



Office of Patents and Licensing DRUG TARGETS

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Novel Class of Compounds to Control Chronic Hepatitis C Virus (Dr. Neerja Kaushik-Basu, 06-49 UMDNJ) *Therapeutic*

Background

Chronic Hepatitis C virus (HCV) infection is the leading cause of severe hepatitis that often progresses to cirrhosis, stasis, and hepatocellular carcinoma. Current therapies against HCV are limited in efficacy and have adverse side effects thus necessitating the development of new antiviral agents against this pathogen. The HCV RNA-dependent RNA polymerase (NS5B) is the key enzyme involved in the replication of the viral genome is unique to the virus and therefore represents an attractive target for drug development. **The present technology relates to a discovery of a novel class of compounds to control chronic Hepatitis C virus by inhibiting its replication.**

Description of the Technology

Researchers at UMDNJ have identified a class of compounds capable of inhibiting HCV NS5B. This has been shown utilizing a purified, functionally active recombinant NS5B in *in vitro* RNA dependent RNA polymerase (RdRp) activity of HCV NS5B on homopolymeric poly rA-U12 template primer. UMDNJ researchers have addressed the mechanism of inhibition by these compounds and identified that they compete with the template-primer in order to inhibit NS5B RdRp activity. In addition to inhibiting the HCV replicase, this family of compounds can potentially inhibit other RNA-dependent RNA/DNA polymerases of viral origin such as HIV-1RT, BVDV NS5B, Poliovirus RdRp, etc. Further studies are under way utilizing cell cultures and animal models.

Applications

- For the treatment of chronic Hepatitis C viral infection

Patent Status

United State provisional patent application filed

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A novel class of nuclear receptor co-repressors and their uses (*Tsai, RWJ 06-03*)
Therapeutic Target

Background

Nuclear receptors (NRs) comprise one of the largest known families of transcription factors. NRs regulate many processes during development and in normal physiology. In insects, NRs such as the ecdysone receptor control the molting and metamorphic processes. Aberrant NR signaling causes a variety of endocrine disorders, metabolic diseases and cancer. The majority of identified NRs are orphan, without a known ligand. A major function of NRs is transcriptional repression. This repression is mediated by co-repressors of the SMRT/N-CoR/SMRTER protein family.

Description of Technology

A novel class of closely related proteins was identified that acts as NRs co-repressors. The interactions between these new co-repressors and several NRs are sensitive to treatment with native or synthetic hormones, both agonists and antagonists. Thus, these novel co-repressors proteins are ideal targets in identifying new ligands for various nuclear receptors involved in endocrine disorders, metabolic diseases and cancer.

Applications

- This new technology can be used to identify new pharmaceutical compounds with clinical utility in the treatment of human diseases cause by aberrant nuclear receptor signaling.
- This technology can also be used to screen for new pesticides with agricultural value.

Patent Status

United States Provisional Application for Patent was filed

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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*) 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.

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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

Deliverables

- Expression vectors; Purified protein; Polyclonal antibody

Patent Status

United States patent application filed

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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.

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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 overexpressed 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.

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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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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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A New Superfamily of Protein Kinases (Alexey G. Ryazanov, RWJ 97-28) Therapeutic Target

Background

The best-characterized superfamily of eukaryotic protein kinases is called the serine/threonine/tyrosine family of kinases. Members of this family share a similar structural organization in their catalytic domains. These kinases phosphorylate amino acid residues located in the loops or turns of their substrates. In prokaryotes, the histidine kinase superfamily has been described and is involved in signal transduction acting as sensor components. Recently, several protein kinases lacking homology with either superfamily of kinases has been reported. Among these, eukaryotic elongation factor-2 kinase (eEF-2), which specifically phosphorylates the elongation factor 2 and shows no homology to any of the well-known superfamily of kinases. Preliminary evidence suggests that eEF-2 kinase is up-regulated in human cancers. Thus, the unique structure of eEF-2 kinase makes it an ideal target for the development of inhibitors with potential use as therapeutic agents. The present invention discloses additional members of the novel superfamily of eukaryotic protein kinases. The discovery and characterization of this superfamily of kinases has both therapeutic and diagnostic implications for diseases associated with cell cycle progression and malignant transformation.

Description of the Technology

UMDNJ researchers have discovered a new superfamily of protein kinases related to eEF-2 kinase that lacks homology with either serine/threonine/tyrosine kinase or histidine kinase superfamily. The new superfamily of protein kinases phosphorylates α -helical regions of proteins instead of β -turns. Additionally, using a novel α -helical 16-amino acid peptide derived from the myosin heavy chain protein as a phosphorylation substrate, an assay has been developed that can be used in the high-throughput screen of inhibitors of protein kinases. These inhibitors can be used for the therapy of malignant transformations, including, but not limited to, cancers. The present technology provides gene sequence of eEF2, heart, melanoma, ch4 protein kinases; clones of eEF-2 kinase gene, assay for inhibitor screening of these protein kinases.

Applications

- For a high-throughput screen for inhibiting of the novel protein kinases
- For the design and development of diagnostic and therapeutic formulations to inhibit eEF-2 kinase activity

Patent Status

- US Pat No. 6,346,406 B1 issued on February 12, 2002

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Translational Control of Longevity (*Dr. Alexey Ryazanov, 04-27 RWJMS*) Therapeutic & Drug Target

Background

The progressive decrease in protein synthesis and degradation leading to an increase in the concentration of damaged proteins is one of the major factors controlling aging. Thus, by regulating the rate of protein turnover, the rate of aging can be modulated. The present invention relates to increasing the life span in mice by modulating the function of eukaryotic elongation factor 2 (eEF-2) kinase, a negative translational regulator that phosphorylates and inactivates elongation factor-2. eEF-2 kinase is regulated by IGF-1/mTOR pathway and plays a role in the control of rate of protein synthesis at the elongation stage.

Description of the Technology

Knockout mice lacking a functional eEF-2 kinase gene were generated to study the effect of loss of eEF-2 kinase activity on longevity. These mice were viable, lacked any phenotypic abnormalities and produced normal progeny. Interestingly, male mice exhibited a 30% (36.6 months) increase in life span compared to normal mice. Furthermore, the complete elimination of eEF-2 kinase was not required for extension of life span. Thus, downregulation of eEF-2 kinase could be used as a means to increase lifespan.

Advantages

- eEF2-kinase has no homology to the majority of eukaryotic protein kinases and is not required for viability
- Complete elimination of eEF-2 kinase is not essential for life span extension

Applications

- eEF-2 Kinase can be used as a target for the design of therapeutic reagents to overcome aging
- To retard aging

Patent Status

United States Provisional Patent application filed

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A novel class of mTOR inhibitors (Zheng, RWJ 06-34) Therapeutics/Drug Target

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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