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WHO Advisory Committee on Variola Virus Research

Report of the second meeting

Geneva, Switzerland
15-16 February 2001

WORLD HEALTH ORGANIZATION
Department of Communicable Disease Surveillance and Response

Contents

Summary

The committee was assembled to evaluate the progress of research on variola virus. Analysis of the various areas of research shows that considerable progress has been made. These areas are: state of strain collections and viability studies, phylogenetic analysis using DNA amplification technologies, detection and differentiation of orthopoxvirus DNA, nucleotide sequence analysis of variola virus DNA, serological procedures for the detection of variola virus, antiviral agents and animal models of smallpox.

1. Introduction

1.1 Dr David Heymann, Executive Director, Communicable Diseases welcomed participants to the meeting and indicated that the main aims were to:

- review progress on the agreed programmes of research on variola viruses
- determine if the research was progressing at the pace necessary for the work to be completed before the planned destruction date in 2002
- identify if there were any significant gaps in the present research programme
- advise, as appropriate, on other possible directions of research.

1.2 Dr Heymann asked the Committee to keep in view the proposed destruction timetable for live virus stocks and the summary conclusions of the previous meeting of the Advisory Committee during their discussions. He also thanked the members of the scientific subcommittee for their help in reviewing the submitted research protocols from those engaged in smallpox virus studies.

1.3 Dr Robert Drillien was unanimously appointed Chairman and Dr Peter Greenaway was appointed Rapporteur. Meeting participants are listed in Annex 2.

1.4 Dr Drillien thanked WHO for organizing the meeting and encouraged broad discussion of the research findings that were to be presented. Following discussion, the initial agenda was modified to accommodate several unlisted presentations. The modified agenda is in Annex 3.

2. Working paper submitted by Drs Henderson and Fenner

2.1 A working paper submitted to the Committee by Drs Henderson and Fenner, who were unable to attend the meeting was presented. The Committee noted the critical views of the authors with respect to the usefulness of conducting further research on variola virus and their concern about respecting the destruction deadline.

3. State of strain collections and viability studies

3.1 It was noted that the Centers for Disease Control and Prevention (CDC), Atlanta, held 451 virus isolates derived from a number of different national collections. The majority of these were variola virus isolates and a database has been developed linking these with available diagnostic and epidemiological data. 49 strains, selected on the basis of geographical area and year of isolation and low passage history, were taken for further analysis. Of these, 45 were subsequently shown to be viable. These covered isolates from Asia (21), Africa (16), Europe (5), South America (2) and North America (1). Many of the viable isolates showed uniform plaque morphology and grew to high titre in tissue culture. 37/45 viable isolates were from *in vitro* cultured material; the remainder were from crust (non-passaged) samples.

3.2 Collection of the samples currently held at the State Research Center of Virology and Biotechnology ("VECTOR"), Koltsovo, Novosibirsk region, first began in Moscow in the mid 1950s. This collection was augmented with isolates obtained by the WHO Collaborating Centre in Moscow during the diagnostic studies that supported the smallpox eradication programme. The collection includes primary scab material, frozen liquid cultures and lyophilised samples. Not all samples in the collection have been tested for viability. 5 primary scab isolates, 4/9 frozen cultures and 6/6 lyophilised strains have demonstrable viability. Difficulties have been experienced in obtaining support for further work but funding is now anticipated.

3.3 Collaboration between staff at CDC and "VECTOR" has been initiated to ensure that any future work on virus characterization is adequately coordinated, including the transfer of reagents.

3.4 The Committee concluded that additional work may be needed to assess the viability of the stocks held in "VECTOR". There may also be benefit in undertaking further molecular characterization of additional strains. This would help to identify strains from which further DNA sequences could be determined.

4. Phylogenetic analysis using DNA amplification technologies

4.1 A number of PCR-based amplification technologies were described to facilitate the characterization and phylogenetic analysis of variola virus isolates. These included restriction enzyme fragment length polymorphism (RFLP) of PCR amplified products using a variety of primers and multiplex PCR analysis. As a general rule, primers in the central conserved genomic region were used for the comparison of all orthopoxviruses whereas those located towards the genomic termini were used to provide species and strain specific data.

4.2 RFLP analysis of some 20 amplicons that covered the entire variola virus genome was shown to be capable of discriminating between different orthopoxvirus species and different variola virus strains. Separation of DNA fragments on agarose

gels after either HincII, BstUI or HpaII digestion followed by analysis using pattern recognition software was used to develop phylogenetic maps of the different variola viruses and other orthopoxviruses analysed. These were used to demonstrate that camelpox virus was phylogenetically closer to variola virus than first thought.

4.3 Parameters such as position tolerance and optimization of the electrophoretically separated fragments were investigated to determine the reliability of this analytical procedure. Dendograms generated following bootstrap analyses of the data demonstrated that the variola virus minor strains could be separated from the major strains and that there was some sub-clustering of individual African and Asian isolates. It was felt that the technology had potential for gaining further insight into strain divergence and for grouping different isolates in a way that avoided direct DNA sequencing. It was also a procedure that could be applied using relatively small amounts of material and one that could be easily automated.

4.4 It was noted that this technology could potentially be used to trace any future outbreaks back to a particular source. This provided a further incentive to use this approach to characterize all existing isolates. However, members of the Committee drew attention to the fact that there would always be a necessity to correlate molecular findings with any clinical data obtained at initial disease presentation.

4.5 It was also noted that this technology could be used to analyse molecular differences that may occur as a result of initial adaptation to tissue culture or on subsequent passage. This had not been done in a rigorous manner but initial data indicated that there was a high degree of sequence conservation when moving from a primary isolate to a tissue culture adapted strain. Available sequence analyses have already identified some microheterogeneity but the significance of this has yet to be determined.

4.6 A related procedure involving multiplex PCR analysis was described for the species-specific differentiation of orthopoxviruses. This used the variable sequences present at the termini of orthopoxvirus genomes to facilitate species differentiation. The methodology had general applicability for diagnostic testing and could be configured to provide results within approximately 4 hours.

4.7 The Committee concluded that significant progress had been made in using PCR technology to investigate phylogenetic relationships between the orthopoxviruses, particularly variola viruses.

5. Detection and differentiation of orthopoxvirus DNA

5.1 A number of presentations described methodologies for the detection and subsequent diagnosis of orthopoxvirus infections using DNA amplification technologies. A major objective for this work is the real time identification of smallpox viruses. The basic procedures used are similar to those already described for the phylogenetic analyses of different variola virus isolates. The detection and

differentiation of orthopoxvirus strains and individual strains of variola virus generally involve the generation of PCR amplified products from both conserved and variable regions of the genome. Different groups have developed different platforms for the detection of amplified DNA products.

5.2 One of the detection procedures described involved the manufacture of 'Biochips' composed of polyacrylamide pads on a glass slide support. These 'Biochips' have a relatively long shelf life and can be manufactured by automated procedures. Specific polynucleotides, capable of differentiating orthopoxvirus species after hybridization, were incorporated into different polyacrylamide pads. Fluorescent-labelled PCR product was hybridized to the 'Biochips' and the intensity of fluorescence measured. The method was capable of differentiating different orthopoxvirus strains following analysis of the fluorescent patterns obtained. The procedure was capable of delivering results within several hours. The procedures have been validated using laboratory-based analysers and further work is being done to produce a portable analyser that could be used in field conditions. The Amplification Refractory Mutation System (ARMS) was described as another diagnostic procedure. This multiplex PCR uses a primer pair that amplifies a large conserved region of the orthopoxvirus genome and variola virus-specific primers that bind within this region to initiate amplification of a smaller product. The procedure is capable of differentiating orthopoxvirus species and is suitable for deployment using several different platform technologies.

5.3 Similar work was described using TaqMan PCR technology in which the evolution of a fluorescent signal was used for detection. The procedure is reasonably rapid and could be used in a high throughput format. The specificity of the test was 100% with the sensitivity being dependent on the concentration of DNA in the starting material. It was noted that the procedure had been validated against a panel of orthopoxviruses. The equipment used was presently laboratory-based but work to develop a portable analyser was in progress.

5.4 PCR methodologies, targetting individual orthopoxvirus genes, for the laboratory identification of orthopoxviruses (including variola virus) were presented. These methodologies have been published, and use restriction fragment length polymorphism as a specificity control.

5.5 The Committee noted that enormous progress had been made in this area. However, a major limitation of these procedures was the methodology for obtaining the initial DNA samples; some reliable and rapid procedures using commercially available reagents are becoming available. It was also noted that the specificity of the procedures was totally dependent on the sequences of the primers used for amplification. The detection of nucleotide sequences in cowpox virus that were previously considered to be variola virus specific, emphasized the point that the use of a single locus for PCR amplification would be insufficient to provide an unambiguous identification. Members of the Committee questioned the need for rapid analytical procedures that were sufficiently sensitive to differentiate between variola sub-species when the clinical management of infected individuals would be the same. It was noted

that the ability to detect the presence or absence of any orthopoxvirus in real time would be needed in emergency public health situations.

6. Nucleotide sequence analysis of variola virus DNA

6.1 The Committee was informed that the nucleotide sequences of three complete variola virus genomes were currently available. Substantial parts of the genomes of three other variola virus strains – Congo 70, Somalia 77 and India 7124 – had also been determined. The full sequence of camelpox virus, the closest known relative of variola virus, was described. It was noted that a large amount of sequence data was also available for individual genes of a variety of other orthopoxviruses.

6.2 The data obtained so far has confirmed the suspected evolutionary relationships between orthopoxviruses and have facilitated the further classification of different variola isolates into sub-species. The work has also demonstrated that the conserved sequences present in the centre of the virus genomes code for proteins that are essential for virus replication, such as enzymes involved in DNA and RNA metabolism. Some of the less conserved sequences located towards the termini code for proteins that are involved in host range determination and immunomodulation. Some of the immunomodulation functions could be markers of pathogenicity but further work was needed to confirm this.

6.3 It was anticipated that at least 6 complete variola virus genome sequences would be available by the end of 2002. It may also be possible to obtain sequence information from scab material that had not been passaged *in vitro*. The Committee felt that very good progress had been made in the sequence analyses of smallpox virus genomes.

7. Serological procedures for the detection of variola virus

7.1 Work using monoclonal and polyclonal antibodies against vaccinia virus proteins in ELISA formats to detect orthopoxviruses was described. These reagents and tests were capable of detecting a range of orthopoxviruses including camelpox, cowpox, monkeypox, vaccinia and variola viruses. Some difference in the relative sensitivity for detecting the different viruses was observed. Strain differentiation was not possible using this system. Work is in progress to determine if tests using these reagents are able to differentiate live variola major and minor strains.

7.2 Monoclonal and polyclonal antibodies are required for the production of serological assays capable of diagnosing infection with different orthopoxviruses. A series of reagents have been prepared using live variola virus preparations. These include both rabbit hyperimmune sera and mouse hyperimmune ascitic fluid. These reagents are all capable of neutralizing live virus *in vitro* tests. Work has started on the production of mouse monoclonal antibodies using inactivated variola virus as the

antigen. Stocks of virus inactivated by gamma irradiation may need to be maintained by the WHO Collaborating Centres after the proposed destruction date in order to characterize these reagents. However, some Committee members were concerned by the possibility that live virus could be isolated from such preparations.

7.3 The available serological reagents have been used to develop ELISA based assays for IgG detection and work has been started on the development of a corresponding IgM test. The reagents have also been shown to be useful for diagnosis using electron microscopy in association with immuno gold labelling.

7.4 The Committee felt that it would be important for any generated antibodies to be thoroughly characterized with respect to the variola virus proteins against which they react. The Committee concluded that much useful work was being done in the development of serological procedures for the detection of variola virus and encouraged its continuation

8. Antiviral agents

8.1 Cidofovir inhibits a wide variety of DNA viruses including orthopoxviruses. The mechanism of action of this drug is through selective inhibition of the viral DNA polymerase. The current status of work on the use of Cidofovir for the treatment of smallpox virus infections and adverse vaccinia virus reactions was discussed. *In vitro* tests for antiviral activity have been developed. These have demonstrated that the agent inhibits both vaccinia virus and 35 different isolates of variola virus. Each of these isolates had similar sensitivity to the drug. Preliminary data on cowpox virus suggests that development of resistance does not appear to be a problem. Poxviruses other than variola virus could therefore be used as surrogate models for the continuation of antiviral drug screening programmes after variola virus stocks have been destroyed.

8.2 An animal model based on the infection of mice with cowpox virus has been used to generate *in vivo* data. Two challenge systems, intranasal administration and small particle inhalation, have been used to investigate drug efficacy. Drug treatment before infection was shown to be effective. It was also shown that co-administration of drugs with vaccine did not affect the efficacy of the vaccine preparation. The animal model work has now been extended using monkeypox virus-infected cynomolgous monkeys where prevention of mortality has been demonstrated.

8.3 Work is in progress to improve the formulation of Cidofovir so that it can be delivered orally in a prodrug form. Aerosol delivery has already demonstrated that the drug is more effective at lower concentrations than that used in systemic treatments. It also completely prevents the development of lung lesions. This work is being supported by a drug discovery programme. An initial evaluation of some 274 compounds identified 27 agents with significant anti-variola virus activity. These included different classes of drugs, some of which showed improved therapeutic indices.

8.4 The use of Cidofovir for the treatment of severe adverse reactions that may occur upon vaccination with vaccinia virus has been submitted for approval for a vaccination study in the United States of America. A similar application is being prepared for the unlikely situation where treatment of smallpox is required.

8.5 The Committee noted that considerable progress had been made in this area.

9. Animal models of smallpox

9.1 Much of this work has concentrated on the aerosol infection of cynomolgous monkeys with the Yamada and Lee strains of variola virus. Clinical signs occur in infected animals by 6 days after infection. Clinical disease is apparent and seroconversion occurs but there is no mortality. It was concluded that this model was not sufficient to assess efficacy of new vaccines or drugs. Further work is anticipated using different strains of variola virus and different primate species. There is the possibility of creating a collaborative project between United States and Russian scientists using baboons as the animal model.

9.2 Further work has been done characterizing the infection of monkeys with monkeypox virus. All infected monkeys develop multi-sytem disease, severe bronchopneumonia and skin lesions. The pathogenesis of disease closely follows that of variola virus infection of man. It was concluded that this would provide a suitable surrogate model to assess the efficacy of cell culture-derived vaccines.

9.3 The Committee concluded that work was progressing satisfactorily in this area but that the rate was slow. The proposed work on the infection of baboons with variola virus strains was noted. It was felt that additional work may be required to identify and further characterize surrogate models in comparison to variola virus infection models so that a validated system for drug and vaccine assessments could be established.

10. Ectromelia virus recombinant expressing mouse IL-4

10.1 The Committee took note of the published work describing a recombinant ectromelia virus expressing the mouse IL-4 gene, which made the virus more virulent for mice. The Committee was of the opinion that with the data available, the implications of these findings for other poxviruses was impossible to assess.

Annex 1: Agenda

15 February 2001

9:00-9:15 Welcome, Purpose of the meeting
Dr David L. Heymann
Executive Director, Communicable Diseases

9:15-9:40 Review of strains in collection, results of viability studies

Presentation by Dr Inger Damon: "Inventory of variola strains at the CDC" (20 min).

9:40-10:00 PCR and extend PCR/RFLP analysis of orthopoxvirus DNA

Presentation by Dr Joseph Esposito: "Extend PCR/RFLP for orthopoxvirus genome DNA diagnostics and inference of phylogeny" (20 min).

10:00-10:30 COFFEE BREAK

10:30-12.00 PCR and extend PCR/RFLP analysis of orthopoxvirus DNA (cont.)

Presentation by Dr Inger Damon: "Extend PCR/RFLP analysis as a tool for phylogeny inference: variola" (15 min).

Presentation by Dr Vladimir Mikhailovich: "Identification of orthopoxvirus species by hybridization on biochip" (7 min)

Presentation by Dr Hermann Meyer: "Amplification of 'variola virus-specific' sequences in cowpox virus isolates " (5 min).

Presentation by Dr Inger Damon: " Development of PCR assays for variola" (20 min)

Presentation by Dr Peter Jahrling: " Real-time identification of the smallpox virus" (20min)

Presentation by Dr Igor Babkin: "Multiplex PCR for species-specific differentiation of orthopoxviruses" (10min)

12:00-13:30 L U N C H

13:30-14:30 Sequence analysis of variola virus DNA

Presentation by Dr Joseph Esposito: "Orthopoxvirus E-PCR amplicon, robotics-assisted, primer-walking genome sequencing" (30min)

Presentation by Dr Geoffrey Smith: "Sequence analysis of various virus DNA" (20min)

14:30-15:30 Progress in development of serological assays

Presentation by Dr David Ulaeto: "UK Programme for detection and diagnosis of variola virus" (20 min)

Presentation by Dr Inger Damon: " Development of serologic assays for variola" (15 min)

15:30-16:00 COFFEE BREAK

16:00-17:30 Review of antiviral candidate drugs
Presentation by Dr John Huggins: "Interim report on joint DHHS-DoD research project " Antiviral therapy of smallpox and other orthopoxvirus infections from terrorist or biological warfare release" (30 min).

16 February 2001

8:30-10:00 Review of animal model developments

Presentation by Dr Peter Jahrling: "Exposure of cynomolgus monkeys to variola virus" (30 min)

9:30-10:00 General Presentations

Presentation by Dr Geoffrey Smith: "The sequence of camelpox virus and recombinant ectromelia virus expressing IL-4" (20 min).

Presentation by Dr Isao Arita: "Working paper submitted by Drs Henderson and Fenner (10 min)

10:00-10:30 COFFEE BREAK

10:30-12:00 General discussion

12:00-13:30 L U N C H

13:30-15:00 General discussion (cont.)

15:00-15:30 **COFFEE BREAK**

15:00-17:00 Conclusions, time lines

Annex 2: List of participants

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