Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (§ 314.162 (21 CFR 314.162)). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

Cysteine HCl is the subject of NDA 19–523, most recently held by Hospira, Inc. (Hospira), and initially approved on October 22, 1986. Cysteine HCl is indicated for use as an additive to amino acid solutions to meet the nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN. It can also be added to amino acid solutions to provide a more complete profile of amino acids for protein synthesis. Hospira notified FDA in a letter dated May 26, 2005, that it had not commercially manufactured and marketed Cysteine HCl, and voluntarily asked that the NDA be withdrawn. The drug product was moved to the "Discontinued Drug Product List" section of the Orange Book, and FDA withdrew approval of NDA 19–523 effective June 16, 2006 (71 FR 34940). In previous instances (see, e.g., 74 FR 63404, December 3, 2009; 72 FR 9763, March 5, 2007; 61 FR 25497, May 21, 1996), the agency has determined that, for purposes of §§ 314.161 and 314.162, never marketing an approved drug product is equivalent to withdrawing the drug from sale. Regulus Pharmaceutical Consulting, Inc., submitted a citizen petition, dated April 30, 2008 (Docket No. FDA–2008–P–0278), under 21 CFR 10.30, requesting that the agency determine whether Cysteine HCl was withdrawn from sale for reasons of safety or effectiveness.

FDA has reviewed its records and, under § 314.161, has determined that Cysteine Hydrochloride Injection, USP, 7.25%, was not withdrawn for reasons of safety or effectiveness. We have also independently evaluated relevant literature and have found no information that would indicate that this product was withheld from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list Cysteine Hydrochloride Injection, USP, 7.25%, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to Cysteine Hydrochloride Injection, USP, 7.25% may be approved by the agency if all other legal and regulatory requirements for the approval of ANDAs are met. If FDA determines that the labeling for this drug product should be revised to meet current standards, the agency will advise ANDA applicants to submit such labeling.

Dated: May 27, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–13463 Filed 6–3–10; 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 United States 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.

888-mel: A Target for Anti-Tumor Immune Responses

Description of Invention: Scientists at the National Institutes of Health (NIH) have developed a human melanoma cell line designated 888-mel from the resected tumor of a 26-year old Caucasian female (patient 888) diagnosed with metastatic melanoma, a frequently terminal cancer. The 888-mel cell line was derived from three separate subcutaneous melanoma lesions on the patient and possesses many characteristics representative of melanoma cell lines developed by these researchers. Most prominently, the 888-mel cell line was used to develop a tumor infiltrating lymphocyte (TIL) culture with high affinity for the tumor cells of patient 888. When the TIL 888 culture was provided as an autologous adoptive immunotherapy treatment to patient 888 in combination with interleukin-2 (IL–2), a complete remission of subcutaneous, lung, and mucosal metastases was observed in the patient for over three years.

Since this medical breakthrough, the 888-mel cell line has been well characterized through various laboratory procedures and data involving this cell line has been published as part of numerous articles. Studies have shown that the cell line expresses a variety of tumor associated antigens (TAAs), including tyrosinase, TRP1, TRP2, gp100, MART–1, p15, gp75, mutated beta-catenin, and p53. However, 888-mel does not normally express the MAGE 1, 2, or 3 TAAs. Many melanoma cell lines are HLA–A2 restricted, but the 888-mel cell line is HLA–A2 negative. The HLA class I typing for this cell line is as follows: HLA–A0101, A2402, B55, B62, Cw5201, Cw55, DRbl*1502, DRbl*1610, DQbl*0601, DRb5*0102, DRb5*0203. 888-mel is a validated source of HLA class I peptides utilized in screens that test the reactivity of TIL cultures that are candidates for adoptive immunotherapy trials. 888-mel is also a standard cell line for studying immune responses in cancer, particularly T cell responses. Other experiments show that roscovitine, a cyclin-dependent kinase inhibitor, can induce apoptosis in the 888-mel cell line, so these cells may be useful in various cell death studies.

Applications

• Research tool for investigating the key immune responses required to mediate the remission of metastatic melanoma in order to identify the immune cell types necessary to produce an effective immunotherapy.

• Research tool for investigating the tumor associated antigens that contribute to the dampening of the immune response in many melanoma tumors so that researchers can better understand how to boost immunogenicity against these antigens.

• Source material for tumor associated peptides that could serve as melanoma vaccine candidates or utilized to determine the reactivity of tumor infiltrating lymphocyte (TIL) cultures being considered for clinical trials.

• Source material for the development of TIL cultures for use in adoptive immunotherapy protocols to treat melanoma patients.

Advantages

• *Cell line is derived from a melanoma patient that underwent complete tumor remission:* Immune cell cultures capable of treating melanoma patients in adoptive immunotherapy protocols could be derived from the tumor associated antigen epitopes found on the 888-mel cell line. This cell line may be a source of novel antigenic peptides capable of triggering immune responses in melanoma patients that lead to tumor regression or stabilization. 888-mel cells have been shown to retain many features of primary melanoma samples, including the expression of common tumor associated antigens.

• *888-mel is an HLA–A2 negative cell line:* A majority of the cancer vaccines and immunotherapies developed to date have focused on utilizing HLA–A2 restricted tumor epitopes since this HLA allele is largely expressed in the human population. However, therapies restricted to HLA–A2 recognition will not be successful in melanoma patients that do not express this allele. For these patients, additional therapies are needed that are directed against melanoma tumor epitopes presented by different HLA alleles.

• *The 888-mel cell line has been well characterized through multiple years of study and is a fundamental cell line for melanoma studies:* The collection of tumor associated antigens expressed by this cell line have been determined through multiple studies, many of which were performed by researchers in the inventors' laboratory. A significant amount of data has also been compiled detailing the immune responses triggered by 888-mel cells.

Inventors: Steven A. Rosenberg (NCI) *et al.*

Selected Publications

1. J Weber *et al.* Expression of the MAGE–1 tumor antigen is up-regulated by the demethylating agent 5-aza-2[1]-deoxycytidine. Cancer Res. 1994 Apr 1; 54(7):1766–1771. [PubMed: 7511051]

2. PF Robbins *et al.* Recognition of tyrosinase by tumor-infiltrating lymphocytes from a patient responding to immunotherapy. Cancer Res. 1994 Jun 15; 54(12):3124–3126. Erratum in: Cancer Res. 1994 Jul 15; 54(14):3952. [PubMed: 8205528]

3. PF Robbins *et al.* Multiple HLA class II-restricted melanocyte differentiation antigens are recognized by tumor-infiltrating lymphocytes from a patient with melanoma. J Immunol. 2002 Nov 15; 169(10):6036–6047. [PubMed: 12421991]

Patent Status: HHS Reference No. E–070–2010/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for licensing under a Biological Materials License Agreement.

Licensing Contact: Samuel E. Bish, PhD; 301–435–5282; *bishse@mail.nih.gov.*

Collaborative Research Opportunity: The Surgery Branch, National Cancer Institute, is seeking statements of capability or interest from parties interested in collaborative research to carry out genotypic as well as phenotypic analysis of the 888-mel cell line in order to better understand the nature of tumor cells that respond to therapy. In addition, this cell line can be used as a target of humoral or cell mediated immune responses as a part of studies characterizing the nature of immune responses directed against tumor cells. Please contact John Hewes, PhD at 301–435–3131 or *hewesj@mail.nih.gov* for more information.

UOK171, A Spontaneous Clear Cell Type Renal Cell Carcinoma (ccRCC) Human Cell Line Derived From a Surgically Removed Tumor

Description of Invention: Scientists at the National Institutes of Health (NIH) have developed a renal cell carcinoma (RCC) cell line designated UOK171 from the resected tumor of a patient diagnosed with stage IV high nuclear grade clear cell type renal cell carcinoma (ccRCC). The UOK171 cell line was immortalized spontaneously by mincing the resected tumor into pieces followed by propagation of the cells over more than twenty generations. One of the most prominent characteristics of this cell line is its intact, nonmutated von Hippel-Lindau (VHL) tumor suppressor gene. In the majority of sporadic and hereditary ccRCC cases, the VHL gene is functionally disrupted due to hypermethylation or the gene is completely lost. Thus, the UOK171 cell line is very useful as a positive control for VHL gene expression in studies of the genetic and molecular mechanisms underlying advanced ccRCC, a disease for which there is no effective treatment. Specifically, this cell line has been used as a non-methylated control cell line in studying the effects of 5–Aza-dCyd and Zebularine on VHL re-expression from methylated-VHL cell line models. These agents do not affect the methylation status of the VHL gene in UOK171. This cell line also exhibits decreased fibroblast growth factor 5 (FGF5) expression, unbalanced chromosome 3 translocations, translocations involving chromosome 14, the losses of chromosome 14 and 22, and chromosome structural aberration 1(8)(q10). UOK171 is also one of the 40-member cell lines in the National Cancer Institute (NCI) Urologic Oncology Branch (UOB) Tumor Cell Line Repository.

Applications

• Research tool for investigating the underlying molecular mechanisms contributing to advanced ccRCC, including the identification of new RCC tumor antigens for immunotherapy.

• Research tool for studying the methylation status of genes involved in ccRCC to reveal the genetic processes occurring in ccRCC tissues that may contribute to advanced disease.

• Positive control cell line for VHL gene expression and function studies, including cytogenetics, gene mutation research, and examination of chromosomal structural abnormalities that may contribute to ccRCC.

• Research tools for testing the activity of potential anti-cancer drugs against ccRCC, a disease which has no effective treatment options.

• Possible starting material for developing a cancer vaccine against RCC.

Advantages

• *Cell line is derived from a ccRCC patient:* These cell lines are anticipated to retain many features of primary ccRCC samples and novel ccRCC antigens identified from this cell line are likely to correlate with antigens expressed on human ccRCC tumors. Studies performed using these cell lines may have a direct correlation to the initiation, progression, treatment, and prevention of ccRCC in humans.

• *Expresses a non-mutated VHL gene:* In the majority of advanced ccRCC patients the VHL gene has been mutated or deleted. The UOK171 cell line represents a tool that can be utilized to study the impact of this VHL gene and various mutations on advanced ccRCC.

• *Molecular and genetic features are well characterized:* This cell line is part of NCI Urologic Oncology Branch's Tumor Cell Line Repository. The inventor has elucidated many physical characteristics of the cell line, including chromosomal attributes and important ccRCC genes, under various conditions.

Inventor: W. Marston Linehan (NCI).

Related Publications

1. WG Alleman *et al.* The *in vitro* and *in vivo* effects of re-expressing methylated von Hippel-Lindau tumor suppressor gene in clear cell renal carcinoma with 5-Aza-2′-deoxycytidine. Clin Cancer Res. 2004 Oct 15; 10(20):7011–7021. [PubMed: 15501981]

2. CP Pavlovich *et al.* Patterns of aneuploidy in stage IV clear cell renal carcinoma revealed comparative genomic hybridization and spectral karyotyping. Genes Chromosomes Cancer. 2003 Jul; 37(3):252–260. [PubMed: 12759923]

3. K Hanada *et al.* Identification of fibroblast growth factor-5 as an overexpressed antigen in multiple human adenocarcinomas. Cancer Res. 2001 Jul 15; 61(14):5511–5516. [PubMed: 11454700]

4. C Stolle *et al.* Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. Hum Mutat. 1998; 12(6):417–423. [PubMed: 9829911]

5. P Anglard *et al.* Molecular and cellular characterization of human renal cell carcinoma cell lines. Cancer Res. 1992 Jan 15; 52(2):348–356. [PubMed: 1345811]

Patent Status: HHS Reference No. E–033–2010/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for licensing under a Biological Materials License Agreement.

Licensing Contact: Samuel E. Bish, Ph.D.; 301–435–5282; *bishse@mail.nih.gov*.

Collaborative Research Opportunity: The Urologic Oncology Branch, Center for Cancer Research, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize UOK171. Please contact John Hewes, Ph.D. at 301–435–3131 or *hewesj@mail.nih.gov* for more information.

Delivery of Transthyretin (TTR) Across the Blood Brain Barrier as a Treatment for Alzheimer's Disease

Description of Invention: The invention describes products and methods of treating Alzheimer's disease. Alzheimer's disease is characterized by the formation of amyloid plaques and tangles in areas of the brain critical for learning and memory. The products are a transthyretin and other blood brain barrier impermeable proteins transformed into blood brain barrier permeable forms by the coupling of an Inter-Cellular Adhesion Molecule-1 (ICAM-1) targeting agent. Transthyretin binds to, and inhibits amyloid protein from forming plaque deposits. Deposition of amyloid is thought to underlie the disease pathology of Alzheimer's. Thus, this invention treats Alzheimer's by inhibiting the formation of amyloid plaques, which normally would result in amyloid plaque formation, inflammation, and neuronal cell death.

Applications

• Therapeutic for Alzheimer's disease.

• Therapeutic for other amyloid-related diseases.

Development Status: Early stage.

Market: As of 2007 over 5 million people in America are living with Alzheimer's disease.

Inventors: Juan Marugan *et al.* (NHGRI)

Patent Status: U.S. Provisional Application No. 61/286,205 filed 14 Dec 2009 (HHS Reference No. E–268–2009/0–US–01).

Licensing Status: Available for licensing.

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

Collaborative Research Opportunity: The NIH Chemical Genomics Center (NCGC) is open to collaborating in order to further develop this invention. Please contact Dr. Juan Marugan at *maruganj@mail.nih.gov* for more information about collaborative research opportunities.

Vaccines Comprising Sand Fly Salivary Proteins for Control of Leishmania Infection

Description of Invention: This invention relates to the use of several peptides from the salivary glands of various sand fly species for the control of leishmania infection. Many of these peptides were shown to be effective in eliciting potent immune responses in animal models and are excellent candidates for the development of vaccines against the disease. A vaccine comprising one of the peptides was used to protect mice challenged with parasites and salivary gland homogenates. A DNA vaccine containing the cDNA for this same peptide also provided protection that lasted at least 3 months after immunization and produced both intense humoral and delayed-type hypersensitivity reactions. Other experiments have shown that B cell-deficient mice immunized with the plasmid vaccine also successfully controlled leishmania infection. Current in-vivo studies continue to explore the use of these sand fly salivary peptides for use as animal vaccines.

Leishmania parasites are transmitted to their vertebrate hosts by infected sand fly bites. Sand fly saliva helps to enhance infection but immunity to the saliva protects against the infection, allowing the possibility of vaccine development. A number of major salivary proteins from sand fly species such as *Lutzomyia longipalpis, Phlebotomus ariasi,* and *Phlebotomus perniciosus* are claimed in the invention.

Leishmania infection affects as many as 12 million people worldwide, with 1.5–2 million new cases each year. Control of this disease will be a major milestone for public health efforts in endemic areas of the world. The current invention provides a potential means to achieve widespread vaccination that may lead to significantly control of the disease in areas such as South America, South Asia, and the Mediterranean where it is still a significant health problem. An effective veterinary vaccine will be of benefit to veterinary medicine and may pave the way for human vaccines against Leishmaniasis. The vaccination of animals may also have a positive impact on the epidemiology of the disease by reducing the number of animal reservoirs and the possibility of human infection.

Applications

• Vaccines to control leishmania infection.

• Use of peptides to elicit potent immune responses.

Development Status: Early stage.

Inventors: Jesus G. Valenzuela *et al.* (NIAID).

Related Publications

1. Oliveira F, Jochim RC, Valenzuela JG, Kamhawi S. Sand flies, Leishmania, and transcriptome-borne solutions. Parasitol Int. 2009 Mar; 58(1):1–5. [PubMed: 18768167]

2. Valenzuela JG, Garfield M, Rowton ED, Pham VM. Identification of the most

abundant secreted proteins from the salivary glands of the sand fly *Lutzomyia longipalpis,* vector of *Leishmania chagasi.* J Exp Biol. 2004 Oct; 207(Pt 21):3717–3729. [PubMed: 15371479]

3. Valenzuela JG, Belkaid Y, Garfield MK, Mendez S, Kamhawi S, Rowton ED, Sacks DL, Ribeiro JM. Toward a defined *anti-Leishmania* vaccine targeting vector antigens: Characterization of a protective salivary protein. J Exp Med. 2001 Aug 6; 194(3):331–342. [PubMed: 11489952]

4. Belkaid Y., Valenzuela JG, Kamhawi S., Rowton E., Sacks DL, Ribeiro JM. Delayed-type hypersensitivity to Phlebotomus papatasi sand fly bite: An adaptive response induced by the fly? Proc Natl Acad Sci U S A. 2000 Jun 6; 97(12):6704–6709. [PubMed: 10841567]

Patent Status

- U.S. Patent Application No. 60/422,303 filed October 29, 2002 (HHS Ref. No. E–285–2002/0–US–01).
- PCT Application No. PCT/US2003/03453 filed October 29, 2003 (HHS Ref. No E–285–2002/0–PCT–02). Application filed in the following countries: the USA, Europe, Brazil, Japan, Mexico, India and Israel.
- U.S. Patent No. 7,485,386 issued February 3, 2009 (HHS Reference No. E–285–2002/0–US–03).
- European Patent Number No. 1572968 issued April 22, 2009 (HHS Reference No. E–285–2002/0–EP–04).
- PCT Application No. PCT/US2009/042980 filed May 05, 2009 (HHS Reference No. E–189–2008/2–PCT–01).
- U.S. Patent Application No. 60/421,327 filed September 19, 2002 (HHS Ref. No. E–130–2002/0–US–01).
- PCT Application No. PCT/US03/29833 filed September 18, 2003 (HHS Ref. No. E–130–2002/0–PCT–02). Application filed in the following countries: USA, Europe, Brazil, Japan, Mexico, India and Israel.

Licensing Status: Available for licensing.

Licensing Contact: John Stansberry, PhD; 301–435–5236; *stansbej@mail.nih.gov*.

Collaborative Research Opportunity: The NIAID, OTD is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize "Vaccines Comprising Sand Fly Salivary Proteins for Control of Leishmania Infection". Please contact Dana Hsu at 301–451–3521 for more information.

Dated: May 26, 2010.

Richard U. Rodriguez,

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

[FR Doc. 2010–13480 Filed 6–3–10; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–D–0406]

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs; Frequently Asked Questions—Statement of Investigator (Form FDA 1572); Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of an information sheet guidance entitled, "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs; Frequently Asked Questions—Statement of Investigator (Form FDA 1572)." This guidance is intended to assist sponsors, clinical investigators, and institutional review boards (IRBs) involved in clinical investigations of investigational drugs and biologics in completing the Statement of Investigator form (Form FDA 1572). FDA developed this information sheet guidance in response to numerous questions from the research community regarding Form FDA 1572. This information sheet guidance provides FDA's responses to the most frequently asked questions.

DATES: Submit either written or electronic comments on agency guidances at any time.

ADDRESSES: Submit written requests for single copies of the guidance to the Division of Drug Information (HFD–240), 10903 New Hampshire Ave., Silver Spring, MD 20993 or to the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist the office in processing your requests. Submit electronic comments to *http://www.regulations.gov*. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the information sheet guidance document.

FOR FURTHER INFORMATION CONTACT: Joseph Salewski, Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring MD 20993, 301–796–3395.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of an information sheet guidance entitled, "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs; Frequently Asked Questions—Statement of Investigator (Form FDA 1572)." This guidance is intended to assist sponsors, clinical investigators, and IRBs involved in clinical investigations of investigational drugs and biologics in complying with the requirement that each investigator complete and sign a Form FDA 1572 before participating in an investigation. This guidance describes how to complete the Statement of Investigator form (Form FDA 1572).

FDA developed this information sheet guidance in response to numerous questions from the research community regarding the Form FDA 1572. In this guidance, we provide answers to frequently asked questions concerning the purpose of this form, when this form needs to be completed and signed by the investigator, how to best complete the various blocks within the form, and when the form might need to be updated. In addition, we clarify questions related to the use of Form FDA 1572 by clinical investigators participating in studies conducted outside the United States that may or may not be under an investigational new drug application.

This information sheet guidance is part of the Information Sheet Guidance Initiative, announced on February 3, 2006, in the **Federal Register** (71 FR 5861), which describes FDA's intention to update the process for developing, issuing, and making available guidances intended for IRBs, clinical investigators, and sponsors. Known as "Information Sheets," these guidances have provided recommendations to IRBs, clinical investigators, and sponsors to help them fulfill their responsibilities to protect human subjects who participate in research regulated by the FDA since the early 1980s. The Information Sheet Guidance Initiative is intended to ensure that the Information Sheets are consistent with the FDA's good guidance practices (GGPs). As part of the initiative, which will be ongoing, the agency plans to rescind Information Sheets that are obsolete, revise and reissue Information Sheet Guidances that address current issues, and develop