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United States Patent [19][11] **Patent Number:** **5,817,491**

Yee et al.

[45] **Date of Patent:** **Oct. 6, 1998**

- [54] **VSV G PSEUDOTYPED RETROVIRAL VECTORS**
- [75] **Inventors:** Jiing-Kuan Yee, Del Mar; Nobuhiko Eml, Nagoya; Theodore Friedmann, La Jolla; Douglas J. Jolly, Leucadia; Jack R. Barber, San Diego, all of Calif.
- [73] **Assignees:** The Regents of the University of California, Oakland; Chiron Viagene, Inc., Emeryville, both of Calif.
- [21] **Appl. No.:** 361,839
- [22] **Filed:** Dec. 22, 1994

Related U.S. Application Data

- [63] Continuation-in-part of Ser. No. 344,743, Nov. 23, 1994, abandoned, and Ser. No. 283,704, Aug. 1, 1994, which is a continuation of Ser. No. 114,288, Aug. 30, 1993, abandoned, which is a continuation of Ser. No. 740,766, Aug. 8, 1991, abandoned, which is a continuation-in-part of Ser. No. 658,632, Feb. 19, 1991, abandoned, said Ser. No. 344,743, is a continuation of Ser. No. 139,994, Oct. 20, 1993, abandoned, which is a continuation of Ser. No. 965,084, Oct. 22, 1992, abandoned, which is a continuation of Ser. No. 586,603, Sep. 21, 1990, abandoned.
- [51] **Int. Cl.⁶** C12N 15/86; C12N 5/10; C12N 5/08
- [52] **U.S. Cl.** 435/172.3; 435/320.1; 435/325; 435/366; 424/93.2
- [58] **Field of Search** 435/172.3, 320.1, 435/240.1, 240.2, 325, 326; 424/93.2

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Primary Examiner—George C. Elliot
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Attorney, Agent, or Firm—Karl Bozicevic; Carol Francis; Bozicevic & Reed

[57] **ABSTRACT**

An enveloped vector particle contains gag and pol proteins from a retrovirus, a nucleic acid sequence and an envelope that includes VSV G envelope glycoprotein. The vector particle can be used to introduce nucleic acids into cells.

22 Claims, 10 Drawing Sheets



US005591624A

United States Patent [19][11] **Patent Number:** **5,591,624****Barber et al.**[45] **Date of Patent:** **Jan. 7, 1997**[54] **RETROVIRAL PACKAGING CELL LINES**[75] **Inventors:** Jack R. Barber, San Diego; Douglas J. Jolly, La Jolla; James G. Respass; Stephen M. W. Chang, both of San Diego, all of Calif.[73] **Assignee:** Chiron Viagene, Inc., Emeryville, Calif.[21] **Appl. No.:** 156,789[22] **Filed:** Nov. 23, 1993**Related U.S. Application Data**

[63] Continuation of Ser. No. 800,921, Nov. 27, 1991, abandoned, which is a continuation-in-part of Ser. No. 586,603, Sep. 21, 1990, abandoned, which is a continuation-in-part of Ser. No. 565,606, Aug. 10, 1990, abandoned, which is a continuation-in-part of Ser. No. 395,932, Aug. 8, 1989, abandoned, which is a continuation-in-part of Ser. No. 170,515, Mar. 21, 1988, abandoned.

[51] **Int. Cl.⁶** C12N 5/10; C12N 5/08[52] **U.S. Cl.** 435/240.2; 435/172.3; 435/240.1; 435/320.1[58] **Field of Search** 435/320.1, 240.1, 435/240.2, 172.3[56] **References Cited****U.S. PATENT DOCUMENTS**4,650,764 3/1987 Temin et al. 435/240.2
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Primary Examiner—Mindy Fleisher*Assistant Examiner*—Johnny F. Railey, II*Attorney, Agent, or Firm*—Seed & Berry; Norman J. Kruse; Robert P. Blackburn[57] **ABSTRACT**

The invention described herein allows the production of recombinant retroviruses (retroviral vector particles) from producer cells which are safer and of higher titer than normal. In addition, methods are provided for making helper cells which, when a recombinant retrovirus genome is introduced to make a producer line, produce particles that are targeted toward particular cell types. Methods are also provided for making recombinant retrovirus systems adapted to infect a particular cell type, such as a tumor, by binding the retrovirus or recombinant retrovirus in the particular cell type. Methods are also provided for producing recombinant retroviruses which integrate in a specific small number of places in the host genome, and for producing recombinant retroviruses from transgenic animals.

9 Claims, 10 Drawing Sheets



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Barber et al.

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[54] PACKAGING CELLS

[75] Inventors: Jack R. Barber, San Diego; Douglas J. Jolly, La Jolla; James G. Respass; Stephen M. W. Chang, both of San Diego, all of Calif.

[73] Assignee: Chiron Viagene, Inc.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,591,624.

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[22] Filed: Jun. 5, 1995

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[63] Continuation of Ser. No. 156,789, Nov. 23, 1993, Pat. No. 5,591,624, which is a continuation of Ser. No. 800,921, Nov. 27, 1991, abandoned, which is a continuation-in-part of Ser. No. 586,603, Sep. 21, 1990, abandoned, which is a continuation-in-part of Ser. No. 565,606, Aug. 10, 1990, abandoned, which is a continuation-in-part of Ser. No. 395,932, Aug. 18, 1989, abandoned, which is a continuation-in-part of Ser. No. 170,515, Mar. 21, 1988, abandoned.

[51] Int. Cl.⁶ C12N 15/00; C12N 5/10

[52] U.S. Cl. 435/172.3; 435/235

[58] Field of Search 435/172.3, 235, 435/69.7, 240.2, 320.1; 935/32, 33, 34, 47, 57

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Primary Examiner—Mindy Fleisher

Assistant Examiner—Robert Schwartzman

Attorney, Agent, or Firm—Seed & Berry; Norman J. Kruse; Robert P. Blackburn

[57] ABSTRACT

The invention described herein allows the production of recombinant retroviruses (retroviral vector particles) from producer cells which are safer and of higher titre than normal. In addition, methods are provided for making helper cells which, when a recombinant retrovirus genome is introduced to make a producer line, produce particles that are targeted toward particular cell types. Methods are also provided for making recombinant retrovirus systems adapted to infect a particular cell type, such as a tumor, by binding the retrovirus or recombinant retrovirus in the particular cell type. Methods are also provided for producing recombinant retroviruses which integrate in a specific small number of places in the host genome, and for producing recombinant retroviruses from transgenic animals.



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Kingsman et al.

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(54) **RETROVIRAL VECTORS**

(75) Inventors: **Alan John Kingsman; Susan Mary Kingsman**, both of Oxon; **Narry Kim; Kyriacos Mitrophanous**, both of Oxford, all of (GB)

(73) Assignee: **Oxford BioMedica plc**, Oxford (GB)

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(58) Field of Search **435/320.1, 455, 435/325, 91.4; 424/93.21, 93.2; 536/23.1; 514/44**

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(57) **ABSTRACT**

Retroviral vector production systems for producing lentivirus-based vector particles which are capable of infecting and transducing non-dividing target cells, wherein one or more of the auxiliary genes such as vpr, vif, tat, and nef in the case of HIV-1 are absent from the system. The systems and resulting retrovirus vector particles have improved safety over existing systems and vectors.

71 Claims, 3 Drawing Sheets



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Kingsman et al.

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(54) **RETROVIRAL VECTORS**

(75) **Inventors:** **Alan John Kingsman, Oxon (GB); Susan Mary Kingsman, Oxon (GB); Narry Kim, Oxford (GB); Kyriacos Mitrophanous, Oxford (GB)**

(73) **Assignee:** **Oxford Biomedica (UK) Limited (GB)**

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.⁷** **A61K 48/00**

(52) **U.S. Cl.** **424/93.2; 435/69.1; 435/91.4; 435/320.1; 435/325; 435/455; 514/44; 536/23.72**

(58) **Field of Search** **435/320.1, 69.1, 435/91.4, 324, 455; 424/93.2; 514/44; 536/23.72**

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(57) **ABSTRACT**

Retroviral vector production systems for producing lentivirus-based vector particles which are capable of infecting and transducing non-dividing target cells, wherein one or more of the auxiliary genes such as vpr, vif, tat, and nef in the case of HIV-1 are absent from the system. The systems and resulting retrovirus vector particles have improved safety over existing systems and vectors.

75 Claims, 3 Drawing Sheets



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(12) **United States Patent**
Kingsman et al.

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(45) **Date of Patent:** **May 22, 2001**

- (54) **LENTIVIRAL VECTORS**
- (75) **Inventors:** **Alan John Kingsman; Susan Mary Kingsman**, both of Oxon (GB)
- (73) **Assignee:** **Oxford Biomedica (UK) Limited**, Oxford (GB)
- (*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) **Appl. No.:** **09/284,011**
- (22) **PCT Filed:** **Oct. 17, 1997**
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- (87) **PCT Pub. No.:** **WO95/32300**
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- (52) **U.S. Cl.** **435/320.1; 435/235.1; 435/455; 435/456; 526/24.1**
- (58) **Field of Search** **435/320.1, 455, 435/456, 235.1; 536/24.1; 424/93.2**

- (56) **References Cited**
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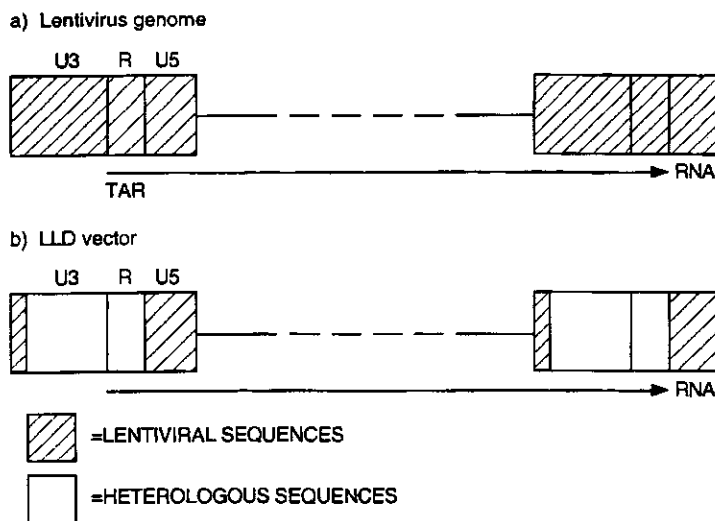
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(57) **ABSTRACT**

Retroviral vector particles capable of infecting and transducing non-dividing mammalian target cells, which vector particles may be based on lentiviruses such as HIV and which have an RNA genome constructed so as to provide in the DNA provirus a non-lentiviral expression control element in the 5'LTR of the provirus.

15 Claims, 4 Drawing Sheets





US006924123B2

(12) **United States Patent**
Kingsman et al.

(10) **Patent No.:** **US 6,924,123 B2**
(45) **Date of Patent:** ***Aug. 2, 2005**

- (54) **LENTIVIRAL LTR-DELETED VECTOR**
- (75) **Inventors:** **Alan John Kingsman, Appleton (GB); Susan Mary Kingsman, Appleton (GB)**
- (73) **Assignee:** **Oxford BioMedica (UK) Limited, Oxford (GB)**
- (*) **Notice:** **Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 186 days.**

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

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(58) **Field of Search** **424/93.1, 93.2, 424/93.6; 435/235.1, 320.1, 69.1, 325, 366**

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(57) **ABSTRACT**

A vector capable of transducing non-dividing and/or slowly dividing cells is provided, wherein the vector is a lentiviral LTR-deleted vector. Also provided is a method for producing a protein of interest in a non-dividing or slowly dividing cell by transducing the cell with a lentiviral LTR-deleted vector and expressing the protein of interest in the cell. In addition, target cells containing the lentiviral LTR-deleted vector are provided.

6 Claims, 6 Drawing Sheets