Analogs of Thalidomide as Potential Angiogenesis Inhibitors

William D. Figg, Erin Lepper (NCI)
U.S. Provisional Application No. 60/486,515 filed 11 Jul 2003 (DHHS Reference No. E–272–2003/0–US–01)
Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@mail.nih.gov.*

The present disclosure relates to anti-angiogenesis compositions and methods, and particularly thalidomide analogs that actively inhibit angiogenesis in humans and animals.

Angiogenesis is the formation of new blood vessels from pre-existing vessels. Angiogenesis is prominent in solid tumor formation and metastasis. A tumor requires formation of a network of blood vessels to sustain the nutrient and oxygen supply for continued growth. Some tumors in which angiogenesis is important include most solid tumors and benign tumors, such as acoustic neuroma, neurofibroma, trachoma, and pyogenic granulomas. Prevention of angiogenesis could halt the growth of these tumors and the resultant damage due to the presence of the tumor.

The subject application discloses active thalidomide analogs that exhibit enhanced potency in the inhibition of undesirable angiogenesis, and methods for using these compounds to treat angiogenesis and solid tumors. In particular, the presently disclosed method provides for inhibiting unwanted angiogenesis in a human or animal by administering to the human or animal with the undesired angiogenesis a composition comprising an effective amount of the active thalidomide analogs. According to a more specific aspect, the method involves inhibiting angiogenesis by exposing a mass having the undesirable angiogenesis to an angiogenesis inhibiting amount of one or more compounds, or pharmaceutically acceptable salts of such compounds.

Serine Protease Inhibitors

Peter P. Roller, Peng Li (NCI)
U.S. Provisional Application No. 60/507,583 filed 30 Sep 2003 (DHHS Reference No. E–272–2002/0–US–01)
Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@mail.nih.gov.*

This disclosure concerns novel serine protease inhibitors and methods for using the inhibitors to reduce tumor progression and/or metastasis. Embodiments of the inhibitors are highly effective, selective inhibitors of matriptase, which has been implicated in tissue remodeling associated with the growth of cancerous tumors and cancer metastasis.

Angiogenesis and tumor invasion require that the normal tissue surrounding the tumor be broken down in a process referred to as tissue remodeling. Tissue remodeling is accomplished by a host of enzymes that break down the proteins in the normal tissue barriers comprising the extracellular matrix. Among the enzymes associated with degradation of the extracellular matrix and tissue remodeling are a number of proteases. The expression of some of these proteases has been correlated with tumor progression.

The disclosed compounds can be used to inhibit matriptase, MTSP1, or both, *in vitro* and *in vivo* and thus can be used in the prevention or treatment of conditions characterized by abnormal or pathological serine protease activity. For example, the compounds are useful for prevention or treatment of conditions characterized by the pathological degradation of the extracellular matrix, such as conditions characterized by neovascularization or angiogenesis, including cancerous conditions, particularly metastatic cancerous conditions where matriptase is implicated. The disclosed compounds can be used to decrease the degradation of the cellular matrix and thereby reduce concomitant tumor progression and metastasis. Conditions characterized by abnormal or pathological serine protease activity that can be treated according to the disclosed method include those characterized by abnormal cell growth and/or differentiation, such as cancers and other neoplastic conditions. Typical examples of cancers that may be treated according to the disclosed inhibitors and method include colon, pancreatic, prostate, head and neck, gastric, renal, and brain cancers.

Methods for Inhibiting Chaperone Proteins

Monica Marcu, Leonard Neckers, Theodor Schulte (NCI)
U.S. Patent Application No. 09/936,449 filed 20 Dec 2001 (DHHS Reference No. E–084–1999/0–US–07), with priority to 12 Mar 1999
Licensing Contact: George Pipia; 301/435–5560; *pipiag@mail.nih.gov.*

This invention is directed to depletion of the Heat Shock Protein (HSP)–90 with novobiocin. Hsp90 is an essential and abundant chaperone in eukaryotes. It is considered today an exciting molecular target for cancer therapy. NIH inventors demonstrated previously that the gyrase-B inhibitor, novobiocin, and its related coumarin derivatives interact with Hsp90, causing *in vitro* and *in vivo* depletion of key regulatory Hsp90-dependent proteins. Using deletion/mutation analysis, the inventors have identified the novobiocin binding domain on Hsp90 and demonstrated that it overlaps a functional ATP binding site, which was previously unknown. These results identify a second site on Hsp90 where the binding of small molecule inhibitors can significantly impact this chaperone's function, and thus support the hypothesis that both N- and C-terminal domains of Hsp90 interact to modulate chaperone activity. The inventors have performed preliminary *in vivo* experiments, treating mice carrying tumor xenografts with novobiocin encapsulated in Alzet pumps (slow, constant release for one month). The treated mice exhibited significantly slower tumor growth. Results of these studies demonstrated a significantly slower growth of tumors.

Dated: January 23, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–1994 Filed 1–29–04; 8:45 am]
BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Notice of Meeting; Chairpersons, Boards of Scientific Counselors for Institutes and Centers at the National Institutes of Health

Notice is hereby given of a meeting scheduled by the Deputy Director for Intramural Research at the National Institutes of Health (NIH) with the Chairpersons of the Boards of Scientific Counselors. The Boards of Scientific Counselors are an advisory group to the Scientific Directors of the Intramural Research Programs at the NIH. This meeting will take place on February 6, 2004 from 9 a.m. to 3 p.m., at the NIH, 9000 Rockville Pike, Bethesda, MD, Building 1, Wilson Hall. The meeting will include a discussion of policies and procedures that apply to the regular review of NIH intramural scientists and their work, with special emphasis on clinical research.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should contact Ms. Colleen Crone at the Office of Intramural Research, NIH, Building 1, Room 103, Telephone (301) 496–1921 or

FAX (301) 402–4273 in advance of the meeting.

The meetings is being published less than 15 days prior to the meeting due to scheduling conflicts.

Dated: January 21, 2004.

Raynard Kington,

Deputy Director, NIH.

[FR Doc. 04–1995 Filed 1–29–04; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

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 meeting.

The meeting 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 Cancer Institute Initial Review Group, Subcommittee F—Manpower & Training.

Date: March 1–2, 2004.

Time: 8:30 a.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn Georgetown, 2101 Wisconsin Avenue, NW, Washington, DC 20007.

Contact Person: Lynn McAmende, PhD, Scientific Review Administrator, Resources and Training Review Branch, Division of Extramural Activities, National Cancer Institute, National Institutes of Health, 6116 Executive Boulevard Room 8105, Bethesda, MD 20892, 301–451–4759, *amendel@mail.nih.gov.*

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: January 23, 2004.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–2003 Filed 1–29–04; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Meeting

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 meeting of the National Cancer Advisory Board.

The meeting will be open to the public as indicated below, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

A portion of the meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4), and 552b(c)(6), 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 Cancer Advisory Board.

Open: February 18, 2004, 8:30 a.m. to 4:20 p.m.

Agenda: Program reports and presentations; business of the Board.

Place: National Cancer Institute, 9000 Rockville Pike, Building 31, C Wing, 6th Floor, Conference Room 10, Bethesda, MD 20892.

Contact Person: Dr. Paulette S. Gray, Executive Secretary, National Cancer Institute, National Institutes of Health, 6116 Executive Boulevard, 8th Floor, Room 8141, Bethesda, MD 20892–8327, (301) 496–4218.

Name of Committee: National Cancer Advisory Board.

Closed: February 18, 2004, 4:20 p.m. to recess.

Agenda: Review of grant applications.

Contact Person: Dr. Paulette S. Gray, Executive Secretary, National Cancer Institute, National Institutes of Health, 6116 Executive Boulevard, 8th Floor, Room 8141, Bethesda, MD 20892–8327, (301) 496–4218.

Name of Committee: National Cancer Advisory Board.

Open: February 19, 2004, 8:30 a.m. to adjournment.

Agenda: Program reports and presentations; Business of the Board.

Contact Person: Dr. Paulette S. Gray, Executive Secretary, National Cancer Institute, National Institutes of Health, 6116 Executive Boulevard, 8th Floor, Room 8141, Bethesda, MD 20892–8327, (301) 496–4218.

This meeting is being published less than 15 days prior to the meeting due to scheduling conflicts. Any interested person may file written comments with the committee by forwarding the statement to the Contact Person listed on this notice. The statement should include the name, address, telephone number and when applicable, the business or professional affiliation of the interested person.

Information is also available on the Institute's/Center's home page: *http://www.deainfo.nci.nih.gov/advisory/ncab.htm,* where an agenda and any additional information for the meeting will be posted when available.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: January 23, 2004.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–2004 Filed 1–29–04; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

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 meeting.

The meeting 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 Cancer Institute Special Emphasis Panel, Small Animal Imaging (SAIRP).

Date: March 9–10, 2004.

Time: 8 a.m. to 5 p.m.