Conformationally Locked Nucleoside Analogs as Antiherpetic Agents

Victor E. Marquez, Juan B. Rodriguez, Marc C. Nicklaus, Joseph J. Barchi, Jr., Maqbool A. Siddiqui (NCI).

U.S. Patent 5,840,728 issued 23 Nov 1998 (DHHS Reference No. E–100–1996/0–US–03).

The compounds of the present invention represent the first examples of carbocyclic dideoxynucleosides that in solution exist locked in a defined N-geometry (C3′-endo) conformation typical of conventional nucleosides. These analogues exhibit increased stability due to the substitution of carbon for oxygen in the ribose ring. The invention includes 4′–6′-cyclopropane fused carbocyclic dideoxynucleosides, 2′-deoxynucleosides and ribonucleosides as well as oligonucleotides derived from these analogues; the preferred embodiment of the invention is carbocyclic-4′–6′-cyclopropane-fused analogues of dideoxypurines, dideoxypyrimidines, deoxypurines, deoxypyrimidines, purine ribonucleosides and pyrimidine ribonucleosides. In addition, oligonucleotides derived from one or more of the nucleosides in combination with the naturally occurring nucleosides are within the scope of the present invention.

The second invention discloses a method for the treatment of herpes virus infections by the administration of cyclopropanated carbocyclic 2′-deoxynucleosides to an affected individual. This invention is a method of administration of the compounds described above. The compounds of this invention are particularly efficacious against herpes simplex viruses 1 and 2 (HSV–1 and HSV–2), Epstein-Barr Virus (EBV) and human cytomegalovirus (CMV), although the nucleoside analogues of the invention may be used to treat any condition caused by a herpes virus. Specifically, the N-methanocarba-T (Thymidine) analogue has been shown to exhibit strong activity against HSV–1 and HSV–2, and moderate to strong activity against EBV. Significantly, the anti-HSV activity of the Thymidine analogue is stronger than that of Acyclovir (shown in a plaque reduction assay), a widely used anti-HSV therapeutic. Furthermore, the Thymidine analogue is also non-toxic against stationary cells and is potent against rapidly dividing cells. Dosage amounts for the compounds are similar to those of Acyclovir.

Descriptions of these inventions may be found in Rodriguez *et al., J. Medicinal Chemistry* 37:3389–3399 (1994) and Marquez *et al., J. Medicinal Chemistry* 39:3739–3747 (1996).

Dated: November 6, 2003.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Research Resources; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Center for Research Resources Special Emphasis Panel, Comparative Medicine.

Date: November 24, 2003.

Time: 1 p.m. to Adjournment.

Agenda: To review and evaluate grant applications.

Place: 6701 Democracy Blvd., One Democracy Plaza, Room 1078, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Marc Rigas, PhD, Scientific Review Administrator, National Center for Research Resources, Office of Review, 6701 Democracy Boulevard, 1 Democracy Plaza, Room 1080, Bethesda, MD 20817–4874, (301) 435–0806, *rigasm@mail.nih.gov.*

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: National Center for Research Resources Special Emphasis Panel, Comparative Medicine.

Date: November 25, 2003.

Time: 2:30 p.m. to Adjournment.

Agenda: To review and evaluate grant applications.

Place: 6701 Democracy Blvd., Room 1080, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Marc Rigas, PhD, Scientific Review Administrator, National Center for Research Resources, Office of Review, 6701 Democracy Boulevard, 1 Democracy Plaza, Room 1080, Bethesda, MD 20817–4874, 301–435–0806, *rigasm@mail.nih.gov.*

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine; 93.333, Clinical Research; 93.371, Biomedical Technology; 93.389, Research Infrastructure, 93.306, 93.333, National Institutes of Health, HHS)

Dated: November 10, 2003.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 03–28644 Filed 11–14–03; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Mental Health; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

*Name of Committee:*National Institute of Mental Health Special Emphasis Panel, Developing Disaster Mental Health Research Capacity through Education RFA.

Date: December 1, 2003.

Time: 8:30 a.m. to 1 p.m.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn Select Bethesda, 8120 Wisconsin Ave, Bethesda, MD 20814.

Contact Person: Richard E. Weise, PhD, Scientific Review Administrator, Division of Extramural Activities, National Institute of Mental Health, NIH, Neuroscience Center, 6001 Executive Boulevard, Room 6140, MSC 9606, Bethesda, MD 20892–9606, (301)–443–1225, *rweise@mail.nih.gov.*

This notice is being published less than 145 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: National Institute of Mental Health Special Emphasis Panel, From Intervention Development to Services: Exploratory Research Grants.

Date: December 1, 2003.