EXHIBIT 3—ESTIMATED COST OF THE EVALUATION

Cost component	Total cost	Annualized cost
Protocol Development	$40,278	$20,139
Data Collection Activities	91,104	45,552
Data Analysis	45,252	22,626
Publication of Results	24,370	12,185
Travel for Site Visits	8,823	4,412
Total	209,827	104,914

Request for Comments

In accordance with the above-cited Paperwork Reduction Act legislation, comments on AHRQ's information collection are requested with regard to any of the following: (a) Whether the proposed collection of information is necessary for the proper performance of AHRQ healthcare research and healthcare information dissemination functions, including whether the information will have practical utility; (b) the accuracy of AHRQ's estimate of burden (including hours and costs) of the proposed collection(s) of information; (c) ways to enhance the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information upon the respondents, including the use of automated collection techniques or other forms of information technology.

Comments submitted in response to this notice will be summarized and included in the Agency's subsequent request for OMB approval of the proposed information collection. All comments will become a matter of public record.

Dated: December 10, 2009.

Carolyn M. Clancy,

Director.

[FR Doc. E9–30957 Filed 12–30–09; 8:45 am]

BILLING CODE 4160–90–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.

Synergy of ABT–737 With an Immunotoxin To Kill Cancer Cells

Description of Technology: Programmed cell death (*i.e.,* apoptosis) represents an attractive approach for treating cancer. However, anti-apoptotic proteins that are frequently active in cancer cells can allow the cells to survive induction of apoptosis. While inhibiting anti-apoptotic proteins has shown promise in combination with apoptosis-inducing treatments, current inhibitors only show incomplete effectiveness in promoting the induction of apoptosis.

ABT–737 is one such inhibitor; it can only inhibit the function of three of the four major anti-apoptosis proteins. The fourth member, known as a MCL1, is a short-lived protein that can still prevent apoptosis in the presence of ABT–737. Importantly, because MCL1 is a short-lived protein, it requires protein synthesis to maintain levels that are sufficient to continue blocking apoptosis.

This technology uses a combination approach in the treatment of cancer. The inventors considered that combining ABT–737 with a protein synthesis inhibitor might completely inhibit anti-apoptotic proteins, leading to efficient induction of apoptosis. Specifically, NIH inventors found that combining ABT–737 and immunotoxins did result in enhanced killing of cancer cells. Because immunotoxins function by inhibiting protein synthesis, the two agents in combination are able to inhibit all of the anti-apoptotic proteins simultaneously. Furthermore, immunotoxins can be specifically targeted to cancer cells, thereby increasing their effectiveness over a non-specific protein synthesis inhibitor. The results suggest that the combination could represent an effective approach to enhancing the induction of apoptosis as an anti-cancer therapy.

Application: Combination anti-cancer therapy.

Advantages:

- Overcomes the anti-apoptotic proteins frequently associated with inducing apoptosis, thereby leading to an effective therapeutic approach.
- Synergistic effect improves toxicity of both the apoptosis-inducing agents and immunotoxins.
- Selective inhibition of protein synthesis by immunotoxins increases effectiveness versus using non-specific inhibitors.

Development Status: Preclinical stage of development.

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

Patent Status: U.S. Provisional Application No. 61/238,032 (HHS Reference No. E–279–2009/0–US–01).

For more information, see:

- Pastan *et al.,* US Patent 4,892,827.
- Pastan *et al.,* US Patent 5,705,163.
- Pastan *et al.,* PCT Application PCT/US2008/075296 (WO 2009/032954).
- JE Weldon *et al.* A protease-resistant immunotoxin against CD22 with greatly increased activity against CLL and diminished animal toxicity. Blood 2009 Apr 16;113(16):3792–3800.
- DJ FitzGerald *et al.* Recombinant immunotoxins for treating cancer. Int J Med Microbiol. 2004 Apr;293(7–8):577–582.

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 D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

A Device for Sterile Removal of a Biological Sample From a Cryopreserved Bag

Description of Technology: Cryopreservation through freezing in liquid nitrogen allows the storage of biological materials for extended periods while maintaining their activity and viability. It is commonly used in the clinic to store blood cells, semen, and umbilical cord blood (UCB) for future use. These materials are typically only obtainable in limited quantities and may be of great therapeutic value, as is the case of hematopoietic stem cells from UCB which can be used to treat and cure a number of different life-threatening illnesses. It is common practice to cryopreserve viably in bags a variety of different cells obtained from the blood. Currently, even if only a small portion of the cryopreserved sample is needed the whole bag must be thawed, wasting much of the sample since it cannot be effectively refrozen. There is a need for a method of retrieving a small sample from a frozen sample of cells in a bag while preserving the cryopreserved state and integrity of the rest of the cellular material.

Researchers at the National Heart, Lung, and Blood Institute in collaboration with the American Fluoroseal Corporation (AFC) have invented an apparatus that separates a small portion of a cryopreserved biological material stored in a collection bag while maintaining the cryopreserved integrity, sterility, and viability of the original cryopreserved material. This device could be used to retrieve small aliquots samples of various cryopreserved cellular products and biological materials such as UCB, blood mononuclear cells, stem cells, semen, and plasma while maintaining the viability and sterility of both the retrieved sample and the original cryopreserved material.

Applications: The apparatus can be used for:

- Retrieving hematopoietic stem cells from cryopreserved UCB unit to reconstitute the bone marrow of cancer patients undergoing radiotherapy and chemotherapy;
- retrieving portions of cryopreserved blood cells for expansion of antigen reactive T-cells, NK cells, and hematopoietic stem cells in the laboratory;
- retrieving portions of cryopreserved semen for assisted reproductive technology;
- sampling of cryopreserved blood plasma for detection of cytokines, chemokines, or other proteins, infectious agents or performance-enhancing drugs.

Advantages:

- Ability to isolate portions or cryopreserved biological materials while retaining viability, sterility, and cryopreserved integrity of remaining material.
- Compatibility with thousands of blood bags presently stored in commercial and public blood banks.

Development Status: A prototype of the device has been built and successfully tested.

Market: This novel apparatus has commercial potential in diverse markets such as: Blood banking and blood products, human reproductive technologies, hematopoietic stem cell and tissue transplantation, medical devices, stem cells, and cancer therapy.

Inventors: Richard W. Childs (NHLBI), Herbert Cullis (AFC), Sumi Vasu (NHLBI).

Patent Status: U.S. Provisional Application No. 61/175,131 filed 04 May 2009 (HHS Reference No. E–173–2009/0–US–01).

Licensing Status: Available for licensing.

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

Collaborative Research Opportunity: The National Heart, Lung, and Blood Institute, Hematology Branch, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the Device for Sterile Removal of a Biological Sample from a Cryopreserved Bag. Please contact Cecilia Pazman, PhD, 301–402–5579; *pazmance@mail.nih.gov* for more information.

Optimizing Chemotherapeutic Performance: Three Newly-Identified Classes of Tyrosyl-DNA Phosphodiesterase (Tdp1) Inhibitors

Description of Technology: During replication, DNA is structurally modified and cleaved by a host of enzymes, including topoisomerases. Some chemotherapeutic agents generate their anti-cancer activity by inducing DNA damage in rapidly replicating tumor cells, resulting in cell death. Topoisomerase I (top1) inhibitors, such as camptothecins, are common chemotherapeutics that prevent the religation of DNA after cleavage during replication.

Tyrosyl-DNA phosphodiesterase (Tdp1) counteracts the action of these chemotherapeutic agents and can reduce their effectiveness in eliminating tumor cells. Tdp1 is an enzyme that repairs DNA lesions and chemotherapeutic-mediated DNA damage, such as the DNA breaks induced by top1 inhibitors. Therefore, Tdp1 is a rational anticancer target whose inhibition should enhance the activity of common cancer chemotherapeutics by permitting greater DNA damage in tumor cells.

Scientists at the National Institutes of Health (NIH) have discovered three classes of compounds that specifically inhibit Tdp1, including cephalosporin derivatives like beta-lactam antibiotics, ellagic acid derivatives such as polyphenol antioxidants, and verteporfin derivatives including protoporphyrins. The compounds were identified as specific Tdp1 inhibitors via a high-throughput screening assay (AlphaScreen™) of the NIH Roadmap Molecular Libraries Small Molecule Repository (MLSMR). One current goal of the scientists is to identify the compounds with the greatest Tdp1 specificity and highest inhibitory activity against cancer cell proliferation. Some of the compounds identified are widely used to treat a variety of other diseases, including bacterial infections (beta-lactam antibiotics) and neurodegenerative and cardiovascular disorders (polyphenol antioxidants).

Now, through studies at the NIH, these compounds identified as Tdp1 inhibitors could be utilized to potentiate the pharmacological action of top1 inhibitors in the treatment of cancer with combination drug therapies. Top1 inhibitor/Tdp1 inhibitor combination chemotherapies are anticipated to be more selective against tumor tissues than top1 inhibitors alone. In addition, since Tdp1 is involved in repairing DNA damage caused by oxygen radicals and tumors are known to contain excess free radicals, Tdp1 inhibitors may also prove useful as anticancer agents independent of their use in conjunction with top1 inhibitors.

Applications:

- Cancer therapeutics administered in combination with known cancer drugs, such as topoisomerase I inhibitors, to enhance the activity and selectivity of these chemotherapeutics. Various types of cancer could be treated with this combination therapy, including lung cancer, colon cancer, breast cancer, prostate cancer, melanoma, lymphomas, ovarian cancer, and pancreatic cancer to name a few.

• Compounds utilized as a strategy to overcome chemotherapy resistance in cancer patients.

• Cancer drug administered alone as a sole chemotherapeutic regimen for patients.

Advantages:

• *Positive S&E History with the FDA:* Some compounds found within each of these three newly-identified classes of Tdp1 inhibitors are used to treat other health problems like bacterial infections and cardiovascular disease. The FDA approval process for these inhibitors in a combination therapy may be shortened given their proven track record in other indications.

• *Different Approach to Combination Chemotherapy:* Combination chemotherapy is a widely accepted treatment strategy for cancer patients, but many combinations lead to more side effects and toxicities due to multiple drug activities. These Tdp1 inhibitors aim to enhance the activity and selectivity of the other drug used in combination, which could lead to greater anticancer activity without an increase in side effects.

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

Market: Cancer continues to be a medical and financial burden on U.S. public health. According to U.S. estimates, cancer is the second leading cause of death with over 565,000 deaths reported in 2008 and almost 1.5 million new cases were reported (excluding some skin cancers) in 2008. In 2007, the NIH estimated that the overall cost of cancer was $219.2 billion dollars and $89 billion went to direct medical costs. Despite our increasing knowledge of cancer treatment and diagnosis methods, the fight against cancer will continue to benefit from the development of new technologies aimed at treating individuals with disease and diagnosing susceptible patients.

Inventors: Yves Pommier (NCI) *et al.*

Selected Publications:

1. C Marchand, *et al.* Identification of phosphotyrosine mimetic inhibitors of human tyrosyl-DNA phosphodiesterase I by a novel AlphaScreen high-throughput assay. Mol Cancer Ther. 2009 Jan;8(1):240–248.

2. S Antony, *et al.* Novel high-throughput electrochemiluminescent assay for identification of human tyrosyl-DNA phosphodiesterase (Tdp1) inhibitors and characterization of furamidine (NSC 305831) as an inhibitor of Tdp1. Nucleic Acids Res. 2007;35(13):4474–4484.

3. Z Liao, *et al.* Inhibition of human tyrosyl-DNA phosphodiesterase I by aminoglycoside antibiotics and ribosome inhibitors. Mol Pharmacol. 2006 Jul;70(1):366–372.

4. TS Dexheimer, *et al.* Tyrosyl-DNA phosphodiesterase as a target for anticancer therapy. Anticancer Agents Med Chem. 2008 May;8(4):381–389.

Patent Status: U.S. Provisional Application No. 61/268,130 filed 08 Jun 2009 (HHS Reference No. E–093–2009/0–US–01).

Licensing Status: Available for licensing.

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

Collaborative Research Opportunity: The National Cancer Institute, Laboratory of Molecular Pharmacology is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize topic of invention or related laboratory interests. Please contact John D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Biomarkers for Osteoarthritis

Description of Technology: Osteoarthritis is chronic, often progressive and substantially disabling condition that becomes more common with advanced age. Osteoarthritis commonly involves the knees, hands, hips, neck and back resulting in pain and limitations of movement.

Unfortunately clinically available tests are neither capable of detecting osteoarthritis early in its development, nor sensitive enough to adequately assess disease progression. A better means of diagnosing early osteoarthritis and its progression that can be used to assess the response to therapeutic treatments is needed. The currently available laboratory techniques are highly sensitive but either lack specificity or require large volumes of sample. Rolling Circle Amplification (RCA) is new technology that precisely localizes unique signals arising from single reporter molecules. RCA has been incorporated into antibody-based microarray system protein chips that enable testing with high sensitivity and specificity for hundreds of proteins simultaneously, using small sample volumes.

This invention describes a method of using RCA technology for detecting the expression of serum proteins that are perturbed in osteoarthritis patients. The results of this testing can be used to identify proteins associated with osteoarthritis presence, prediction of osteoarthritis development and prognosis, predict response to osteoarthritis treatment and potentially also identify future anti-osteoarthritic drugs.

Inventors: Shari M. Ling *et al.* (NIA).

Patent Status: U.S. Patent Application No. 11/573,711 filed 14 Feb 2007 (HHS Reference No. E–354–2004/0–US–07) and related international applications.

Licensing Status: Available for licensing.

Licensing Contact: Charlene A. Sydnor, PhD; 301–435–4689; *sydnorc@mail.nih.gov.*

VAC–BAC Shuttle Vector System for Generating Recombinant Poxviruses

Description of Technology: This invention relates to a VAC–BAC shuttle vector system for the creation of recombinant poxviruses from DNA cloned in a bacterial artificial chromosome. A VAC–BAC is a bacterial artificial chromosome (BAC) containing a vaccinia virus genome (VAC) that can replicate in bacteria and produce infectious virus in mammalian cells.

Applications:

• VAC–BACs can be used to modify vaccinia virus DNA by deletion, insertion or point mutation or add new DNA to the VAC genome with methods developed for bacterial plasmids, rather than by recombination in mammalian cells.

• It can be used to produce recombinant vaccinia viruses for gene expression.

• It can be used for the production of modified vaccinia viruses that have improved safety or immunogenicity.

Advantages:

• VAC–BACs are clonally purified from bacterial colonies before virus reconstitution in mammalian cells.

• Manipulation of DNA is much simpler and faster in bacteria than in mammalian cells.

• Modified genomes can be characterized prior to virus reconstitution.

• Only virus with modified genomes will be produced so that virus plaque isolations are not needed.

• Generation of a stock of virus from a VAC–BAC is accomplished within a week rather than many weeks.

• Multiple viruses can be generated at the same time since plaque purification is unnecessary.

Inventors: Bernard Moss and Arban Domi (NIAID).

Related Publications:

1. A Domi and B Moss. Cloning the vaccinia virus genome as a bacterial artificial chromosome in Escherichia coli and recovery of infectious virus in mammalian cells. Proc Natl Acad Sci USA. 2002 Sep 17;99(19):12415–12420.

2. A Domi and B Moss. Engineering of a vaccinia virus bacterial artificial

chromosome in Escherichia coli by bacteriophage lambda-based recombination. Nat Methods. 2005 Feb;2(2):95–97.

Patent Status: U.S. Patent No. 7,494,813 issued 24 Feb 2009 (HHS Reference No. E–355–2001/2–US–02).

Licensing Status: Available for licensing.

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

Dated: December 23, 2009.

Richard U. Rodriguez,

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

[FR Doc. E9–31075 Filed 12–30–09; 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.

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Fourier X-ray Scattering and Phase-Contrast Imaging: Enhanced Contrast and Sensitivity of X-ray Images

Description of Technology: The invention offered for licensing is broadly applicable to medical diagnostic imaging, biological imaging, industrial non-destructive testing, security screening, and other routine x-ray inspections. The invention provides a method and apparatus that can significantly improve and enhance the contrast and sensitivity of x-ray images. More specifically, the method described in the invention provides a technique to obtain in a single shot x-ray diffraction, differential phase-contrast, as well as the conventional absorption images. X-ray diffraction reveals information about microscopic structures in the imaged object from nanometer to micrometer scales which enables detection of specific materials and disease pathologies that are invisible in conventional x-ray images. The main advantage of the invention over prior art is the single-shot capability without the need to scan an analyzer crystal or grating, and without the need for any hardware beyond standard radiography equipment. It also offers flexibility in hardware configuration to target specific materials by their diffraction signature. For this reason the invention is highly adaptable and well suited for day-to-day applications of x-ray radiography and computed tomography.

In one of the embodiments of the invention for example, a scattering imaging method uses a transmission grid to modulate the intensity of a beam of an x-ray radiation source. A detector captures a raw image from the modulated intensity pattern. A diffraction image can be automatically generated from the detected modulated intensity pattern.

In yet another embodiment, both a diffraction image and a differential phase-contrast image are obtained in a single exposure. Advantageously, commercially available x-ray grids and radiography machines can be used for this method, and exact positioning of the grid is unnecessary, as the method works for any non-zero distance between the grid and the detector. Thus, the speed and ease of implementation makes it suitable for both planar radiography and 3D computed tomography. In addition to its medical diagnostics significance, the invention can be utilized in other, non-medical applications such as non-destructive inspections and security screening.

Applications

- Medical diagnostic radiography and computed tomography. For example, imaging blood vessels, imaging of bones (*i.e.,* osteoporosis, fractures).
- Non-invasive characterization of material microscopic structures by planar radiography or 3D computed tomography implementations of the invention.
- Detection of materials by their diffraction signature in x-ray inspections and security screening.

Advantages: Although x-ray diffraction and phase-contrast imaging can detect materials and structures that are invisible by conventional absorption images, current techniques remain difficult to implement due to requirements for specialized x-ray optical components and/or brilliant sources, and lengthy scanning of analyzer components such as perfect crystals or high-density gratings. A recent publication (US2007/0183563 A1) mentioned that by using a detector with elements less than ⅓ of the pitch of an analyzer grating, it is possible to obtain differential phase-contrast images in one measurement without the need to scan. US2007/0183580 A1 further elaborates on this technique and specifies that the detector elements are an integer fraction of the grating pitch so that sub-groups of the detectors can report x-ray intensities of different portions of a grating period, from which the phase shift of the grating pattern is measured. Such detectors are highly challenging to realize, and are not able to cope with varying pitches or patterns of x-ray beam modulation.

It is additionally known in the art to remove the effects of scattering with the use of grids, gratings, or other masks of periodically arranged opaque areas. Specifically, a mask or multiple masks of periodically arranged opaque areas are placed in the x-ray path, such that periodic dark shadows are created on a recorder surface either by direct geometric shadowing or by wave-interference effects. The shadow areas only receive x-ray which is scattered in the object. The signals of these shadow areas are subtracted from the raw image to yield an image free of the effects of scattering.

Nonetheless, the above variations require exacting procedures or are expensive, making the prior art ill-suited for today's routine x-ray imaging applications, including non-destructive testing (*e.g.,* component inspection without damage), security screening, and medical diagnostic exams.

The present technology overcomes the drawbacks of the prior art by allowing the acquisition of x-ray diffraction, differential phase-contrast and absorption images all in a single exposure without the need for scanning or any hardware beyond commercial radiography equipment.

It is particularly flexible when compared to prior art in that the number of transmission grids, their patterns and their positions can all be adjusted to selectively detect or enhance specific materials, such as contrast agents in medical diagnostic imaging or explosive materials in security screening.

Development Status: The invention is fully developed.