

BASIC RUBELLA RESEARCH LEADING TO IMPROVED RUBELLA VACCINES

NIH GUIDE, Volume 22, Number 20, June 4, 1993

PA NUMBER: PA-93-090

P.T. 34

Keywords:

Vaccine

Infectious Diseases/Agents

Viral Studies (Virology)

Immunology

National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite investigator-initiated research grant applications to pursue the development of safer vaccines to protect women against rubella infection (German measles). Multidisciplinary approaches, including basic research in virology and molecular immunology, are needed to identify and characterize the rubella virus gene products that are required for induction of durable immunity and those that are associated with adverse effects, particularly manifestations of joint disease. Research in this area also might lead to an understanding of the high female/male incidence ratio of adverse reactions in adults. In addition to vaccines with fewer adverse side-effects, a further goal is to develop safe vaccines that can be used in pregnant women to prevent fetal infection and congenital rubella syndrome (CRS).

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Program announcement (PA), Basic Rubella Research Leading to Improved Rubella Vaccines, is related to the priority area of immunization and infectious diseases. Potential

applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-0325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Research grant applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal Government. Applications from minority individuals and women are encouraged. Foreign institutions are not eligible for the First Independent

Research Support and Transition (FIRST) (R29) award.

MECHANISMS OF SUPPORT

Applications considered appropriate responses to this announcement are the investigator-initiated research project grant (R01) and the FIRST award (R29).

RESEARCH OBJECTIVES

Background

Until the introduction of a live attenuated vaccine in 1970, rubella was a common febrile disease of childhood. The most serious effects of rubella--abortions, miscarriages, stillbirths and fetal anomalies--follow infection during early pregnancy. The average cost of a single case of CRS, caused by infection of the fetus with rubella, is estimated to be well over \$200,000.

The current licensed vaccine works well in children. By blocking the spread of rubella, it has been effective in dramatically reducing, but not eliminating, the yearly incidence of CRS in the United States. From 1970 to 1989, there was a steady reduction in the number of annual cases of rubella. However, compared to 1988, the yearly incidence of rubella cases and rubella in patients 15 years of age or older, increased twofold in 1989, and threefold in 1990. Although the total number of cases was still small (0.4 cases per 100,000 in 1990), this re-emergence of natural rubella led to a campaign to increase vaccination coverage in all age groups, and thus more and more adult women are being immunized against rubella.

Unfortunately, as a public health tool, the current vaccine has some deficiencies. This live vaccine, like natural rubella, causes transient joint symptoms in a significant proportion of women vaccinees. Historical reports of natural epidemics also mention increased arthropathy predominantly in adult women. Currently in the U.S., an increasing percentage of women entering child-bearing age have not been immunized against rubella. When these adult women receive rubella vaccine, acute joint complaints are common, occurring in up to 25 percent of previously seronegative vaccinees. These symptoms usually last from one day to three weeks. Investigators in Canada recently reported that 5 to 11 percent of adult female vaccinees develop a more severe, persistent or recurring arthropathy. There also have been reports that these complications increase with the age of the vaccinee, and/or the presence of low or incomplete rubella immunity (perhaps representing a waning antibody response from an earlier childhood immunization). Another limitation of the current vaccine is that it is not recommended for use in women who may be pregnant, because the vaccine virus can be transmitted to the fetus.

Research Objectives and Experimental Approaches

Basic research on rubella is now at a low level in the U.S. Our primary objective is to stimulate research on rubella so that data are available to develop improved vaccines which would protect women of childbearing age without causing undesirable side effects and without fear of fetal infection. Success in this endeavor will require basic research in virology, immunology, genetics, and pathogenesis. Studies are needed to identify and characterize rubella virus gene products required for induction of durable immunity, and those associated with adverse effects. Research is encouraged to discover the role of viral components, and the importance of the response of the host, in the induction of inflammation and symptoms of acute and persistent arthritis. Studies would include genetic analysis of clinically characterized vaccine strains to determine if strain-specific variation leads to a propensity for growth in human synovial cells and association with persisting joint symptoms in adult vaccinees. Research in this area also might provide an understanding of the high female/male incidence ratio of adverse reactions in adults.

Research projects are sought which investigate topics including, but not limited to those listed below.

- o Establishment of the quantitative and qualitative differences between vaccine-induced and naturally-induced immunity against rubella.

- o Determination of which rubella antigens are required to safely elicit long-lasting protective humoral and cellular immunity.

- o Characterization of the viral correlates of virulence and attenuation.

- o Elucidation of those factors contributing to vaccine-induced adverse events. Analysis of the host and viral factors that contribute to immune and inflammatory responses associated with arthritis, and establishment of the molecular and cellular mechanisms causing joint inflammation.

- o Development of an animal model of rubella which parallels human disease, and allows elucidation of viral and host factors contributing to immunity and immunization-induced adverse events.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that applicants for NIH clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions that disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 (rev. 9/91) in Sections 1-4, of the Research Plan AND summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans (including American Indians or Alaskan Natives), Asian/Pacific Islanders, Blacks, Hispanics). The rationale for studies on single minority population groups must be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the review will be deferred until the information is provided.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

APPLICATION PROCEDURES

Applications are to be submitted on the research grant application form PHS 398 (rev. 9/91) and will be accepted at the standard application deadlines February 1, June 1 and October 1.

Application kits are available at most institutional offices of sponsored research and may be obtained from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892, telephone (301) 594.7248. The title and number of the announcement must be typed in Section 2a on the face page of the application.

The original and five legible copies of the application must be sent or delivered to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

FIRST (R29) applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or Principal Investigator could be included with the application.

REVIEW CONSIDERATIONS

Applications in response to this announcement will be assigned on the basis of established PHS Referral Guidelines. Applications will be reviewed for scientific and technical merit by study sections of the Division of Research Grants, NIH, and in accordance with the standard NIH peer review procedures. Following scientific-technical review of the applications considered to have significant and substantial merit, a secondary review will be by the appropriate national advisory council or board.

AWARD CRITERIA

Applications will compete for available funds with all other R01 and R29 applications considered to have significant and substantial merit. The following will be considered when making funding decisions: relative scientific merit, program relevance, availability of funds.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Dr. James M. Meegan

Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
Solar Building, Room 3A16
Bethesda, MD 20892
Telephone: (301) 496-7453
FAX: (301) 496-8030

Dr. Susana A. S. Sztein

Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 405
Bethesda, MD 20892
Telephone: (301) 594-9953
FAX: (301) 594-9673

Direct inquiries regarding fiscal matters to:

Mr. Todd Ball

Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4B35
Bethesda, MD 20892
Telephone: (301) 496-7075

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.856, Microbiology and Infectious Disease Research. Grants will be awarded under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grants policies and Federal Regulations at 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

[Return to 1993 Index](#)

[Return to NIH Guide Main Index](#)

