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STATE-OF-THE-ART MANAGEMENT OF CANCER

PROSTATE CANCER, PART II

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MEETING COVERAGE

NEW DEVELOPMENTS IN THE TREATMENT OF ADVANCED COLORECTAL CANCER

FROM THE 32ND ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY PHILADELPHIA, PA, MAY 18-21, 1996

STATE-OF-THE-ART MANAGEMENT OF CANCER

PROSTATE CANCER, PART II

This report completes the monogram on prostate cancer; for detailed information on epidemiology, etiology, pathogenesis, staging, and treatment options for early, organ-confined prostate cancer; preventative approaches; and various advances in the treatment of prostate cancer reported at the 32nd Annual Meeting of the American Society of Clinical Oncology (ASCO96), please see FO, V2 #1, May 1996.

RESEARCH FUNDING SOURCES

The realization that the risk for prostate cancer is much higher than previously suspected and that it is likely to affect younger men, has brought this malignancy to the forefront, spurring funding from both public and private sources and accelerating basic, applied and clinical research. The proposed fiscal 1997 National Institutes of Health (NIH) budget of $3 billion provides "sufficient" funding for prostate cancer research compared to the current NIH reauthorization bill that earmarked $72 million for prostate cancer research, equal to that allocated for ovarian cancer, but 1/3 of the $225 million mandated for breast cancer. Also, in June 1996, an amendment was added to a Department of Defense (DOD) appropriations bill that would re-allocate $100 million ($93 million of new funding to supplement $7 million that had been allocated for intramural research) earmarked for peer-reviewed prostate cancer research to be administered by the U. S. Army. Intramural research on prostate cancer is being performed at the Uniform Services University (Bethesda, MD) where researchers maintain a comprehensive database of over 2,500 prostate cancer patients treated at Walter Reed Army Medical Center (Washington, DC).

Another new source of research moneys is the Association for the Cure of Cancer of the Prostate (CaP CURE; Santa Monica, CA), founded in 1993 by Michael Milken and supported by the Milken Family Foundation. Leading the effort at the institutional side is Dr. Leroy Hood of the University of Washington (Seattle, WA). To date CaP CURE has awarded $10 million in grants and is currently soliciting additional proposals for basic and/or clinical research in advanced prostate cancer. CaP CURE is also providing funding for a national tissue bank to procure prostate tissue samples to aid researchers in their search for cancer-related compounds. CaP CURE is also supporting the Prostate Cancer Genetic Research Study (PROGRESS) spearheaded by Fred Hutchinson Cancer Center (Seattle, WA) that is aiming to identify genetic patterns of prostate cancer by studying as many as 1,000 families with three or more members diagnosed with the disease at an early age. The Center of Genome Research at the NIH (Bethesda, MD) is also trying to map the location of prostate cancer genes as part of the Hereditary Cancer Study in collaboration with Johns Hopkins (Baltimore, MD) that has established a hereditary prostate cancer registry containing 2,000 families (also see FO, V2 #1, p 284).

UPDATE ON TREATMENT TRENDS

As indicated in Part I of this article, early prostate cancer is treated either by prostatectomy (and other options with localized effects) or by watchful waiting, when aggressive interventions do not seem to confer a survival benefit. Although more and more American men are diagnosed with early prostate cancer, the rate of prostatectomies did not increase proportionally, as was originally feared. Actually, statistics recently released by the National Center for Health Statistics, indicate a 15% decrease in radical prostatectomy procedures, from 53,000 reported in 1993 (see FO, V2 #1, Exhibit 10) to 45,000 in 1994.

Patients with advanced disease at presentation are treated by hormonal therapies and those who relapse or are diagnosed with hormone-refractory prostate cancer (HRPC), are treated with various chemotherapy and radiotherapy modalities. Exhibit 1 estimates that approximately 195,000 patients are treated by such therapies annually in the USA, Europe and Japan.

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Exhibit 1
Patients with Prostate Cancer Treated by Drug Therapy (1995)

Country	Deaths (excl. 1st year) (#)	Advanced Stage (#)	Other Stages (#)	Total Drug Candidates (#)
Western Europe EEC	46,888	29,429	180,777	76,317
Western Europe non-EEC	6,524	3,924	24,107	10,449
Eastern Europe[1]	7,966	4,398	27,016	12,364
Total Europe[1]	61,378	37,751	231,900	99,129
Total Former USSR	8,766	6,655	40,881	15,421
Total North America	42,612	46,949	288,401	89,561
Triad (Europe[1], Japan, N. America)	108,103	87,589	538,045	195,691

[1]Excluding the former USSR

HORMONAL THERAPIES

The endocrine control of prostate growth is complex. Luteinizing hormone-releasing hormone (LHRH) stimulates pulsatile production and release of luteinizing hormone (LH). LH, in turn, stimulates production of testosterone by the Leydig cells of the testis, through regulation of a series of biosynthetic enzymes which convert cholesterol to testosterone. Within the prostate gland, testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5 α-reductase. DHT is a more potent androgen than testosterone in the prostate. The prostate is dependent on DHT for growth and normal function. For instance, in men with hereditary deficiencies of 5 α-reductase, prostate size is significantly reduced. DHT mediates its activity through the androgen receptor (AR), resulting in prostate cancer growth.

Hormonal Manipulation Options

All forms of hormonal manipulation of prostate cancer, presently in use, can be placed within this framework. Orchiectomy removes the major source of testosterone, and thus the major source of DHT. Low dose estrogens such as diethylstilbestrol (DES), inhibit LHRH secretion by the hypothalamus and LH secretion by the pituitary, inhibiting testosterone secretion.

Luteinizing hormone-releasing hormone (LHRH) agonists inhibit LH secretion from the pituitary through abolition of pulsatile LHRH stimulation. Luprolide acetate (see Exhibit 2), an LHRH analog, is currently available in more than 50 countries for the treatment of prostate cancer. It is sold as Lupron or Lupron Depot by TAP Pharmaceuticals (Deerfield, IL) in the USA, and as Leuplin by Takeda in Japan, where it was launched in September 1992 as a once-monthly injectable formulation Abbott Laboratories markets leuprolide in Canada, Latin America and Europe. An application for a dual-chamber prefilled syringe (CPS) kit designed for easier handling, was filed in Japan in March 1995, and in the USA and Europe; it was approved in Germany in March 1995. An application for a once-quarterly injection dosage formulation for treating prostate cancer was filed in December 1994 in the USA and in Europe. Additional indications for the drug include endometriosis and central precocious puberty, breast cancer and uterine fibroids. Other LHRH analogs on the market include Decapeptyl, marketed by various companies outside North America and Zoladex (Zeneca).

Antiandrogens include:

- "mixed" agents such as cyproterone or medroxyprogesterone that inhibit LHRH secretion by the hypothalamus, LH secretion by the pituitary, and DHT binding to its receptor
- "pure" antiandrogens such as flutamide, nilutamide, and bicalutamide that directly inhibit binding of DHT to its receptor

Adrenal suppression by aminoglutethamide or ketoconazole inhibits adrenal androgen synthesis and thus can block up to 40% of DHT present in the prostate. Finally, "combined" therapy with hormone ablation and a pure antiandrogen can both suppress testosterone production as well as DHT binding to its intraprostatic receptor.

Hormonal Ablation Therapy

Hormone ablation therapy (HAT) represents one of the most effective palliative therapies in medical oncology, with at least 80% of patients responding to HAT with decreased bone pain, shrinkage of metastatic lesions, and improved sense of well being. Low dose estrogens, LHRH agonists, and orchiectomy are equivalent in terms of rate of response, failure-free survival, and overall survival. The pure antiandrogens flutamide (Eulexin; Schering) and bicalutamide (Casodex; Zeneca) when used in combination with LHRH agonists result in a modest failure-free survival and overall survival benefit compared to LHRH agonists alone in men with metastatic (stage D2) prostate cancer and low disease burden. In particular, bicalutamide and flutamide may be equivalent in terms of failure-free survival advantage with LHRH agonists alone (Proc ASCO 15: 245, Abstr #619, 1996).

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Exhibit 2
Commercially Available Drugs for the Treatment of Prostate Cancer

Brand/Generic/(Number) Developer/ Affiliate(s)	Description/ Indication	Delivery/Dosage/Average Wholesale Price (AWP)	Comments
Casodex/bicalutamide (ICI 176334)/Zeneca	Antiandrogen/advanced prostate cancer in combination with an LHRH agonist (also under development as a monotherapy in early disease)	PO/50 mg/daily/$10.25 per 50 mg tablet (USA); $8.6 per 50 mg tablet (Italy)	Launched in the UK (5/95), the USA (10/95), and Ireland; approved in France, Canada, Finland, Denmark, Italy (6/96) and Switzerland (8/95); filed worldwide outside Japan; sales in 1995 are estimated at $15 million
Cyprostat, Androcur/ cyproterone acetate/ Schering AG	Antiandrogen/to mitigate side effects (testosterone flare, hot flashes) of HAT or orchiectomy and in refractory disease	PO	Available outside the USA since 1980; in early 1995, it was reported that cyproterone was associated with 66 incidences of serious hepatotoxicity resulting in 33 deaths in the UK, mostly in elderly patients on long-term therapy; it is currently recommended that cyproterone is used for only short-term therapy and in patients unresponsive to other agents
Cytadren/aminoglutethimide tablets USP/Novartis (Ciba-Geigy)	Adrenal steroidogenesis inhibitor	PO/initial therapy of 250 mg orally four times daily at 6-hour intervals/$1.085 for 250 mg	250 mg given 2x/day for 2 weeks followed by escalation over 3 months in 84 castrated prostate cancer patients resulted in no CR, 14% PR and 49% SD
Decapeptyl/triptorelin (AY-25650, BIM-21003, BN-52104,WY-42422)/ Debio Recherche Pharmaceutique/Tulane U (licensor), Pharmacia & Upjohn (licensee, NA)	Gonadorelin analog, LHRH agonist	PO (CR, SR) and depot	Launched in over 85 countries outside North America; NDA pending in the USA (1992 revenue was over $100 million)
Emcyt/estramustine phosphate sodium/ Pharmacia & Upjohn/ Hoffmann-La Roche (manufacturer)	Estramustine phosphate sodium, estradiol and nornitrogen mustard linked by carbamate/metastatic and/ or progressive prostatic carcinoma	PO/140 mg/kg given in 3 or 4 divided doses daily/ $2.92 for 140 mg	Launched in the USA (82) and worldwide
Eulexin (also Drogenil, Euflex, Eulexine, Flucinom, Flutamide, Fugerel, Odyne)/ flutamide (NK-601, Sch-13521)/Schering-Plough/ Nippon Kayaku	Acetanilid, non-steroidal active antiandrogen/ metastatic prostatic carcinoma (in combination with LHRH agonists)	PO/two capsules (125 mg each) three times a day (total daily dose of 750 mg) for all indications/ $1.55 for 125 mg	Launched WW for metastatic prostate cancer; launched outside the USA for metastatic (stage D2) prostate cancer; $290 million worldwide sales in 1995; supplemental NDA was approved in the USA on June 21, 1996 for the treatment of locally-confined stage B2-C prostate cancer
Doridamina/lonidamine (AF-1890, KN-228)/ Angelini and various licensees	Derivative of indazole carboxylic acid, potentiates anticancer drug activity/ prostate and breast cancer		Launched in Europe (Italy 86, Portugal 90)

— *continued on next page*

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Lupron Depot/leuprorelin/ TAP Pharmaceuticals (Abbott/Takeda jv)	Leuprolide acetate, an LHRH agonist/potent inhibitor of gonadotropin/advanced prostate cancer	Depot suspension/7.5 mg (depot formulation) monthly/$496.25 for 7.5 mg	Also approved in a three-month (84-day) 22.5 mg formulation in December 1995, based on an ANDA filed in December 1994; TAP will conduct phase IV to compare the two dosage forms
Lupron/leuprorelin (TAP-144SR)/TAP Pharmaceuticals (Abbott/ Takeda jv); Abbott and Takeda	Leuprolide acetate, an LHRH agonist/potent inhibitor of gonadotropin/advanced prostate cancer	Subcutaneous injection/1 mg (0.2 ml) daily/ $278.12 for 2 weeks	Launched in the USA (85) and in over 50 countries worldwide; marketed by TAP in the USA, Abbott in Canada, Latin America and Europe (Enantone) and Takeda (Leuplin, launched in Japan in 1992) elsewhere; patent expires in 1996; 1995 global sales (prostate cancer and gynecological diseases) for all formulations are estimated at $667 million
Metastron/strontium-89, strontium-89 chloride/ Zeneca, Amersham International (co-promoter)	Radiopharmaceutical/ pain palliation	IV (slow)/148 MBq, 4 mCi/ $241.5 for 10.9-22.6 mg/ml	Launched (9/95)/USA for bone pain associated with prostate cancer; ASCO96, Abs. 1748
Nilandron (USA), Anandron/ nilutamide (RU-23908)/ Roussel Uclaf (Hoechst)	Antiandrogen with a long duration of action	PO/50 mg tablet	Launched outside the USA, in France (87), South America; recommended for approval in the USA (2/95) for metastatic prostate cancer in combination with surgical or chemical castration
Stilphostrol/diethylstilbestrol (DES) diphosphate/Bayer (distributor); Akorn (manufacturer)	Diethylstilbestrol diphosphate/ prostate carcinoma	PO/starting dose 50 mg 3x/day; increase to 4 or more 50 mg tablets 3x/day; maximum daily dose must not exceed 1 gram/ $1.5 for 50 mg	
Suprefact/buserelin (Hoe-766, S-746766)/ Hoechst	Synthetic gonadorelin analog/ advanced prostatic cancer		Launched outside the USA, in Germany (84) and most European countries, the Far East
Zoladex/goserelin/Zeneca, Zeneca Yakuhin KK (Zeneca & Sumitomo jv; Japan)	Goserelin acetate implant, potent synthetic decapeptide analog of LHRH/prostate carcinoma, endometriosis, uterine fibroids	Subcutaneous injection/3.6 mg every 28 days administered into the upper abdominal wall/ $383.65 for 3.6 mg	Launched in the USA in 1989; available in 40 countries; launched in Japan in 1991; patent expires in 1997; WW sales were $223.5 million in 1993, $308 million in 1994 and $403.5 in 1995
Zoladex LA	Long acting formulation of goserelin	Long-acting 10.8 mg depot formulation administered every four weeks/UK cost is £366.81 per injection	Launched in Sweden and the UK and approved in France Finland and the Netherlands in 1995; ANDA filed in the USA (10/94)

The timing of HAT in the course of prostate cancer is controversial. Initiating HAT in earlier stage disease, or prior to metastatic symptoms, may lengthen the time to progression, but there is no evidence that early versus delayed hormonal therapy improves overall survival. Investigators who feel that allowing the tumor to grow increases the chances of random genetic instability in the tumor cells, resulting in a higher probability of devel-

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opment of an androgen resistant clone in the tumor, initiate HAT earlier in the course of the disease.

Maximal androgen blockade (MAB) consisting of an LHRH analog plus an antiandrogen, was first proposed in 1945. However, there is still unresolved controversy regarding the benefits of MAB versus LHRH analogs alone in the management of incurable prostate cancer. A meta-analysis of 22 randomized trials that compared conventional castration (surgical or medical) versus MAB (castration plus prolonged use of an antiandrogen such as flutamide, cyproterone acetate, or nilutamide), reported by the Prostate Cancer Trialists' Collaborative Group (Lancet, 1995 Jul 29, 346(8970):265-9), did not show that MAB results in longer survival than conventional castration. Within a median follow-up of 40 months, 3,283 (57%) of 5,710 patients studied died; crude mortality rates were 58% for castration alone and 56% for MAB and 5-year survival rates were 22.8% and 26.2%, respectively, representing a non-significant improvement of 3.5%.

Side effects associated with HAT include impotence, hot flashes, gynecomastia, weakness, and anemia. Most of these side effects are caused by reduction of serum testosterone. This has led to efforts at intraprostatic blockade of testosterone action with an antiandrogen which preserves peripheral testosterone levels. Flutamide monotherapy at 250 mg PO TID and Casodex monotherapy at 50 mg PO qD are likely inferior to LHRH agonist or orchiectomy in terms of progression-free survival, although patients who were sexually potent prior to therapy generally remained potent (Urology 46: 849, 1995). Current studies are underway to compare Casodex at a dose of 150 mg qD with orchiectomy or LHRH agonist. In addition, novel combinations of flutamide and finasteride (Proscar, Merck) have been tested as potency sparing HAT for prostate cancer (J Urol 154: 1642, 1995; Brufsky A, etal, Proc ASCO 15: 252 Abstr #645, 1996).

Costs of various forms of HAT vary widely. LHRH agonists are usually given as depot formulations monthly, although three-month formulations of Lupron Depot and Zoladex are also available. The average wholesale price (AWP) of one month of an LHRH agonist is approximately $300-$400. Monthly AWP of Casodex is approximately $250 and of Eulexin approximately $220. In contrast, generic DES is $6.30 for a one-month supply. It is estimated that HAT costs approximately $20,000 per year at the patient level; in contrast, the cost of an orchiectomy is approximately $4,000.

New Hormonal Therapies

Various hormonal therapies are in development including vaccine-like approaches discussed in the vaccine section of this report.

Alza (Palo Alto, CA) and its sister company, Therapeutic Discovery Corporation (TDC), are developing an implantable delivery system (DUROS) for luprolide. The DUROS implant has the capability of delivering large molecules, such as proteins and peptides, for up to one year.

Asta Medica (Frankfurt am Main, Germany) is developing cetrorelix, a LHRH antagonist, originally synthesized by A.V. Schally and colleagues at Tulane University (New Orleans, LA). Cetrorelix is a decapeptide containing 5 unnatural D-amino acids and was shown to be a potent LHRH-antagonist in various animal models; in animal models of sex-hormone dependent tumors (prostate and breast), a profound antitumor response was observed. The safety of cetrorelix was also confirmed in about 100 volunteers. Even in supraoptimal doses and after intravenous injections, none of the subjects had to be excluded due to side effects. Good bioavailability was also observed after subcutaneous injections (Reissmann T, etal, 15th World Congress on Fertility and Sterility, Bologna, Italy, September 15-16, 1995). The drug was shown effective as single therapy in patients with advanced carcinoma of the prostate and paraplegia caused by metastatic invasion of the spinal cord. In five patients cetrorelix, administered at two different dose regimens, resulted in regression of neurologic symptoms and improvement continued during treatment; at three months all of the patients were able to walk with the aid of a cane. These results show that cetrorelix causes an immediate lowering of serum testosterone levels in patients with prostate cancer metastasized to the spinal cord, in whom LHRH agonists cannot be used as monotherapy because of the possibility of flare-up and appears to be appropriate for long-term therapy (Gonzalez-Barcena D, etal, Urology, 1995 Feb, 45(2):275-81). In mid-1995 Asta Medica and Nippon Kayaku (Tokyo, Japan) extended their collaboration by forming a joint venture in Japan, Kayaku Asta Medica (Tokyo, Japan), to develop and market cetrorelix. Cetrorelix is in development for sex-hormone dependent tumors, stimulation of ovulation and BPH. Asta also formed a collaboration at the end of 1995 to develop and market Sugen's (Redwood City, CA) oncology products in Europe.

Boehringer Ingelheim (Ingelheim am Rhein, Germany) is developing novel potent steroidal inhibitors (CB7630) of the key enzyme, cytochrome P450(17) α, involved in androgen biosynthesis. Inhibition of this enzyme could prevent androgen production from both the testes and the adrenals, not achievable by medical or surgical castration. When such steroidal inhibitors were compared with castration, ketoconazole and flutamide in animal models, both flutamide and surgical castration significantly reduced the weight of ventral prostate and seminal vesicles, and CB7630 (abiraterone acetate) and CB7627, administered once daily for 2 weeks, also significantly reduced the weight of these organs, as well as that of kidneys and testes. Ketoconazole, on the same schedule, had no such effect. Plasma testosterone was reduced

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to ≤ 0.1 nM by CB7630, despite a 3- to 4-fold increase in the plasma level of LH. Adrenal weights, that remained unchanged following treatment with CB7630 or CB7627, were raised significantly following ketoconazole, indicating no inhibition of corticosterone production by these steroidal compounds (Barrie SE, etal, Journal of Steroid Biochemistry and Molecular Biology, 1994 Sep, 50(5-6):267-73). Boehringer Ingelheim is developing CB7630, under a license from BTG, currently in phase I clinical trials in hormone-dependent prostatic cancer.

Janssen Pharmaceutica Research Foundation (Johnson & Johnson; Titusville, NJ) is developing R 75251 (liarozole), which, like the orally-active antifungal ketoconazole (Nizoral), is an imidazole derivative. In high doses (400 mg three times a day), liarozole inhibits the biosynthesis of testicular and adrenal androgens. Liarozole binds to cytochrome P-450-dependent hydroxylating enzymes involved in steroid biosynthesis and retinoic acid catabolism. Ketoconazole, although also active in high doses, is associated with gastrointestinal side effects that limit its routine use. Liarozole's side effects are milder and, unlike ketoconazole therapy, adrenal androgen and cortisol levels are not modified. Liarozole is in phase III clinical trials in metastatic prostate cancer. In a phase I/II clinical trial involving 44 patients with metastatic prostatic cancer in clinical relapse, objective responses, including tumor volume reduction, occurred in approximately 30% of patients with measurable disease, PSA reduction of 50% or more was observed in approximately 50% and pain relief occurred in most patients (Mahler C, etal, Cancer, 1993 Feb 1, 71(3 Suppl):1068-73). Among 45 patients, administered liarozole (300 mg orally twice daily), there were three CRs, three more patients experienced reductions in PSA levels of ≥50%, and disease stabilized in 9 and progressed in 10 (Smith J, etal, ASCO96, Abs. 636:250).

Ligand Pharmaceuticals (San Diego, CA) is funding a sex steroid development program to identify agonists, partial agonists and antagonists of sex steroid receptors as drugs for hormonally-responsive cancers of men and women, hormone replacement therapies and treatment and prevention of diseases affecting women's health. Ligand has exclusively licensed the cloned human androgen receptor and is employing it to identify novel androgen receptor agonists and antagonists for the treatment of cancer and other indications. As of March 1996, Ligand had identified non-steroidal lead compounds from its internal screening program. An internally directed medicinal chemistry effort has produced potent, selective, patentable androgen receptor agonists and antagonists which show pharmacological activity *in vivo* in rodents. Ligand intends to pursue internally cancer applications of any compounds emerging from this research.

Organon (West Orange, NJ) acquired, in February 1996, an option to develop long-acting formulations of ganirelix, a GnRH antagonist originally under development by Roche Bioscience (previously Syntex; Palo Alto, CA) for the treatment of prostate, uterine and breast cancer and endometriosis and BPH. Organon is seeking a partner to co-develop this formulation. Ganirelix is in phase II clinical trials. Organon has also acquired an exclusive worldwide license to develop a short-acting form of ganirelix for the treatment of infertility.

Pharmacia & Upjohn (P&U; Kalamazoo, MI) acquired, in August 1995, exclusive marketing rights in the USA and semi-exclusive in Canada and Mexico to triptorelin, an LHRH agonist developed by Debio Recherche Pharmaceutique (Martigny, Switzerland), a subsidiary of the Debio Group (Lausanne, Switzerland). Treptorelin is marketed in Europe (in 85 countries worldwide) for the treatment of prostate cancer and endometriosis. It is in phase III clinical trials in the USA in prostate cancer.

CURRENT THERAPEUTIC APPROACHES FOR LOCALLY ADVANCED AND LATE-STAGE PROSTATE CANCER

When prostate cancer spreads beyond the capsule, surgery is no longer curative. Rather, multimodality approaches combining external beam radiation with hormonal ablation therapy (HAT), or various chemotherapy regimens, alone or in combination, are used in an attempt to improve long-term disease-free and overall survival. Approximately 200,000 patients in the USA, Europe and Japan, progress to advanced disease annually and become candidates for chemotherapy (Exhibit 1). Hormonal and other therapies approved for the treatment of prostate cancer worldwide are listed in Exhibit 2. Use of these agents, alone or in combination, is predicated by the stage of the cancer and patient age and health status. Additional information on combination chemotherapy and multimodality therapy is presented in Exhibit 3 and also reported in FO, V2 #1, pp 298-300.

Treatment of Locally Advanced Prostate Cancer

Patients with locally advanced (stage C or T3N0M0/T4N0M0) disease who have a poorer prognosis than those with earlier stage disease, generally do not benefit from radical prostatectomy. Long term control of disease and failure-free survival are achieved with external beam radiotherapy, but more than 50% of patients eventually die of their disease. HAT, consisting of an LHRH agonist and an antiandrogen, is an option in these patients, especially those with urinary obstruction. Therapeutic modalities currently in clinical trials for locally advanced prostate cancer include immunotherapy with PEGylated IL-2 followed by radical prostatectomy, three-dimensional conformal radiotherapy, neoadjuvant HAT followed by radical prostatectomy, cryotherapy, and combination of interferon-α and 13-cis retinoic acid.

Schering-Plough's Eulexin (flutamide, oral) was approved by the FDA on June 21, 1996, in combination with LHRH agonists, for the management of locally con-

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Exhibit 3
Selected Combination Chemotherapy and Multimodality Therapy in Prostate Cancer

Phase/Type of Therapy	Results	Reference
Phase I/estramustine (140 mg PO tid on days 1-14) + vinorelbine (escalating dose 15-25 mg/m^2 IV on days 1 and 8), repeated first every 28 days and then every 21days	Among 12 evaluable patients with HRPC, PSA declined > 50% in six (50%), pain scores improved in seven (58%); toxicity was mild	Reese D, etal, ASCO96, Abs. 673:259
Phase II/estramustine (2 140 mg capsules three times a day) + etoposide (one 50 mg capsule twice a day) for 21 days every 28 days	This was an active regimen in hormone-refractory prostate cancer	Pienta KJ, etal, ASCO96, Abs. 681:261
Phase II/estramustine (600 mg/m^2/day IV during weeks 1-4 and 6-10) + vinblastine (4 mg/kg weekly as above) + strontium-89 (2.2 MBq/kg every 12 weeks)		Wehbe T, etal, ASCO96, Abs. 682:261
Phase I/estramustine (600 mg/m^2/day IV) + escalating doses of paclitaxel (70, 135, 175, 210 mg/m^2) by 3-hour infusion every three weeks	This regimen demonstrated some activity against HRPC, but was associated with significant GI toxicity	Peereboom DM, etal, ASCO96, Abs. 690:263
Estramustine (12 mg/kg/day PO for 6 weeks) + vinblastine (4 mg/m^2 IV weekly for six weeks) on an 8-week cycle (minimum 3 cycles)	Among 4 patients with prostate cancer metastasized to the bone, 3 had a major response (PSA decline of >90% and at least 40% decrease of prostate gland), disease stabilized in one and morphine therapy was discontinued in two of the four	Kankonde, etal, AACR96, Abs. 662:256
Estramustine (600 mg/day) + doxorubicin (20 mg/m^2/ week by injection)	Among 21 chemotherapy-naive patients with HRPC, there were 3 PRs, disease stabilized in six, serum PSA normalized in five and declined by over 50% in eight; within a median duration of about one year 52% of patients died	Culine S and Theodore C, ASCO96, Abs. 700:266
[Ketoconazole (400 mg PO tid) + hydrocortisone (30 mg PO daily) on days 1-28] + [cyclophosphamide (100 mg /m^2 PO) added on days 1-14], every 28-days	Among 27 evaluable patients with elevated PSA, 78% experienced a ≥ 50% decline in PSA levels; this outpatient oral treatment was well tolerated	Pavlick AC, ASCO96, Abs. 698:265
Diethylstilbesterol (200 mg/day) + UFT (400 mg/day) continued for one year	Among 70 patients with newly diagnosed prostate cancer having undergone bilateral orchiectomy, cause-specific survival and non-progression was more favorable in this group compared to patients treated by DES alone	Kuryama M, etal, ASCO96, Abs. 707:267
Cis-platinum + adriamycin + carboquone	Among sixteen patients with stage D advanced prostate cancer (14 who relapsed from antiandrogen therapy and 2 with hormone-resistant disease), there were three PRs, disease stabilized in nine and progressed in four patients; mean response duration among patients with PR and with stable disease was 11.6 months; PR and stable patients survived significantly longer than nonresponders	Ito H, Nippon Ika Daigaku Zasshi Journal of the Nippon Medical School, 1995 Oct, 62(5):456-68

fined stage B2-C prostate cancer. Labeling recommends that this combination therapy should start eight weeks prior to initiating radiation therapy and last through its completion. The recommended dose is 750 mg daily, administered in three divided doses. Eulexin is commercially available for the treatment of stage D2 metastatic carcinoma of the prostate. The supplemental NDA was approved within six months of submission, illustrating FDA's intention to step up the approval process of oncology drugs that demonstrated activity in clinical trials. Multimodality therapy combining flutamide and LHRH agonists with radiation extended median disease-free survival of patients with stage B2 or C prostate cancer by 1.8 years (4.4 years compared to 2.6 for those on radiation

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therapy alone). When PSA levels were used as a criterion of disease-free status, median survival was 2.7 years for those on multimodality therapy compared to 1.5 years among controls.

The supplemental application incorporated results of a 471-patient randomized controlled clinical trial performed by the Radiation Therapy Oncology Group (Pilepich MV, etal, Urology, 1995 Apr, 45(4):616-23). Patients with large T2, T3, and T4 prostate tumors, but no evidence of osseous metastasis, were randomized to goserelin (3.6 mg subcutaneously every 4 weeks) and flutamide (250 mg orally three times daily) two months before and during the radiation therapy course compared with radiation therapy alone. Total pelvic irradiation administered was 65 to 70 Gy. Among 456 evaluable patients, 226 were treated with multimodality therapy and 230 by radiation alone. With a median potential follow-up of 4.5 years, cumulative incidence of local progression at 5 years was 46% among those on multimodality therapy compared to 71% in controls and 5-year incidence of distant metastasis was 34% and 41%, respectively. Progression-free survival rates, including normal PSA levels for 396 patients with at least one PSA recorded, were 36% and 15% at 5 years, respectively. In this trial no significant difference in overall survival could be detected but short-term androgen deprivation with radiation therapy resulted in a significant increase in local control and disease-free survival compared with pelvic irradiation alone in patients with locally advanced carcinoma of the prostate. There were no serious toxicities associated with the treatment.

Treatment of Metastatic Prostate Cancer

Metastatic prostate cancer (stage D or TXN1M0/TXNXM1) is presently incurable. Treatment is palliative, mostly involving HAT to reduce levels of intraprostatic androgens to castration levels, thereby reducing prostate cancer growth.

Treatment of Recurrent and Hormone-Refractory Prostate Cancer

Prostate cancer that recurs after radical prostatectomy or radiation therapy is considered incurable. Therapeutic options include careful observation, or early initiation of HAT. Some men will have a prolonged indolent course, but many will progress to overt metastatic disease within 5 years. If the recurrence is localized to the prostate, salvage radical prostatectomy can be attempted after radiation failure, but results are usually poor and complications frequent. Salvage radiation therapy after radical prostatectomy may provide some benefit for tumor bed recurrence in selected patients.

Prostate cancer, recurring after HAT, is usually associated with a poor prognosis, with a median survival of 9-12 months. If a patient has been on combined hormonal blockade, then a trial of antiandrogen withdrawal is warranted. PSA levels will decline in 25% of men and symptoms improve for a period of months after discontinuation of the antiandrogen. Androgen deprivation therapy before and during radiation therapy could, by reducing tumor volume, increase local tumor control, disease-free survival, and overall survival in patients with locally advanced adenocarcinomas of the prostate. The likely mechanism is stimulation of clones of tumor cells within the cancer which contain mutant androgen receptors, which then regress when the antiandrogen is withdrawn.

Secondary hormonal manipulation provides a modest benefit in a minority of patients. Ketoconazole appears to be modestly active in patients who have failed antiandrogen withdrawal (see FO, V2 #1, pp 299-230). A fraction of patients who have failed Casodex monotherapy, may respond to orchiectomy (ASCO96, Abs. 624:247). Megace (160 mg/day or 640 mg/day) has only modest activity in patients who have failed primary hormonal therapy (ASCO96, Abs. 601:241).

Finally, traditional cytotoxic chemotherapy provides little apparent benefit in hormone-refractory prostate cancer (HRPC). Many men with refractory prostate cancer are elderly with poor performance status, and trials of cytotoxics are difficult to perform in this population. Most agents exhibit minimal activity. Future advances in the therapy of recurrent and refractory prostate cancer will require a better understanding of the growth of the prostate cancer cell and also a better definition of HRPC. Great variability of responses among HRPC patients treated by various chemotherapeutic regimens suggest a need to classify patients on the basis of hormonal sensitivity based on objective criteria. Patients with a spectrum of prostate cancer subtypes and treatment histories are often classified as being "hormone-refractory" in clinical trials, confusing analysis of responses. A new classification based on hormonal sensitivity has been proposed to recognize that androgen-independent proliferation or progression of disease despite castration levels of testosterone does not necessarily mean that a tumor is refractory to hormonal manipulations (Scher HI, etal, Urology, 1995 Aug, 46(2):142-8). AntiCancer (San Diego, CA) reported in early 1995 that it developed a three-dimensional *in vitro* histoculture assay of androgen sensitivity in benign and malignant prostate disease.

Immunex (Seattle, WA) filed a supplemental NDA in May 1996 for Novantrone (mitoxantrone) for the treatment of HRPC, seeking priority review. The filing is based on two phase III trials, a pivotal 161-patient trial conducted in 11 centers, comparing Novantrone plus prednisone to prednisone alone, and a 245-patient trial of D2 hormone refractory prostate cancer, completed in 1995 (see FO, V2 #1, p 299) that compared Novantrone plus hydrocortisone with hydrocortisone monotherapy. Results of both trials showed that treatment with Novantrone demonstrated clinical benefit in reduction of pain and improvement in quality of life. Novantrone is already on the market in the USA as first-line therapy for acute myelogenous leukemia.

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Parke-Davis (Ann Arbor, MI) is developing suramin, a polysulfonated napthylamine, first synthesized by Bayer AG (Leverkusen, Germany) in 1916 and extensively used for the treatment of trypanosomiasis and onchocerciasis, for the treatment of HRPC. Suramin is in phase III clinical trials. Suranim appears to block growth factor signaling, competitively inhibit protein-kinase C activity, resulting in cell differentiation and decreased cell proliferation, and affect other proteins such as tumor necrosis factor and IL-2, among others. Suramin and many of its analogs were also shown to inhibit angiogenesis *in vitro* (Gagliardi A, etal, AACR96, Abs. 379:55). Suramin may induce apoptosis by inhibition of growth factor signaling and, in combination with adriamycin, circumvents bcl-2-associated drug resistance and may induce apoptosis in resistant malignant cell types with defective apoptotic pathways (Tu SM, etal, Cancer Letters, 1995 Jul 13, 93(2):147-55). Suramin also reduces bone resorption, hence its bone palliation effect in advanced prostate cancer.

A multicenter phase III, double-blind, placebo-controlled trial of suramin and hydrocortisone versus placebo and hydrocortisone began in February 1994, for metastatic HRPC using a fixed dosing schedule. As of early 1996, this ongoing study had accrued 304 (65%) of its 466 patient goal and remained blinded. Among 141 patients, grade 3/4 adverse effects occurred in 40%, with the most common being edema (9%), neurologic effects (9%), hematologic effects (8%), and malaise/fatigue (6%). The most common grade 1/2 adverse effects have been edema (46%), malaise/fatigue (42%), nausea/vomiting (40%), and rash (39%). Treatment was discontinued in 9% (Marshall ME, etal, AACR96, Abs. 1188). Suramin is administered either as a bolus injection (150-250 mg/ml) or as a continuous infusion (280-300 µg/ml).

British Biotech's (Oxford, UK) marimastat (BB-2516), a broad-spectrum matrix metalloproteinase inhibitor (MMPI), is the first orally available MMPI to be tested in humans. In a phase I/II study, 11 patients with advanced rapidly progressive HRPC following androgen deprivation, as confirmed by a rise in PSA levels of 25% or more over the 4-week period preceding study entry, were administered an escalated (25 to 50 mg) twice daily oral schedule of marimastat for a 4-week period or until dose limiting toxicity. There were no drug-related serious adverse events or deaths. Over comparable 4-week periods, median rate of PSA rise decreased from 44% before to 11% during treatment with marimastat. Marimastat produced an effect on PSA levels in 55% of the patients with minimal toxicity (Boasberg P, etal, ASC96, Abs. 671). Marimastat is in evaluation for a variety of solid tumors (also see FO, V1 #7/8, p 194).

ADJUVANT AND COMBINATION THERAPIES

Adjuvant Therapy Post Surgery/Radiotherapy

Various strategies are under development as adjuvant therapy for prostate cancer after radical prostatectomy or radiotherapy to eliminate any residual cancer, extend disease-free survival and prevent disease recurrence. Most promising among such approaches is immunotherapy/vaccination, discussed later in this report. Others include various immunoconjugates (prostate-specific monoclonal antibodies tagged with radioisotopes or toxins), and various gene therapy approaches.

Chemotherapy and Combination and Multimodality Therapies in Advanced Disease

Generally, monotherapy and combination chemotherapy have little activity in advanced disease (see Exhibit 3). Agents with modest activity against prostate cancer include estramustine, vinblastine, doxorubicin, and mitomycin-C. Combinations with modest activity currently in phase II trials include estramustine and vinblastine, estramustine and etoposide, and doxorubicin and ketoconazole. Newer agents, such as vinorelbine (Navelbine), taxol, and taxotere, alone or in combination with other agents, may also have activity against prostate cancer, as reported in preliminary clinical trials.

BONE PAIN PALLIATION

At presentation, approximately 25%-30% of prostate cancer patients have bone metastases that often cause deep, unremitting pain. Initiation of HAT relieves bone pain for a period of 16-18 months in about 75% of cases. (Parenthetically, painful bone metastases are also experienced by breast and lung cancer patients.) When HAT fails, palliative options for pain control include analgesics, chemotherapeutics, external-beam radiotherapy and radionuclide therapy. Chemotherapy usually results in a moderate, short-term effect. Radiotherapy is used when all else fails. Half-body irradiation may be effective in up to 70% of cases with diffuse painful metastases but it is associated with considerable toxicity. Intravenously-injected radioisotopes that preferentially localize to bone offer an effective means of bone pain palliation. One such agent, Metastron (Amersham), using strontium-89, is on the market and several companies are developing competitive products.

Researchers at the Department of Radiation Oncology, Wayne State University (Detroit, MI) conducted a survey among members of the American Society for Therapeutic Radiology and Oncology, to assess the impact of recent developments, including the introduction of Metastron, on the radiotherapeutic management of painful osseous metastases. Responses from 817 physicians indicated that strontium-89 was administered at a dose of 4 mCi (73%) or 10.8 mCi (26%) whereas the most commonly used external beam fractionation protocol was 30 Gy in 10 fractions (59%). Survey results suggested a new trend in the radiotherapy of bone metastases that used local-field radiation for site-specific bone palliation combined with systemic radionuclide administration for occult metastasis (Ben-Josef E, etal, ASCO96, Abs. 1655:514).

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Other products in late stages of development use rhenium-188 or samarium-153; an agent based on Sn-117 is in an earlier stage of development. One advantage of the new agents is that they can be imaged in bone because the isotopes are gamma-ray emitters. The ability to obtain an image offers an immediate quality control check assuring that the injected therapeutic dose is delivered properly. Metastron does not offer this capability. Also, all of the bone pain palliation agents cause bone marrow toxicity but, at the dose levels administered, this effect is usually not clinically significant.

Some of the information presented below has been obtained from attendance at the 43rd Annual Meeting of the Society of Nuclear Medicine, held in Denver, CO, on June 3-6, 1996.

Amersham International

Amersham International (Buckinghamshire, UK) markets Metastron, the first radionuclide-based agent to be approved for bone pain palliation. The active therapeutic isotope in Metastron is strontium-89 which is a pure beta-emitter with bone penetration of 0.8 cm. It is a calcium analog radionuclide that imitates the biodistribution of calcium *in vivo* and is selectively absorbed at bone locations with increased osteoblastic activity, such as bony metastases, where it has a biologic half-life of just over 50 days. Metastron was introduced in the USA in mid-1994 and has been well received clinically. In multiple clinical trials of systemic radionuclide therapy using strontium-89, response rates exceeded 80% resulting in a significant improvement in analgesia requirement, time to further radiotherapy, and a reduction in tumor markers in patients with prostate cancer. Use of Metastron is not without retractors, however. Some investigators report only a 33% response and that 20% of those treated experience more severe pain.

Mallinckrodt

Mallinckrodt (St. Louis, MO) is developing a bone pain palliation agent using rhenium-188 which has completed phase III clinical trials; an NDA was filed in mid-1995. This agent comprises a phosphate compound which exhibits an affinity for bone, labeled with rhenium; it functions similarly to MDP (labeled with technetium) used for bone imaging. Rhenium is shorter-lived than strontium so that onset of pain relief with rhenium is earlier, but the duration is shorter and more injections are required to get the same therapeutic effect. Two injections are usually administered, separated by about a month, to allow the clinician to assess the agent's effectiveness before administering the second dose. If the agent does not work effectively, a second dose is not delivered, thus minimizing total radiation exposure.

Cytogen

Cytogen (Princeton, NJ) acquired, in 1994, rights to a bone pain palliation agent developed by Dow Chemical (Midland, MI). This product, Quadramet (samarium-153 EDTMP), is a stable complex of samarium and a tetraphosphonate chelator, EDTMP, that targets bone and concentrates in areas that have been invaded with tumor. Quadramet emits both a beta particle (therapeutic component) and a gamma photon (imaging element) and has a physical half-life of 46.3 hours. The beta particles in Quadramet are less energetic than those in strontium and do not injure tissue that is remote from the source. Quadramet has completed all three phases of human clinical studies, and an NDA was filed in August 1995. Cytogen has licensed DuPont Merck (Wilmington, DE) as its primary marketing partner for Quadramet. Cytogen has the right to supplement DuPont's efforts by co-promoting the product to nuclear medicine specialists. DuPont Merck will be the commercial supplier of the product, which will be ordered by the patient's physician and administered by the nuclear medicine physician on an outpatient basis. Eventually, Quadramet may be distributed by Syncor (Chatsworth, CA) under its agreement with DuPont (see FO, V1 #12, p 279).

Diatide

Diatide (Londonderry, NH) is developing a bone pain palliation agent, Sn-117m DTPA, under a worldwide license from Brookhaven National Laboratories (NY). According to Diatide, the significant difference between this agent and all others described here, is that the latter are beta emitters that presumably travel a longer distance and go through the cortex of the bone (and through the bone marrow), thereby depleting white blood cells in the process. These dose-limiting toxicities may compromise their potential effectiveness. In contrast, Sn-117m DTPA, acts via a conversion electron, which has a penetration of approximately 0.3 mm. Tin has a natural affinity for bone and, because the conversion electron of tin has a very short range, it does not go through the bone marrow. Diatide researchers have demonstrated that this agent produces less myelosuppression than other products in development. Diatide's product may also have a wider application potential because it may be effective in the treatment of breast or lung cancer patients who may not tolerate bone marrow toxicities of radionuclides such as strontium, samarium or rhenium. Sn-117m DTPA is administered by infusion on an outpatient basis and provides pain relief for 6 to as long as 15 months without requiring reinjection. The agent has recently completed phase II trials, and Diatide is evaluating the results prior to entering phase III trials.

NOVEL DRUGS IN DEVELOPMENT

New biologic therapies such as PSA vaccines, human autologous prostate tumor vaccines expressing granulocyte-macrophage colony stimulating factor (GM-CSF), novel steroid hormone receptor ligands, and antisense oligonucleotide drugs, all represent potential approaches for the treatment of recurrent and refractory prostate

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cancer. Numerous agents targeting solid tumors based on various mechanisms (anti-angiogenesis, apoptosis promotion, cell cycle regulation, etc.), currently in research, preclinical, and early-phase clinical trials will also have applications in the treatment of all stages of prostate cancer. Exhibit 4 presents a database of selected drugs in development for the treatment of prostate cancer.

Identification of Genes Implicated in Prostate Cancer

Genes implicated in prostate cancer may either be inherited, resulting in familial patterns of disease transmission, or be involved in tumorigenesis because of acquired defects such as mutations, or deletions, among others (see FO, V2 #1, pp 284-286). Discoveries in this area promise not only to potentially lead to gene therapy-based treatments for prostate cancer in the long-term, but also improve how the disease is diagnosed and treated in the short-term. For instance, a recent finding by researchers at Dana-Farber Cancer Institute (Boston, MA) lead by Philip Kantoff, that structural variations in the gene encoding the androgen receptor (AR) molecule is a heritable factor that affects the development of prostate cancer, may improve prognostic evaluations of the disease. Androgens bind to this receptor, which regulates expression of certain genes in prostate gland cells and influences cell growth. The AR gene contains a polymorphic CAG repeat sequence, with repeats ranging normally from 8-31 (average 20) in different men. By testing blood samples collected from men participating in the 22,0710-member Physicians' Health Study, researchers compared findings from 368 patients with prostate cancer to an equal number of age-matched controls and discovered that GAG repeat length inversely correlated with cancer stage, i. e. the shorter the repeat the more advanced or more aggressive was the cancer. For every six fewer repeats, the relative risk of either stage C or D prostate cancer and/or high grade disease was 0.66 and the relative risk of developing distant metastasis was 0.41 (Giovannucci E, etal, ASCO96, Abs. 646:252).

One strategy for the development of novel therapeutics with broad applications is modulation of signal transduction pathways determined by human genes that play pivotal roles in the initiation and/or progression of prostate cancer. Once such genes are identified by structural genomics, their signal transduction pathways are elucidated by functional genomics and various approaches may then be employed to inhibit or enhance their activities. Various oncogenes and tumor suppressor genes have been implicated in prostate cancer (see FO, V2 #1), including the ubiquitous p53 tumor suppressor gene. Mutations of p53, found in over 50% of all human cancers, are implicated in aberrant cell cycle regulation and inhibition of apoptosis (see FO, V1 #1, pp 22-32). Numerous companies are pursuing programs associated with various approaches to mitigate p53-associated tumorigenesis and malignant progression, that may give rise to therapeutics with broad applications.

Centocor (Malvern, PA) was awarded a CRADA by the National Institute of Environmental Health Sciences (NIEHS) in 1995, to develop antibodies to a 267-amino acid glycoprotein belonging to the TM4 family of cell proteins, produced by a recently cloned prostate-specific metastasis suppressor gene on human chromosome 11p11.2 (Science 268: 884, 1995). The gene, named kang-ai (Chinese for anti-cancer) or KAI1, is identical to the gene product recognized by the antibody to the mononuclear cell antigen CD82, and may be involved in transmembrane signaling to the intracellular cytoskeleton to inhibit prostatic epithelial cell growth. Loss of such a molecule may render a prostatic epithelial cell unable to sense surrounding cells that would normally inhibit its growth. A reduction of KAI1 RNA was observed in prostate cancer samples compared to normal tissues; in 82% of cases of primary and metastatic prostate cancer samples, KAI1 expression was significantly reduced and was absent in four samples of metastatic prostate cancer (Dong J-T, etal, AACR96, Abs. 4084). Centocor and NIEHS are collaborating in the development and commercialization of monoclonal and polyclonal antibodies to KAI1 glycoprotein which will be used to correlate expression of this glycoprotein with the clinical course of prostate cancer and, possibly, other malignancies in patients with localized disease.

Genset (Paris, France), established in 1989 issued an IPO in May 1996. Genset, which specializes in genomics research, has entered into a strategic alliance with Synthelabo (Paris, France) to discover prostate cancer-associated genes. The company has exclusive access to a large collection of DNA samples from affected families and unrelated individuals, as well as DNA and RNA samples from healthy and diseased prostate tissues provided by urologists at the Hôpital Saint-Louis (Paris, France). These samples, together with related clinical data, were collected from a network of facilities throughout France. This network is being expanded to include samples from other European countries. Synthelabo has agreed to fund this alliance for up to $69 million if certain milestones are achieved, culminating in the commercialization of at least two small molecule drugs for prostate disease. Genset retains rights to development of therapeutics based on oligonucleotides and gene and cell therapies for prostate and other diseases and diagnostics.

LXR Biotechnology (Richmond, CA) is developing mammary proteinase inhibitor (maspin), LXR023, for the treatment of metastatic breast cancer and other solid tumors such as prostate cancer, under an exclusive license from Dana-Farber Cancer Institute. Diagnostic applications are also being pursued under a co-exclusive arrangement. In February 1996 the U.S. Patent and Trademark Office issued a patent to LXR covering maspin.

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Exhibit 4
Novel Drugs in Development for the Treatment of Prostate Cancer

Primary Developer/ Affiliates	Generic Name/ Number/Brand Name	Drug Type/Target/ Mechanism/Delivery	Status/Location/ Indication	Comments
Abbott Laboratories	A63162	Selective inhibitor of the arachidonic acid metabolizing enzyme, 5-lipoxygenase/inhibits human prostate cancer cell proliferation and induces apoptosis	Preclin (5/95)/USA/ androgen-independent prostate cancer	ASCO95; Abs. 22:79
Agouron Pharmaceuticals/Cancer Research Campaign, U Newcastle	AG337/Thymitaq	Thymidylate synthase inhibitor/ IV, PO, IP, oral	Phase II (c4/96)/USA (AACR96, Abs. 1176: 171)	Phase III (11/95)/ USA/head & neck and primary liver cancer; also see FO,V1 #2/3, #4, #12
Alfacell/NIH	P-30/Onconase	Microtubule inhibitor/15 kD protein isolated from oocytes and early embryos of Rana pipiens	Preclin (4/96)/USA	See FO,V1 #2/3, #4
Allergan Ligand Retinoid Therapeutics	9-cis-retinoic acid/ ALRT-1057, LG-1057, LGN-1057, LGD-1057	Chemically synthesized retinoid analog/binds to both retinoic acid receptors (RARs) and retinoid "X" receptors (RXRs)/inhibits cell proliferation and induces apoptosis and cell differentiation/PO	Phase IIb (planned)/ USA	LGD-1057 analogs are also being developed
Alza (Therapeutic Development Corporation)	DUROS	Drug delivery implant to administer leuprolide for one year	Clinical/USA	
Amira (Repligen)	Cyclocreatine (Ccr)	Creatine analog; substrate for creatine kinase (CK), an enzyme involved in cellular ATP homeostasis and may play a role tumorigenesis	Phase I/USA/solid tumors high in CK	Ara G and Teicher BA, AACR96, Abs. 2695; Winslow ER, etal, AACR95, Abs. 2336; Hoosein NM, etal, Anticancer Research, 1995 Jul-Aug, 15(4):1339-42
Aphton	Gonadimmune	Antihormone immunogen/ blocks GnRH secretion	Phase I/USA, UK	
Asta Medica/ Nippon Kayaku, Tulane U (licensor)	Cetrorelix/SB-075, SB-75	Decapeptide LHRH antagonist/ SC	Phase II (4/96)/ Germany/hormone-dependent prostate cancer	
Avigen/U Manitoba; Baylor College of Medicine	(Avipro)	Immunostimulant/AAV vector delivers an IL-2 gene directly into tumor using prostate-specific promoter (PSP)	Preclin (5/96)/USA	
British Biotech	Marimastat/BB-2516	Matrix metalloproteinase inhibitor/oral	Phase I/II (3/96)/ UK, USA	ASCO96, Abs. 671; also see FO,V1 #2/3, #4
BTG/Boehringer Ingelheim (licensee), Cancer Research Campaign	Abiraterone acetate/ CB7630	Steroid/inhibits cytochrome P450(17) α (17 α-hydroxylase/ C17-20 lyase)/prevents androgen production by the adrenal glands/ parenteral	Phase I (2/96)/UK/ hormone-dependent prostate cancer	
Cambridge Antibody Technology and Techniclone International (50/50 jv)		Humanized MAb immunoconjugates using Techniclone's Tumor Necrosis Technology to anchor a toxic payload (e.g. a radioisotope or drug) to the necrotic core of solid tumors	Preclin/USA, UK	

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Canji (Schering Plough)	PTSG	Gene therapy	Research (2/96)/USA	
Carrington Laboratories	Acemannan/CARN 750/ Alvonex	Highly acetylated, polydispersed linear mannan obtained from the mucilage of *Aloe vera*/injectable	Phase I (12/95)/USA	
Cellcor (Cytogen)	Autolymphocyte therapy, ALT, CD8	Extracted lymphocytes such as killer and helper T cells are activated non-specifically *ex vivo* and then returned to the patient to target cancer cells/*ex vivo*	Phase I/USA	
Cell Genesys		Stem cell gene therapy/stem cells genetically-engineered *ex vivo* with tumor specific receptors	Preclin/USA	
Cell Pathways	FGN-1	Sulfone metabolite of the NSAID sulindac; organic molecule/ apoptosis inducer	Preclin (2/96)/USA	See FO,V1 #1 & #2/3
Cell Therapeutics/ Cancer Research Campaign, Memorial Sloan-Kettering	CT-2584, CT-2583, CT-2586, CT-3536	Low molecular weight phospholipid signaling inhibitors/ alter production of phosphatidic acid (PA), an intracellular second messenger involved in a variety of agonist stimulated cell growth and activation responses/parenteral	Phase I (12/95)/UK, USA/refractory prostate cancer	See FO,V1 #2/3 & #5
Cel-Sci	Multikine	Immunotherapy/consists of IL-2 and a number of different cytokines manufactured by harvesting the supernatant in which white blood cells are stimulated to elicit these cytokines as part of natural immune responses/intralesional	Phase I (5/96)/USA;	Clinical (2/96)/USA, Canada/head and neck cancer
Centocor/National Institute of Environmental Health Sciences (NIEHS) (CRADA 1995)		Monoclonal and polyclonal antibodies to glycoprotein produced by KAI1, a prostate-specific metastasis suppressor gene on human chromosome 11p11.2/may be involved in transmembrane signaling to the intracellular cytoskeleton to inhibit prostatic epithelial cell growth	Preclin/USA/ localized prostate cancer and possibly other malignancies	
Cephalon & Kyowa Hakko (licensor)/ TAP Pharmaceuticals (USA rights)	KT-8391, CEP-2563 (ester of CEP-751)	Small-molecule/receptor tyrosine kinase (RTK) inhibitor	Phase I (b96)/USA	
Cytel/Sequel	Theradigm-MAGE 3/ CY-2010	Small antigenic peptides/targets MAGE-3/injectable	Phase II/USA/ solid tumors	
Cytel	Theradigm-PSA	Targets PSA/injectable	Research/USA	
Cytel/Takara Shuzo (Japan)		Adoptive immunotherapy/ *ex vivo*	Research/USA	
Cytogen	OncoRad PR/ CYT-356-Y-90		Phase II (4/96)/USA	
Cytogen/Dow Chemical (licensor), U Missouri (developer), DuPont Merck Pharmaceutical (licensee, USA manufacturing & marketing)	Samarium, samarium EDTMP/Sm-153-EDTMP, CYT-424/Quadramet	Beta-emitting radionuclide with chelating agent/injectable	Phase III (c3/95)/USA, Europe; NDA (8/95)/ bone pain from metastatic prostate cancer; phase II (b95)/ USA/treatment of prostate cancer metastasized to the bone	ASCO96, Abs. 1654:514

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Diatide/Brookhaven National Laboratories (licensor)	Sn-117m DTPA	Radionuclide; tin radioisotope combined with DTPA chelating agent/injectable	Phase II (c96)/USA	
Elan/NCI	Phenylacetate, NaPA, NaPB, phenylbutyrate, sodium phenylacetate, sodium phenylbutyrate/EL-530	Metabolite of phenylalanine/ regulates gene expression through DNA hypomethylation; activates nuclear receptors that act as transcriptional factors, inhibits mevalonate decarboxylation and protein isoprenylation; depletes glutamine/parenteral (bolus and IV)	Phase II (b8/94)/ USA/HRPC; preclin (b8/94)/USA/ adenocarcinoma of the prostate	See FO, V1 #6; ASCO96, Abs. 288, 1539, 1542
Eli Lilly	LY320236		Phase I/USA	Also phase I for BPH
EntreMed/Children's Hospital, Boston (developer); Bristol-Myers Squibb (ww licensor)	Thalidomide analogs	Angiogenesis inhibitor/ blocks TNF-α formation	Phase II/USA	See FO, pp 190, 195, 196, 269 & 275
Europeptides (Mediolanum/ Pharmascience jv)	Antarelix/EP-24332	LHRH antagonist peptide	Phase I (5/94)/Italy	
Europeptides (Mediolanum/ Pharmascience jv)	EP-23904/Meterelin	Nine amino acid LHRH agonist	Phase I (5/94)/Italy	Phase I (5/94)/Italy/ breast cancer, endometriosis
Genome Therapeutics		Identification of genes associated with prostate cancer		
Glaxo Wellcome	1209W95	MAb	Preclin (11/95)/USA	Preclin (9/95)/USA/ lung, gastric cancers
Glaxo Wellcome	3622W94	MAb	Preclin (11/95)/USA	Preclin (9/95)/USA/ lung, gastric cancers
Glaxo Wellcome	GG211, GI-147211A, GI-147211C	Water soluble topoisomerase I inhibitor/bolus	Phase I/II (11/94)/ USA	Phase I/II (11/94)/ USA/breast, colon cancers (FO,V1 #2/3)
Glaxo Wellcome	GI-111924	C17-20 lyase inhibitor	Phase I (11/95)/USA	
Harrier	HAR7	Synthetic camptothecin derivative	Preclin/USA	
Hoffmann-La Roche	Vitamin D3 analogs	19-*nor* hexafluoride analogs/ bind to vitamin D_3 receptor/ inhibit clonal growth	Research/USA	AACR96, Abs. 1688:247
Idun Pharmaceuticals	Bcl-2 inhibitor	Small molecule bcl-2 inhibitors	Preclin (1/95)/USA	
ILEX Oncology	Dihydro-5-azacytidine (DHAC)	Developed as an alternative to 5-azacytidine/inhibits methylation of ribosomal and transfer RNA/ may convert androgen receptor-negative prostate cancer cells into androgen receptor-positive cells/ injectable	Preclin/USA	Phase II (1/96)/USA/ mesothelioma
ILEX Oncology/ Hoechst Marion Roussel (licensor)	DFMO/Ornidyl (antiparasitic)	Ornithine decarboxylase (ODC) inhibitor/inhibits both tumor growth and progression/ injectable, PO	Phase II (1/96)/USA	Also being studied by the NCI as a chemopreventative
ILEX Oncology/Sanofi	Mitoguazone (MGBG), methy-G, methyl-GAG/ NSC-32946	Antimetabolite/polyamine biosynthesis inhibitor	Phase II (4/96)/USA/ HRPC	Produced minimal activity (ASCO96, Abs. 702:266); also see FO, V1 #11
ImClone Systems	Anti-EGFr chimeric MAb/ C225	Chimeric MAb against epidermal growth factor receptor (EGFr)/ inhibits uncontrolled cancer cell growth associated with this receptor's activity	Phase I (b12/94-c3/95) USA; phase II/ USA/in conjunction with doxorubicin	See FO, V1 #2/3, #4

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The Immune Response Corporation		Radiosensitizer; genetically modified fibroblasts to produce interleukin-3 (IL-3)/intratumoral	Preclin/USA	
Immunex	Mitoxantrone/Novantrone	Anthracenedione/IV	Supplemental NDA (5/96)/USA/HRPC	See FO,V2 #1, p 299; approved as first line treatment for acute myelogenous leukemia
ImmunoTherapeutics	GMDP-GDP/ImmTher	Immunomodulator/lipophilic disaccharide peptides related to muramyl dipeptide/liposome encapsulated:injectable	Phase II (5/95)/USA	See FO, V1 #2/3, #6
ImmunoTherapeutics	Longer acting version of ImmTher/ Theramide	Vaccine/induces cellular immunity	Phase I (5/95)/USA	See FO, V1 #2/3, #6
Janssen Pharmaceutica Research Foundation (Johnson & Johnson)	Liarozole, liarozote fumarate/R-75251, Ro-85264/Liazal	Imidazole derivative; cytochrome P450 inhibitor	Phase III (1/95)/USA, Europe	ASCO96, Abs. 636:250
Jenner Technologies/ Lankenau Hospital	OncoVax-P/JT 1001	PSA-based vaccine/purified recombinant PSA and adjuvant delivered in a liposome carrier	Phase I/II (10/95)/ USA	AACR96, Abs. 3258:477; ASCO96, Abs. 1809
Leo Pharmaceutical Products	KH1060, KH1266, CB1093 and CB1267 (most potent)	20-epi-1,25$(OH)_2D_3$ analogs/ inhibit clonal proliferation, reduce bcl-2 and increase bax expression	Research/USA	AACR95, Abs. 2640:387
Ligand Pharmaceuticals	3-methyl-TTNEB/ LGD-1069/Targretin Oral	Retinoid/binds selectively to RXR/PO	Phase II (planned)/ USA	See FO, V1 #4, #11
Ligand Pharmaceuticals	LG2293 series	Androgen antagonist	Preclin (95)/USA	
LXR Biotechnology/ Dana-Farber Cancer Research Institute, NCI	Maspin/LXR023	Tumor suppressor protein and gene; mammary serine protease inhibitor/binds to surface of invasive and metastatic tumor cells and restores normal function	Research (94)/USA/ metastatic prostate cancer	Preclin (94)/USA/ metastatic breast cancer
Mallinckrodt	Rhenium-186 editronate	A phosphate compound labeled with rhenium-186	NDA (95)/USA	
Matritech/ John Hopkins U School of Medicine, NCI	PC-I	Nuclear matrix protein/diagnosis, monitoring and possible treatment of prostate cancer	Research (96)/USA	See FO, V2 #1, p 290
Matrix Pharmaceutical	5-FU and epinephrine/ Intradose-FU injection/ MPI-5011	5-FU (300mg) in 10 ml of biodegradable gel-like matrix (purified bovine collagen)/intratumoral injection	Phase II (c95)/USA	See FO, V1 #2/3, p 61
Matrix Pharmaceutical	Cisplatin IntraDose/ IntraDose-CDDP injectable gel	Biodegradable gel-like matrix/ intratumoral injection	Phase II (b3/95)/USA	See FO, V1 #2/3, pp 56, 61
McNeil (Johnson & Johnson)/ NCI (NIH)	Fenretinide/McN-R-1967, HPR	Orally-active retinoid with antiproliferative activity/PO	Phase I (5/94)/USA	Phase III (5/94)/ USA, Italy/breast cancer
Medarex/Novartis (Ciba-Geigy; exclusive WW marketing rights), Chiron	MDX-210 Bispecific	Bispecific MAb conjugated to a trigger MAb/induces tumor cell killing by simultaneously binding to Her-2 on the surface of cancer cells and to a key receptor on immune system killer cells	Phase I/II (b5/95)/ USA	See FO,V1 #2/3 & #4
Medarex/Merck KGaA	H-447 Bispecific	Bispecific MAb/binds to epidermal growth factor receptor (EGFr)	Phase I (b9/95)/USA/ prostate cancer that overexpesses EGFr	

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Merck/Yamanouchi, Banyu, Neopharmed, Sigma-Tau, S. Riesel	Finasteride/MK-0906, MK-906, Ym-152/Proscar, Finastid, Procure, Prostide	Testosterone 5 α-reductase inhibitor/blocks conversion of testosterone to DHT	Phase III (5/94)/USA/ prostate cancer; phase II (b10/93)/ USA/chemoprevention	Launched WW for BPH; patents expire in 2006
Millennium Pharmaceuticals/Baylor College of Medicine		Identification of genetic changes associated with progression of human prostate cancer using position cloning techniques	Research/USA	
National Cancer Institute	Pyrazoloacridine(PZA)	DNA intercalating agent/IV	Phase II (5/95)/USA	Phase II (5/95)/USA breast and colon cancer
NeoRx	Avicidin	Antibody-mediated pretargeting technology/antibody covalently linked to streptavidin and biotin	Phase I/II (96)/USA/ solid tumors	See FO, V1 #2/3, #4
Organon (exclusive WW licensee)/Roche Bioscience (was Syntex)	Ganirelix/RS-26306	Gonadorelin antagonist; GnRH antagonist/SC, oral, nasal; long-acting formulations	Phase II (10/94)/ Switzerland	
Parecelsian	Andrographolide/PN 27,1	Natural product isolated from the Chinese medicinal herb *Andrographis paniculata*/oral	Phase I (4/96)/USA	
Parke-Davis (Warner-Lambert)/ U. S. Bioscience, NIH, Dainippon	Trimetrexate/CI-898, JB-11, NSC-249008, NSC-328564, NSC-352122/Neutrexin	Cytostatic antifolate, lipid soluble analog of methotrexate/ dihydrofolate reductase inhibitor/ IV, topical	Phase II (5/94)/USA	
Parke-Davis (Warner-Lambert)/NIH	Suramin/CI-1003	Polysulfonated naphthathylamine derivative/parenteral	Phase III (b2/94)/ USA/metastatic HRPC	AACR96, Abs. 1188:173
Parke-Davis (Warner-Lambert)	CI-958	Benzothiopyranoindazole/DNA intercalator (planar moiety of the ligand inserted between adjacent DNA pairs)	Phase III (b96)/USA	ASCO96, Abs. 649
Pharmacia & Upjohn/ Taiho, NCI (NIH), Evanston Hospital	Menogaril, menogarol, methylnogarol/7-OMEN, U-52047, NSC-269148, TUT-7/Tomosar	Nogalamycin derivative, antibiotic/DNA antagonist/ PO, IV	Phase I (2/95)/USA	Recommended dosage is 160-200 mg/m^2
PharmaMar	Kahaladide F (KF)	Natural product isolated from a Hawaiian mollusk	Research (1/96)/ Spain	
Pherin		Nasal drug delivery methodology/ vomeropherins applied to the nose/affect CNS function without entering the systemic circulation or the brain	Research/USA	
Pierre Farbre/ Pasteur Merieux, Rhône-Poulenc Rorer, Glaxo Wellcome, Boehringer Ingelheim, Gedeon Richter, Kyowa Hakko	Vinorelbine/KW-2307/ Navelbine, NVB	Semisynthetic vinca alkaloid	Phase II (4/95)/ France	
Prizm Pharmaceuticals	hbFGF-toxin	Immunoconjugate; mitotoxin; hbFGF-saporin fusion protein	Preclin/USA	
Proteus Molecular Design/ML Laboratories (licensee)	LHRH immunacine, gonadorelin analog, LHRH analog/014L, PM-OV-92, Sterovac 92	Vaccine containing gonadorelin analog/stimulates antibody response cross-reacting with naturally-produced LHRH	Phase II (7/96)/UK	

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Research Corporation Technologies/NeXstar, U Arizona, Arizona Cancer Center	Azonafide compounds	Anthracene analogs/ topoisomerase inhibitor	Preclin/USA	Phase I (3/95)/USA/ leukemia
Roberts Pharmaceutical/Salk Institute (licensee)	Deslorelin, gonadorelin analog, LHRH analog/ Somagard	LHRH analog/SC injection	Reg (12/94)/Ireland; await reg/UK; phase III/USA, France	Reg (12/94)/UK/ central precocious puberty; phase II (12/94)/UK/ endometriosis
Sankyo/Fuji Chemical Industries	FO-152	Thymidylate synthase inhibitor	Phase II (discontinued 2/95)/Japan	See FO, V1 #2/3
Scotia Pharmaceutical	LiGLA/EF-13	IV, PO	Phase II (2/95)/UK	Phase II (2/95)/UK/ HIV, colorectal, lung, and breast cancer; phase III (2/95)/UK/ pancreatic cancer; phase II (2/95)/NA, Africa/HIV (see FO, V1 #2/3, #4)
Scotia Pharmaceutical	Mesotetrahydroxy-phenylchlorin, mTHPC/EF9	Photodynamic therapy (PDT)	Preclin/UK	Demonstrated efficacy in clinical trials in head and neck tumors
Searle (Monsanto)	SC-41661A	3H-thymidine inhibitor	Preclin (5/95)/USA/ androgen-independent prostate cancer	Anderson KM, etal, ASCO95, Abs. 22:79
Sequana Therapeutics/ Canji (Schering-Plough)		Identification and characterization of prostate cancer-related genes	Research/USA	
Sequus Pharmaceuticals	Pegylated liposomal doxorubicin/Doxil (USA), Dox-sl (Europe)	Doxorubicin encapsulated in sterically stabilized liposomes	Clinical/USA	A95/USA/AIDS-related Kaposi's sarcoma
Seragen/Lilly	Epidermal growth factor (EGF) fusion toxin/ $DAB_{389}EGF$	Fusion toxin	Phase II (95)/USA	See FO,V1 #2/3, #4
Serono Laboratories	Recombinant interferon-β, rIFN-β/R-Frone, Rebif	Recombinant interferon-β	Phase I/II (5/95)/USA	Phase I/II (5/95)/ USA/breast, brain and lung cancer
Sheffield Medical Technologies/Baylor College of Medicine	UGIF (urogenital sinus derived growth inhibitory factor)	Isolated from rat fetal urogenital sinus organ cells/involved in cellular differentiation	Preclin(9/95)/USA	
Somatix/ Johns Hopkins U	GVAX	Gene therapy/multiple gene transfer in which tumor cells are removed from patients, transduced *ex vivo* with the gene for GM-CSF, irradiated, and then reinfused into patients/ subcutaneous injection	Phase I/II/USA	RAC #9408-082
SRI International/NCI (NIH), Roberts Pharmaceutical, HN Pharma AG, DuPont Merck, Taisho	Etanidazole/DuP-453, SR-2508, NSC-301467, NSC-314055/Radinyl	Hydrophilic radiosensitizer/ IV infusion	Phase II (5/95)/USA	See FO,V1 #4, #5
Sugen/NCI (CRADA)	Platelet derived growth factor (PDGF) antagonist/ SU101	PDGF receptor antagonist/ inhibits PDGF tyrosine kinase (TK)-mediated cell signalling/oral	Preclin/USA	Phase I (96)/USA/ brain, refractory ovarian cancers, melanoma (see FO, V1, #4, p 108)

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Sugen	Pan-Her (formerly Her2)	Small molecule inhibitor of Her-2 receptor tyrosine kinase (RTK)	Preclin (2/96)/USA	
Therion Biologics/ NCI (NIH)	PROSTVAC	Gene transfer using live recombinant pox virus vector/expresses tumor-specific antigen to elicit cellular immune response	Preclin/USA	In development under a 5 year CRADA with the NCI (see FOV1 #4)
United Biomedical	$SUIS_{LHRH}$	Synthetic peptide immunotherapeutic/targets and immunoneutralizes LHRH	Phase I (b10/95)/USA/ androgen-dependent prostate cancer	
U. S. Bioscience/ NCI (NIH), Warner-Lambert	Diaziquone, AZQ, aziridinyl-benxoquinon/ CI-904, NSC-182986	Cytostatic with high CNS bioavailability	Phase III (5/94)/USA	Myelosuppression and anemia are dose-limiting
U Wisconsin/NCI	Perillyl alcohol	Natural product, monoterpene/ induces apoptosis and phase I and II hepatic detoxification enzymes; selectively inhibits protein isoprenylation, inhibits CoQ synthesis, and induces mannose 6-phosphate/IGFII receptor and TGF β	Phase I/USA	AACR96, Abs. #1815; also limonene, another monoterpene, is in phase I in the UK

Maspin is a protein related to the serpin family of protease inhibitors expressed by a gene identified as a candidate tumor suppressor gene that may play a role in human breast and other cancers. Maspin is expressed in normal mammary epithelial cells but not in most mammary carcinoma cell lines. Transfection of mammary carcinoma cells with the maspin gene does not alter a cell's growth properties *in vitro*, but reduces its ability to induce tumors and metastasize in nude mice and to invade through a basement membrane matrix *in vitro.* Analysis of human breast cancer specimens revealed that loss of maspin expression occurred most frequently in advanced cancers (Zou Z, etal, Science, 1994 Jan 28, 263(5146):526-9). Maspin was identified by Dr. Ruth Sager at Dana-Farber Cancer Institute. In animal models genetically engineered forms of maspin can bind to invasive and metastatic breast tumor cells and block their growth throughout the body. Maspin is likely to be involved in the control of apoptosis in metastatic breast tumor cells. Therapy with genetically engineered maspin may restore normal control of cell death to these malignant cells. LXR intends to enter into a CRADA with the National Cancer Institute to investigate maspin's role in breast, prostate and other highly metastatic cancers. LXR intends to develop maspin both as a prognostic marker for metastatic potential in tumor biopsies and as a therapeutic for the suppression of tumor metastasis. Unlike most known tumor suppressors, which exert their effect only from within the cell, maspin appears to act by binding to the outer surface of cancer cells. This ability makes it attractive as a potential therapeutic because it can be administered directly to the patient. LXR is currently pursuing preclinical studies with purified recombinant maspin in established models of metastatic breast cancer.

Millennium Pharmaceuticals (Cambridge, MA) is engaged in commercializing a broad range of diagnostics and therapeutics based on its proprietary genetics, genomics and bioinformatics technologies. In the oncology field, the company is identifying genes related to a variety of cancers, including prostate, breast and colorectal cancer, and melanoma. The company is currently pursuing five projects in the field of oncology, one using human genetics approaches and four based on cDNA methodologies. Millennium is identifying genetic changes that underlie the progression of human prostate cancer through the use of positional cloning techniques and has entered into a collaboration with Baylor College of Medicine (Houston, Texas) to obtain tumor samples required for this study. The company has begun target validation studies on these genes, including gene transfer into animal models of cancer progression.

In April 1996, Millennium and Eli Lilly entered into a strategic alliance in selected areas in oncology, expanding a previous agreement entered in October 1995, in the atherosclerosis area. Lilly agreed to purchase $3.5 million of Millennium's common stock and fund a five-year program of cancer research which may be extended for up to eight years. Lilly is obligated to make additional milestone payments to the company and pay royalties on sale of certain therapeutic products that may result from the alliance. The agreement provides Lilly with exclusive worldwide royalty-bearing rights to develop and commercialize small molecule drugs and therapeutic proteins and co-exclusive rights to develop and commercialize gene therapy products based on Millennium's gene discoveries; Millennium has retained exclusive rights to all antisense drug applications. Lilly has also granted Millennium non-exclusive rights to use certain

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of its combinatorial chemistry libraries and high-throughput screening technologies to conduct a limited number of screens with Millennium's targets to identify product candidates for medical indications other than those designated by Lilly as being of strategic importance. Millennium has exclusive worldwide rights to develop and commercialize such product candidates and pay Lilly royalties on sales. Millennium also granted Lilly a non-exclusive right to use certain genomics technologies.

Sequana Therapeutics (La Jolla, CA) is collaborating with Canji (San Diego, CA), recently acquired by Schering-Plough, to sequence and identify genes within a region believed to contain a gene involved in prostate cancer. Schering-Plough has an option to acquire a license to certain genes discovered through this collaboration.

Tissue-Targeted Toxic Therapy

Use of the herpes simplex virus-thymidine kinase (hsv-tk) "suicide gene" (see FO, V1 #6, pp 151-152) may allow targeting toxic therapies to malignant tissues, thus, sparing patients systemic exposure to toxic chemotherapeutics. Researchers at Baylor College of Medicine obtained approval (RAC # 9601-144) in January 1996 to begin human trials using the hsv-tk as a means of activating, in a tissue-selected mode, an inert prodrug of systemically introduced ganciclovir. Using an adenovirus vector, the hsv-tk gene is delivered by intratumoral/intraprostatic injection. In preclinical trials locally invasive, rapidly growing tumors with metastases to regional lymph nodes and lung, induced in mice, were inoculated with a replication deficient, recombinant adenovirus expressing either the hsv-tk gene or the 13-galactosidase gene as a control. Each group was administered ganciclovir or saline twice daily for 6 days. By day 14, treated tumors were reduced in volume and weight by 80% relative to controls and only 12.5% (1/8) of treated animals developed metastases compared to 81.2% (13/16) of controls. Tumor growth suppression continued with a 50% reduction in tumor size in treated animals compared to controls. Also metastasis occurred in 14% (2/14) of treated animals versus 93% (14/15) of controls and ganciclovir-treated tumors grew to a size similar to that of controls at day 14 when 80% of the animals had metastasis. These results indicate that monotherapy using intratumoral administration of the hsv-tk gene and systemic ganciclovir results in short-term local tumor growth suppression and reduction in metastatic activity. Metastasis suppression may not be caused exclusively by killing of premetastatic cells but may involve systemic effects such as induction of an antitumor immune response (Hall, SJ, AACR96, Abs. 2350).

In a similar approach, researchers used a tissue-specific PSA promoter to drive a thymidine kinase (tk) gene that can convert the antiviral agent acyclovir into a toxic metabolite. By using the long PSA promoter-driven tk, cell-specific killing occurred only in PSA-producing cells *in vitro.* Long PSA promoter was a potent tissue-specific promoter that could efficiently drive any gene in tissue-specific manner only in PSA secreting cell lines. For efficient gene delivery, the construct comprised a recombinant adenovirus containing 6.1 kb of long PSA promoter, 1.2 kb of tk gene, and 0.2 kb of polyadenylation signal. Even though this new virus can efficiently deliver its toxic tk gene into different target cells, high tk gene expression was observed only in PSA-producing cells *in vitro.* When acyclovir was added, presence of thymidine kinase was very detrimental during the long phase of PSA producing cells but long-phase killing was not observed in non-PSA producing cells (Ko SC, AACR96, Abs 2379).

Immunotherapy/Vaccines

New screening techniques are identifying millions of men with latent disease who are at risk of developing full-blown prostate cancer but who cannot be treated during this latent stage because of lack of effective organ-sparing preventative therapies. These individuals would greatly benefit from availability of effective low-cost prophylactic approaches such as immunotherapies or vaccines. Interest in cancer vaccines has surged in the 1990s because screening techniques that can identify individuals at risk for cancer with a high degree of confidence, are creating populations candidate for interventions that must be highly effective, easy to administer and associated with minimal toxicity. Prostate cancer represents a unique paradigm in cancer vaccine deployment. Although costly therapeutic vaccines, administered in advanced cases, will be the first to enter the market and originally compete with chemotherapy approaches (see Exhibit 5) in this area, low-cost prophylactic vaccines are expected to make a significant market impact in the long run (see Exhibit 6).

Aphton (Woodland, CA) is a public biopharmaceutical company developing therapeutics using a vaccine-like technology to treat diseases, both malignant and nonmalignant, in the gastrointestinal and reproductive systems. Aphton's approach is to neutralize, or block, hormones which play a critical role in such diseases by using a vaccine-like process to harness and direct the body's immune system to generate a controlled antibody response against administered immunogens. 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 products may be administered in much smaller doses and less frequently, typically twice a year, which virtually eliminates the problem of

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Exhibit 5
Estimated Potential Annual Market for Therapeutic and Prophylactic Vaccines for Prostate Cancer (Five Years Post-Introduction)

Region	Rx Vaccine[2]		Rx Vaccine with Annual Booster[3]		Prophylactic Vaccine[4]		Prophylactic Vaccine with Annual Booster[5]	
	(#)	Market ($ mil)	(#)	Market ($ mil)	(#)	Market ($ mil)	(#)	Market ($ mil)
USA	44,394	111.0	361,494	428.1	317,100	158.6	1,585,500	602.5
N. America	46,949	117.4	382,299	452.7	335,350	167.7	1,676,750	637.2
Europe[1]	37,751	94.4	307,402	364.0	269,651	134.8	1,348,255	512.3
Japan	2,889	7.2	23,522	27.9	20,633	10.3	103,165	39.2
Triad	87,589	219.0	713,223	844.6	625,634	312.8	3,128,170	1,188.7

[1] Excluding the former USSR, [2] AWP is estimated at $2,500, [3] AWP is estimated at $1,000, [4] AWP is estimated at $500, [5] AWP is estimated at $350

patient compliance. The company's two lead cancer immunotherapy agents are Gastrimmune and Gonadimmune. Gonadimmune uses a synthetic peptide sequence which is identical to a portion of gonadotropin-releasing hormone (GnRH) targeted to be neutralized, resulting in blocking production of testosterone, estrogen and progesterone. Aphton has already demonstrated in animals Gonadimmune's ability to block, or inhibit, production of testosterone in prostate cancer. Preclinical animal trials with Gonadimmune were completed as of September 1995 and clinical trials in breast and prostate cancer are currently underway in the UK.

Avigen (Alameda, CA), in collaboration with investigators at Baylor College of Medicine, is pursuing gene therapy as a treatment for early-stage prostate cancer (Avipro) using its AAV vector technology that appears to be particularly well suited for treatment of prostate cancer because prostate tumor cells are often localized and usually divide extremely slowly. In addition, these tumors can be readily accessed by direct injection. Avigen also developed a model of prostate cancer in mice. Following injection of an AAV vector containing a "marker" gene directly into the prostate in mice, expression of the marker protein was observed within the prostate epithelium. As of May 22, 1996, Avigen was evaluating antitumor effects of direct injection of an AAV vector containing the tk and IL-2 genes into these tumors. The company is also developing other strategies using AAV vectors containing tumor suppressor genes. These vectors will incorporate a prostate-specific promoter designed to limit gene expression. In February 1994, Avigen entered into agreement with the University of Manitoba (Canada) for an exclusive, worldwide license to patented applications relating to such a prostate-specific promoter for use in gene therapy. Under this agreement, Avigen paid an initial license fee and has agreed to make additional cash payments on achievement of certain development milestones and to make royalty payments based on net sales of products which use the licensed technology.

CEL-SCI (Alexandria, VA) started a prostate cancer study with its immunotherapy drug Multikine at Thomas Jefferson University Hospital (Philadelphia, PA) in May 1996. The study will enroll up to 15 prostate cancer patients who have failed hormonal therapy. Multikine, a natural mixture of cytokines, contains IL-2 and other cytokines, several of which are being investigated individually as potential cancer treatments. The goal of the treatment is to generate therapeutically effective systemic anti-tumor immunity to eventually reduce the need for radical surgery.

Cellcor (Newton, MA) is developing *ex vivo* autolymphocyte therapy (ALT), currently in phase III clinical trials in metastatic renal cell carcinoma. In ALT, lymphocytes such as killer and helper T cells are extracted from patients, activated non-specifically *ex vivo* and then returned to the patient to search out foreign targets such as cancer cells or viruses. Cellcor has also conducted clinical trials of ALT in prostate cancer and melanoma and is evaluating ALT in infectious diseases such as chronic hepatitis. In March 1994, Cellcor entered into a non-exclusive agreement with SRL (Tokyo, Japan), Japan's largest diagnostic reference laboratory, to introduce ALT in Japan. Cellcor was acquired in October 1995 by Cytogen (Princeton, NJ) in exchange of $20 million-worth of Cytogen common stock.

Cytel (San Diego, CA), a public company incorporated in 1987, is pursuing an extensive cancer vaccine program using a variety of approaches. As part of its antigen recognition program, originally developed in collaboration with Sequel Therapeutics, a joint venture with Scripps Research Institute (La Jolla, CA) which was subsequently acquired by Cytel in October 1995, the company is developing both injectable and *ex vivo* cancer immunotherapeutics.

Cytel has developed a proprietary process to sequence tumor antigens and uses computers to search the sequence to identify a 9-10 amino acid-binding peptide that interacts with MHC Class I molecules, increasing the potency of these peptides by linking them to proprietary

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carrier and helper components. Because HLA molecules are polymorphic in humans, a typical vaccine contains a mixture of 7 or 8 of these small peptides, in order to be effective in a majority of populations. Combining these peptides with epitopes that induce helper T cells may yield an even better vaccine response.

The company's proprietary vaccine technology, Theradigm, selectively stimulates the immune system to produce disease-specific responses from cytotoxic T-lymphocytes (CTL or CD8+ cells). Theradigm consists of small antigenic peptides which are segments of foreign proteins that induce a cellular immune response. Theradigm-MAGE 3 (CY-2010) which targets advanced solid tumors and melanoma is in phase II trials. Theradigm-MAGE 3 has been studied by Dr. Steven Rosenberg at the National Cancer Institute since July 1994 and by Dr. Jeff Weber at the University of California, Irvine. Theradigm-PSA, a vaccine based on PSA specifically addressing prostate cancer, is in research.

Exhibit 6
Estimated Potential Annual Market for Prophylactic Vaccines for Prostate Cancer
Five Years Post-Introduction

Region	Prophylactic Vaccine Administered Once		Annual Booster[1]		Total
	(#)	Market ($ mil)	(#)	Market ($ mil)	Market ($ mil)
USA[1]	250,000	17.5	9,775,159	244.4	261.9
N. America	268,350	18.8	10,938,796	273.5	292.3
Europe[2]	269,651	18.9	21,704,487	542.6	561.5
Japan	20,633	1.4	6,013,792	150.3	151.7
Triad	558,634	39.1	38,657,075	966.4	1,005.5

[1] Annual booster administered to cases in five years including latent prostate cancer cases
[2] Excluding the former USSR
Note: AWP prices for preventive vaccines are estimated at $70 for the initial immunization and $25 for the annual booster

Cytel is also pursuing an *ex vivo* therapeutic vaccine using adoptive immunotherapy, which involves the removal, activation, expansion, and reintroduction of antigen-specific peripheral blood lymphocytes in patients with advanced disease who may not be immunocompetent to mount an adequate response to the vaccine. The *ex vivo* vaccine consists of human antigen-presenting cells engineered to express HLA-1(A)2 molecules on their surfaces that can complex with antigenic peptides derived from cancer-specific proteins. When incubated with a patient's isolated T cells in an *ex vivo* setting, the antigenic peptide/HLA-1(A)2 complex that forms stimulates the proliferation of only those T cells that express a receptor specific for the HLA-1(A)2/antigenic peptide complex. This expanded population of T cells is then reinfused back into the patient, where it seeks out and destroys cancer cells that also express the HLA-1(A)2/antigen complex. The company entered into a collaboration in this area with Takara Shuzo in early 1995.

Medarex (Annandale, NJ) is developing bispecific MAbs that typically consist of two antibody fragments, each of which is specific for a different site, that are fused into one construct. One fragment, the Trigger, is a humanized antibody fragment proprietary to Medarex, that is specific for the Fc receptor and, consequently, is capable of binding to and triggering a macrophage. Medarex obtained exclusive worldwide rights (on a royalty-fee basis) from Dartmouth University (Hannover, NH) to the Trigger component. The target fragment, which is licensed to Medarex by a third party, is specific for a particular antigen on a tumor cell or pathogen. In January 1996, the company announced the result of a new scientific study showing that its bispecific technology stimulates a potent immune response against targeted antigens, causing a vaccine-like effect.

The company's lead product is MDX-210 that targets breast cancer and other tumors such as ovarian, prostate and colon cancers, among others, that overexpress Her-2. MDX-210 combines the Trigger antibody fragment with a target fragment specific for Her-2 antigen licensed from Chiron. In May 1995, Medarex began a phase I clinical trial of MDX-210 in refractory metastatic prostate cancer at the Norris Cotton Cancer Center (Lebanon, NH), supported by a grant from the CaP CURE Foundation. MDX-210 is already in phase I/II trials for breast and ovarian cancer. In May 1995, Medarex entered into a collaborative arrangement with Novartis (was Ciba-Geigy) to jointly develop and market MDX-210. Medarex is primarily responsible for phase II clinical trials; thereafter, Ciba is primarily responsible for phase III clinical trials, regulatory approvals and commercial launch. Under the terms of the agreement, Medarex sold 899,888 shares of common stock to Ciba in June 1995, for an aggregate price of $4 million. Medarex also granted Ciba worldwide exclusive rights to MDX-210 in exchange of purchase of additional equity in the amount of $4 million, milestone and R&D payments of up to $31 million and royalties on product sales. Medarex has retained certain rights with respect to the manufacture of MDX-210.

Another Medarex Bispecific, MDX-447, is designed to induce tumor cell killing by simultaneously binding to EGFr found on the surface of various types of tumors and to Fc receptors on macrophages and other white blood cells. Both the Trigger and target components of MDX-447 are humanized. A phase I/II clinical trial of MDX-447

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to treat cancers that overexpress EGFr, such as head and neck, breast, non-small cell lung, prostate and ovarian cancer, commenced in 1995 at Memorial Sloan-Kettering Cancer Center. The EGFr targeting component of MDX-447 was contributed by Merck KGaA. Under the terms of a collaboration established in 1994, Merck KGaA purchased 450,000 shares of Medarex common stock at $7.00 per share for an aggregate purchase price of $3.15 million in lieu of R&D funding and may also provide up to $1.25 million to fund clinical trials. Upon achievement of certain milestones, Merck may provide Medarex with up to $25 million to fund phase III clinical trials. After Merck's funding reaches $29 million, the parties will share future development costs equally. Medarex retains exclusive commercialization rights in the USA, subject to royalties payable to Merck, for the EGFr Bispecific and any other Bispecific developed by this collaboration. Merck has exclusive commercialization rights in Europe, subject to royalties payable to Medarex, and the two companies jointly hold commercialization rights for the rest of the world. In addition to the EGFr Bispecific, other products covered by the collaboration include a Bispecific for the treatment of other tumors employing a different Merck targeting molecule and proprietary Bispecific technology developed by Merck capable of triggering the killing of tumors by T cells.

Jenner Technologies (Danville, CA), a private company founded in 1992, is developing cancer vaccines for colorectal, lung, and prostate cancer. Jenner vaccines use pure recombinant tumor-associated antigens combined with adjuvants and Jenner's proprietary carrier technology which targets the vaccine to the reticuloendothelial system (RES). The recombinant antigens consist of many epitopes to increase their chances of reacting with intrinsic corresponding sites. Liposomes target the vaccine to the appropriate sites and facilitate antigen presentation to enhance a cellular immune response. Adjuvants also enhance CTL production. Jenner's prostate cancer vaccine (OncoVax-P) is based on purified recombinant PSA, encapsulated in a liposome, which serves as a carrier. Jenner has filed patent applications covering key components of its vaccine approach. A phase I/II clinical trial in prostate cancer was initiated in October 1995, at Lankenau Hospital (Philadelphia, PA) and will initially involve five immunocompetent patients with prostate cancer who failed HAT.

Proteus Molecular Design (Macclesfield, Cheshire, UK), a Proteus International unit, is developing a GnRH immunotherapeutic for treatment of prostate and breast cancer. Preclinical toxicology studies were successfully completed as of September 1995, and phase II trials in prostate cancer are to begin under the auspices of ML Laboratories (Liverpool, UK), the drug's licensee. Animal models showed reductions in testosterone concentration comparable to those achieved by an existing GnRH agonist but with less frequent dosing and without the hormonal surge associated with such agonists. Proteus has filed patent applications for this product in several jurisdictions including the USA, where it is in discussion with the inventors with a view to obtaining necessary declarations, and in Europe, where it is addressing issues relating to prior disclosure.

Somatix Therapy (Alameda, CA) in collaboration with Bristol-Myers Squibb, is developing a cancer vaccine, GVAX, based on an *ex vivo* approach involving extraction of tumor cells from patients which are then transduced with the gene for GM-CSF, irradiated and reinfused into patients to elicit an immune response. In March 1995, Somatix began a phase I/II clinical trial with GVAX in the treatment of melanoma at the Dana-Farber Cancer Institute and Massachusetts General Hospital (Boston, MA) and at the Netherlands Cancer Institute in Amsterdam. In April 1996, the FDA approved initiation of a phase III clinical study of GVAX. A phase I study is also being pursued at John Hopkins Oncology Center (Baltimore, MD) using GVAX to treat renal cell carcinoma. In January 1996, a phase I/II clinical trial was initiated with GVAX for the treatment of prostate cancer (RAC approval #9408-082). Study end-points include safety and induction of an immune response. Circulating levels of PSA will also be monitored as an indication of efficacy. Eventually, Somatix Therapy intends to use one tumor cell line to create a standardized vaccine applicable to any patient with prostate cancer. The company also plans to begin trials in colorectal cancer.

Therion Biologics (Cambridge, MA) is a privately held biopharmaceutical company developing vaccines which stimulate a full range of antibody and cell-mediated immune responses for the prevention and treatment of cancer and AIDS. Through genetic manipulation, the company can incorporate several genes in a single vector to maximize antigen-specific immune responses. The company's vaccines are based on gene transfer involving genes that express tumor-associated antigens and/or other immunomodulators such as cytokines. Antigens incorporated in Therion's vaccines were isolated through a technology developed by Dr. Steven Rosenberg at the NCI. This technology uses tumor infiltrating lymphocytes (TILs) which can recognize antigens specific to malignant cells. The company's leading product is Magevac, a recombinant therapeutic vaccine for treatment of melanoma. In collaboration with Jeffrey Schlom, PhD, also of the NCI, the company has been evaluating TBC-CEA vaccine, in phase I/II trials, for treatment of advanced gastrointestinal, breast and lung cancer. TBC-CEA is a live recombinant poxvirus expressing the CEA gene. Therion and Schlom are also collaborating on several other vaccines including a prostate cancer vaccine containing PSA (Prostvac), Rasvac for colorectal cancer and TBC-NEU and Muvac for breast and ovarian cancers.

United Biomedical (UBI; Hauppauge, NY), a public company founded in 1983, is developing synthetic peptide-based immunotherapeutics with potential applications in

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the treatment of infectious diseases and cancer. UBI's technology, Synthetic Universal Immune Stimulator (SUIS), significantly augments the protective or therapeutic immune responses elicited by synthetic peptide antigens. UBI has validated this technology in preclinical studies with hormonal, regulatory, and pathogen-specific antigens, and has conducted comprehensive studies to optimize formulations for human and veterinary use. The company has manufactured clinical lots of a prototype prostate cancer therapeutic, $SUIS_{LHRH}$, which is virtually 100% effective in stimulating antibodies that neutralize the action of LHRH, causing testosterone levels to reach castration levels. This construct will also be clinically evaluated for treatment of BPH. $SUIS_{LHRH}$ entered phase I clinical trials in late 1995 at Dana-Farber Cancer Institute. SUIS technology may also serve as a platform technology for development of human and veterinary therapies by targeting neutralization of defined epitopes of other regulatory hormones.

In the treatment of prostate cancer, UBI has developed a combination immunotherapeutic approach, targeted at both androgen-dependent and independent prostate tumor cells. The first component of the therapy has as its basis the immunoneutralization of LHRH. Inhibition of the action of LHRH is achieved by immunization with synthetic LHRH covalently linked to immunoregulatory peptides and additional groups that have defined adjuvant effects. These modifications to the LHRH molecule are specifically designed to stimulate potent antibody responses to LHRH within a few weeks following initiation of treatment, thereby blocking the action of the hormone and, as a direct consequence, preventing production of testosterone. In the absence of testosterone, androgen-dependent tumor cells undergo apoptosis, resulting in a significant reduction of tumor burden.

$SUIS_{LHRH}$ consists of a mixture of four different synthetic LHRH constructs, including different T cell epitopes required to stimulate hormone neutralizing immune responses in the genetically diverse human population, each 25-50 amino acids in length. An additional synthetic peptide domain which has been shown to mobilize helper T cells and, thus, act as an adjuvant, is linked to the LHRH T cell epitope construct to optimize antibody responses to the LHRH sequence. This second component of the immunotherapy focuses directly on the destruction of androgen-independent prostate tumor cells by inducing CTLs capable of destroying tumor cells expressing antigens which are highly induced under conditions of androgen deprivation. UBI has developed a method for modifying synthetic peptides representing CTL epitopes, so that they are presented to the immune system through the MHC Class I pathway and generate high levels of specific CTL activity. UBI's technology for inducing CTL responses with lipid-modified synthetic peptides is currently being evaluated in phase I clinical-trials using model human immunodeficiency virus (HIV) CTL epitopes, and has already effectively demonstrated the capacity to stimulate epitope-specific CTL responses in both preclinical studies and preliminary clinical trials. Additionally, UBI is using genetic immunization by combining minigenes for selected tumor-specific antigens with plasmids coding for adjuvants capable of enhancing the induction of tumor-specific CTLs.

Immunotoxins

Prizm Pharmaceuticals (San Diego, CA) is developing growth factor-targeted cytotoxic molecules (mitotoxins) that are compounds composed of a growth factor conjugated to a biological modifier. These conjugates bind to high affinity receptors on the surface of cells and cause a change in metabolic activity or cell death. Mitotoxin conjugates under development link saporin (SAP) and other toxic molecules, such as small molecular weight DNA cleaving compounds and antisense, to FGF, VEGF and hbEGF. SAP is a ribosome-inactivating protein (RIP) derived from the plant *Saponaria officinalis*. RIPs are enzymes which work by removing a nucleotide base from specific sequences of ribosomal RNA, preventing the interaction of ribosomes with other factors, thus inhibiting protein synthesis resulting in cell death. SAP is a type 1 RIP, a class characterized by single polypeptide chains possessing no cell-binding domain, which are very stable and safer to handle. In the FGF-SAP conjugate, FGF enables SAP to penetrate selected cell types. Since FGF receptors are only expressed in specific situations, this expression is generally localized, and since SAP cannot enter cells on its own, this mitotoxin strategy produces a highly targeted, effective therapy with a low side effect profile. In preliminary *in vitro* and *in vivo* studies Prizm's mitotoxin eliminated malignant melanoma and prostatic adenocarcinoma cells with no effect on normal tissue. Prizm is currently proceeding with additional animal studies on melanoma, prostate cancer and other tumor cell lines using FGF-SAP and also plans to develop conjugates of FGF linked to other drugs such as small organic DNA cleaving molecules, antisense RNA and DNA, and photoporphyrins. VEGF-SAP, a potentially specific antiangiogenic agent, will also be evaluated against human malignancies.

Natural Products

Carrington Laboratories (Irving, TX) specializes in the development of OTC skin care products, wound care products and pharmaceuticals derived from the Costa Rican *Aloe vera* plant. In late 1995, Carrington began a phase I clinical trial at the University of Texas Health Science Center (Houston, TX) of Alvonex (CARN 750), an injectable formulation of acemannan, a natural product derived from *Aloe vera*, in patients with advanced melanoma, hypernephroma, soft tissue sarcoma, and breast, prostate and colon cancer. Patients are treated weekly with a one-month, ascending dose protocol. This product has resulted from the company's bulk injectable

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mannans (BIM) technology that also produced Carimmune (CARN 700), an acemannan immunostimulant for the treatment of feline and canine fibrosarcoma.

Paracelsian (Ithaca, NY), a biotechnology company developing oncology diagnostics and therapeutics, is applying its signal transduction core technology to the Chinese pharmacopoiea of natural products. The company has identified herbal extracts using its screens to detect downregulation of cyclic-dependent kinases (CDKs) and particularly CDK1 whose overexpression has been associated with abnormal cell proliferation. Various of these extracts are currently being preclinically evaluated, in cooperation with Roswell Park Cancer Institute's Department of Experimental Therapeutics (Buffalo, NY), in prostate cancer cell lines. One such extract, andrographolide (PN 27,1), isolated from the Chinese medicinal herb *Andrographis paniculata,* and various of its analogs, demonstrated similar anticancer activity as cisplatin against three prostate cancer cell lines but without similar toxicity. PN 27,1 is well tolerated in oral dosage forms for extended periods of time. A patent was filed in December 1994 covering applications of this agent for the treatment of cancer. Other herbal extracts are also in development for the treatment of prostate cancer.

In May 1996, Paracelsian announced that it will expand its compassionate use trial of PN 27,1, initiated in March 1995, to enroll 300 cancer patients because of very encouraging preliminary results seen in six of seven patients who participated in the trial. Approximately 30 additional patients were already enrolled at the time of the announcement. Among seven treated patients with advanced disease (two for non-Hodgkin's lymphoma, two for breast cancer and two for prostate cancer), after three months of therapy, a 75% positive response rate was observed as measured by traditional clinical variables.

University of Wisconsin (Madison, WI) investigators are evaluating, in clinical trials, monoterpenes that are extracts of orange peel (limonene) and lavender oil (perillyl alcohol), shown to possess anticancer properties in mice. A phase I clinical trial is underway in the UK with limonene and another with perillyl alcohol at the University of Wisconsin in 14 patients with advanced solid tumors unresponsive to conventional therapy. More settings are expected to participate in phase I trials under the auspices of the NCI. To date, no adverse reactions were observed and phase II clinical trials are being planned in breast, ovarian and prostate cancer. In preclinical trials, oral administration of monoterpenes caused about 85% of rat mammary carcinomas to regress, presumably via the induction of apoptosis. Another mechanism may involve activation of a tumor suppressor gene encoding the receptor for mannose 6-phosphorate/insulin-like growth factor II (M6P/IGFII) which inactivates IGFII and activates transforming growth factor-β (TGF-β) that in turn prevents cancer cell proliferation. Menoterpenes may also prove useful in prostate cancer prevention.

Other Drugs Therapies

Cephalon (West Chester, PA) is a public company focusing in drug development in neurology. One of its core projects is the development of receptor tyrosine kinase (RTK) effectors that mediate actions of a variety of growth and neurotrophic factors. Cephalon licensed from Kyowa Hakko (Tokyo, Japan) patent rights to these RTK effectors in 1992. Under the terms of the license, Cephalon has exclusive marketing rights to these compounds in the USA and has an option to acquire semi-exclusive marketing rights in Japan. Each of the two companies have semi-exclusive marketing rights throughout the rest of the world, including Europe. Under the agreement a milestone payment from Cephalon is due upon the filing of an IND with the FDA for a licensed molecule. Kyowa Hakko will supply the molecules in bulk form and Cephalon will pay for commercial supplies as well as royalties on product sales.

RTKs activate a tyrosine kinase which, in turn, activates (phosphorylates) other proteins, in sequence, mediating their activity. For example, activation of a growth factor receptor such as platelet-derived growth factor (PDGF), leads to cellular growth and proliferation. The company's small molecule RTK effectors, either activate specific tyrosine kinase-mediated events, or act as antagonists or inhibitors of such effects. The company's small neurotrophic RTK effectors were shown in preclinical studies to cross the blood-brain barrier and promote the survival of neurons.

Cephalon has also developed a number of RTK effectors that act as antagonists that may prove useful in treating certain types of cancer, such as prostate cancer, where tumor growth and development may be mediated by the activity of an endogenous growth factor. Under a recent amendment to the agreement with Kyowa Hakko, Cephalon has obtained an option to acquire the exclusive rights to develop compounds for prostate cancer in Europe, Canada, Mexico and the USA, that are now being developed in the USA in collaboration with TAP Pharmaceuticals. In return for exclusive European rights, Kyowa Hakko will receive exclusive rights to develop the compound for prostate cancer in Asia and would receive a royalty on Cephalon European sales. In April 1994 Cephalon entered into an agreement with TAP Pharmaceuticals to commercialize its RTK-based products for prostate cancer for the USA. TAP made an initial investment of $19.4 million ($5 million in cash and $14.4 million in Cephalon common stock) in May 1994 and may eventually invest as much as $50 million.

Elan (Athlone, Ireland) is investigating under an NCI CRADA, phenylbutyrate (NaPB; EL 530), currently in phase II clinical trials in prostate cancer, conducted by the NCI. NaPB and the related compound phenylacetate (NaPA) are potent differentiating agents. NaPB was more

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potent than NaPA in preclinical studies and has cytotoxic effects similar to sodium butyrate (NaBU) which induces apoptosis and differentiation through histone acetylation (Carducci M, AACR95, Abs. 2339).

Harrier (Durham, NC), established in the mid-1980s, is a virtual company developing novel topoisomerase I inhibitors that are glycosylated derivatives of camptothecin, in collaboration with the Institute for Drug Development (San Antonio, TX) and the University of Michigan (Ann Arbor, MI). Using a proprietary glycosylation process, Harrier developed HAR7, the glucal derivative of 7-(hydroxymethyl) camptothecin. HAR7 was efficacious against the PC-3 prostate carcinoma cell line on five-day and one-day schedules, causing 77% and 79% tumor growth inhibition, respectively, and modestly active against the DU-145 prostate tumor on single administration (Dexter, D, etal, 9th NCI-EORTC Symposium on New Drugs in Cancer Therapy, March 12-15, 1996, Abs. 444).

Ilex Oncology (San Antonio, TX), a private company, is developing three drugs for the treatment of solid tumors, including prostate cancer. As of April 1996, Ilex was evaluating, in an ongoing clinical trial, mitoguazone in patients with hormone refractory prostate cancer. To ensure enrollment of patients with very resistant disease into the study, in order to be eligible, patients must have failed up to two prior chemotherapy regimens. Study endpoints include PSA levels, pain (by assessment of a visual analog scale and analgesic consumption) and performance status. A clinical trial of chemotherapy-naive patients with HRPC is in planning stages.

Another agent, DFMO, originally developed to treat parasitic infections (i.e., African sleeping sickness), marketed as Ornidyl by Hoechst Marion Roussel (HMR), was also shown to inhibit both tumor cell growth and promotion and progression phases of carcinogenesis. DFMO is a potent, irreversible inhibitor of the activity of the enzyme ornithine decarboxylase (ODC) which controls a critical step in the synthesis of polyamines which play an important role in cell proliferation (i.e., high levels of ODC and polyamines are seen in tumor and other proliferating cells). Phase II trials of DFMO are underway in colon, bladder, breast, prostate and cervical cancer. ILEX has obtained exclusive worldwide rights from HMR for DMFO in cancer applications. DFMO was well tolerated in phase I clinical trials, with such side effects as diarrhea, anemia, leukopenia, nausea, and dizziness occurring in only 2% of patients on therapeutic doses. NCI's Division of Cancer Prevention and Control (DCPC) is currently sponsoring a number of phase II clinical trials of DFMO in patients who are at risk of developing cancer and/or in patients who are at risk of recurrence of various cancers (e.g., colon, bladder, cervix and prostate). The NCI also sponsored a completed trial which demonstrated that DFMO can be given at doses which effectively inhibit ODC for more than one year without toxicity. Another drug, DHAC (dihydro-5-azacytidine), that was developed as an alternative to 5-azacytidine, an antimetabolite with demonstrated antitumor activity in acute non-lymphocytic leukemia, may convert AR-negative prostate cancer cells into AR-positive cells.

ImClone Systems (New York, NY) is developing C225, a chimeric MAb EGFr antagonist, currently in phase Ib/IIa clinical trials against various solid tumors that overexpress EGFr. C225 blocks EGFr and, in combination with chemotherapy or radiation, eliminates cancerous cells through a mechanism which is believed to involve the induction of apoptosis. In animal studies, C225 exhibited pronounced anti-tumor activity, completely destroying human tumor cells in these animals and resulting in long-term tumor-free survival. In January 1996, ImClone announced the initiation of a phase Ib/IIa clinical trial of C225, in conjunction with Adriamycin (doxorubicin), in patients with advanced prostate carcinoma. This clinical trial is being conducted at Memorial Sloan-Kettering Cancer Center and the University of Virginia Cancer Center (Charlottesville, VA). The protocol calls for a total of 15 patients to receive C225 and Adriamycin by weekly intravenous administration based on a multiple injection dose escalation schedule. A similar phase Ib/IIa study of C225 is currently underway in patients with advanced head and neck, and lung carcinomas, as monotherapy or in combination with cisplatin. ImClone obtained exclusive worldwide rights to the patented C225 anti-EGFr antibody from the University of California in April 1993 and, in July 1994, also licensed intellectual property rights, including pending patent applications, from Rhône-Poulenc Rorer, to use EGFr MAbs in combination with FDA-approved chemotherapeutic regimens such as doxorubicin and cisplatin, to treat tumors that overexpress EGFr.

The Immune Response Corporation (Carlsbad, CA) is developing a technology designed to sensitize tumor cells to chemotherapy or radiation treatment. The therapy involves intratumoral injection of genetically modified fibroblasts to produce IL-3 prior to radiation therapy. In a preclinical study, tumors in rats treated with IL-3 expressing tumor cells were sensitized to radiation. In this study, all 10 of the treated rats demonstrated tumor regression, while controls did not show any improvement. Technology to use cytokine- modified fibroblasts for radiation sensitization was licensed from the University of California, Los Angeles (UCLA).

Matrix Pharmaceutical (Menlo Park, CA) announced in March, 1995 the initiation of phase II clinical testing of its IntraDose-CDDP injectable gel construct for the treatment of prostate cancer. IntraDose-CDDP is designed to provide local, sustained administration of cisplatin and to serve as a minimally invasive, non-surgical outpatient procedure for the treatment of prostate cancer.

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This study is intended to provide histologic evidence of clinical response. Approximately fifteen patients with prostate cancer, scheduled for radical prostetectomy, are administered three IntraDose-CDDP treatments over a period of six weeks. The gel is introduced using the standard long needle biopsy technique under ultrasound guidance, performed on an outpatient basis. Examination of the excised prostates is expected to provide information on histologic response, drug distribution, safety and intraprostatic dose requirements, which may then be used to optimize selection criteria for candidate patient populations for later-phase clinical trials. Matrix is using its proprietary drug delivery technology to develop products designed to improve the effectiveness and reduce the toxicity of established chemotherapeutic agents for the treatment of cancer and serious skin diseases. In the urological area, in addition to IntraDose-CDDP, the company is also developing other potential treatments for prostate cancer and BPH.

Pherin (Menlo Park, CA), founded in 1991, is developing pharmaceuticals based on discoveries in chemosensory neurobiology and human neuroanatomy. Pherin has identified a new family of compounds (vomeropherins) that are applied within the nasal passage. Pherin scientists have demonstrated that humans have specialized vomeropherin receptors in the nose located in a small structure, a functional sensory organ known as the vomeronasal organ (VNO), that may be used as a pathway for regulating brain functions. Vomeropherins exert a physiological or pharmacological effect on receptors in the VNO. Mammalian pheromones are naturally occurring, species-specific vomeropherins.

Pherin's technology may enable clinicians to manipulate various psychotropic and psychophysical functions controlled by the hypothalamus, a region of the brain responsible for the regulation of anxiety, fear, aggression, sex drive, water and salt balance, blood pressure, sugar and fat metabolism, endocrine function, appetite, and body temperature, among others. In the nose, vomeropherins bind to specific chemosensory receptors and generate bioelectrical impulses that are transmitted through neural pathways directly to the brain. Vomeropherins do not have to enter the general circulation nor the brain to evoke a therapeutic response. Pherin has identified and synthesized dozens of these substances and is testing them in human pilot studies to characterize their therapeutic properties. One class of these compounds has demonstrated the ability to evoke changes in specific hormone levels and may be used to treat hormone-dependent tumors such as prostate cancer.

Double-blind human trials have shown Pherin's compounds to be safe and efficacious. They may be delivered by a simple and minimal dosage mode of delivery through the nasal route and act through signal transduction to the hypothalamus, therefore limiting or eliminating systemic toxicity. In contrast to therapeutics that must enter the brain to exert their effect, vomeropherins trigger specialized nerves in the nose that connect to the hypothalamus region of the brain and, therefore, do not have to overcome the effects of the blood-brain barrier.

Vomeropherins bind to receptors in the VNO that have complementary specificity and initiate action potentials in sensory nerves, causing a signal to be transmitted through specific neural pathways to the brain. By binding to specific receptors, vomeropherins act rapidly and affect only the region of the brain which is targeted by the stimulated afferent nerve. This greatly reduces the potential for deleterious side effects. One patent has been issued, another has recently been allowed, and eight patent applications are pending in the USA and corresponding applications are pending worldwide.

Sheffield Medical Technologies (New York, NY), in collaboration with researchers at Baylor College of Medicine, characterized and isolated, originally from rat fetal urogenial sinus organ cells, a novel protein responsible for the production of urogenital growth inhibitory factor (UGIF), a protein that has been shown to inhibit the proliferation of prostate cancer cells. Sheffield, in collaboration with Baylor, is developing UGIF as a potential therapeutic for prostate cancer and BPH. The protein, termed ps20, has biological properties responsible for UGIF activity. Human cell lines exposed to ps20 *in vitro* were significantly growth-inhibited, indicating that the rat protein was biochemically similar to its human counterpart. Researchers theorize that a reduction in UGIF production may lead to poor cell differentiation that is associated with the progression of prostatic carcinomas, while the presence of UGIF activity may induce changes in cellular differentiation and lead to growth inhibition of poorly-differentiated or abnormal cells. It is believed that if UGIF activity can be enhanced, cancer cells may be inhibited from typical patterns of progression. Preclinical studies were initiated in late 1995. In December 6, 1995, Sheffield announced that researchers at Baylor sequenced the gene for ps20 and are now assessing the biological activity of a recombinant form compared to the proven activity of its natural counterpart. Sheffield also announced that a patent application claiming the use of UGIF for the treatment of prostate cancer has been allowed by the U. S. Patent and Trademark Office. Sheffield has an option to exclusively license the Baylor technology regarding ps20 and UGIF.

UroCor (Oklahoma City, OK) provides a broad range of diagnostic services for the clinical management of certain urological cancers and diseases. The company intends to complement its diagnostic services with therapeutic products and information systems to become an integrated disease management provider in the urology market to serve the needs of urologists and managed care organizations for the care of patients throughout a disease cycle. UroCor operates through four business units, Uro-

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Diagnostics, UroSciences, UroTherapeutics and Disease Management Information Systems. UroDiagnostics provides comprehensive diagnostic, prognostic and monitoring services to over 1,400 urologists nationwide. According to UroCor there are over 7,500 office-based urologists in the USA, including those affiliated with managed care organizations. UroCor believes that the urology market is particularly well-suited for an integrated disease management approach because urological diseases typically require extensive and prolonged diagnosis, prognosis and monitoring throughout the course of the disease.

UroCor deploys its own direct sales force to market its services to urologists' offices and managed care organizations. In the prostate cancer area, UroCor intends to develop and license technologies and products to enhance its product and services offerings. UroDiagnostics offers serum-based (PSA, PSA velocity and free/total PSA) and tissue-based (sextant biopsy and UroScore) tests for the management of prostate cancer. UroSciences is developing serum-based tests based on reverse transcriptase/polymerase chain reaction (RT-PCR) approaches and novel gene discoveries and tissue-based tests that employ molecular and antibody markers and computer-assisted image analysis of individual cancer cells. UroSciences combines access to external resources at academic centers and research institutions with the company's internal product development capabilities. UroSciences has developed a database of thousands of cellular tissue and serum specimens of patients that were provided by its clients and via contractual relationships with academic and research centers.

UroTherapeutics provides selected therapies to urologists for the care of patients in an office environment and plans to license, acquire from others or co-market urological pharmaceutical products. Disease Management Information Systems provides urologists and managed care organizations with access to the company's proprietary urological disease database, disease management models and practice management guidelines for the diagnosis and treatment of patients.

MEETING COVERAGE

NEW DEVELOPMENTS IN THE TREATMENT OF ADVANCED COLORECTAL CANCER

FROM THE 32ND ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY PHILADELPHIA, PA, MAY 18-21, 1996

- Advanced colorectal cancer is diagnosed in over 100,000 patients annually, in North America, Europe and Japan (see FO, V1 #12, p 273).
- Mainstay of treatment of advanced colorectal cancer is 5-fluorouracil (5-FU), in combination with folinic acid.
- Combinations of 5-FU with various other chemotherapeutic agents have resulted in higher response rates.
- 5-FU is expected to face competition as first-line treatment of advanced colorectal cancer from several new chemotherapeutics, including the newly approved agents, irinotecan and Tomudex, and several others in late stages of development (see FO, V1 #2/3 and #12).

5-FLUOROURACIL COMBINATIONS

5-Fluorouracil plus Leucovorin Calcium

When compared to 5-FU and levamisole combination, 5-FU plus leucovorin is at least as effective and, possibly, results in both longer overall survival and disease-free survival in patients with colon cancer. In a large-scale phase III clinical trial conducted between July 1989 and December 1990, 2,151 patients with Dukes' B and C colon cancer were randomly assigned to:

- 5-FU (500 mg/m^2) plus leucovorin (500 mg/m^2), weekly, for six weeks for six cycles
- 5-FU (450 mg/m^2, daily, for five days and, weekly, after day 29) plus levamisole (50 mg, orally, three times daily, for three days, repeated every 14 days) for one year
- 5-FU (500 mg/m^2) plus leucovorin (500 mg/m^2), weekly for six weeks for six cycles plus levamisole (50 mg, orally) three times daily for three days, repeated every 14 days for one year

Average time on the study was 63.4 months, with 49% of patients contributing survival information for at least five years. Grade 3 or higher toxicity was reported in 36% of 5-FU plus leucovorin patients; 38% of those on 5-FU, leucovorin and levamisole; and 28% of those on 5-FU plus levamisole. While there was no significant difference in overall or disease-free survival among the three arms, in pairwise comparisons, 74% of patients treated with 5-FU plus leucovorin lived over 5 years and 64% experienced five-year disease-free survival compared to 69% and 60%, respectively, for those treated by the 5-FU plus levamisole combination (Wolmark N, etal, Proc ASCO, Vol. 15, May 1996, Abs. 460:205).

5-Fluorouracil and Folinic Acid

A regimen of bi-weekly high-dose folinic acid combined with a 5-FU 48-hour infusion achieved a response rate comparable to that seen with more complex regimens in patients with metastatic colorectal cancer. Low enough toxicity also allows other drugs to be combined with this approach. In a multi-center phase II trial, 101 patients with metastatic colorectal cancer were treated with a two-hour infusion of folinic acid (500 mg/m^2), repeated on day two, followed by 5-FU (3 to 4 g/m^2) administered over 48 hours, every two weeks. The initial 5-FU dose of 3 g/m^2 for two cycles, was increased to 4

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g/m² if toxicity did not exceed grade 2. Cycles were repeated until disease progression. Overall, among 89 evaluable patients, the objective response rate was 33.7%, with two CRs (2.2%) and 28 PRs (31.5%) and disease stabilized in 43 patients (46.7%). Median progression-free survival was eight months and median overall survival was 16 months, with 62% of patients surviving for one year. Neutropenia was the major hematologic toxicity (4.3%), with three patients experiencing febrile neutropenia episodes. Non-hematologic toxicities included 5-FU-related encephalopathy (1.1%), nausea (2.2%), mucositis (3.2%), diarrhea (2.2%), and 5-FU-related angina pectoris (1.1%) (Beerblock Y, etal, Proc ASCO, Vol. 15, May 1996, Abs. 490:212).

5-Fluorouracil and Trimetrexate

Trimetrexate (Neutrexin; U.S. Bioscience), a nonclassical dihydrofolate reductase inhibitor which potentiates the cytotoxicity of 5-FU but does not compete with leucovorin for cellular uptake, has been shown to be highly active and well tolerated when combined with 5-FU and leucovorin in the treatment of advanced colorectal cancer. While standard therapy with 5-FU modulated with leucovorin usually results in an overall objective response rate of about 23%, adding trimetrexate to this regimen increases the response rate to 48% in patients with unresectable or metastatic colorectal cancer. In this study, 36 previously untreated patients with unresectable or metastatic colorectal cancer received trimetrexate (110 mg/m²) on day one as a 60-minute IV infusion; leucovorin (200 mg/m²) on day two as a 60-minute IV infusion 24 hours after initiation of trimetrexate; 5-FU (500 mg/m²) as an IV bolus on day two immediately following leucovorin; and then oral leucovorin (15 mg) every six hours times seven doses starting six hours after 5-FU. Treatment was repeated weekly for six weeks, followed by two weeks rest (one cycle). Patients were treated until their disease progressed or they experienced unacceptable toxicity.

Among 29 evaluable patients, there were two (7%) CRs, 12 (41%) PRs and disease stabilized in 12 (41%). With median follow-up of 51.8 weeks, median time to disease progression was 25.7 weeks and, while median survival was not reached at the time results were presented, it was estimated at 53.4 weeks. Toxicities of the combination were generally manageable. Hematologic toxicity was mild, with only three patients experiencing grade 3/4 neutropenia; no cases of grade 3/4 thrombocytopenia were observed. Gastrointestinal toxicity was somewhat more of a problem with grade 3 or 4 diarrhea being reported in 58% of treated patients (Blanke C, etal, Proc ASCO, Vol. 15, May 1996, Abs. 433:198).

5-Fluorouracil and Azidothymidine (AZT, zidovudine)

The combination of AZT (Retrovir; Glaxo Wellcome), 5-FU and leucovorin exhibits promising activity in patients with metastatic colorectal cancer. In initial phase I/II studies, chemotherapy-naive patients with metastatic colorectal cancer were enrolled to determine maximum tolerated dose of AZT, pharmacokinetics of the drug combination, and activity of AZT when combined with 5-FU and leucovorin. In the first study, 35 individuals received 5-FU (500 mg/m²) as an IV bolus once-a-week in the middle of a two-hour infusion of leucovorin (500 mg/m²), with AZT (0.5 to 10 g/m²) administered as a 90- to 120-minute IV infusion starting 60-minutes after 5-FU, in successive cohorts of three patients. Among 34 evaluable patients, overall response rate was 44%, with five (15%) CRs and 10 (29%) PRs. Median duration of response was 44 weeks, and median survival time was 15 months. Hematologic toxicities were manageable; only 3% of patients experienced grade 3/4 leukopenia. Other grade 3/4 toxicities included diarrhea (17%) and stomatitis (3%). Hypotension occurred only in patients treated at AZT doses above 7 g/m² and became dose-limiting at 10 g/m². Based on these findings, a phase II study enrolled 28 patients with metastatic colorectal cancer treated with the same doses of 5-FU and leucovorin as in the phase I study and AZT doses up to 8 g/m² (MTD). Among evaluable patients, the initial objective response rate (all PRs) was 42% (11/26) (Brunetti I, etal, Proc ASCO, Vol. 15, May 1996, Abs. 493:213).

5-Fluorouracil and 776C85

A combination of 776C85 (776; Glaxo Wellcome), a potent inactivator of dihydropyrimidine dehydrogenase, the rate limiting enzyme in fluorouracil catabolism, and 5-FU, shows significant anti-tumor activity in patients with 5-FU-refractory colon and breast cancer. Animal studies had demonstrated that 776 increased the antitumor efficacy and therapeutic index of 5-FU. Based on these findings, a phase I trial was designed to determine the maximal dose of IV 5-FU that could be safely administered with oral 776 with or without leucovorin, any toxicities associated with this treatment, and the pharmacokinetics of the 776 and 5-FU combination. Forty-five patients with refractory cancers (29 colorectal, 5 pancreatic, 4 breast, 3 renal, 3 biliary and one sarcoma) enrolled in the study, were treated with three successive dosing periods each followed by a 2-week interval as follows: first, 776 days one to seven; second, 776 days one to three with 5-FU on day two; and, third, 776 days one to seven with 5-FU on days two to six. The drug 776 was tested at doses of 0.74 mg/m², 3.7 mg/m², and 18.5 mg/m² in the first nine patients with 5-FU at 10 mg/m² or 20 mg/m². Subsequent patients received a fixed daily dose of 776 at 10 mg with 5-FU at 15-30 mg/m². Leucovorin (50 mg daily oral dose) was administered to 19 patients who were treated according to the following regimen: seven with 5-FU at 10 mg/m², four at 15 mg/m², six at 20 mg/m², and two at 25 mg/m².

Toxicities included grade 3/4 neutropenia, experienced by 10 patients, and grade 3/4 diarrhea, by seven, as well as lesser grades of nausea, vomiting, stomatitis, and fatigue. Also, there were three treatment-related deaths

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from sepsis at 5-FU doses of 20 mg/m^2 and 25 mg/m^2. With regard to the pharmacokinetics of the drug combination, 776 decreased the clearance of 5-FU, prolonging its half-life, and reducing MTD. Based on these findings, drug doses recommended for phase II/III testing are 25 mg/m^2 for 5-FU alone or 20 mg/m^2 with leucovorin given on days two to six with 776 (10 mg) administered daily on days one to seven, every 28 days (Schlisky RL, etal, Proc ASCO, Vol. 15, May 1996, Abs. 1544:485).

IRINOTECAN

Irinotecan (CPT-11), a semisynthetic analog of camptothecin, is a new topoisomerase I inhibitor with considerable activity as a single agent in both chemotherapy-naive and 5-FU-refractory patients with advanced colorectal cancer. Irinotecan is a prodrug that changes to an active metabolite (SN-38) which is 100-fold more active than the parent compound. Originally developed by Yakult Honsha in Japan, in collaboration with Daiichi Pharmaceutical (Tokyo, Japan), the compound was cleared for marketing in Japan in January 1994 as Campto/Topotecin, for primary lung, cervical and ovarian cancers. Although the drug is more active than any other as second-line therapy, approval of irinotecan generated controversy in Japan, where the product was reported to be associated with serious ADRs, such as reduced white blood cell counts, and a number of fatalities, during clinical testing. Certain use precautions have been applied to the product in Japan.

In January 1994, Pharmacia & Upjohn (P&U) acquired USA and Canadian marketing rights to irinotecan from Yakult Honsha and Daiichi. Under the agreement, P&U will develop, register and market irinotecan in North America and Daiichi will continue to collaborate and copromote it with P&U in the USA. P&U filed an NDA in October 1995 to market the drug as Camptosar for refractory colorectal, cervical and lung cancer and non-Hodgkin's lymphoma in an IV formulation; an oral formulation is also under development. Irinotecan was approved by the FDA on June 14, 1996, under accelerated approval, 28 hours after it was recommended by the Oncologic Drugs Advisory Committee for the treatment of refractory (metastatic) colorectal cancer. Following approval of Hycamptin on May 28, 1996, irinotecan is the second camptothecin analog to gain approval within one month. Actually, irinotecan is the first drug in 40 years to be approved for the treatment of colorectal cancer in the USA.

Irinotecan is marketed in Europe as Campto by Roger Bellon (Rhône-Poulenc Rorer) which submitted a PLA in its first European market, France, in late 1994, for the treatment of advanced colorectal cancer which progressed after standard treatment; Campto was launched in France in September 1995 for this indication. At the same time, Rhône-Poulenc Rorer amended its marketing agreement with Yakult Honsha (Tokyo, Japan) and now has rights to develop and market irinotecan in over 100 countries outside Japan, the USA and Canada.

P&U in the USA and RPR in Europe are also investigating irinotecan as first-line therapy of metastatic colorectal cancer because its efficacy for this indication appears to be comparable to 5-FU. Forty-one chemotherapy-naive patients with measurable metastatic colorectal cancer were treated at Memorial Sloan-Kettering Cancer Center, Cornell University Medical College (New York, NY) with a 90-minute infusion of irinotecan (125 mg/m^2) administered weekly for 4 weeks every 6 weeks. There were thirteen (32%) PRs. Median response duration was 8.1 months and median survival time was 12.1 months (2.1 to 21.7) for all 41 patients. Grade 3 or 4 diarrhea occurred in 29% of patients and neutropenia in 22%. Strict adherence to an anti-diarrheal regimen of loperamide and diphenyldramine significantly reduced the incidence of severe diarrhea to 9%. No correlations were seen between pharmacokinetics of irinotecan/SN-38 and the clinical parameters of response, survival, or incidence of diarrhea (Conti JA, etal, Journal of Clinical Oncology, 1996 Mar, 14(3):709-15). In a much larger European study, involving 213 chemotherapy-naive and pretreated patients, overall response rate in evaluable patients was 20.5%.

Major dose-limiting toxicities of irinotecan are delayed diarrhea and neutropenia. Diarrhea is adequately managed by prophylactic treatment with high dose loperamide. A new anti-secretory anti-diarrheal agent, acetorphan (Tiorfan; Bioprojet), a specific enkephalinase-inhibitor, is also under evaluation for the treatment of irinotecan-induced diarrhea (Extra JM, etal, ECCO8, Abs. 727:S152). Use of prophylactic antibiotics is also expected to mitigate the effects of neutropenia.

5-Fluorouracil and Irinotecan Combinations

Investigators are also evaluating irinotecan, with a promising measure of success, in combination with 5-FU for the treatment of metastatic colorectal cancer (Rixe O, etal, ECCO8, Abs. 955:S197). In a recent study, irinotecan was administered on a dose escalation schedule (100 mg/m^2, 125 mg/m^2, 150 mg/m^2, and 175 mg/m^2) as a 90-minute infusion on days one and 15. A fixed dose of 5-FU (600 mg/m^2) daily was given sequentially as a continuous IV infusion from day three on, for five consecutive days. Six patients with advanced colorectal cancer were enrolled into each dose level of irinotecan, with the treatment cycle repeated every four to five weeks. Among the 20 patients who had entered the trial at the time of this report, 19 receiving doses of irinotecan of 100 mg/m^2 to 150 mg/m^2 were evaluable. MTD was not reached at these levels. Partial responses were achieved in five patients for a preliminary response rate of 26.3%. Toxicities were relatively well managed; one patient in the group receiving irinotecan at the 125 mg/m^2 dose level experienced grade 4 neutropenia and one grade 3 diarrhea (Yamao T, etal, Proc ASCO, Vol. 15, May 1996, Abs. 1527:481).

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ZD1694

Final results and survival data comparing ZD1694 (Tomudex; Zeneca), a direct and specific thymidylate synthase inhibitor, with conventional 5-FU and leucovorin therapy, point out that the two approaches have comparable efficacy but that Tomudex has a much better safety profile. Of 439 previously untreated patients with advanced colorectal cancer, 222 were randomly assigned to Tomudex (3 mg/m^2 IV) once every three weeks, and 212 to 5-FU (425 mg/m^2) and leucovorin (20 mg/m^2) administered as an IV bolus daily for five days, repeated every four to five weeks. Five randomized patients did not receive therapy, but all others under treatment, whether eligible or evaluable, were included in the efficacy analysis. The overall objective response rates were 20% for Tomudex and 16.5% for conventional therapy. Median time to disease progression was 4.9 months and 3.5 months, respectively, while median survival was 10.3 months and 10.5 months, respectively. There were no statistically significant differences between the two treatments in any of the efficacy endpoints. There was, however, a significant difference in the safety profiles of the two treatment approaches. Those treated with Tomudex experienced much lower rates of potentially life-threatening toxicities than did patients treated with the 5-FU/leucovorin combination. Toxicities included higher rates of grade 3/4 leucopenia which occurred in 30% of those treated by 5-FU/leucovorin versus 14% of those on Tomudex, and mucositis (22% and 2%, respectively). There was also a much higher incidence of alopecia among those treated by 5 FU/leucovorin (Seitz JF, etal, Proc ASCO, Vol. 15, May 1996, Abs. 446:201)

A more comprehensive analysis of the safety profiles of the two treatment approaches used in the Tomudex Advanced Colorectal Cancer trial, confirmed an association of increasing age and female gender with grade 3 and 4 leucopenia and mucositis, among patients treated with modulated 5-FU. On multivariate analysis, among patients treated by 5-FU and leucovorin, female gender predicted for increased grade 3/4 leucopenia, while increasing age (over 60) was associated with both increased grade 3/4 leucopenia and increased grade 3/4 mucositis. Among those treated by Tomudex, the only association noted was an increase in transaminase in females, which appeared to be of limited clinical significance. On univariate analysis, there was a statistically significant inverse relationship between lean body mass and grade 3/4 leucopenia among persons treated with 5-FU and leucovorin (Zalcberg J, etal, Proc ASCO, Vol. 15, May 1996, Abs. 447:201).

OXALIPLATIN

Oxaliplatin (Debiopharm), a diamminecyclohexane (DACH) platinum derivative, which has demonstrated responses in preliminary studies of patients with metastatic colorectal cancer, was shown to be safe and active in an ongoing clinical trial. To date, 24 patients with metastatic colorectal cancer, six of whom had previous adjuvant chemotherapy, received oxaliplatin (130 mg/m^2) as a two-hour IV infusion, without hydration, every three weeks. During the trial, no dose reduction was required and only four of 77 evaluable cycles were delayed. Among 14 patients evaluable for efficacy, an objective response rate of 21.4% (3 PRs) was observed and disease stabilized in six (43%). Among 19 patients evaluable for safety, all had mild peripheral sensitive neuropathy (grade 1/2) that subsided completely between treatment cycles. One patient suffered grade 3/4 anemia, two had grade 3/4 nausea, and three grade 3/4 vomiting. Generally, oxaliplatin was well tolerated (Diaz-Rubio E, etal, Proc ASCO, Vol. 15, May 1996, Abs. 468:207).

5-Fluorouracil and Oxaliplatin

Treatment with oxaliplatin in combination with 5-FU and leucovorin resulted in 25 (25.5%) objective responses among 98 patients (Louvet C, etal, Proc ASCO, Vol. 15, May 1996, Abs. 467:206#).

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