(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 September 2004 (10.09.2004)

PCT

(10) International Publication Number
WO 2004/075836 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/005047

(22) International Filing Date: 20 February 2004 (20.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/372,076 21 February 2003 (21.02.2003) US
10/677,074 1 October 2003 (01.10.2003) US

(71) Applicant: **APOVIA, INC.** [US/US]; 11125 flintkote, Suite A, San Diego, CA 92121 (US).

(72) Inventors: **PAGE, Mark**; 57 Lambourn Drive, Allestree, Derby DE22 2UT (GB). **FRIEDE, Martin**; 2386 Newport Avenue, Cardiff, California (GB). **SCHMIDT, Annette, Elisabeth**; Fuerstenrieder Strasse 4, 82152 Planegg (DE). **STOBER, Detlef**; Avenariusstrasse 16, 81243 Muenchen (DE).

(74) Agents: **GAMSON, Edward, P.** et al.; Welsh & Katz, Ltd., 120 South Riverside Plaza, 22nd floor, Chicago, IL 60606 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: STABILIZED HBc CHIMER PARTICLES AS THERAPEUTIC VACCINE FOR CHRONIC HEPATITIS

(57) Abstract: A method of treating chronic hepatitis B is disclosed that comprises administering a T cell-stimulating amount of a vaccine to a patient. The vaccine comprises an immunogenic amount of chimeric, carboxy-terminal truncated hepatitis B virus nucleocapsid (core) protein (HBc) that is engineered for both enhanced stability of self-assembled particles and the substantial absence of nucleic acid binding by those particles. The chimeric protein molecule can include one or more immunogenic epitopes peptide-bonded to one or more of the N-terminus, the immunogenic loop or the C-terminus of HBc. The enhanced stability of self-assembled particles is obtained by the presence of at least one heterologous cysteine residue near one or both of the amino-terminus and carboxy-terminus of the chimer molecule.

A

```
Ground Squirrel   mylfhlclvf acvpcptvqa sklclgwlwd

                    1
  HBc AYW           mdidpykefg atvellsflp sdffpsvrdl ldtasalyre
  HBc ADW           mdidpykefg atvellsflp sdffpsvrdl ldtasalyre
  HBc ADW2          mdidpykefg atvellsflp sdffpsvrdl ldtasalyre
  HBc ADYW          mdidpykefg atvellsflp sdffpsvrdl ldtaaalyrd
  Woodchuck         mdidpykefg ssyqllnflp ldffpdlnal vdtatalyee
  Ground Squirrel   mdidpykefg ssyqllnflp ldffpdlnal vdtaaalyee

                   41
  HBc AYW           alespehcsp hhtalrqail cwgelmtlat wvgvnledpa
  HBc ADW           alespehcsp hhtalrqail cwgelmtlat wvgnnlgdpa
  HBc ADW2          alespehcsp hhtalrqail cwgelmtlat wvgnnledpa
  HBc ADYW          alespehcsp hhtalrqail cwgdlmtlat wvgtnledpa
  Woodchuck         eltgrehcsp hhtairqalv cwdeltklia wmssnitseq
  Ground Squirrel   eltgrehcsp hhtairqalv cweeltrlit wmsentteev
```

B

```
                   81
  HBc AYW           srdlvvsyvn tnmglkfrql lwfhiscltf gretvieylv
  HBc ADW           srdlvvnyvn tnmglkirql lwfhiscltf gretvleylv
  HBc ADW2          srdlvvnyvn tnvglkirql lwfhiscltf gretvleylv
  HBc ADYW          srdlvvsyvn tnvglkfrql lwfhiscltf gretvleylv
  Woodchuck         vrtiivnhvn dtwglkvrqs lwfhlscltf gqhtvqeflv
  Ground Squirrel   rriivdhvnn twglkvrqtl wfhlscltfg qhtvqeflvs

                  121
  HBc AYW           sfgvwirtpp ayrppnapil stlpettvvr rrgrsprrrt
  HBc ADW           sfgvwirtpp ayrppnapil stlpettvvr rrdrgrsprr
  HBc ADW2          sfgvwirtpp ayrppnapil stlpettvvr rrdrgrsprr
  HBc ADYW          sfgvwirtpp ayrppnapil stlpettvvr rrgrsprrrt
  Woodchuck         sfgvwirtpa pyrppnapil stlpehtvir rrggarasrs
  Ground Squirrel   fgvwirtpap yrppnapils tlpehtvirr rggsraarsp

                  161
  HBc AYW           psprrrrsqs prrrrsqsre sqc
  HBc ADW           rtpsprrrrs qsprrrrsqs resqc
  HBc ADW2          rtpsprrrps qsprrrrsqs resqc
  HBc ADYW          psprrrrsqs prrrrsqsre sqc
  Woodchuck         prrrtpsprr rrsqsprrrr sqc
  Ground Squirrel   rrrtpsprrr rsqsprrrrs qspasnc
```

WO 2004/075836 A2

GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.