



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

(10) **Patent No.:** **US 6,355,271 B1**
(45) **Date of Patent:** **Mar. 12, 2002**

(54) **THERAPEUTIC CALCIUM PHOSPHATE PARTICLES AND METHODS OF MANUFACTURE AND USE**

FOREIGN PATENT DOCUMENTS

(75) Inventors: **Steve J. D. Bell**, Marietta; **Tulin Morco**, Decatur; **Qing He**, Atlanta, all of GA (US)

FR	7212036	12/1973
FR	7924948	4/1981
GB	1422973	1/1976
WO	WO 90/11092	10/1990
WO	WO 93/17706	9/1993
WO	WO 93/24640	12/1993
WO	WO98/35562	8/1998
WO	WO00/15194	3/2000
WO	WO 00/46147	8/2000

(73) Assignee: **Biosante Pharmaceuticals, Inc.**, Smyrna, GA (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.

OTHER PUBLICATIONS

(21) Appl. No.: **09/496,771**

Academic Press Dictionary of Science and Technology. <http://www.harcourt.com/dictionary/def/2/2/3/1/2231200.html>, Nov. 2000.*

(22) Filed: **Feb. 3, 2000**

Abstracts of Papers Presented at the 1992 meeting on Modern Approaches to New Vaccines, Including Prevention of AIDS, Cold Spring Harbor), *Vaccine* 11: 92 (1993).

Related U.S. Application Data

(60) Provisional application No. 60/118,356, filed on Feb. 3, 1999, provisional application No. 60/118,364, filed on Feb. 3, 1999, and provisional application No. 60/118,355, filed on Feb. 3, 1999.

Aldovini and R. A. Young, "Humoral and cell-mediated immune responses to live recombinant BCG-HIV vaccines," *Nature* 351: 479-482 (1991).

(51) **Int. Cl.**⁷ **A61K 9/14**

Ascadi et al., "Human dystrophin expression in mdx mice after intramuscular injection of DNA constructs," *Nature* 352: 815-818 (1991).

(52) **U.S. Cl.** **424/489**; 424/491; 424/493; 424/499; 424/278.1; 514/770

Bartus et al., "Sustained Delivery of Proteins for Novel Therapeutic Products," *Science*, 281(5380): 1161-1162 (1998).

(58) **Field of Search** 424/184.1, 204.1, 424/490, 493, 489, 453, 278.1, 499, 491; 514/2, 770, 951, 970

Bastin, et al., "Use of Synthetic Peptides of Influenza Nucleoprotein to Define Epitopes Recognized by Class I-Restricted Cytotoxic T Lymphocytes," *J. Exp. Med.*, 165(4): 1508-1523 (1987).

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,925,545 A	12/1975	Relyveld
4,016,252 A	4/1977	Relyveld
4,350,686 A	9/1982	Relyveld et al.
4,500,512 A	2/1985	Barme
4,552,756 A	11/1985	Relyveld et al.
5,178,882 A	1/1993	Kossovsky et al.
5,219,577 A	6/1993	Kossovsky et al.
5,306,508 A	4/1994	Kossovsky et al.
5,334,394 A	8/1994	Kossovsky et al.
5,364,838 A	11/1994	Rubsamen
5,460,830 A	10/1995	Kossovsky et al.
5,460,831 A	10/1995	Kossovsky et al.
5,462,750 A	10/1995	Kossovsky et al.
5,462,751 A	10/1995	Kossovsky et al.
5,464,634 A	11/1995	Kossovsky et al.
5,506,203 A	4/1996	Backstrom et al.
5,549,973 A	8/1996	Majetich et al.
5,580,859 A	12/1996	Felgner et al.
5,593,875 A	1/1997	Wurm et al.
5,595,762 A	1/1997	Derrieu et al.
5,620,896 A	4/1997	Herrmann et al.
5,629,021 A	5/1997	Wright
5,641,515 A	6/1997	Ramtoola
5,648,097 A	7/1997	Nuwayser
5,695,617 A	12/1997	Gravier et al.
5,747,001 A	5/1998	Wiedmann et al.
5,785,975 A	7/1998	Parikh
5,827,822 A	10/1998	Floc'h et al.
5,866,553 A	2/1999	Donnelly et al.
5,891,420 A	4/1999	Cutie
5,898,028 A	4/1999	Jensen et al.
5,902,789 A	5/1999	Stolz

Benvenisty, N., and Reshef, L. *PNAS* 83, 9551-9555, (1986).

Bennink and J. W. Yewdell, "Recombinant Vaccinia Viruses as Vectors for Studying T Lymphocyte Specificity and Function," *Curr. Top. Microbiol. Immunol.*, 163:153-184 (1990).

(List continued on next page.)

Primary Examiner—Donna C. Wortman

Assistant Examiner—Robert A. Zeman

(74) *Attorney, Agent, or Firm*—Bruce D. Gray; Kristin D. Mallatt; Kilpatrick Stockton LLP

(57) **ABSTRACT**

Novel calcium phosphate core particles, methods of making them, and methods of using them as vaccine adjuvants, as cores, as carriers of biologically active material, and as controlled release matrices for biologically active material are disclosed. The core particles may have a surface modifying agent and/or biologically active material, such as antigenic material or natural immunoenhancing factor, polynucleotide material, or therapeutic proteins or peptides, partially coating the particle or impregnated therein. The core particles have a diameter between about 300 nm and about 4000 nm, more particularly between about 300 nm and about 2000 nm, and even more particularly between about 300 nm and about 1000 nm, are substantially spherical in shape, and have a substantially smooth surface.