hospital's anti-dumping statute obligations and should clearly inform the patient that, notwithstanding the patient's ability to pay, the hospital stands ready and willing to provide a medical screening examination and stabilizing treatment, if necessary. Hospital staff should encourage any patient who believes that he or she may have an emergency medical condition to remain for the medical screening examination and any necessary stabilizing treatment. Staff should also encourage the patient to defer further discussion of financial responsibility issues, if possible, until *after* the medical screening has been performed. If the patient chooses to withdraw his or her request for examination or treatment, a staff member with appropriate medical training should discuss the medical issues related to a ''voluntary withdrawal.''

- *Voluntary Withdrawal*

If an individual chooses to withdraw his or her request for examination or treatment at the presenting hospital, and if the hospital is aware that the individual intends to leave prior to the screening examination, a hospital should take the following steps: (1) Offer the individual further medical examination and treatment within the staff and facilities available at the hospital as may be required to identify and stabilize an emergency medical condition; (2) Inform the individual of the benefits of such examination and treatment, and of the risks of withdrawal prior to receiving such examination and treatment; and (3) Take all reasonable steps to secure the individual's written informed consent to refuse such examination and treatment. The medical record should contain a description of risks discussed and of the examination, treatment, or both, if applicable, that was refused. If an individual leaves without notifying hospital personnel, the hospital should, at a minimum, document the fact that the person had been there, what time the hospital discovered that the patient had left, and should retain all triage notes and additional records, if any. However, the burden rests with the hospital to show that it has taken appropriate steps to discourage an individual from leaving the hospital without evaluation.

Dated: November 4, 1999.

June Gibbs Brown,

Inspector General, Office of Inspector General.

Dated: November 3, 1999.

Michael M. Hash,

Deputy Administrator, Health Care Financing Administration.

[FR Doc. 99–29390 Filed 11–9–99; 8:45 am]

BILLING CODE 4150–04–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Licensing Opportunity and/or Cooperative Research and Development Agreement (''CRADA'') Opportunity; Certain Live Attenuated Respiratory Syncytial Viruses (RSV) and Parainfluenza Viruses (PIV) for Use as Human Vaccines

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) is seeking Licensee(s) and/or a commercial collaborator(s) to further develop, test, and commercialize as live attenuated vaccines certain recombinant RSV and PIV strains and associated intellectual property developed in the Laboratory of Infectious Diseases (LID), Division of Intramural Research, National Institute of Allergy and Infectious Diseases (NIAID).

DATES: There is no date by which license applications must be received. Respondents who wish to be considered for the CRADA opportunity must submit a Capability Statement (described below in **SUPPLEMENTARY INFORMATION**) to the NIAID. Only written Capability Statements received by the NIAID on or before December 27, 1999 for consideration. Capability Statements should be forwarded to Michael R. Mowatt, Ph.D. at the address specified below.

FOR FURTHER INFORMATION CONTACT: Inquiries about these licensing opportunities should be addressed to Robert Benson, Ph.D., Patent Advisor, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804, Telephone: (301) 496–7056 ext. 267; Facsimile: (301) 402–0220; Email: rb20m@nih.gov. Information about Patent Applications and pertinent information not yet publicly described can be obtained under the terms of a Confidential Disclosure Agreement. Respondents interested in licensing the inventions will be required to submit an ''Application for License to Public Health Service Inventions''.

Inquiries about the CRADA opportunity should be addressed to Michael R. Mowatt, Ph.D., Technology Development Manager, Office of Technology Development, NIAID, Building 31 Room 3B62, 31 Center Drive MSC 2137, Bethesda, MD 20892–2137, Telephone: (301) 435–8618, Facsimile: (301) 402–7123; Email: mmowatt@nih.gov. Respondents interested in the CRADA opportunity should be aware that it might be necessary to secure a license to the above-mentioned patent rights in order to commercialize products arising from a CRADA.

SUPPLEMENTARY INFORMATION: The inventions described below are owned by an agency of the U.S. Government and are available for licensing—in accordance with 35 U.S.C. 207 and 37 CFR part 404 to achieve expeditious commercialization of results of federally-funded research and development—and/or further development under one or more CRADAs in the clinically important applications described below.

Human Respiratory Syncytial Viruses (HRSV), subgroups A and B (HRSV–A and HRSV–B, respectively), are the most common cause of serious respiratory tract infection in children and infants less than one year of age. RSV is responsible for more than 20% of all pediatric hospital admissions due to respiratory tract disease, and in the US is the cause of 91,000 hospitalizations and 4,500 deaths. No licensed vaccine is available to prevent disease by these viruses.

Attenuated RSV strains for intranasal administration are the most promising candidate vaccines because they are efficacious even in the presence of passively transferred antibodies, the very situation found in the target population of infants with maternally derived anti-HRSV antibodies. Designed mutations can be introduced into the RSV genome or antigenome utilizing cDNA technology as a means of engineering suitably attenuated RSV strains. See Collins *et al.*, Proc. Nat. Acad. Sci. USA *92* 11563–11567, 1995, and PCT/US96/15524, ''Production of Infectious Respiratory Syncytial Virus From Cloned Nucleotide Sequences'', which is available from NIH for licensing nonexclusively.

Human Parainfluenza Viruses (HPIV), serotypes 1, 2, and 3 (HPIVs, HPIV2, and HPIV1, respectively), are in aggregate the second most common

cause of serious respiratory tract infection in children and infants less than one year of age. No licensed vaccine is available to prevent disease by any of these viruses. Attenuated HPIV strains are the most promising candidate vaccines for the same reasons noted above for attenuated RSV vaccines. The following seven recently filed patent applications are available for licensing for certain virus vaccine strains.

Production of Attenuated Chimeric Respiratory Syncytial Virus Vaccines From Cloned Nucleotide Sequences

Inventors: Peter L. Collins, Stephen S. Whitehead and Brian R. Murphy.
Serial Number: 09/291,894 (CIP of 08/892,403, PCT/US97/12269).
Filing Date: April 13, 1999.

This patent application broadly describes and claims RSV strains that are attenuated recombinant chimeras of two different RSV parental strains. The chimeras comprise a background genome or antigenome from one strain into which is isnerted or substituted genes or genomic segments from a heterologous RSV strain. Introduction of the heterologous gene can serve to (a) attenuate the background strain, and/or (b) change the immunogenicity of the background strain to the heterologous strain or (c) form a chimera with the immunogenicity of both the background and heterologous strains. A chimeric virus consisting of a RSV Group A background strain into which the F and G genes of the RSV Group B virus were substituted was shown to be infectious and to raise protective antibodies against RSV Group B in chimpanzees. Thus a candidate RSV vaccine strain of one Group with the proper balance of attenuation and immunogenicity can now be used to make a vaccine against the other Group just by switching the F and/or G genes. Certain candidate RSV vaccine strains are not available for licensing.

Production of Attenuated, Human-Bovine Chimeric Respiratory Syncytial Virus Vaccines

Inventors: Ursula Buchholz, Peter L. Collins, Brian R. Murphy and Stephen S. Whitehead.
Serial Number: 60/143,132.
Filing Date: July 9, 1999.

The inventors have shown that genes may be switched between human RSV (HRSV) and bovine RSV (BRSV) and a live, infectious and immunogenic chimeric virus can result. Based on this discovery, two approaches are contemplated to produce chimeric strains that are vaccine candidates, balanced in attenuation and immunogenicity. The first is to start with BRSV and substitute in the HRSV F and G genes; this has been done and the resulting chimeric strain shown to be highly attenuated in chimpanzees. Other HRSV genes or genome segments may be inserted to decrease attenuation. The other approach is to start with HRSV and introduce BRSV genes, other than the BRSV F and G genes. These host range mutants should be extremely stable because of the large number of nucleotide and amino acid sequence differences between bovine and human RSV genes.

Production of Recombinant Respiratory Syncytial Viruses Expressing Immune Modulatory Molecules

Inventors: Peter L. Collins, Alexander R. Bukreyev, Brian R. Murphy and Stephen S. Whitehead.
Serial Number: 60/143,425.
Filing Date: July 13, 1999.

With the goal of producing attenuated RSV vaccine strains with new and favorable properties, the cytokines, Interferon-gamma (IFN-γ), Interleukin-2 (IL–2), Interleukin-4 (IL–4) and Granulocyte-Macrophage Colony Stimulating Factor (GM–CSF) were inserted into the RSV genome. Utilizing murine versions of the cytokines and mice as animals models, all four recombinant RSVs were infectious, immunogenic, protective against RSV challenge, and produced substantial quantities of the given cytokine. RSV/IFN-γ and RSV/GM–CSF were particularly interesting because both were attenuated but with enhanced immunogenicity, a very desirable phenotype in attenuated virus vaccine strains. IL–2 insertion resulted in attenuation but no change in immunogenicity.

Production of Attenuated Respiratory Syncytial Viruses Vaccines Involving Modification of M2 Open Reading Frame (ORF) 2

Inventors: Alison Bermingham, Peter L. Collins and Brian R. Murphy.
Serial Number: 60/143,097.
Filing Date: July 7, 1999.

This application describes two inventions, both involving knocking out or ablating the expression of the second translational open reading frame encoded by the M2 gene (M2 ORF2) of RSV. The first invention is the finding that M2 ORF2 knockout viruses are infectious and immunogenic but are attenuated from 100–1000 fold in vitro. Thus, the M2 ORF2 knockout represents another attenuating mutation that can be mixed with other known mutations to produce RSV vaccine strains with the proper balance of attenuation and immunogenicity. The second invention involves the finding that while the implication of M2 ORF2 knockouts is restricted compared to wildtype, the production of mRNA and viral proteins is increased 175–300%. Thus, even though the virus is attenuated, the expression of viral antigens is increased. As another application, these knockouts can be used to produce the immunogenic F and G proteins for use in subunit vaccines.

Recombinant PIV Vaccines Attenuated by Deletion or Ablation of a Non-Essential Gene

Inventors: Anna P. Durbin, Peter L. Collins and Brian R. Murphy.
Serial Number: 09/350,821.
Filing Date: July 9, 1999, with priority to September 19, 1997.

The present invention concerns the discovery that knocking out one or more of the non-essential C, D and/or V genes results in attenuated and immunogenic virus strains. A C knockout and DV double knockout of a human PIV3 (JS wildtype) strain were attenuated and protective in African Green Monkeys. Knockouts of the C, D and/or V genes represent another type of attenuation to be mixed with the other known mutations to generate PIV vaccine strains with the appropriate balance of attenuation and immunogenicity.

Attenuated, Human-Bovine Chimeric Parainfluenza Virus (PIV) Vaccines

Inventors: Jane E. Bailly, Peter L. Collins, Brian R. Murphy and Anna P. Durbin.
Serial Number: 60/143,134.
Filed: July 9, 1999.

The essence of the present invention is that bovine PIV (BPIV) gene(s) other than the hemagglutinin-neuraminidase (HN) and fusion (F) glycoprotein genes can be substituted for their counterparts in a NPIV genome or antigenome as a means of attenuation based on host range restrictions. Conversely, the genes that encode HPIV protective antigens, *e.g.*, the HN and F genes, can be inserted into a BPIV genome or antigenome. Either approach can yield human/bovine PIV chimeras that are infectious and immunogenic but attenuated, due to host range effects, and thus are candidate vaccine strains. BPIV genes may serve as another means of modulating viral attenuation, *e.g.*, in combination with other known attenuating mutations, as described above, in order to derive a suitably attenuated HPIV. Alternatively, starting from BPIV and inserting the antigenic HPIV F and/or NH genes, along with other HPIV genes or other attenuating mutations represents another path one

can take to an attenuated HPIV vaccine. Certain candidate human-bovine chimeric PIV vaccine strains are not available for licensing.

Production of Attenuated Negative Stranded RNA Virus Vaccines From Cloned Nucleotide Sequences

Inventors: Brian R. Murphy, Peter L. Collins, Anna P. Durbin, and Mario H. Skiadopoulos.

Serial Number: 60/129,006.

Filling Date: April 13, 1999.

Negative stranded RNA viruses (the Mononegavirales) include RSV, PIV, measles, mumps and rabies as human pathogens. Recombinant production of live attenuated virus strains as vaccine candidates has involved, for each virus, identifying attenuating mutations and producing recombinant virus strains with different combinations of mutations in a hunt for the right balance of attention and immunogenicity. This invention dramatically increases the number of mutations available. The inventors have shown that attenuating mutations in one negative stranded RNA virus can be ''transferred'' to homologous locations in other negative stranded RNA viruses, resulting in a transfer of the attenuation phenotype. Now, many of the attenuating mutations known for RSV or PIV can be transferred between each of these viruses, or into the other less studied members of this family. Also mutations identified in other paramyxoviruses, such as measles virus, can be transferred to RSV and PIV. Such transformations have been performed and show that this general approach works. Certain candidates RSV and PIV vaccine strains are not available for licensing.

The CRADA will employ attenuated human-animal chimeric RSV and PIV strains developed in LID using recombinant DNA methodologies to (1) identify and characterize the mutations responsible for attenuation, (2) engineer viral strains suitably attenuated for use as human vaccines, and (3) evaluate the attenuated viruses as live vaccines in animals and humans.

The LID has extensive experience in evaluating the safety, antigenicity, immunogenicity and efficacy of various human viral pathogens and vaccines thereof both in experimental animals and human volunteers. The Collaborator in this endeavor is expected to commit several scientists off-site to support the activities defined by the CRADA Research Plan.

These scientists, in collaboration with investigators in the LID, would coordinate the production and release testing of the candidate vaccines, generate monoclonal antibodies needed for manufacture of clinical lots and for their clinical evaluation, and use molecular virologic techniques to generate attenuating mutations suitable for use in live vaccine candidates. In addition, it is expected that the Collaborator will provide funds to supplement LID's research budget for the project and would make a major funding commitment to support the safety, immunogenicity and efficacy studies for candidate vaccines developed under the CRADA.

The capability statement must address, with specificity, each of the following selection criteria: (1) The technical expertise of the Collaborator's Principal Investigator and laboratory group in molecular virology, (2) Ability of Collaborator to manufacture experimental vaccine lots for parental administration under Good Manufacturing Practices (GMP) conditions, and (3) Ability to provide adequate and sustained funding to support the requisite vaccine safety and efficacy studies.

Dated: October 26, 1999.

Mark Rohrbaugh,

Director, Office of Technology Development, NIAID.

Dated: October 29, 1999.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, NIH.

[FR Doc. 99–29368 Filed 11–9–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Drug Research and Development of a Novel Vacuolar-Type (H+)-ATPase-Inhibitory Compound Class

AGENCY: National Cancer Institute, National Institute of Health, PHS, DHHS.

ACTION: Notice of opportunity for cooperative research and development (CRADA).

An opportunity is available for a Cooperative Research and Development Agreement (CRADA) for the purpose of collaborating with the NCI intramural Laboratory of Drug Discovery Research & Development (LDDRD) on further research and development of U.S. government-owned technology encompassed within U.S. Patent Application Serial No. 60/122,953, entitled ''Novel Vacuolar-Type (H+)-ATPase-Inhibitory Compounds and Compositions, and Uses Thereof.''

SUMMARY: Pursuant to the Federal Technology Transfer Act of 1986 (FTTA, 15 U.S.C. 3710; and Executive Order 12591 of April 10, 1987, as amended by the National Technology Transfer and Advancement Act of 1995), the National Cancer Institute (NCI) of the National Institutes of Health (NIH) of the Public Health Service (PHS) of the Department of Health and Human Services (DHHS) seeks a Cooperative Research and Development Agreement ((CRADA) with a pharmaceutical or biotechnology company to develop new drugs, therapeutic and/or preventative methods based on selective inhibition of vacuolar-type (H+) ATPases. The CRADA would have an expected duration of one (1) to five (5) years. The goals of the CRADA include the rapid publication of research results and timely commercialization of products, methods of treatment or prevention that may result from the research. The CRADA Collaborator will have an option to negotiate the terms of an exclusive or non-exclusive commercialization license to subject inventions arising under the CRADA and which are subject of the CRADA Research Plan, and can apply for background licenses to the existing patent described above, subject to any pre-existing licenses already issued for other fields of use.

ADDRESSES: Proposals and questions about this CRADA opportunity may be addressed to Dr. Bjarne Gabrielsen, Technology Development & Commercialization Branch, National Cancer Institute-Frederick Cancer Research & Development Center, Fairview Center, Room 502, Frederick, MD 21701 (phone: 301–846–5465, fax: 301–846–6820).

Scientific inquiries should be directed to Dr. Michael R. Boyd, Chief Laboratory of Drug Discovery Research & Development, National Cancer Institute-Frederick Cancer Research & Development Center, Bldg. 1052, Rm 121, Frederick, MD 21702–1201 (phone: 301–846–5391; fax: 301–846–6919; e-mail boyd@dtpax2.ncifcrf.gov).

EFFECTIVE DATE: Inquiries regarding CRADA proposals and scientific matters may be forwarded at any time. Confidential preliminary CRADA proposals, preferably two pages or less,