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.

Improving the Therapeutic Effectiveness of Foreign Proteins

Description of Invention: Foreign proteins are recognized by the immune system, which typically responds by creating neutralizing antibodies to the foreign protein. While this is helpful in response to an infection or the administration of a vaccine, it is troublesome when foreign proteins are administered for the treatment of disease in a non-vaccine capacity (*e.g.,* an immunotoxin, therapeutic antibody, protein replacement therapy, etc.). These neutralizing antibodies decrease the therapeutic effectiveness of the protein, ultimately resulting in the inability to administer the foreign protein to a patient with any benefit. Thus, if a particular disease requires multiple administrations, the chance of achieving a successful response with the foreign protein becomes unlikely.

A particular instance where neutralizing antibodies have reduced therapeutic effectiveness is the use of immunotoxins for treatment of cancer. Immunotoxins comprise an antibody domain for targeting a surface antigen on a cancer cell and a toxin domain that is capable of killing the targeted cell. The toxin domain is typically a modified form of a bacterial toxin, such as Pseudomonas exotoxin A, and is therefore recognized as a foreign protein by the patient's immune system. Although immunotoxins have an initial therapeutic effect, the effectiveness is ultimately mitigated by neutralizing antibodies against the toxin domain of the immunotoxin. Thus there is a clear need to reduce the formation of neutralizing antibodies in patients who are administered a foreign protein like an immunotoxin.

This technology addresses this need by reducing the formation of neutralizing antibodies through the co-administration of the immunosuppressive agent CP–690,550 with a therapeutic foreign protein. Specifically, the inventors found that co-administering CP–690,550 and an immunotoxin to a mouse model reduced the production of neutralizing antibodies to the immunotoxin. These results suggest that the use of CP–690,550 in combination with any foreign protein therapeutic could allow multiple cycles of therapy and result in improved therapeutic efficacy.

Applications:

- Improved efficacy of treatments that utilize the foreign proteins that can be neutralized by patient immune systems.
- Administration of CP–690,550 with an immunotoxin, for the treatment of cancers such as mesothelioma, lung cancer, leukemia, lymphoma, ovarian cancer, etc.

Advantages:

- Broad applicability to any treatment where a foreign protein is used as a therapeutic agent.
- Overcomes a persistent challenge to the use of protein biologics as therapeutics.
- Reduction of the immune response by a patient reduces the production of neutralizing antibodies, increasing the success rate of the treatment.
- Fewer neutralizing antibodies increases the duration in which a foreign protein can achieve a therapeutic concentration.
- Fewer neutralizing antibodies also allows multiple rounds of effective administration of the foreign protein.
- Longer duration for a therapeutic concentration and the ability to administer multiple doses increase the chances of a therapeutic response.

Development Status: Preclinical stage of development; preliminary mouse model data.

Inventors: David J. FitzGerald (NCI) *et al.*

Patent Status: U.S. Provisional Application No. 61/304,293 (E–082–2010/0–US–01).

For more information, see:

1. Pastan *et al.* PCT Publication WO 2009/032954 "Deletions in Domain II of Pseudomonas Exotoxin A that Reduce Non-Specific Toxicity."
2. Pastan *et al.* U.S. Patent Publication 2009/0142341 "Mutated Pseudomonas Exotoxins with Reduced Antigenicity."
3. Changelian *et al.* Science 2003 Oct 31;302(5646):875–878. "Prevention of organ allograft rejection by a specific Janus kinase 3 inhibitor." [PubMed: 14593182].
4. Pastan *et al.* U.S. Patent 7,355,012 "Mutated Anti-CD22 Antibodies with Increased Affinity to CD22 Expressing Leukemia Cells."

Licensing Status: Available for licensing.

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

Collaborative Research Opportunity: The Center for Cancer Research, Laboratory of Molecular Biology, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact John Hewes, PhD at 301–435–3131 or *hewesj@mail.nih.gov* for more information.

Parkin and PINK1-Based Therapies for Parkinson's Disease and Other Mitochondrial Diseases

Description of Invention: This technology provides methods for treating Parkinson's disease and other diseases associated with mitochondrial dysfunction.

Mutations in mitochondrial DNA (mtDNA) are responsible for a broad spectrum of inherited diseases, with symptoms that can range from mild to very severe. Accumulated mutations in mtDNA have also been linked to the pathogenesis of common diseases such as cancer, diabetes mellitus, and neurodegenerative disorders. In Parkinson's disease, for example, the accumulation of defective mitochondria appears to be responsible for the loss of midbrain neurons that produce dopamine neurotransmitter, which is a key feature of this disease.

In their recent work, Dr. Richard Youle and co-investigators have linked the fields of mitochondrial quality control and the genetics of Parkinson's disease. They have discovered that the Parkin protein is selectively recruited to damaged mitochondria, and promotes autophagic degradation of these mitochondria; ablation of Parkin increases levels of damaged mitochondria in cells. They have also discovered that another protein associated with mitochondrial disease,

the mitochondrial PTEN-induced kinase-1 (PINK1), accumulates on the surface on damaged mitochondria, and that the presence of full-length PINK1 is necessary and sufficient for Parkin recruitment to the mitochondria. Thus, both Parkin and PINK1 play specific and important roles in mitochondrial quality control and disposal.

This technology describes methods of treating Parkinson's disease or other mitochondrial diseases such as KSS (Kearns Sayre syndrome), MERRF (Myoclonus epilepsy ragged-red fibers), MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), NARP (Neuropathy ataxia, retinitis pigmentosa), and LHON (Leber hereditary optic neuropathy) by increasing PINK1 or Parkin expression or activity, as well as methods of reducing the number of defective mitochondria in a cell by increasing PINK1 or Parkin expression or activity.

Applications:

• Development of therapies for Parkinson's disease and other diseases associated with mitochondrial dysfunction.

• Development of individualized treatment regimens for mitochondrial diseases through *ex vivo* or *in vitro* testing of candidate drugs.

Inventors: Richard J. Youle *et al.* (NINDS).

Related Publications:

1. A Abeliovich. Parkinson's disease: Mitochondrial damage control. News and Views, Nature 2010 Feb 11:463:744–745. [PubMed: 20148026].

2. D Narendra *et al.* PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. 2010 Jan 26;8(1):e1000298. [PubMed: 20126261].

3. D Narendra *et al.* Parkin-induced mitophagy in the pathogenesis of Parkinson disease. Autophagy. 2009 Jul;5(5):706–708. [PubMed: 19377297].

4. D Narendra *et al.* Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol. 2008 Dec 1;183(5):795–803. [PubMed: 19029340].

Patent Status: U.S. Provisional Application No. 61/256,601 filed 30 Oct 2009 (HHS Reference No. E–225–2009/0–US–01).

Licensing Status: Available for licensing.

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

Collaborative Research Opportunity: The National Institute of Neurological Disorders and Stroke is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize methods of treating mitochondrial diseases by increasing PINK1 or Parkin expression or activity. Please contact Dr. Martha Lubet at 301–435–3120 or *lubetm@mail.nih.gov* for more information.

A Highly Sensitive ELISA for Detection of Serum Levels of Soluble IL-15 Receptor Alpha

Description of Invention: The invention is an ELISA based assay that can be used in the clinical setting to detect the presence of soluble human IL-15 receptor (IL-15R) in the serum or plasma.

Interleukin-15 (IL-15), a cytokine has potential as an immunotherapeutic agent for cancer treatment because it is a critical factor for the proliferation and activation of natural killer (NK) and CD8+ T-cells.

In addition to studies directed toward augmenting IL-15 action to increase patient immune responses to their tumor, IL-15R alpha play a pathogenic role in leukemia and autoimmune disorders. IL-15 and IL-15R alpha are coexpressed in association with a number of autoimmune disorders including rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, chronic liver disease, and refractory celiac syndrome including that disease associated with the development of enteropathy associated CD8 T-cell lymphoma. An assay for the released serum form of IL-15R alpha is required to evaluate these IL-15R alpha inducing agents.

Applications:

• The assay has the potential of being a commercial assay for clinical use to detect soluble human IL-15R alpha (sIL-15R alpha) in serum or plasma.

• The assay will help in predicting the efficacy of IL-15-based therapies since high levels of IL-15R are thought to be necessary to optimize the therapeutic effects of IL-15.

• The assay can be used to identify patients who can be good candidates for IL-15 therapy.

• The assay may also help clinicians identify patients susceptible to diseases associated with disorders of IL-15R expression.

Advantages:

• The assay is in the industry accepted ELISA format.

• This non-radioactive ELISA assay has a sensitivity of 1pg/ml that is significantly more sensitive than the current industry detection level of 20 pg/ml.

Development Status: Developed at the proof-of concept level and laboratory setting. Clinical validation of the assay is currently being planned.

Market: The assay can be used in the clinical setting to detect very low levels of IL-15R alpha in the serum or plasma of patients.

IL-15R alpha disorders have been demonstrated in leukemia and autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, celiac disease, and psoriasis as well as those with disorders associated with the retrovirus, HTLV-I. Additionally, select lymphomas express IL-15R alpha.

Inventors: Thomas A. Waldmann and Jing Chen (NCI).

Related Publication: Waldmann TA. The biology of interleukin-2 and interleukin-15: Implications for cancer therapy and vaccine design. Nat Rev Immunol. 2006 Aug;6(8):595–601. [PubMed: 16868550].

Patent Status:

• U.S. Provisional Application No. 61/241,265 filed 10 Sep 2009 (HHS Reference No. E–079–2009/0–US–01).

• U.S. Provisional Application No. 61/242,595 filed 10 Sep 2009 (HHS Reference No. E–079–2009/1–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Sabarni Chatterjee, PhD; 301–435–5587; *chatterjeesa@mail.nih.gov.*

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

Dated: June 1, 2010.

Richard U. Rodriguez,

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

[FR Doc. 2010–13606 Filed 6–4–10; 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