

delivery. AAV is not considered pathogenic and transduces stably dividing and non-dividing cells; and shows good serotype specificity to various cell types for targeted gene delivery.

This invention is a highly scalable AAV vector production method in insect cells. This production method produces virus particles much more efficiently than the standard mammalian cell culture system. For example, to produce  $10^{15}$  rAAV particles may require 5,000 175cm<sup>2</sup> flasks. With this new production method, 10 to 50 liters of Sf9 insect cells are required to produce the same quantity of AAV particles. This is a striking improvement in production efficiency. In addition, all serotypes of AAV can be produced, with the respective AAV serotype vectors available for the immediate scale up of AAV production.

This invention coupled with NIH invention E-308-2001, titled "Scalable Purification of AAV2, AAV4 or AAV5 Using Ion-Exchange Chromatography," gives a licensee a highly scalable production and purification system for efficient clinical trial development and commercialization of AAV.

#### Scalable Purification of AAV2, AAV4 or AAV5 Using Ion-Exchange Chromatography

Nikola Kaludov (NIDCR)

John Chiorini (NIDCR)

Serial No. 60/381,180 filed 17 May 2002; Serial No. 10/166,347 filed 17 May 2003 (DHHS Reference No. E-308-2001/0).

Licensing Contact: Jeffrey Walenta; 301/435-4633; walentaj@mail.nih.gov.

Adeno-associated viruses (AAVs) constitute, as a group, the vehicle of choice for gene therapy because of several attractive features. Among others, AAVs are less pathogenic than other viruses, and they can be used for the long-term expression of therapeutic genes.

This invention describes a simple ion-exchange (HPLC) methodology to purify different AAV serotypes. The protocol, which can be readily scaled up, details the efficient concentration of fully infective AAV particles, and is applicable to a number of promising serotypes for which efficient purification methodologies are currently lacking. Significantly, the method consistently produces higher infectivity per particle ratios than standard methods.

This invention, coupled with NIH invention E-325-2001, entitled "Highly Scalable Production of AAV in Insect Cells," would give a licensee a

purification system that can be readily scaled-up to efficiently produce recombinant adeno-associated viruses for clinical trial development.

This work is further described in Kaludov *et al.*, *Hum. Gene Ther.* (2002) 13:1235-43.

Dated: June 16, 2003.

**Steven M. Ferguson,**

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

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## 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 agencies 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.

#### Oligodeoxyribonucleotides Comprising O<sup>6</sup>-Benzylguanine and Their Use

Robert Moschel *et al.* (NCI)

U.S. Patent 6,060,458 issued 09 May 2000,

Licensing Contact: George Pipia; 301/435-5560; pipia@mail.nih.gov.

The DNA repair protein, O<sup>6</sup>-alkylguanine-DNA alkyltransferase (alkyltransferase) is the primary source of tumor cell resistance to alkylating chemotherapeutic drugs that modify the O<sup>6</sup>-position of DNA guanine residues. Inactivators of alkyltransferase are currently in use to enhance

chemotherapy by these alkylating drugs. The prototype inactivator, O<sup>6</sup>-benzylguanine is currently in Phase II and III clinical trials as an adjuvant to improve chemotherapy. Although O<sup>6</sup>-benzylguanine is a promising inactivator, it is not an ideal drug since it is only sparingly soluble in water and it is not effective in inactivating some mutant alkyltransferase proteins that could possibly be produced after repeated chemotherapy cycles.

Oligodeoxyribonucleotides containing O<sup>6</sup>-benzylguanine residues represent another class of alkyltransferase inactivators. They are extremely water soluble alkyltransferase inactivators that can efficiently inactivate the alkyltransferase protein at much lower concentrations than O<sup>6</sup>-benzylguanine. In addition, oligodeoxyribonucleotides containing O<sup>6</sup>-benzylguanine are effective in activating several mutant alkyltransferase proteins that are highly resistant to inactivation by O<sup>6</sup>-benzylguanine. For example, oligodeoxyribonucleotides between 7 and 11 nucleotides in length containing multiple O<sup>6</sup>-benzylguanines are effective in inactivating several alkyltransferase molecules per oligonucleotide molecule at 300 fold lower concentrations than O<sup>6</sup>-benzylguanine. These same substrates are also effective inactivators of mutant alkyltransferase molecules that are resistant to inactivation by O<sup>6</sup>-benzylguanine. In addition, positioning O<sup>6</sup>-benzylguanine near the 3'-or 5'-terminus of these oligodeoxyribonucleotides improves their resistance to degradation by cellular nuclease proteins. Therefore, oligodeoxyribonucleotides containing multiple O<sup>6</sup>-benzylguanine residues may be more effective chemotherapy adjuvants than O<sup>6</sup>-benzylguanine as the free base.

#### Imidazoacridones with Anti-Tumor Activity

Christophe Michejda *et al.* (NCI) DHHS Reference No. E-289-1999 (and related U.S. and foreign patents/applications) and U.S. Patent 6,541,483 issued 01 April 2002 (and related U.S. and foreign patents/applications),

Licensing Contact: George Pipia; 301/435-5560; pipia@mail.nih.gov.

The present invention relates to novel bifunctional molecules with anti-tumor activity. These agents are composed of an imidazoacridone moiety linked by a nitrogen containing aliphatic chain of various length and rigidity to another aromatic ring system capable of intercalation to DNA.

Previous studies on related symmetrical bis-imidazoacridones revealed that only one planar imidazoacridone moiety intercalates into DNA. The second aromatic moiety, which is crucial for biological activity, along with the linker resides in DNA minor groove, and is believed to interact with DNA-binding proteins (most likely, transcription factors and /or repair proteins). The symmetrical bis-imidazoacridones arrest the growth of sensitive cancers (especially colon cancers) but do not kill the tumors. It was hypothesized that the growth arrest was due to the inability of the affected tumor cells to repair DNA damage caused by the compounds. Remarkably, bis-imidazoacridones are very well tolerated, are very tissue selective and do not appear to damage normal tissues.

Since the binding of the symmetrical bis-imidazoacridones to DNA was unsymmetrical, the inventors have developed unsymmetrical compounds in which one imidazoacridone moiety was replaced by other intercalating groups, with the expectation that this would enhance biological activity while retaining the remarkable tissue selectivity and low systemic toxicity. The new compounds contain intercalating moieties such as 3-chloro-7-methoxyacridine or naphthalimide along with the original imidazoacridones.

These new compounds, especially those containing naphthalimide moiety, are extremely cytotoxic against variety of tumor cells in vitro (IC<sub>50</sub> at low nanomolar range) and kill tumor cells by inducing apoptosis. In vivo, in nude mice xenografted with human tumors, the compounds significantly inhibited the growth of such tumors as colon tumor HCT116 and Colo205 as well pancreatic tumors (lines 6.03 and 10.05 freshly established from a patient). These compounds are extremely potent agents against hepatocellular carcinoma as evidenced by their ability to eradicate liver cancer in an orthotopic liver cancer model in rats. The primary molecular target of these very potent compounds is the inhibition of both topoisomerase I and II, although other targets may be important as well. Remarkably, no toxicity was observed at the therapeutic doses. These are among the most potent agents known against cancers of the GI tract and appear to be tolerated very well.

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**Steven M. Ferguson,**

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

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#### Zap70 Protein Expression as a Marker for Chronic Lymphocytic Leukemia (CLL)

Louis M. Staudt *et al.* (NCI) Serial No. 60/375,966 filed 25 Apr 2002 and Serial No. 10/309,548 filed 03 Dec 2002

*Licensing Contact:* Catherine Joyce; 301/435-5031; [joycec@mail.nih.gov](mailto:joycec@mail.nih.gov).

The presence or absence of somatic mutations in the expressed immunoglobulin heavy chain variable regions (IgVH) of chronic lymphocytic leukemia (CLL) cells provides prognostic information. Patients whose leukemic cells express unmutated IgVH regions (Ig-unmutated CLL) often have progressive disease whereas patients whose leukemic cells express mutated IgVH regions (Ig-mutated CLL) more often have an indolent disease. Given the difficulty in performing IgVH sequencing in a routine diagnostic

laboratory, this prognostic distinction is currently unavailable to most patients.

The present invention relates to the discovery that ZAP-70 expression also distinguishes the two CLL subtypes. Ig-unmutated CLL expressed ZAP-70 5.54-fold more highly than Ig-mutated CLL. ZAP-70 expression correctly predicted IgVH mutation status in 93% of patients, and ZAP-70 expression and IgVH mutation status were comparable in their ability to predict time to treatment requirement following diagnosis. Clinically applicable RNA and protein-based assays for ZAP-70 expression have been developed. These assays would yield important prognostic information for CLL patients.

The above-mentioned invention is available for licensing on an exclusive or non-exclusive basis.

#### ABCA13 Nucleic Acids and Proteins, and Uses Thereof

Michael Dean *et al.* (NCI)

DHHS Reference No. E-304-2000/0 filed August 20, 2003

*Licensing Contact:* Catherine Joyce; 301/435-5031; e-mail: [joycec@mail.nih.gov](mailto:joycec@mail.nih.gov).

This technology relates to the identification of a novel gene in the ABC (ATP-binding cassette transporter) gene superfamily, the ABCA13 gene. The ABC proteins are involved in extra- and intracellular membrane transport of various substrates such as ions, amino acids, peptides, sugars, vitamins, or steroid hormones and at least 14 members of the ABC gene superfamily have been described as associated with human disease. ABCA13 has high similarity with other ABCA subfamily genes that are associated with human inherited diseases. This includes ABCA1, the gene responsible for the cholesterol transport disorders Tangier disease and familial hypoalphalipoproteinemia, and ABCA4, the gene responsible for several retinal degeneration disorders. The ABCA13 gene is expressed in trachea, testes, and bone marrow. The ABCA13 gene maps to chromosome 7p12.3, a region that contains an inherited disorder affecting the pancreas and bone marrow (Shwachman-Diamond syndrome) as well as a locus involved in T-cell tumor invasion and metastasis (INM7), and therefore is a positional candidate for these disorders.

The above-mentioned invention is available for licensing on an exclusive or non-exclusive basis.