that refers to that listed drug may be approved. FDA may not approve an ANDA that references a listed drug that the agency has determined was withdrawn for reasons of safety or effectiveness (§ 314.127(a)(11)).

CERNEVIT–12 (multivitamins for infusion) is the subject of NDA 20–924, held by Baxter Health Corp. (Baxter). FDA approved the NDA on April 6, 1999, as an application under section 505(b)(2) of the act (21 U.S.C. 355(b)(2)), relying in part upon literature and the agency's prior findings of safety and efficacy for a listed parenteral multivitamin drug product. CERNEVIT–12 (multivitamins for infusion) is indicated as a daily multivitamin maintenance dosage for adults and children age 11 years and older receiving parenteral nutrition, and for situations in which administration by the intravenous route is required.

Adult parenteral multivitamin drug products were reviewed for efficacy under the Drug Efficacy Study Implementation (DESI) program. Under this program, implemented in response to the 1962 amendments to the act requiring demonstration of effectiveness (The Kefauver-Harris Amendments, Public Law No. 87–781 (1962)), the National Academy of Sciences-National Research Council (NAS-NRC) undertook a study of some 4,000 drug formulations for the express purpose of assessing the efficacy of the products. Upon consideration of the findings and recommendations of the NAS-NRC, FDA set forth in the **Federal Register** its conclusions and assessment of whether and under what circumstances a drug product is considered "effective" for use as required by the act.

In the initial DESI notice of July 27, 1972, addressing parenteral multivitamin preparations, FDA announced its conclusion that parenteral multivitamin preparations as then formulated lacked substantial evidence of effectiveness because they did not contain certain essential vitamins, or they contained certain vitamins in doses that were too high or too low (37 FR 15027, July 27, 1972). Because of the critical medical importance of these preparations and the lack of alternative drug products, FDA notified manufacturers and distributors of parenteral multivitamin products in December 1972 that the agency would allow these products to remain on the market pending the development and testing of new formulations and the resolution of complex technical and medical issues (37 FR 26623, December 14, 1972).

On September 17, 1984, FDA announced the parenteral multivitamin formulations the agency had determined to be effective and the conditions for marketing those products (49 FR 36446, September 17, 1984). The agency subsequently modified the conditions for marketing an effective adult parenteral multivitamin drug product in 2000 (65 FR 21200, April 20, 2000). In that "upgrade" notice, FDA announced several changes to the product formulation including increases in the dosage amounts of Vitamins B_1, B_6, C, and folic acid, and amended portions of the "Conditions for Marketing and Approval" for parenteral multivitamin products set forth in the September 17, 1984, notice to reflect the changes (Id. at 21201).

In the **Federal Register** of August 18, 2003, FDA announced that it was withdrawing approval of NDA 20–924 in response to Baxter's withdrawal request dated December 18, 2002 (68 FR 49481, August 18, 2003). As a result, CERNEVIT–12 (multivitamins for infusion) was moved to the "Discontinued Drug Product List" section of the Orange Book.

Strides Arcolab Limited submitted a citizen petition under § 314.161(b) of the regulations (Docket No. FDA–2009–P–0318) requesting that FDA determine whether the NDA for CERNEVIT–12 (multivitamins for infusion) had been withdrawn from sale for reasons of safety or effectiveness. After considering the citizen petition and reviewing agency records, FDA has determined that CERNEVIT–12 (multivitamins for infusion) was withdrawn from sale for reasons of safety or effectiveness.

Specifically, we have carefully reviewed our files for records concerning the withdrawal of CERNEVIT–12 (multivitamins for infusion), including the NDA file for this product. We also have independently evaluated relevant literature and data for possible postmarketing adverse event reports. Agency records did not contain any clinical reviews describing safety issues associated with CERNEVIT–12 (multivitamins for infusion), and postmarketing safety reports did not raise any safety concerns.

FDA has determined, however, that CERNEVIT–12 (multivitamins for infusion) was not reformulated to comply with the April 20, 2000, **Federal Register** upgrade notice before it was withdrawn from the market. As described in that notice, adult parenteral multivitamin drug products must contain higher doses of Vitamins B_1, B_6, C, and folic acid than the dosages contained in CERNEVIT–12 (multivitamins for infusion) (65 FR 21201).

Because CERNEVIT–12 (multivitamins for infusion) is not in compliance with current FDA standards for adult parenteral multivitamin drug products, the agency has determined under § 314.161 that CERNEVIT–12 (multivitamins for infusion) was withdrawn from sale for reasons of safety or efficacy. (57 FR 17950 at 17956, April 28, 1992) ("if the NDA or ANDA holder fails to comply with [the DESI upgrade] notice, the NDA or ANDA product is not considered to be approved for effectiveness and cannot be a listed drug"). The Discontinued Drug Product List delineates, among other items, products that have been discontinued from marketing for reasons other than safety or effectiveness. Therefore, CERNEVIT–12 (multivitamins for infusion) will be removed from the Discontinued Drug Product List section of the Orange Book (§ 314.162(a)(2)). In addition, FDA will not accept or approve ANDAs that refer to CERNEVIT–12 (multivitamins for infusion) (21 CFR 314.127(a)(11)).

Dated: March 11, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–5748 Filed 3–16–10; 8:45 am]

BILLING CODE 4160–01–S

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.

Caspase Inhibitors Useful for the Study of Autoimmune or Inflammatory Diseases

Description of Invention: Novel and potent caspase 1 inhibitors are available for licensing. In particular, this technology discloses potent and selective caspase 1 inhibitors that target the active site of the enzyme. Caspase 1 is known to play a pro-inflammatory role in numerous autoimmune and inflammatory diseases and therefore represents an excellent target for treatment of a broad range of diseases, including but not limited to Huntington's, amyotrophic lateral sclerosis, ischemia, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, and sepsis. Not surprisingly this enormous potential has resulted in at least three caspase 1 inhibitors entering clinical trials (VX–740, IDN–6556, and VX–765) in recent years.

Applications

• Potential therapeutic for a broad range of autoimmune diseases.

• Potential therapeutic for a broad range of inflammatory diseases.

Development Status: Early stage.

Market: The market size is potentially very large. For instance, rheumatoid arthritis alone affects 1% of the population, or about 2.5–3 million Americans. Further, it is estimated that osteoarthritis affects at least 16 million people in America.

Inventors: Craig J. Thomas and Matthew B. Boxer (NHGRI).

Publication: Boxer MB, Quinn AM, Shen M, Jadhav A, Leister W, Simeonov A, Auld DS, Thomas CJ. A highly potent and selective caspase 1 inhibitor that utilizes a key 3-cyanopropanoic acid moiety. Chem Med Chem., accepted.

Patent Status: U.S. Provisional Application No. 61/299,790 filed 29 Jan 2010 (HHS Reference No. E–308–2009/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Steve Standley, PhD; 301–435–4074; *sstand@od.nih.gov.*

Collaborative Research Opportunity: The NIH Chemical Genomics Center is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize appropriate lead compounds described in U.S. Provisional Application No. 61/299,790. Please contact Dr. Craig J. Thomas via e-mail (*craigt@nhgri.nih.gov*) for more information.

Defensin-Based Therapeutics for the Treatment of Pulmonary Disease

Description of Invention: Investigators at the National Heart, Lung and Blood Institute have developed modified defensins that are resistant to degradation, have improved characteristics compared to unmodified defensins, and are promising candidates for pulmonary disease therapeutics.

Defensins are small cationic peptides that defend the lung against pathogenic microorganisms and play an important role in innate immunity. However, during lung inflammation, defensin concentrations can reach levels that are cytotoxic for airway epithelial cells. Therefore, the development of methods to produce modified defensins that exhibit reduced cytotoxicity, while retaining the ability to stimulate the innate immune response, would be of potential therapeutic benefit for pulmonary diseases.

The inventors have previously shown that a defensin, human neutrophil peptide 1 (HNP–1), is elevated in samples from the lungs of patients with inflammatory lung disease, and that the HNP–1 in these samples is ADP-ribosylated at one or both of two arginine residues within the protein. *In vitro* studies by the inventors show that ADP-ribosyl-HNP–1 has reduced cytotoxic activity compared to HNP–1, while retaining its T cell chemotactic properties and ability to promote neutrophil recruitment, and thus ADP-ribosyl-HNP–1 may play an important role as a regulator of the inflammatory response. These properties would also be useful for treatment of pulmonary inflammation and lung diseases. However, ADP-ribosylated HNP–1 and other defensins are degraded rapidly in vivo due to the susceptibility of the ADP-ribose moiety to attack by hydrolases and pyrophosphatases, which limits their therapeutic potential.

The inventors have recently discovered that the ADP-ribosylated arginine residues in HNP–1 can be converted to ornithine through a non-enzymatic process that results in a peptide with an altered pharmacological profile. The investigators have also successfully generated ornithine-substituted ADP-ribosyl HNP–1 and ornithine-HNP–1 in vitro, which are currently being characterized. Thus, ornithine-substituted ADP-ribosyl HNP–1 and ornithine-HNP–1 may be promising candidates for the development of therapeutics to treat pulmonary disease, and the strategy of replacing ADP-ribosylated residues with ornithine to enhance stability and therapeutic efficacy may also be extended to other defensins

Through an earlier, related invention, the inventors have also demonstrated that recombinant proteins wherein tryptophan or phenylalanine residues substitute for ADP-ribosylarginine have a similar stabilizing impact on polypeptides, making them more suitable as therapeutic agents.

The inventors also hypothesize that it would be possible to develop a treatment that increases levels of an ADP-ribosylated therapeutic protein, such as HNP–1, in the lung via inhalation administration of the therapeutic protein in conjunction with nicotinamide adenine dinucleotide (NAD), which is required for ADP-ribosylation. This could represent a unique therapeutic strategy for treating pulmonary disease.

Applications: Development of defensin-based therapeutics that enhance the immune response in pulmonary disease patients, without damaging the epithelial cells lining the airway.

Advantages

Modified defensins are less cytotoxic, while retaining ability to stimulate innate immunity.

Ornithine-substituted defensins are resistant to enzymatic degradation, making them more promising as drug candidates.

Development Status: In vitro studies, as well as analysis of patient samples, have been performed.

Inventors: Joel Moss et al. (NHLBI).

Relevant Publication: Stevens LA, Levine RL, Gochuico BR, Moss J. ADP-ribosylation of human defensin HNP–1 results in the replacement of the modified arginine with the noncoded amino acid ornithine. Proc Natl Acad Sci U S A. 2009 Nov 24;106(47):19796–19800. [*PubMed:* 19897717.]

Patent Status: U.S. Provisional Application No. 61/241,311 filed September 10, 2009 (HHS Reference No. E–243–2009/0–US–01).

Related Technologies

• HHS Reference No. E–080–2002/0, "Modified Defensins and Their Use."

• HHS Reference No. E–160–2002/0, "Tryptophan as a Functional Replacement for ADP-ribose-arginine in Recombinant Proteins."

Licensing Status: Available for licensing.

Licensing Contact: Tara Kirby, PhD; 301–435–4426; tarak@mail.nih.gov.

Collaborative Research Opportunity: The National Heart, Lung and Blood Institute Translational Medicine Branch is seeking statements of capability or

interest from parties interested in collaborative research to further develop, evaluate, or commercialize defensin-based therapeutic agents to treat pulmonary diseases. Please contact Brian W. Bailey, PhD at 301–494–4094 or *bbailey@mail.nih.gov* for more information.

HTLV–II Vector and Methods of Use

Description of Invention: The invention hereby offered for licensing is in the field of vaccines and vaccine vectors. More specifically the invention provides compositions and methods of use of HTLV–II viral vector. The vector comprises at least a portion of the HTLV–II genome encoding the gag, pro, and pol genes and lacking all or a portion of the pX region. A heterologous gene is inserted within the deletion of the pX region. The gene of interest may encode all or a portion of a protein that corresponds to a viral protein of a foreign virus. The viral vectors thus constructed are useful for inducing immune response to the viral protein from the foreign virus. In particular the invention claims vaccines against HIV and SIV.

Applications: The technology can be used for DNA-based vaccines.

Advantages

• Vaccines based on HTLV–II vectors have exhibited the capability to eliciting T cell response effectively. In particular they induce specific CD4+ and CD8+ T cell response. Antibody response to the HTLV–II vector is almost undetectable. The vector is infectious, but highly attenuated, with respect to the wild type HTLV–II. Desirably, the HTLV–II viral vector induces antibodies that can participate in Antibody-Dependent-Cell-Mediated Cytotoxicity (ADCC), a mechanism that enhances its effectiveness.

• Most of the T-cell vaccines developed for HIV are based on microbial vectors that have limited replication capacity and do not persist in the host. Such vaccines do not protect macaques from SIV infection and their ability to protect against high virus load is merely transient (approximately six months). They are perceived to elicit too "small T-cell responses" that expand "too late". In addition, few of these vectors target mucosal sites, the first portal of HIV entry. In contrast, an HTLV II based vaccine is anticipated to infect macaques and replicate at very low level in lymphoid tissue and particularly in the gut which may enable them to maintain sufficient level of effectors CD8 memory cells to decrease early seeding of the virus, and sufficient level of central memory cells in lymph nodes that may limit the broadcasting of the virus at distal sites. These features make an HTLV–II based vaccine for HIV an excellent unique candidate to target mucosal tissues and provide long lasting mucosal immunity to HIV. In addition, the HTLV II infects dendritic cells both in vivo and in vitro, and the HTLV II infected dendritic cells have a mature phenotype, suggesting that HIV antigens expressed within dendritic cells could be effectively presented to the immune system.

• HTLV II is a human retrovirus with no clear disease associations neither in healthy nor in HIV infected individuals

• HTLV shares many biological and molecular characteristics of HIV, including routes of transmission, a T-cell tropism and gut tropism.

• Based on the above, it is believed that HIV vaccines based on HTLV II vector will exhibit superiority compared to other vaccines in development.

Development Status: At the present only in vitro as well as animal (macaques) data that demonstrate the proof of concept are available. The data indicates that an HTLV II based vaccine could replicate in the appropriate body compartment and confer immunity in humans. The inventors continue to work on the development of this approach.

Market: In spite of major global efforts of more than 25 years in developing a vaccine against HIV/AIDS, such a vaccine is still not in existence but yet very much needed for the fight against the global epidemic of HIV/AIDS. The market for HIV/AIDS drugs is currently at the level of approximately $6 billion a year and is expected to grow to $13 billion by the year 2015. Should an effective vaccine be developed the market for such a vaccine may exceed this level. The instant technology may offer superiority to existence approaches in the area of HIV vaccines and thus a huge commercial opportunity for pharmaceutical/vaccine enterprises as well as a major contribution for global public health.

Inventors: Genoveffa Franchini *et al.* (NCI).

Publications: Paper in preparation.

Patent Status: PCT Application No. PCT/US2009/051138 filed 20 Jul 2009, which published as WO 2010/009465 on 21 Jan 2010 (HHS Reference No. E–269–2008/1–PCT–01).

Related Technologies: RhCMV SIV vaccine (Picker *et al.*)

Licensing Status: Available for licensing.

Licensing Contact: Susan Ano, PhD; 301–435–5515; *anos@mail.nih.gov.*

Collaborative Research Opportunity: The National Cancer Institute, Animal Models & Retroviral Vaccine Section, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize HTLV–II vectored HIV vaccines. Please contact John D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Prevention and Treatment of Cancer With Kinase Inhibitors Targeting the PH Domain of AKT

Description of Invention: Activation of the PI3K/Akt signaling pathway has been implicated in the development of cancer. Akt, a kinase that is central to this pathway, is found at elevated levels in many tumors and is associated with a poor disease prognosis. Further research has validated Akt as a therapeutic target for the development of anti-cancer drugs. Most efforts of drug development targeting Akt have focused on inhibitors of the ATP-binding domain which have the drawback that they interfere with other physiologically important kinases. This is reflected in that no Akt inhibitors have been clinically approved. However, investigators at the National Institutes of Health (NIH) and Georgetown University (GU) have developed an alternative strategy that improves Akt specificity by targeting the unique pleckstrin homology (PH) domain of Akt.

Scientists at NIH and GU have discovered several lipid-based inhibitors of Akt called phosphatidylinositol ether lipid analogues (PIAs) that target the pleckstrin homology (PH) domain of Akt. These PIAs, which are analogues of the products of phosphatidylinositol 3-kinase (PI3K), inhibit Akt within minutes and selectively kill cancer cells that contain high levels of Akt activation. The mechanism of action of these compounds has been intensively studied providing much insight into how PIAs inhibit the growth of cancer cells. In addition, several molecular targets have been identified that highly correlate with cancer cell sensitivity to PIA that potentially could serve as clinical biomarkers predictive of responsiveness to PIAs. U.S. and Australian patents issued for this invention have composition and method of use claims.

Applications

• Treating or preventing development of cancer or preventing progression of premalignant lesions to cancer.

• Used as single agents or in combination with other anti-cancer treatments like chemotherapy, biological therapy, or radiation.

Advantages: Targeting the PH domain improves specificity against Akt kinase in comparison to inhibitors of the ATP domain which typically are unspecific.

Inventors: Phillip A. Dennis (NCI) *et al.*

Relevant Publications

1. Memmott RM, Gills JJ, Hollingshead M, Powers MC, Chen Z, Kemp B, Kozikowski A, Dennis PA. Phosphatidylinositol ether lipid analogues induce AMP-activated protein kinase-dependent death in LKB1-mutant non small cell lung cancer cells. Cancer Res. 2008 Jan 15;68(2):580–588. [*PubMed:* 18199555.]

2. Gills JJ, Castillo SS, Zhang C, Petukhov PA, Memmott RM, Hollingshead M, Warfel N, Han J, Kozikowski AP, Dennis PA. Phosphatidylinositol ether lipid analogues that inhibit AKT also independently activate the stress kinase, p38alpha, through MKK3/6-independent and -dependent mechanisms. J Biol Chem. 2007 Sep 14;282(37):27020–27029. [*PubMed:* 17631503.]

3. Gills JJ, Holbeck S, Hollingshead M, Hewitt SM, Kozikowski AP, Dennis PA. Spectrum of activity and molecular correlates of response to phosphatidylinositol ether lipid analogues, novel lipid-based inhibitors of Akt. Mol Cancer Ther. 2006 Mar;5(3):713–722. [*PubMed:* 16546986.]

4. Carón RW, Yacoub A, Li M, Zhu X, Mitchell C, Hong Y, Hawkins W, Sasazuki T, Shirasawa S, Kozikowski AP, Dennis PA, Hagan MP, Grant S, Dent P. Activated forms of H–RAS and K–RAS differentially regulate membrane association of PI3K, PDK–1, and AKT and the effect of therapeutic kinase inhibitors on cell survival. Mol Cancer Ther. 2005 Feb;4(2):257–270. [*PubMed:* 15713897.]

5. Castillo SS, Brognard J, Petukhov PA, Zhang C, Tsurutani J, Granville CA, Li M, Jung M, West KA, Gills JG, Kozikowski AP, Dennis PA. Preferential inhibition of Akt and killing of Akt-dependent cancer cells by rationally designed phosphatidylinositol ether lipid analogues. Cancer Res. 2004 Apr 15;64(8):2782–2792. [*PubMed:* 15087394.]

6. Kozikowski AP, Sun H, Brognard J, Dennis PA. Novel PI analogues selectively block activation of the pro-survival serine/threonine kinase Akt. J Am Chem Soc. 2003 Feb 5;125(5):1144–1145. [*PubMed:* 12553797.]

Patent Status: U.S. Patent No. 7,378,403 issued 27 May 2008 (HHS Reference No. E–245–2002/0–US–03), and related international filings.

Licensing Status: Available for licensing.

Licensing Contact: Surekha Vathyam, PhD; 301–435–4076; *vathyams@mail.nih.gov.*

Dated: March 10, 2010.

Richard U. Rodriguez,

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

[FR Doc. 2010–5764 Filed 3–16–10; 8:45 am]

BILLING CODE 4140–01–P

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.

Spontaneously Transformed Mouse Epithelial Cancer Cell Lines Serving as Mouse Models: A New Model for Cancer Research

Description of Invention: Investigators at the NIH have created a collection of 45 mouse epithelial cancer cell lines derived from six organs: Bladder, cervix, colon, lung, kidney, and mammary glands. These cells lines were obtained from spontaneously transformed primary cell cultures without genetic, viral or chemical manipulation so they can serve as mouse models for studying the natural process of oncogenesis.

The cell lines were characterized cytogenetically during their transformation from normal to spontaneously immortalization and were found to recapitulate many of the changes observed in human cancer cells such as the deregulation of oncogenes (Myc, Mdm2) and tumor suppressor genes (Cdnk4a/Ink4a/p16, Rb).

Carcinomas that arise from the epithelial cells lining organs lead to the most common cancers in humans. However, research on cellular transformation has largely relied on fibroblast cells which are not of epithelial origin and therefore, may not reflect the changes that lead to epithelial oncogenesis. The availability of these mouse epithelial cancer cell lines should allow for a more accurate analysis of this process.

Applications: These cell lines serve as "ideal" murine tumor models as they show evidence of progression, permitting analysis of the genetic and biological changes observed in the equivalent human carcinomas and associated with tumor progression. Their tumor histology is comparable to human cancers.

The cell lines have unique properties that make them suitable for study of the following:

• Unlimited replicative potential.

• Exhibit tumorigenic potential and EMT (Epithelial Mesencymal Transition).

• Exhibit high degree of chromosome instability (chromosome rearrangements, amplifications) in regions orthologous to those altered in human cancers.

• Use in mapping mouse genes homologous to human cancer genes and for the study of the effects of deregulation of cancer associated genes, through silencing or overexpression.

• For use in gene expression studies of tumor progression, comparing profiles to human cancers involving the same tissue types.

• Use as experimental controls in the analysis of oncogene signaling pathways.

• Use in the studying telomerase pathway regulation (200-fold expression difference between cell lines).

• Use of mouse as model of epithelial carcinomas and specifically cancers of the bladder, cervix, colon, lung, mammarys and kidney cancers.

• These mouse models serve as vehicles to test the efficacy of new therapies, targeting specific targets associated with the transformation of six different mouse epithelial tissues.