

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),

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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.

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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,

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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),

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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.