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STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

BREAST CANCER — PART V
NOVEL DRUGS IN DEVELOPMENT

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Numerous agents are in development (see Exhibit 1) for the treatment of all stages of breast cancer. Clinical trials of agents approved for other indications that are being investigated alone or in combination for the treatment of various stages of breast cancer, were described in Part IV of this article (see FO, V2 #7/8). Currently, the NCI alone is supporting nearly 200 clinical trials that relate to breast cancer. In terms of novel approaches, agents in preclinical and early clinical development listed in Exhibit 1, may not specifically target breast cancer but are generally considered potentially effective against most solid tumors. Because of the importance of breast cancer in terms of incidence and prevalence, the majority of these agents are being developed for the treatment of various stages of this malignancy. References are provided in Exhibit 1 regarding information about the nature and status of many of these agents being developed for multiple tumor targets that was presented in previous issues of FUTURE ONCOLOGY.

NEW HORMONAL THERAPIES

Hormonal therapy has been a pivotal treatment and maintenance approach in every manifestation of breast cancer, both extending survival and increasing disease-free survival of breast cancer patients. The aim of hormonal therapy is to deprive tumors of estrogen and progesterone without affecting estrogen levels in other tissues to avoid osseous and cardiovascular complications. Hormonal therapy for breast cancer involves various agents and strategies depending on patient attributes and disease stage. Tamoxifen-based anti-estrogen therapy is commonly used in both pre- and post-menopausal women, as first-line hormonal therapy. However, this drug is primarily effective in estrogen receptor-positive (ER+) or progesterone-receptor-positive (PgR+) breast cancer. Progestins, such as megestrol acetate (Megace; Bristol-Myers Squibb) or medroxyprogesterone (Provera; Pharmacia & Upjohn), usually associated with more serious side effects than tamoxifen, are currently relegated to third-line treatment in both pre- and post-menopausal women. Aromatase inhibitors, such as the recently launched anastrozole (Arimidex; Zeneca), are used in post-menopausal women as second-line hormonal therapy in patients who failed tamoxifen. LHRH antagonists such as leuprolide (Lupron; TAP Pharmaceutical) and goserelin (Zoladex; Zeneca) are only used in pre-menopausal women as an alternative to surgical removal of the ovaries. Another approach pursued by Aphton (Miami, FL) uses a vaccine-like product, Gonadimmune, to induce an immune response (active immunization) to elicit antibodies that neutralize GnRH and, in turn, suppress the production of female steroids estrogen and progesterone.

Currently, more than 550,000 women with breast cancer are treated with hormonal therapies in North America, Europe and Japan (see Exhibit 2). Tamoxifen, the standard hormonal treatment, however, is associated with various side effects, the most serious being an increased risk of developing endometrial cancer. In view of tamoxifen's large market and the fact that its patent has expired in most countries outside the USA, developers of alternative anti-estrogen approaches are being lured by a potentially lucrative opportunity in the management and chemoprevention of breast cancer. However, developing agents that interfere with hormonal activity that are superior to tamoxifen, has proven a very

Exhibit 1
Novel Drugs in Development for the Management of Breast Cancer

Primary Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Drug Type ❑ Target ❑ Mechanism ❑ Delivery	Status ➢ Location ❑ Indication	Comments
Aastrom Biosciences	Cell Production System (CPS)	Expansion of lymphoid blood cells for gene and cell therapies ❑ *ex vivo*	Phase I (2/95)➢ USA	Collaboration with RPR Gencell was terminated 9/96
Abgenix (Cell Genesys)	Humanized anti-EGFR MAb	Fully human MAb directed against a cell-surface receptor for EGF	Preclin (6/96)➢ USA	
Aeson Therapeutics (Research Corporation Technologies) ❑ Temple U Fels Institute for Cancer Research and Molecular Biology (developer); NCI	Fluasterone	Dehydroepiandrosterone (DHEA) analog	Preclin (96)➢ USA	Clinical trials planned to start in Europe; Aeson is negotiating with NCI to test fluasterone in breast cancer prevention
Agouron Pharmaceuticals ❑ Hoffmann-La Roche (licensee outside NA; co-promoter NA)	AG-3340	Small, synthetic molecule ❑ selectively inactivates certain members of the family of matrix metalloprotease (MMP) enzymes (gelatinases, stromelysins and collagenase-3) ❑ PO	Phase I➢UK ❑ solid tumors	
Agouron Pharmaceuticals	AG2034	Small, synthetic molecule ❑ inactivates glycinamide ribonucleotide transformylase (GART) that promotes cancer cell proliferation	IND (10/96)➢USA	
Alfacell ❑ NIH, Scientific Protein Laboratories (American Home Products)	P-30 ❑ Onconase	Rnase; novel enzyme (smallest member of the superfamily of pancreatic ribonucleases) ❑ causes degradation of RNA within cancer cells, preventing cell growth and proliferation ❑ IV	Phase II (4/96)➢ USA ❑ metastatic breast cancer	Scientific Protein Laboratories will supply both phase III clinical and future commercial quantities of Onconase for Alfacell (5/95)
Allergan Ligand Retinoid Therapeutics (Allergan/ Ligand joint venture) ❑ NCI	9-cis-retinoic acid (9cRA) ❑ 1057, LG-1057, LGN-1057) ❑ Panretin Oral	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	Preclin➢USA (plans are underway for the NCI to evaluate ALRT1057 Oral in breast cancer)	Phase II/III (95)➢USA ❑ APL; (see FO, pp 31 and 250); LGD-1057 analogs also being developed
AltaRex		Anti-idiotypic MAb ❑ binds with high affinity to CA15.3; stimulates the immune system through the generation of autologous antigen mimics ❑ IV	Preclin➢Canada	
Andrulis Pharmaceutical	GB-21	Platinum polymer complex with prolonged half life *in vivo* ❑ IV	Preclin (5/96)➢ USA	Demonstrated selectivity for breast and renal cancer (Fiebig HH, AACR96, Abs. 2021: 297)
Ansan ❑ Bar-Ilan Research and Development (Israel)	AN9 ❑ Pivanex	Butyric acid analog ❑ promotes cellular differentiation; induces apoptosis ❑ injectable	Phase I (3/96)➢ USA	

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AntiCancer ❑ Shionogi	Methioninase ❑ AC9301 ❑ ONCase	Water soluble enzyme ❑ breaks down methionine in blood; arrests tumor cell growth before mitosis ❑ IV	Phase I (1/96)➢ USA ❑ advanced breast cancer	May be used to modulate the effects of paclitaxel; also see FO, p 253
Aphton	Gonadimmune	Antihormone immunogen ❑ blocks GnRH secretion ❑ IV	Preclin➢USA	See FO, pp 313 and 320
Applied Immune Sciences (Rhône-Poulenc Rorer)	IL-2 gene transfer ❑ Avectin	Active immunotherapy ❑ irradiated autologous human tumor cells modified to express IL-2 delivered by a cationic liposome complex ❑ subcutaneous injection	Phase I (1/27)➢ USA ❑ refractory or recurrent metastatic breast cancer	Lyerly HK, Duke U Medical Center (Durham, NC); RAC# 9409-086, approved 9/12/94
Applied Immune Sciences (Rhône-Poulenc Rorer)	CEA-based vaccine	Active immunotherapy; CEA peptide (CAP)-pulsed autologous human cultured dentritic cells ❑ IV	Phase I➢USA ❑ CEA-expressing metastatic solid tumors	Lyerly HK, Duke U Medical Center
Aquila (was Cambridge Biotech)	QS-21 adjuvant ❑ Stimulon	Adjuvant used in cancer vaccines	Clinical➢USA	Has been tested in over 500 people
Aronex Pharmaceuticals ❑ Boehringer Mannheim (Corange; worldwide licensee, 1/97)	AR209	Antibody-toxin complex containing ligand and *Pseudomonas* exotoxin ❑ binds to cancer cells expressing erbB-2 oncoprotein, is transported intracellularly and kills the cell ❑ IV	Preclin (5/96)➢ USA ❑ solid tumors	
Aronex Pharmaceuticals ❑ M. D. Anderson Cancer Center (licensor)	Annamycin	Anthracycline analog; liposomal formulation of DOX analog; active against cancer cells that do not respond to DOX ❑ IV	Phase I/II(5/96)➢ USA ❑ breast cancer refactory to DOX	Potential use in solid tumors, leukemias and lymphomas; see FO, p 132
Asta Medica ❑ Kayaku Asta Medica (jv with Nippon Kayaku, Japanese rights)	D-21266	Alkylphospholipid analog; miltefosine analog	Phase I (8/96)➢ Europe	
Asta Medica ❑ Tulane U (licensor), Kayaku Asta Medica (jv with Nippon Kayaku) and Shionogi (Japanese rights)	Cetrorelix ❑ SB-075, SB-75	Decapeptide LHRH-antagonist ❑ SC	Phase II (8/96)➢ Germany	See FO, p 306; also phase II in infertility
Atrix	Atrigel delivery system (incorporating cisplatin, vinblastine or DOX)	Drug delivery system ❑ intralesional	Preclin➢USA	
Axis Genetics ❑ Oxford U	Epicoat chimeric virus particle (CVP) technology	Plant production of proteins ❑ genetically-modified plant (cowpea) mosaic viruses express foreign peptides on their surface; when inoculated into cowpea plants the latter produce large quantities of the virus	Research (12/96) ➢UK	See FO, p 392
Banyu (Merck)	NB-506	Topoisomerase I inhibitor and DNA and RNA polymerase inhibitor; indolocarbazole	Phase I (11/96) ➢Japan	Suggested dose is 350-450 mg/m^2 for phase II clinical trials

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BASF Bioresearch (BASF AG)		Novel peptide-like synthetic compounds ❑ IV	Preclin➢USA	Induced complete regression of breast cancer *in vivo* even when treatment started after extensive tumor growth; also, 80-100% long-term, tumor-free survivors (more than 90 days) were observed (Nelson C, etal, AACR95, Abs. 2334:392)
BASF Bioresearch/ Knoll Pharmaceutical (BASF AG)	Dolastatin ❑ LU 103793 (NSC D-669356)	Synthetic derivative of dolastatin 15, an antiproliferative compound isolated from the Indian Ocean sea hare *Dolabelia auricularia* ❑ interferes with the tubulin system	Phase I➢USA	
Baxter ❑ Yeda (developer)		MAbs combined with CTL to produce cells known as T bodies ❑ *ex vivo* cellular therapy	Research➢USA, Israel	
Biomeasure (Beaufour-Ipsen) ❑ Tulane U (Dr. David Coy, licensor)	Lanreotide ❑ BIM-23014 ❑ Angiopeptin, Dermopeptin, Somatuline	Octapeptide; somatostatin analog ❑ hormone and growth factor antagonist ❑ IM, depot	Phase I/II (95) ➢Europe (Italy)	
Biomira ❑ Ribi ImmunoChem Research (licensor-adjuvant)	Theratope STn-KLH+ Detox-B adjuvant	Active specific immunotherapy (ASI); synthetic cancer-associated carbohydrate antigen containing versions of mucins found on the surface of tumor cells, combined with keyhole limpet hemocyanin (protein carrier) and adjuvant ❑ IV	Phase II (c2/96) ➢USA, UK; phase II/III (2/96)➢ Canada	Theratope in combination with IFN-α and low dose mitomycin C boosts responsiveness of T cells in breast and GI cancers; also see FO, pp 51, 233, 348; phase III is in combination with cyclophosphamide
Biomira ❑ Imperial Cancer Research Technology (licensor)	BP1-7 (MUC-1 peptide)-KLH	Synthetic peptide antigen ASI; ❑ IV	Phase I (b2/95) ➢USA; phase I/II ➢Canada	
Biomira	BLP-25 (MUC-1 peptide)	Peptide antigen formulated in liposomes ❑ IV	Phase I (2/96) ➢Canada	
Biomira		ASI; glycopeptide technology that combines both peptide and carbohydrate cancer epitopes into a single molecule which has been shown to be highly immunogenic ❑ IV	Preclin➢Canada	
Biotherapies Incorporated	Recombinant mammastatin	Protein that inhibits growth of normal and transformed human mammary cells; it is not produced in breast cancer	Preclin➢USA	Ervin PR and Wicha MS, AACR96, Abs. 2722:399
Boehringer Mannheim (Corange)	BBR 2778 (also derivatives BBR 3376, 3390, 3409, 3438, 3456 and 3479)	9-AZA-anthrapyrazole	Phase I (5/96) ➢Italy	Menta E, etal, AACR96, Abs. 2015:296
Bone Care International	LR-103	Natural vitamin D metabolite	Preclin➢USA	Phase I (planned for 1997) (8/96)➢USA ❑ psoriasis
Boston Life Sciences	CDI	Naturally-occurring protein ❑ inhibits new capillary formation	Preclin (96) ➢USA ❑ solid tumors	

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Bristol-Myers Squibb ❑ Genzyme Transgenics (manufacture) and Ixsys (R&D)	BR96-DOX immunoconjugate ❑ BMS-182248	Chimeric MAb BR96 that recognizes a Le^y-related carbohydrate antigen bound by eight DOX molecules	Phase II (9/96) ➢USA	BMS entered an agreement with Genzyme Transgenics for the production of BR96 MAb in transgenic goats
Bristol-Myers Squibb	BR96 sFv-PE40 immunotoxin	Single-chain immunotoxin fusion protein; MAb BR96 linked to truncated form of *Pseudomonas* exotoxin, PE40	Phase I (9/96)➢ USA ❑ solid tumors	
Bristol-Myers Squibb ❑ Manitoba Cancer Treatment and Research Foundation, U Manitoba (licensor), NCI (Canada)	DPPE	Chemosensitizer ❑ enhances effects of chemotherapeutics	Phase II➢Canada, USA ❑ hormonally-resistant breast cancer	Phase II in metastatic breast cancer in combination with DOX is being conducted by the NCI (Canada); see FO, p 393
Bristol-Myers Squibb ❑ NCI	Bryostatin 1	Natural macrocyclic lactone derived from murine bryozoam *Bugula neritina* ❑ activates protein kinase C; triggers release of reactive oxygen radicals by polymorphonuclear neutrophils (PMN) and monocytes ❑ IV	Phase I➢USA	Among 11 patients treated with an MTD of bryostatin of 60 $\mu g/m^2$ and a fixed oral dose of all-trans retinoic acid (75 mg/m^2), there were no responses and no significant toxicity (Toppmeyer D, etal, ASCO96, Abs. 1530:482); also phase II (b94)➢USA ❑ renal cancer and NHL
Bristol-Myers Squibb	BMS-181174 (BMY-25067)	Mitomycin C analog ❑ IV	Phase I (5/96) ➢USA	MTD was 65 mg/m^2 in a single 30-minute infusion q 4 weeks (Johnson CA, etal, ASCO96, Abs. 1535:483)
British Biotech ❑ Tanabe (licensee, Japan, 9/96)	Marimastat ❑ BB-2516	Matrix metalloproteinase inhibitor ❑ oral	Phase III (5/96) ➢UK, USA ❑ solid tumors; phase I➢ UK, USA ❑ breast cancer metastasized to the bone	Combination with carboplatin to be evaluated in the UK; also see FO, pp 104, 194, 196, 310 and 313
British Biotech	BB-10010	Macrophage inflammatory protein-1α analog; bone marrow protector, mobiliser	Phase I➢USA	Administered at doses of 5, 10, 30 and 100 mg/kg SC daily for 3 days with cyclophosphamide (3 gm/m^2) on day 1; G-CSF support given in cycles 2-6 (Gordon, MS, etal, ASCO96, Abs. 728:273)
BTG/EORTC	C-1311, BTG-1760	Novel substituted imidazoacridinone ❑ completely arrests cells in G2; causes irreversible tumor cell inhibition and death; inhibits catalytic activity of DNA topoisomerase I and II *in vitro*	Preclin (6/96)➢UK	
BTG ❑ SmithKline Beecham (exclusive licensee); Cancer Research Campaign Centre for Cancer Therapeutics, Institute of Cancer Research	Idoxifene (pyrrolidino-4-iodo-tamoxifen) ❑ CB-7386, CB-7432	Improved analog of tamoxifen; estrogen antagonist	Phase II (6/96)➢UK	SmithKline Beecham will take full responsibility for development after completion of phase II
BTG	Pyridoglutethimide; rogletimide	Aromatase inhibitor (first generation) ❑ lowers plasma estrogen ❑ PO	Phase II (6/96) ➢UK, USA	U. S. Bioscience discontinued development; agent available for license by BTG

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Cangene (acquired by Apotex 11/95)	Allevorin; recombinant interleukin-3 (rIL-3) produced using Cangenus, a proprietary gene expression system	Cytokine ❑ stimulates precursor blood cells to accelerate bone marrow recovery after radiation and chemotherapy; most effective when administered with another growth factor, such as GM-CSF	Phase I/II (b9/94) ➢Canada	Project is on hold, the company is looking for a partner (8/96)
Canji (Schering-Plough) ❑ Geraldine Brush Cancer Research Institute at California Pacific Medical Center	Brush-1	Gene therapy	Preclin (95)➢USA	
Canji (Schering Plough)	H-NUC TSG	Gene therapy	Preclin➢USA	
Canji (Schering Plough)	ACN53	Gene therapy ❑ delivery of p53 gene by AAV vector		Phase I➢USA ❑ hepatic cancer (RAC# 9412-097 for intra-arterial delivery, approved in 12/94)
CarboMed	CM101 ❑ GBS toxin	Polysaccharide exotoxin produced by Group B Streptococcus	Phase I (c12/94) ➢USA ❑ solid tumors, including breast cancer	Phase II to start in 1996 in collaboration with the NCI
Carrington Laboratories ❑ U Texas Medical School	Acemannan ❑ CARN 750 ❑ Carravex	Highly actetylated, polydispersed linear mannan obtained from the mucilage of Aloe vera/injectable	Phase I (12/95) ➢USA	Phase II planned for 1997; see FO, pp 324-325
Cascade Oncogenics		Genomics; identification of genes that are transcriptionally regulated by p53	Research➢USA	
CEL-SCI	Multikine	Immunotherapeutic, multicytokine combination ❑ intralesional	Phase I (c87) (12/95)➢UK	See FO, p 321
Cell Genesys ❑ Ludwig Institute for Cancer Research and Sloan-Kettering Institute for Cancer Research		Gene therapy ❑ engineered T cells that recognize a specific protein on the surface of tumor cells ❑ *ex vivo*	Preclin (3/96) ➢USA ❑ solid tumors	
Cell Genesys ❑ Dana-Farber Cancer Institute		Gene therapy	Preclin (1/97) ➢USA	
Cell Genesys ❑ Arizona Cancer Center, U Arizona		Gene therapy	Preclin (1/97)➢USA ❑ solid tumors	
Cell Genesys ❑ NCI (CRADA)		Gene therapy; use of MAb gene CC49 to construct immune cells that target tumor-associated antigen TAG-72	Preclin➢USA ❑ solid tumors	
Cell Pathways ❑ NCI	FGN-1	Sulfone metabolite of the non-steroidal anti-inflammatory drug (NSAID) sulindac; organic molecule ❑ apoptosis inducer ❑ PO	Preclin➢USA	Phase I (3/95)➢USA ❑ colon cancer (orphan drug); see FO, p 31
Cell Therapeutics ❑ Christie Hospital, Cancer Research Campaign, Memorial Sloan-Kettering Cancer Center	CT-2584, CT-2583, CT-2586, CT-3536	Low molecular weight phospholipid signaling inhibitors ❑ alter production of the intracellular second messenger, phosphatidic acid (PA), which is involved in a variety of agonist-stimulated cell growth and activation responses ❑ infusion	Phase I➢USA	See FO, p 129

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CellPro	CEPRATE SC stem cell concentration system	Provides selected stem cells to repopulate the immune and blood systems	A (12/96)➢USA, Europe, Canada ❑ autoBMT in breast cancer	Also used in gene therapy trials to enhance gene insertion to treat cancer and AIDS
Celltech ❑ American Cyanamid (American Home Products)	Calicheamicin ❑ CMB401 (was CDP 671)	Cytotoxic conjugate; rhMAb linked to calicheamicin, a synthetic enediyne and sequence-specific DNA ligand; anti-polymorphic epithelium mucin (PEM/ muc-1) conjugate ❑ IV	Phase I/II (96) ➢UK	
Centocor ❑ Apollon (licensor)	GeneVax	DNA-based vaccine	Preclin➢USA	Centocor plans to focus initially on vaccines for prostate, breast and colorectal cancer; see FO, pp 248 and 395
Centocor ❑ Glaxo Wellcome (worldwide rights)	Panorex ❑ 17-1A MAb	Immunotherapy ❑ binds to colon cancer cells and destroys them using various immunologic mechanisms including complement and/ or antibody dependent cellular cytotoxicity (ADCC)	Preliminary studies indicate potential in solid tumors including breast cancer	L (2/95)➢Germany; prereg➢Austria, Switzerland, Finland, Sweden; phase III➢NA, Europe ❑ adjuvant therapy for post-operative colorectal cancer; see FO, pp 52 and 351
Chiron	2B-1	Bispecific murine MAb; immunostimulant ❑ effects lysis of tumor cells expressing c-erb-2 protein by binding to both c-erb-2 and CD16	Phase I/II➢USA	Phase I➢USA ❑ various malignancies (in combination with IL-2)
Chiroscience	D3967	Hormonal therapy; single isomer compound	Phase II (b2/96) ➢Europe	
Ciba-Geigy (licensee) ❑ SRI (developer)	Edatrexate (10-ethyl-deaza-aminopterin) ❑ EDAM ❑ NSC-626715	Methotrexate analog; anti-folate; dihydrofolate reductase inhibitor	Phase I (5/96) ➢USA ❑ advanced breast cancer	In preclinical trials it demonstrated greater anti-tumor activity and improved therapeutic index than MTX
Corange	LMB-7	Wholly recombinant immunotoxin composed of the Fv portion of MAb B3 fused to PE38	Phase I/II (96) ➢USA	LMB-7 is about ten-fold more active than LMB-1 and well tolerated by monkeys
Corixa	HER2/neu peptides		Preclin (1/95) ➢USA	
Corixa ❑ U Pittsburgh	MUC-1 tumor antigen	Immunotherapeutic ❑ activates tumor-reactive T cells	Phase I (5/95) ➢USA	See FO, p 52
Cytel	Theradigm-P53	Immunotherapeutic ❑ elicits CTL; targets p53 ❑ injectable	Research➢USA	See FO, p 352
Cytel	Theradigm-HER2	Immunotherapeutic ❑ elicits CTL; targets HER2/neu ❑ injectable	Research (2/95) ➢USA	See FO, p 352
Cytel ❑ Sequel, NCI (NIH)	Theradigm MAGE-3 ❑ CY-2010	Small antigenic peptide ❑ targets MAGE-3 ❑ injectable		Phase I/II (4/95) under investigator initiated IND (b12/97)➢USA; ❑ melamona; see FO, pp 322 and 352
Cytoclonal Pharmaceutics ❑ Montana State U (licensor)	Fungal Taxol Production System	Compounds related to Taxol produced by microbial fermentation using the fungus *Taxomyces andreanae*	Preclin (3/96) ➢USA	

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Cytoclonal Pharmaceutics ❑ Wadley Technologies (WadTech; licensor)	BC-1 MAb	Genetically engineered human MAb ❑ targets BC-1 protein on breast tumors	Research (3/96) ➢USA ❑ breast cancer	May also be developed as an *in vivo* imaging agent for breast cancer by linking to a radioactive isotope; also being considered as a cancer vaccine
Cytoclonal Pharmaceutics ❑ Wadley Technologies (WadTech; licensor); Sloan-Kettering	IL-T	Fusion protein; interleukin and TNF	Preclin➢USA ❑ prevention of radiation and chemotherapy damage	
Cytoclonal Pharmaceutics ❑ Enzon	TNF-PEG	Pegylated TNF	Preclin➢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		NDA (8/95)➢USA ❑ bone pain from metastatic prostate cancer (see FO, pp 311 and 314)
CytRx ❑ Rush-Presbyterian-St-Luke's Medical Center, Peter MacCallum Cancer Institute of Australia	CRL-1336	Multi-drug resistant reversing agent ❑ inhibits P-glycoprotein and other transporters	Phase I (2/95) ➢USA	See FO, p 129
Daiwa Pharmaceutical	MGN-3	Immunomodulator; modified arabinoxylane from rice bran	Phase II (96) ➢Japan ❑ solid tumors	
Depotech ❑ Chiron	DepoCyt	DepoFoam formulation of cytarabine (ara-C)	Phase III (8/95) (b4/94)➢USA ❑ solid tumors and neoplastic meningitis	See FO, p 253
Diatide ❑ Brookhaven National Laboratory	Sn-117m DTPA	Tin radioisotope Sn-117m combined with DTPA, a common chelating agent	Phase II/III (5/96) USA ❑ pain palliation caused by metastatic cancer to the bone	See FO, p 311
Dong-A Research Lab (Seoul, Korea)	DA-125	Anthracycline derivative ❑ IV	Phase II (5/96) ➢Korea	MDT was 100 mg/m^2 q 3 weeks; toxicities were mild nausea and vomiting and myelosuppression
DuPont Merck	DMP-840	Bis-naphthalimide ❑ binds DNA with high affinity; has sequence specificity to multiple G and C bases, and is a potent inhibitor of RNA synthesis	Phase II (9/95) ➢USA	
DuPont Merck (licensee) ❑ Warner-Lambert, NCI	Teloxantrone HCl moxantrazole ❑ CI-937, NSC-355644, PD-113309	Anthrapyrazole derivative	Phase I/II(c92) ➢USA	
DuPont Merck (licensee) ❑ Warner-Lambert, NCI	Losoxantrone, bintrazole ❑ CI-941, DuP-941, NSC-357885, PD-113785	5-aminoanthrapyrazole; DNA-intercalating agent ❑ induces single- and double-stranded breaks in DNA and is a potent DNA synthesis inhibitor ❑ IV	Phase II (c93) ➢USA ❑ advanced breast cancer	

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Eisai	ER-37328	Carbazole ❑ topoisomerase II inhibitor	Preclin (11/96) ➢Japan	Showed greater anti-tumor activity than etoposide in preclinical studies (Uenaka T, etal, AACR96, Abs. 2670:391)
Eisai	E-7010	Sulfonamide ❑ dihydroteroate synthesis inhibitor; tubulin polymerization inhibitor ❑ IV, PO, IP	Phase II (7/96) ➢Japan	
Eli Lilly ❑ U Newscastle	Lometrexol ❑ LY-264618	Antifolate; inhibitor of *de novo* purine biosynthesis	Phase II➢UK	Escalation dose of 12-45 mg/m^2 for 4 weeks or 45-130 mg/m^2 for 3 weeks with oral folic acid (5 mg/d) for 7 days prior to and after administration; folic acid allows repeated courses at higher doses, with hematologic toxicity as the major side effect (Bailey N, etal, ASCO96, Abs. 1552:487)
Eli Lilly	LY23154 ❑ Tifolar/ Rolazar (proposed)	Multi-targeted antifolate; inhibitor of TS and other enzymes	Phase II (96)➢USA ❑ solid tumors	
Eli Lilly ❑ Chugai Pharmaceutical	Raloxifene	Anti-estrogen		Phase III➢WW ❑ osteoporosis
EntreMed ❑ Bristol-Myers Squibb (first refusal rights)	Endostatin	Antiangiogenic factor; collagen-derived protein ❑ blocks new vessel formation	Phase I➢USA	See FO, pp 397-398
EntreMed ❑ Bristol-Myers Squibb (licensee)	Angiostatin	Natural protein derived from metastasis-limiting tumors ❑ angiogenesis and metastasis inhibitor ❑ IV	Preclin (7/96) ➢USA ❑ solid tumors	
EntreMed ❑ Bristol-Myers Squibb (licensee)	Thalidomide analogs	Antiangiogenic compounds ❑ block TNF-α formation	Phase II (4/96) ➢USA	See FO, pp 195-96
Enzon	PEG-hemoglobin	Hemoglobin based oxygen carrier; radiosensitizer ❑ delivers oxygen to solid hypoxic tumors	Phase I (9/95) ➢USA ❑ solid hypoxic tumors	Obtained FDA clearance (12/95) for a multicenter multi-dose clinical trial in advanced solid tumors
Ergo Science ❑ Louisiana State U	ERGOSET/ serotonin agonist	Neurotransmitter modulating drug to address abnormalities of the neuroendocrine system and increase the body's immune activity against cancer	Phase II (8/96) ➢USA ❑ metastatic breast cancer	
Ergo Science ❑ Louisiana State U	ERGOSET/ neurotransmitter	See ERGOSET (above)	Phase II (8/96) ➢USA ❑ metastatic breast cancer	Patients are dosed using ERGOSET and the neuro-transmitter alone or adjunctively with chemo-therapy or radiation therapy
Ergo Science ❑ Rowland Institute for Sciences		Photodynamic therapy	Research (8/96) ➢USA	
Fuji Photo Film ❑ Dana Farber Cancer Institute	MKT-077 (formerly FJ-776)	Rhodacyanine dye (newly synthesized, highly water soluble) ❑ causes selective mitochondrial damage ❑ IP	Phase I➢USA, Japan	Koya K, etal, Cancer Research, 1 Feb 1996, 56(3):538-43

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Genentech	Anti-HER2 4D5 MAb, rhuMAb HER2	Humanized recombinant MAb ❑ IV	Phase III (3/96) ➢WW ❑ metastatic breast cancer	5/43 evaluable patients experienced CR or PR on an IV loading dose of 250 mg, followed by 10 weekly doses of 100 mg
Genentech	Anti-p185HER2 immunoliposomes-mediated delivery of DOX	DOX-loaded anti-p185HER2 immunoliposomes	Preclin➢USA	Results in less systemic toxicity and higher regression of established tumors than free DOX (Park, JW,etal, ASCO96, Abs. 1605:501)
Genetic Therapy (Novartis) ❑ NIH		Chemoprotection ❑ retroviral-mediated transfer of human multi-drug resistance (MDR-1) gene into hematopoeitic stem cells during autologous transplantation after intensive chemotherapy ❑ IV	Phase I (1/27) ➢USA ❑ breast cancer	O'Shaughnessy J, Kentuckiana Medical Oncology Association (Louisville, KE); RAC# 9309-054, approved 9/9/93
Genetic Therapy (Novartis vector supplier) ❑ U Southern California (USC) and Kenneth Norris Comprehensive Cancer Center and Hospital		Gene marking ❑ retroviral mediated transfer of neomycin phosphotransferase gene into autologous peripheral blood cells/bone marrow transplantation	Phase I➢USA ❑ breast cancer and lymphoma	Douer D, USC and Kenneth Norris Comprehensive Cancer Center and Hospital (Los Angeles, CA); RAC#9411-092, approved 11/18/94
Genetics Institute (American Home Products)	RhIL-11 ❑ Neumega	Recombinant human interleukin-11 (IL-11) ❑ increases platelet counts of patients undergoing chemotherapy	Phase III (3/96) ➢USA	
Genetix Pharmaceuticals ❑ Applied Immune Sciences (RPR)	MDR gene	Chemoprotection ❑ retroviral mediated transfer of MDR gene into autologous bone marrow cells	May be applicable to advanced breast cancer	Hesdorffer C and Antman K, Columbia U College of Physicians and Surgeons (New York, NY); RAC# 9306-051, approved 6/8/93; Phase I (1/97)➢USA ❑ ovarian and brain cancer
Geniva (Oxford Biosciences) ❑ US Army Medical Research and Material Command (funding)	Interleukin-12 (IL-12)	Cytokine ❑ may inhibit proliferation of breast cancer	Preclin (11/96) ➢USA	Geniva is to receive $960,000 for a three-year period
Genta ❑ NCI	Anti-BCL-2 Anticode oligonucleotide ❑ G3139	Oligonucleotide ❑ bcl-2 inhibitor	Preclin (3/96) ➢USA	Phase I/IIa (b 95) (3/96) ➢UK ❑ drug resistant non-Hodgkin's lymphoma; NCI intends to sponsor phase I trials in several solid tumors; see FO, pp 26-27 and 252
GenVec	$Ad_{GV}CD.10$	Gene therapy; insertion of the cytosine deaminase gene selectively into cancer cells to convert prodrug 5-fluorocytosine, an orally-administered antifungal agent, into 5-FU *in situ* ❑ intratumoral		Phase I (b5/96)➢USA ❑ colon cancer that has metastasized to the liver
Genzyme Molecular Oncology (was PharmaGenics) ❑ Boehringer Mannheim-Therapeutics (3/95)		Agents that restore normal p53 function identified by screening a library of compounds and bioactive substances from natural sources	Research➢USA, Germany	

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Genzyme Molecular Oncology (was PharmaGenics) ❑ Xenova (licensee outside North and South America, 12/95)		Agents that restore normal p53 function	Research➢USA, UK	
Genzyme Molecular Oncology (was PharmaGenics) ❑ Genetic Therapy (Novartis; sub-licensed rights in 1993)		p53-and DCC-based gene therapy	Research➢USA	
Glaxo Wellcome	GG211, GI-147211A, GI-147211C	Topoisomerase I inhibitor (water soluble) ❑ bolus	Phase I/II (8/96) ➢USA	MTD is 0.5 mg/m^2 daily for 21 days; recommended phase II dose is 0.4 mg/m^2 daily with provision for dose escalation; dose-limiting toxicity is thrombocytopenia (Khater C, etal, ASCO96, Abs. 1536: 483); see FO V1 #2/3, p56
Glaxo Wellcome	5-ethynyluracil (5-EU) ❑ 776C85 or 776C	Potent mechanism-based inactivator of dihydropyrimidine dehydrogenase; catalyzes the rapid catabolism of 5-FU; improves anti-tumor activity of 5-FU ❑ PO	Phase I/II (11/95) ➢USA	Phase II/III clinical trials were ongoing in colorectal cancer in 1996
Glycomed (Ligand Pharmaceuticals)	GM 1306	Small, sulfated carbohydrate molecule ❑ inhibits growth factors implicated in angiogenesis and metastasis	Preclin (2/96) ➢USA ❑ estrogen-dependent breast cancer	See FO, p 187
Hoechst Marion Roussel	MDL 101731	Ribonucleoside diphosphate reductase inhibitor ❑ IV, PO	Phase I (9/96) ➢USA	
Hoffmann-La Roche	Capecitabine	5-FU prodrug; tumor-selective fluoropyrimidine ❑ PO	Phase II➢Europe ❑ solid tumors	
Idun Pharmaceuticals	Bcl-2 inhibitor	Small molecule inhibitors of bcl-2 gene	Preclin (1/95) ➢USA	See FO, p 326
Ilex Oncology	Dihydro-5-azacytidine (DHAC)	Alternative to 5-azacytidine ❑ inhibits methylation of ribosomal and transfer RNA ❑ injectable	Preclin(1/96) ➢USA	See FO, p 326
Ilex Oncology ❑ Hoechst Marion Roussel (licensor)	DFMO ❑ Ornidyl (antiparasitic)	Ornithine decarboxylase (ODC) inhibitor ❑ inhibits tumor growth and progression ❑ injectable, PO	Phase II (1/96) ➢USA	NCI is sponsoring a number of phase II studies of DFMO in patients who are at risk of recurrence of various cancers; see FO, p 326
Ilexus ❑ Austin Research Institute		Conjugated vaccine technology; modulates the immune response from an antibody response to a cytotoxic immune response	Phase I (11/96) ➢Australia	Strong dose response relationship to a breast cancer antigen was demonstarted in initial phase I trial
ImClone Systems		Immunotherapy ❑ targets p53 mutation sites	Research (3/96) ➢USA	
ImClone Systems ❑ Memorial Sloan-Kettering Cancer Center	Anti-EGFR chimeric MAb/C225	Epidermal growth factor receptor (EGFR) antagonist/ blocks EGFR overexpressed on several types of cancer cells ❑ eliminates cancerous cells through induction of apoptosis ❑ IV	Phase Ib/IIa (b3/96) ➢USA	Phase Ia/IIb dose escalation study will evaluate C225 in conjunction with paclitaxel in patients with EGFR-positive breast cancer; see FO, pp 52-53 and 326

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Immunex ❑ Wyeth-Ayerst (Canadian rights)	Levoleucovorin ❑ Isovorin	Modulates 5-FU ❑ PO, IV	NDA (3/96) ➢USA; phase II/III ➢Canada	
Immunomedics ❑ School of Pharmacy, Memorial U Newfoundland	DOX-CEA	DOX immunoconjugates ❑ selectively toxic to CEA-positive cells	Preclin (95)➢USA	Lau A, etal, Bioorganic and Medicinal Chemistry, 1995 Oct, 3(10):1305-12
Inex ❑ Duke U, Purdue U	Onco TCS	Drug delivery system; small lipid-based particulates carrying vincristine		Phase II (2/96)➢Canada ❑ pancreatic and colorectal cancer
Inex ❑ Duke U, Purdue U	Onco-L TCS	Ligand-targeted transmembrane carrier system containing a potent anti-cancer compound	Research (4/96) ➢USA	The targeting agent is a MAb in breast cancer
Inex	p53 TCS	Transmembrane carrier system-based gene therapy to deliver p53 gene to tumor cells	Research (4/96) ➢USA ❑ tumors associated with defective p53	Schering-Plough Research Institute opted not to license the product as of 2/97; see FO, p 26
Ingenex	SG-94	Gene therapy	Preclin (3/95)➢USA	See FO, p 26
Ingenex ❑ CellPro, U Chicago	MDRx1	Chemoprotection ❑ hematopoietic stem cells transduced with the MDR-1 gene in a retroviral expression vector ❑ *ex vivo*	Phase I (1/27) ➢USA ❑ enhance tolerance to chemotherapy	Deisseroth A, etal, M. D. Anderson Cancer Center; RAC# 9406-077, approved 6/9/94; Hanania EG, etal, ASCO96, Abs. 583: 236; see FO, pp 112-113
Introgen ❑ Rhône-Poulenc Rorer; NCI	Ad-p53	Gene therapy	Preclin (10/96) ➢USA	Signed letter of intent with the NCI to conduct phase I/II clinical trials under an NCI CRADA; see FO, pp 28 and 98
Isis Pharmaceuticals	Isis 2503	Antisense compound ❑ targets cancers that overexpress Ha-ras	Preclin (3/96) ➢USA	
Isis Pharmaceuticals		Antisense compound ❑ targets cancers that overexpress Ki-ras	Preclin (3/96) ➢USA	
Isis Pharmaceuticals ❑ Novartis (Ciba-Geigy)	Isis 3521 ❑ CGP64128A	20-mer phosphorothioate oligodeoxynucleotide ❑ targets PKC-α protein inhibitor	Phase I (b1/96) ➢USA ❑ refractory breast cancer	
Isis Pharmaceuticals ❑ Novartis (Ciba-Geigy)	Isis 5132 ❑ CGP69846A	C-raf kinase antisense inhibitor	Phase I (b4/96) ➢USA ❑ refractory breast cancer	
Janssen Pharmaceutica/ Janssen-Cilag (Johnson & Johnson)	Vorozole ❑ R-76713, R-83842 ❑ Rivizor	Aromatase inhibitor ❑ PO	Phase III➢USA, UK ❑ relapsed/advanced breast cancer	
Janssen Pharmaceutica Research Foundation (Johnson & Johnson)	Liarozole, liarozote fumerate ❑ R-75251, R-85264 ❑ Liazal	Imidazole derivative ❑ inhibits cytochrome P_{450} retinoic acid hydroxylase; blocks the P_{450} -dependent breakdown of retinoic acid catabolism and estrogen biosynthesis	Phase II (1/96) ❑ ER+ or ER- post-menopausal metastatic breast cancer	Gross PE, etal, ASCO96, Abs. 156:123; phase III (1/95)➢USA, Europe ❑ prostate cancer; see FO, pp 217, 307, 446; NDA (1/97)➢USA ❑ prostate cancer

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Johns Hopkin's Oncology Center (Baltimore, MD)	Novobiocin	Coumeromycin antibiotic that enhances alkylating agent cytotoxicity ❑ may modulate repair of DNA damage	Phase I➢USA ❑ metastatic breast cancer	38 patients were treated with an escalating oral dose of novobiocin (0.5 to 5 g/d) on days -10 to -3, and cyclophosphamide (6 g/m^2) and thiotepa (800 mg/m^2) on days -8 to -5 and bone marrow infusion on day 0 (Armstrong, DK, etal, AACR96, Abs. 1975:290)
Kyowa Hakko (licensee) ❑ Hoechst Marion Roussel	FMDC ❑ KW-2331	Antimetabolic agent ❑ inhibits growth of cancer cells ❑ PO	Phase I (1/95) ➢Japan	First oral cytidine anti-cancer agent for solid tumors
Kyowa Hakko (ww rights) ❑ EORTC (licensor); U Amsterdam	EO-9 ❑ NSC-382456	Alkylating indoloquinone; mitomycin-C analog ❑ activates DT-diaphorase to inhibit cell division	Phase II (10/95) ➢Europe ❑ solid tumors	
Kyowa Hakko	7-hydroxystau-rosporine ❑ UCN-01	Protein kinase inhibitor, staurosporine analog with higher specificity ❑ induces apoptosis	Preclin➢USA, Japan	Schwartz, GK, etal, ASCO96, Abs. 1604:501
Laboratoires AEterna	AE-941 ❑ Neovastat	Angiogenesis inhibitor ❑ PO	Phase III➢Canada ❑ terminally ill patients with solid tumors; phase II➢Canada ❑ breast cancer	
Lidak Pharmaceuticals ❑ Medical Biology Institute (licensor)	Large Multivalent Immunogen (LMI) ❑ LP-2307	Immunostimulant ❑ induces CTLs	Preclin➢USA	See FO, pp 147 and 352
Ligand Pharmaceuticals	LGD1069 ❑ Targretin	Small organic compound ❑ activates retinoid receptors, RXRs ❑ topical and PO formulations	Preclin➢USA ❑ treatment/prevention of breast cancer	Phase II (PO)➢USA ❑ lung, head & neck, ovarian, prostate and renal cancer and Kaposi's sarcoma; see FO, pp 312 and 251
Ligand Pharmaceuticals ❑ Wyeth-Ayerst (American Home Products) (exclusive ww rights)	LG2527 & LG2716	Progesterone receptor agonists ❑ hormonal therapy	Research (95) ➢USA	Lead compounds selected
Liposome Company ❑ Pfizer (licensee, ww rights), U British Columbia, Canada; McGill U	TLC D-99, TLC-DOX99	Doxorubicin in liposomal formulation ❑ IV	Phase III (7/96) ➢USA, Europe ❑ metastatic breast cancer	
Liposome Company		Hydrophobic taxane-derivative prodrugs; liposomal formulation	Preclin➢USA	Ahmad I, etal, AACR96, Abs. 2044:300
LXR Biotechnology ❑ Dana-Farber Cancer Institute, NCI (licensees); Boehringer Mannheim (Corange; 12/96 collaborative agreement)	Maspin/LXR-023	Tumor suppressor gene and protein located in cell membrane and extracellular matrix; mammary serine protease inhibitor ❑ binds to surface of invasive and metastatic tumor cells and restores normal function ❑ regulates apoptosis in the intestinal epithelial cells that maintain nutrient absorption	Preclin (5/96) ➢USA ❑ metastatic breast cancer	Gene is down-regulated in invasive breast carcinomas; maspin does not behave as a classical inhibitory serpin against any known target protease (Sager R, etal Current Topics in Microbiology and Immunology, 1996, 213 (Pt 1):51-64); exogenous recombinant maspin blocks growth, motility, and invasiveness of breast tumors *in vitro* and *in vivo;* see FO, p 29

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Matrix Pharmaceutical	Cisplatin IntraDose ❑ IntraDose-CDDP injectable gel	Biodegradable gel-like matrix ❑ intratumoral injection	Phase III (4/96) (b6/95)➢USA, Europe ❑ recurrent chest wall metastases from breast cancer	See FO, pp 20-21, 56 and 326-327
Matrix Pharmaceutical		Tubulin-binding, topoisomerase inhibitors ❑ therapeutic implants	Preclin (4/96) ➢USA	
McNeil (Johnson & Johnson) ❑ NCI	Fenretinide, retinamide (4-HPR) ❑ McN-R-1967	Orally active retinoid ❑ inhibits proliferation of cancer cells; induces apoptosis in certain cancer cells ❑ PO	Phase III (6/96) ➢USA, Italy ❑ breast cancer prevention	See FO, p 288
Medac	Titanocene dichloride	Early-transition metal complex of titanium ❑ suppresses angiogenesis	Phase II (9/95) ➢Germany	
Medarex ❑ Novartis (Ciba-Geigy; licensor, exclusive ww rights), Chiron	MDX-210	Bispecific MAb with humanized trigger and murine target components ❑ targets HER2 and induces immune responses through target-trigger mechanism	Phase II (96)➢USA, Europe ❑ cancers that overexpress HER2/neu	Also in phase I/II (b7/95) in combination with Amgen's G-CSF, Neupogen; see FO, pp 99, 322 and 395
Medarex ❑ Merck KGaA; Memorial Sloan-Kettering Cancer Center	MDX 447	Bispecific MAb ❑ binds EGF receptors (EGFR)	Phase I/II (b9/95) ➢USA	Medarex retains USA market rights while sharing worldwide rights to non European countries; see FO, pp 99 and 322
Medisperse (Unimed/ Sterilization Technical Services partnership) ❑ NCI	Paclitaxel	Submicron particle formulation	Preclin (4/95) ➢USA	
Memorial Sloan-Kettering Cancer Center (Andrew D Seidman)	Gossypol and derivatives ❑ inhibits protein kinase C	Naturally occurring (in cottonseed) polyphenolic binaphthyl dialdehyde ❑ PO	Phase I/II (6/96) ➢USA ❑ refractory breast cancer	Also extensively tested in clinical trials as a male contraceptive agent
MethylGene (Hybridon) ❑ McGill U	Antisense compounds	Inhibit methyltransferase, a regulatory protein	Research (3/96) ➢Canada	
MGI Pharma ❑ Dainippon Pharmaceuticals (licensee, Japan)	MGI 114, 6-HMAF	Alkylating agent; acylfulvene; semi-synthetic compound; natural product isolated from mushrooms of the genus *Omphalotus* ❑ inhibits growth of tumor cells without excessive toxicity to healthy cells	Phase I (b12/95) (12/96)➢USA	
MGI Pharma ❑ U Rochester (licensor)	Phosphoramidate fluorodeoxyuridine monophosphate (PF-dUMP) analog	Antimetabolite; thymidylate synthase inhibitor/IV	Preclin (12/96) ➢USA	
MicroGenSys	Recombinant carcinoembryonic antigen (CEA) vaccine	Immunotherapy; CEA recombinant immunogen	IND (95)➢USA ❑ metastatic breast cancer	
Mitotix ❑ DuPont Merck		p53 degradation inhibitor ❑ blocks selected elements of the ubiquitin-mediated pathway	Research (12/95) ➢USA	See FO, p 27
Mitotix ❑ DuPont Merck		Mimetics of tumor suppressor gene, p16; Cdk4 ❑ Cyclin D1 inhibitor	Research (12/95) ➢USA	See FO, pp 253-254

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Mitotix ❑ Fred Hutchinson Cancer Research Center, and Memorial Sloan-Kettering Cancer Center (licensors)	p27	Natural cell cycle inhibitor ❑ anti-proliferative	Research (1/97) ➢USA	Mitotix is also evaluating p27 as a prognostic indicator in cancer
Mitotix ❑ Fred Hutchinson Cancer Research Center (licensor), Rockefeller U (co-owner of patents)	Cyclin E	Key regulator of cell cycle	Research (1/97) ➢USA	Diagnostic rights owned by Cascade Oncogenics
National Cancer Institute	Etanidazole, EF5	Nitroimidazole; radiosensitizer (hypoxic cell sensitizer)	Phase II➢USA	
NCI (NIH) ❑ Genetic Therapy (Novartis), vector supplier; Chiron, TNF supplier		Immunotherapy ❑ genetically modified irradiated autologous cancer cells for tumor necrosis factor (TNF) *in vitro* ❑ subcutaneous injection	Phase I (1/97) ➢USA ❑ melanoma and renal cell, colon and breast cancer	Rosenberg SA, NIH; RAC# 9110-010 approved 10/7/91
NCI (NIH) ❑ Genetic Therapy (vector supplier)		Gene marking ❑ retroviral-mediated gene transfer of bone marrow and peripheral blood stem cells during autologous bone marrow transplantation (ABMT) ❑ IV	Clinical➢USA ❑ metastatic breast cancer	Dunbar C, NIH; RAC# 9206-024 approved 6/2/92
NCI-Frederick Cancer Research and Development Center	Genistein	Component of soy; natural product ❑ inhibits protein tyrosine kinase; binds estrogen receptor	Preclin➢USA	Wand TT, etal, Carcinogenesis, 1996 Feb,17(2):271-5
NCI (NIH)	CP-IL4-toxin	Fusion toxin; interleukin-4 receptor (IL-4R) linked to *Pseudomonas* exotoxin (PE)	Research➢USA ❑ breast cancer expressing IL-4R	Puri RK, etal, AACR96, Abs. 2848: 417
NCI (NIH)	LMB-1	Immunotoxin; MAb B3 which recognizes carbohydrate antigen Le^Y, chemically linked to PE38, a genetically engineered form of *Pseudomonas* exotoxin	Phase I➢USA ❑ solid tumors	10-100 mg/kg/day administered as a 30-minute bolus on days 1, 3 and 5 and repeated every 4 weeks if patient has no antibodies against LMB-1 (Pai, LH, etal, ASCO96, Abs. 1528:481)
NCI (NIH)	Discodermolide	Natural product derived from the Caribbean sponge *Discodermia dissoluta* ❑ stabilizes microtubules	Preclin➢USA	Balachandran R, etal, AACR96, Abs. 2996:439
NCI-Navy Medical Oncology Branch (Bethesda, MD)	90Y-B3 MAb ❑ NSC-643714	Radioimmunotherapy; indium-111-labeled MAb B3	Phase I (2/96) ➢USA ❑ metastatic breast cancer	
Neopharm	DOX ❑ LED	Liposome encapsulated DOX	Phase II (8/96) ➢USA	
NeoPharm ❑ Georgetown U	LET	Liposome-encapsulated taxol	Preclin (1/96) ➢USA	
NeoPharm ❑ Georgetown U	LE-AON	Liposome encapsulated antisense oligodeoxynucleotides	Preclin (1/96) ➢USA	
NeoPharm ❑ NCI (CRADA)	Broxuridine ❑ BUdR	Radiosensitiser ❑ replaces thymidine in DNA of actively dividing cells ❑ IV	Phase III (8/96) ➢USA	Also diagnostic applications (see FO, p 383)

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NeoPharm ❑ NCI (CRADA)	Idoxuridine ❑ IUdR	Radiosensitiser ❑ replaces thymidine in DNA of actively dividing cells ❑ IV	Phase III (8/96) ➢USA	Also diagnostic/imaging applications (see FO, p 383)
Neoprobe ❑ Cellcor	RIGS/ACT	Immunotherapy ❑ harvesting of positive lymph nodes, *ex vivo* activation, multiplication and reinfusion	Phase I (b12/96) ➢USA	Phase II (b12/96)➢USA ❑ late-stage metastatic colorectal cancer
NeoRx	Avicidin	Humanized MAb ❑ uses a pretargeting technique whereby the MAb component and radioactive element (yttrium-90) are injected separately	Preclin➢USA	Phase I/II (3/96)➢USA ❑ NSCLC; see FO, p 69 and 99
NeXstar Pharmaceutical		Angiogenesis inhibitor; aptamer antagonist of vascular endothelial factor (VEGF); liposomal formulation	Preclin➢USA	
NeXstar Pharmaceutical	Daunorubicin ❑ VERSUS-103 ❑ DaunoXome	Liposomal formulation of daunorubicin	Phase II (3/96) ➢USA	Approved (3/96)➢USA, 13 European countries ❑ advanced Kaposi's sarcoma; see FO, pp 56, 132, and 367-368
Nippon Kayaku; Snow Brand Milk Products (joint development)	NKS-01	Aromatase inhibitor ❑ PO	Phase II (2/95) ➢Japan	
Novartis (Sandoz)	Interleukin-3, rhIL-3 ❑ SDZ ILE-964	Cytokine ❑ reduces adverse effects of chemotherapy	Phase II➢USA ❑ metastic breast cancer	In clinical trials, IL-3 followed by GM-CSF reduced post-chemotherapy myelosuppression
Novartis (Sandoz)	Interleukin-6, rhIL-6 ❑ SDZ ILS-969	Cytokine ❑ reduces adverse effects of chemotherapy	Phase II➢USA	In combination with G-CSF (Neupogen; Amgen) IL-6 enhanced platelet and neutrophil recovery
Novartis (Sandoz)	Cyclosporin analog ❑ PSC-833	Third generation immunosuppressant; chemotherapy protectant; MDR modifier	Phase II/III (95) ➢Europe	Reduced nephrotoxicty; see FO, p 115
Novartis (Sandoz)	Octreotide ❑ SMS 201-995 ❑ Sandostatin	Octapeptide somatostatin analog ❑ growth hormone antagonist	Phase III➢USA ❑ metastatic breast cancer	Also available microencapsulated in poly (lactide-glucolide)-glucose for long-acting release (Sandostatin LAR)
Novartis (Ciba-Geigy)	Zoledronate ❑ CGP-42446	Third generation bisphosphonate, potent osteoclast inhibitor	Phase I➢USA ❑ osteolytic bone lesions in breast cancer; phase II/ USA ❑ in comparison with pamidronate	
Novopharm ❑ Alabama U	NOVOMAb-G2	Pancarcinoma specific human MAb		Phase I (5/96)➢USA ❑ melanoma
Onyx Pharmaceuticals	ONYX-015	Genetically engineered adenovirus ❑ replicates and kills p53-deficient cells ❑ intratumoral injection	Preclin (96) ➢USA, UK ❑ p53-deficient cancer	Phase I (b4/96)(5/96)➢ USA, UK ❑ p53-deficient head and neck cancer
Onyx Pharmaceuticals ❑ Bayer		Small molecule inhibitors ❑ targets mutations in ras	Discovery (5/96) ➢USA	
Onyx Pharmaceuticals ❑ Warner-Lambert		Small molecule inhibitors; cell cycle regulators	Discovery (5/96) ➢USA	

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Osiris Therapeutics ❑ Ireland Cancer Center and Case Western Reserve U		Human mesenchymal stem cells expanded *ex vivo* and re-infused with hematopoietic stem cells ❑ differentiate into connective tissue	Phase I (investigator-sponsored)➢USA ❑ advanced breast cancer following high-dose chemo-therapy	
Otsuka Pharmaceuticals	BOF-A2 ❑ Emitefur	5-FU derivative; fluorinated pyrimidine ❑ PO	Phase II (95) ➢Japan ❑ advanced and recurrent breast cancer	
Oxis	C-1	Pro-oxidant free radical generators linked to delivery molecules	Research (9/96) ➢USA	
Paracelsian ❑ NCI (CRADA)		Natural products; screen herb extracts for agents that modulate cell signaling pathways	Research➢USA	
Paracelsian ❑ Rosewell Park Cancer Insitiute	Andrographolide ❑ PN27.1	Immunostimulant; natural product isolated from *Andrographis paniculata* ❑ PO	Preclin➢USA	Phase I (4/96)➢USA ❑ prostate cancer; see FO, p 325
Parke-Davis (Warner-Lambert)	PD 158780	Pyridopyrimidine ❑ suppresses epidermal growth factor receptor (EGFR) tyrosine kinase	Research➢USA	Fry D, AACR96, Abs. 2893:424
Parke-Davis (Warner-Lambert) ❑ NCI	Pyrazoloacridine (PZA) ❑ NSC-366140, PD115934	DNA intercalator; anti-tumor activity may be attributed to an enzymatic nitro reduction pathway; induction of nascent and parental DNA damage appears to be caused by avid binding of PZA to DNA that interferes with the access of replication, repair, and trans-cription enzyme complexes ❑ infusion	Phase II (5/95) ➢USA ❑ metastatic breast cancer	
Parke-Davis (Warner-Lambert)	CI-958	Benzothiopyranoindazole ❑ DNA intercalator (planar moiety of the ligand inserted between adjacent DNA pairs)	Phase II (5/95) ➢USA	
Parke-Davis (Warner-Lambert) ❑ DuPont Merck	Teloxantrone HCl, moxantrazole ❑ CI-937, DuP-937, NSC-355644, PD-113309	Anthrapyrazole derivative ❑ potent topoisomerase II inhibitor at the molecular and cellular level ❑ IV, IP	Phase II (2/95) ➢USA, Canada ❑ advanced breast cancer	
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 methotrex-ate ❑ dihydrofolate reductase inhibitor ❑ IV, topical	Phase II (5/94) ➢USA	L (5/94)➢USA; reg (90) ➢Canada; prereg➢EC ❑ *Pneumocystis carinii pneumonia* (PCP)
Parke-Davis (Warner-Lambert) ❑ NIH	Suramin ❑ CI-1003, NSC-34936	Polysulfonated naphthathy-lamine derivative; growth factor antagonist	Phase II (10/95) ➢USA ❑ advanced breast cancer	Northwestern U Robert H. Lurie Cancer Center
PDT/Pharmacia & Upjohn (licensee)	SnET2	Photodynamic therapy; tin ethyletioporpuria ❑ nonthermal light activates SnET2 to produce free oxygen radicals	Phase III➢France ❑ cutaneous metastatic breast cancer	Filing planned for late 1997 or early 1998; see FO, pp 296-297 and 369
Pfizer ❑ Fujisawa (Klinge Pharma), licensor; Ligand Pharmaceuticals, collaborator	Droloxifene ❑ FK-435, K-060, K-21060, RP 60850	Tissue-selective estrogen agonist-antagonist ❑ anti-estrogen ❑ PO	Phase III (8/96) ➢USA; prereg (95)➢Germany; phase II➢(9/94) ➢Japan	

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Pfizer ❑ Ligand Pharmaceuticals, collaborator	CP-336,156	Anti-estrogen, partial agonist ❑ PO	Preclin➢USA	Phase I (11/96) ➢Europe ❑ osteoporosis
PharmaMar	Ecteinascidin 743/ET-743	Tetrahydroisoquinoline ❑ binds to DNA and inhibits DNA, RNA and protein synthesis, blocks cell cycle progression at G2/M phase ❑ IV	Phase I (b7/96) ➢Europe, USA	See FO, pp 173-174
PharmaMar	Kahaladide F (KF)	Marine depsipeptides isolated from a Hawaiian mollusk, *Elysia rubefescens*	Research (1/96) ➢Europe	
PharmaMar ❑ NCI	Didemnin B ❑ NSC-325319, IND-4505	Depsipeptide isolated from the Caribbean tunicate *Tridemnun solidum*; protein synthesis inhibitor ❑ inhibits G1 cell cycle progression by acting on the guanine nucleotide binding factor EF-1 alpha; induces apoptosis ❑ IP, IV	Phase I (11/95) ➢USA	A dehydro-derivative of didemnins (DDB) isolated from *Aplidium albicans* appears to be more active and less toxic than the parent compound; in phase II trials didemnin was not effective in hormonally refractory prostate cancer (Williamson SK, etal, Investigational New Drugs, 1995, 13(2): 167-70) but appears effective in lymphoma
Pharmacia & Upjohn	Exemestane ❑ FCE-24304	Aromatase inhibitor ❑ PO, SC	Phase III (7/96) ➢USA, Sweden; phase II➢Japan ❑ advanced breast cancer	Filing of NDA is planned in 1997
Pharmacia & Upjohn	Tallimustine, distamycin ❑ FCE-24517	Sulfonic distamycin derivative; DNA antagonist	Phase II➢USA ❑ solid tumors	Two other distamycin derivatives, FCE 27266, that inhibits lung and liver metastasis (Sola F, etal, Journal: Invasion and Metastasis, 1995, 15(5-6): 222-31) and FCE 26644, a growth-factor complexing molecule (Sola F, etal, Cancer Chemotherapy and Pharmacology, 1995, 36(3):217-22), have also been identified
Pharmacia & Upjohn ❑ NIH	Carzelesin ❑ NSC-D-619020; U-80244	Rachelmycin analog ❑ DNA antagonist	Preclin➢USA	
Pharmacia & Upjohn ❑ NIH, Yakult Honsha (licensee)	Adozelesin ❑ U-73975 ❑ Adosar	Alkylating agent; rachelmycin derivative ❑ P-glycoprotein inhibitor; DNA minor groove binder ❑ IV	Phase II (7/96) ➢USA, Japan	CC-1065 analog
Pharmacia & Upjohn ❑ Taiho, NCI (NIH)	Menogaril, menogarol, methylnogarol ❑ 7-OMEN, NSC-269148, U-52047, TUT-7 ❑ Tomosar	Anthracycline; nogalamycin derivative ❑ DNA antagonist ❑ PO, IV	Phase II (7/96) ➢USA	
Pharmacia & Upjohn	Methoxymorpholino DOX ❑ FCE 23762	Anthracycline; highly lipophilic DOX derivative ❑ IV, PO	Phase I (95) ➢Europe ❑ solid tumors	More active and less cardiotoxic than DOX (Angiuli P, etal, Annals of Oncology, 7 (suppl. 5), 1996)

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Pharmacyclics ❑ Hoechst Celanese	Lutetium-texaphyrin ❑ Lu-Tex	Texaphyrin-based photosensitizer activated by red light (720-760 nanometers) to generate cytotoxic singlet oxygen molecules	Phase I (9/96) ➢USA ❑ cutaneous metastasis of breast cancer	See FO, p 239
Pherin		Nasal drug delivery methodology ❑ vomeropherins applied to the nose	Research (96) ➢USA	See FO, p 327
U Pittsburgh (vector supplier) ❑ Human Applications Laboratory		Gene therapy ❑ autologous fibroblasts transduced with retroviral vectors carrying human IL-12 genes/intratumoral injection	Phase I (1/27) ➢USA ❑ solid tumors	Lotze MT, U Pittsburgh (Pittsburgh, PA); RAC# 9406-081 approved
Prizm Pharmaceuticals	hbEGF-toxin	hbEGF-saporin mitotoxin (heparin binding epidermal growth factor)	Preclin➢USA	See FO, p 324
Proscript ❑ NCI		Small molecule drugs; proteasome inhibitors ❑ inhibit degradation of p53 and cyclins *in vivo* ❑ PO	Research➢USA	
Protein Design Labs ❑ Sandoz (licensor)	SMART ABL 364 ❑ HuABL-364 (replaces murine ABL 364 discontinued in phase II)	Humanized IgG1 MAb against Le^y antigen; immunostimulant	Preclin (2/96) ➢USA, Japan ❑ epithelial cell cancers; metastatic breast cancer	Terminal half-life of a single IV dose of 0.8 mg/kg of the selected variant K, that has affinity within 2-fold of the chimeric IgG_1 MAb, was 14-20 days (mean of 16.3 days) in rhesus monkeys compared to 1.9 days of the parent murine MAb (Co MS, Cancer Research, 1996 Mar 1, 56(5):1118-25); see FO, p 100
Protein Design Labs		Bispecific MAb constructed using PDL's proprietary leucine zipper technology	Preclin (5/96)➢USA	
Proteus Molecular Design ❑ Strathclyde U (co-developer) ❑ ML Laboratories (licensee)	Hormone therapy, LHRH immunacine, gonadorelin analog, LHRH analog ❑ 014L, PM-OV-92, Sterovac 92 ❑ Prolog	GnRH immunotherapeutic; vaccine-like construct containing gonadorelin analog ❑ stimulates antibody response by cross-reacting with naturally-produced LHRH	Phase I (4/96) ➢Europe	See FO, p 323
QLT PhotoTherapeutics ❑ Ligand; Lederle (American Home Products)	Porfimer sodium ❑ Photofrin	Photodynamic therapy	Phase I/II/USA ➢metastatic breast cancer	Marketed (7/96)➢Canada, Europe, Japan ❑ esophageal and bladder cancer; approved/USA ❑ esophageal cancer; see FO, pp 29, 101-103 and 271-272
Research Triangle Institute	RTI-3021-020	Anti-progestin; PgR modulator; manifests cell- and promoter-specific agonist and antagonist activities	Research (5/96) ➢USA	
Rhône-Poulenc Rorer	RPR-109881	Taxane analog; highly potent ❑ crosses the blood-brain barrier and is active against MDR tumors, including those resistant to paclitaxel ❑ PO, IV	Phase I (6/96) ➢USA	
Roussel-Uclaf/National Cancer Institute of Canada ClinicalTrials Group (NCIC CTG) Breast Cancer Site Group	Mifepristone (RU-38486, RU486)	Anti-progestin	Phase II (94) ➢Canada ❑ adjuvant therapy of breast cancer	

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Royal Postgraduate Medical School		Gene therapy; prodrug activation system; P-ERCY plasmid carries genes for cytosine deaminase and erbB-2, into tumor cells ❑ activates 5-fluorocytosine prodrug into 5-FU	Phase I➢UK ❑ metastatic skin nodules in breast cancer	
Sanofi Winthrop	Tirapazamine ❑ WIN 59075, SR 4233	Radiosensitizer; bioreductive drug preferentially toxic to hypoxic cells ❑ interrupts cell cycle progression and induces apoptosis	Phase II (96) ➢USA➢refractory breast cancer	
Sanofi Winthrop	WIN 33377	Thioxanthone derivative	Phase I➢USA	
Schering AG	Onapristone ❑ ZK-98299, ZK299	Antiprogestin; steroid hormone antagonist	Phase III (94) ➢Europe	See FO, p 446
Schering-Plough		Peptidomimetics; novel tricyclic inhibitors of farnesyl protein transferase ❑ act on ras oncogene	Preclin➢USA	Also colon and pancreatic cancer
Schering-Plough ❑ Endorecherche		Oral anti-estrogen compound	Clin (b95) ➢Canada	Study headed by Dr. Fernand Labrie at the Research Center of Laval U Medical Center
Scotia Pharmaceuticals	EF27	Fatty acid product (mixture of EFAs from evening primrose and fish oils)	Phase III (11/95) ➢USA; license filed (11/95)➢UK ❑ alleviation of side effects of radiotherapy	
Scotia Pharmaceuticals	Temoporfin ❑ EF9 ❑ Foscan	Photodynamic therapy		Phase II➢UK ❑ head and neck cancer
Scotia Pharmaceuticals ❑ St Bartholomew's Hospital	Lithium gamma-linolenic acid ❑ LiGLA ❑ EF-13	Prostaglandin synthase inhibitor ❑ IV, PO	Phase II (5/95) ➢UK	Developing new form of EF-13 using LipidTeknik technology to allow 10-15 times higher dose via peripheral veins and SC-101 as EF-13 follow-up
Sequana/Memorial Sloan-Kettering Cancer Center (jv)		Gene therapy	Research (8/96) ➢USA	
Sequus	STEALTH pegylated-liposomal DOX ❑ Doxil (USA), Dox-sl, Caelyx (Europe)	Liposome encapsulated drug for delivery to targeted areas (20-month shelf-life approved 7/96) ❑ IV	Phase II (4/96) ➢Europe, USA	Approved (11/95) ➢Europe, UK, USA ❑ Kaposi's sarcoma; see FO, p 367
Seragen ❑ Lilly	EGF fusion toxin ❑ $DAB_{389}EGF$	EGF antagonist linked to diptheria toxin ❑ becomes internalized in EGFR expressing cells; comes apart within the cytosol and releases diphtheria toxin that kills the cell	Phase II (95)➢USA	See FO, pp 53 and 245-246
SmithKline Beecham	Topotecan, hycaptamine ❑ NSC-609699; SK&F-104864 ❑ Hycamtin	Water-soluble camptothecin analog ❑ DNA topoisomerase II inhibitor ❑ IV, PO	Phase III (injectable) ➢USA; phase I (oral)➢USA	Approved (5/96)➢USA ❑ refractory ovarian cancer
SoloPak Laboratories	Gallium nitrate ❑ NSC-15200	Antiresorptive therapy ❑ SC	Phase III (4/96) ➢USA ❑ bone metastases from breast cancer	

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Somatix (Cell Genesys) ❑ Johns Hopkins U, Bristol-Myers Squibb	GVAX cancer vaccine	Immunotherapy ❑ multiple gene transfer in which tumor cells are removed from patients, transduced with the gene for GM-CSF, irradiated, and then reinfused into patients ❑ *ex vivo*	Phase I/II➢USA	See FO, pp 53, 149, 323 and 355
Southern Research Institute ❑ NCI	Penclomedine (PEN) ❑ NSC-338720	Synthetic pyridine derivative ❑ activated in cells to free a radical that binds DNA/IV, IP, PO	Phase I (96)➢USA	Struck RF, AACR96, Abs. 2585:379
Sparta Pharmaceuticals	Spartaject DOX	Anthracycline-based delivery system ❑ injectable	Preclin➢USA	See FO, p 56
Sparta Pharmaceuticals	Spartaject taxane	Taxane-based delivery system ❑ injectable	Preclin (3/96) ➢USA	
Sparta Pharmaceuticals	L.A.D.D. 5-FP	Oral drug delivery technology	Preclin (3/96) ➢USA	
Sparta Pharmaceuticals	PT-523	Antifolate	Preclin (3/96) ➢USA	See FO, p 135
Sparta Pharmaceuticals ❑ Cancer Research Campaign (CRC)	Asulacrine (formerly CI-921 or Amsalog)	IV, PO	Phase I (3/96) ➢UK	Oral formulation entered phase I in the UK (8/96)
StressGen ❑ British Columbia Cancer Agency	Oncocine	Combination of tumor antigens with microbial stress proteins, hsp65 and hsp71	Preclin (6/95) ➢USA, Canada	Uses StressGen's Unigen technology; see FO, pp 53-54, 147-148 and 353
Sugen	Flk-1 TK antagonist	Anti-angiogenesis agent ❑ Flk-1 receptor	Preclin (96)➢USA ❑ solid tumors	Clinicals are slated for mid-97
Sugen ❑ Asta Medica (greater Europe and South America rights)	Pan-Her (formerly HER2) antagonist	Tyrosine kinase inhibitor	Preclin (95)➢USA	
Sugen	90K antigen	Tumor-derived glycoprotein; immunostimulatory antigen in mammary carcinoma	Research (96) ➢USA	Jallal B, etal, Cancer Research, 1995 Aug 1, 55(15):3223-7
SunPharm ❑ U Florida	Parabactin	Polyamine analog ❑ ribonucleotide reductase inhibitor	Research (96) ➢USA ❑ mammary tumor cells	
Taiho Pharmaceutical	S-1 (tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate)	Thymidylate synthase inhibitor ❑ PO	Phase II➢Japan; phase I➢Europe ❑ solid tumors and advanced breast cancer	
Taiho Pharmaceutical	TAT-59	Anti-estrogen	Phase II➢Japan	
Targeted Genetics (RGene Therapeutics) ❑ Groupe Fournier (Dijon, France)	RGG-0853 (E1A tumor suppressor gene complexed with DC-cholesterol)	Gene therapy ❑ autologous tumor cells modified to express E1A ❑ suppress HER2/neu *in vivo* ❑ intraperitoneal, intrapleural	Phase I (6/96) ➢USA ❑ metastatic breast cancer	Hortobagyi GN, etal, M. D. Anderson Cancer Center; RAC# 9512-137 approved 12/4/95; NIH approved 2/2/96
Techniclone International ❑ Cambridge Antibody Technology		Drug delivery system ❑ delivers diagnostic and therapeutic agents to the inner core of solid tumors	Preclin (7/96) ➢USA, Europe	
Techniclone International ❑ U Southern California (licensor)	Vasopermeation Enhancement (VE)	Vascular dilators ❑ increase permeability of toxic drugs across blood vessels and capillaries serving tumors	Preclin (96)➢USA ❑ solid tumors	

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Terrapin Technologies	TER199	Glutathione S-transferase (GST) inhibitor ❑ potentiates cytotoxicity of standard alkylating agents in cultured cells and xenografts	Preclin (8/96) ➢USA	See FO, pp 18 and 134
Terrapin Technologies	TER286	Alkylating agent activated by GST; GST-activated cytotoxin	Preclin (8/96) ➢USA	See FO, pp 18 and 323
Therion Biologics ❑ NCI (NIH)	TBC-CEA (rV-CEA)	Immunotherapy ❑ live recombinant vaccinia virus ❑ expresses CEA	Phase I/II (b6/93) ➢USA (2/97)	
Therion Biologics ❑ NCI	rF-CEA	Immunotherapy ❑ recombinant fowl pox virus ❑ expresses CEA	Preclin (2/97) ➢USA	
Therion Biologics ❑ NCI (NIH)	rV-MUC-1	Immunotherapy ❑ gene transfer using live recombinant vaccinia virus ❑ expresses tumor-specific antigen to elicit cellular immune response	Preclin (2/97) ➢USA	
Transgene (BioMerieux)		Vector delivery system; vaccinia virus expressing MUC-1 and IL-2 genes	Preclin (7/95) ➢France	See FO, p 99
U.S. Bioscience	Hexamethylmelamine ❑ Hexalen	DNA antagonist ❑ IV	Phase II➢USA	
U. S. Bioscience ❑ Ganes Chemicals, Ben Venue Laboratories, Parke Davis (Warner-Lambert), NCI	Sparfosate sodium, sparfosic acid, N-phosphonoacetyl-L-aspartic acid ❑ CI-882; NSC-224131 ❑ PALA disodium salt	Fluorinated pyrimidine enhancer ❑ enhances 5-FU ❑ injectable	Clinical (b89) ➢USA	
U. S. Bioscience ❑ Southern Research Institute (licensor); Schering-Plough (overseas), Eli Lilly (Canada), ALZA (USA)	Amifostine ❑ NSC-29696, WR-2721 ❑ Ethyol, Ethiofos, Gammaphos	Selective cytoprotective agent ❑ protects healthy cells from the damaging effects of chemotherapy	Clinical (10/95) ➢USA	L (4/96)➢USA, Canada, Mexico, S. Africa, France, Germany, UK ❑ advanced ovarian cancer, NSCLC; see FO, pp 21, 111 and 173
U Washington ❑ NCI	Perillyl alcohol and/or limonene	Natural products, monoterpenes ❑ induce apoptosis	Phase I➢USA; phase I (limonene) ➢UK ❑ advanced solid tumors	Phase II planned in breast, ovarian and prostate cancer; see FO, p 325
Vanderbilt Cancer Center (Nashville, TN)	Retroviral vector expressing antisense c-fos RNA	*In vivo* gene therapy	Phase I (6/96) ➢USA ❑ metastatic breast cancer	
Vical ❑ U. Michigan (Dr. Gary Nabel), U. Chicago Med Center, Arizona Cancer Center, Mayo Clinic	Allovectin-7	Immunotherapy ❑ transfer of gene encoding a mismatched transplantation antigen (HLA-B7) causing the malignant cells to bear the foreign antigen on their surface ❑ intratumoral injection	Phase II (b9/95) ➢USA, Canada	See FO, pp 54, 150 and 355
Vical	Leuvectin	Gene therapy ❑ IL-2 gene in a plasmid-lipid complex ❑ intratumoral injection	Phase I/II (b4/95-c5/96)➢USA ❑ solid tumors	
Vincent T. Lombardi Cancer Research Center, Georgetown U Medical Center	Thalidomide ❑ NSC-66847	Anti-angiogenesis therapy ❑ PO	Phase II (5/96) ➢USA ❑ metastatic breast cancer	

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Vincent T. Lombardi Cancer Research Center, Georgetown U Medical Center		Mitomycin-C analog	Preclin➢USA	
The Wistar Institute ❑ Sandoz (Novartis)		Chimeric anti-idiotype MAbs produced by immunization with anti-tumor MAbs	Phase I/II➢USA	
The Wistar Institute	TALL-104	Human major histocompatibility complex nonrestricted cytotoxic T-cell line that posseses a uniquely potent MHC nonrestricted tumoricidal activity	Preclin➢USA ❑ advanced, refractory malignancies of various histologic types	
Xenova ❑ Cancer Research Campaign	XR5000 (DACA)	Topoisomerase I & II inhibitors; may overcome drug resistance	Phase I (c9/96) ➢UK, New Zealand ❑ metastatic cancer	
Xenova ❑ Parke-Davis (collaboration and exclusive license outside Europe 10/96)		Natural products discovery technology, QTC, to identify anti-cancer agents	Research➢UK	
Xenova ❑ Bristol-Myers Squibb (research and licensing agreement)		Natural products; screening of microbial extract library	Research➢UK	
Xytronyx ❑ Wound Healing of Oklahoma (developer and R&D partner)	Laser/Sensitizer Assisted Immunotherapy (LSAI)	Photodynamic immunotherapy (PDIT) ❑ intratumoral	Preclin➢USA	
Xytronyx ❑ Binary Therapeutics	Lipophilic cationic compounds (LCCs)	Compounds used for PDT ❑ may be highly tumor-selective, light activated at substantially longer wavelengths to treat larger and deeper tumors and are effective in the presence or absence of oxygen	Preclin➢USA ❑ solid tumors	
Zeneca Group	ICI-182,780	Pure anti-estrogen steroid ❑ blocks stimulatory activity of the IGF-1 system ❑ PO	Phase II (1/96)➢UK ❑ advanced breast cancer	See FO, p 217
Zeneca Group	ZK 119010	Pure anti-estrogen		
Zeneca Group	ICI 164,384	Pure steroidal anti-estrogen		
Zeneca Group ❑ Institute of Cancer Research	ZD-1694 ❑ ICI-D-1694 ❑ Tomudex	Quinazoline antifolate; direct and specific thymidylate synthase inhibitor ❑ IV	Phase III (96) ➢USA, UK	See FO, pp 55 and 331
Zeneca ❑ CRC Technology	ZD-2767 ADEPT	Immunoconjugate; conjugated to MAbs that recognize tumor-selective antigens ❑ prodrug generates corresponding active drug upon interaction with a bacterial nitroreductase	Preclin➢USA	

challenging task. The objective is to develop tissue-specific anti-estrogens with increased efficacy and decreased toxicity but, to date, there is no clear evidence that any of the new non-steroidal anti-estrogen (NSAE) competitors to tamoxifen offer improved clinical efficacy, despite favorable preclinical results.

None of the new NSAEs appear to be significantly less toxic than tamoxifen. Steroidal anti-estrogens and the new aromatase inhibitors that are not expected to have proliferative effects on the endometrium, do not exhibit the beneficial cardiovascular and skeletal effects of tamoxifen and the other NSAEs (Howell A, etal, European Journal of Cancer, 1996 Apr, 32A(4):576-88). Therapeutic effectiveness of the new aromatase inhibitors seems to be equivalent to tamoxifen or the anti-progestins, despite improved estrogen suppression associated with these agents. If all the results of endocrine therapy are therapeutically similar, the final strategy may rest on patient

choice based on quality of life considerations.

Estrogen, a steroid hormone, is a key intracellular modulator of processes involved in female reproductive function. Estrogens are produced by the primary steroidogenic tissues such as the ovaries, testes, adrenals and placenta. Conversion of androgens to estrogens also occurs in a variety of cells and tissues, such as ovarian granulosa and testicular cells, placenta, adipose tissue, and certain sites in the brain. Various peripheral tissues that possess all the required enzymatic systems, also form active androgens and estrogens (intracrinology) from a relatively large supply of precursor steroids such as dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), provided by the adrenals. Extragonadal synthesis of estrogens is pathophysiologically important; estrogens produced by adipose tissue are implicated in the pathogenesis of certain forms of breast cancer. Effective anti-hormonal treatment needs to take into consideration these additional sources of hormone production (Labrie F, etal, Annales D Endocrinologie, 1995, 56(1):23-9).

Estrogen enters the cell's fatty outer membrane and exerts its biological activity through a specific estrogen receptor (ER) located within cell nuclei. ER-mediated gene transcription occurs when, upon interaction with its cognate hormone, latent ER binds to a DNA sequence called the estrogen response element (ERE). Transcriptional activation is mediated via two transactivation ER domains, AF-1 and AF-2. Because estrogen stimulates tumor growth, anti-estrogen therapy aims to deny breast tumors estrogens.

According to recent discoveries (Katzenellenbogen, Benita S, AACR96, Extended Abstracts, p 630) the level and activity of ER and progesterone receptors (PgR) is influenced by hormones, anti-hormones, growth factors and activators of protein kinases. For instance, estrogens stimulate gene transcription that leads to cell proliferation. Their activity is in turn modulated by progestins and antagonized by anti-estrogens. Various interactions, precipitated by factors that regulate or modulate expression and degradation of ligand-receptor complexes, must take place in order for signaling pathways to become activated. Many of these modulators alter the magnitude of ER phosphorylation and also, specific sites of phosphorylation alter transcriptional activity and other receptor properties. The biological activity of ER and the effectiveness of anti-estrogens as estrogen antagonists are probably determined by changes in cellular phosphorylation. Estrogens, as well as protein kinase activators such as cyclic adenosine monophosphate (cAMP) and certain growth factors, increase phosphorylation of the ER and/or proteins involved in the ER-specific response pathway and, thus, alter the biological effectiveness of ER-modulated activities. In several cell systems, estrogens and cAMP act synergistically to enhance ER transcriptional activity in a promoter-specific manner. In addition, cAMP changes the agonist/antagonist balance of NSAEs like tamoxifen, increasing their agonist and reducing their antagonist activity.

Response to estrogen alters production of growth factors, growth factor receptors and proto-oncogenes and stimulates PgR production which increases the cells' sensitivity to progestin, and its production of intracellular and secreted proteins, including plasminogen activators, that may play a role in increasing the cell's metastatic potential. Anti-estrogens, interacting with the ER, effect conformational changes in the ER and inhibit estrogen activity. Although binding of estrogens and anti-estrogens is mutually competitive, some of the contact sites of estrogens and anti-estrogens are different. Receptors may become altered in their ability to bind and mediate the actions of estrogens versus anti-estrogens by mutations in the hormone binding domain of the ER and deletions of carboxyl-terminal regions. Mutant receptors also suppress the activity of the wild type ER by acting at multiple steps in the ER-response pathway.

It appears that a single ER type, which is biochemically identical in all cell types examined, is involved in all diverse biological processes regulated by estrogen. However, although ER exists as a single protein, it is selectively modulated by synthetic ER modulators with cell-specific agonist and antagonist activities. ER modulators are classified into a single class of agonists and into three distinct classes of antagonists represented by tamoxifen, raloxifene and ICI 164,384. Although agents belonging to each class of antagonist appear to interact with the same ER domain, they affect transcriptional activity differently. One possible explanation for this difference is that the cell recognizes each stable conformation created by these ER-ligand interactions as a unique structure eliciting a distinct response.

Another explanation for how the same drug may cause different effects in different tissues, based on molecular signaling between a cell's ER and its genes, has been proposed by Eli Lilly scientists studying the mechanism of action of raloxifene, a drug that antagonizes estrogen action in the breast but imitates it in bone. Raloxifene, it seems, uses a different route to signal genes depending on cell type. This, coupled with input from diverse gene-activating estrogen pathways, results in the agonist/antagonist activity of raloxifene. These findings may eventually lead to drugs that act along certain pathways to selectively achieve desired effects.

However, other possibilities, such as additional receptors, may also need to be considered to explain the various contradictory actions of ER-binding agents in different cells. For instance scientists at the Karolinska Institute (Huddinge, Sweden) recently identified and cloned a novel receptor (clone 29) expressed in rat prostate and ovary. The cDNA of clone 29 encodes a protein of 485 amino acid residues with a calculated molecular weight of 54.2 kDa which is highly homologous to the rat ER protein, particularly in the DNA-binding domain (95%) and in the C-terminal ligand-binding

domain (55%). This novel rat ER is referred to as rat ERβ to distinguish it from the previously cloned ERα from rat uterus (Kuiper GG, etal, PNAS USA, 1996 Jun 11, 93(12):5925-30).

Non-steroidal Anti-estrogens

Currently various NSAE competitors of Tamoxifen are in development and one, toremifine (Orion), has been approved and launched abroad. Tamoxifen, a triphenylethylene-derived, NSAE, functions as an estrogen antagonist in the breast but manifests estrogen like activities in the bone and the cardiovascular system. Unfortunately, however, in a large proportion of patients, tamoxifen also manifests partial ER agonist activity in the endometrium by stimulating uterine cell proliferation. It is this latter activity of tamoxifen that has tainted its role as a long-term approach in the chemoprevention of breast cancer and spurred the development of competitive hormonal therapies. Tamoxifen is also associated with other toxic side effects, among them hepatic carcinogenicity which arises from the formation of DNA adducts. Lack of DNA adducts observed in the tamoxifen analogs toremifene, droloxifene and idoxifene, may account for the species variation in hepatic carcinogenicity (Potter GA, etal, Carcinogenesis, 1994 Mar, 15(3):439-42). Also, unfortunately, in many cases tumors become resistant to tamoxifen during therapy, allowing disease to progress.

Toremifene (Fareston; Orion), a triphenylethylene, is currently the only other anti-estrogen marketed for use in advanced breast cancer; it is available in the UK and Japan for the treatment of breast cancer in postmenopausal women who have progressed on tamoxifen. It was launched in Japan by Nippon Kayaku (Tokyo, Japan) in June 1995. Toremifene appears to be therapeutically equivalent to tamoxifen but its clinical profile differs somewhat. Toremifene has been evaluated in phase I and II clinical trials in over 1,500 patients in Europe, Japan and the USA as first-line therapy in ER+ breast cancer and as second- and third-line therapy in patients who failed tamoxifen. Overall response rates (35% CR+PR in unselected patients) observed with toremifene, are similar to those of tamoxifen. However, doses evaluated (up to 200 mg daily) and the recommended 60 mg daily dose, are significantly higher than the recommended daily 20 mg regimen for tamoxifen. Unlike tamoxifen that produces DNA adducts, toremifene appears to be only weakly active which may explain why it does not induce liver tumors in rats (Jordan VC, Journal of Cellular Biochemistry, Supplement, 1995, 22:51-7). Also see FO, pp 174 and 426.

Droloxifene (Pfizer), another triphenylethylene, is an estrogen antagonist/partial agonist in phase III clinical trials for breast cancer and in phase II clinical trials in osteoporosis. Again, dose regimens of droloxifene (100 mg daily) are much higher than those of tamoxifen. Side effects are comparable with toremifene. Droloxifene also appears to be weakly active in producing DNA adducts. Pfizer licensed droloxifene from Klinge Pharmaceuticals (Munich; Germany), a subsidiary of Fujisawa (Osaka, Japan). In April 1996 Ligand (San Diego, CA) settled a suit against Pfizer, filed in December 1994, claiming that, under the Pfizer-Ligand collaboration in the field of osteoporosis established in 1991, Ligand was entitled to receive milestone payments and royalties upon commercialization of droloxifene. According to the settlement Ligand received milestone payments of approximately $1.25 million in 1996 in Ligand common stock held by Pfizer, and will be entitled to royalties of 1% on sales of droloxifene for breast cancer or 3% for all indications. A similar agreement was concluded for CP-336,156, an estrogen partial agonist resulting from the Pfizer-Ligand collaboration. In *in vitro* and *in vivo* studies, CP-336,156 proved to retain bone-sparing and cardioprotective attributes without increasing the risk of uterine cancer. The drug, currently in preclinical development, also appears to exhibit good oral bioavailability at low doses.

One of the actions of droloxifene is reduction of plasma levels of insulin-like growth factor (IGF) in a dose-related manner. Plasma levels of IGF-I decreased by a mean value of 20% in 6 women with breast cancer treated with droloxifene (40 mg daily) while plasma levels of insulin-like growth factor binding protein (IGFBP)-1 increased by 45%; these variables were 42% and 70%, respectively in 7 women treated with a daily dose of 100 mg. As IGF-I is a potent mitogen for breast cancer cells *in vitro,* a decrease in the plasma level of IGF-I with an increase in the concentration of IGFBP-1, may contribute to the anti-tumor effects of droloxifene (Helle SI, etal, Journal of Steroid Biochemistry and Molecular Biology, 1996 Feb, 57(3-4):167-71).

Idoxifene (CB-7386, CB-7432), a new tamoxifen analog synthesized by Cancer Research Campaign Centre for Cancer Therapeutics and the Institute of Cancer Research (ICR; Sutton, Surrey, UK), was licensed by BTG (London, UK), the patent holder, exclusively to SmithKline Beecham (SKB). As of June 1996, idoxifene was in phase II clinical trials in the UK. SKB will assume further development after completion of phase II clinical trials. Idoxifene was designed to be metabolically stable to minimize any carcinogenic potential. A phase I clinical trial of idoxifene conducted at the Department of Medical Oncology, Charing Cross and Westminster Medical School (London, UK), treated 20 women with metastatic breast cancer, 19 of whom had received tamoxifen previously, with doses between 10-60 mg. Idoxifene was well tolerated at a maintenance daily dose of 20 mg; 11 patients complained of mild symptoms similar to those seen with tamoxifen. Fourteen patients continued idoxifene therapy for 1-56 weeks; there were two PR and disease stabilized for 6-56 weeks in 4 patients (Coombes RC, etal, Cancer Research, 1995 Mar 1, 55(5):1070-4). The CRC Centre for Cancer Therapeutics

of the ICR also synthesized a series of idoxifene homologs and tested them for antagonism of the calmodulin-dependent activity of cAMP phosphodiesterase and for binding affinity to rat uterine ER (Hardcastle IR, etal, Journal of Medicinal Chemistry, 1996 Feb 16, 39(4):999-1004).

Raloxifene (Evista; Eli Lilly) is being clinically evaluated in the treatment of osteoporosis. If the drug becomes generally available to prevent osteoporosis in post-menopausal women, it may also play a role as a chemopreventative in breast cancer (Jordan VC, Journal of Cellular Biochemistry, Supplement, 1995, 22:51-7). Like tamoxifen, raloxifene antagonizes estrogen's effects in breast tissue but acts like an estrogen in bone. However, unlike tamoxifen, raloxifene does not promote excess growth of uterine tissue, implying that it might prevent osteoporosis without increasing the risk for endometrial cancer. Researchers investigating the mechanisms of action of raloxifene have come up with some intriguing findings that may pave the way for the development of more specific anti-estrogens. For instance, it appears that some of raloxifene's regulatory effects in bone appear to be mediated by pathways independent of ERE binding. A new binding domain on TGF-β3 was discovered, the raloxifene response element (RRE), a polypurine sequence that did not resemble either the ERE binding site or another site, AP-1 involved in gene regulation by estrogen. This finding implies that two regulatory pathways, mediated by the ERE and RRE, control gene expression *in vitro*. Products of various genes that contain RRE-like sequences, some known to be regulated by estrogen, appear to have important roles in the effects of anti-estrogens on various tissues (Yang NN, etal, Science, 30 August 1996, 273:1222-25).

Exhibit 2
Breast Cancer Patients on Hormonal Therapy in 1996

Region	Prevalence of Breast Cancer (#)	Rate per 100,000	New Patients on Hormonal Therapy (#)	All Patients on Hormonal Therapy (#)
EEC	1,863,230	1,042.2	138,017	279,484
Non-EEC	178,979	1,036.1	13,768	26,846
Eastern Europe	204,260	368.0	17,508	30,369
Europe[1], Total	2,246,469	893.1	168,234	
USA	1,412,000	1,048.3	103,208	185,000
Canada	154,314	1,021.5	10,416	20,215
North America	1,566,314	1,045.6	114,040	
Japan	199,216	312.8	11,953	26,097
Triad[1]	4,011,999	862.7	294,227	562,129

[1] Excludes the former USSR

Steroidal (Pure) Anti-estrogens

The new pure anti-estrogens exhibiting a distinct mechanism of action may be valuable either as a first-line therapy for advanced breast cancer or as second-line endocrine therapy after failure of long-term adjuvant tamoxifen therapy (Jordan VC, Breast Cancer Research and Treatment, 1995, 36(3):267-85). In contrast to toremifene or droloxifene that do not appear to have greater activity than tamoxifen in the treatment of advanced disease and, therefore, may ultimately offer no advantages over current therapy, the pure anti-estrogens may produce a more profound inhibitory effect on the tumor, and the response may be maintained longer. An orally active, pure anti-estrogen, would be an important advance (Tellez C and Jordan VC, Surgical Oncology Clinics of North America, 1995 Oct, 4(4):751-77).

ICI 182,780 (Zeneca), a specific steroidal anti-estrogen, is being investigated in an oral formulation for the treatment of breast cancer patients who have relapsed on tamoxifen. *In vitro* studies of ICI 182,780 demonstrated that the drug suppresses ER without a concomitant rise in either EGFR or TGF α (McClelland RA, etal, European Journal of Cancer, 1996 Mar, 32A(3):413-6). ICI 182,780 is in phase II clinical trials (see FO, p 217).

Anti-progestins

Anti-progestins exhibit potent anti-tumor activity in hormone-dependent experimental breast cancer models. Although the underlying mechanism is not clear, it may be primarily attributed to induction of functional differentiation, similar to that observed with ER-based modulation. Anti-progestins may be classified into two categories based on differences in how they interact with and inactivate PgR. Type I compounds, represented by onapristone (ZK-98299; Schering AG), impair PgR association with DNA, while Type II compounds, such as RU 38486 (mifepristone), ZK-112993 and ZK-98734 (lilopristone), promote PgR binding to DNA. Type II agents that appear to inhibit PgR activity at a step downstream of DNA binding, presumably do not induce conformational changes in PgR structure required for enhancement of transcription. Although both types inhibit progestin induction substoichiometrically, Type II anti-progestins are more potent, inhibiting at lower ratios of antagonist to agonist than onapristone. Furthermore, onapristone minimally stimulates phosphorylation of PgR which may contribute to its antagonist action in contrast to mifepristone that increases site-specific phosphorylation of PgR in a manner indistinguishable from that of a hormone agonist. Also, onapristone is not susceptible, *in vivo*, to

functional switching to a partial agonist by interacting with cAMP signal transduction pathways, as occurs with Type II compounds. Thus, onapristone, under certain conditions, may be a purer antagonist than Type II compounds (Edwards DP, etal, Journal of Steroid Biochemistry and Molecular Biology, 1995 Jun, 53(1-6):449-58). For more information on onapristone, see FO, p 446. Numerous anti-progestins have been synthesized but, despite favorable activity *in vitro* and in animal models, results with anti-progestins in clinical trials have been disappointing.

Mifepristone (RU 38486; Roussel-Uclaf), first synthesized in 1980, exhibits high affinity for PgR and cortisol receptors. When linked to the receptor, mifepristone temporarily blocks the action of the corresponding hormone. Mifepristone has a powerful anti-progesterone and anti-glucocorticoid effect and a less powerful but nevertheless important anti-androgen effect (Serfaty D, Presse Medicale, 1995 Apr 29, 24(16):775-8). In a phase II clinical trial, among 28 post-menopausal women with PgR-positive recurrent breast cancer who had received no prior therapy for recurrence (prior adjuvant hormonal treatment was permitted if a disease-free interval of at least 24 months had been observed), treated with mifepristone (200 mg daily), there were three PRs, for an overall response rate of 10.7%. Although toxic effects were generally mild to moderate, consisting primarily of nausea, lethargy, anorexia, and hot flashes, mifepristone had minimal activity in this optimal group of patients. Therefore, although it may have a role in combination with anti-estrogens on the basis of preclinical studies, clinical data does not support its use as monotherapy in the management of breast cancer (Perrault D, etal, Journal of Clinical Oncology, 1996 Oct, 14(10):2709-12).

RTI-3021-020 that belongs to a family of chemically novel PgR antagonists developed at Research Triangle Institute (RTI; Research Triangle Park, NC), is a new class of PgR modulators which exhibit cell- and promoter-specific agonist and antagonist activities. *In vitro* biochemical and cell-based assays demonstrated that RTI-3021-020 stabilized into a unique PgR-structure which is recognized by the cell in such a way as to yield partial agonist activity (McDonnell, DP, AACR96, Extended Abstracts, p 630-631). Another antiprogestin synthesized by RTI, RTI-3021-012 (CDB-2914) is being developed as a contraceptive agent. The National Institute of Child Health and Human Development is soliciting CRADA proposals for the development of this agent as a contraceptive.

LG2527 and LG2716 are PgR agonists under development by Ligand Pharmaceuticals, in collaboration with Wyeth-Ayerst (American Home Products) that has acquired exclusive worldwide rights. Ligand is also pursuing an active program in hormonal therapy for breast and prostate cancer (see FO, p 307).

Aromatase Inhibitors

Numerous steroidal and non-steroidal aromatase inhibitors are in development and several have reached the clinic (see FO, pp 445-446). Aromatase, an enzyme localized in the endoplasmic reticulum, catalyzes biosynthesis of estrogens. Aminoglutethimide, a nonspecific reversible competitive non-steroidal aromatase inhibitor, is the pioneering drug that set the stage for the synthesis of a number of structural analogs such as rogletimide which, although slightly less potent, does not inhibit the cholesterol side-chain cleavage and is devoid of sedative action. A new generation of much more potent non-steroidal aromatase inhibitors, include fadrozole (CGS16949A, Afema; Novartis), launched in Japan in 1995, and the imidazole and triazole derivatives that are highly selective for aromatase. Triazoles such as vorozole (R76713; Johnson & Johnson), anastrozole (Arimidex; Zeneca) and letrozole (Femara; Ciba-Geigy/Novartis) reduce serum estradiol concentration to undetectable levels in breast cancer patients. Among steroidal aromatase inhibitors in development are the 7 alpha-substituted androstenedione derivatives including MDL 18962 and FCE 24304. Also, Janssen Research Foundation (Titusville, NJ and Beerse, Belgium) filed an NDA in January 1997 for its differentiation agent liarozole fumarate (Liazal), an imidazole derivative that blocks the P_{450}-dependent breakdown of retinoic acid catabolism and estrogen biosynthesis, for the treatment of hormone-dependent cancer refractory to standard hormonal therapy. For additional information see FO, pp 174, 217, 426 and 445-6.

Exemestane (FCE 24304; Pharmacia & Upjohn), an androstenedione derivative, is an orally active irreversible steroidal aromatase inhibitor. In a dose escalating study, 56 post-menopausal women with advanced breast cancer were divided into four consecutive groups and administered exemestane at daily doses of 25, 12.5, 5 and 2.5 mg. After 7 days of treatment, mean estrone and estradiol levels decreased by 64% and 65% (a decrease which was maintained over time), respectively; in the 2.5 mg group, estrone sulphate levels also decreased by 74%. Treatment tolerability was satisfactory with nausea and dyspepsia reported in 16% of patients. The overall objective response rate was 18% (Zilembo N, etal, British Journal of Cancer, 1995 Oct, 72(4):1007-12). Exemestane is currently in phase III clinical trials.

Luteinizing Hormone-releasing Hormone (LHRH) Agonists

LHRH agonists have been used as a treatment modality in patients with disseminated breast cancer since 1982. Administration of LHRH agonists to pre-menopausal patients produces a chemical oophorectomy. These agonists have been successfully used in the treatment of pre-menopausal women with breast cancer resulting in response

rates of 31%-63%. LHRH agonists integrated into the general treatment plan for young pre-menopausal patient taking tamoxifen whose menstrual cycles may have not stopped by combination chemotherapy, would block the reflex rise in estradiol caused by tamoxifen therapy and ultimately resulting in a more efficient anti-hormonal therapy. For a detailed review of LHRH agonists and related approaches, see FO, V2 #2/3.

Other Developments

D3967, a treatment for hormone sensitive breast cancers which is expected to offer significant advantages over racemic drug treatment through reduced side effects and a dual mode of action, is under development by Chiroscience (Cambridge, UK), a chiral pharmaceutical company. Phase I studies were completed in early 1996 and regulatory approvals were obtained for two phase II studies involving 145 patients, with recruitment initiated in Norway, Poland and the Czech Republic at the end of April 1996. D3967 may exhibit a dual mechanism of action, and may be effective in combination with other anti-cancer drugs.

Fluasterone, a dehydroepiandrosterone (DHEA) analog, is under development by Aeson Therapeutics (Tucson, Arizona), a company formed by Research Corporation Technologies (RCT; Tucson, Arizona) to assume ongoing development of potential therapeutic agents from a synthetic version of DHEA. DHEA, a steroid hormone, is produced in large quantities by the human adrenal gland, but its biological role in humans is only partially understood. In animal tests, DHEA inhibits development of breast, lung, colon, liver and skin tumors and also exhibits antiobesity, antidiabetic, antiatherosclerotic and cholesterol-lowering effects. Male hormonal side effects of the steroid limit the use of DHEA in humans, particularly women. Fluasterone, A patented DHEA analog developed by Dr. Arthur G. Schwartz and others at the Temple University Fels Institute for Cancer Research and Molecular Biology (Philadelphia, PA), lacks these side effects and shows greater efficacy in animals. Aeson plans to evaluate the potential efficacy of fluasterone in preventing breast cancer, among other indications. Aeson is negotiating to carry out a clinical trial with the Cancer Chemoprevention Program of the NCI to test fluasterone as a breast cancer preventive.

GROWTH FACTOR MODULATION

Various polypeptide growth factors have been implicated in cell division and cell growth in solid tumors, in general, and breast cancer, in particular.

Polyamine Depletion

Polyamines have been proposed as specific mediators of estrogen action in breast cancer cells, but their exact role in this process remains unclear. However, *in vitro*, polyamine depletion is an efficient complementary strategy to block the mitogenic action of peptide growth factors, which are only partly antagonized by anti-estrogens (Huber M and Poulin R, Journal of Clinical Endocrinology and Metabolism, 1996 Jan, 81(1):113-23).

Epidermal Growth Factor (EGF) Blockade

The role of EGF in breast cancer remains obscure. The epidermal growth factor (EGF) receptor (EGFR) is a transmembrane receptor that contains an extracellular portion that binds natural ligands EGF or TGF α and an intracellular portion which contains a tyrosine kinase that is activated by EGF/TGF α binding. Oncogene erbB-2 and EGFR are often co-expressed in human tumors and have been shown to act synergistically in the transformation of cells in experimental model systems. Transactivation of erbB-2 can occur via ligand-induced heterodimerization with EGFR or other members of the erbB family of receptor tyrosine kinases.

In an attempt to assess the prognostic value of EGFR expression and its biological role in ER+ and ER- primary breast cancer, 26 patients with primary breast tumors were evaluated in terms of ER status and EGFR expression. ER+ tumor cells were detected in 22 (69%) and EGFR+ tumor cells were detected in 11 (34%) of primary breast carcinomas. Expression of ER and EGFR was inverse in both primary tumor cells and metastases, and a relationship was observed between EGFR expression and poorly differentiated or large breast tumors. Primary tumors with a predominant lobular component were ER+ and, with one exception, EGFR-, while invasive ductal carcinomas were more frequently EGFR+. No apparent differences in receptor expression were observed between primary tumors and lymph node metastases or chronously or metachronously occurring bilateral breast cancers, implying that expression of EGFR is not a prerequisite for development of metastases (van Agthoven T, etal, International Journal of Cancer, 1995 Dec 11, 63(6):790-3).

Researchers have also observed that natural interferon-β (IFN-β) and recombinant IFN-α 2b inhibit EGF-stimulated cell growth and reduce EGF binding in estrogen-sensitive human breast cancer cells (Iacopino F, etal, Anticancer Research, 1996 Jul-Aug, 16(4A):1919-24).

Abgenix (Foster City, CA), a subsidiary of Cell Genesys, was established in June 1996 to consolidate all interests related to agreements with Japan Tobacco (Osaka, Japan) and the joint venture with JT Immunotech USA (San Mateo, CA), a medical subsidiary of Japan Tobacco established in 1991, and preclinical antibody research originally handled by the Xenotech Division of Cell Genesys which was phased out in 1996. Up to the time of the establishment of Abgenix, Cell Genesys received approximately $38 million in funding through agreements with JT Immunotech and Japan Tobacco which remain in effect, with committed funding into 1997. New agreements have been transferred to

Abgenix. Abgenix is focused on the development and commercialization of antibody therapies for inflammation, autoimmune disorders and cancer, as well as in a licensing program of gene activation technology. In the cancer area, Abgenix is developing a fully human MAb directed against an EGF cell-surface receptor to block EGF activity.

ImClone Systems (New York, NY) has completed a phase I clinical trial of human chimeric anti-EGFR MAb C225 (see FO, p 315 and 398-99). Single doses of 100 mg/m^2 achieved receptor-saturating MAb levels in the blood for more than a week, without eliciting a human anti-mouse antibody (HAMA) response. No serious toxicities were observed. A second phase I trial with repeated weekly doses of MAb C225 is nearing completion. In xenograft models, MAb C225 therapy was successful only when initiated within a week of tumor cell implantation because most xenografts larger than 1 cm in diameter did not respond to MAb C225. Combination of MAb C225 with chemotherapy may prove a more effective strategy in attacking cells damaged by chemotherapy that might be susceptible to further injury, if they were deprived of essential signal transduction mechanisms by blocking growth factors receptors. Preclinical studies demonstrated strong synergistic effects of MAbs 225 or 528 combined with doxorubicin, cisplatin or paclitaxel. Well-established tumors, resistant to treatment with either MAb alone or toxic doses of chemotherapy, were eradicated when the treatments were combined. Because response to combined EGFR blockade and chemotherapy does not appear to be elicited by a particular chemotherapeutic agent, it is hypothesized that it is attributed to a generalized mechanism involving dual checkpoint activation. When malignant epithelial cells are deprived of the EGFR tyrosine kinase-medicated pathway (G1 checkpoint) and are concurrently damaged by a drug (G2 checkpoint, primarily), it is postulated that the growth factor pathway becomes a requirement for survival. Based on these findings, ImClone started two phase Ib/IIa clinical trials of C225 in mid-1995, one to test C225 alone in patients with EGFR+ cancers, and the second to evaluate C225 in combination with paclitaxel in patients with breast cancer. In both studies, 24 patients are treated with C225 weekly by intravenous injection in a dose escalation protocol over four weeks. Treatment is continued for another eight weeks in patients with stable disease.

Investigators also treated athymic mice with a combination of anti-EGFR C225 MAb, and 8-Cl-cAMP, a selective cAMP analog that inhibits type I cAMP-dependent protein kinase (PKAI), a protein overexpressed in cancer cells. The combination proved effective in suppressing tumor growth and angiogenesis without signs of toxicity and may be a feasible long-term (chronic) maintenance approach to chemotherapy-treated survivors (Ciardiello F, etal, JNCI, 4 Dec 1996, 88(23):1770-76).

NEW CHEMOTHERAPEUTICS

Gemcitabine

Gemcitabine (Gemzar; Eli Lilly), launched in the USA in May 1996 for the treatment of pancreatic cancer generated domestic sales of $31.6 million in 1996 and worldwide sales of $62 million. At the current rate (worldwide sales in the last three months of 1996 were $26.3 million), the drug is expected to generate worldwide sales of $150 million in 1997 for this and other possible indications. Analysts see gemcitabine evolving into a broad anti-cancer agent with a potential worldwide market estimated at between $500 million and $700 million in the year 2000. Gemzar was launched in several European countries in 1996 and is currently available in over 19 countries worldwide. Based on the 1.2 g/m^2 thrice monthly regimen, cost of treatment at the current average wholesale price of $347 for 1 g of gemcitabine, would be $2,160 per cycle.

Gemcitabine has demonstrated activity in many solid tumors including breast cancer (see FO, pp 47, 98, 110 and 263). In a phase II European study, among 40 patients with metastatic or locally-advanced breast cancer evaluable for response (26 had received chemotherapy with seven in the adjuvant setting), administered gemcitabine (1200 mg/m^2) as a 30-minute intravenous infusion on days 1, 8, and 15 of a 28-day cycle, there were three CRs and seven PRs, for an overall response rate of 25%. Median duration of survival was 11.5 months. Hematologic toxicity was generally mild, with Grade 3 and 4 leukopenia occurring in 6.8% and 2.3% of patients and neutropenia in 23% and 7% of patients, respectively. Nonhematologic toxicity was minimal. Flu-like symptoms were mild and transient and only one patient developed alopecia. In a 36-patient, phase II clinical trial in the USA that included patients with Stage IV breast cancer who had been heavily pretreated, among 26 evaluable patients, there were two CR and 10 PRs, for an overall response rate of 46% (Blackstein M, etal, ASCO96, Abs. 135:117). The safety profile was similar to that in the European study, although myelosuppression was greater. Responses were observed in both chemotherapy-naive and previously treated patients. The drug was extremely well tolerated in both studies, even in heavily pretreated patients. Therefore, its modest toxicity profile, novel mechanism of action and, in particular, relative lack of myelotoxicity render gemcitabine an ideal candidate for combination chemotherapy in breast cancer (Carmichael J and Walling J, Seminars in Oncology, 1996 Oct, 23(5 Suppl 10):77-81). Gemcitabine's mode of action involves a number of intracellular changes, shared by other radiation sensitizers, that may be particularly useful in combination with radiotherapy for the treatment of solid tumors. *In vitro*, gemcitabine produces radiation enhancement ratios at low noncytotoxic concentrations that are higher than those of other radiosensitizers. Radiosensitization increases with dose and duration of exposure, and is greatest when

exposure precedes radiation (Shewach DS and Lawrence TS, Seminars in Oncology, 1996 Oct, 23(5 Suppl 10):65-71).

Anthracyclines-Novel Approaches and Analogs

Numerous anthracycline analogs have been synthesized and many have been clinically evaluated in the USA and abroad, particularly in Japan. This activity is spurred by the importance of anthracyclines as key components of adjuvant chemotherapy in the management of breast cancer and by the fact that the application of currently approved agents such as doxorubicin (DOX), is seriously compromised by their cumulative cardiotoxicity that limits their usefulness as long-term therapy, particularly in the elderly.

Liposomal encapsulation of currently approved anthracyclines is one approach used to limit their toxicity. Among such products are various approved liposomal formulations of DOX such as Sequus Pharmaceuticals' (Menlo Park, CA) Doxil/Caelyx and of daunorubicin, such as NeXstar Pharmaceuticals' (Boulder, CO) DaunoXome, both approved for Kaposi's sarcoma and in clinical trials in metastatic breast cancer together with TLC D-99, a liposomal formulation of DOX under development by The Liposome Company (Princeton, NJ), currently in phase III clinical trials.

Annamycin, a new anthracycline antibiotic under development by Aronex (The Woodlands, TX), exhibits high affinity for lipid membranes and is significantly more active than DOX. Also, annamycin was not affected by P-glycoprotein (P-gp)-related multidrug resistance (MDR) *in vitro* when compared with idarubicin and DOX (Consoli U, etal, Blood, 1996 Jul 15, 88(2):633-44). Annamycin is currently in a phase I/II dose-escalating study in breast cancer patients who have failed treatment with other anthracyclines, being conducted in collaboration with M. D. Anderson Cancer Center (Houston, TX). In addition to breast cancer, Annamycin may be effective in a wide variety of solid tumors, leukemias and lymphomas. Aronex has acquired exclusive rights from M. D. Anderson to an issued patent covering Annamycin, that claims its composition and its use in treating cancer. Six patents covering Annamycin and certain related compounds have been non-exclusively sublicensed to Aronex by M. D. Anderson Cancer Center (Houston, TX), which licensed them from Ohio State University (Columbus, OH). In addition, a patent application has been filed regarding an improved process for preparing Annamycin.

Anthrapyrazoles are newer anthracycline derivatives that are closely related to mitoxantrone at the molecular and cellular levels. They are potent topoisomerase II inhibitors but, unlike anthracyclines, they do not seem to produce free radicals and, therefore, they were expected to be less cardiotoxic than DOX. Originally it was thought that anthrapyrazoles may be useful for the same indications as mitoxantrone, especially for patients with cardiac risks, for pediatric patients, and for those treated with intensified protocols. In clinical trials conducted by the NCI, a very high response rate (50%-60% CR+PR) was observed in women with previously treated advanced breast cancer. However, further clinical development of these drugs was stymied by the fact that they did not seem to be totally devoid of cardiotoxicity. Among clinically evaluated anthrapyrazoles are several developed by Warner-Lambert (Morris Plains, NJ), in collaboration with the NCI, and licensed to DuPont Merck (Wilmington, DE), such as teloxantrone (DuP 937), losoxantrone (DuP 941) and piroxantrone (DuP 942).

Other anthracycline analogs in development include menogaril (Tomosar), an orally administered agent currently in phase II trial, and FCE 23762, a novel, highly lipophilic DOX analog that demonstrated potent *in vitro* and *in vivo* anti-tumor activity including efficacy in multidrug-resistant tumor cell lines, both under development by Pharmacia & Upjohn. FCE 23762 becomes metabolically activated *in vivo* resulting in an 80-fold increase in potency over the parent drug. In a phase I clinical trial involving 53 patients with refractory solid tumors, FCE 23762, was administered by IV bolus injection at 3-week intervals at doses ranging from 30 μg/m^2 to 2250 μg/m^2. MTD using this schedule was 1500 μg/m^2. Dose limiting toxicity was reversible myelosuppression (granulocytopenia and thrombocytopenia), demonstrating a delayed nadir and recovery compared to DOX. Other toxicities included transient elevation of hepatic transaminases, delayed and prolonged nausea and vomiting, mucositis, anorexia, fatigue, and diarrhea. No cardiotoxicity was observed. Four objective tumor responses were seen in solid tumors other than breast cancer. Recommended phase II dose for previously untreated patients using this schedule is 1250 μg/m^2 which may actually be below optimal dose (Vasey PA, etal, Cancer Research, 1995 May 15, 55(10):2090-6).

Anthracyclines-Novel Delivery Approaches

Drug delivery approaches are also in development to enhance tumor effects of approved anthracyclines like DOX by delivering them *in situ*, thus avoiding systemic toxicities. Also, the effect of chemotherapeutics, such as DOX, may be enhanced by linking the drugs to various targeting molecules.

Atrix Laboratories (Fort Collins, CO) is developing such an approach using its drug delivery system Atrigel, a biodegradable sustained release drug delivery system, for the local delivery of certain anti-cancer agents. Atrigel can release an agent into solid tumors at higher concentrations and for longer periods than feasible by the systemic route because of dose-limiting toxicity. Preclinical studies with the Atrigel system and cisplatin, vinblastine, as well as DOX, resulted in reduced tumor volume, increased survival and lower toxicity. Sustained

release of these agents for periods up to 28 days has been demonstrated preclinically.

Bristol-Myers Squibb is developing BR96-DOX (BMS-182248), an immunoconjugate designed as a delivery vehicle for chemotherapeutics such as DOX or toxins. BR96-DOX combines BR96 MAb, a chimeric (mouse/human IgG_1) MAb which binds a Le^y-related tumor-associated antigen abundantly expressed on the surface of many tumors including breast cancer, in a DOX:MAb molar ratio of 8:1. BR96 is tumor-selective rather than tumor-specific and also binds to cells of several normal tissues, primarily differentiated cells of the esophagus, stomach, and intestine as well as acinar cells of the pancreas. BR96 MAb is rapidly internalized into the acidic environment of endosomes and lysosomes after binding to cells expressing the antigen. This characteristic was used to produce DOX immunoconjugates which use an acid-labile hydrazone linker to DOX, which undergoes lysosomal hydrolysis and rapidly releases DOX *in vivo*, following antigen-specific internalization, and a thioether bond to the MAb for acceptable plasma stability. BR96-DOX is stable in solution for long-term refrigerated storage (Barbour NP, etal, Pharmaceutical Research, 1995 Feb, 12(2):215-22).

In preclinical studies BR96-DOX was shown to produce complete regressions and cures of a variety of subcutaneous and disseminated Le^y-expressing tumors in athymic mice in which the tissue distribution of Le^y is similar to that seen in humans and was both more active and more potent than optimized unconjugated DOX. In two phase I trials in patients whose primary tumors express Le^y and who have failed conventional therapy, BR96-DOX was administered at escalating doses (66-875 mg/m^2) by 2- or 24-hour infusion at a given dose on either an every 3-week or weekly schedule. Although biopsies performed 24-hours after the end of conjugate infusion demonstrated that both the MAb and DOX components of the conjugate localized to small, metastatic, subcutaneous tumors, there was no evidence to date of a significant antibody response to the BR96-DOX conjugate, BR96 MAb, linker, or DOX. Pharmacokinetic studies demonstrated that immunoreactive conjugate remained in circulation through 7 days post-infusion. Circulating conjugate retained the ability to mediate antigen-specific cytotoxicity *in vitro* through 3 days post-infusion. The major toxicity has been gastrointestinal (GI), including nausea, vomiting and gastritis and is most likely mediated by the protein part of the immunoconjugate, as indicated also by toxicology studies in dogs which express high levels of Le^y in the GI tract. GI toxicity remained a problem despite various adjunct treatments (omeprazole, H2 receptor antagonists or metoclopramide, dexamethasone, 5-HT3 receptor antagonists and lorezepam). No CR was observed but there were 2 PR and disease stabilized in several patients.

Additional preclinical studies suggest that anti-tumor activity of BR96-DOX is more closely related to total drug exposure than to the peak drug concentration. It is unlikely that peak concentrations which are curative in rodent models, would be achieved with single doses in patients because of GI toxicity. However, modification of the dose and schedule of administration of BR96-DOX may allow for total exposure to be substantially increased while minimizing GI toxicity (Trail, PA, etal, AACR96, Abs. 3212:471 and Extended Abstract, p 626). A phase II study in breast cancer with BR96-DOX was initiated in late 1996. In May 1995, Genzyme Transgenics (Framingham, MA) entered into a contract with BMS to provide goats that secrete BR96 MAb as a low cost alternative for the production of biologicals.

Genentech (South San Francisco, CA) researchers have been investigating use of anti-p185HER2 immunoliposomes as a delivery approach to enhance localization of DOX. Anti-p185HER2 immunoliposomes consist of Fab' fragments of a humanized anti-p185HER2 MAb (rhuMAb-HER2) with anti-proliferative properties, conjugated to either conventional or sterically-stabilized liposomes. DOX-loaded anti-p185HER2 immunoliposomes are significantly and specifically cytotoxic against p185HER2-overexpressing tumor cells *in vitro* and were shown to deliver DOX to tumors *in vivo* (Park JW, etal, PNAS USA, 1995 Feb 28, 92(5):1327-31). Systemic administration in nude mice bearing p185HER2-overexpressing tumor xenografts resulted in tumor localization of DOX and in less systemic toxicity and higher regression of established tumors than free DOX (Park, JW, etal, ASCO96, Abs. 1605:501).

5-fluorouracil Analogs/Thymidylate Synthase Inhibitors

Anti-tumor effects of such commonly used antimetabolites as methotrexate and 5-fluorouracil (5-FU) are partly attributed to thymidylate synthase (TS) inhibition. However these drugs also have non-specific, non TS effects on RNA and purine synthesis. Newer TS inhibitors, and various analogs, prodrugs and enhancers of 5-FU are being pursued by various developers to improve efficacy and reduce toxicities. These novel drugs will undoubtedly prove useful in the treatment of breast cancer, as well as many other tumors.

776C85 (776C), a uracil analog, is a mechanism-based inactivator of dihydropyrimidine dehydrogenase (DPD), the rate limiting enzyme in 5-FU catabolism. Co-administration of 776C85 and 5-FU improves the latter's anti-tumor activity. The drug, under development by Glaxo Wellcome, is in phase II/III clinical trial in colorectal cancer, and studies are planned for other cancers that respond to 5-FU. Based on a phase I clinical trial with intravenous 5-FU, oral leucovorin and oral 776C85, the recommended dose for phase II/III in patients with solid tumors is 25 mg/m^2 for 5-FU alone or 20 mg/m^2 with leucovorin (50 mg), administered on days 2-6, and 776C85 (10 mg) on days 1-7, every 28 days (Schilsky, RL, etal,

ASCO96, Abs. 1544:485). Side effects associated with a combination of oral 5-FU at 1.35 mg/m^2 twice daily administered for 14, 21 or 28 days or 1.8 mg/m^2 twice daily for 28 days, in combination with daily oral 776C85 (10 mg), were mild; Grade 4 diarrhea occurred in 1 of 3 patients at the highest dose level (Baker SD, etal, ASCO96, Abs. 1547:486). Combination of oral 5-FU/776C85 that would be equally effective to prolonged IV infusions of 5-FU, would provide a welcome treatment alternative.

Capecitabine (Ro 09-1978) is an oral tumor-selective fluoropyrimidine developed by Hoffmann-La Roche as a more effective and less toxic alternative to doxifluridine (Furtulon; Roche), a 5-FU prodrug commercially available in Japan, Korea and China. In phase I clinical trials capecitabine alone or in combination with leucovorin demonstrated activity against several solid tumors including breast cancer. Patients were treated with daily capecitabine doses ranging from 1004-1657 mg/m^2, in combination with a fixed 60 mg daily dose of oral leucovorin (Dirix, LY, etal, ASCO96, Abs. 1821:496).

Ralitrexed (Tomudex; Zeneca) is a specific folate-based quinazoline TS inhibitor developed in collaboration with the UK Institute of Cancer Research (Sutton, UK). Eight phase II trials of Tomudex (3.0 mg/m^2), administered as a short 15-minute infusion thrice weekly, demonstrated this drug's activity in a range of tumor types, including breast cancer (objective response rate was 26% (Cunningham D, etal, Tomudex International Study Group, Annals of Oncology, 1996 Feb, 7(2):179-82). Among 43 evaluable patients from a total of 46 patients (74% of patients were previously treated with systemic therapy either as adjuvant cytotoxic or hormonal therapy or hormone therapy for advanced disease and 39% with adjuvant cytotoxic chemotherapy) with advanced breast cancer who entered a phase II study of ZD1694, 26% achieved CR or PR. A response rate of 44% was seen in liver metastases. Two patients achieved CR lasting 265 and 301 days, respectively, one in locoregional disease, and one in liver metastases. The most common Grade 3/4 adverse events were nausea and vomiting (11%), diarrhea (11%) and leukopenia (20%); Grade 3/4, self-limited and reversible increases in transaminases were seen in 22% of patients. ZD1694 monotherapy appears to be comparably active as other antimetabolites in patients with hormone-refractory advanced breast cancer, with acceptable tolerability (Smith I, etal, British Journal of Cancer, 1996 Aug, 74(3):479-81).

S-1, a new oral fluorinated pyrimidine developed by Taiho Pharmaceutical (Saitama, Japan), is designed to biochemically modulate 5-FU and inhibit its degradation in the liver and phosphorylation in the digestive tract. S-1 consists of tegafur (FT), a prodrug of 5-FU that is absorbed orally and metabolized *in vivo* to 5-FU, 5-chelo-2,4-dihydroxypyridine (CDHP), and potassium oxonate (OXO), combined in a molar ratio of FT:CDHP:OXO, 1:0.4:1; FT releases 5-FU continuously in the liver, CDHP inhibits degradation and OXO inhibits phosphorylation (Shirasaka T, etal, Cancer Research, 1996 Jun 1, 56(11):2602-6). In a phase II clinical trial conducted in Japan by the S-1 Cooperative Study Group, among 27 evaluable patients with advanced breast cancer administered S-1 (50 or 75 mg) twice daily for 28 consecutive days with 14 days interval after first course and repeated every 6 weeks for courses 2-4, the response rate was 40.7% with 4/27 (14.8%) CR and 7/27 (25.9%) PR (Taguchi T, etal, ASCO96, Abs. 151:121). Also see FO, p 261.

UFT (Ftorafur), developed by Taiho (an Otsuka Group company), is a fixed-ratio combination of uracil and tegafur (see FO, p 55). It is currently being developed for colorectal cancer by Bristol-Myers Squibb that has obtained exclusive rights to UFT in North and Latin America, Europe, and all other countries except Japan where it is marketed by Taiho and the Philippines and other Asian countries and Spain, where it is marketed by Otsuka (Tokyo, Japan) In these countries UFT is marketed for a variety of indications, among them colorectal, gastric, breast, and other cancers. An NDA for colorectal cancer is expected to be filed in the USA in 1998.

Topoisomerase I inhibitors

Topoisomerase I inhibitors have become commercially available for the first time in 1996 for various indications other than breast cancer (see FO, pp 56, 111, 251) and are also being clinically evaluated for the treatment of advanced breast cancer. A detailed review of the status of topoisomerase I inhibitors in the treatment of cancer will be presented in FO, V2 #11.

Taxanes

Taxanes are increasingly becoming more important in the treatment of advanced breast cancer. A thorough discussion of the use of taxanes in cancer, in general, has been presented in FO, pp 175-185 and 275-276, and in breast cancer, in particular, in FO, pp 217-219 and 436-437. In 1996, the two taxanes on the market, paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Rhône-Poulenc Rorer) reported sales of $813 million and $89 million, respectively, for a total worldwide revenue of $902 million.

In February 1997 the Alberta Cancer Board and Rhône-Poulenc Rorer (RPR) announced the creation of the International Taxotere Breast Cancer Study Group, a $15 million, five-year worldwide research collaboration to study the effects of docetaxel-based combination chemotherapy on overall and disease-free survival in early-stage breast cancer. Headed by Dr. Jean-Marc Nabholtz of the Cross Cancer Institute (Edmonton, Alberta), this randomized clinical trial is expected to begin enrolling its target of 1,600 women in April 1997 in 73 centers worldwide. Two docetaxel-based combination regimens are to be investigated. One regimen, combining docetaxel with Adriamycin and cyclophosphamide (TAC), will be compared to the standard 5-FU, Adriamycin

and cyclophosphamide (FAC) protocol, and the other will combine docetaxel with high-dose chemotherapy and peripheral stem cell transplantation.

Retinoids

Retinoids exhibit anti-proliferative effects in human breast cancer cells and share some characteristics with anti-estrogens, although the molecular targets involved have yet to be identified. For instance, estrogen elicits up-regulation of retinoic acid receptor-α (RAR-α) RNA and protein levels in human breast cancer cells. Retinoids are currently being evaluated alone and in various combination in the treatment of breast cancer. For more information on retinoids, see FO, pp 144, 368, 398.

LGD1069 (Targretin; Ligand Pharmaceuticals), a small organic compound that selectively activates retinoid X receptors (RXR), is being clinically investigated in topical (phase III in the treatment of cutaneous T cell lymphoma) and oral (phase II in the treatment of solid tumors) formulations. In addition to its activity against other solid tumors, LGD1069 reduced incidence of breast tumor formation in a carcinogen-induced rat mammary carcinoma by 90% versus an 85% reduction observed with tamoxifen. LGD1069 also reduced the number of tumors by 85% compared to tamoxifen's 75%. No dose-limiting toxicities were observed. Also see FO, p 31.

Interferon/retinoid combinations have also proven effective in promoting apoptosis and blocking angiogenesis. It has been shown that retinoids and interferon-γ (IFN-γ) act synergistically to amplify growth inhibition in cultured breast cancer cells (Widschwendter M, etal, Cancer Research, 1995 May 15, 55(10):2135-9). Also, a combination of 9-cis-retinoic acid (9-cis RA) and IFN-γ increased radiosensitivity of breast cancer cells *in vitro*. These results suggest that a regimen of IFN-γ, 9-cis RA, and radiotherapy may be a promising combination in the therapy of solid tumors, conventionally treated by radiation therapy (Windbichler GH, etal, Gynecologic Oncology, 1996 Jun, 61(3):387-94). Use of combinations of retinoids with interferon-α (IFN-α) may also prove effective in the treatment of angiogenesis-dependent malignancies (Majewski S, etal, Cancer Letters, 1995 Feb 10, 89(1):117-24).

Vitamin D derivatives, in combination with 9-cis RA, were also shown to promote apoptosis in breast cancer cells. A novel vitamin D analog, EB1089, alone or in combination with 9-cis RA, reduced bcl-2 and increased p53 protein levels in cell cultures after 96 hours of exposure. In the presence of 9-cis RA, EB1089 was more effective in down-regulating bcl-2 and up-regulating p53. EB1089 also induced DNA fragmentation in breast cancer cells either alone or in combination with 9-cis RA *in situ* (James SY, etal, Journal of Molecular Endocrinology, 1995 Jun, 14(3):391-4). Agents such as EB1089 may prove useful in combination with anti-estrogens in the treatment of ER+ breast tumors, and as monotherapy in ER- breast tumors.

Fenretinide (4-HPR), an orally available retinoid developed by McNeil (Johnson & Johnson), is in phase III clinical trials as a breast cancer chemopreventative in the USA and in Italy. Its mode of action at the molecular level, however, remains elusive. The agent does not bind to the retinoid acid receptors RAR or RXR. The drug induces a significant decline in IGF-I levels which appears to be more pronounced in women under the age of 50 (Formelli F, AACR95, Abs. 1263;185).

Metalloprotease Inhibitors

Most cancer deaths, including those of breast cancer patients, are attributable to metastasis. Metalloprotease inhibitors have shown to prevent metastasis of a rat breast carcinoma (Eccles S, etal, AACR96, Abs. 505:73). MPIs are in clinical development for various solid tumors, including breast cancer. Among developers of MPIs is British Biotech (Crowley, Oxford, UK), with its oral MPI, Marimastat; Agouron with the oral selective agent, AG-3340; CollaGenex (Newtown, PA) in collaboration with Boehringer Mannheim, and Chiroscience.

ALTERATION/REPAIR OF ONCOGENES/TUMOR SUPPRESSOR GENES AND RELATED PATHWAYS

p53

Ten years after the discovery of p53 located on the short arm of chromosome 17, Dr. Bert Vogelstein and colleagues at Johns Hopkins University (Baltimore, MD) reported, in 1989, that p53 was subtly mutated in many different tumors and that wild type p53 acted as a tumor suppressor preventing development and progression of many solid tumors including breast cancer. Based on findings from several studies, alterations in p53 are considered to be the most common changes identified to date in breast cancer, occurring in 25% to 45% of cases. Also, p53 mutations are associated with aggressive tumors and a poor patient prognosis regarding disease-free and overall survival. Using Sequence-Based Diagnosis (SBD), researchers sequenced the complete coding region of p53 gene from 316 consecutively presented breast cancers (97 lymph node positive and 206 node negative). The whole coding sequence identified 69 individual mutations, 29 in node-positive tumors. Mutation sites were partly different for node-positive and node-negative patients. p53 status was related to prognosis and effect of adjuvant therapy; mutations in the evolutionary conserved regions II and V were associated with significantly worse prognosis. Adjuvant systemic therapy, especially with tamoxifen, along with radiotherapy seemed to be of less value in lymph node-positive patients with tumors carrying p53 mutations (Bergh J, etal, Nature Medicine, 1995 Oct, 1(10):1029-34). Also see FO, pp 24.

Numerous developers, among them Lynx Therapeutics (Hayward, CA) which is using antisense approaches (see FO, p 27), Onyx Pharmaceuticals (Richmond, CA), Mitotix (see FO, P 27), and the companies listed below, among others, are testing a variety of approaches to affect the status of p53. Strategies in use involve replacement of mutant forms of p53 gene with wild-type p53, selectively killing cells lacking normal p53 and interfering with pathways affecting expression of p53, or genes that are transcriptionally regulated by p53, such as those involved in cell-cycle control, DNA damage repair or cell apoptosis.

Canji (San Diego, CA), a Schering-Plough business unit, is introducing normal p53 into tumors with mutant p53. The efficacy of a recombinant p53 adenovirus (p53 Ad) was tested in nude mice injected with three human breast cancer cell lines (MDA-MB-468, -231 and -435) expressing mutant p53. Mice were treated by intratumoral/peritumoral injection of p53 Ad, β-galalactosidase Ad or vehicle alone. Tumor growth inhibition averaged 74% (61 % was p53-specific) for 468 tumors and 86% (43% was p53-specific) for 231 tumors, but was not significant for 435 tumors. At the same virus concentrations, 468 cells were slightly more infectable than 231 cells, while 435 cells were resistant to adenovirus infection. The same dose of p53 Ad killed almost all 468 and 231 cells. In another group of experiments to examine the continued efficacy of p53 Ad over multiple cycles of therapy, efficacy decreased with continued dosing. Although insertion of normal p53 appears to curtail cancerous cell growth *in vivo* in tumors expressing mutant p53 and adenovirus appears to be an efficient delivery vehicle for the p53 gene when target cells express the appropriate viral receptor, development of host resistance to Ad infection must be addressed in any clinical protocol using an Ad-based gene delivery system (Nielsen L, etal, AACR96, Abs. 2317:340). In February 1997, Schering-Plough Research Institute declined to sign a worldwide license for p53 TCS, a transmembrane carrier system-based approach to deliver p53 gene to tumor cells, being developed in collaboration with Inex (Vancouver, Canada). The two companies may enter into a less formal alliance to continue research in this area.

Genzyme Molecular Oncology (GMO; Cambridge, MA) was formed by Genzyme in February 1997 by combining PharmaGenics (Allendale, NJ), acquired by Genzyme, with its own cancer-related drug development operations. Currently a division of Genzyme, GMO will eventually be spun off as a public company through an IPO. PharmaGenics' involvement in the cancer area is based on research in tumor suppressor genes, in general, and p53, in particular, conducted by a team of researchers at Johns Hopkins University. PharmaGenics has licensed certain patent rights from Johns Hopkins University, including methods to screen for drugs that restore p53 function covered by a U. S. patent (#5,362,623) issued in November 1994. PharmaGenics has forged alliances with Xenova (Slough, UK), Boehringer Mannheim Therapeutics (Penzberg, Germany), Hofmann-La Roche and Genetic Therapy (Novartis). The new company's focus will be genomics, combining PharmaGenics' Serial Analysis of Gene Expression (SAGE) with Genzyme's expertise in positional cloning; gene therapy, including Genzyme's melanoma vaccine development program; gene-based diagnostics; and small-molecule combinatorial chemistry drug discovery.

Introgen Therapeutics (Austin, TX) and Rhône-Poulenc Rorer have a letter of intent to establish a CRADA with the NCI to conduct a phase II clinical trial of Introgen's Ad-p53 product in the treatment of p53-expressing, locally recurrent breast cancer involving the chest wall. Preclinical results suggest that Ad-p53 infects and kills cancer cells (including those exhibiting MDR) of diverse tissue origin and that Ad-p53 may enhance mitomycin C- or Adriamycin-induced cell death in tumors with p53 mutations (Blagosklonny MV and el-Deiry WS, International Journal of Cancer, 1996 Jul 29, 67(3):386-92).

Onyx Pharmaceuticals (Richmond, CA) scientists found that injection of a mutant virus into p53-deficient human cervical carcinomas grown in nude mice, caused a significant reduction in tumor size and complete regression of 60% of the tumors. This mutant form of human adenovirus E1B that does not express a 55-kilodalton protein that inactivates p53, can replicate in and lyse p53-deficient human tumor cells but not cells with functional p53. It is, therefore, possible to use this mutant adenovirus to treat certain cancers (Bischoff JR, etal, Science, 1996 Oct 18, 274(5286):373-6). The agent was administered to cotton rats with no apparent toxicity and is now in phase I clinical trials for head and neck cancer, which has a high incidence of p53 abnormality. Patients selected were those with recurrent disease that was not amenable to chemotherapy or radiation therapy. The trial began in early 1996. Also see FO, pp 27-28.

HER2/neu

HER2 (erbB-2 or neu), which is expressed at low levels in various tissues, is a member of the EGFR family of receptor tyrosine kinases. HER2 appears to be activated by two basic mechanisms, heterodimerization of HER2 with other EGFR family members and constitutive activation that results from HER2 overexpression. Early laboratory studies suggest that amplification and overexpression of HER2/neu are associated with poor prognosis in both node-positive and node-negative breast cancer. The protein, a receptor tyrosine kinase produced by HER2/neu, is overexpressed in approximately 30% of breast and ovarian carcinomas. Its presence may also be predictive of metastasis and might help identify patients who would benefit from more aggressive treatment.

When activated by a point mutation in its transmembrane domain, HER2/neu is an extremely potent transform-

ing oncogene when expressed in rodent mammary parenchyma. This extreme potency led researchers to suggest the possibility that HER2/neu might transform mammary cells by a single step. Based on the premise that transformation efficiency cannot be modulated, it was shown that, at least in the rat, mutated HER2/neu is not a single-step transformer but a very potent event in the multistage process of mammary carcinogenesis. A hormonal promotion protocol also increased the yield of mammary carcinomas following the introduction of the mutated HER2/neu gene (Tai YT and Gould MN, Carcinogenesis, 1995 Jul, 16(7):1455-9).

Targeted Genetics (Seattle, WA) is using a cationic lipid vector technology, acquired with RGene Therapeutics in 1996, to deliver a proprietary therapeutic gene, E1A, into breast cancer cells. E1A acts as a tumor suppressor that can decrease or eliminate expression of the HER2/neu oncogene. In mouse models of cancer, E1A suppressed the function of HER2/neu, significantly increasing long-term survival. In a phase I clinical trial now in progress, two groups of patients, (one suffering from breast cancer and the second from ovarian cancer) are administered the cationic lipid-E1A gene product (RGG0853) at weekly doses for up to six months. No major toxic side effects have been observed to date. In October 1996, Targeted Genetics obtained an SBIR grant of approximately $100,000 to conduct laboratory studies in support of a phase I clinical trial of RGG0853. Also in October 1996, the company received a $1 million milestone payment from Groupe Fournier (Dijon, France), its European partner, relating to the initiation of the phase I clinical trial. The collaborative agreement with Groupe Fournier involving the development of RGG0853 for the treatment of cancer, was forged by RGene Therapeutics in July 1996. The two companies are to coordinate development of RGG0853 in the USA and Europe through a joint clinical program. Under terms of the agreement, Fournier could pay up to $25 million in the form of an up-front licensing fee, milestone payments and development costs. Fournier has received exclusive rights to develop and commercialize RGG0853 in Europe and certain African countries; RGene retains exclusive rights elsewhere. Groupe Fournier also plans to begin a phase I clinical trial of RGG0853 in Europe.

Cell Cycle Regulation

It is believed that understanding changes in expression of cell cycle regulators will enable oncologists to determine the degree of tumor aggression, the likely response to therapy and the outlook for survival for women with breast cancer. Two proteins, p27 and cyclin E that are essential to cell cycle regulation, have been shown to have prognostic and possibly therapeutic value in breast cancer. p27 prevents entry into the DNA replication phase of the cell cycle by binding to cyclin E when complexed with another protein called cyclin-dependent kinase (CDK). The cyclin/CDK complex is required for the cell to undergo DNA replication, and binding of p27 blocks progression through the cell cycle. Cyclin E regulates the process by which cells divide and multiply while p27 protein acts as an inhibitor of cell division; high level of p27 in cells halts their proliferation. Cyclin E production was found to correlate with disease stage and tumor grade. p27 and its role in the cell cycle was originally described by scientists at Memorial Sloan-Kettering Cancer Center (New York, NY), and Fred Hutchinson Cancer Center (Seattle, WA). Scientists at Rockefeller University (New York, NY) discovered cyclin E and its role in controlling cell cycle. The technology for cyclin E is co-owned by Rockefeller University and Fred Hutchinson Cancer Center.

Cascade Oncogenics (Portland, OR), a private, development-stage biotechnology company, is applying discoveries about the role of cell cycle regulation in malignancy to develop assays for the diagnosis/prognosis of cancer. Assays in development include measurement of cyclin E (therapeutic applications of cyclin E have been licensed to Mitotix), which is indicative of a defect within the cell-cycle; detection of genetic defects such as mutations in the AT (ataxia-telangiectasia) gene; and assays establishing the role and effect of other biochemical pathways on the cell cycle to guide selection of therapy.

In a project funded partially by Cascade Oncogenics and led by Peggy L. Porter, MD and James M. Roberts, MD, PhD at Fred Hutchinson Cancer Center and the University of Washington (Nature Medicine, 1 Feb, 1997), investigators discovered that women whose breast tumors exhibited high levels of p27 and low levels of cyclin E (similar to normal breast tissue levels) had the best rates of survival and that those with an opposite pattern faced a nine-fold increased mortality risk. In view of these findings, these two proteins may serve as potential prognostic indicators and guide management of young women with breast cancer, especially in indentifying subgroups that would benefit from more aggressive treatment and excluding those that would not. The study involved 278 women diagnosed with breast cancer between 1983 and 1992, identified through the Cancer Surveillance System (CSS) of Western Washington located at the Hutchinson Center. During a follow-up period averaging 5.2 years, investigators characterized the expression of cyclin E and p27 in breast tumors and compared cyclin E and p27 levels of expression to other tumor characteristics and risk factors. Four different combinations of p27 and cyclin E protein levels (both markers at high levels, both markers at low levels, high cyclin E and low p27, and low cyclin E and high p27) were evaluated regarding their relative impact on survival.

Cascade Oncogene is also attempting to identify biologically important genes transcriptionally regulated by p53, that are related to DNA repair and the cell-cycle. These genes are isolated using a proprietary DNA amplification technology, Targeted Inverted Repeat DNA Amplification (TIRA), which permits rapid amplification

of unknown DNA flanking a p53 binding sequence to identify a non-characterized region of DNA. In October 1996, the company was awarded a $750,000 SBIR grant from the NCI to identify p53-regulated genes important in cancers of the breast, ovary, prostate, and colon. The company has isolated one novel full-length gene and is evaluating the clinical significance of the gene and its associated protein.

Mitotix (Cambridge, MA) acquired an exclusive worldwide license from Memorial Sloan-Kettering Cancer Center and Fred Hutchinson Cancer Research Center to p27 for all anti-proliferative therapeutic and diagnostic applications. Mitotix also holds an exclusive worldwide license from the Hutchinson Center to cyclin E for all therapeutic applications. Mitotix is currently pursuing further research to define the prognostic value of p27 and identify potential therapeutic applications for p27 and cyclin E to treat tumors and other cell proliferative disorders. Similarly with the breast cancer findings, Mitotix researchers and their collaborators found that colorectal cancer patients with higher levels of p27 expression had better survival rates while those with low levels of p27 had poorer outcomes. Mitotix is also applying p27 technology as part of its program to evaluate approaches for the treatment of restenosis.

CELL MODIFICATION USING GENE TRANSFER

Gene transfer and genetic therapy have broad applications in breast cancer. In addition to correcting gene expression, gene transfer may be used to insert genes into specific cells to enhance their immunogenicity, and either render them more sensitive or protect them from systemic chemotherapy.

Prevention of Myelosuppression

Bone marrow suppression is the biggest dose-limiting toxicity factor in the treatment of cancer because chemotherapy must be interrupted or reduced to allow bone marrow recovery. Various approaches are in development to protect the bone marrow from myelosuppressive toxicities of various chemotherapeutics. In the case of trimetrexate (TMTX), an anti-cancer drug with potential advantages over the more commonly used antifolate, methotrexate (MTX), but with severe myelosuppressive effects, researchers have used retroviral vectors containing mutant dihydrofolate reductase (DHFR) genes to protect bone marrow cells from TMTX. In an animal model, a variant of human DHFR containing a Leu-to-Tyr mutation in the 22nd codon (L22Y) was deemed best, allowing a 100-fold increase in resistance over controls. L22Y vector was highly effective in protecting hematopoiesis from TMTX toxicity (Spencer HT, etal, Blood, 1996 Mar 15, 87(6):2579-87).

Ingenex (Menlo Park, CA) and its collaborators are developing a product, MDRxl, based on the human-multi drug resistance gene (MDRl) which encodes P-gp. MDRx1 involves the insertion of the MDR1 gene *ex vivo* into autologous stem cells to render some portion of these cells resistant to myelotoxic high dose chemotherapy. These modified stem cells are then reinfused into patients to repopulate the blood system with chemoresistant blood cells. If it proves successful, MDRx1 may be also used as a co-selective gene to help introduce and maintain other genes of potential therapeutic value in human cells. In clinical testing of a preliminary form of MDRx1 in breast cancer patients, initiated in January 1995, at M. D. Anderson Cancer Center, the MDR1 gene was successfully introduced into a fraction of the donor bone marrow of most or all of the patients in the study. There are still a number of issues that need to be addressed to optimize this gene transfer approach before it becomes clinically feasible. Ingenex has an issued United States patent involving a nucleic acid encoding the human MDR1 protein and has obtained exclusive worldwide license for certain issued patents and patent applications, including the human MDRl gene license agreements with the University of Illinois (Chicago, IL). In addition, Glaxo Wellcome holds a non-exclusive right to transfect cell lines with the MDRl gene and to use the transfectants for research purposes. Ingenex has also acquired an exclusive license from the Massachusetts Institute of Technology (Cambridge, MA) for an issued patent relating to the use of MDR genes for creating and selecting drug resistant mammalian cells. In January 1995, Ingenex assigned its various rights relating to the human MDR1 gene and associated patents to Aberlyn Capital Management Limited Partnership in exchange for a $2 million payment which, in turn, sublicensed back to Ingenex the rights of the assigned licenses for six monthly payments of $25,000, beginning in February 1995, and 42 monthly payments of $60,060 thereafter.

Enhancement/Sensitization of Chemotherapy

Transfer of drug susceptibility genes into specific tumor cells may potentiate anti-tumor activities of conventional cancer chemotherapeutics. A distinct advantage of such an approach is permitting a potent cytotoxic to be delivered in a very localized fashion thus minimizing systemic toxicity. Various gene-activating methodologies are in development. One approach is to enhance metabolism of certain chemotherapeutics *in situ*. For instance, cyclophosphamide (CPA), a drug used in almost all adjuvant combination therapies in breast cancer, and its isomer ifosfamide (IFA), are alkylating agent prodrugs whose anti-tumor activity is the result of metabolism by liver cytochrome P_{450} enzymes. However, therapeutic effectiveness of these oxazaphosphorines is limited by hematopoietic, renal, and cardiac toxicity that results from systemic distribution of liver-derived activated drug metabolites. Transfer of a liver cytochrome P_{450} gene into breast cancer cells *in vitro* greatly sensitized them to oxazaphosphorine toxicity because of enhanced intratumoral CPA and IFA activation. Only

tumor cells were affected but a strong bystander cytotoxicity effect that does not require direct cell-cell contact. Intratumoral expression of cytochrome P_{450} gene in nude mice also increased the *in vivo* cytotoxicity of CPA 15-20-fold without any apparent increase in host toxicity (Chen L, etal, Cancer Research, 1996 Mar 15, 56(6): 1331-40).

Another way to limit systemic toxicity is to convert a systemically-delivered low toxicity prodrug into its cytotoxic counterpart in selected cells *in situ*.

GenVec (Rockville, MD) is selectively introducing the cytosine deaminase gene into cancer cells to convert the prodrug 5-fluorocytosine, an orally-administered antifungal agent, into 5-FU *in situ*. GenVec obtained RAC approval in September 1995, to begin clinical trials in colon cancer that has metastasized to the liver, using a gene therapy construct ($Ad_{Gv}CD.10$) consisting of an adenovirus vector modified to carry the cytosine deaminase gene. Once administered directly into a hepatic tumor, the gene expresses an enzyme that converts 5-fluorocytosine into 5-FU. A phase I clinical trial that will enroll 18 patients began in May 1996 at New York Hospital-Cornell Medical Center (New York, NY). A similar prodrug activation approach is in development for breast cancer.

IMMUNOTHERAPY/VACCINES

Vaccines are in development based on various antigens and on gene transfer techniques to alter tumor cells in order to amplify the immune response and block malignant cell proliferation. Almost all constructs identified are therapeutic vaccines addressing advanced disease. However, because most of breast cancer involves treatable early disease, the most promising immunotherapy approach is a prophylactic/maintenance vaccine that can be safely administered to the thousands of breast cancer survivors (see Exhibit 3). Also see FO, pp 345-355.

Theratope

Theratope, a non toxic, synthetic sialyl-Tn-KLH (keyhole limpet hemocyanin) therapeutic cancer vaccine emulsified in Detox adjuvant under development by Biomira (Edmonton, Canada), has completed phase II clinical trials. In November 1996 Biomira reported final phase II clinical trial data of Theratope in patients with metastatic or recurrent breast cancer. Median survival for 25 breast cancer patients who were treated according to the standard Theratope program, was 26.5 months, compared with 9.2 months for a retrospective control group treated by conventional approaches. The control group, selected from the National Oncology DataBase, included breast cancer patients who were frequency matched according to prognostic variables, including prior treatment, with the breast cancer patients who were treated with Theratope. In two parallel clinical trials in patients with metastatic or recurrent breast cancer treated with Theratope vaccine, 50 patients with metastatic or recurrent breast cancer were prospectively randomized to different strategies for the administration of cyclophosphamide prior to immunotherapy. When these 50 patients treated with Theratope were compared with the matched control group, a significant survival difference, 19.1 months versus 9.2 months, was observed. Phase II studies also demonstrated a correlation between the strength of the antibody response to Theratope and increased survival in 125 cancer patients with breast, colorectal, ovarian or pancreatic cancer. Phase III clinical trials will use a standard protocol which involves Theratope administered following pretreatment with low-dose intravenous cyclophosphamide, that resulted in the longest median survival. While continuing with plans for phase III clinical trials, the company intends to present phase II data to the Canadian and USA regulatory authorities in hope of proceeding with a submission requesting accelerated marketing approval. Discussions are also continuing with potential partners for the Theratope program.

CEA-based Vaccines

The human carcinoembryonic antigen (CEA), which is expressed on approximately 50% of breast cancers, is a target in various vaccines in development for the management of breast cancer. Scientists have learned how to evoke a good immune response to CEA, a weak immunogen, by combining it with a portion of genetic material from vaccinia and other viruses.

Applied Immune Sciences (AIS; Santa Clara, CA), a Rhône-Poulenc Rorer company, is using tumor associated antigens, MART-1 expressed on melanoma, and CEA expressed on colon, lung, pancreas and breast tumors, in combination with dendritic cells, to generate antigen specific CTL for adoptive immunotherapy (Gadea, J, etal, AACR96; Abs. 3154). AIS is pursuing two approaches to generate tumor antigen specific CTL. Dendritic cells are either pulsed with MART-1 or CEA peptides (in the peptide-based approach) or transfected with cDNA constructs for MART-1 and CEA (in the gene-based approach). MART-1 specific CTL from peripheral blood mononuclear cells (PBMC) of normal donors and melanoma patients as well as CEA specific CTL from pancreatic and breast cancer patients, have been generated using the peptide-based strategy. AIS has also achieved 10-30% transgene expression of MART-1 and CEA genes in dendritic cells using a system consisting of a plasmid containing complexes of inverted terminal repeats of adeno-associated virus and cationic liposomes (Godea J, AACR96, Abs. 3154:462).

Therion Biologics (Cambridge, MA) is collaborating with J. Schlom and colleagues at the Laboratory of Tumor Immunology and Biology of the NCI in the development of rV-CEA (TBC-CEA), a recombinant CEA-vaccinia vaccine that was shown to be immunogenic and safe in both rodents and primates, and to elicit good antitumor responses in the rodent model. In a phase I clinical

trial, enhancement of T-cell and antibody responses to vaccinia virus proteins were observed with no toxicity in metastatic breast, lung, and colorectal cancer patients immunized with three dose levels of rV-CEA (Schlom J, etal, Breast Cancer Research and Treatment, 1996, 38(1):27-39). Also, enhanced CEA-specific immune response, coupled with the improved experimental therapeutic outcome, was observed in mice bearing palpable CEA-positive colon adenocarcinoma tumors treated with a single vaccine dose in combination with IL-2. A single rV-CEA immunization resulted in complete tumor regression in approximately 20% of the mice while the addition of a course of low-dose IL-2 resulted in complete tumor regression in 60-70% of the mice (McLaughlin JP, etal, Cancer Research, 1996 May 15, 56 (10):2361-7). Therion's TBC-CEA has been evaluated in phase I clinical trials in colorectal, lung and breast cancer. Another version, using recombinant fowl pox virus instead of vaccinia, is in preclinical development.

Exhibit 3
Estimated Potential Market for Prophylactic Vaccines for Breast Cancer in Selected World Regions
(Estimates are based on 5th year post-launch)

Region	Prophylactic Vaccine		Prophylactic Vaccine with Annual Booster	
	(#)	Market	(#)	Market
USA	184,300	92.2	921,500	350.2
N. America	202,900	101.5	1,014,500	385.5
Europe 1	297,786	148.9	1,488,930	565.7
Japan	24,902	12.4	124,510	47.4
Triad	525,588	262.8	2,627,940	998.6

1 Excluding the former USSR
2 Based on initial vaccine price of $500 and annual booster price of $350

MUC-1-based Vaccines

Polymorphic epithelial mucin (PEM) encoded by the mucin gene (MUC-1), is a high molecular weight integral membrane glycoprotein that is present on the apical surface of most simple secretory epithelial cells. MUC-1 which is expressed on normal breast epithelium and in 90% of breast cancers, is highly expressed and aberrantly glycosylated in most carcinomas and metastatic lesions. Numerous functions have been proposed for this molecule, including protection of the epithelial cell surface, an involvement in epithelial organogenesis, and a role in tumor progression. A humoral immune response to PEM protects against disease progression, and further supports the idea of using synthetic peptides or glycopeptides containing the immunogenic core of the mucin as cancer vaccines (von Mensdorff-Pouilly S, etal, European Journal of Cancer, 1996 Jul, 32A(8):1325-31). Also, because MUC-1 was found to be a ligand for intercellular adhesion molecule 1 (ICAM-1), interaction between MUC-1 and ICAM-1 may be critical to the process of bloodborne metastases in breast cancer (Regimbald LH, etal, Cancer Research, 1996 Sep 15, 56(18): 4244-9). Researchers report that stable high-level expression of MUC-1 was achieved on human dendritic cells (DCs) by retroviral transduction of CD34+ progenitor cells and their subsequent cytokine-induced differentiation into DCs. MUC-1 + DCs are expected to be a valuable tool in the immunotherapeutic treatment of patients with tumors that express MUC-1 (Henderson RA, etal, Cancer Research, 1996 Aug 15, 56(16):3763-70).

Various development programs involving MUC-1 are ongoing. Investigators at the University of Pittsburgh School of Medicine, Department of Surgery, tested a 105 amino acid synthetic MUC-1 peptide with 5 repeated immunodominant epitopes to evaluate toxicity and detect mucin-specific immune responses in patients with adenocarcinoma. Enhancement of response by vaccination with MUC-1 admixed with BCG was also assessed. A 100 mg of MUC-1 mixed with BCG was administered to 63 patients with two more vaccinations at 3-week intervals. All patients tolerated vaccination, with most experiencing local ulceration at the vaccination site. Vaccination with MUC-1 appeared safe and may serve to enhance specific responses to tumor antigens (Goydos JS, eat, Journal of Surgical Research, 1996 Jun, 63(1):298-304).

Biomira is developing several MUC-1-based vaccines for breast cancer, among them BPI-7 and BLP-25 (formulated in liposomes), in phase I clinical trials in the USA and Canada. In late 1991, Biomira acquired the worldwide, exclusive option to license patents relating to MUC-1 peptide antigen held by the Imperial Cancer Research Fund (ICRF; London, UK). In December 1996, Biomira also licensed patent rights from the Dana-Farber Cancer Institute (Boston, MA), pertaining to MUC-1 use in peptide cancer vaccines.

Gene Transfer/Immunotherapy

There are various genetic approaches used to engineer killer T cells to enhance the immune response (see FO, pp 148-150, 354-355) being exploited by numerous developers of cancer immunotherapeutics.

Cell Genesys (Foster City, CA) is engineering killer T cells by using genes that express cancer-specific antibodies. These proprietary genes are introduced into a T cell causing the cell to produce a novel cell surface receptor that targets and binds a specific disease antigen, or protein,

on a cancer cell, thereby signaling the T cell to kill the cancer cell through normal immune system mechanism. The Company's lead cancer effort, targeting various solid tumors including breast cancer, is being conducted in collaboration with the NCI under a CRADA. Cell Genesys is using an antibody gene, CC49, to construct immune cells that specifically target a tumor-associated antigen, TAG-72, which is associated with a variety of cancers. Preclinical studies demonstrated highly specific killing of colon tumor cells *in vitro* by these engineered immune cells. Additionally, a breast cancer therapeutic is in preclinical development under an option agreement with the Dana-Farber Cancer Institute, and another gene therapy product which targets multiple cancers, is being developed in collaboration with Evan Hersh, MD, Chief of Oncology, Arizona Cancer Center at the University of Arizona (Tuscon, AZ). The company also has a collaboration with Dr. Lloyd Old of the Ludwig Institute for Cancer Research and Sloan-Kettering Institute for Cancer Research, signed in 1995.

In January 1997, Cell Genesys and Somatix Therapy (Alameda, CA), announced that they signed a definitive agreement to merge. Under the terms of the merger agreement, anticipated to be completed in April 1997, Somatix will become a wholly- owned subsidiary of Cell Genesys in a tax-free reorganization and stock-for-stock merger. Both companies have been developing *ex vivo* and *in vivo* gene therapies to treat various diseases with an emphasis on cancer.

Immunomodulation

AntiCancer's (San Diego, CA) ONCase, a universal modulator, greatly potentiates the action of chemotherapy agents when used in combination regimens. ONCase targets a metabolic defect found in tumor cells but not in normal tissue and is effective against all types of solid and hematological tumors (see FO, p 253).

Daiwa Pharmaceutical (Tokyo, Japan) is clinically evaluating MGN-3, an enzymatically-modified arabinoxylane from rice bran, in multiple myeloma, leukemia and breast, prostate and cervical cancer (Ghoneum, Mamdooh and Namatalla, Galal, AACR96, Abs. 3062:449) as an adjunct to conventional chemotherapy. Treatment of 27 cancer patients with 3 g of MGN-3, daily, increased natural killer (NK) cell activity (low basal level of 10.8-40%) at 2 weeks with percentages of induction for breast cancer at 154-332%, prostate cancer at 174-385%, leukemia at 100-240%, multiple myeloma at 100-537% and cervical cancer at 100-275%. Enhanced NK activity was observed 3 and 6 months after treatment.

Ergo Science (Charlestown, MA), is evaluating the application of its temporal neuroendocrine regulation technology to treat breast and other cancers. Preclinical studies suggest that temporal neuroendocrine regulation may play an important role in the body's regulation of immune function and its ability to fight cancer. The company also believes that tumors may suppress the body's immune response, in part by altering patterns of neurotransmitter activity. Ergo has demonstrated that alteration of daily neuroendocrine patterns through timed administration of neurotransmitter modulating drugs, can stimulate the immune system and limit growth of tumors in mice.

As of 8/96, the company was enrolling patients in a small phase II clinical trial of ERGOSET, a low-dose, fast-release, oral tablet formulation, in combination with a serotonin agonist. A similar trial of ERGOSET with an undisclosed neurotransmitter in patients with metastatic breast cancer, to evaluate whether the treatment can increase the body's immune activity against the cancer, is also ongoing. Patients in this trial are treated either by ERGOSET and the neurotransmitter alone or, adjunctively, with chemotherapy or radiation therapy. The company is a co-owner of certain patents and patent applications relating to ERGOSET and its other technologies, based on a licensing agreement with Louisiana State University (New Orleans, LA), signed in 1990. The company is also evaluating use of phototherapeutic dyes in photodynamic therapy to treat various tumors and has licensed the rights to patents covering these phototherapeutic dyes from The Rowland Institute for Sciences (Cambridge, MA).

Other Strategies

The Wistar Institute (Philadelphia, PA) has been evaluating the potential applicability of the human TALL-104 cell line, endowed with a uniquely potent MHC nonrestricted tumoricidal activity across several species, as an anti-cancer agent. An animal study enrolled 19 dogs with advanced, refractory malignancies of various histologic types that had failed all other available treatments and had very limited life expectancy, to evaluate the possible toxicity and efficacy of TALL-104. Lethally irradiated TALL-104 cells (10^8/kg) were administered systemically based on two treatment schedules. TALL-104 cells were given every other day for two weeks in a row and then once a week for three additional weeks or daily for a total of 5 days. No significant clinical or laboratory toxicity was observed and none of the animals had to be withdrawn from the study because of immediate adverse reactions to the infusions, such as the commonly-encountered capillary leak syndrome associated with cytokine administration. TALL-104 therapy induced various degrees of anti-tumor effects in 37% (7/19) of the animals, including 1 CR (continuing at +13 months), three PR (duration of 2, 3, and continuing at +2 months), and three transient responses. Clinical responses and immunological parameters correlated well in each case. Cyclosporin A was administered orally (10 mg/kg/day), starting from the day before TALL-104 cell administration and continued throughout the treatment to prevent rejection of the xenogeneic effectors (Cesano A, Cancer Research, 1996 Jul 1, 56(13):3021-9).

MONOCLONAL ANTIBODIES AND IMMUNOCONJUGATES/IMMUNOTOXINS

New laboratory techniques have made it possible to produce monoclonal antibodies (MAbs) that target special antigens on the surface of breast cancer cells to increase selectivity and efficacy of cancer therapy. Use of MAbs directed against tumor associated antigens as therapeutic agents and to deliver chemotherapeutic drugs, toxins, and radionuclides to tumors, has been under investigation for many years. However, before MAbs can be effectively used as drug delivery vehicles such treatment parameters as conjugate dose and schedule, target tumor size, antigenic heterogeneity, and drug sensitivity, must be addressed. MAbs may also be used as tumor vaccines and may offer a way to eliminate micrometastasis to prevent the disease from recurring after surgery or radiation.

In December 1996, the NIH offered to license a patented (U.S. #4,522,918) process, developed by NCI researchers, to produce eleven MAbs from hybridoma cultures for the detection, prognosis, and treatment of human breast cancer. These MAbs are activated only by tumor cells from human mammary cancer and not by apparently normal human tissues. The isotypes of ten of the MAbs are IgG of various subclasses and one is IgM.

MAbs Against HER2/neu

Genentech (South San Francisco, CA) is clinically evaluating a humanized MAb, 4D5, for the treatment of HER2 overexpressing breast cancer. Humanization of 4D5 was accomplished by incorporating the complementarity determining regions (CDR) of 4D5 onto a human IgG_1 framework. Decided by molecular modeling considerations, the final form of the humanized MAb (rhuMAb HER2) which retained the biochemical and biological properties of 4D5, was capable of mediating antibody-dependent cellular cytotoxicity (ADCC). Three phase I and two phase II studies in metastatic breast cancer were completed with rhuMAb HER2 as of mid-1996. In the phase II study, conducted at Memorial-Sloan Kettering Cancer Center, 46 patients with extensive metastatic breast cancer exposed to a median of two prior chemotherapy regimens for metastatic disease, were treated with a 90-minute intravenous loading dose of 250 mg of rhuMAb HER2, followed by 10 weekly doses of 100 mg. Treatment with rhuMAb HER2 alone was well tolerated with transient fever and chills encountered during or after the first administration in five patients. Among 44 evaluable patients on day 77, there was 1 CR and 5 PR. Patients with no disease progression at the completion of this treatment period were offered a weakly maintenance treatment of 100 mg until disease progression. Adequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no HAMA was elicited against rhuMAb HER2. Responses were observed in lesions in the liver, mediastinum, lymph nodes, and chest wall. Minor responses, seen in two patients, and stable disease, which occurred in 14 patients, lasted for a median of 5.1 months (Baselga J, etal, Journal of Clinical Oncology, 1996 Mar, 14(3):737-44).

In a second phase II study, rhuMAb HER2 was co-administered with cisplatin (75 mg/m^2) on days 1, 29 and 57, to ascertain any synergistic effects. Enrolled patients suffered from metastatic breast cancer that progressed on standard chemotherapy regimens. Grade 3 or 4 toxicity, consistent with cisplatin therapy in a pretreated population, was observed at some point in 21 of 39 patients (54%). Among 36 evaluable patients, 9 (25%) experienced PR. Ongoing clinical trials are addressing the utility of rhuMAb HER2 in combination regimens for the treatment of metastatic breast cancer (Sliwkowski, etal, AACR96, Extended Abstracts, p 625-626). It has been suggested that the effectiveness of MAb against HER2/neu may be compromised by the presence of soluble HER2/neu that was shown *in vitro* to neutralize the inhibitory impact of anti-HER2/neu MAbs on breast cancer cell proliferation (Brodowicz T, etal, Annals of Oncology, 7(Suppl. 5), 1996, Abs. 27P:8).

Amgen (Thousand Oaks, CA) scientists generated a panel of MAbs against the purified soluble form of erbB-2/HER2 receptor, corresponding to the receptor's extracellular region. Some of the MAbs strongly induced tyrosine phosphorylation of 180-185 kDa proteins, including not only HER2 but also HER3 and HER4 receptors, when they were expressed on the surface of breast cancer cells. These MAbs do not cross-react with HER3 or HER4 as demonstrated by a competition study. Receptor phosphorylation was also observed with the cell lines transfected with HER2 or a chimeric receptor consisting of the extracellular domain of HER2 and the transmembrane and cytoplasmic domains of EGFR. Selected MAbs were tested for their ability to change cell morphology, and one specific MAb, mAb74, induced cell morphology changes and apoptosis (Kita Y, etal, Biochemical and Biophysical Research Communications, 1996 Sep 4, 226(1):59-69).

Bispecific MAbs

Bispecific MAbs incorporate two binding sites, one targeting an antigen on tumor cells and the other any one of various receptors on such immune system killer cells as monocytes or macrophages. However, although bispecifics present tumor cells to killer cells, these latter cells do not always interact with their targets. In order to ensure that killer cells destroy the targeted cancer cell, bispecifics are engineered to not only lock onto effector cells but also to activate them.

Medarex (Annandale, NJ) is developing MDX-210, a bispecific MAb that recognizes type I Fc receptors for IgG (FcγRI or CD64) on monocytes and macrophages and the cell surface product of the HER2/neu oncogene. MDX-210 is constructed by chemically cross-linking F(ab')

fragments of MAb 520C9 to HER2/neu and F(ab') fragments of MAb 22 to FcγRI. MDX-210 mediated effective lysis of HER2/neu overexpressing breast cancer cell lines *in vitro* by effectively directing FcγRI-positive effector cells to phagocytose or kill tumor cells that overexpress HER2/neu. In clinical trials, MDX-210 was both immunologically and clinically active and well tolerated. Optimization of the dose and schedule of MDX-210 and development of combination treatment with cytokines that modulate immune effector cells are expected to greatly enhance efficacy of MDX-210 for treatment of tumors that overexpress HER2/neu, especially in the minimal disease setting (Valone FH, etal, Journal of Hematotherapy, 1995 Oct, 4(5):471-5).

In a phase Ia/Ib trial of MDX-210, conducted to determine the maximum-tolerated dose (MTD) and/or the optimal biologic dose (OBD) in patients with advanced breast or ovarian cancer that overexpressed HER2/neu, cohorts of three patients were administered a single infusion of MDX-210 at increasing dose levels from 0.35 mg/m^2 to 10.0 mg/m^2. Treatment was well tolerated, with most patients experiencing only transient Grade 1 to 2 fevers, malaise, and hypotension; two patients experienced transient Grade 3 hypotension at 10.0 mg/m^2. Transient monocytopenia and lymphopenia developed at 1 to 2 hours, but no other hematologic changes were observed. Doses of MDX-210 ≥3.5 mg/m^2 saturated ≥80% of monocyte FcγRI and produced peak plasma concentrations ≥1 μg/ml, which is greater than the concentration for optimal monocyte/macrophage activation *in vitro*. Elevated plasma levels of the monocyte products tumor necrosis factor alpha (TNF α), interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), and neopterin, were observed with maximal levels at doses ≥7.0 mg/m^2. Localization of MDX-210 in tumor tissue was demonstrated in two patients. One partial and one mixed tumor response were observed among 10 assessable patients. MDX-210 is immunologically active at well-tolerated doses with an MTD and OBD at 7 to 10 mg/m^2 (Valone FH, etal, Journal of Clinical Oncology, 1995 Sep, 13(9):2281-92).

Because *in vitro* assays showed that FcγRI-positive neutrophils constitute a major effector cell population during G-CSF therapy, a combination of G-CSF and MDX-210 was tested in breast cancer patients. A multicenter phase I/II clinical trial was initiated in June 1995 in collaboration with Amgen, to evaluate MDX-210 in combination with Amgen's G-CSF, Neupogen. In this study, patients treated with G-CSF are administered an escalating single doses of MDX-210. This therapy was generally well tolerated with side effects including fever and short periods of chills, which were temporally related to elevated plasma levels of IL-6 and TNF α. Transient decreases in total white blood count and absolute neutrophil count (ANC) were observed, and elevated plasma levels of soluble HER2/neu increased after MDX 210 treatment and fell below baseline at the end of the study in most patients, suggesting tumor cell lysis *in vivo*. During G-CSF treatment, isolated neutrophils were highly cytotoxic in the presence of MDX-210 *in vitro* (Repp R, etal, Journal of Hematotherapy, 1995 Oct, 4(5):415-21). At one site at the University of Erlangen in Germany, patients were treated with G-CSF for 8 consecutive days while cohorts were also treated with escalating, single doses of MDX 210 (Valerius, T, etal, ASCO96, Abs. 97:108).

Chiron (Emeryville, CA) is developing 2B-1, a bispecific murine MAb that binds to both c-erbB-2 and CD16 (FcγRIII) extracellular domains. CD16, the low-affinity Fcγ receptor for aggregated immunoglobulins, is expressed by polymorphonuclear (PMN) leukocytes, natural killer (NK) cells and differentiated mononuclear phagocytes. 2B-1 potentiates *in vitro* lysis of tumors overexpressing c-erbB-2, by NK cells and mononuclear phagocytes expressing the FcγRIIIA isoform. 2B-1 is in phase I/II clinical trials as monotherapy and in combination with interleukin-2 (IL-2). In a phase I clinical trial, 15 patients with c-erbB-2-overexpressing tumors were treated with a 1-hour IV infusion of 2B-1 on days 1, 4, 5, 6, 7, and 8 of a single treatment course. Three patients were treated with daily doses of 1.0 mg/m^2, while six patients each were treated with 2.5 mg/m^2 and 5.0 mg/m^2, respectively. Principal non-dose-limiting transient toxicities were fever, rigor, nausea, vomiting, and leukopenia. Thrombocytopenia was dose limiting at the 5.0 mg/m^2 dose level in two heavily pretreated patients. Initial 2B-1 treatment induced more than 100-fold increases in circulating levels of TNF-α, IL-6, and IL-8 and lesser rises in GM-CSF and IFN-γ. HAMA responses were induced in 14 of 15 patients. Several minor clinical responses were observed, with reductions in the thickness of chest wall disease in one patient with disseminated breast cancer. The maximum tolerated dose and the recommended phase II daily dose for patients with extensive prior myelosuppressive chemotherapy is 2.5 mg/m^2 (Weiner LM, etal, Cancer Research, 1995 Oct 15, 55(20):4586-93).

Recombinant Immunotoxins

Immunotoxins combine MAbs with various bacterial or plant toxins. Newer recombinant versions of these immunoconjugates have replaced whole MAbs with the Fv fragment, in a single chain or in a disulfide-linked form, as the targeting component that is fused directly to a toxin. Toxins in development include Seragen's (Hopkinton, MA) $DAB_{389}EGF$, a diptheria fusion toxin targeting EFGR that completed phase II clinical trials in solid tumors in late 1995 (see FO, pp 53 and 245-246) and Prizm Pharmaceuticals' saporin-based fusion toxins also targeting EFGR and other growth factors and angiogenesis effectors. The clinical limitations of BR96 sFv-PE40, as well as other immunotoxins, depend on the management and/or prevention of neutralizing anti-immuno-

toxin antibodies and the onset of toxicities, specifically vascular leak syndrome.

BR96 sFv-PE40 is a single-chain immunotoxin composed of the carcinoma-reactive antibody BR96 and a truncated form of *Pseudomonas* exotoxin. MAb BR96 recognizes a Le^y-related carbohydrate antigen expressed on a wide range of carcinomas. Immunotoxins composed of BR96 and a binding defective form of *Pseudomonas* exotoxin A were constructed both as chemical conjugates and as fusion proteins. While both forms of BR96 immunotoxin were equally cytotoxic to human carcinoma cell lines *in vitro*, the fusion protein form, BR96 sFv-PE40, was >10-fold more active *in vivo* as an anti-tumor agent. BR96 sFv-PE40 was used to target established human tumor xenografts in both mice and in rats. The rat which displays the Le^y antigen on the same normal tissues as humans, appears to be an appropriate model for the preclinical evaluation of this immunotoxin. Complete regressions of lung, breast and bladder carcinomas were obtained in these models upon administration of well-tolerated doses of BR96 sFv-PE40. (Siegall CB, Seminars in Cancer Biology, 1995 Oct, 6(5):289-95).

Immunotoxin LMB-1, developed by NCI scientists, is composed of MAb B3 chemically linked to PE38, a genetically engineered form of *Pseudomonas* exotoxin A. LMB-1 causes complete regression of tumors in nude mice, is well tolerated by monkeys, and is completing a phase I trial in humans. MAb B3 recognizes carbohydrate antigen Le^y and demonstrates excellent anti-tumor activity in nude mice bearing Le^y-positive tumors. In a phase I study of 38 patients with colon and breast cancer expressing Le^y, who failed conventional therapy, objective responses were observed in 5 patients, and disease stabilized in 18 and progressed in 15. There was one CR in a patient with metastatic breast cancer to the supraclavicular nodes. Maximum tolerated dose of LMB-1 is 75 µg/kg administered intravenously three times every other day. The major toxicity is vascular leak syndrome (Pai LH, etal, Nature Medicine, 1996 Mar, 2(3):350-3).

Immunotoxin LMB-7, a wholly recombinant immunotoxin composed of the Fv portion of monoclonal antibody B3 fused to PE38, is under development by Corange. LMB-7 is about ten-fold more active than LMB-1, is very well tolerated by monkeys, and is also in a phase I trial.

ScFv2(FRP5/225)-ETA and ScFv(FRP5)-TGF α-ETA, under development by the Institute for Experimental Cancer Research, Tumor Biology Center (Freiburg, Germany), are bivalent, single-chain immunotoxins specific for erbB-2 and EGFR, and erbB-2 and the natural EGFR ligand, TGF α, respectively. Bispecific scFv2(FRP5/225)-ETA consists of two scFv domains specific for erbB-2 and EGFR linked to a modified *Pseudomonas* exotoxin A. ScFv2(FRP5/225)-ETA displayed *in vitro* cell killing activity of tumor cells overexpressing either erbB-2 or EGFR similar to that of the monospecific toxins, but was more potent *in vitro* and *in vivo* in inhibiting the growth of tumor cells expressing both receptors (Schmidt M, etal, International Journal of Cancer, 1996 Feb 8, 65(4):538-46). Bispecific scFv(FRP5)-TGF α-ETA consists of the antigen-binding domain of the erbB-2-specific MAb, FRP5, and the natural EGFR ligand, TGF α, inserted at different positions in truncated *Pseudomonas* exotoxin A. ScFv(FRP5)-TGF α-ETA protein displayed binding to EGFR and erbB-2, thereby inducing activation of the receptors, which was dependent on the cellular context and the level of EGFR and erbB-2 expression. This bispecific was cytotoxic *in vitro* for tumor cells expressing various levels of the target receptors. *In vivo,* scFv(FRP5)-TGF α-ETA potently inhibited the growth of established tumor xenografts in nude mice (Schmidt M and Wels W, British Journal of Cancer, 1996 Sep, 74(6):853-62).

AR209, currently under development by Aronex Pharmaceuticals is an antibody-toxin complex composed of a targeting ligand and a fragment of *Pseudomonas* exotoxin. It is being developed initially for breast cancer, but may be applicable to other solid tumors including lung, ovarian and stomach cancers. AR209 is designed to bind to cancer cells that contain erbB-2, become internalized and kill the cell. Preclinical studies indicate that AR209 causes regression of solid human tumors and is well tolerated. The product is currently in preclinical development. Aronex intends to seek a corporate partner to develop and commercialize AR209. Aronex has a worldwide license from the NIH to the *Pseudomonas* exotoxin used in the design of AR209. Aronex also has an exclusive license to a United States government patent application covering antibodies targeting erbB-2. Patent applications covering sequences of the antibody used in the formulation of AR209 have also been filed. In January 1997, Aronex awarded an exclusive worldwide license to Boehringer Mannheim (Corange) for the development of AR209 for the treatment of cancer, in exchange of licensing fees, milestone payments and royalties. Aronex retained an option for marketing rights in the USA and the specific right to the binding ligand of AR209 to allow the company to develop additional products.

CP-IL4-toxin, targeting interleukin-4 receptor (IL-4R) in human breast carcinoma cells, is a circular permuted IL4-pseudomonas exotoxin under preclinical evaluation by the NCI. Human breast carcinoma cell lines have been shown to express IL-4R. Three breast cancer cell lines were sensitive to the cytotoxic effect of CP-IL4-toxin but two normal breast cell cultures were least sensitive (Puri RK, etal, AACR96, Abs. 2848:417).

NATURAL PRODUCTS

Numerous entities are evaluating agents derived from natural products or synthesized to mimic their activity. Natural products are specifically important sources of anti-

cancer agents. Also, agents derived from natural products are of particular interest in the development of chemopreventatives for cancer, in general, and breast cancer, in particular.

Novel Therapeutic Agents

Paracelsian (Ithaca, NY) signed a two-year CRADA with the Laboratory of Tumor Cell Biology of the NCI in January 1997 that extends a pre-existing relationship initiated in 1995 under a letter of intent. The objectives of this CRADA are to screen the company's library of herb extracts used in traditional Chinese medicine, in order to identify unique, pharmacological agents capable of modulating a cell signaling pathway induced in certain HIV and pancreatic, Kaposi's sarcoma and breast cancer cell lines and develop an understanding of the molecular interactions of the various screen-positive agents with the cells' signaling pathways. Paracelsian recently announced plans to launch in 1997, its first dietary supplement product, AndroCar, that improves general well-being of cancer patients.

PharmaMar [Tres Cantos (Madrid), Spain], is developing numerous anti-cancer agents derived from marine sources. The company initiated phase I clinical trials of Ecteinascidin-743 (ET-743) in Europe, in collaboration with EORTC, and in the USA. ET-743, a tetrahydroisoquinoline alkaloid isolated from the tunicate *Ecteinascidia turbinata*, was active in *in vivo* xenograft tests against various solid tumors including breast cancer (Hendriks HR, etal, AACR96, Abs. 2653:389 and Eckhardt SG, etal, AACR96, Abs. 2791:409). In October 1996, PharmaMar signed a research and option agreement with Bristol-Myers Squibb for the evaluation and development of up to 12 unidentified compounds from PharmaMar's marine products portfolio, excluding ET-743.

Chemoprevention

Identifying possible prevention approaches in breast cancer is a research priority. Naturally, development of pharmacologic approaches targeting the general population is a formidable task, because any drugs that may need to be administered to large, asymptomatic populations on a chronic base, must be proven safe beyond any shred of doubt. However, a favorable benefits to risk ratio may be sufficient in chemopreventatives targeting only high risk populations such as those who survived cancer or were diagnosed with a genetic predisposition to certain cancers. High prevalence of breast cancer survivors (see Exhibit 2) and increasing genetic susceptibility testing to identify women at risk for breast cancer renders this indication particularly suitable for chemoprevention approaches.

Currently, a large trial, the Breast Cancer Prevention Trial, being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), is evaluating tamoxifen in post-menopausal women ≥60 years-of-age and women between the ages of 35 and 59 who are considered at sufficiently high risk to develop breast cancer. This double-blinded trial, slated to enroll 16,000 women randomized to be administered either tamoxifen (20 mg daily) or placebo, is expected to last 5 years. In view of tamoxifen's association with uterine cancer, its evaluation as a potential chemopreventative illustrates the benefits versus risks dilemma. However, tamoxifen also has cardiovascular and bone benefits, which raises its benefits to risk ratio. Newer NSAEs may prove even more favorable by providing all of tamoxifen's benefits without any cell proliferative action in the uterus. Other pharmacologic approaches in clinical trials include:

- a comparison of tamoxifen and tamoxifen plus fenretinide in women >65 years-of-age with ER+, node-positive breast cancer, being conducted by the Eastern Cooperative Oncology Group
- a phase III clinical trial of the effects of beta carotene, vitamin E and aspirin on incidence of various epithelial tumors among 40,000 women health professionals over 45 years-of-age, being conducted at Brigham and Women's Hospital (Boston, MA)
- a phase III randomized clinical trial involving 3,000 node-negative patients with breast cancer treated with daily fenretinide (200 mg) for five years, being conducted at the National Tumor Institute (Milan, Italy)

Other approaches to chemoprevention include the possible use of anti-angiogenesis agents as a chronic maintenance therapy for those at risk of developing metastasis. However, although non-toxic in the acute setting, chronic administration of anti-angiogenics may impair wound healing. A most desirable approach involves once-in-a-lifetime immunization, perhaps also involving a periodic booster, but no vaccine able to prevent cancer recurrence has been identified to date.

However, although chemoprevention using pharmacologic agents appears feasible, the most attractive approach would involve use of natural products which are not expected to have any untoward effects. An ideal scenario would involve a dietary regimen that would stop or slow carcinogenesis at a very early stage and keep it in check through an individual's lifetime. Unfortunately, although numerous food components/additives have been looked at, there is no hard scientific data to support benefits of any specific compound in cancer prevention.

Monoterpenes, such as the unsubstituted monocyclic monoterpene limonene, described in FO, p 325, have been shown to prevent carcinogen-induced mammary cancer at both the initiation and promotion/progression stages and cause complete regression of the majority of advanced rat mammary cancer when added to the diet. Modification of limonene by hydroxylation at various positions increases both its chemopreventive and therapeutic efficacy. For example, the naturally occurring

hydroxylated limonene analog, perillyl alcohol, is 5-10 times more potent than limonene and has a similar therapeutic index (Gould MN, Journal of Cellular Biochemistry, Supplement, 1995, 22:139-44). Phase I clinical trials are in progress in the UK and the USA.

Genistein, an isoflavone, may have some role as a cancer chemopreventive. In Japan, where breast cancer rates are low compared to those in Western nations, daily consumption of dietary genistein, found in soybeans and related products, is calculated to be 1.5-4.1 and 6.3-8.3 mg/person, respectively. These levels are much higher than those for Americans or Western Europeans (Fukutake M, etal, Food and Chemical Toxicology, 1996 May, 34(5):457-61).

Resveratrol, a phytoalexin found in grapes and other foods, demonstrated cancer chemopreventive activity in various assays and may merit investigation as a potential cancer chemopreventive agent in humans. In various mouse models of carcinogenesis, resveratrol reduced the number of tumors per mouse and the percentage of mice with tumors without any overt signs of toxicity (Meishiang Jang, etal, Science, Vol. 275, January 10, 1997).

ANGIOGENESIS/ANTI-VASCULAR APPROACHES

Angiogenesis is considered one of the key mechanisms of tumor growth and metastasis in most solid tumors including breast cancer. Several groups have shown that quantitation of tumor angiogenesis by counting blood vessels in primary breast cancer, provides an independent assessment of prognosis with poor prognosis associated with high blood vessel counts. Various techniques are in development to use angiogenesis as a diagnostic/prognostic marker (see FO, pp 195-199, 254 and 274-275) and as a therapeutic target (see FO, p 185-195, 275 and 397-398) in solid tumors and breast cancer. Researchers at the University of Maastricht in the Netherlands have developed an animal model to evaluate angiogenic properties of biopsized tumor tissue from breast cancer patients to evaluate the tumors' angiogenic potential (Lichtenbeld HC, etal, Annals of Oncology 7(Suppl. 5), 1996, Abs. 5O:4).

Angiogenesis Inhibition

Anti-angiogenesis approaches in the treatment of cancer are in early stages of development. Although angiogenesis inhibitors were effective in animal models, early human trials have not produced similar results. The most recent agent to prove effective in shrinking tumors in mice is endostatin, discovered by Judah Folkman and his colleagues at Harvard Medical School (Boston, MA). Endostatin, like angiostatin, is an antiangiogenic factor purified from a metastasis-limiting tumor. It exhibits potent anti-tumor activity in mice and is now being prepared for testing in humans.

It will probably take a long time to fine-tune the application of optimal anti-angiogenesis therapy in humans. It is unlikely that angiogenesis inhibitors will be useful as short-term monotherapy and will probably be employed in combination therapies and, perhaps, as long-term maintenance therapy and chemoprevention. The good news is that most agents tested to date were not associated with any untoward side effects. Therefore, the possible requirement that anti-angiogenesis need be administered simultaneously with other cytotoxic drugs in the short-term to effect a cure, and then on a chronic basis to prevent a recurrence, appears feasible. Although angiogenesis mechanisms appear to be the same across tumor types, many anti-angiogenesis agents act on specific factors and pathways. For instance, factors implicated in angiogenesis in breast cancer include VEGF, placenta growth factor, pleiotrophin, TGF β1, acidic and basic FGF, and platelet-derived endothelial cell growth factor. In view of this plethora of effectors, it would probably be more effective to inhibit angiogenesis using a non-specific inhibitor rather than by blocking vascular growth factors using highly specific agents. Several suramin analogs (which are less toxic than suramin *in vivo* but more potent in inhibiting angiogenesis) have been developed for phase I clinical trials (Harris AL, etal, Breast Cancer Research and Treatment, 1996, 38(1):97-108).

In animal models, although inhibition of angiogenesis shrank tumors, they quickly grew back after drug withdrawal. This implies that anti-angiogenesis approaches may require life long administration. On the positive side, tumors in mice shrank every time drug was administered, precluding development of resistance. One of the challenges in treating human tumors is that, unlike those in mice, they have been growing for many years and their vascular supply is probably fully established by the time they become clinically detectable. Anti-angiogensis may prevent new tumor formation but other techniques may be necessary to cut-off tumor access to existing vasculature. In view of these findings, use of multiple types of assaults in combination with inhibition of angiogenesis appears to be a possible strategy in treating human tumors.

Laboratoires Aeterna (Quebec, Canada) is evaluating Neovastat, an orally administered angiogenesis inhibitor that prevented growth of various cancers in preclinical studies. Daily administration of Neovastat for 54 days, produced a statistically significant decrease in the volume and weight of breast tumors (DA3 breast tumor cells) in mice compared to controls. Also, there was no apparent significant toxicity associated with the administration of the product. Neovastat is currently in phase III clinical trials in terminally ill patients with solid tumors in Canada and in phase I/II clinical trials in breast cancer in Canada and the USA. Patients have been treated with Neovastat on a compassionate basis since August 1996.

Anti-vascular Approaches

In addition to approaches to inhibit the development of new vessels that supply tumors, researchers are also

using techniques to occlude existing vascular conduits to tumors using a variety of techniques. One such technique, successfully applied to mice, is to administer drugs that induce formation of clots in vessels feeding tumors. Although such a technique was successfully employed by Philip Thorpe and colleagues at the University of Texas Southwestern Medical Center (Dallas, TX) to shrink or even eliminate tumors in animals, application to humans would require significant more understanding as to how to selectively promote clots in certain vessels and not in others. One suggested approach is to target effectors participating in new vessel development. Such an approach, however, will face the same problem encountered by the anti-angiogenesis approaches, namely how to deal with the established vasculature.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) may be used to treat superficial breast tumors and skin metastases of breast cancer. Unfortunately, although initial results with PDT are very effective, PDT-induced tumor regressions are not long lasting. Various strategies are, therefore, being tried to improve long-term effects of PDT. For more information on PDT in cancer, see FO, pp 29, 56 and 64, 101-102, 239, 271-272, 296 and 369).

PDT in Combination with Chemotherapeutics

In preclinical tests in mice, an additive effect was observed for the combination of mitomycin C and PDT in the treatment of subcutaneous tumors. When interstitial PDT was combined with a low dose of mitomycin C, administered 15 minutes before illumination, the Photofrin (QLT Phototherapeutics; Vancouver, Canada) dose or light dose could be reduced by a factor of two to maintain equivalent cure rate or growth delay of PDT alone (Baas P, etal, British Journal of Cancer, 1996 Apr, 73(8):945-51).

PDT and Immunotherapy Approaches

Xytronix (San Diego, CA) is developing PDT for the treatment of breast and other cancers. In May 1996 Xytronix entered into an agreement with privately-held Wound Healing of Oklahoma (WHO) which grants Xytronyx an exclusive worldwide license to WHO's proprietary Laser/Sensitizer Assisted Immunotherapy (LSAI) a new photodynamic immunotherapy (PDIT) approach for cancer treatment. LSAI or PDIT involves co-injection of an infrared absorbing dye (photosensitizing drug) and an immunoadjuvant directly into a tumor, followed by illumination with an infrared laser. Similar to traditional PDT, LSAI is intended to destroy the tumor in the primary area of treatment but it is also intended to trigger an immune reaction against the primary tumor and any metastases. This approach is expected to be applicable for the treatment of advanced stages of breast, lung and prostate cancer. High response rates have been achieved with this therapy in conjunction with a very challenging animal breast tumor model. Xytronyx expects initially to target breast cancer with LSAI. SAI was principally developed by two founders of WHO, Dr. Robert Nordquist and Dr. Wei Chen. Patent applications encompassing the LSAI technology have been filed in the USA and abroad. In conjunction with the license agreement, Xytronyx and WHO have also entered into a research agreement under which WHO will perform further research to assist with the development and commercialization of LSAI. Xytronyx is also collaborating with Dr. Stephen Kahl, Professor of Chemistry and Pharmaceutical Chemistry at the University of California, San Francisco to develop novel cancer drugs.

In June 1996 Xytronix also entered into an agreement which granted the company the option to purchase at anytime prior to April 30 1997, privately held Binary Therapeutics, Inc. (BTI; Westwood, MA) by issuing common stock to BTI stockholders with an aggregate acquisition value of $6 million. BTI holds rights to certain proprietary technologies in the areas of both PDT and a related area, Boron Neutron Capture Therapy (BNCT). BTI's technologies may offer advantages over other existing PDT technologies in terms of selectivity (the ability to specifically target tumors) and the potential to target deeper-seated tumors. One drug, BTI's boronated porphyrin compound (BOPP), is currently being prepared for human clinical trials as a photosensitizer for PDT treatment of brain cancer. Under terms of the agreement, Xytronyx will assist BTI with certain product development efforts and in exchange has received an option to acquire the company.

BTI also holds rights to technologies encompassing the use of a second family of compounds, lipophilic cationic compounds (LCCs), for cancer treatment with PDT. As demonstrated in certain laboratory models, the degree of tumor selectivity of LCCs may prove to be substantially higher than that achieved by competitive products. LCCs may be activated by light at substantially longer wavelengths, allowing penetration of skin and tissue for the treatment of larger and deeper tumors. Unlike current PDT drugs, LCCs may be effective in the presence or absence of oxygen because they do not rely solely upon the production of cytotoxic oxygen free radicals for their killing mechanism. BTI believes that LCCs may be applicable to all major forms of solid tumors. Patents encompassing the LCC technology have been issued in the USA and abroad. BTI is currently evaluating various LCCs for the purpose of selecting a lead LCC compound for preparation for clinical trials. BTI has targeted mouth cancer as an initial demonstration of the safety and efficacy of its lead LCC compound in PDT because of the favorable (in terms of ease of reach and diagnosis) location of this cancer, although the ultimate indication selected for treat-ment may be changed based on the characteristics of the LCC selected for initial development.

PDT and Anti-angiogenesis Approaches

It is speculated that tumor regrowth after treatment may be mainly attributed to neovascularization in response to continued angiogenic stimuli from damaged tumor cells. When using angiogenic inhibitors such as paclitaxel and suramin at low anti-angiogenic doses against mammary carcinoma *in vitro* and in xenografts, researchers discovered that combined treatment with PDT and either chemotherapeutic agent was superior to that of PDT or either drug alone (Sharma A, etal, AACR96, Abs. 1980:291).

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