➢Spain ❑ solid tumors
Pherin ❑ Organon	Vomeropherins (see FO, p 327)	Compounds that activate chemosensory cells in the vomeronasal organ (VNO) in nasal passages to transmit a message to the hypothalamus that may regulate various functions ❑ nasal	Preclin (97)➢USA
Praecis ❑ Hoffmann-La Roche (NA, Asia, Japan), Synthelabo (Europe)	PPI-149 ❑ Abarelix	LH-RH antagonist; rapidly reduces serum levels of testosterone without an androgen surge	Phase II (c5/98)➢USA, phase I/II (o4/98)➢Europe ❑ hormone-dependent prostate cancer
Praecis		Antagonist of bFGF	Preclin (6/98)➢USA ❑ HRPC

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Procyon BioPharma ❑ Massachusetts General Hospital		Non-pathogenic antinuclear autoantibodies (ANAs) discovered in the blood of healthy aged animals that bind to nucleosomes and enhance the body's natural immunological cancer fighting mechanisms	Preclin (9/98)➢Canada, USA
Procyon BioPharma	Prostate Secretory Protein (PSP94)	PSP94 binds to specific receptors on the surface of prostate cancer cells	Preclin (9/98)➢Canada ❑ HRPC
Proteus Molecular Design ❑ Strathclyde Institute for Drug Research (SIDR), U Strathclyde, ML Laboratories	014L, PM-OV-92, Sterovac 92 ❑ Prolog (see FO, p 323)	GnRH immunotherapeutic vaccine (LH-RH immunacine); vaccine-like construct containing a gonadorelin analog which stimulates an antibody response by cross-reacting with naturally-produced LH-RH ❑ injection	Phase IIa (b96; o6/98) ➢UK ❑ advanced prostate cancer
Schering-Plough	SCH 66336	Small molecule tricyclic farnesyltransferase inhibitor (FTI) ❑ PO	Phase I (b3/98)➢USA ❑ solid tumors
Scotia ❑ Boehringer Ingelheim, Kyowa Hakko Kogyo	EF-9 ❑ Temoporfin, Foscan	Meso-tetrahydroxyphenylchlorine-based photodynamic therapy (m-THPC-PDT)	Phase III (c98)➢USA ❑ head and neck cancer (may have application in prostate cancer)
Seragen (Ligand Pharmaceuticals)	EGF Fusion Protein	Recombinant fusion protein in which the receptor-binding domain of diphtheria toxin has been replaced by human EGF ❑ IV	Phase I/II (98)➢USA ❑ solid tumors espressing EGFr
Somatix Therapy (Cell Genesys) ❑ Johns Hopkins U, U Texas, Bristol-Myers Squibb, Whitehead Institute	Allogeneic GVAX	GM-CSF-transduced allogeneic tumor cell vaccine ❑ subcutaneous	Preclin (8/96)➢USA
Somatix Therapy (Cell Genesys) ❑ Johns Hopkins U, U Texas, Bristol-Myers Squibb, Whitehead Institute	Autologous GVAX (see FO, p 323)	GM-CSF-transduced autologous tumor cell cell vaccine ❑ subcutaneous	Phase I (b1/96, o3/97) ➢USA
Stanford Rook	SRL 172	Immunotherapeutic consisting of heat-killed *Mycobacterium vaccae* ❑ injection	Phase I/II (2/97)➢UK ❑ advanced prostate cancer
Sugen ❑ Asta Medica	Pan-Her Antagonist (formerly Her2 Antagonist)	Small molecule inhibitors of the HER receptor family which includes the EGF receptors, HER2, and HER 4	Preclin (97)➢USA
Sugen ❑ NCI, Taiho Pharmaceutical	SU101	Small synthetic molecule that inhibits the platelet-derived growth factor (PDGF) tyrosine kinase (TK) signaling pathway; structurally similar to leflunomide ❑ IV, subcutaneous	Phase II (o3/98)➢USA ❑ HRPC
Sugen ❑ Taiho Pharmaceutical	SU5416	Small molecule drug targeting VEGF-mediated Flk-I TK pathway; blocks angiogenesis ❑ IV, PO	Phase I (o3/98)➢USA; phase I/II (b6/98)➢UK ❑ solid tumors (IV)
SuperGen ❑ Stehlin Foundation for Cancer Research, U Texas M.D. Anderson Cancer Center, NCI	9-nitrocamptothecin (9NC) ❑ RFS 2000	Water-insoluble topoisomerase I inhibitor ❑ PO	Phase I➢USA
Taiho Pharmaceutical	TAS-103	Novel dual topo I and II inhibitor ❑ IV	Phase I (b10/96)➢USA ❑ refractory solid tumors
Targon (Elan)	Phenylbutyrate ❑ NSC-657802, EL 532	Phenylbutyrate, an aromatic fatty acid, is a prodrug of phenylacetate that demonstrates potent differentiating effects ❑ IV, PO	Phase I (o3/98, PO) ➢USA ❑ solid tumors
Teikoku Hormone	Osaterone acetate	Antiandrogen	Phase II (98)➢Japan
The Liposome Company (TLC)	Liposomal ether lipid ❑ TLC ELL-12	Liposomal form of ether lipid; anticipated not to possess many toxicities, particularly myelosuppression	Preclin (8/98)➢USA
The Population Council		GnRH analog ❑ implant	Phase I➢USA
Therion Biologics ❑ NCI CRADA	Prostvac (see FO, p 323)	Live recombinant vaccinia-vectored vaccine (rV-PSA) that expresses epitopes of amino acids 141-150 and 154-163 of PSA ❑ injection	Phase I (b11/96)➢USA ❑ metastatic prostate cancer

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Transgene ❑ Imperial Cancer Research Fund (ICRF), Imperial Cancer Research Technology (ICRT)		Attenuated vaccinia virus modified with the human MUC1 and IL-2 genes ❑ intramuscular	Phase II (b3/98)➢France
Trilex Pharmaceuticals		Prostate cancer vaccine that targets PSA 773	Research (5/97)➢USA
Tulane U	AN-201; AN-163 and AN-258; AN-162 and AN-238	Cytotoxic hybrid analogs of somatostatin (SST) and doxorubicin	Preclin (7/97)➢USA
Tularik ❑ Cold Spring Harbor Laboratory		Representational difference analysis (RDA) to discover cancer-associated genes	Research (98)➢USA
United Biomedical	Synthetic Universal Immune Stimulator (SUIS) LH-RH (see FO, pp 323-24)	Synthetic peptide immunotherapeutic; synthetic LH-RH covalently linked to immunoregulatory peptides and groups with defined adjuvanting effects ❑ injection	Phase I (11/97)➢USA ❑ androgen-dependent prostate cancer
U Alabama	GRO15A	G-rich oligonucleotide which can completely inhibit the growth of DU145 prostate cancer cells in culture relative to untreated cells and cells treated with other G-rich oligonucleotides	Preclin (98)➢USA
U Alabama	GRO29A	See above	Preclin (98)➢USA
U Kentucky	NF681	Synthetic diphenylurea compounds that are more potent inhibitors of angiogenesis than suramin	Preclin (o7/98)➢USA
U Michigan	Vaccinia-PSA	Vaccinia (poxvirus) vectors linked to PSA ❑ intradermal	Phase I/II (b7/97)➢USA ❑ androgen-modulated minimal volume prostate cancer recurring after post-prostatectomy
U Michigan	AdMXI1	Plasmid expression vector containing HA-tagged human MXI1 under control of an RSV LTR promoter, resulting in a replication-incompetent adenovirus with the MXI1 gene as an insert; causes arrest at the G_2/M phase of the cell cycle	Research (o3/98)➢USA
U Pittsburgh	Curacin A	A thiazoline ring-containing lipid, is a potent antitubulin marine cyanobacterial natural product that causes cell cycle arrest in mitosis	Preclin (98)➢USA
U Texas M. D. Anderson Cancer Center	Interferon β (IFN-β)	Daily administration of low-dose IFN-β or pegylated IFN-β, administered on a chronic basis ❑ injection	Clinical (o8/98)➢USA
University of Maryland School of Medicine		17-azolyl compounds that are novel inhibitors of the androgen synthesis pathway	Preclin (3/98)➢USA
Vanderbilt Cancer Center, Vanderbilt U Medical School ❑ U Tennessee, Emory U School of Medicine		Retroviral vectors containing mouse mammary tumor virus expressing antisense c-myc RNA	Preclin (6/96)➢USA
Vertex Pharmaceuticals ❑ BioChem Therapeutic	Biricodar dicitrate ❑ VX-710 ❑ Incel	Blocks activity of the MDR-1 protein to combat multidrug resistance; resensitizes cancer cells to chemotherapy ❑ IV	Phase II (b6/98)➢USA (in combination with mitoxantrone) ❑ HRPC
Vical	Leuvectin	A gene-based product consisting of a gene encoding IL-2 and a lipid to facilitate uptake ❑ intratumoral	Phase I/II (b6/97; o3/98) ➢USA
Virogenetics ❑ Washington U School of Medicine		Recombinant canarypox viruses carrying DNA sequences encoding interleukin 2 (ALVAC-IL-2), interferon γ (ALVAC-IFN γ), tumor necrosis factor-α (ALVAC-TNF-α), or the co-stimulatory molecule B7.1 (ALVAC-B7.1) ❑ intratumoral	Preclin (97)➢USA

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Wisconsin Genetics (WGI, Endorex) ❑ Wisconsin Alumni Research Foundation (WARF)	Perillyl alcohol ❑ NSC 641066 (see FO, p 325)	Synthetic analog of the naturally occurring hydroxylated limonene, a monoterpene; induces apoptosis ❑ PO	Phase II (b3/98)➢USA ❑ HRPC
Wyeth-Lederle Vaccines-Malvern ❑ Centocor	GeneVax	DNA vaccine encoding a MHC-1-directed peptide that mimics a live attenuated virus	Phase I (b97)➢USA ❑ colorectal cancer (may be applicable to prostate cancer)
Yamanouchi Pharmaceutical	YM116	Non-steroidal inhibitor of cytochrome P_{450} ❑ PO	Preclin (3/98)➢Japan

Source: NEW MEDICINE Oncology KnowledgeBASE (nm|OK), August 1998.

MAb. Without any other intervention about 50% of the mice were cured. It appears that appropriate manipulation of T cell costimulatory and inhibitory signals may provide a fundamental and highly adaptable basis for prostate cancer immunotherapy (Kwon ED, etal, PNAS USA, 22 July 1997, 94(15):8099-103).

PSA-based Strategies

Several clinical trials are ongoing using vaccinia virus expressing PSA, sponsored by the NCI. In a phase I clinical trial (protocol IDs: NCI-94-C-0118C, NCI-T94-0007N, NCI-NMOB-9401), under PI AP Chen of the NCI, vaccinia virus genetically engineered using a pT1001 plasmid vector to contain a copy of the PSA gene (NSC-697729), is being used to treat 45-60 HRPC patients. The study has been designed to determine the antitumor activity of this construct, the optimal biologic dose based on humoral and cellular immune response and, when possible, tumor biopsy results and any side effects.

A phase I/II clinical trial (protocol IDs: CCUM-9618, NCI-T97-0007) being conducted at the University of Michigan Comprehensive Cancer Center under PI Martin G. Sanda, is evaluating the safety and biological activity of a recombinant vaccinia PSA vaccine in 21-24 chemotherapy-naive patients with serological recurrence of prostate cancer following radical prostatectomy. Endpoints include determination of MTD of vaccinia-PSA administered intradermally and evaluation of its immunological and serological antitumor effects. MDT is to be established in the phase I clinical trial. In the phase II trial, patients undergo 2 cycles of androgen deprivation interruption; cycle 1 determines the baseline measurements and cycle 2 is accompanied by vaccination. The last 8 patients accrued in this phase II trial are administered a second dose of vaccinia-PSA, 4 weeks after the first dose.

Immunization with microbial vectors expressing PSA such as the attenuated vaccinia virus (NYVAC) and adenovirus type 5, produced anti-PSA T cells in Balb/c mice (H-2d) with antitumor ability *in vitro* and *in vivo*, according to researchers at the University of Iowa (Iowa, IA). Splenocytes from mice immunized with both viruses gave strong anti-PSA CTL responses but initial experiments indicate that the adenoviral vector induced a stronger response than did the NYVAC vector. Therefore, a single dose of NYVAC or adenovirus type 5 expressing PSA can induce, within 14 days, an efficient anti-PSA CTL response in Balb/c mice (Lubaroff DM, etal, AACR98, Abs. 70:11).

BCG-based immunotherapeutic vaccines that express PSA are being evaluated by investigators at the New York Medical College (Valhalla, NY) and Albert Einstein College of Medicine (Bronx, NY). In order to stimulate the immune system to destroy prostate cancer cells recombinant BCG-based vaccines are used that express and secrete prostate specific molecules, such as PSA and PSMA. The ability of BCG, engineered to intracellularly express 2/3 of the PSA molecule, to generate antitumor immunity is currently being evaluated in mice. The anticipated application is to treat patients who have undergone radical prostatectomy and are at risk for recurrence (Zeoli CD, etal, AACR98, Abs. 2426:355-6).

Prostvac, a live recombinant vaccinia-vectored vaccine (rV-PSA) that expresses epitopes of amino acids 141-150 and 154-163 of PSA, being developed by Therion Biologics (Cambridge, MA), is under evaluation in metastatic prostate cancer in two separate phase I clinical trials (NCI-T95-0086H and DFCI-96079) initiated in November 1996 at the NCI and Dana Farber/Partners Cancer Care, headed by Drs. Jeffrey Schlom and Donald Kufe, respectively. Both trials are sponsored by the NCI under a five-year CRADA and in partnership with Dr. Schlom.

In one phase I clinical trial, rV-PSA was administered in 3 consecutive monthly doses (2.65 million, 26.5 million, and 265 million pfu) to 24 men with a rising PSA after radical prostatectomy or radiation therapy, or both. No patient experienced any effects beyond Grade 1 cutaneous toxicity. Pustule formation occurred after the first dose in all 18 men who were treated with 26.5 million pfu. Patients were removed from protocol for clinical progression or 3 monthly rises in PSA > 50% of baseline. Twelve of 23 men (52%) remained on the study for 1-10+ months with stable disease (Eder JP Jr, etal, ASCO98, Abs. 1672:434a).

ProstaRex, under development by AltaRex (Edmonton, Alberta, Canada) in collaboration with investigators at the Noujaim Institute for Pharmaceutical Research in Oncology, Faculty of Pharmacy, University of Alberta in

Canada, is a specific anti-PSA antibody that elicits an anti-idiotypic response against prostate cancer. Murine MAbs are used to facilitate this anti-idiotype induction therapy (AIT) which is directed against specific tumor-associated antigens (TAA). Injecting appropriate antibody generates a mixture of surrogate antigens and/or results in a more effective presentation of the existing native antigen to the immune system, thus giving the immune system a choice to select the appropriate antigen form. Among a large panel of anti-PSA MAbs produced and evaluated for their potential therapeutic efficacy against prostate cancer in mice, one was selected that induced a specific immunity against PSA itself (Leveugle B, etal, AACR98, Abs. 2424:355).

OncoVax-Pr, under development by Jenner Biotherapies (San Ramon, CA), is a liposome-encapsulated formulation of baculovirus-derived recombinant PSA (100 mg/ml) and lipid A (200 mg/ml), administered with or without AdjuVax-100a, a proprietary emulsion formulation. In July 1998, Jenner initiated a phase II clinical trial of OncoVax-Pr with AdjuVax-100a, in patients with HRPC in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF, Leukine; Immunex). A second phase II trial involving patients who have had primary treatment for prostate cancer and are experiencing a rising PSA will also commence shortly.

In a phase I clinical trial, conducted at Thomas Jefferson University (Philadelphia, PA) and Walter Reed Army Institute of Research (Washington, DC) sequential groups of patients with surgically incurable prostate cancer were treated with OncoVax-Pr with four different schedules of administration (see Exhibit 2). No toxicity was noted in regimen A; 2/5 patients in regimen B experienced transient neurologic symptoms and 1/5 had fever. Local erythema and induration were seen in all patients in regimen C and abscesses developed at BCG injection sites. C and D regimens generated immunity against PSA (Harris DT, etal, ASCO98, Abs. 1647:428a).

Vaccines Based on Other Prostate Cancer-Associated Antigens

Globo H, a hexasaccharide detected originally by MAb Mbr1 that is expressed on the surface as a glycolipid, O-linked to mucins or N-linked to other proteins and expressed on cancers of epithelial origin, is being studied at Memorial Sloan-Kettering Cancer Center as a target for potential carbohydrate-based vaccines against prostate cancer. Globo-H-KLH conjugate plus QS21 produced high titer IgM and IgG responses against Globo H *in vitro* and *in vivo.* In a phase I clinical trial (protocol IDs: MSKCC-96055A1, NCI-V97-1119), 20 patients were immunized at 4 different dose levels on weeks 1, 2, 3, and 7. Patients without progressive disease and acceptable antibody titers were administered a fifth vaccination on week 19. Over a 26 week period, following four immunizations, all patients generated high titer IgM and IgG responses by week 13. Preliminary studies showed a decline in PSA, indicating that the vaccine affects the rate of disease progression (Slovin SF, etal, AACR98, Abs. 2518:370).

MUC1 and MUC2 antigens are being employed in vaccines in clinical trials also at Memorial Sloan-Kettering Cancer Center. A phase II clinical trial (protocol IDs: MSKCC-97122, NCI-G98-1378) of vaccination with mucin peptide (MUC2) KLH conjugate plus Q21, is being conducted by PI Susan Slovin, MD, in 20 patients with histologically confirmed recurrent prostate cancer. This is a dose escalation, two group study with Group A comprised of patients who have progressed after primary surgery or radiation (with or without neoadjuvant ablation) and who have noncastrate levels of testosterone (greater than 50 ng/mL), and Group B comprised of patients with progressive, androgen-independent disease with castrate levels of testosterone (less than 30 ng/mL). Four cohorts of 5 patients, enrolled sequentially from either group A or B, are treated with escalating doses of MUC2-KLH vaccine plus QS21 administered subcutaneously to random sites on the upper arm and upper leg, at three weekly intervals, and then at weeks 7 and 19. After 5 patients have undergone two vaccinations and there is no unacceptable toxicity at that dose level, additional patients proceed to the next higher level. There are no dose escalations in the same patient.

Trial objectives include determination of an optimal dose of gastrointestinal MUC2-KHL vaccine plus QS21 that induces an antibody response to MUC2 and a helper T and/or cytotoxic T cell response against MUC2, the safety of MUC2-KLH conjugate prepared using a myocin-binding subunit heterobifunctional linker plus QS21, and assessment of postimmunization changes in PSA levels and other objective disease parameters.

Tn(c)-KLH conjugate plus QS21 immunization is also being evaluated in a phase II clinical trial (protocol IDs: MSKCC-98002, NCI-G98-1440) in 15 patients with progressive prostate cancer, ongoing at Memorial Sloan-Kettering Cancer Center under PI Howard I. Scher, MD. Three sequential cohorts of 5 patients each are treated with escalating subcutaneous doses of Tn(c)-KLH plus QS21 at the same dose, at weekly intervals, for 3 weeks and then at weeks 7 and 19. After 5 patients have undergone two vaccinations, and there is no unacceptable toxicity at that dose level, additional patients proceed to the next higher dose level until MDT. There are no dose escalations in the same patient. Patients are followed every 3 months after the first vaccination and then for 1 year or until disease progression is documented.

Trial objectives are to determine the optimal dose of Tn(c)-KLH plus QS21 needed to induce an optimal antibody response, the safety of this type of immunization, postimmunization changes in PSA levels and other objective disease parameters and any effects of Tn(c)-KLH dose on helper and/or CTL response against Tn(c).

Exhibit 2
Results of a Phase I Clinical Trial of OncoVax-Pr

	Treatment Regimen	Patients (#)	Clinical Response	Delayed-type hypersensitivity (DTH)	Antibody to human vesicle-seminal derived PSA
A	1 ml of OncoVax-Pr on days 0, 30, 60, intramuscularly	5	2 SD 3 PD	1/5	1/5
B	1 ml on days 0, 30, 60, intravenously	5	2 SD 3 PD	1/5	0/5
C	1 ml of OncoVax-Pr on days 0, 30, 60 + subcutaneous GM-CSF (125 mg) on days 0-4, 30-34, 60-64	10	7 SD 3 PD	4/4	9/10
D	1 ml of OncoVax-Pr on days 0, 1, 2, 15, 30 plus intradermal BCG (1-8 x 10^6 CFU) on days 0, 15, 30, plus pre-treatment with IV cyclophosphamide (300 mg/m^2) on day 3	5	2 SD 3 PD	4/5	5/5

Source: Harris DT, etal, ASCO98, Abs. 1647:428a

Transfection of Cytokine Genes into Tumors

Gvax, under development by Cell Genesys (Foster City, CA), in collaboration with Johns Hopkins University (Baltimore, MD), consists of autologous irradiated prostate cancer cells transduced *ex vivo* with the gene for GM-CSF using a retrovirus vector. Gvax has been shown to induce potent T-cell-mediated antitumor immune responses in poorly immunogenic preclinical animal cancer models including prostate cancer. In a phase I clinical trial in metastatic prostate cancer discovered at radical prostatectomy, 8 patients were treated in the outpatient setting with 3 to 6 cycles of this vaccine. In 3/11 cases one limitation of this approach was *ex vivo* vaccine cell expansion. However, *ex vivo* GM-CSF gene transfer was 100% successful in all patients. No DLT was observed. Among 41 fully evaluable vaccinations, biopsies showed perivascular inflammatory infiltrates similar to those seen in preclinical models, with a prominence of dendritic cells, macrophages, and degranulating eosinophils surrounding vaccine cells. Histologically confirmed DTH reactivity to untransduced, autologous PCA target cells was also observed. Median serum PSA declined from 28.85 ng/ml (range=6.7-75) before surgery to 0.65 ng/ml (range of 0.1-30.4) at first vaccination. However, within a follow-up of 51-83 weeks, 6/8 patients progressed after surgery and vaccination based on ultrasensitive serum PSA levels (Simons JW, etal, ASCO98, Abs. 1205:313a and AACR98, Abs. 2517:369).

Autologous Cells Activated *Ex Vivo*

Use of autologous cells activated *ex vivo* is evolving into an effective immunization approach for advanced, metastatic prostate cancer. Particularly effective are autologous dendritic cells that express costimulatory molecules and high levels of MHC proteins. Dendritic cells are the most efficient APCs *in vivo* and are the APCs involved in primary T cell activation.

Cancer Biotherapy Research Group (Franklin, TN), under Robert O. Dillman at Hoag Cancer Center (Newport CA) is conducting a phase II randomized clinical trial (protocol IDs: NBSG-9212, NCI-V92-0155) of an autologous tumor cell vaccine, to enroll 20 to 30 patients with advanced solid tumors, including prostate cancer. All patients are vaccinated on week 1 with irradiated autologous tumor cells, with one group also treated with interferon γ as an immunologic adjuvant, while the other is treated with GM-CSF. In both groups, additional vaccine plus adjuvant is administered at rotating sites on weeks 2 and 3, then monthly from weeks 8-24. Another phase II clinical trial (protocol IDs: NBSG-9115, NCI-V93-0342), being conducted by the same group, uses autologous activated lymphocytes plus immunomodulation with high-dose cimetidine to treat up to 50 patients with metastatic cancer, including prostate cancer. Patients are treated monthly with autologous lymphocytes that have been activated *in vitro* with anti-CD3 antibody and expanded *in vitro* with cimetidine and indomethacin. In addition, patients are administered oral cimetidine throughout the treatment period that may involve up to 6 courses, in the absence of unacceptable toxicity or rapid disease progression.

Dendreon (Mountain View, CA) is developing dendritic cell-based immunotherapy (APC8015) for HRPC, involving harvested autologous dendritic cells that are activated *ex vivo* with prostate tumor antigens, and returned to the patient. APC8015 is an autologous dendritic cell product prepared by isolating DC precursors from peripheral leukapheresis products by buoyant density centrifugation, followed by incubation for 40 hours in serum-free, cytokine-free media with PA2024 (a fusion protein composed of a PSA and a DC targeting element). Creation of APC8015 is based on three proprietary technologies developed by Dendreon:

- Dendritic Cell Enrichment - collection and enrichment (in less than two hours) of precursor dendritic cells from patients' blood
- Tumor Antigen Engineering - genetically engineered antigens to be expressed as proteins that efficiently target dendritic cells
- Antigen Presentation - optimal loading and processing of antigen by dendritic cells

An 18-patient phase II clinical trial was in progress as of October 1997 at the University of California, San Francisco, and data from this trial is expected by the end of 1998. Researchers are now focusing on appropriate dosage. Starting dose is 1.2 x 10^9 cells/m^2 (Valone FH, etal, ASCO98 Abs. 1334:346a).

In a phase I clinical trial, completed at UCSF, 12 patients with HRPC were treated with monthly IV infusion of APC8015 (0.3, 0.6 and 1.2 x 10^9 cells/m^2) for 3 months. APC8015 was well tolerated with Grade 1-2 myalgias occurring in 3 patients. Following one infusion of APC8015, all patients developed strong T cell proliferation responses to PA2024. Detection of IFN-γ but not IL-4 suggests a TH-1 response to PA2024. Weak antibody responses to PA2024 were detected in only two patients (Valone FH, etal, AACR98, Abs. 1186:173).

In June 1997, Dendreon acquired an exclusive worldwide license from Immune Response (Carlsbad, CA) to issued and pending patents concerning dendritic cell therapy for cancers and other diseases. Immune Response originally received the exclusive patent rights to the technology from the University of Brussels in Belgium. Dendreon believes this is the only patent yet to be issued covering the clinical use of dendritic cells.

In October 1997, Dendreon formed a research collaboration with the Mayo Clinic (Rochester, MN) to further develop its cell therapy technology. As part of the agreement, a cell processing facility employing Dendreon's proprietary cell isolation and enrichment technology will be established at the Mayo Clinic, to be jointly operated by the two partners. Financial details of the collaboration were not disclosed. As an initial clinical focus of the collaboration, the Mayo Clinic will initiate phase I/II trials of Dendreon's dendritic cell therapy for the treatment of advanced prostate cancer.

Northwest Biotherapeutics (Seattle, WA) is using dendritic cells pulsed with PSMA-derived peptides (PSM-P1 and PSM-P2) as autologous vaccines against advanced prostate cancer (see FO, p 399). In March 1998, Dr. Gerald Murphy and colleagues at Northwest Hospital (Seattle, WA), reported that among 33 men with metastatic HRPC there were 9 PR defined as a greater than 50% decline in PSA. There was also evidence of tumor regression on bone scans and other tests in some of the study participants. The combined average response duration of 4 of these men was 225 days; disease progressed in 13 patients and 7 died during the study. Five men who did not respond to treatment in the phase I trial, responded in the phase II, with PRs lasting 196 days. No serious adverse effects were noted during treatment, despite that fact that patients must sit through procedures that last several hours. The main side effects are fatigue, pain, and local reactions, primarily related to injections of GM-CSF.

As of mid-1998, at least five other cancer research centers have initiated clinical trials with this approach, including Cedars/Sinai UCLA (Los Angeles, CA), St. Luke's Medical Center (Milwaukee, WI), M.D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, and the University of Michigan Medical Center. A planned multicenter trial will use purified recombinant PSMA in contrast to the initial trials that used peptides from PSMA. This trial will split participants into 15 groups in order to compare different doses and delivery methods of PSMA, along with the effects of adding GM-CSF or Flt-3 ligand.

GENE THERAPY

Adeno-associated Viral (AAV) Vectors

Avigen (Alameda, CA), in collaboration with investigators at Baylor College of Medicine, is evaluating the use of its AAV vectors as a treatment for early stage prostate cancer. AAV vectors are well suited for treatment of prostate cancer because prostate tumors can be easily accessed by direct injection, tumor cells divide extremely slowly and tumors are frequently localized to a particular site. Investigators have demonstrated that following injection of an AAV vector containing a "marker" gene directly into the prostate in mice, expression of the marker protein is observed in the prostate epithelium. Recently, they have also developed a model of prostate cancer in mice. Currently, these investigators are evaluating the antitumor effects of direct injection of an AAV vector containing the tk and IL-2 genes into these tumors. They are also developing other strategies using AAV vectors containing tumor suppressor genes. These vectors will incorporate a prostate-specific promoter designed to limit gene expression to prostate cells.

Adenovirus Vectors (ADV)

According to Leland W. Chung, PhD, of the University of Virginia, speaking at CaP CURE97, adenovirus:

- has a well-characterized genome
- can carry DNA of up to 35 kb
- exhibits episomal expression (does not integrate into the genome) with reduced immunogenicity is rendered replication defective
- results in high titer high infectivity even in non-dividing cells

In order to determine the most efficient delivery route for adenoviral gene transfer to the prostate, investigators at the University of Tennessee (Memphis, TN) constructed a replication deficient recombinant adenoviral vector (AdRS VlacZ) expressing bacterial β-galactosidase (lacZ) under the control of Rous sarcoma virus (RSV) promoter and treat-

ed canine prostates *in vivo* by three different routes, IV, intra-arterial and intraprostatic (Steiner MS, etal, AACR98, Abs. 3531:519). Optimal delivery was achieved by intraprostatic administration as determined by:

- the percentage of prostate cells expressing β-gal *in situ*
- β-gal enzymatic activity from prostate genomic DNA from prostate tissue using primers specific for the adenoviral genome

Calydon has created a prostate-specific attenuated replication competent adenovirus (ARCA) containing a prostate tissue-specific enhancer (PSE) gene that only infects and grows on the subtype of prostate cells that express PSA. This PSE-containing virus, CN706, was created by inserting minimal enhancer/promoter constructs derived from the 5' flank of the human PSA gene (PSE) into adenovirus type 5 DNA so as to drive the E1A gene.

When injected into the prostate, the virus infects and, as a result, destroys any PSA-producing cells both normal as well as cancerous. In this behavior it may be considered an alternative to surgery, chemotherapy or radiation therapy that also destroy the gland. However, because its effects concentrate solely on the prostate gland it is not expected to affect fertility, potency, or continence that are serious complications of surgery and/or radiotherapy. Also, CN706 is not expected to affect non-PSA producing cells. In preclinical trials conducted in mice, a single injection of the virus, directly into the gland, shrunk tumors dramatically within six weeks, without side effects (Rodriguez R, etal, Cancer Res, 1 Jul 1997, 157(13):2559-63).

A phase I clinical trial that is to enroll 30 men with T3 prostate cancer, started in July of 1998 at the Brady Urological Institute of the Johns Hopkins Hospital Oncology Center. The study is expected to enroll 3 patients per month to be treated at each dose level. Endpoints include PSA levels, tumor volumes, as well as safety. Patients will be closely monitored for two months with follow-up for a total of two years.

University of Michigan researchers used a plasmid expression vector containing HA-tagged human MXI1 under control of an RSV LTR promoter, and produced a replication-incompetent adenovirus with the MXI1 gene as an insert (AdMXI1). In the myc/max regulatory network, c-myc activates transcription and stimulates cell proliferation while MXI1 negatively regulates these actions. AdMXI1-infected DU145 human prostate tumor cells, in comparison with controls, showed:

- a significant reduction in cell number 3-4 days following infection
- a significantly reduced doubling time (4 days, as compared to 1-1.5 days for controls)
- a significantly reduced BrdU incorporation 48 hours after infection, indicating reduced cellular proliferation
- a significantly higher proportion of cells in the G_2/M phase of the cell cycle, suggesting a G_2/M arrest
- a significantly reduced ability to form colonies in soft agar (less than one third the number of colonies seen with controls)

These studies demonstrate that expression of MXI1 can suppress growth of a prostate tumor cell line, possibly by inducing a G_2/M arrest, and raise the possibility that an MXI1 adenovirus might be useful as part of a gene therapy approach for prostate cancer (Taj MM, etal, AACR98, Abs. 4393:645).

Suicide Gene Therapy using Adenovirus Vectors

In a study conducted at the Baylor College of Medicine, researchers reported on the experimental evidence of antitumor activity *in vitro* and *in vivo* of HSV-tk delivered using an adenoviral vector injected directly into the tumor, followed by ganciclovir. In a phase I clinical trial patients with rising PSA levels less than 20 ng/ml, and biopsy-proven recurring tumors after irradiation therapy, were treated with a single intraprostatic injection of ADV/HSV-tk followed by 14 days of intravenous ganciclovir (5 mg/kg), administered every 12 hours. PSA declined by >50% in 3 patients and 1 patient's biopsy converted to negative. Toxicities associated with the treatment were mild (Scardino PT, etal, ASCO 98 Abs. 1186:308a).

MONOCLONAL ANTIBODIES

PSMA MAb Immunoconjugates

BZL Biologics licensed the exclusive rights to four new MAbs (J591, J533, J415 and E99), all IgG isotypes, which target the extracellular domain of PSMA, as well as Prost 30 (anti-PSA), designed by researchers at New York Hospital-Cornell Medical Center (New York, NY). These constructs are being used either unconjugated or conjugated in the treatment of prostate cancer. According to Neil H. Bander, MD, of New York Hospital-Cornell Medical Center, speaking at CaP CURE97, prostate cancer is ideally targeted by MAb-based therapies because:

- MAbs localize well in the prostate
- prostate cancer is radiosensitive
- lymph and bone metastases are of small volume and, therefore, may be killed by radioimmunoconjugates

The MAbs developed by these investigators, after binding to their target, become internalized which makes them candidates as immunotoxins (ricin A chain-J591 is highly specific and highly toxic to LINCaP cells) or drugs. They may also be applicable to many different tumors because PSMA has been found to be expressed in many other epithelial cell tumors but not on normal cells.

As of September 1997, four clinical trials were conducted with Prost 3 (both conjugated and unconjugated) involving about 60 patients. In a phase I/II clinical trial with

naked Prost 30, conducted in 1996, there were 14 responses, lasting 2-27 months, among 22 treated patients. In a phase I/II clinical trial of Prost 3, conjugated with ^{131}I, which began enrolling patients in January 1997 (it was open in September 1996), heavily pretreated HRPC were administered Prost 3 (5-10 mg) and escalating doses of ^{131}I (30 mCi/m^2 to 105 mCi/m^2). Accrual was slow because patients treated at each dose level were monitored for hematopoietic toxicity for at least one month before new patients were treated at the subsequent dose level. Two of 6 evaluable patients responded among 7 patients accrued as of mid-1997.

In completed phase I/II clinical trials, unconjugated Prost 30 yielded a 23% response rate based on a PSA decline of >50%. The longest responder continued without progression at 36+ months. In an adjuvant trial involving high-risk patients post-prostatectomy, those treated with Prost 30 experienced a 60% decrease in progression rate at a median of 2 years. Despite this good data, Prost 30 is being phased out in favor of anti-PSMA MAbs which not only target a much better defined antigen but have substantially more compelling preclinical data in combination with bismuth-213 or ricin conjugates.

Clinical trials of the anti-PSMA MAbs are expected to begin at Cornell Medical Center and at Memorial Sloan-Kettering Cancer Center in the fourth quarter of 1998, an IND having been filed in late August 1998. The lead antibody has been already humanized.

Antibody-Directed Cytotoxicity

Medarex is clinically evaluating the bispecific MAb MDX-H210 which combines a recognition site for HER2/neu with a triggering sequence for the high affinity IgG Fc receptor CD64. MDX-H210 is administered with systemic GM-CSF either in metastatic HRPC or locally-advanced or metastatic renal cell cancers that express HER2/neu. In a phase II clinical trial, being conducted in the USA and the UK, GM-CSF (5 µg/kg/day) was administered subcutaneously for 4 days, followed by IV MDX-H210 (15 mg/m^2), repeated weekly for 3 weeks, with each cycle lasting 18 days. Responding patients who do not experience DLT may repeat the 18-day cycle following a 24-day rest.

Among 5 patients with renal cancer and 18 patients with prostate cancer who completed at least one cycle, there were 2 objective responses in patients with renal cancer (a 52% reduction in tumor size in one patient and a 49% reduction in the size of a pulmonary metastasis with clearing of non-measurable lesions in another). Among those with prostate cancer, there were 5 objective responses (>50% decline in PSA ; 104 to <0.1, 20 to <0.1, 118 to 11, 872 to 207 and 126 to 58 ng/ml) and QoL improvements were also noted. Toxicity with GM-CSF was mild and little or no additional toxicity was seen in the majority of patients after infusion of MDX-H210. However, in responders, Grade 3 toxicity was seen in both renal cancer patients and in one prostate cancer patient (James N, etal, ASCO98, Abs. 1681:434a).

MDX-H210 is also being investigated in a phase Ia/Ib trial (protocol IDs: MDX-DMS-9318, NCI-V94-0450), administered by IV infusion on days 1, 3, and 5, plus interferon γ (IFN-γ) on days 0, 2, and 4 of weeks 1-3, to patients with metastatic adenocarcinomas expressing the HER2/neu antigen, including prostate cancer. Medarex is also clinically evaluating another bispecific, MDX-447, in solid tumors that overexpress EGFr (see FO, pp 322-23), including HRPC.

ANTISENSE STRATEGIES

Genta

Genta (San Diego, CA) is developing Anticode G3139, an 18-base fully phosphorothioated antisense oligonucleotide that targets the anti-apoptosis bcl-2 gene. In December 1997 Genta initiated a phase I/IIa clinical trial (MSKCC-97096, NCI-G97-1337, GENTA-G3139-97/01) in HRPC at Memorial Sloan-Kettering Cancer Center under PI Howard Scher, MD. Part 1 of this trial will accrue a maximum of 30 patients, and Part 2, 15 patients, for a maximum of 45 patients. Patients are entered in cohorts of 3 to be administered G3139 IV for 14 days, followed by a 4 week rest for up to 3 courses of therapy. Dose is then escalated in a new cohort until MDT.

In July 1998, the company initiated a new phase I/IIa clinical trial of G3139 at the Sidney Kimmel Cancer Center in metastatic HRPC, under the direction of John Gutheil, MD, to be funded under a CRADA the company established with the NCI in June 1998. The agent will be administered over longer periods of time than in previous trials, in combination with an androgen-receptor blocker.

Isis Pharmaceuticals

Isis Pharmaceuticals (Carlsbad, CA) is clinically evaluating two antisense constructs, ISIS 3521/CGP 64128A, a 20-base antisense phosphorothioate oligonucleotide inhibitor of protein C kinase (PKC)-α expression and ISIS 5132/CGP69846A, an inhibitor of C-raf kinase, in HRPC. In the phase II trials of ISIS 5132/CGP69846A, the compound is evaluated as a single-agent in a variety of solid tumors, including prostate cancer. This trial being conducted by cooperative groups in as many as 12 medical centers the USA, Canada and Europe, is enrolling up to 30 patients and will take about one year to complete.

A phase II randomized clinical trial (protocol ID CAN-NCIC-IND111) of ISIS 5132 and ISIS 3521 is also planned in HRPC under the auspices of the National Cancer Institute of Canada. This randomized study is to enroll 15-30 chemotherapy-naive patients who may continue LH-RH therapy while participating in this trial. Patients are stratified according to measurable disease (presence or absence) at the time of randomization and treated either with IV ISIS 3521 or ISIS 5132 for 21 days, repeated every 4 weeks in the absence of unacceptable toxicity or disease progression. Patients are followed at 4 weeks, then every 3 months until disease relapse or progression.

OTHER TREATMENT STRATEGIES

Cytotoxic Analogs of Somatostatin Containing Doxorubicin or its Derivative, 2-Pyrrolinodoxorubicin

Investigators at Tulane University and the Veterans Affairs Medical Center (New Orleans, LA) have created cytotoxic hybrid analogs of somatostatin (SST) such as octapeptides vapreotide (RC-160) or RC-121, linked to doxorubicin or its superactive derivative, 2-pyrrolino-DOX (AN-201). The respective cytotoxic conjugates are AN-163 and AN-258 for RC-160 and AN-162 and AN-238 for RC-121 *In vitro* tests on cell line PC-3, as well as several other cell lines from other tumors, demonstrated that the cytotoxic radicals in these conjugates retained their antiproliferative activity. Preliminary studies in animal models of breast and prostate cancer showed that AN-238 is less toxic than AN-201 but more potent in inhibiting tumor growth. These highly active cytotoxic analogs of SST are designed as targeted antitumor agents for the treatment of various cancers expressing receptors for SST octapeptides (Nagy A, etal, PNAS USA, 17 Feb 1998, 95(4):1794-9).

Macrophage Activating Factor

Investigators at Albert Einstein Cancer Center (Philadelphia, PA) and Hyogo College of Medicine (Hyogo, Japan) have successfully treated prostate cancer patients with vitamin D-binding protein (Gc protein)-derived macrophage activating factor (MAF). When activated via inflammation, macrophage can eliminate tumor cells but the inflammation-primed macrophage activation cascade requires serum vitamin D-binding protein (Gc protein). The MAF precursor activity of Gc protein is lost or reduced in cancer patients because Gc protein is deglycosylated by serum α-N-acetylgalactosaminidase (NaGalase) secreted from tumor cells and cannot be converted to MAF. Exogenously administered MAF can bypass the deglycosylated Gc protein and act directly on macrophages. Treatment of Gc protein with immobilized β-gal and sialidase generated the most potent MAF (GcMAF) ever discovered that produces no side effects in humans. When the efficacy of GcMAF was assessed by measuring serum NaGalase activity (serum NaGalase level is proportional to tumor burden), after 35 weekly administrations of 100 ng GcMAF the majority of 32 prostate cancer patients treated exhibited insignificantly low serum NaGalase levels equivalent to healthy controls. Undifferentiated/hormonally refractory cancers responded more favorably than differentiated and hormonally sensitive tumors. Symptoms associated with bone pain or urination difficulty improved after several weeks of therapy (Yamamoto N, etal, AACR98, Abs. #2425:355).

Photodynamic Therapy

Miravant Medical Technologies (formerly PDT; Santa Barbara, CA) is developing, in collaboration with Pharmacia & Upjohn, a photodynamic therapy system, PhotoPoint, which integrates the use of proprietary light-activated (photoselective) drugs, and proprietary light producing and delivery devices, to achieve selective photochemical destruction of diseased cells. Miravant obtained FDA approval in August 1998 to begin a clinical study of PhotoPoint using the photosensitized tin ethyl etiopurpurin (SnET2, Purlytin) for the treatment of localized prostate cancer. When SnET2 is exposed to the appropriate light wavelength, it acts as a catalyst to generate a highly reactive form of oxygen that destroys the membrane of the cells containing the drug. In animal studies, SnEt2 demonstrated greater uptake in the prostate than in surrounding tissues. In this application, SnEt2 is administered intravenously and light is delivered locally to the entire prostate to destroy cancer cells. PhotoPoint/Purlytin is under late stage clinical trials in several other cancers, including basal skin carcinoma, breast cancer and Kaposi's sarcoma.

PREVENTION STRATEGIES

Risk factors associated with prostate cancer include age, race, family history and such environmental factors as diet. Because of the observation that differences in the detection of latent cancer/prostatic intraepithelial neoplasia (PIN) do not vary as widely as do incidence and mortality associated with prostate cancer between a country of relatively low such rates as Japan, and high such rates as the USA, it has been assumed that environmental factors, primarily diet, plays a significant role in the accelerated transformation of PIN into bona fide prostate cancer. However, age remains the highest risk factor for prostate cancer; by the age of ≥70 incidence rates of prostate cancer are virtually the same for all races.

Aromatase Inhibitors

Because a role for estrogen in prostate neoplasia has been postulated, one chemopreventive strategy for this cancer is to decrease estrogen production (see liarozole, above).

Antioxidants

According to Warren Heston, PhD, speaking at CaP CURE97, investigators at Memorial Sloan-Kettering Cancer Center have come up with a scenario that links advancing age and the increased presence of oxidative species in aging cells, implicating oxidants in the development of prostate cancer. Processes in the prostate associated with aging that may increase risk of cancer, include:

- higher production of oxidants
- lower production of antioxidants
- enhancement of oxidant production by exposure to androgens
- increased production of nitric oxide
- folate deficiency

It was shown that oxidative byproducts of normal metabolism cause extensive damage to DNA, proteins and lipids. Mitochondrial DNA is damaged more than nuclear DNA (Ames B, etal, PNAS USA 1995, 92:5255) and mitochondria of aged animals produce higher levels of oxidants

than those of young ones (Hagen and Ames, PNAS USA 1997, 94:3064-69). Mitochondria in a "leaky" state in the aged are able to produce an increasing amount of oxidative molecules. Also, exposure of mitochondria in the prostate to androgen increases oxidation. In concert with increased production of antioxidants, the aged cell's antioxidant capabilities, which are present in all cells, diminishes. There is also significant nitric oxide synthase activity in the rat dorsolateral prostate with considerable nitric oxide being produced. Such activity was also detected in the transition zone but was much higher in the peripheral zone of the prostate where most human cancers develop. Nitric oxide can combine with superoxide anions to form peroxynatrate, a potent DNA damaging agent and a mutagen. Also, folate defficiency acts as a carcinogen. Folate deficiency in the prostate is the result of high levels of folate hydrolase (PSMA). Among antioxidants considered in prostate cancer are vitamins A and E.

Vitamin A originates from both plant (carotenoids) and animal sources. Studies using this vitamin remain inconclusive as to its benefits in preventing prostate cancer. Among the over 500 different carotenoids, one that is not converted to vitamin A is lycopene, a highly effective blocker of singlet oxygen found in various tissues including the prostate. One of the major dietary source of lycopene are tomatoes and tomato-based products that were shown to benefit men who include them in their diet. The role of another carotenoid, β-carotene, in prostate cancer is less well understood.

Vitamin E is also under investigation as a risk reducer in various cancers, as well as prostate cancer. For instance, a-tocopherol, one of eight naturally occurring forms of vitamin E and the most common source of dietary vitamin E, was found to have a protective effect in prostate cancer. In a clinical trial carried out in Finland, a modest daily dose of 50 mg of a-tocopherol reduced prostate cancer incidence and deaths by 32% and 41%, respectively (Heinonen OP, etal, JNCI, 18 Mar 1998, 90(6):440-6). The NCI is planning a follow-up trial to confirm these findings.

BRACHYTHERAPY VERSUS PROSTATECTOMY-AN UPDATE

Controversy regarding the merits of prostatectomy versus brachytherapy (see FO, pp 790-4) will continue in view of the results of a recent analysis of outcomes of 1,872 patients treated for prostate cancer between January 1989 and October 1997, with prostatectomy, radiotherapy or brachytherapy. This retrospective analysis concluded that, although men with low-risk disease faired equally well when treated with any of the three modalities, intermediate- or high-risk patients did somewhat better with either prostatectomy or radiotherapy (D'Amico AV, etal, JAMA, 16 Sep 1998, 280(11):969:74).

Editor's Note: *Because of space limitations the second part of our special review will continue in the next issue of FUTURE ONCOLOGY that will also incorporate Part I of an article on cervical cancer.*

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