Utilization of Non-Viral Sequences for Minus-Strand DNA Transfer and Gene Reconstitution

Wei-Shau Hu, Vinay K. Pathak (NCI)
DHHS Reference No. E–134–00/0 filed 19 May 2000

This technology relates to novel retroviral vectors for the introduction of heterologous nucleic acid into a host cell. Integration of these vectors into the nucleic acid of a host cell results in reconstitution and duplication of the heterologous nucleic acid in the cellular genome. The invention describes a method to efficiently reconstitute genes during virus replication. Vectors have been developed that enable gene reconstitution, by including two halves of a gene, each half having a small region of homology. The 3′ half of the gene is inserted into the 5′ terminal repeat, before the ''R'' region, and the 5′ half of the gene is inserted into the 3′ terminal repeat, between the ''U3'' region and the ''R'' region. Upon transfer into a cell and viral integration into the genome, two complete copies of the gene are reconstituted (gene duplication), one in the 5′ long terminal repeat (LTR) and one in the 3′ LTR. The virus can be used to transfer two copies of genes, such as toxic genes, into a desired cell population, or can be used to detect the presence of competent retroviruses (as a detection system). This technique can be utilized for delivery of toxic genes for cancer gene therapy or for high-sensitivity detection of replication-competent retroviruses during propagation of viral stocks.

Gadd45a-Null Mice (45C Clone) and Cells Derived from Them

MC Hollander, MS Sheikh, D Bulavin, LA Henmueller (NCI)
DHHS Reference No. E–129–00/0

This technology relates to the creation of a mouse cell line that harbor homozygous deletions of the Gadd45 gene. Gadd45 was the first gene discovered to be controlled by another gene, p53, the most highly mutated gene in human cancer. Cells lacking Gadd45 are less able to deal with DNA damage and are prone to alternations in genomic integrity. Both of these attributes are critical for the prevention of cancer. Gadd45 null mice have a high frequency of parturition failure.

The mice can be used to investigate the effect that the aforementioned attributes have a cell growth and integrity and carcinogenesis. As the Gadd45a-null nice show defects in cell cycle control and DNA repair, they will be useful in toxicology and drug screening. For pharmaceutical studies using chemical libraries, these mice and their derived cells may be useful in identifying inhibitors of specific molecular pathways. Also, the mice will be a useful model for studying delivery failure and cervical dilation.

Usage of Two Yeast Strains in the Identification of Specific Inhibitors of Polo Kinases

Kyung S. Lee, Sukgil Song (NCI)
DHHS reference No. E–100–00/0 filed 23 May 2000

This technology relates to the usage of two yeast strains in the identification of specific inhibitors of polo kinases. Polo kinases are characterized by the presence of a distinct region of homology in the non-catalytic C-terminal domain termed the ''polo-box''. The polo subfamily of protein kinases appears to play a critical role in cell proliferation and cell division. The polo-box domain of mammalian polo kinase, Plk, and the budding yeast functional homolog, Cdc5, are essential for their subcellular localization and functions. The two yeast mutants can be used to screen for inhibitors of polo-box function.

A Transgenic Mouse Model for Tetracycline Regulated Gene Expression in the Mouse Epidermis

Adam B. Glick (NCI)
DHHS Reference No. E–226–99/0

This technology related to the creation of several transgenic mouse lines that will produce conditional overexpression of foreign genes in the mouse epidermis. Foreign genes are frequently expressed in mice to create models of human disease by using a promoter or regulatory region that is tissue specific. In previous models expression of the target gene is always on. In these new models expression is conditional such that timing and level of expression can be completely controlled by the investigator. The inventor has taken advantage of the bigenic tetracycline regulatory system first described by Grossen and Bujard to create the present transgenic mouse lines. The system utilizes two transgenic lines that are then bred together to create a double transgenic mouse. One transgenic line expresses the tetracycline regulated transcriptional transactivator tTA or rTA linked to keratin 5 (K5) promoter. These transgenic lines have been designated K5/tTA and K5/rTA. The K5 promoter is expressed in the epidermis hair follicles and several other squamous epithelia such as tongue trachea and forestomach. The second transgenic line carries the target gene linked to the tetO binding sites for the tTA or rTA proteins. In double transgenic mice, the tTA binds to the tetO sequence and causes high levels of expression of the target gene. However, the ability of the tTA to bind to DNA is prevented by the antibiotic tetracycline. If animals are maintained on tetracycline in the drinking water or fed, the expression of the target gene is suppressed; upon removal of the antibiotic, gene expression is induced. In contrast tetracyclines are required to induce expression of the target by the rTA. The ability of this bigenic system to suppress expression of the target gene is crucial for a functional analysis of genes which produce an embryonic or neonatal lethal phenotype when expressed at high levels during gestation. In addition, different levels of gene expression can be achieved through titration of the tetracycline dose. Studies in the inventor's laboratory has confirmed that the K5/tTA and rTA can transactivate expression of target genes in the epidermis at high levels, uniformly throughout the tissue, and that transactivation is tightly controlled by tetracycline analogues. The mouse epidermis is a useful system for modeling for human fibrotic and blistering skin diseases, dissecting the critical factors in would healing and multistage carcinogenesis in lining epithelia. This conditional expression system should greatly enhance the ability to assess function of specific target genes in these processes, and to create useful *in vivo* models for the development of novel therapeutics.

Dated: December 12, 2000.

Jack Spiegel,

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

[FR Doc. 00–32366 Filed 12–19–00; 8:45 am]

BILLING CODE 4140–01–P

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 contract proposals and the discussions could disclose confidential trade secrets or commercial

property such as patentable material, and personal information concerning individuals associated with the contract proposals, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Institute Special Emphasis Panel Human Papillomavirus Type 16 Vaccine Trial in Costa Rica.

Date: January 8, 2001.

Time: 9 a.m. to 5 p.m.

Agenda: To review and evaluate contract proposals.

Place: National Cancer Institute, 6130 Executive Boulevard, Conference Room F, Rockville, MD 20852, (Telephone Conference Call).

Contact Person: Lalita D. Palekar, PhD, Scientific Review Administrator, Special Review, Referral and Resources Branch, Division of Extramural Activities, National Cancer Institute, National Institutes of Health, 6116 Executive Boulevard, Room 8066, Bethesda, MD 20892–7405, (301) 496–7575.

(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: December 13, 2000.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 00–32358 Filed 12–19–00; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Research Resources; Notice of 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 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.

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: Scientific and Technical Review Board on Biomedical and Behavioral Research Facilities.

Date: January 23–25, 2001.

Open: January 23, 2001, 8:00 am to 9:00 am.

Agenda: To discuss program planning and issues.

Place: DoubleTree Hotel, 1750 Rockville Pike, Rockville, MD 20852.

Closed: January 23, 2001, 9:00 am to Adjournment.

Agenda: To review and evaluate grant applications.

Place: DoubleTree Hotel, 1750 Rockville Pike, Rockville, MD 20852.

Contact Person: D.G. Patel, PhD., Scientific Review Administrator, Office of Review, National Center for Research Resources, National Institutes of Health, 6705 Rockledge Drive, Room 6018, Bethesda, MD 20892–7965, (301) 435–0824, dgpatel@ncrr.nih.gov.

Name of Committee: National Center for Research Resources Initial Review Group, Comparative Medicine Review Committee.

Date: February 13–14, 2001.

Open: February 13, 2001, 8:00 am to 9:00 pm.

Agenda: To discuss program planning and other issues.

Place: Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, MD 20878.

Closed: February 13, 2001, 9:00 am to Adjournment.

Agenda: To review and evaluate grant applications.

Place: Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, MD 20878.

Contact Person: Camille M. King, Scientific Review Administrator, Office of Review, National Center for Research Resources, National Institutes of Health, One Rockledge Centre, MSC 7965, 6705 Rockledge Drive, Suite 6018, Bethesda, MD 20892–7965, (301) 435–0815, kingc@ncrr.nih.gov.

Name of Committee: National Center for Research Resources Initial Review Group, General Clinical Research Centers Review Committee.

Date: February 13–15, 2001.

Closed: February 13, 2001, 8:00 am to Adjournment.

Agenda: To review and evaluate grant applications.

Place: Gaithersburg Marriott, Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, MD 20878.

Open: February 14, 2001, 8:00 am to 9:30 am.

Agenda: To discuss program planning and other issues.

Place: Gaithersburg Marriott, Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, MD 20878.

Closed: February 14, 2001, 9:30 am to Adjournment.

Agenda: To review and evaluate grant applications.

Place: Gaithersburg Marriott, Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, MD 20878.

Contact Person: John L. Meyer, PhD, Deputy Director, Office of Review, National Center for Research Resources, National Institutes of Health, One Rockledge Centre, Room 6018, 6705 Rockledge Drive, MSC 7965, Bethesda, MD 20892–7965, 301–435–0806, meyerj@ncrr.nih.gov.

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

Dated: December 13, 2000.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 00–32360 Filed 12–19–00; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Research Resources; 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 following meeting.

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.

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 Center for Research Resources Initial Review Group, Research Centers in Minority Institutions Review Committee.

Date: February 22–23, 2001.

Open: February 22, 2001, 8 a.m. to 10 a.m.

Agenda: To discuss program planning and other issues.

Place: Residence Inn, 7335 Wisconsin Avenue, Bethesda, MD 20814.

Closed: February 22, 2001, 10 a.m. to Adjournment.