



US006261787B1

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

(10) **Patent No.:** **US 6,261,787 B1**
(45) **Date of Patent:** ***Jul. 17, 2001**

(54) **BIFUNCTIONAL MOLECULES FOR DELIVERY OF THERAPEUTICS**

(75) Inventors: **Pamela B. Davis**, Cleveland heights;
Thomas W. Ferkol, Jr., Concord, both of OH (US); **Elizabeth Eckman**, Ponte Vedra Beach, FL (US)

(73) Assignee: **Case Western Reserve University**, Cleveland, OH (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/264,032**

(22) Filed: **Mar. 8, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/957,333, filed on Oct. 24, 1997, now Pat. No. 6,072,041, which is a continuation-in-part of application No. 08/655,705, filed on Jun. 3, 1996, now Pat. No. 5,972,900, and a continuation-in-part of application No. 08/656,906, filed on Jun. 3, 1996, now Pat. No. 5,972,901.

(51) **Int. Cl.**⁷ **G01N 33/53**; G01N 33/567; C07K 16/00; A61K 38/00; C07H 21/02

(52) **U.S. Cl.** **435/7.1**; 435/7.21; 435/69.7; 530/391.1; 530/391.7; 530/402; 530/807; 530/866; 514/12; 536/23.1

(58) **Field of Search** 530/866, 867, 530/402, 391.1, 391.7; 514/12; 536/23.1; 435/7.1, 7.21, 69.7

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,100,788 3/1992 Lofdahl et al. 435/69.7

5,108,921 4/1992 Low et al. 435/260.1
5,521,291 5/1996 Curiel et al. 530/391.7
5,763,192 6/1998 Kauffman et al. 435/7.1
5,871,974 2/1999 Huse 435/69.7

OTHER PUBLICATIONS

Ernst Wagner et al. "Transferrin-polycation-DNA complexes: The effect of polycations on the structure of the complex and DNA delivery to cells" Proc. Natl. Acad. Sci. USA vol. 88, pp. 4255-4259, May 1991.

Elizabeth Eckman et al., Pediatric Pulmonology 14 (Suppl.): A229 "Targeting the Polymeric Immunoglobulin Receptor as a Means of Directing Therapeutic Proteins to the Airway" 1997.

Elizabeth Eckman et al., Pediatric Pulmonology 13 (Suppl.): A242 "Structure and Function of Anti-Human Secretory Component FV/Human Alpha-1-Antitrypsin Fusion Proteins" 1996.

Amedeo Cafilisch "Computational combinatorial ligand design: Application to human α -thrombin" Journal of Computer-Aided Molecular Design 10 (1996) 372-396.

(List continued on next page.)

Primary Examiner—Hankyel T. Park

(74) *Attorney, Agent, or Firm*—Banner & Witcoff LTD

(57) **ABSTRACT**

A bifunctional molecule consisting of a therapeutic molecule and a ligand which specifically binds a transcytotic receptor can be transported specifically from the basolateral surface of epithelial cells to the apical surface. This approach provides the ability to deliver a therapeutic molecule directly to the apical surface of the epithelium, by targeting the transcytotic receptor with an appropriate ligand. Thus, the highest concentration of the therapeutic molecule will be at the apical surface, where it can have the greatest therapeutic effect.

16 Claims, 18 Drawing Sheets

