TECHNOLOGY COMMERCIALIZATION OPPORTUNITIES

A one page non-confidential disclosure is available for each technology. Please cite the MDA reference number (located to the right of the technology’s name) when requesting information. The technologies are arranged in the following categories: Therapeutics, Drug Delivery, Preventives, Diagnostics, Devices, Research Tools/Reagents/Cell Lines, and Imaging and Other.

Technology Reference Codes -
+ Denotes that an issued patent is available for that invention
^ Denotes patent pending

THERAPEUTICS

- Highly Potent Anthracycline-based Anti-Tumor Agents 591^

Anthracyclines are one of the most active classes of anti-neoplastic agents. These drugs are DNA intercalating agents and generally exert their cytotoxic effects by inhibiting DNA synthesis through inhibition of topoisomerase II. Two well known members of this class of drugs are doxorubicin and daunorubicin. Significant side effects of this class of drugs include myelosuppression and cumulative dose-related cardiotoxicity, thus limiting their effectiveness over time. In addition, higher toxicities have been recently seen when these drugs are combined with other chemotherapeutics for the treatment of tumors. A series of doxorubicin and daunorubicin analogs have been synthesized that have unique structures and biological activity significantly above that of the parental compounds. In vitro testing of these analogs in several different cell lines have revealed potencies of greater than 500 fold that of the parental compounds and it is believed that this high activity is due to covalent crosslinking of the DNA. Thus the potential advantages of these new compounds include an increased overall therapeutic index through the use of lower doses for longer periods of time while achieving clinically relevant effects and limiting dose-related toxicity. The use of specialized drug delivery vehicles such as lipid-based vectors could further enhance drug targeting and delivery thereby further increasing the therapeutic index of these drugs.
A Novel Tumor Suppressor Gene 99-05
A gene with novel tumor suppressing activity has been identified. It is a previously identified gene that encodes a nuclear phosphoprotein and is known to interact with several cell cycle, signal transduction and differentiation regulatory molecules such as Rb, E2F-1, and a p53 binding protein. These interactions may be responsible for the subsequent transcriptional inhibition of the genes whose transcriptional activation depends on these molecules. Constitutive expression of the gene in normal growth arrested fibroblasts has been shown to prevent entry into the cell cycle when the cells were stimulated to proliferate. The inventors have now discovered that this gene is associated with anti-transformation activity and anti-tumor activity on human prostate, breast and ovarian cancer cells both in vitro and in vivo. Additional preclinical animal data is currently being generated. The discovery of the tumor suppressor activity of this gene makes it an attractive candidate for use as a gene therapeutic.

Synthetic Coactivators of Hormone – Mediated Transcription 99-12
Nuclear receptors are hormone-dependent transcription factors that regulate cell growth, development, differentiation and homeostasis. Binding of a hormone to its receptor causes a conformational change in the receptor increasing the affinity of it for DNA, thus enabling it to bind tightly to specific nucleotide sequences in the gene that the hormone regulates, resulting in transactivation domain-mediated activation or suppression of transcription of the gene. Coactivator molecules assist in this transactivation process. Artificial coactivators have been developed which can strongly enhance hormone receptor transactivity. This activity is hormone-dependent and receptor-specific. This discovery provides the opportunity to direct any protein into the DNA-bound hormone receptor complex to modulate transcriptional activity and gene expression of hormone regulated genes.
- **Development of an Adenovirus Vector With Tetracycline-regulatable Human TNF-α Gene Expression**  
  The modified multiple-plasmid tetracycline repressor/operator-based mammalian gene expression system warrants lower constitutive expression of the tetracycline-responsive transactivator (tTA), resulting in a system with no squelching effect on host cells. The novel system is contained within a single plasmid and is readily convertible to tetracycline-responsive adenoviral and other viral vectors. It would be possible to turn off the therapeutic gene expression before the adenovirus vectors or adenovirally transduced effector cells reach the tumor deposits. The advantages of regulatable gene delivery are: 1) greatly reduce the systemic toxicity of high-dose therapeutic gene products during the period when the vectors or genetically modified effector cells have been administered to patients but the majority of them are still in the blood circulation; 2) minimize the impact of therapeutic gene expression on the survival, specificity or distribution (homing pattern) of the effector cells in vivo.

- **Water Soluble Raloxifene Analogs**  
  Because raloxifene is not very soluble in water, a ligand has been synthesized that is more hydrophilic. This conjugate can be chelated with technetium or indium for SPECT evaluation of ER(+) lesions. By attaching the conjugate raloxifene to a water-soluble polymer that can be used as a drug carrier, it can be sustained released through the intravenous injection route. This offers the advantage of reducing systemic toxicity. Because the raloxifene conjugate can be chelated with other inorganic metals, it has the potential application in the detection of ER(+) lesions by MRI. The labeled raloxifene conjugate may non-invasively identify ER(+) recurrences without resorting to surgical procedures. Because it is more hydrophilic than raloxifene, it has less uptake in the liver and lung, which may interfere with the interpretation of breast cancer lesion since breast lesions are in the vicinity of the liver. In addition to the treatment of cancer, the raloxifene conjugate can be used as a preventing agent.
Bioactive Biodegradable Nerve Conduit 97-12 *
Tumor removal, traumatic injuries and congenital anomalies often result in injuries to critical nerves. Failure to restore injured nerves can result in the loss of muscle function. Currently, nerve repair involves autografting nerves to the injured site and is limited by the availability of donor tissue and the morbidity related to the sacrifice of donor nerve. A nerve conduit provides the physical and physiological structures necessary for nerve regeneration. This bioactive and biodegradable polymer nerve conduit is seeded with support cells and induction factors through a novel timed delivery system, to reproduce all the necessary components of a nerve graft and thus avoid the morbidity of autografts.

Inhibition Of Bcl-2 Protein Expression 504 ^
Bcl-2 is an oncogene with tumorigenic potential due to its capacity to block programmed cell death. By blocking the production of the bcl-2 protein, the tumor cells are able to regain the capacity to enter programmed cell death. More than 90% of follicular lymphoma patients have a translocation of the bcl-2 gene to the immunoglobulin heavy chain gene. Therefore, the bcl-2 gene is under the influence of the immunoglobulin heavy chain enhancer, and is consequently overexpressed. Antisense oligos specific for the translation initiation site of the human bcl-2 mRNA are incorporated into liposomes and transported into the cellular cytoplasm. These liposomal oligos inhibited the proliferation of cell lines derived from human B-cell lymphomas.

Aerosolized Lipofection 96- 41
This is a non-toxic, non-immunogenic, cationic lipid formulation that can be used to transfact specific genes in the bronchial epithelium by aerosolization. It is intended to be used to correct genetic defects in premalignant lesions in the bronchial epithelium of patients at risk of lung cancer, and as a result, delay or prevent lung cancer. Viruses are more efficient than liposomes in transfecting cells but are also more toxic and immunogenic, therefore, repeated administration is unrealistic. Liposome composition and size are major determinants of the transfection efficiency. Specific liposome formulations have been identified as having a higher transfection efficiency and, therefore, a greater potential as therapeutic agents. The invention has been successfully tested in models of endobronchial human lung cancer in nude mice.
New Agents for the Prevention and Treatment of Fungal Infections  495

Fungi are the major cause of infection-related mortality in patients with hematologic malignancy and in patients undergoing bone marrow transplantations. In addition, fungi utilize certain substances not only for their growth, but also as fungal virulence factors. Recent laboratory studies have demonstrated that a non-antimicrobial inhibitor of these substances has significant inhibitory growth activity against several pathogenic species of fungi, predominantly the species causing invasive sinopulmonary fungal infections in cancer patients. This agent showed synergistic activity when combined with amphotericin B in inhibiting the growth of these pathogens. At higher concentrations, the combination was sufficient to cause total inhibition of all the pathogens tested.

Ceramide's Emerging Role As A Pathway Regulator  004GA

Ceramide appears to act as a potential mediator of the effects of extracellular agents on cell growth, differentiation, and apoptosis. In addition, the role of the Rb gene product in mediating ceramide effects intracellularly has been examined. A novel ceramide-dependent pathway of signal transduction is beginning to emerge, and research has shown that cell-permeable ceramides will cause cytotoxicity in a broad spectrum of human adherent tumor cell lines, irrespective of their TNF sensitivity and MDR or HER-2 expression. Liposomal ceramide demonstrates cytostatic and/or cytotoxic activity against a variety of human tumor cell lines both in vitro and in vivo.

Increasing The Therapeutic Efficacy Of Antimycobacterial Agents  007GA

These antimicrobials, particularly clofazimine, show very good activity against Mycobacterium avium-intracellular complex (MAC) in both the free and liposomal form. Their antibacterial activity is increased after encapsulation and the lipid composition has no toxic side effects as demonstrated in other clinical studies. They are also very effective against drug resistant strains of Mycobacterium tuberculosis.

Platinum complexes  099/214/294/308/369

The platinum complexes represent a new generation of water-soluble platinum anti-cancer compounds, which show high activity against platinum resistant cell lines.

Ovarian cancer: therapeutic human monoclonal antibody  216/436

This human monoclonal antibody is the first determined to be reactive with human ovarian carcinomas; both therapeutic and diagnostic applications are expected. Radioimmunoconjugate formulation is beginning clinical trials.
- **Novel stem cell inhibiting protein**  360
  This molecule causes dose-dependent reversible suppression of bone marrow stem cells in vitro, with potential use as a stem cell protective agent during chemotherapy and radiotherapy.

- **Cytotoxic T Lymphocytes Based Cancer Therapies and Vaccines**  98-40
  Previously, only HER2/neu has been shown to be the source of naturally occurring, MHC-restricted cytotoxic T lymphocyte (CTL)-recognized peptides in epithelial tumors. However, the investigators demonstrate that the human high affinity folate binding protein (FBP) is a source of antigenic peptides recognized not only in ovarian cancer but also in breast cancer. These peptides are efficient at amplifying the response of tumor-associated lymphocyte (TAL) populations producing enhanced proliferation and peptide-specific IFN-\(\gamma\) release. Furthermore, on a per cell basis TAL stimulated with the FBP peptides exhibit enhanced cytotoxicity not only against peptide-loaded targets but also against FBP-expressing epithelial tumors of different histologies suggests the exciting potential of a widely applicable FBP-based vaccine in epithelial cancers.

**DRUG DELIVERY**

- **Inhibition Of Bcl-2 Protein Expression**  504 ^
  Bcl-2 is an oncogene with tumorigenic potential due to its capacity to block programmed cell death. By blocking the production of the bcl-2 protein, the tumor cells are able to regain the capacity to enter programmed cell death. Antisense oligos specific for the translation initiation site of the human bcl-2 mRNA are incorporated into liposomes and transported into the cellular cytoplasm. These liposomal oligos inhibited the proliferation of cell lines derived from human B-cell lymphomas.

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PREVENTATIVES

Cancer-preventing compounds

This patented technology describes a unique class of compounds that can neutralize the damaging effects of carcinogens.

Sunscreen Adjunct

A method for preventing UV radiation-induced immunosuppression by topical application of a specific, liposomally encapsulated, DNA repair enzyme to sunlight exposed skin.

DIAGNOSTICS

Animal Tumor Marker Assay

This technology describes a tumor marker, which appears to be a diagnostic and prognostic indicator for a number of different cancers. The marker is present in blood plasma and other body fluids (as well as the tumors themselves), regardless of the primary tumor site or type. The assay will find use as a kit both in veterinary offices and veterinary reference laboratories for the companion animal market and agricultural sector.

Ovarian Cancer: Diagnostic Human Monoclonal Antibody

This human monoclonal antibody is the first determined to be reactive with human ovarian carcinomas; both therapeutic and diagnostic applications are expected.
DEVICES

- **Self Anchoring Coils for Vascular Occlusion 97-14, 97-20**
  This coil anchoring system is attached to stainless steel Gianturco macrocoils and tested in a short-term and long-term pilot study with use in a high-flow arterial model. The anchor remained partially compressed when placed in a vessel with a smaller diameter than the unconstrained device. Consequently, the anchor leaned against the vessel at multiple points, resulting in a stable position. Use of the anchoring system makes it possible to achieve precise, reliable delivery of the attached occluding coil. Deployment of the anchor is accomplished in two stages. With use of this delivery technique, precise deployment of the anchor can be achieved. Optimal positioning and arrangement of the coil prevents migration. The anchoring coil would not only be able to extend the use of coils to lesions with large diameters, but it would increase the safety of this type of vessel occlusion. This anchoring system makes coil embolization safer by virtually eliminating the risk of migration. The anchor itself does not require a larger delivery system for coil placement and the presence of the anchor within the lumen of the catheter does not restrict catheter manipulation.

- **A Method to Prevent Signal-Pile up in Scintillation Detectors 531 ^**
  When a radiation particle is detected in a scintillation detector, the detector emits light which is then converted into electronic signal by a photo-sensor. When incoming radiation flux is high, signal pileup may occur as the next radiation particle(s) arrives while the present event is still emitting light. As a result, the particles will merge into a larger signal. Therefore, the performance of conventional scintillation detectors is greatly inhibited as they are not capable of taking a higher count of signal. The invention relates to a novel hybrid processing method to prevent and correct signal pile up. A 10-12 fold improvement in count-rate capability over conventional detector was observed with the new method, and most of the scintillation light is collected. Additionally, the new method allows the use of a 10x stronger radiation source, which enables the data collection time to be reduced by 90%.
Fiber Optic Probe For Thermal Injury Detection 95-50

This fiber optic based device will detect and monitor the full extent of deep lethal thermal injury in living biological tissues during or within seconds of heating by various sources. Up until now, the full extent of deep thermal damage could only be detected one or more days after heat treatment by observation of tissue necrosis using pathologic techniques on tissues removed from the body. The use of this device coupled to the heat source will allow control of the size and/or extent of lethal thermal damage deep in tissue during any thermal coagulative treatments. Two visibly distinct zones develop within seconds of heating and the boundary of lethal thermal damage is determined by measurements of changes and rates of change of back-reflected light intensity due to increased light absorption by hemoglobin accumulating at the outer boundary of the red thermal damage zone.

- Cell-cell Adhesion Quantitation System using Computer Assisted Microscopy 157

This novel method of characterizing and quantifying lymphocyte function and aggregate structure using video microscopy and digital image processing represents significant advantages over existing methods such as flow cytometry.

- Superior Resolution, Low Cost PET Camera 462

This invention relates to a high resolution and low cost Positron Emission Camera (PET) that is excellent for imaging tumors in localized areas such as breast cancer, brain tumors, lymph nodes metastasis and others.

Equipped with radially translating detector segments and a rotation motion to tailor detector rings to the size of the object, the camera is able to image both large (whole body) and small objects (brain, breast and limb) with high detection sensitivity.

Most importantly, the cost of producing a new PET is significantly lower than that of a standard one. It is estimated that the price of a new PET will be less than $1 million, while a standard camera is currently sold at $2.7 million. Further saving could be realized if the camera is used with a new detector design invented by the same inventor.

- Subcutaneous Endoscopic Dissector 549

The dissector is designed to allow minimally invasive surgery in anatomic locations not amenable to the usual endoscopic techniques. For an example, in order to operate subcutaneously, one must have surgical instruments that are capable of 1) retraction, 2) irrigation, 3) suction, 4) cautery for dissection and coagulating small blood vessels, and 5) visualization. To date, all these functions require separate instruments.
- **Self-Expanding Y-Shape Stent 98-22, 98-21, 98-20**
  This bifurcated stent consists of a common body and two legs that are made as a whole of one coherent element. The radially expandable and flexible tubular bodies of the stent are made of nitinol wires and utilizes nitinol's superelastic properties. The design makes it possible to use the stent in several vascular and non-vascular territories where bifurcated anatomical structures are present. The stent design makes it possible to change the angles between the crossing wires, thereby creating a tighter mesh and/or a tapering shape, and resulting in a controlled expansile force. The expansile force of the stent can be increased to the point that a virtually incompressible stent can be created.

- **Nitinol Basket Occlusion Device 98-26**
  One of the advantages of the vascular occluding device is that it achieves a better coverage of the given segment of the vessel than the stainless steel coil does. Therefore, the mechanical blocking of the blockage of the blood stream along with the thrombosis induced by the entrapped blood within the basket leads to quicker vascular occlusion. The strength of the nitinol wires with thermal memory and superelasticity significantly facilitates the self-anchoring of the occluder and greatly reduces the possibility of migration. The occluder can be repositioned offering a prompt correction of misplacement. The guide wire compatible version of the design makes the deployment of the occluder safer and more controllable. In addition to causing a prompt and reliable ureteral occlusion, there is no need for injecting other embolic agents to complete the obstruction. This type of occluder can also be used for vascular occlusion.
RESEARCH TOOLS/REAGENTS/CELL LINES

- **First Inducible/Reversible Mouse Model for Osteoporosis**  98-23
  Bone remodeling is characterized by osteoclastic resorption of pre-existing bone followed by formation of new bone by osteoblasts. To define the role of bone formation in the control of bone resorption in vivo, investigators generated an inducible osteoblast ablation mouse model. This model strikingly mimics characteristics of osteoporosis as it has reduced amount of bone mass and density. More importantly, it is not only inducible through administering a drug which kills bone forming cells-osteoblast, but also reversible if a compound is given to arrest the function of the bone-resorbing osteoclast. It has great utilities for both scientific research and pharmaceutical development. It serves as a great model to study the genetic mechanism of osteoporosis and relevant genes that may be closely associated with the disease. In addition, it is a great animal model to screen and test anti-osteoclast drug candidates.

- **Human Prostate Cancer Cell Lines MDA Pca 2a and MDA Pca 2b**  97-07
  These cell lines were derived from a bone metastasis of a single patient with androgen-independent prostatic adenocarcinoma. They were obtained from different samples of the same specimen and have different genotypes and phenotypes. They are androgen sensitive, expressing PSA, PAP, and grow in vitro as minelayers and in vivo when injected into nude mice. Therefore, it may serve as a useful model to study the biology of prostate cancer, to test sensitivity to different drugs, to develop vaccines and new therapies. To date, the only major human prostate cancer cell lines available as a model for the androgen-independent, androgen sensitive phenotype is LNCap. Conceivably, the use of three cell lines (MDA PCa 2a, MDA PCa 2b and LNCap) provides a more adequate model system of androgen-sensitive prostate cancer.
Rapid Analysis of Gene Expression (RAGE) 98-11

There are currently several methods of determining changes in gene expression. Most of them depend on selecting a small subset of the transcribed genes, developing specific probes for each of these genes and estimating mRNA levels by either hybridization methods or RT-PCR. Among them, RAGE offers a unique approach to determine the frequency distribution of virtually all polyadenylated mRNAs in a cell population or tissue at a selected point in time. It is best suited for determining global changes in gene expression patterns subsequent to some stimulus, but can also be applied to comparisons of tissue samples, e.g., tumor vs. normal tissue. In addition to providing quantitative global data, it can be tailored to look at a particular subset of the transcriptome, and it can be used for gene discovery. Initial feasibility studies have been successfully conducted in a human breast cancer cell line.

Long-Term Human Breast Carcinoma Cell Lines of Metastatic Origin 98-25

Nineteen human breast carcinoma cell lines have been established as continuous cultures and published in *In Vitro*, Vol. 14 No. 11, 1978. Sixteen of our lines were obtained from pleural effusions, two from brain metastases, and one from pericardial fluid. All lines have been shown to be distinct entities and are uncontaminated by HeLa cells or each other. A Iq marker chromosome is present in all but one of the lines examined. They are: MDA-MB-134, 157, 175, 231, 253, 309, 330, 331, 361, 390, 411, 415, 416, 431, 435, 436, 453, 461, 468 and 469. A summary of their morphological, cytogenetic and biochemical characteristics is provided in the same paper.

Method for Increased Transfection Efficiency in Cells 516

One of the major obstacles to successful *in vivo* gene therapy using first-generation, replication-defective adenovirus vectors is low transfection efficiency. Even though transgene expression can be increased by administration of a high dose of vectors, the accompanying severe local inflammatory response and the natural antiviral defense mechanism of cells, which includes production of interferons, limits clinical effectiveness. Interferons are a family of multifunctional proteins with potent antiviral activities. Macrophages that express endogenous IFN-alpha and -beta are resistant to viral infection, but this property can be compromised by antibodies against IFN-beta. Treatment of cells with exogenous IFN-alpha or IFN-inducing agents can suppress replication of DNA and RNA viruses.
IMAGING

**A Method to Prevent Signal-Pile up in Scintillation Detectors**  
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OTHER

- **CHEQ-Cancer and Health Evaluation Questionnaire**  
  This simple copyrighted questionnaire helps determine one's risk for cancer; it is used at MDA and in industry.

- **Chelators in Combination with Biocides**  
  Studies have shown that chelators, when added to antibiotics and antimicrobials, improve the activity against multi-drug resistant microbial organisms through synergistic mechanisms. Other studies have shown that chelators alone can inhibit and suppress the growth of several multi-drug resistant bacteria. The chelators help certain antimicrobials to overcome the intrinsic resistance of organisms. They result in the dissolution of the biofilm layer, hence exposing the organisms to the synergistic activity of the combination of antibiotics and/or antifungals with chelators. From the industrial perspective, all oil and gas pipelines, in addition to others carrying water and/or other chemicals, become contaminated with bacterial and fungal microorganisms. The method of treatment of these gas, oil, and water pipelines is by flushing these pipes with biocides such as chlorine or antimicrobial agents such as gentamicin. It has been shown that the addition of chelators to biocides and antimicrobial agents causes the biofilm layers to disintegrate and dissolve. This improves the activity of biocides against the embedded bacteria.