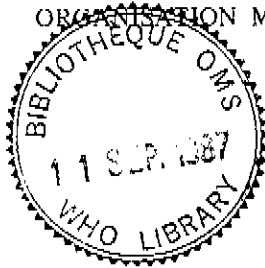




WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE



13229
DISTR.: GENERAL(E)

WHO/MIM/PVD/INF.DOC./87.1

ENGLISH ONLY

PROGRAMME FOR VACCINE DEVELOPMENT
RESEARCH PRIORITIES

The WHO Programme for Vaccine Development is a goal-oriented programme which funds research only in the following priority areas:

1. Acute viral respiratory diseases of childhood

- (a) Analysis of the genome structure and evolutionary relationships of pneumoviruses and paramyxoviruses by molecular cloning and nucleotide sequencing.
- (b) Application of molecular techniques in the study of epidemiology and pathogenesis. Study of the variability of RS virus and PI3 virus using monoclonal antibodies and by gene cloning and sequencing. Assessment of the role of strain variation in reinfection and in disease severity.
- (c) Expression of cloned viral genes in prokaryotic systems (to produce high yields of unprocessed polypeptides) and in eukaryotic systems (for modified proteins).
- (d) Characterization of the function and immunogenic potential of individual virus proteins. Development of individual gene vectors (by recombination into adenovirus, baculovirus, vaccinia virus, Salmonella, yeast or mammalian cells) for study of immune responses in animal models.
- (e) Study of the protective immune response with emphasis on the role of cell-mediated immunity.
- (f) Production and characterization of monoclonal antibodies for definition of epitopes and for use in affinity chromatography for purification of viral proteins. Production of monoclonal antibody neutralization-resistant variants. Location of immunogenic sites on viral proteins, and evaluation as immunogens of synthetic peptides representing linear determinants.
- (g) Investigation of the function of structural and non-structural proteins by reverse and conventional genetics. Study of the targeting and translocation of proteins by site-specific mutagenesis and protein engineering.
- (h) Vector engineering and design, e.g. reduction of the lesion-producing potential of vaccinia virus without loss of reproductive capacity, incorporation of auto-destruct and replication-limiting features, etc.
- (i) Support of other initiatives, e.g. development of live attenuated strains, antivirals, passive immunization, etc.

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale or use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.

Ce document n'est pas une publication officielle de l'Organisation mondiale de la Santé (OMS) et tous les droits y afférents sont réservés par l'Organisation. S'il peut être commenté, résumé ou cité sans aucune restriction, il ne saurait cependant être reproduit ni traduit, partiellement ou en totalité, pour la vente ou à des fins commerciales.

Les opinions exprimées dans les documents par des auteurs cités nommément n'engagent que lesdits auteurs.

2. Dengue

The main aim is to produce second generation vaccines by using the following approaches:

- (a) Identification of critical (protective, neutralizing and enhancing) epitopes.
 - (i) Human sera targets (viral protein exposure)
 - (ii) Mouse monoclonal antibody production and characterization
 - (iii) Active mouse immunization (with isolated viral proteins)
 - (iv) Passive mouse immunization (with monoclonal antibodies).
- (b) Expression of critical (protective/neutralizing) epitopes.
 - (i) cDNA cloning and sequencing
 - (ii) Expression and/or synthesis of viral proteins and/or peptides
 - (iii) Immunization experiments
 - (iv) Challenge experiments
- (c) Optimization of immunization.
 - (i) Adjuvants/immuno-enhancers
 - (ii) Expression systems (E. coli, yeast etc.)
 - (iii) Self-replicating vectors (yellow fever, vaccinia etc)
- (d) Molecular definition of virulence.
 - (i) Cloning, sequencing and comparison of parent vs vaccine strain pairs
 - (ii) Cloning, sequencing and comparison of "classical" dengue vs dengue haemorrhagic fever strain pairs
- (e) Construction of engineered live attenuated vaccines.
- (f) Similar lines of research will be supported on Japanese encephalitis.

3. Diseases caused by encapsulated bacteria

- (a) Epidemiological studies of epidemic/endemic disease, with emphasis on immune responses to Meningococcus. Screening at a particular point in time for the spectrum of antibody specificities as well as for antibody isotype.
- (b) Development of standardized isotype-specific serological tests for bactericidal (protective) antibody.
- (c) Development of serogroup (i.e. capsular polysaccharide) and serotype (i.e. LPS and/or class I membrane protein) vaccines.
- (d) Manipulation of the immune response so as to give long-lasting immunity and the development of bactericidal complement-fixing antibodies.
- (e) Delineation of the chemical structure of epitopes in capsular polysaccharides and LPS vaccines. Synthesis of oligosaccharides.
- (f) Transfer of genes for oligosaccharide expression in potential vector organisms.

4. Hepatitis and Polio

4.1 Hepatitis A

- (a) The collection of well-characterized strains of hepatitis A and other enterically transmitted hepatitis viruses of diverse geographical and epidemiological origin;
- (b) Studies towards an improved understanding of the pathogenesis and primary sites of replication of these viruses.

- (c) Study of cell-mediated and humoral (local and systemic) immunity to these infections;
- (d) Establishment of a panel of monoclonal antibodies against hepatitis A virus strains for use in virus characterization and antigen analysis;
- (e) Identification of critical antigenic sites of hepatitis A virus relevant to protective immunity using a combination of selection of non-neutralized mutants in the presence of monoclonal antibodies and recombinant DNA technology;
- (f) Further cloning and sequencing studies on carefully selected hepatitis A strains in order to (i) determine the genetic basis of antigenicity and virulence of the virus and (ii) to rescue infectious virus by transfection, to facilitate construction of attenuated strains by strategic modifications of the virus genome;
- (g) Development of experimental vaccines against hepatitis A using antigens prepared by controlled gene expression and synthesis of oligopeptides;
- (h) Studies aimed at improving virus yields from cell types suitable for vaccine production;
- (i) To maintain contact with manufacturers of biological products, including those taking a conventional approach to vaccine development, and to establish an effective interface between the Steering Committee and industry.

4.2 Polio

- (a) Determination of the molecular basis of virulence of types 1, 2 and 3 poliovirus with special reference to the Sabin strains and their reversion to virulence;
- (b) Evaluation of prospects for the preparation of new attenuated strains of virus by precise genetic modification (e.g. of Sabin strains) and "rescue" of infectious virus through cDNA;
- (c) Evaluation of intratypic recombinant viruses as vaccines, including the use of the attenuated Sabin type 1 strain as a carrier of genetic information encoding foreign antigens (e.g. polio type 3 and hepatitis A);
- (d) Further definition of the basis of immunity to polioviruses as generated by infection or immunization, particularly concerning the relative importance of local versus systemic and cell-mediated versus humoral immunity;
- (e) To provide for the free availability of reagents critical to the programme, including: (1) maintenance of a bank of well-characterized monoclonal antibodies to poliovirus, and (2) establishment of a bank of poliovirus genes (cDNA clones);
- (f) Study of the immunological properties and value as vaccines of polypeptides, derived by controlled gene expression or chemical synthesis, representative of antigenic sites of the poliovirus;
- (g) Collection of further data on the molecular basis of antigenicity of poliovirus and the preparation of new immunogens, e.g. by protein engineering;
- (h) Application of information from (a) for the development of safety tests of live vaccines employing molecular methods.

4.3 Hepatitis Non-A, Non-B

- (a) Identification of the etiological agent(s) from cases of hepatitis A-like disease in populations which are immune to hepatitis A virus in the Indian subcontinent, Central Asia and North Africa.

- (b) Evaluation of serological responses and sero-epidemiological surveys to investigate antigenic heterogeneity amongst the aetiological agents.
- (c) Development of specific diagnostic tests.
- (d) Development of reliable animal models for studies of infection pathogenesis and immunity.
- (e) Studies of the role of anti-HAV on pathogenesis of HAV-like non-A, non-B infection.
- (f) Molecular biological studies relevant to diagnosis and vaccine development.

5. Tuberculosis

- (a) Molecular biology and genetics.
 - (i) To isolate genes in order to understand their involvement in mycobacterial growth, pathogenesis and resistance to intracellular killing.
 - (ii) To produce potential protective antigens in suitable hosts.
 - (iii) To clone antigens in mycobacteria.
 - (iv) To develop DNA probes for use in diagnosis.
 - (v) To select mutants which have lost pathogenicity and to identify the genetic changes responsible for this.
- (b) Characterization of possible mechanisms and in vitro assays relevant to protection in vivo.
- (c) T cells and protective epitopes.
- (d) Immunoregulation in human tuberculosis.
- (e) Development of simple and specific immunodiagnostic techniques.

Acute respiratory viruses	Dengue	Encapsulated bacteria	Hepatitis/ polio	Tuberculosis
<u>Deadlines for applications</u>				
24 March 1988	9 April 1988	25 February 1988	19 March 1988	18 February 1988
<u>Dates of Steering Committee meetings</u>				
24-25 May 1988	9-10 June 1988	25-26 April 1988	19-20 May 1988	18-19 April 1988
