Subject name	Address	Effective date
WETTEROW, MELANIE	PHOENIX, AZ	2/20/2005
WHITE, SEAN	GLENDALE, AZ	2/20/2005
WHITTENTON, ANGELA	COATS, NC	2/20/2005
WILD, LISA	COLUMBIA, CT	2/20/2005
WILLIAMS, PATRICIA	ANNANDALE, VA	2/20/2005
WILLIAMS, WARREN	OAKLAND, CA	2/20/2005
WOOLLEY, TODD	OLYMPIA, WA	2/20/2005
ZIBA, GRACE	LOMA LINDA, CA	2/20/2005
FRAUD/KICKBACKS/PROHIBITED ACTS/SETTLEMENT AGREEMENTS		
GLANZER, ELROY	IDAHO FALLS, ID	2/18/2004
OWNED/CONTROLLED BY CONVICTED ENTITIES		
MONTECINO'S DRUGS, INC	MARRERO, LA	2/20/2005
VALLEY COUNTRY CARE	EDEN VALLEY, MN	2/20/2005
DEFAULT ON HEAL LOAN		
BUKOWSKI, TODD	WASHINGTON, DC	11/19/2004
MANRIQUEZ, ANTONIO	COACHELLA, CA	2/20/2005
RICHARDS, JOHN	WASHINGTON, DC	2/20/2005

Dated: February 1, 2005.

Katherine B. Petrowski,

Director, Exclusions Staff, Office of Inspector General.

[FR Doc. 05–2369 Filed 2–7–05; 8:45 am]

BILLING CODE 4150–04–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, DHHS.

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.

Methods for Treating Active Uveitis

Robert Nussenblatt (NEI) and Thomas Waldmann (NCI), Zhuqing Li (NEI), Ronald Buggage (NEI).

U.S. Provisional Patent Application No. 60/616,760 filed 06 Oct 2004 (DHHS Reference No. E–328–2004/0–US–01).

Licensing Contact: Susan Carson; 301/435–5020; *carsonsu@mail.nih.gov.*

Intraocular inflammatory disease (uveitis) is characterized by pain and a decrease in vision that can lead to blindness if not treated appropriately. The incidence and prevalence of the disease are approximately 52/100,000 and 112/100,000, and this translates into an incidence of 151,000 per year and a prevalence of 322,000. The numbers are expected to increase as the population ages. Treatment of severe uveitis often focuses on the control of the inflammatory symptoms using high dose corticosteroids, cytotoxic drugs or other immunosuppressive agents and there is a need for therapies that reduce the major side effects associated with the prolonged use of systemic steroids (*e.g.* hyperglycemia, osteoporosis and loss of immunocompetence).

Daclizumab is a humanized anti-Tac (HAT) antibody that specifically binds to the alpha subunit (CD25 or Tac subunit) of the human high affinity interleukin-2 (IL–2) receptor expressed on the surface of activated lymphocytes. Dr. Nussenblatt and colleagues at the NEI have previously shown that daclizumab can be used to successfully treat quiescent uveitis. Long term daclizumab therapy at a dose of 1mg/kg can be used instead of standard immunosuppressive agents to treat severe uveitis for more than 4 years with no adverse effects attributable to the medication, and subcutaneously administered daclizumab also appeared to be clinically effective. However, subjects with active uveitis were less likely under this regimen to have their disease controlled (J. Autoimmunity (2003) 21, 283–293).

The present invention targets patients with refractory, active uveitis and consists of a high dose intravenous induction therapy using daclizumab at two different doses and times followed by a longer term maintenance therapy. Positive therapeutic effects have been seen with this protocol in a small group of patients within 4–6 weeks after the initiation of therapy. As previous work indicated that IL–2R receptors have a slow turnover rate on CD4 positive subpopulation of lymphocytes, a possible mechanism of action of this new protocol is saturation of CD25 (TAC) receptors on cells in sequestered sites.

Available for licensing are methods directed to this treatment of active uveitis using a high dose pulsatile induction protocol of an interleukin-2 (Il–2) receptor antagonist. Methods are also provided for the treatment of corneal transplant rejection, limbal stem cell rejection following transplantation, optic neuritis and dry eye.

Novel Thermostable Y-Family DNA Polymerases

Roger Woodgate (NICHD), John P. McDonald (NICHD), and Wei Yang (NIDDK).

U.S. Provisional Patent Application No. 60/573,684 filed 20 May 2004 (DHHS Ref No. E–166–2004/0–US–01); U.S. Provisional Patent Application No. 60/623, 490 filed 29 Oct 2004 (DHHS Ref No. E–166–2004/1–US–01).

Licensing Contact: Susan Carson; 301/435–5020; *carsonsu@mail.nih.gov.*

Y-family polymerases are able to bypass lesions in DNA that would otherwise block replication by high fidelity DNA polymerases and are key to the effective study of ancient DNA and for use in forensic medicine. These enzymes are ubiquitous and are found in all kingdoms of life: bacteria, archaea and eukaryotes. The number of proteins related to the Y-family polymerases is well over 200 orthologs and despite being closely related at the phylogenetic level, the few polymerases now characterized, each show a unique set of properties including processivity, fidelity, and the ability to bypass certain types of DNA. Y-family polymerases from thermostable organisms are of particular interest because the enzymes isolated from such species tend to be more stable, easy to work with and may have more utility in assays at higher temperatures, such as Polymerase Chain Reaction (PCR). For example, the thermostable archeal *Sulfolobus solfataricus* DinB-like polymerase Dpo4 can bypass lesions by generally inserting the correct complementary nucleotide opposite a variety of damaged bases and can, under appropriate conditions substitute for Taq polymerase in PCR applications [NAR (2001) 29, 4607–4616; DHHS Ref. No. E–232–2001/0]. Additionally, functional and structural organization of this family of polymerases permits domain swapping designed to optimize specific properties of use in novel applications [J. Biol. Chem. (2004) 279, 32932–32940].

Dr. Woodgate's group at the National Institute of Child Health and Development have expanded their earlier work and have now discovered several additional thermostable dpo4 homologs from other strains found in the *Sulfolobaceae* family, some of which have optimal growth temperatures higher than 80°C. These novel DinB-like proteins have thermostable DNA polymerase activity and are capable of: (1) PCR amplifications over 1kb in length, (2) replication past DNA lesions such as abasic sites and CPD (cis-syn cyclobutane pyrimidine dimer) lesions and (3) incorporation of several different labeled DNA nucleotides into DNA during replication. These enzymes may therefore be a good substitute for Taq polymerase in applications utilizing fluorescent nucleoside triphosphate derivatives. These lesion-bypassing Dpo4-like polymerases could also be included along with a conventional thermostable polymerase in a PCR protocol designed to amplify old or damaged DNA samples which could greatly increase recoverability, accuracy and length of products. Other applications could include labelling or tagging DNA, real-time PCR, detection of SNPs, mismatches or DNA lesions, mutagenic PCR, directed-evolution methods and expanding the ''DNA alphabet'' utilizing non-natural nucleotides.

Available for licensing are seven novel Y-family polymerases. Claims are directed to these sequences and chimeras, as well as to methods of identifying other Y-family polymerases and generating other chimeric Y-family polymerases and methods of use. These enzymes and methods of identifying and generating novel Y-family polymerases should be of interest to forensic DNA service companies as well as to research reagent companies pursuing novel thermophlic enzymes for use in ancient and damaged DNA analysis and for novel applications with modified nucleotides.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Related technologies available for licensing as research tools include: DHHS Ref. No. E–232–2001/0 (dpo4 Y-family polymerase) and DHHS E–229–2001/0 (pol iota Y-family polymerase).

Rapid, Efficient In Vivo Site-Directed Mutagenesis Using Oligonucleotides

Francesca Storici, Michael A. Resnick, Lysle Kevin Lewis (NIEHS).

PCT Application No. PCT/US02/23634 filed 26 July 2002, which published as International Publication No. WO03/012036 on 13 Feb 2003 (DHHS Reference No. E–204–2001/0–PCT–02).

National Stage Entry: EPC, CA, AU, US, JP.

U.S. Patent Application No. 10/484,989 filed 26 Jan 2004 (DHHS Reference No. E–204–2001/0–US–07).

Licensing Contact: Susan Carson; 301/435–5020; *carsonsu@mail.nih.gov.*

The rapid modification of genes provides opportunities to study gene function and evaluate drug responsiveness. Scientists at the National Institute for Environmental and Health Sciences have developed a new system in yeast, *delitto perfetto,* which provides for rapid, efficient and accurate in vivo genomic mutagenesis using oligonucleotides (IROs) and involves the complete removal of the heterologous sequence previously integrated at the target locus (Nature Biotechnol. (2001) 19, 773–776). They have demonstrated that synthetic oligonucleotides can target a desired mutation to almost any chromosomal locus where a marker cassette has been previously integrated. The oligonucleotides, which are designed with short sequence homology to sites up- and down-stream of the marker cassette, replace the marker cassette with the chosen mutation without leaving any heterologous sequence in the targeted locus. Since the system always provides selection for the clones containing the desired mutation, it can be used to generate any kind of modification: *i.e.*, it is not constrained by the generation of mutations that provide a detectable phenotype. Additionally, induction of double-strand breaks (*delitto perfetto-DSB*) in vivo before standard transformation procedures provides 1,000 to 10,000 fold stimulation of oligonucleotide targeting, resulting in 5–20% of all cells in the population being efficiently targeted by small oligonucleotides (PNAS (2003), 100, 14994–14999). With such a high stimulation of targeting even gross rearrangements, like large DNA deletions, chromosome fusions, circularizations, reciprocal or non reciprocal translocations are obtained with high frequency and direct selection.

The core invention is a novel self-cloning system for simple and high-throughput in vivo site-directed mutagenesis applicable to all organisms capable of homologous recombination and developed in the non-pathogenic yeast *Saccharomyces cerevisiae.* Since changes are created through a self-cloning process, this system could represent a highly versatile tool to generate modifications of genes in yeasts for commercial application in the food and beverage industries (such as, baking, brewing, wine and sake) without the resulting organisms being classified as GMO (genetically modified organisms). This approach could also be well positioned within drug discovery protocols where the need to mutagenize particular target sequences forms an integral part of the drug development process.

Delitto perfetto-DSB is efficient for targeting homologous sequences that are close or distant to the DSB and in the presence of a competing homologous chromosome in diploid cells, and can strongly stimulate recombination with single-stranded DNA, without strand bias. The mechanism of DSB repair with oligonucleotides follows primarily a single-strand annealing pathway of recombinational repair. This novel system is also independent of restriction sites, requires minimal sequence

analysis. This method has been used in *S. cerevisiae* for many yeast chromosomal genes and the human gene p53 and has obvious potential for use with YAC and TAR clones. Claims are directed to several methods for generating DNA nucleic acid mutations in vivo and are applicable to any organism that has a homologous recombination system, as well as to kits. This methodology is available for licensing and is a highly versatile tool of direct use to drug discovery, pharma and research reagent companies as well as to companies working with industrial yeast strains.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Related technologies also available for licensing include: DHHS Ref. No. E–121–1996/0–US–06, Transformation-Associated Recombination Cloning (U.S. Patent No. 6,391,642 issued 21 May 2002); and DHHS Ref. No. E–262–1984/0–US–03, Process for Site Specific Mutagenesis Without Phenotypic Selection (U.S. Patent No. 4,873,192 issued 10 Oct 1989).

The Whey Acidic Protein (WAP) Promoter and Its Use to Express Therapeutic Proteins in the Milk of Transgenic Mammals

Lothar Hennighausen (NIDDK), Heiner Westphal (NICHD), *et al.* U.S. Patent No. 6,727,405 issued 27 Apr 2004 (DHHS Reference No. E–411–1987/0–US–03).

Licensing Contact: Susan Carson; 301/435–5020; *carsonsu@mail.nih.gov.*

Transgenic animals can be engineered to express complex human proteins at high concentrations in milk. Protein replacement therapy is often the only treatment available for congenital diseases such as hemophilia or lysosomal storage disease, and the cost of treatment can be high with the therapeutic protein market estimated to reach more than $50 billion by 2010.

U.S. Patent No. 6,727,405 has recently been issued (expiry date 2021) to NIH scientists and their collaborators. This patent provides for a non-human mammal such as mouse, sheep, pig, goat and cow whose genome contains a DNA sequence comprising a milk serum protein (whey acidic protein) promoter linked to a heterologous gene sequence and secretory peptide, as well as methods for producing a secreted protein into the transgenic animal's milk and claims directed to the DNA construct. The invention permits the production of any desired protein in an easily maintained, stable, mammalian bioreactor, which is capable not only of producing the desired protein in milk, but can also pass the ability to do so to its female offspring. Although other methods of obtaining recombinant protein products are available, these require inefficient, expensive purification of the protein from the blood or from cell culture media and there remains a need for an efficient and cost effective method for producing therapeutic proteins.

This WAP promoter platform technology provides a viable alternative to other milk protein promoters and is available for non-exclusive licensing.

Dated: January 31, 2005.

Steven M. Ferguson,

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

[FR Doc. 05–2364 Filed 2–7–05; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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ACTION: Notice.

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A3 Adenosine Receptor Agonists

Kenneth A. Jacobson *et al.* (NIDDK).

U.S. Provisional Patent Application No. 60/608,823 filed 09 Sep 2004 (DHHS Reference No. E–248–2004/0–US–01).

Licensing Contact: Marlene Shinn-Astor; (301) 435–4426; *shinnm@mail.nih.gov.*

Researchers have been pursuing compounds that activate or inhibit adenosine A3 receptors because these cell membrane proteins have a wide range of physiological and disease-related effects and are thus considered to be promising drug targets. The adenosine A3 receptors are G-protein-coupled receptors and are found mostly in brain, lung, liver, heart, kidney, and testis. When this receptor is activated moderately, a cytoprotective effect is observed, such as reducing damage to heart cells from lack of oxygen. However, at high levels of stimulation they can cause cell death. Both agonists and antagonists are being tested for therapeutic potential, for example, treatment of cancer, heart conditions, neurological conditions, pain, asthma, inflammation and other immune implications.

Adenosine receptors have provided fertile leads for pharmaceutical development, and there are currently a variety of adenosinergic compounds advancing toward clinical trials. Therapeutics which target the adenosine A3 receptors is now an emerging focus that the major pharmaceutical companies are developing. Smaller companies are also developing drugs that stem from proprietary technology targeting adenosine A3 receptors. These companies have products in clinical trials for colorectal cancer and rheumatoid arthritis.

This invention pertains to highly potent A3 adenosine receptor agonists, pharmaceutical compositions comprising such nucleosides, and a method of use of these nucleosides.

This research has been published, in part, in S. Tchilibon, B.V. Joshi, S.-K. Kim, H.T. Duong, Z.-G. Gao, and K.A. Jacobson, ''N-methano adenosine derivatives as A3 receptor agonists,'' J. Med. Chem., ASAP web release date 23 Sep 2004, doi: 10.1021/jm049580r.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Apparatus for Multifocal Deposition and Analysis

Bradford Wood, Alexander Gorbach, Ziv Neeman, Julia Hvisda (all of NIHCC), *et al.* U.S. Provisional Patent Application No. 60/403,875 filed 16 Aug 2002 (DHHS Reference No. E–248–2001/0–US–01); International Application Number PCT/US03/25575 filed 14 Aug 2003, which