



## Office of Patents and Licensing Oncology

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**dUTPase Enzyme A Marker for Cellular Proliferation Background** (*Robert Ladner, SOM 94-12*) *Diagnostic/Therapeutic Target*

**Background**

dUTPase is an enzyme that hydrolyzes dUTP to dUMP and pyrophosphate. Since dUTPase levels increase during cell proliferation in a cell-cycle dependent manner, it is suggested that this enzyme could be used as a proliferation marker. Other human proteins such as Ki-67, C5F10 and DNA polymerase alpha, which increase during cell proliferation, have been reported to be useful as prognostic indicators of the status of a cell. For example, Ki-67 has been used as a proliferation marker for lymphoproliferative diseases, and central nervous system and breast tumors. The present invention describes the use of dUTPase enzyme as a marker for the determination of proliferation status of a cell in both neoplastic and normal tissues.

**Description of the Technology**

Scientists at UMDNJ have isolated and completely sequenced the human dUTPase gene. In addition, the dUTPase enzyme has been isolated and purified. The invention also provides methods for determining the proliferation status of a cell and the efficacy of antineoplastic agents using dUTPase. The dUTPase enzyme of the present invention can be used as a cellular proliferation marker to diagnose tumors and to determine responses to chemotherapy since dUTPase has been implicated as having a role in cellular response to fluorodeoxyuridine chemotherapy.

**Applications**

- For the determination of the proliferation status of a cell in both neoplastic and normal tissues.
- For the development of antimicrobial and antineoplastic agents
- To determine efficacy of antineoplastic drugs such as fluorodeoxyuridine or drugs that affect thymidylate synthesis.

**Patent Status**

United States Pat. No. 5,962,246 granted on October 5, 1999

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**Hematopoietic Growth Factor Inducible Neurokinin-1 Gene** (*Pranela Rameshwar, NJMS 00-31 & 02-47*) Therapeutic Target/Diagnostic

**Background**

Neurokinin-1 (NK-1) belongs to a family of receptors known to bind neurotransmitters, tachykinins, with different affinities and mediate a range of physiological functions. These receptors are expressed differentially in bone marrow, mammary epithelial cells and neural tissues. While the expression of NK-1 is constitutive in neural tissues, in bone marrow cells its expression is inducible by hematopoietic regulators. NK-1 receptors and its ligands have been implicated in the pathology of several lymphoproliferative disorders such as Hodgkin's and non-Hodgkin's lymphoma, leukemia and inflammatory diseases. The present technology relates to a discovery of NK-1 variant in the bone marrow cells that is differentially expressed in mature hematopoietic cells and peripheral immune cells.

**Description of the Technology**

A novel gene was discovered, termed Hematopoietic Growth Factor Inducible Neurokinin-1 type (HGFIN), because of its expression in differentiated hematopoietic cells and peripheral immune cells and its absence in progenitor bone marrow mononuclear cells. Further research indicated that HGFIN is a cell cycle inhibitor. This reveals a role for HGFIN in hematopoietic proliferation and regulation, and suggests a potential application in the treatment of lymphoproliferative disorders. Human melanoma and breast cancer cell lines also showed expression of HGFIN. HGFIN has been shown to bind substance P, a tachykinin peptide, and may play a role in substance P-mediated early integration of cancer cells to the bone marrow. Thus targeting NK-1 and other NK receptors in combination with HGFIN could be beneficial in the treatment of cancers.

**Applications**

- For the development of small molecule inhibitors, RNAi, gene therapy, peptides or proteins for therapies in the treatment of cancers, inflammatory, neurological or hematopoietic diseases.
- For use as a transdifferentiation marker to follow the path of cells from bone marrow.
- For the development of antibodies for research use.

**Patent Status**

United States patent granted on 9/6/2005 No. 6,939,955.

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## **A Novel Topoisomerase 1 Binding Protein for Use in Cancer Diagnostics and Therapeutics** (*Eric H. Rubin, CINJ 01-46*) Diagnostic/Therapeutic Target

### **Background**

Topoisomerase 1 is a DNA binding protein that regulates DNA topology and is used as a target of antineoplastic agents camptothecins. Several other proteins are presumed to be necessary for top1 functions. Previous studies at UMDNJ have identified a novel topoisomerase 1 and p53 binding protein called topors. This protein was characterized to be a RING protein rich in serine and arginine domains. The RING domain was shown to be similar to SUMO and E3 ubiquitin ligases. Post-translational modification of proteins via covalent attachment of SUMO is known to be important in cell cycle progression, stress response and signal transduction. The present invention relates to further characterization of the novel topors protein and its uses in cancer diagnostics and therapeutics.

### **Description of the Technology**

Expression of topors protein is down-regulated in tumors from kidney, colon, endometrium and lung, as compared to normal tissue samples. Consistent with the protein data, endometrium and colon tumor tissue samples lacking topors protein did not reveal measurable mRNA levels. Furthermore, over-expression of Topors in cervical cancer cell lines leads to cell death. Thus, lack of topors in cancer cells appears to contribute to the selection and persistence of mutant phenotype and progression to tumorigenesis. Additionally, it has been shown that topors functions as an E3-type ubiquitin ligase and E3-type SUMO ligase for topoisomerase and p53. Thus, topors is a dual function ubiquitin and SUMO ligase. Collectively these data indicate that topors is a candidate tumor suppressor gene similar to p53 and the loss of topors SUMO ligase activity could lead to cancer. It is feasible that modulation of topors ubiquitin and/or SUMO ligase activities may be useful in diseases associated with alterations in ubiquitin or SUMO pathways, including cancer.

### **Applications**

- For screening of cancer tissues
- In gene therapy to re-introduce topors gene into cells lacking the gene
- For use in modulation of DNA repair process
- For development of small molecule inhibitors

### **Patent Status**

United States patent application filed

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**Modification of Immunomodulatory Protein** (*Alexey G. Ryazanov, RWJ 04-41*)  
*Diagnostic/Therapeutic Target*

**Background**

TRPM7 is a bifunctional molecule consisting of an ion channel fused to a protein alpha-kinase domain and plays an important role in magnesium homeostasis, proliferation and cell death. Although this channel kinase has been characterized using electrophysiological techniques, the function of the kinase domain as well as its endogenous substrates still remains unknown. Research at UMDNJ has revealed that annexin 1, a member of annexin family of Ca<sup>2+</sup>-regulated phospholipids binding proteins, is a substrate for TRPM7 kinase. This protein has been shown to play a role in proliferation, inflammation, apoptosis and cancer.

**Description of the Technology**

UMDNJ researchers have discovered a novel modification of annexin 1 protein. This protein consists of a Ca<sup>2+</sup> and membrane-binding core and N-terminal tail preceding the core. The N-terminal region is crucial for its interaction with both intracellular and extracellular targets responsible for regulating proliferation and inflammation. TRPM7 phosphorylates annexin at the conserved Ser5 residue within the N-terminus. Since N-terminus is known to interact with other proteins and membranes, phosphorylation of N-terminus may be pivotal in modulating its function.

**Applications**

The development of new therapeutics for modulation of inflammation, cancer, heart diseases, arthritis, skin diseases, and anoxic neuronal cell death  
As a marker of diagnosis of cancer, heart diseases, arthritis, and skin diseases

**Patent Status**

United States Patent application filed

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## **Bone Morphogenetic Protein –2 and Protein-4 in Treatment and Diagnosis of Cancer** (*John Langenfeld, RWJ 01-02*) Diagnostic/Therapeutic Target

### **Background**

BMP-2 expression is linked to cancer invasion and. BMPs are synthesized as inactive proteins of variable length. The precursor BMP-2 and BMP-4 proteins are proteolytically cleaved, producing mature C-terminal proteins of a little more than 100 residues. BMP-2 and BMP-4 interact with the same binding sites: mature BMP-2 and BMP-4 protein signaling is mediated by transmembrane serine/threonine kinases called type IA, IB, and type II receptors. The receptor phosphorylates cytoplasmic targets, which include the Smad family of proteins. In addition, the same molecules including noggin, chordin, DAN, gremlin, and Cerberus 1 homolog, inhibit both BMP-2 and BMP-4, thereby preventing their ability to bind to the receptors. While BMP expression has been noted in a few cancers, such as sarcomas and in pancreatic cancer and in cancer cell lines, the inhibition of BMP-2 activity and/or BMP-4 activity as a potential cancer treatment has never been mentioned.

### **Description of the Technology**

BMP-2 expression is linked to cancer invasion and growth and inhibiting BMP-2 activity reduces the size of cancerous tumors in nude mice and down regulates the expression of VEGF and sonic hedgehog in lung cancer cell lines. The present technology provides amino acid sequence of inhibitors to BMP-2 and BMP-4 and the receptor site for BMP-2 and BMP-4 antibodies.

#### Advantages

Allows for early detection of metastases and treatment

Technology provides novel sequences and receptor sites

### **Patent Status**

3 U.S. patents are in prosecution

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## **Thymidylate Synthase Polymorphisms for Use in Screening for Cancer Susceptibility** (*Robert Ladner, SOM 02-52*) *Diagnostic/Therapeutic/ Cardiovascular*

### **Background**

Thymidylate Synthase (TS) is an important enzyme in the nucleotide synthesis pathway and converts dUMP to dTMP. TS is a target for a variety of chemotherapeutic agents such as 5-FU, raltitrexed (Tomudex and pemetrexed (Alimta)) and inhibition of TS leads to cytotoxicity due to depletion of dTTP pool, a phenomenon dubbed as “thymine-less death.” TS also plays a critical role in cardiovascular diseases and other defects. TS and methylenetetrahydrofolate reductase (MTHFR) compete for folate in the generation of homocysteine. Folate and homocysteine have been associated with cardiovascular risk. Polymorphisms consisting of 28 base pair repeats in the 5'-untranslated region of the TS gene have been identified in certain African and Asian populations and have been shown to predict patient response to 5-FU chemotherapy. **The present invention discloses a novel single nucleotide polymorphism which could be added to existing screening tests thereby enhancing the predictive value of the tests.**

### **Description of the Technology**

A novel single nucleotide polymorphism (SNP) in the 5' tandem repeats of the TS gene has been discovered. Individuals with wild-type form had higher transcription of TS than those with the variant form. In addition, the present invention also discloses a six base pair deletion in the 3' gene of TS which results in mRNA instability and decreased production of TS. It has been shown that in cancer tissues, the reduced production of TS prevents the growth and metastasis of cancerous cells. Taken together, these studies demonstrate that identification of these polymorphisms would enable the prediction of a patient's response to chemotherapy and cardiovascular disease treatments.

### **Applications**

- To assess the risk of cancer and cardiovascular diseases
- To develop screening methods for the base pair deletion in the 3' gene of TS
- To predict the clinical outcome of chemotherapy and anti-cardiovascular treatments

### **Patent Status**

PCT application filed.

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**Monoclonal Antibody for a Prostate-Specific Tumor Suppressor Gene** (*Cory Abate-Shen, CABM 01-10*) *Diagnostic/Research Tool*

**Background**

Relatively little is known about the molecular mechanisms involved in prostate carcinogenesis due to the lack of animal models that mimic human prostate carcinoma. Mutant mouse models lacking genes critical for prostate development could be utilized to understand the molecular pathways involved in prostate cancer initiation and progression. Thus, identification of prostate-specific oncogenes would be extremely valuable in studying prostate carcinogenesis. The present invention relates to: (1) the identification of a prostate-specific tumor suppressor gene, (2) generation of monoclonal antibodies (mouse and human) to the tumor suppressor protein, and (3) mutant mouse models of prostate cancer.

**Description of the Technology**

Knockout mice lacking the functional homeobox gene Nkx3.1 and the lipid phosphatase Pten were generated to study the molecular factors involved in prostate carcinogenesis. These studies showed that the loss of Nkx3.1 protein expression is a hallmark of prostate cancer in mice and humans, and occurs in early stages of the disease. Thus the resultant mouse models mimic early stages of human prostate cancer. Monoclonal antibodies against human NKx3.1 regulatory protein have been produced. A method for detecting the presence of Nkx3.1 in biopsy tissue samples has been developed.

**Applications:**

Mouse anti-human and anti-mouse polyclonal as well as monoclonal antibodies with specificity for the tumor suppresser Nkx3.1 protein are available. These antibodies can be used:

- As tumor marker for early detection of prostate cancer.
- Pre- and post-treatment monitoring of prostate cancer
- As a marker to distinguish between indolent versus aggressive prostate cancer.

The knockout mice can be used to study the molecular mechanisms involved in prostate cancer initiation and progression.

**Patent Status:**

US patent applications filed.

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## **Novel Bi-Functional Alpha-Kinases: Protein Kinases Linked to Ion Channels**

*(Alexey G. Ryazanov, RWJ 00-08) Therapeutic Target*

### **Background**

A superfamily of protein kinases (serine/threonine/tyrosine protein kinases) that phosphorylate amino acid residues located in the loops or turns of their substrates is most well-characterized. Several other protein kinases have been documented that lack homology to this superfamily of kinases. Recently a new class of kinases, alpha kinases, lacking homology to the serine/threonine/tyrosine protein kinase superfamily has been identified. Eukaryotic Elongation Factor 2 Kinase (eEF-2) belongs to this second family of kinase. The alpha kinases differ from serine/threonine/tyrosine protein kinases in that they phosphorylate a threonine amino acid residue located in the alpha helical region of the substrate. The present invention relates to the discovery and characterization of additional members of the family of the alpha kinases that are related to the eEF-2 kinase but possess certain unique characteristics. The characterization of additional members has both therapeutic and diagnostic implications for diseases associated with cell cycle progression and malignant transformation.

### **Summary of Invention**

Genes for tissue specific alpha kinases such as melanoma alpha kinase, heart alpha kinase, skeletal muscle alpha kinase and lymphocyte alpha kinase have been identified, cloned and sequenced. These kinases lack sequence homology to the well-characterized serine/threonine/tyrosine superfamily with partial homology to eEF-2 alpha kinases. In addition, a subfamily of bifunctional alpha kinases was discovered and found to contain an ion channel covalently linked to the catalytic domain of the protein kinase. The presence of an ion channel linked to the kinase molecule is indicative of self-regulation of the molecule and suggests a phosphorylation mechanism that is distinctive from previously characterized mechanisms. The present technology provides vectors encoding and expressing the channel kinases.

### **Applications**

- To generate antibodies (monoclonal or polyclonal) to the kinases
- To develop novel drug for cancer and other malignancies
- To diagnose and treat medical conditions requiring modulations of alpha kinase activities

### **Patent Status**

United States CIP application filed.

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**Oligonucleotide Compositions for the inhibition of Transcription Factors** (*Beverly E. Barton, NJMS 03-02*) Therapeutic

**Background**

The STAT (signal transducers and activators of transcription) family of transcription factors is involved in the signal transduction pathway of growth factors and cytokines. STATs are known to be activated by phosphorylation of tyrosine and serine residues. Phosphorylation of STAT3 is via IL-6 signaling and is tightly regulated in normal cells. However, aberrant signaling of STAT3 is found in many types of malignancies. The persistent activation of STAT3 leads to over-expression of genes involved in anti-apoptotic factors and cellular proliferation. Inhibition of STAT3 has been found to lead to apoptosis of malignant cells. **The present invention provides oligonucleotide compositions for the inhibition of STAT family of transcription factors and, thus, for treatment of diseases wherein aberrant STAT expression plays a critical role in pathophysiology.**

**Description of the Technology**

Oligonucleotide compounds containing sequences capable of binding to transcription factors and inhibiting activity of transcription factors have been shown to modulate cellular responses mediated by STAT family of transcription factors. In the presence of excess amounts of the binding sequences, STAT transcription factors were prevented from binding to genes. These oligonucleotide binding sequences were tested for their ability to inhibit tumor growth in an *in vivo* mouse model for human prostate cancer. Mice injected with these oligonucleotides had significantly smaller tumors compared to control mice. Taken together, these data support the use of these oligonucleotides in the treatment of diseases wherein STAT transcription have a pathophysiological role.

**Applications**

- For the treatment of diseases wherein STAT family of transcription factors have a pathophysiological role. Specific applications include:
- Cancer
- Autoimmune diseases
- Chronic inflammatory diseases
- Alopecia, cosmetic hair removal or suppression

**Patent Status**

United State provisional patent application filed

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## **PNA-Neamine Conjugates for use as Therapeutic agents and Research Tools**

*(Virendra N. Pandey, NJMS 03-37) Therapeutic*

### **Background**

Peptide nucleic acids (PNAs) are analogs of nucleic acid with peptide backbone replacing sugar phosphate backbone in a nucleic acid. These analogs bind to both single stranded and double stranded RNA or DNA in sequence specific manner to inhibit translation and replication. They are gene-specific, nontoxic, and non-immunogenic. However, their therapeutic potential has been limited because of their poor uptake into mammalian cells. Thus, new methods for efficient transfer of therapeutic agents and artificial nucleases with improved cell permeation properties have been extensively investigated.

Aminoglycoside antibiotics such as neomycin B, which are specific to 16S bacterial rRNA, also bind HIV RNA recognition elements, RRE (Rev Responsive Element) and TAR and block HIVRev and HIV-Tat RNA-protein interactions. However, the toxicity of neomycin B and the risk of developing antibiotic resistance due to modification by aminoglycoside-modifying enzyme limits its use as a therapeutic agent. Neamine derivatives with increased affinity to RNA targets or resistance to aminoglycoside modifying enzymes have been prepared by mimetics. **The present invention discloses new methods and compositions for the synthesis of improved PNA-aminoglycoside derivatives.**

### **Description of the Technology**

The aminoglycoside neamine was conjugated to a PNA sequence specific to the TAR region of HIV-1 RNA genome. The TAR specific PNA-neamine conjugate had improved cellular uptake and enhanced binding with the target sequence resulting in robust inhibition of viral replication. Furthermore, the conjugate was also able to block the production of HIV-1 in lymphocyte CEM cells infected with pseudotyped HIV-1 virions. One of the conjugates disclosed in the present invention showed RNA cleavage activity in the absence of magnesium ions. Taken together, these results indicate that aminoglycoside-PNA conjugates could be used as antiviral agents.

### **Applications**

Therapeutics: PNA-aminoglycoside conjugates can be used as antiviral and anticancer agents.

### **Patent Status**

PCT Patent Application filed

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## **Novel Combretastatin A-4 Analogues with Potent Cytotoxicity and Anti-Tubulin Polymerization Activities** (*William J. Welsh, RWJ 04-29*) Therapeutic

### **Background**

The microtubule system of eukaryotic cells is considered to be a target for the development of anti-cancer agents. The  $\alpha$ - and  $\beta$ -tubulin heterodimer is the building block of microtubules and, as such, is the biochemical target for several clinically used chemotherapeutics. Colchicine, paclitaxel and other clinically used anti-tubulin drugs often face limitations such as neural and systemic toxicity, poor water solubility and bioavailability, and complex synthetic pathways and isolation procedures. The present invention describes five novel small-molecule compounds that exhibit anti-tubulin polymerization and anti-cancer activity.

### **Description of the Technology**

The present invention describes the rational design, synthesis and biological evaluation of a series of novel small-molecule compounds that exhibit strong *in vitro* anti-tubulin polymerization activity as well as cytotoxicity in the low nM range against four cancer cell lines isolated from cervical, breast and colon tumors. Moreover, these compounds show significant cytotoxicity in human cervix epithelial adenocarcinoma and colon carcinoma cells which overexpress multiple drug resistance. Furthermore, these novel inhibitors are water soluble and predicted to exhibit good bioavailability. These compounds and their analogues are also attractive from the standpoint of medicinal chemistry and large-scale chemical synthesis, by virtue of the absence of chiral (stereochemical) centers and the efficient 5-step reaction scheme which renders the desired product in high yield employing inexpensive starting materials.

### **Applications**

Compounds of this invention can be used as anti-cancer agents

### **Patent Status**

PCT patent application filed

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**Identification of a Myeloid Precursor Cell for Modulations of Immune Responses**  
(Yacov Ron, RWJ 98-08) *Therapeutic & Oncology*

**Background**

Pluripotential stem cells (PSC) are found in the bone marrow and spleen in mice and are cells that are capable of self-renewal and differentiation into all lineages of the hematopoietic system. Only one in 2,000-5,000 cells in bone marrow are PSC and are present within a narrow subset (Thy-1.1lo LinSca-1+) of bone marrow cells. The current dogma concerning the kinetics of hematopoiesis is that only primitive pluripotential bone marrow stem cells can support hematopoiesis, whereas lineage-committed stem cells can support only a particular lineage. The present invention provides long-lived myeloid-committed stem cell population that can replenish the mature myeloid lineage.

**Description of the Technology**

Researchers at UMDNJ have identified long-lived myeloid-committed stem cells in spleen which replenish the mature myeloid lineage for at least 12 months. Evidence for these findings is provided by the discovery that these cells do not home back to the bone marrow. These stem cells can be targeted with a retroviral vector following LPS stimulation of T-cell depleted spleen cells. The ability to introduce exogenous genes into myeloid lineage has several advantages over current methods of retroviral-mediated gene transfer techniques using bone marrow stem cells. For example, the efficiency of gene transfer using bone marrow stem cells is very low (5%), while the efficiency with the present method is extremely high. Another disadvantage of using bone marrow cells includes expression of the exogenous gene in all hematopoietic cell lineages.

**Gene transfer using the cells identified in the present invention results in the targeted expression of the exogenous gene in the desired subset of the myeloid compartment.**

**Applications**

- Gene therapy-based treatment of genetic disorders linked to myeloid lineage such as Gaucher's disease
- Selective immune response against tumor or viral antigens.

**Patent Status**

United States patent issued 4/2007

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**Method of Improving Drugs with Anti-Retroviral and Anti-Cancer Activity** (*Harmut M. Hanauske-Abel, NJMS 04-39, 04-46*) Therapeutic

**Background**

This invention relates to a method of inhibiting the generation of infections viral progeny, or suppressing the proliferation of malignant cells, which comprises interrupting the eIF5A-dependent cellular pathway essential for cellular proliferation. eIF5A is a eukaryotic translation initiation factor 5A, an intracellular protein with two isoforms. eIF5A requires posttranslational modification in order to become biologically active. It has been shown to be over-expressed in cancers and is thought to play an essential role in virally-induced proliferation of cells. This protein is unique in that it contains hypusine, a lysine derivative, which is formed by posttranslational hydroxylation, catalyzed by the non-heme ferrous dioxygenase deoxyhypusine hydroxylase (DOHH). The active site architecture of DOHH can be characterized by an active site cage entombed inside the apoenzyme ('fireplace-with-chimney' model). This invention relates to the discovery that the 'chimney' segment of the DOHH active site can accommodate large hydrophobic moieties which can serve as an anchor for a smaller inhibitor in the 'fireplace' segment of DOHH thereby significantly improving the efficacy of the inhibitor.

**Description of the Technology**

This invention discloses a method used to obtain a suppressive effect on the proliferation of cells occurring within a non-metastatic or metastatic malignancy. The preferred embodiment of the pharmacologically relevant DOHH inhibitor is a compound of a disclosed formula or a derivative thereof with a hexane backbone and a hydrophobic anchor as (C<sub>5</sub>-C<sub>12</sub>) alkyl, (C<sub>3</sub>- C<sub>12</sub>) cycloalkyl, or a hydrophobic aromatic moiety. Other side chains can be hydrogens; alkyl, alkenyl, alkynyl or alkoxy groups; or a peptide or a peptidomimetic moiety containing 10 to 50 carbon atoms particularly positioned on the hexane ring. The disclosed formula for the proposed pharmaceutical agent has been shown to have an improved efficacy as compared to the currently existing DOHH inhibitors.

**Application**

The compounds of this invention can be used in systemic or topical application as anti-neoplastic agents in combination with existing anti-cancer drugs of various clinically introduced chemotypes, as well as, a part of cancer treatment protocols also comprising surgery and radiation.

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## **Activated CDC42-Associated Kinase (Ack) as a Therapeutic Target for Ras Induced Cancer** (*Nur-E-Kamal, RWJ 04-49*) Therapeutic Target

### **Background**

Activation of Ras GTPase function has been shown to be associated with various types of cancer identifying Ras as a target for cancer therapeutics. However, Ras GTPase activity is also essential for multiple normal signaling pathways involved in controlling growth and differentiation of mammalian cells. Thus targeting Ras directly may have deleterious effects on non-cancer cells. This invention is based on the discovery that Ras signal for transformation transduces through the activated CDC42-associated kinase (Ack). This invention validates Ack kinase as an attractive therapeutic target for Ras-induced cancer.

### **Description of the Technology**

The present invention discloses the fact that CDC42 and activated CDC42 associated kinase (Ack) act downstream of Ras signaling in cancer cells. To prove this, the expression of Ack was knocked down using siRNA in v-Ha-Ras NIH 3T3 transformed cells. siRNA knocked down the expression of Ack in a dose-dependent manner in v-Ha-Ras transformed NIH 3T3 and parental NIH 3T3 cells. Additionally, Ack-deficiency in the v-Ha-Ras transformed cells was shown to induce apoptosis. Therefore Ras signals transduced through Ack protect v-Ha-Ras transformed cells from apoptosis. PD 158780 tyrosine kinase inhibitor inhibits the kinase activity of Ack *in vitro* and affects the growth of v-Ha-Ras transformed NIH3T3 cells in a dose-dependent manner. Thus Ras-CDC42-Ack signaling pathway is required for survival of Ras-transformed mammalian cells and Ack kinase is an attractive target to develop a chemotherapeutic agent for Ras-induced cancer.

### **Applications**

CDC42-Ack can be used as a target in search of novel therapeutic agents for Ras-induced cancers, i.e. brain tumors, breast and prostate cancers.

### **Patent Status**

United States Provisional Patent Application filed on 08/09/2005  
Provisional Patent Application Number 60/706,655

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**Mouse Model of Invasive Bladder Cancer** (*Cory Abate-Shen, 06-38 UMDNJ*) Research Tool

**Background**

Despite significant improvements in diagnosis and treatment, neoplasia of the bladder continues to result in significant mortality. Bladder cancers range from being benign to highly aggressive, and most are epithelial in origin and urothelial in nature. They are believed to arise from two distinct precursor lesions, namely, a papillary form (called Papillary Urothelial Neoplasm of Low Malignant Potential or PUNLMP) and carcinoma-in-situ (CIT). However, it is not well understood how these precursors relate to each other or to benign versus invasive disease. The present invention is a double knockout mouse to be used as animal models for bladder cancer.

**Description of the Technology**

The present invention is an autochthonous mouse model of bladder cancer that originates in the urothelium and ultimately progresses to invasive disease. This was accomplished by using adenovirus-Cre delivery system to achieve sporadic deletion of tumor suppressor function specifically in the bladder urothelium. Simultaneous deletion of two tumor suppressor genes leads to the development of invasive bladder tumors with 100% penetrance by 4 months, including distant metastases to the liver and other tissues, which are also sites for bladder cancer metastases in humans. The histological appearance of these tumors is remarkably similar to invasive human bladder cancer.

**Applications**

This invention provides a tool for identifying therapeutic agents, method of observing the effects of treatment, and an animal model for the development of bladder disease, not limited to cancer.

**Patent Status**

United States Provisional Application – 2006.

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**Reversal of Resistance to Anti-Microtubule Drugs in Human Breast Cancer** (*Dr. William Hait, 06-56 CINJ*) *Oncology/Drug Target*

**Background**

Anti-microtubule agents are among the most active drugs in the treatment of breast cancer. They function by inhibiting microtubule dynamics. Resistance to these agents is complex and includes non-specific, as well as, specific mechanisms of drug resistance. General, non-specific mechanisms include those mediated by the over-expression of drug efflux pumps, whereas mechanisms specific to anti-microtubule agents include alterations in tubulin through mutation, differential expression of tubulin isotypes, post-translational tubulin modifications, and altered expression of microtubule regulatory proteins. The present technology relates to a method to overcome resistance to anti-microtubule agents by targeting microtubule regulatory proteins.

**Description of the Technology**

UMDNJ/CINJ researchers have recently shown that cell-cycle kinetics constitute a specific mechanism of resistance to anti-microtubule drugs. Since anti-microtubule drugs produce their deleterious effects predominantly during M phase (the phase in which microtubules display the greatest dynamicity), altering the expression of a protein in favor of G2/M progression sensitizes breast cancer cells to anti-microtubule agents. The present technology provides preliminary methodology with supporting data for reversal of resistance to anti-microtubule agents providing a therapeutic advantage to a subset of cancers that are often aggressive and resistant to conventional therapies.

**Applications**

For the treatment of cancers resistant to conventional therapies.

**Patent Status**

United State provisional patent application filed

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**EMAP II in Cancer Therapy** (*Drs. Margaret & Roderik Schwarz, RWJ 06-08 & 06-27*)  
Oncology

**Background**

Endothelial-Monocyte Activating Polypeptide II (EMAP II) is a 34kD protein that undergoes enzymatic release of its C-terminus resulting in the release of a 19kD fragment that functions as an anti-angiogenic protein. The function of the intracellular proform of EMAP II has been elucidated by UMDNJ researchers, as well as, the conditions by which the protein is cleaved, and the mechanism by which it inhibits vessel formation.

**Description of the Technology**

The mechanism of action of EMAP II has allowed for the assembly of unique combinations of chemotherapeutic agents and anti-angiogenic agents that results in significant enhanced suppression in tumor growth. More specifically, EMAP II in combination with cytotoxic agents such as gemcitabine and in combination with VEGF antibodies or alpha5 integrin blockers resulted in tumor regression. Additionally, using methods of the present invention, one can search for novel cancer drugs that would affect cleavage of EMAP II thereby inhibiting angiogenesis.

**Patent Status**

United State provisional patent application filed

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## **Epigenetic Modulation for Restoration of Drug Sensitivity in Cancer Chemotherapy** *(Dr. Debabrata Banerjee, CINJ 06-06) Oncology*

### **Background**

Colorectal cancer is a second leading cause of cancer-related deaths in the United States. 5-Fluorouracil (5-FU) remains a main regiment used in the clinic for the last decade to treat patients diagnosed with this deadly disease. The response rate to 5-FU is typically less than 30% and the intrinsic or acquired resistance to the drug is the main obstacle to therapeutic success. Two delivery methods of 5-FU are relevant from the clinical point of view: bolus infusion of high doses of the drug given weekly or continuous infusion of low doses. Depending on the schedule of drug administration it may have different mechanisms of action. 5-FU is converted intracellularly to active metabolites, FdUMP, FdUTP and FUTP. These active metabolites can either act as a thymidylate synthase (TS) inhibitor and interfere with DNA synthesis, or may be incorporated into RNA. Significant evidence has accumulated to support the concept that bolus treatment results in metabolism to F-UTP and exerts its cytotoxic effect predominantly through incorporation into the RNA. Researchers at UMDNJ have recently shown that resistance to bolus 5-FU is due to lower incorporation of F-UTP into RNA as a result of lower levels Uridine Monophosphate Kinase (UMP/K).

### **Description of the Invention**

UMP/K (also known as UMP/CMP kinase) is an enzyme that catalyzes the transfer of a phosphate group to UMP, CMP and dCMP using ATP as a cofactor. This enzyme is crucial for the de-novo and salvage synthesis of pyrimidine nucleotides and no other enzymes with the same substrate specificity as UMP/K kinase has been identified so far. The important role of UMP/K in bolus 5-FU resistance was determined by analyzing patient samples of colon cancer metastatic to the liver which lower level of this enzyme, especially in the group of patients, who were previously treated with 5-FU and was further confirmed by modulation of this enzyme level in our in vitro colorectal cancer model. **UMDNJ researchers have found a way to increase the level of this enzyme making the resistant cells sensitive to treatment with 5FU.**

### **Patent Status**

United State provisional patent application filed

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## **A novel class of mTOR inhibitors (Zheng, RWJ 06-34) *Oncology***

### **Background**

Mammalian target of rapamycin (mTOR) is an important drug target for many human diseases, including graft rejection, autoimmunity, restenosis, cancer, heart disease, diabetes, obesity, aging, and also Alzheimer, Parkinson and Huntington diseases. mTOR is a conserved regulator of cell growth and metabolism that integrates energy, growth factor, and nutrient signals. TOR is a phosphatidylinositide 3-kinase-related kinase (PIKK). It forms two multiprotein complexes mTORC1 and mTORC2. Only mTORC1 is sensitive to rapamycin. mTOR localizes to the endoplasmic reticulum (ER) and Golgi. Dysregulation of mTOR signaling occurs in diverse human tumors. Preclinical studies indicate that rapamycins are potent inhibitors of the proliferation of numerous tumor cell lines in culture and of murine syngeneic tumor models or human Xenografts.

### **Description of Technology**

A novel class of mTOR inhibitors targeting both mTORC1 and mTORC2 were identified. The inhibitors are more potent than and distinct from rapamycin and rapamycin-derivatives in their mechanism of action. They block localization of mTOR to the ER and Golgi. They also induce apoptosis in tumor cells a distinctive advantage for cancer therapy. Moreover, because mTORC2, an important regulatory kinase in the aging pathway is inhibited, they can be useful agents to treat aging and aging-related illness.

### **Applications**

- These new inhibitors can be used to develop drugs with clinical utility in the treatment of many human diseases involving mTOR dysregulation.
- This technology can also be used for drug discovery targeting ER and Golgi localization of mTOR.
- The technology can also be applied in the research area to target molecules to the ER and Golgi.

### **Patent Status**

United States Provisional Application for Patent was filed on December 8, 2006

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**Novel Leukotoxin as a Therapeutic Agent** (*Scott C. Kachlany, NJMS 04-38*)  
Therapeutic

**Background**

Current treatment for blood cancers includes the use of synthetic compounds that target the cell division process of nearly all cells of the body, not just cancerous ones. As a result, devastating side effects are all too common in patients. Bone marrow suppression, severe neurologic effects, infertility, pulmonary, and gastrointestinal effects are some of the adverse effects exhibited by the drugs. The present invention presents a novel method of treatment leukemia and lymphoma which comprises the use of a novel form of leukotoxin as a therapeutic agent.

**Description of the Technology**

The present technology discloses a novel leukotoxin secreted in great abundance from a unique strain of *Actinobacillus actinomycetemcomitans*. The isolated protein of the present invention is different from another leukotoxin purified from another strain of Aa in fatty acid modifications and cytotoxic properties against blood cells. The therapeutic composition proposed here has specific activity against white blood cells with no cytotoxic activity against red blood cells or other human cell types. Proof of principle experiments have been carried out *in vitro* and *in vivo* utilizing disease-specific cells and small animals. Experiments utilizing leukemia blast cells from patients are under way.

**Applications**

- As a new class of cancer therapeutics with a specificity for leukemia and lymphoma.

**Patent Status**

United States Provisional Application filed November 2005.

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**Apoptosis-inducing peptides as novel therapeutics for cancer treatment** (*Jianjie Ma, RWJ 05-08, 05-16*) *Oncology*

*ATAPs (Amphipathic Tail-Anchor Peptides)*

The new cancer therapeutic peptides, ATAPs induce apoptotic cell death of diverse cancer cells. ATAPs contain a single amphipathic transmembrane segment and specific targeting property to mitochondrial membrane. By these two linked properties (the amphipathicity and targeting signal peptide), ATAPs specifically accumulate at the mitochondrial membrane and then disrupt mitochondrial membrane potential, causing acute apoptosis of cancer cells. Apoptosis induced by ATAPs is not blocked by anti-apoptotic Bcl-xL and Bfl-1 proteins that are involved in resistance of cancer cells against various cancer drugs. Therefore, these ATAPs have high potential as a new cancer drug.

*PLP (Presenilin-2 Loop Peptide)*

Presenilin-2 is a critical component of  $\gamma$ -secretase which is related to Alzheimer's disease. It is a membrane protein with eight predicted transmembrane (TM) domains and a hydrophilic loop of approximately 120 amino acids between the sixth and seventh TM domains. Presenilin-2 loop region could be cleaved by presenilinase and caspase -3 into a small, 22 amino acid peptide, presenilin-2 loop peptide (PLP). Through our combination of biochemistry, confocal microscopy, and cell culture method, we found that PLP when coupled with a membrane penetrating peptide (TAT) can readily enter the cell, and cause perturbation of intracellular Ca homeostasis. Cells treated with TAT-PLP (~1  $\mu$ M) quickly undergo apoptosis within 6 hours after treatment. As control, a scrambled peptide, TAT-PSP, is not effective in triggering apoptosis. TAT-PLP interacts with the IP3 receptor Ca release channel located on the endoplasmic reticulum, and triggers release of cytochrome c release from mitochondria. These results demonstrate that PLP can be used as a potential therapeutic agent for the treatment of cancer cells.

**Patent Status**

United States Provisional Applications –2006.

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## **Nitric Oxide Synthase Inhibitors** (*Laskin, RWJ 98-23*) *Research Tools & Oncology*

### **Background**

Nitric oxide synthase (NOS) - mediated diseases include sunburn, rheumatoid arthritis, ulcerative colitis, Crohn's disease, septic and toxic shock, asthma, hypertension, myocarditis, diabetes and autoimmune and respiratory disorders. Nitric oxide is synthesized via the arginine to citrulline deamination pathway making this pathway a target for the design of therapeutic drugs. The literature describes various N- $\gamma$ -substituted arginines as inhibitors of NOS.

### **Description of the Technology**

This invention relates to a novel class of planar, fused-ring bio-isoteric models of arginine as NOS inhibitors. The synthesis, structure, and utility of eight novel members of triazole families that inhibit NOS have been described. One of the compounds when tested on mammalian PAM 212 cancer cells showed antiproliferative property.

### **Applications**

- For use as NOS inhibitors in diseases requiring inhibition of NOS
- Anticancer agents

### **Patent Status**

United States patent application 10/863,785 was filed in 2004

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**New Erythropoietin Molecule: Erythropoietic Without Immunosuppression** (*Yuan, Rui Rong RWJ 06-73*) *Oncology*

**Background and Description of the Invention**

Anemia is a common complication in patients with cancer, especially in those with advanced disease or who are under intensive chemotherapy or radiotherapy. Erythropoietin (EPO) is a 165 amino acid glycoprotein and the recombinant Human EPO (rHuEPO) has been used extensively for the treatment of anemia in humans. EPO treatment is capable of alleviating therapy-related anemia and improves cancer patient's quality of life (QOL). It represents a safe and effective means to increase the red cell mass and avoid blood transfusions in >50% of the cancer patients with chronic anemia.

In recent years, EPO has received considerable attention because it may have the capability of inducing broad neuroprotective effects in animals following CNS injury. However, long-term use of EPO therapy remains an elusive because EPO treatment may overly stimulate erythropoiesis. To overcome this excessive red cell production, we have created a library of EPO-derived fragments for tissue protection based on the hypothesis that two distinct functions (erythropoiesis and tissue protection) reside in different domains of the molecule. Our studies on small EPO-derived peptides have provided strong evidence to support the notion that there are at least two distinct functional domains co-existing within the whole EPO molecule and that sequences and/or structures within the EPO amino acid sequence will dictate their biological functions. Since we have identified the amino acid sequence of the immunosuppressive EPO-derived small peptides, we hypothesize that the amino acid sequence(s) responsible only for erythropoiesis can be created and characterized. The new type of EPO (EPO-new or EPO-N) for anemia treatment is thus being developed for future clinical use.

**Patent Status**

United States Provisional Application for Patent Filed

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**Local Combination Immunotherapy for Solid Tumors** (*Rui-Rong Yuan, UMDNJ 04-03*) Oncology

**Background**

Despite the significant progress in cancer treatment made over the last two decades, many patients with malignant solid tumors, especially patients with metastatic disease or locally advanced unresectable tumors, die of disease progression. Both SCLC and neuroblastoma are of neuroendocrine origin and express high-levels of the neuron specific nuclear antigen-HuD protein. The HuD-antigen is a neuronal RNA-binding protein. Hu proteins are expressed in the nucleus and cytoplasm of neurons and are thought to play roles in neurogenesis and neuronal maintenance. All SCLC cells express HuD antigen, while there is no expression in normal lung tissue. The HuD-antigen is also expressed in 80% of all human neuroblastomas. A strong correlation between the presence of high titer polyclonal anti-HuD antibodies and occasional spontaneous remissions of SCLC in some patients has suggested that the HuD-antigen might be a good molecular target for specific immunotherapy against SCL.

**Description of the Technology**

We have created a new immunotoxin (named BW-2) using anti-HuD Antibody in complex with a toxin. (For future clinical application, other immunotoxins can be created utilizing humanized SCLC tumor specific monoclonal antibodies or a fragment that can enter into the targeted tumor cells.) We have demonstrated that the immunotoxin aggressively killed SCLC cells in vitro with high specificity while exhibiting minimal toxicity against control cell lines. In contrast to conventional immunotoxin therapy, we injected the immunotoxin compound directly into tumors (subcutaneous) in a nude mouse model of human SCLC. We found that this immunotoxin killed targeted SCLC tumor cells and significantly delayed tumor progression compared to all the control groups. There was no toxicity in the immunotoxin treated animals. Furthermore, following local tumor specific immunotoxin therapy, additional autologous DCs injections into the immunotoxin treated tumor site should improve tumor antigen presentation resulting in a more robust shrinking of the tumor.

**Patent Status**

United States Provisional Application filed on 06/29/2006.

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## **Methods and Compositions for the Regulation of Proliferation of Stem Cells**

*(Pranela Rameshwar, NJMS 02-20) Oncology/Stem Cells*

### **Background**

Chemotherapeutic agents do not distinguish between the aberrant cancerous cells and the rapid growing, but normal stem and immune cells. Hence, both tumor and healthy stem and immune are killed off by the administration of chemo- and radio-therapeutic toxic agents. This leads to a drop in blood count, suppression of the immune response, and to an increased risk of bacterial and/or fungal infection, which can lead to death. Thus, there has been and continues to be, a long felt need for a way to protect the healthy stem and progenitor cells of the body from the toxic effects of chemo- and radio-therapy. The present invention includes novel compositions and methods for showing, and or turning off, stem and progenitor cell growth in a subject, specifically, in a subject about to undergo toxic cancer treatment, thus protecting these cells from the highly toxic effects associated with chemo- and radio-therapy.

### **Description of the Technology**

UMDNJ researchers have discovered that neutral endopeptidase (NEP) utilizes Substance P (SP) to produce a tetrapeptide, SP(1-4), that inhibits proliferation of lymphoid-myeloid stem and progenitor cells, It has been determined, through its interactions with TGF-beta and TNF-alpha, that SP(1-4) can be used as an effective treatment to shield both stem and progenitor cells from the toxic effects of chemo- and radio-therapy thereby protecting a subject's immune system from being compromised and reducing the risk of bacterial or fungal infection, allowing for a greater dosage of chemo- and/or radio-therapy to be administered and/or over a longer administration period, as well as, shortening the recovery period required for new stem cell growth and terminal blood cell replenishment.

### **Patent Status**

US Patent Number 7,119,071 B2 Granted October 10, 2006

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**Methods for Selection of Malignant Cells from Malignant Tissues** (*Pranela Rameshwar, NJMS 04-43*) *Oncology*

**Background**

Breast cancer metastasis to the bone marrow correlates with poor prognosis. Seemingly curative therapies in patients with both metastatic and non-metastatic breast cancer have recurrence of breast cancer cells from the bone marrow. Such resurgence can occur even twenty years after remission. Based on these reports, it is believed that breast cancer cells entering and surviving in bone marrow are either subsets of breast cancer cells with unique properties, or are located in an area, which protects them from treatment modalities. The resurgence of breast cancer cells from the bone marrow is consistent with ability of the bone marrow to maintain survival of growth-arrested cancer cells. Since resurgence occurs even in early stages of breast cancer, it appears that breast cancer cells may enter the bone marrow long before the tumor can be detected by conventional clinical methods. As cancer cell lines can exhibit phenotypes divergent from that of cancer cells in vivo, it is essential to use primary cancer cells in experiments to mimic in vivo behavior of cancer cells. However, surgical tissues are generally small and clinical analysis of excised tissue is of primary importance, leaving little or no sample for experimental analyses. Thus there is a need for a reliable method for selecting and maintaining malignant cells from a small tissue sample to facilitate drug discovery and cancer prevention. The present invention discloses such methods.

**Description of the Invention**

The present invention is a method of selecting an enriched population of malignant cells. The method of the invention involves depleting fibroblasts from a population of cells obtained from a tissue sample, selecting epithelial cells from the fibroblast-depleted population and culturing the selected epithelial cell population in the presence of bone marrow stoma cells so that an enriched population of malignant cells is selected and propagated.

**Patent Status**

Unites States Patent application was filed April 12, 2006 US2006/0234374 A1

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