DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Macrocyclic Grb2 SH2 Domain-Binding Inhibitors: New Anti-Cancer and Anti-Angiogenic Therapeutic Agents

Description of Technology: Growth factor receptor bound 2 (Grb2) SH2 domain is involved in signaling events leading to a variety of proliferative diseases including erb-2 dependent breast cancers and c-met dependent renal cancers. Inhibiting the Grb2 SH2 domain binding has great potential therapeutic utility in the treatment of certain cancers.

This technology discloses the design and synthesis of new macrocyclic inhibitors of Grb2 SH2 domain binding. More specifically, a simple synthetic approach using upper achiral junctions has been utilized that does not require complex stereoselective synthesis. These new series of compounds have synthetic advantage over similar macrocyclic compounds and retain good binding affinity towards Grb2 SH2 domain.

Applications and Modality: (1) New macrocyclic inhibitors of Grb2 SH2 domain binding; (2) New compounds have good binding affinity for Grb2 SH2 domain and can be potential anti-cancer and anti-angiogenic agents; (3) Utilization of simple achiral upper ring junctions that do not require complex stereoselective synthesis; (4) New compounds have synthetic advantage over more structurally complex inhibitors.

Market: (1) In 2006, receptor tyrosine kinase inhibitor drug sales were estimated at more than $1B dollars; (2) In 2006, cancer drug sales were estimated to be $25 billion.

Development Status: The technology is currently in the pre-clinical stage of development.

Inventors: Terrence R. Burke Jr. and Fa Liu (NCI)

Relevant Publications:

1. F Liu *et al.* Utilization of achiral alkenyl amines for the preparation of high affinity Grb2 SH2 domain-binding macrocycles by ring-closing metathesis. Org. Biomol. Chem. 2007;5:367–372.

2. N Atabey *et al.* Potent blockade of hepatocyte growth factor-stimulated cell motility, matrix invasion and branching morphogenesis by antagonists of Grb2 Src homology 2 domain interactions. J. Biol. Chem. 2001 Apr 27;276(17):14308–14314.

3. C–Q Wei *et al.* Macrocyclization in the design of Grb2 SH2 domain-binding ligands exhibiting high potency in whole cell systems. J. Med. Chem. 2003 Jan 16;46(2):244–254.

Patent Status: U.S. Provisional Application No. 60/867,307 filed 27 Nov 2006 (HHS Reference No. E–305–2006/0–US–01)

Licensing Status: Available for exclusive and non-exclusive licensing.

Licensing Contact: Adaku Madu, J.D.; 301/435–5560; *madua@mail.nih.gov*

Collaborative Research Opportunity: The National Cancer Institute Laboratory of Medicinal Chemistry is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize macrocyclic Grb2 SH2 domain-binding antagonists. Please contact John D. Hewes, Ph.D. at 301/435–3121 or *hewesj@mail.nih.gov* for more information.

Cyclic Phosphopeptide Inhibitors of Protein Phosphatase 2C Delta, Wip1

Description of Technology: Wip1 (PP2Cdelta or PPM1D) is a protein phosphatase 2C (PP2C) family member that negatively regulates the p38 MAP kinase pathway. By dephosphorylating p38 kinase, p38 is unable to activate the p53 pathway; this prevents p53-mediated cell-cycle arrest and apoptosis, suggesting that Wip1 overexpression and over-activity may have implications during oncogenesis. Significantly, Wip1 is overexpressed in several human cancers, including breast cancer, ovarian clear cell adenocarcinoma and neuroblastomas. Thus, inhibitors of Wip1 may have promise as anti-cancer therapeutics. Unfortunately, no specific inhibitors have been designed to show proof of this concept.

The instant technology involves the development of specific peptides for the inhibition of the Wip1 catalytic site. The inventors have modified the optimal Wip1 substrate sequence in such a manner that it successfully inhibits Wip1 activity. Importantly, the peptide effectively inhibited Wip1 without significantly affecting the activity of other PP2C family members. Thus, this compound has potential for examination as an anti-cancer agent.

Claims in this technology are directed to compositions comprising the Wip1 inhibitors, as well as methods of using the inhibitors to inhibit Wip1 activity in a cell.

Application: The inhibitors can be developed as anti-cancer therapeutics.

Market: The cancer therapeutic market is expected to reach $27 billion by 2009.

Development Status: The technology is at the pre-clinical stage. Optimization of the peptide sequence for delivery and efficacy, as well as the design of mimetics, are contemplated for further development.

Inventors: Ettore Appella, Stewart R. Durell, Hiroshi Yamaguchi, Yawen Bai (NCI), *et al.*

Publications:

1. H Yamaguchi *et al.* Substrate specificity of the human protein phosphatase 2Cdelta, Wip1. Biochemistry 2005 Apr 12;44(14):5285–5294.

2. DV Bulavin *et al.* Inactivation of the Wip1 phosphatase inhibits mammary tumorigenesis through p38 MAPK-mediated activation of the p16(Ink4a)-p19(Arf) pathway. Nat Genet. 2004 Apr;36(4):343–350.

3. H Yamaguchi *et al.* Development of substrate-based cyclic phosphopeptide inhibitor of protein phosphatase 2Cdelta, Wip1. Biochemistry 2006 Nov 7;45(44):13193–13202.

4. S Shreeram *et al.* Regulation of ATM/p53-dependent suppression of myc-induced lymphomas by Wip1 phosphatase. J. Exp. Med. 2006 Dec 25;203(13): 2793–2799.

Patent Status: U.S. Provisional Application No. 60/850,218 filed 06 Oct 2006 (HHS Reference No. E–288–2006/0-US–01) Licensing Status: Available for non-exclusive or exclusive licensing.

Licensing Contact: David Lambertson, PhD; 301/435–4632; *lambertsond@od.nih.gov*

Collaborative Research Opportunity: The NCI CCR, LCB is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize Cyclic Phosphopeptide Inhibitors of Protein Phosphatase 2C Delta, Wip1. Please contact John D. Hewes, Ph.D. at 301/435–3121 or *hewesj@mail.nih.gov* for more information.

New Tumor Endothelial Markers: Genes That Distinguish Physiological and Pathological Angiogenesis

Description of Technology: Angiogenesis, the formation of new blood vessels, is associated with normal physiological processes such as wound healing, ovulation or menstruation as well as with many diseases. Presently, it is thought to be required for the progressive growth of solid tumors and age-related macular degeneration. Lack of disease-specific endothelial markers has hindered the development of cancer therapies targeted against angiogenesis.

This invention describes specific markers that can be used to identify tumor angiogenesis, separate from normal physiological angiogenesis. Several markers have been identified which may serve as potential targets for tumor vessels by using comparative gene expression analysis on various normal and tumor endothelial cells. Furthermore, the invention describes several organ-specific endothelial markers that can aid in the selective delivery of molecular medicine to specific sites. For example, brain endothelial markers (BEMs) and liver endothelial markers (LEMs) described herein could potentially be used to direct molecular medicine specifically to these tissues.

The novel tumor endothelial markers (TEMs) described in this invention also have potential diagnostic ability. These markers can be used to distinguish between normal and tumor tissues. Some of the secreted TEMs can serve as surrogate markers in the determination of the optimum biological dose (OBD) for the current anti-angiogenic drugs in clinical trials.

Applications and Modality: (1) Novel therapeutic targets associated with tumor vessels; (2) New agents can be developed against these novel targets; (3) Novel endothelial markers that distinguish pathological angiogenesis from normal physiological angiogenesis; (4) Surrogate tumor endothelial markers that can be used to determine optimal biological dose (OBD) of anti-angiogenic drugs.

Market: (1) Sales of the first FDA approved anti-angiogenic drug Avastin™ has reached $600 million; (2) Another promising anti-angiogenic molecule, Thalidomide™, has been approved as an anti-cancer agent and for other use in Europe and Australia.

Development Status: The technology is currently in the pre-clinical stage of development.

Inventors: Brad St.Croix and Steven Seaman (NCI)

Relevant Publication: A Nanda and B St. Croix. Tumor endothelial markers: new targets for cancer therapy. Curr Opin Oncol. 2004 Jan;16(1):44–49.

Patent Status: U.S. Provisional Application No. 60/858,068 filed 09 Nov 2006 (HHS Reference No. E–285–2006/0-US–01) Licensing Status: Available for exclusive and non-exclusive licensing.

Licensing Contact: Adaku Madu, J.D.; 301/435–5560; *madua@mail.nih.gov*

Collaborative Research Opportunity: The NIH National Cancer Institute, Tumor Angiogenesis Section, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize specific biomarkers that can be used to identify tumor angiogenesis. Please contact John D. Hewes, PhD at 301/435–3121 or *hewesj@mail.nih.gov* for more information.

A New Method for Improving the Therapeutic Efficacy of L-Asparaginase in Multiple Types of Cancer

Description of Technology: For the last several decades, L-asparaginase (L-ASP) has been widely used as a clinical treatment for leukemias. Studies show that cancer cells that contain less asparagine synthetase (ASNS) are more susceptible to L-ASP. The response to L-ASP therapy is often better when the expression of ASNS is limited.

The present invention describes a new method for enhancing L-ASP activity by combining it with antagonists of ASNS—such as siRNAs, antisense nucleotides, antibodies or small-molecule inhibitors—for treatment of cancers. Reducing or suppressing the expression of ASNS potentiates the growth inhibitory activity of L-ASP.

Additionally, the invention discloses a novel biomarker screening tool to identify leukemia, ovarian, and other cancer patients that would be most likely to respond to L-ASP treatment.

Applications and Modality: A new method for improving the therapeutic efficacy of L-asparaginase.

ASNS antagonists such as siRNA, antibodies, antisense nucleotides, or small-molecule inhibitors can potentially be used in combination with L-ASP in the treatment of cancers.

ASNS gene or protein expression can serve as a therapeutic response biomarker for personalization of cancer therapy with the aforementioned combinations.

Market: There were more than 500,000 deaths from cancer in 2006. The current technology has the potential of being used in conjunction with L–ASP in treating cancer patients.

Oncaspar™, the PEG-derivitized L-ASP developed by Enzon Pharmaceuticals, registered annual sales of about $25 million in 2006, largely on the basis of treatment of acute lymphoblastic leukemia. The present invention may make L–ASP applicable to treatment of types of cancers that are much more common.

Development Status: The technology is currently in the pre-clinical stage of development. With respect to L–ASP treatment of patients with solid tumors, Phase I clinical trials have been initiated (Principal Investigator Daniel D. Von Hoff, TGen, Inc.) at three institutions using L–ASP in combination with gemcitabine.

Inventors: Philip L. Lorenzi, *John N. Weinstein* and *Natasha J. Caplen* (NCI)

Publication: PL Lorenzi *et al.* Asparagine synthetase as a causal, predictive biomarker for L-asparaginase activity in ovarian cancer cells. Mol Cancer Ther. Nov; 5(11):2613–2623. Epub 2006 Nov 6, doi 10.1158/1535–7163.MCT–06–0447.

Patent Status: U.S. Provisional Application No. 60/779,143 filed 03 Mar 2006 (HHS Reference No. E–132–2006/0–US–01); U.S. Provisional Application No. 60/833,027 filed 25 Jul 2006 (HHS Reference No. E–132–2006/0–US–02).

Licensing Status: Available for exclusive and non-exclusive licensing.

Licensing Contact: Mojdeh Bahar, J.D.; 301/435–2950, *baharm@mail.nih.gov*

Collaborative Research Opportunity: The National Cancer Institute's Genomics & Bioinformatics Group in the Laboratory of Molecular Pharmacology is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the combination therapies described in this abstract. Please contact John D. Hewes, Ph.D. at 301/435–3121 or *hewesj@mail.nih.gov* for more information.

Dated: November 8, 2007.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

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