

Detection of Mutations in Heterogeneous Tissues (*James S. Goydos, CINJ 03-15*)

Diagnostic

Background

The detection of point mutations in genes from heterogeneous biological samples is often complicated by the presence of both mutated and wild type cells. Methods currently in use such as DNA chips, single strand conformation polymorphism (SSCP), and Denaturing Gradient Gel Electrophoresis (DGGE), are expensive, cumbersome, not amenable to high throughput analyses, and involve the performance of electrophoresis. Other methods such as immunohistochemistry and Western blotting approaches used to detect the mutant protein, although useful, require diagnostic antibodies. Thus, there is a long felt need for techniques that can rapidly distinguish a normal allele from a disease causing allele in a specific and sensitive manner. **The present invention relates to a diagnostic strategy for the detection of mutant alleles in heterogeneous tissue sample.**

Description of the Technology

UMDNJ researchers have developed a method to detect point mutations in genes derived from heterogeneous biological samples containing both mutated and wild type cells. Normally, point mutations introduce new restriction site(s) in genes, which could then be identified using restriction enzymes that cut PCR products at specific sites of the DNA. Thus, the ability to detect these mutations depends on the presence of restriction sites within the site of mutation. However, the three most commonly found point mutations (Q61K, Q61R N-Ras and V599E B-Raf) in the N-Ras and B-Raf components of the MAPK pathway do not introduce restriction sites. Based on this observation, a strategy that introduces restriction sites via site directed mutagenesis has been developed to enable the detection of as low as 100 copies/ μ l of the mutant mRNA

Applications

- For the diagnosis of cancers and genetically determined diseases.
- For the screening of disease carriers.
- To predict patient outcome and plan therapy.

Patent Status

United States Provisional Patent application filed

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

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.

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

A Novel Gene Associated with Glioblastoma (*Randall D. McKinnon, RWJ 02-18*)
Diagnostic/Therapeutic Target

Background

The most malignant and common of brain tumors, Glioblastoma multiforme (GBM), has a median survival of less than one year. Despite extensive research the etiology of GBM remains unknown, there are few reliable molecular or genetic markers, and diagnosis is based on histopathology with many limitations. Since GBM is highly infiltrative surgery removes only part of the tumor, while the efficacy of radiotherapy and chemotherapy is limited by quiescent tumor cells that escape treatment. The classification of gliomas including GBM is difficult under current guidelines and available markers. Several tumor suppressor genes have been implicated in malignant glioma progression, but specific genes or gene products have not been identified to date. **The current invention identifies a novel gene product with applications in the diagnosis and potential for therapeutic treatment of malignant brain tumors including GBM.**

Description of the Technology

We have identified an expressed sequence tag (EST) that is a molecular marker for the classification of malignant glioma and GBM, with potential application to assess and quantify a candidate's risk of progression into the malignant phenotype. Based on the analysis of RNA transcripts elevated during rodent glioblast transformation, a novel gene has been identified that is associated with glioblast immortalization, an early step in the progression of malignant glioma. Subsequent analysis of the human homologue of this gene, termed GliTEN, mapped it to chromosome 10 locus q25, a site of common genetic rearrangements in malignant gliomas and GBM. The potential role of GliTEN in tumor progression suggests it may provide a molecular target for therapeutic intervention in malignant glioma progression.

Applications

- To enable diagnosis and classification of brain tumors including GBM
- To identify patients at risk for progression into malignant phenotype
- To develop diagnostic kits to detect GliTEN mRNA.
- To generate therapeutic or diagnostic monoclonal antibodies
- To generate therapeutic RNAi vectors for gene therapy

Patent Status

United state patent application and a CIP on the full length GliTEN gene.

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

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

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

Hematopoietic Growth Factor Inducible Neurokinin-1 Gene (*Pranela Rameshwar, NJMS 00-31*) 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.

Deliverables

- Sequence of HGFIN; Vectors and Expression Systems; Purified Protein

Patent Status

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

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

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

Deliverables

- Expression vectors; Purified protein; Polyclonal antibody

Patent Status

United States patent application filed

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

Novel 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 Ca²⁺-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 Ca²⁺ 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

Licensing Opportunity

This technology is available for exclusive license.

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

Human Preprotachykinin-I Gene Promoter (*Pranela Rameshwar, NJMS 97-16*)
Diagnostic/Therapeutic Target

Background

Neurokinins belong to a family of receptors known to bind neurotransmitters, tachykinins, with different affinities and mediate a range of physiological functions such as neurotransmission, hematopoietic homeostasis, angiogenesis, cell transformation and immune modulation. The Preprotachykinin-I (PPT-I) gene encodes the tachykinin family of neurotransmitters. Further, PPT-I gene has been shown to be over-expressed in breast and other endocrine cancers that metastasize to the bone marrow. Since tachykinins are involved in the maintenance of homeostasis and neoangiogenesis, imbalance in SP and NK-A can lead to tumor metastasis. **The present invention relates to the use of PPT-I as a novel target in the development of therapies and diagnostics for a multitude of diseases.**

Description of the Technology

Using vectors and expression systems containing promoter regions involved in transcription for the PPT-I, NK-2 and SP-R genes, a role for PPT-I encoded gene products and corresponding receptors, in breast cancer has been established. Certain mutations in the promoter region that could be associated with breast cancer and breast cancer metastasis have been identified. Knock-out and knock-in studies with breast cancer cells revealed that PPT-I is important in cell transformation and also in having a central role in the integration of cancer cells as part of the bone marrow microenvironment. The present invention provides vectors with PPT-I promoter regions and receptor genes NK-1 and NK-2; deletion mutants; expression systems; vectors containing RNAi for PPT-I, NK-1 or NK-2; knock-in and knock-out breast cancer cell lines.

Applications

- For development of therapeutic and diagnostic applications in cancer and hematopoietic diseases
- For the development of small molecules, antisense molecules, antibodies, peptide or proteins for therapeutic interventions in the treatment of cancers, inflammatory diseases, neurological disorders, and hematopoietic diseases.

Patent Status

United States patent application filed.

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

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

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu

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

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.

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

University of Medicine and Dentistry of New Jersey

335 George Street, New Brunswick, NJ 08901

Direct Phone: (732)-235-9355 Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu