

form of trafficking in persons, a special needs child with a disability, a child who has been a victim of physical or sexual abuse under circumstances that indicate that the child's health or welfare has been significantly harmed or threatened, or a child whose proposed sponsor clearly presents a risk of abuse, maltreatment, exploitation, or trafficking to the child based on all available objective evidence.

9. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008 § 235(c)(3)(B) to conduct follow-up services, during the pendency of removal proceedings, on children for whom a home study was conducted, and to conduct follow-up services for those UAC with mental health or other needs.

10. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008 § 235(c)(4) to cooperate with the Executive Office for Immigration Review (EOIR) to ensure that custodians of UAC receive legal orientation presentations provided through the Legal Orientation Program administered by EOIR.

11. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008 § 235(c)(5) to ensure, to the greatest extent practicable and consistent with section 292 of the Immigration and Nationality Act (8 U.S.C. 1362), that UAC who are or have been in the custody of the Secretary or the Secretary of Homeland Security, and who are not described in § 235(a)(2)(A), have counsel. To the greatest extent practicable, personnel in the Administration for Children and Families shall make every effort to use the services of pro bono counsel who agree to provide representation to such UAC without charge.

12. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008 § 235(c)(6) to appoint independent child advocates for child trafficking victims or other vulnerable UAC.

13. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008 § 235(d)(1) to specifically consent to juvenile court jurisdiction for an unaccompanied alien child who is applying for special immigrant status pursuant to 101(a)(27)(J) of the Immigration and Nationality Act (8 U.S.C. 101(a)(27)(J)) and who is in the custody of the Secretary.

14. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008

§ 235(d)(4)(A) to make eligible for placement and services under a URM program pursuant to § 412(d) of the Immigration and Nationality Act (8 U.S.C. 1522(d)) children granted special immigrant status under section 101(a)(27)(J) of the Immigration and Nationality Act (8 U.S.C. 1101(a)(27)(J)) and who were either in the custody of the Secretary or who were receiving services pursuant to section 501(a) of the Refugee Education Assistance Act of 1980 (8 U.S.C. 1522 note) at the time a dependency order was granted.

15. Authority under the William Wilberforce Trafficking Victims Protection Reauthorization Act of 2008 § 235(e) to train Federal personnel, and upon request, State and local personnel, who have substantive contact with UAC.

I hereby affirmed and ratified any actions taken by the Assistant Secretary for Children and Families or any other Administration for Children and Families officials, which, in effect, involved the exercise of this authority prior to the effective date of this delegation.

#### Limitations

1. This delegation shall be exercised under the Departments' existing delegation of authority and policy on regulations.

2. This delegation shall be exercised under financial and administrative requirements applicable to all Administration for Children and Families authorities.

#### Effective Date

This delegation of authority is effective on date of signature.

Dated: March 23, 2009.

**Charles E. Johnson,**

*Acting Secretary, Department of Health and Human Services.*

[FR Doc. E9-6959 Filed 3-30-09; 8:45 am]

**BILLING CODE 4184-01-M**

## 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.

#### Cell Based Immunotherapy

*Description of Technology:* The invention hereby offered for licensing is in the field of Immunotherapy and more specifically in therapy of autoimmune diseases such as Type I diabetes, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus and immune mediated allergies such as asthma as well as in transplantation-related disorders, such as graft acceptance and graft-versus-host-disease (GVHD).

While the role of FOXP3+ regulatory T cells (Tregs) in the maintenance of self-tolerance and immune homeostasis has been established and thus their use in adoptive immunotherapy has been contemplated, there is still no good way to purify and expand these cells in an efficient and reproducible manner ex vivo for use in human therapy. The subject invention provides a method that allows such purification for use in expansion cultures to generate sufficient numbers of cells and purity for cell-based immunotherapy. The method is based on the finding that Tregs selectively express Latency Associated Peptide (LAP) and CD121b (IL-1 Receptor Type 2) and on the ability to selectively separate these cells from other immune cells that are potentially hazardous, through the use of magnetic particles which specifically bind to either one of these two surface molecules and selectively separate those cells from the non-Tregs.

#### Applications:

Immunotherapy, primarily for autoimmune diseases such as Type I diabetes, hematologic disorders such as aplastic anemia, transplantation-related disorders, such as graft acceptance and graft-versus-host-disease (GVHD) and allergic diseases such as asthma.

Facilitating detailed studies and analysis of human Treg function in health and disease.

Assay to differentiate thymic-derived versus peripheral-derived FOXP3+ Tregs.

Potential assay to monitor disease status, progression and prognosis such as early detection or response to therapy of GVHD after transplantation, solid organ graft rejection post-transplantation or a flare-up of systemic lupus erythematosus.

**Advantages:** The method of purification of FOXP3+ Tregs for human treatment may be superior in efficiency and practicality than currently existing techniques. After the magnetic separation, the final product contains more than 90% fully functional FOXP3+ Tregs. This novel protocol should facilitate the purification of Tregs for both cell-based therapy as well as for detailed studies of human Treg function in health and disease. It is important to note that most of the treatments for specific autoimmune diseases (i.e. hormone replacement therapy, enzyme replacement therapy, corticosteroids, NSAIDs, plasmaphereses, immunosuppressants and intravenous immunoglobulins) do not constitute cure for the specific diseases. Immunotherapy with Tregs has a potential to provide cure or prolonged remission for many of these diseases.

**Development Status:** The purification protocol has been proven simple and efficient in a laboratory setting.

**Market:** As indicated above the technology may be applied to allergies and many human diseases that are characterized by diminished frequency or dysfunction of Tregs, including systemic lupus erythematosus (SLE), type 1 diabetes, multiple sclerosis, aplastic anemia, idiopathic thrombocytopenic purpura, graft-versus-host disease (GVHD) and transplant rejection etc. As noted above treatment with Tregs may have a potential to provide cure to many of these diseases, thus collectively, the commercial market opportunities for the technology are wide-ranging and the contribution to public health may be highly significant.

The following information provides further detail concerning the potential market size for therapeutic use of Tregs:

- As a group, autoimmune diseases afflict millions of Americans. While individually not very common, with the exception of thyroid disease, diabetes and systemic lupus erythematosus (SLE), taken as a whole, autoimmune diseases represent the fourth largest cause of disability among women in the United States. According to the National Women's Health Centre, 75% of cases of autoimmune diseases occur in American women.

- Similarly, Type 1 Diabetes is the second most common chronic disease in children after asthma. About 13,000 new cases are diagnosed in the U.S. alone each year. Patients with Type 1 Diabetes make up about 5% to 10% of all cases of diabetes. It most commonly appears in girls and boys when they are fourteen years old.

- Multiple sclerosis is a chronic disease that starts early in life and as many as 400,000 patients are afflicted with this disease which lasts for decades.

- More than 19,000 transplants are performed in the United States each year. That equates to 1,583 per month, 365 per week, 52 per day, and 2 per hour for a rate of approximately 1 in 14,315 or 0.01% of the U.S population.

**Inventors:** Dat Q. Tran and Ethan M. Shevach (NIAID).

**Publications:**

1. J Andersson, DQ Tran, M Pesu, TS Davidson, H Ramsey, J O'Shea, EM Shevach. CD4+Foxp3+ regulatory T cells confer infectious tolerance in a TGFβ-dependent manner. *J Exp Med.* 2008 Sep 1;205(9):1975–1981.

2. EM Shevach, DQ Tran, TS Davidson, J Andersson. The critical contribution of TGF-beta to the induction of Foxp3 expression and regulatory T cell function. *Eur J Immunol.* 2008 Apr;38(4):915–917.

3. DQ Tran, R Ramsey, EM Shevach. Induction of FOXP3 expression in naïve human CD4+FOXP3- T cells by T cell receptor stimulation is TGFβ-dependent but does not confer a regulatory phenotype. *Blood.* 2007 Oct 15;110(8):2983–2990.

**Patent Status:** U.S. Provisional Application No. 61/090,788 filed 21 Aug 2008 (HHS Reference No. E-312-2008/0-US-01).

**Licensing Status:** Available for licensing.

**Licensing Contacts:** Uri Reichman, Ph.D., MBA; 301-435-4616; [UR7a@nih.gov](mailto:UR7a@nih.gov); John Stansberry, Ph.D.; 301-435-5236; [stansbej@mail.nih.gov](mailto:stansbej@mail.nih.gov).

**Collaborative Research Opportunity:** The NIAID/NIH Laboratory of Immunology is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the use of CD121b or LAP to produce a Treg product for cell-based immunotherapy. Please contact Nicole Mahoney at 301-435-9017 for more information.

### Compositions and Methods for Inhibiting and Treating Herpes Simplex Virus (HSV) Infection and HSV-1 Containing a UL3 Deletion

**Description of Technology:** The invention offered hereby for licensing is in the fields of viral and cancer therapeutics and in particular related to Herpes Simplex Virus. It is based on the finding that Protein Disulfide Isomerase (PDI) family members bind in vitro to the herpes simplex protein UL3 and that HSV entry to the host cell is mediated through HSV's interaction with the host cell's surface protein(s) belonging to PDI family members. Inhibition of virus entry can therefore be accomplished by inhibitors of the PDI protein family members. The inventors demonstrated the following:

- A small molecule such as 5,5'-Dithiobis(2-nitro-benzoic acid) (DTNB) can block HSV infection by blocking PDI-like activity.

- Anti-PDI antibodies can block HSV infection.

- Disulfide Isomerase family members bind in vitro to the herpes simplex protein UL3.

Accordingly, the inventors further suggest that a UL3-like peptide or its analogues and derivatives can be effective as inhibitors of HSV infection.

The invention further provides for methods and kits to screen for new inhibitors, based on the entry mechanism mentioned above.

In another aspect of the invention, it is proposed that such PDI inhibitors or binding proteins can potentially serve as antitumor agents based on the finding that cancer cells express increased levels of PDI compared to healthy cells.

With respect to cancer therapeutics, the invention further claims a recombinant mutant herpes simplex virus devoid of the capability to express UL3 or expressing a mutant HSV UL3 protein. Such a virus can serve as an oncolytic virus for treatment of cancer.

**Applications:**

- Antiviral therapeutics.
- Anticancer therapeutics.
- Screening for new antiviral and anticancer agents.
- Developing of Oncolytic Viruses for cancer therapy.

**Advantages:** Herpes Simplex Viruses are responsible for a wide range of human diseases. Herpes simplex virus is the causative agent of oral and genital herpes, and is associated with sexual transmission. Infections with herpes simplex can be acute, or latent with recurring periodic outbreaks. An infection by herpes simplex is marked by watery blisters in the skin or mucous membranes of the mouth, lips or

genitals that can be painful and thus can severely affect the quality of life of an infected individual. The virus can lead to potentially fatal infections in babies whose mothers are infected, and to permanent neurological damage in adults with herpes encephalitis. The virus may also play a role in the spread of HIV as it can make people more susceptible to HIV infection.

In spite of the severity of diseases caused by HSV and in spite of the many years of efforts to develop effective anti-HSV medications and vaccines, there is still no effective cure for herpes in existence. The existing antiviral medications such as *Acyclovir*, *Valacyclovir* and *Famciclovir* that work by inhibiting the virus' DNA synthesis (targeting the enzyme DNA Polymerase) cannot eradicate the virus from the body, but merely reduce the extent of the symptoms and the frequency of breakouts. Other small molecules in development also aiming at DNA synthesis are targeting another virus enzyme (Helicase-primase complex). The therapeutic strategy described in the subject technology provides a completely different mechanism, *i.e.* inhibition of the virus entry. Thus it may provide advantages compared to the existing drugs with respect to toxicity and efficacy.

With respect to cancer therapy, the subject invention may offer a new class of drugs which act by an alternate mechanism in comparison to conventional cancer drugs. The technology may thus prove to be advantageous with respect to toxicity and efficacy. In addition, drugs developed by this technology may be given to patients in combination with existing drugs.

#### *Development Status:*

- The inhibition of HSV infection by DTNB and antibodies against the PDI surface protein have been demonstrated *in vitro*.
- Pre-clinical or clinical data is not yet available.
- Further development to identify PDI inhibitors applicable for viral therapy and cancer therapy is currently ongoing.

• Further development and optimization of recombinant HSV to be utilized as an oncolytic virus is ongoing. Only *in vitro* data is available at present.

*Market:* The market for anti-herpes drugs is huge. Results of a nationally representative study show that genital herpes is common in the United States. Nationwide, at least 50 million people ages 12 and older, or one of five adolescents and adults, have had a latent or acute genital HSV infection. There are up to 1 million new cases

every year and according to some estimates genital herpes is now more common than diseases like diabetes and asthma. At the same time there is still no effective drug against this virus available, thus the commercial potential in developing a new effective drug is enormous.

With respect to the market for cancer therapeutics the opportunities are also vast. This market has been growing in the last several years by an estimate of 18% a year due to the introduction of many new and innovative drugs, and some reports forecast a market size of close to \$90 billion by 2011.

*Inventors:* Nancy S. Markovitz and Stephen Daniell (FDA).

#### *Publications:*

1. NS Markovitz. The herpes simplex virus type 1 UL3 transcript starts within the UL3 open reading frame and encodes a 224-amino-acid protein. *J Virol.* 2007 Oct;81(19):10524–10531.

2. E Bar, T Kimura, M Kikuchi, NS Markovitz. Protein disulfide isomerase (PDI) family members interact with the UL3 protein of herpes simplex virus-1. 31st International Herpesvirus Workshop, Abstract #8.51, Seattle WA, July 22–28, 2006.

3. KD Nguyen, EE Bar, MJ Dambach, NS Markovitz. Yeast Two Hybrid Identification of the Herpes Simplex Virus-1 UL3 protein domains that interact with cellular target proteins. NIH Research Festival, Abstract #CB-19, Bethesda MD, October 2006.

4. MJ Dambach, J Trecki, N Martin, NS Markovitz. Oncolytic viruses derived from the  $\gamma$ 34.5-deleted herpes simplex virus recombinant R3616 encode a truncated UL3 protein. *Mol Ther.* 2006 May;13(5):891–898.

*Patent Status:* U.S. Provisional Application No. 61/134,566 filed 11 Jul 2008 (HHS Reference No. E-236-2008/0-US-01).

*Licensing Status:* Available for licensing.

*Licensing Contacts:* Uri Reichman, PhD, MBA; 301-435-4616; [UR7a@nih.gov](mailto:UR7a@nih.gov); John Stansberry, Ph.D.; 301-435-5236; [stansbej@mail.nih.gov](mailto:stansbej@mail.nih.gov).

### **Identification of Adaptive Mutations That Increase Infectivity of Hepatitis C Virus JFH1 Strain in Cell Culture**

*Description of Technology:* The technology offered for licensing is in the field of hepatitis C. More specifically the invention discloses an efficient way to grow the virus, a way that may facilitate advanced research in the field of hepatitis C (HCV) and its pathogenesis, as well as provide for convenient and effective ways to screen for new hepatitis C drugs. It also lends

itself to the development of vaccines against hepatitis C.

The invention is based on the finding that certain mutations in the JFH1 strain of HCV, as well as certain chimera of the mutated strain, can lead to an increase in production of infectious virus particles in cell cultures (*i.e.*, Huh-7.5) between 100- to 1000-fold as compared to the wild type virus. Such mutations are introduced to a viral RNA that codes for hepatitis C and the latter is introduced to an appropriate cell to produce a high yield of highly infective virus.

Progress in research in the field of HCV, as well as the development of drugs and vaccines to combat hepatitis C infections, has been hampered for years due to the lack of robust *in vivo* cell culture systems for the study of this virus. Several breakthroughs in the area that occurred in 2005 and thereafter (*i.e.*, the isolation of HCV genotype 2a sequence (JFH1) and the generation of the unique cell line Huh-7.5) contributed significantly to progress in the field, but further optimization and improvements in the culture system have still been needed. The subject invention offers such improvements and thus may lead to enhanced progress in HCV research and in the development of the much needed drugs and vaccines against the virus.

#### *Applications:*

- Research in the field of HCV and its pathogenesis.
- Screening and discovery of drugs that inhibit HCV infections.
- Development of vaccines for HCV.

*Advantages:* 100- to 1000-fold more efficient method to grow virus particles.

*Development Status:* The invention is fully developed and requires no additional work.

*Market:* It is estimated that 170 million people worldwide suffer from HCV infection, with 3 to 4 million new cases each year. The primary causes of new HCV infections worldwide are unscreened blood transfusions and the reuse of syringes, without sterilization (WHO). It is estimated that nearly 4.1 million people in the U.S. are infected with HCV with 3.2 million of the 4.1 million people chronically infected. Approximately 70% of those chronically infected suffer from chronic liver disease (CDC). There has been a major decline in the number of new HCV infections per year in the U.S. from the 1980s (240,000) to 2004 (26,000) (CDC). In the U.S., the primary cause of new infections is needle-sharing by intravenous drug users. Despite the significant decrease in new HCV infections, the number of patients requiring treatment for chronic HCV is

expected to rise as patients with HCV infection age and progress to more serious liver diseases (McHutchison HG, *et al.* Chronic Hepatitis C: An Age Wave of Disease Burden 2005. American Journal of Managed Care. 11: S286–S295). From 2010–2019, it is estimated that direct medical expenditures for HCV will be \$10.7 billion; the costs of decompensated HCV infection (cirrhosis and hepatocellular carcinoma) are estimated to be \$21.3 billion; and indirect costs associated with the loss of life under age 65 are estimated to be \$54.2 billion (McHutchison HG, *et al.* 2005).

Chronic hepatitis C is a serious disease that can result in long-term health problems, including liver damage, liver failure, liver cancer, or even death. It is the leading cause of cirrhosis and liver cancer and the most common reason for liver transplantation in the United States. Approximately 8,000–10,000 people die every year from hepatitis C related liver disease.

Of every 100 people infected with the hepatitis C virus, about 75–85 people will develop chronic hepatitis C virus infection; of those,

- 60–70 people will go on to develop chronic liver disease.
- 5–20 people will go on to develop cirrhosis over a period of 20–30 years.
- 1–5 people will die from cirrhosis or liver cancer.

In spite of the urgent public health need for effective drugs and vaccines against HCV as discussed above, and in spite of the huge market potential for such medical remedies, there are no effective drugs or vaccines in existence as of yet due to technical difficulties, one of them, as mentioned at the outset, is the difficulties in growing and culturing the virus. The only drugs available to treat HCV at the present time are Ribavirin and Interferon but none constitute a real cure for the disease. They also can present severe side effects that make the use of them prohibitive in many cases. The subject technology may therefore present an opportunity for drug and vaccine companies to accelerate their research and development in this area.

*Inventors:* Rodney Russell, Jens Bukh, Robert H. Purcell, and Suzanne U. Emerson (NIAID).

*Publication:* RS Russell, JC Meunier, S Takikawa, K Faulk, RE Engle, J Bukh, RH Purcell, SU Emerson. Advantages of a single-cycle production assay to study cell culture-adaptive mutations of hepatitis C virus. Proc Natl Acad Sci USA. 2008 Mar 18;105(11):4370–4375.

*Patent Status:*

- U.S. Provisional Application No. 60/931,259 filed 21 May 2007 (HHS Reference No. E–171–2007/0–US–01).
- U.S. Provisional Application No. 61/066,773 filed 22 Feb 2008 (HHS Reference No. E–171–2007/1–US–01).
- PCT Application No. PCT/US2008/063982 filed 16 May 2008, which published as WO 2008/147735 on 04 Dec 2008 (HHS Reference No. E–171–2007/2–PCT–01).

*Licensing Status:* Available for licensing.

*Licensing Contacts:* Uri Reichman, PhD, MBA; 301–435–4616; [UR7a@nih.gov](mailto:UR7a@nih.gov); Rung C. Tang, JD, LL.M.; 301–435–5031; [tangrc@mail.nih.gov](mailto:tangrc@mail.nih.gov).

Dated: March 24, 2009.

**Richard U. Rodriguez,**

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

[FR Doc. E9–7207 Filed 3–30–09; 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 any 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.

**Mouse Monoclonal Antibodies to Human Tristetraprolin (TTP)**

*Description of Technology:* TTP has been implicated in autoimmune and inflammatory diseases through its role as a regulator of the transcripts encoding

several pro-inflammatory cytokines, including tumor necrosis factor alpha. However, it has been difficult to study endogenous TTP in man and other animals because it is expressed at very low levels in most cells and tissues, and because of the lack of mouse monoclonal antibodies directed at the human protein.

Scientists at the NIH have developed three mouse monoclonal antibodies (TTP–16, TTP–214 and TTP–409) that react to different regions of the human TTP to allow for the identification and localization of the TTP protein by standard protocols. Although validation has only been conducted at the level of western blotting to date, they do not appear to cross-react with other human members of the TTP protein family.

*Potential Applications:* Mouse monoclonal antibodies to human TTP will be useful in both clinical and basic research on a variety of inflammatory diseases and studies of mRNA destabilization. They can be used to identify or isolate TTP in cells or tissues by Western blotting, immunoprecipitation, immunohistochemistry, immunofluorescence, flow cytometry, and RNA super-shift assays, and can also be used in cross-linking and immunoprecipitation protocols.

*Inventors:* Elizabeth A. Kennington and Perry J. Blackshear (NIEHS).

*Patent Status:* HHS Reference No. E–123–2009/0—Research Tool. Patent protection is not being pursued for this technology.

*Licensing Status:* Available for licensing.

*Licensing Contact:* Fatima Sayyid, M.H.P.M.; 301–435–4521; [Fatima.Sayyid@hhs.nih.gov](mailto:Fatima.Sayyid@hhs.nih.gov).

**Use of Anthrax Lethal Factor To Treat Cancer and Screening Methods for MAPK Kinase Protease Activity**

*Description of Technology:* Anthrax toxin, produced by *Bacillus anthracis*, is composed of three proteins; protective antigen (PA), edema factor (EF), and lethal factor (LF). PA by itself has little or no toxic effect upon cells, but serves to bind cell surface receptors and mediate the entry of EF and LF into the cell. EF has been identified as an adenylate cyclase and together with PA forms a toxin (edema toxin; EdTx) which can induce edema formation when injected subcutaneously. LF and PA together form a toxin (lethal toxin; LeTx) which can cause rapid lysis of certain macrophage-derived cell lines *in vitro* as well as death when injected intravenously.

Indirect evidence had suggested that LF was a metalloprotease. However, the