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WHO Advisory Committee on Variola Virus Research

Report of the third meeting

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World Health Organization
Department of Communicable Disease Surveillance and Response

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Summary

The WHO Advisory Committee on Variola Virus Research reviewed progress of research involving live variola virus. It agreed that considerable progress had been made since it last met. However, despite previous estimates, the Committee noted that significant components of the agreed programme were unlikely to be completed by the end of 2002. Further, during extensive discussion, additional research was identified which would necessitate having access to live variola virus after the anticipated 2002 destruction date. The Committee therefore recommended that the destruction deadline be postponed to enable essential research to be completed. It also recommended that additional research using live variola virus should continue to be carefully monitored and reviewed under the auspices of WHO and that steps should be taken to ensure that all approved research remains outcome focused and time limited.

1. Introduction

1.1 Dr David Heymann, Executive Director, Communicable Diseases welcomed participants to the meeting and asked the Committee to review the progress of research using live variola virus. The main issues to address were :

- The likelihood of completing the research planned prior to this meeting by the end of 2002.
- Any recent developments in variola virus research or in the world situation suggesting the need for additional studies that would extend beyond the end of 2002.

1.2 Dr Peter Greenaway was appointed Chairman and Dr Robert Drillien was appointed Rapporteur. The meeting agenda is given in Annex 1 and meeting participants are listed in Annex 2. The majority of the meeting concemed scientific presentations relating the most recent results from laboratories using live variola virus.

2. Review of variola virus strains in the Russian collection

2.1 The second meeting of this Committee noted that the Centers for Disease Control and Prevention (CDC), Atlanta, held 451 virus isolates derived from a range of continents and countries when smallpox was endemic. The current review and the studies reported concentrated on some 50 isolates, from a total of approximately 120 in the Russian collection, that were not present in the United States collection. Twenty-three isolates from scab material and previously lyophilised samples displayed viability upon tissue culture passage. Isolation of DNA from these strains is ongoing; 2 genomes have been completely cloned, at least 5 others will be cloned by the end of 2002 and other work is being planned.

2.2 The Committee agreed that before the end of 2002 further consideration should be given to the necessity of holding the entire range of isolates currently available in the two repositories.

3. Nucleic acid based diagnostics

3.1 A number of methods have been developed over the last few years to enable very sensitive detection of variola virus DNA and distinguish this DNA from that of other orthopoxviruses. PCR-RFLP analysis, multiplex PCR and real time PCR employing the detection of fluorigenic probes are the most promising methods.

3.2 The Committee was informed of a recent laboratory-acquired infection with a non variola orthopoxvirus which provided a demonstration of the performance of PCR-RFLP and real time PCR methods using clinical material from the skin and vesicular fluid. Analysis of DNA samples from the infected worker by extend PCR-RFLP enabled a very precise definition of the virus responsible for the accidental infection.

3.3 Similar studies have been conducted to more thoroughly investigate a fatal case of laboratory transmitted smallpox that occurred some 20 years ago. In addition, real time PCR has been used to follow viraemia and the presence of virus in tissue in monkeys experimentally infected with variola virus. Finally, it was shown that multiplex PCR can be used to identify variola virus DNA in crust samples and that it can distinguish major and minor strains with as little as 1 pg of sample material. 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 results obtained indicate that single gene PCR-RFLP and multiplex PCR detection methods are useful for detecting variola virus in clinical samples. It was noted that real time PCR has greater sensitivity and can therefore detect infection at an earlier stage, however, it uses expensive equipment and, so far, is not able to consistently distinguish between orthopoxvirus species. Extend PCR-RFLP has proven useful to precisely define the origin of an isolate but may require prior tissue culture passage.

3.5 The Committee agreed that significant progress has been made in the area of molecular diagnosis but that there is still scope to improve the sensitivity of the tests available. For example, it would be useful to know how early a variola virus infection might be detected at the prodromal stage. An ultimate goal is the development of relatively cheap hand held detection equipment for variola virus DNA.

3.6 The Committee recognized that the further development of diagnostic procedures was an important area for further work. It encouraged investigators to share diagnostic reagents, essential primer sequences for PCR detection and protocols. This would be particularly useful for differentiating between, for example, variola and varicella virus infections.

4. Sequence analysis of variola virus DNA

4.1 The Committee was informed that the extend PCR method combined with primer walking has been used to obtain the complete genomic sequences of 7 additional variola virus isolates. This brings the total number of full length sequences to 10 (9 major strains and 1 minor strain). A high degree of sequence conservation was detected between isolates even though some had undergone a number of passages in tissue culture. Whilst this suggests that tissue culture passage may have little influence on genome stability, no comparative data from scab material was available. The Committee indicated that it would be important to obtain DNA sequence information from scab material.

4.2 Hypervariable regions containing long T or AT runs have been detected near the left and right termini respectively. This microheterogeneity is thought to reflect the low passage and non clonal features of the virus populations analysed. The biological meaning of these findings, if any, is unclear. As yet, no sequence variability between isolates could be correlated with their known degree of virulence.

4.3 The Committee noted that a considerable amount of nucleic acid sequence information on variola viruses was now available. After discussion it was agreed that gaining further sequence information from the more variable termini had priority over the derivation of additional whole genome sequences. This would be useful for forensic studies if there was ever a deliberate release of variola virus. Reference DNA should be kept for this purpose.

5. Sequence of the ectromelia virus genome

5.1 The sequence of the highly pathogenic ectromelia virus genome (the causative agent of mousepox) was presented and comparisons were made with other orthopoxviruses, particularly variola virus. The data provides the opportunity to study the role of virus genes, some of which are homologues of variola virus genes, in a severe animal poxvirus infection.

6. Progress in the development of serological assays

6.1 Polyclonal and monoclonal antibodies against vaccinia virus have been used in ELISA and manual threshold assays to evaluate their usefulness in the detection of variola virus isolates. So far some 23 virus samples amplified in tissue culture have been studied. Although the methods available appear relatively sensitive they do not allow the detection of all virus isolates. In this respect, polyclonal sera more readily detected all virus strains while monoclonals missed some.

6.2 A human IgM capture assay has been developed as one means to recognize the presence of an orthopoxvirus infection. This method relies on the use of killed variola virus as antigen and hyperimmune mouse ascitic fluid directed against live variola virus as the capture system. Detection of IgM in monkeys infected experimentally with variola between

4 and 6 days after infection (depending on the infectious dose used) has been achieved. The assay was also used to detect anti-vaccinia IgM 4 days after an accidental human infection.

6.3 The Committee noted that the specificity of the test remains a critical issue but that this could be readily solved by the availability of variola virus specific monoclonal antibodies. The development of such antibodies has been initiated but progress has been slow. The Committee concluded that a variola virus specific serological assay could usefully complement molecular diagnostic techniques, particularly as a second method to detect infection. However, further validation of the test was needed before this goal could be achieved.

7. Animal models

7.1 Adequate animal models using variola virus have been unavailable so far. Recent data demonstrating the infection and lethality of variola virus, administered intravenously or intravenously with an aerosol, in cynomolgus monkeys was presented. It was noted that the induced disease develops at a much faster pace than smallpox in man and that the dose of virus used to date via the intravenous route is particularly high. It was shown that a number of the pathological features of the disease produced in monkeys appear to be similar to those of smallpox in man.

7.2 Additional studies are needed to improve and validate this model. However, for this to be done, the work would need to extend beyond 2002. It was clear that the monkey model has the potential to be employed for testing therapeutic drugs and novel vaccines. It could also provide access to clinical specimens for testing diagnostic procedures. Other surrogate animal models are being pursued in parallel, in particular the infection of monkeys with monkeypox virus and the infection of rodents with cowpoxvirus.

8. Drug development

8.1 Most studies have focused so far on the efficacy of cidofovir as an anti-poxvirus drug. This compound has demonstrable activity against cowpox in mice and against monkeypox in monkeys. The United States currently allows cidofovir to be used in emergencies as an investigational new drug to treat adverse effects following immunization with the current smallpox vaccine and in the unlikely event of smallpox re-emerging.

8.2 A drug development programme based on the chemical modification of cidofovir has been initiated to identify compounds with improved activity and to allow oral administration. Other work involving the *in vitro* screening of other chemical entities has identified additional compounds with anti-poxvirus activity. Further work on these compounds is needed.

8.3 Most of the anti-poxvirus compounds identified so far target the viral DNA polymerase and it was considered important to identify other viral gene products susceptible

to drug intervention. A number of molecules were identified in a subsequent survey which inhibit a range of orthopoxviruses, including variola virus. Some drugs have selective activity, inhibiting one or more of the orthopoxviruses but not necessarily variola virus. This finding supports the premise that access to live variola virus is necessary if the effective screening of additional lead compounds is to be achieved.

8.4 Further discussion considered the potential use of variola virus recombinants encoding green fluorescent protein as a tool for rapid detection of virus multiplication in drug inhibition assays. It was agreed that an extensive and reasoned risk analysis was needed before this approach could be considered by the Committee's peer review panel. Approval from WHO's Biosafety Advisory Group would also be needed before work of this nature can be undertaken.

9. Vaccine development

9.1 The Committee agreed that the best safeguard against smallpox was vaccination. It noted that this strategy had been deployed successfully during the eradication programme but that the smallpox vaccine currently available was associated with a significant number of adverse side reactions. This suggested that, although the current vaccine had proved efficacy and utility, improvements were needed particularly to facilitate the safe and effective immunization of vulnerable sectors of different populations (the immunocompromised, the elderly, pregnant women and children with eczema).

9.2 The Committee therefore encouraged the identification of further research into vaccine strategies that might employ more attenuated vaccinia virus strains, sub-unit vaccines or other promising recombinant DNA methodologies. Results reported at the meeting and in numerous publications with attenuated vaccinia virus recombinants encoding antigens from other pathogens indicate the potential value of deploying alternative vaccine development strategies. It was recognized that access to live variola virus would be necessary to assess the efficacy of new, improved smallpox vaccines and, ultimately, to obtain approval from the regulatory authorities.

10. Fundamental studies

10.1 Some fundamental research with variola virus has been pursued although this area has purposely not received high priority. Research investigating the involvement of chemokine receptors in the spread of variola virus in tissue cultures was described. The Committee took note of these interesting findings.

11. Conclusions and recommendations

11.1 The Committee acknowledged that important progress has been made since its last meeting in health-oriented research involving variola virus. However, it was concluded that

much essential research will not be completed by the end of 2002, the currently proposed deadline for variola virus destruction.

11.2 One area of particular concern was the current low level of smallpox immunity in the world population and the consequent necessity to undertake further research on future strategies for dealing with an unexpected outbreak. The Committee therefore felt that further goal oriented research, extending beyond the anticipated 2002 destruction deadline, is justified so that the world population can be adequately prepared for such an unlikely event.

11.3 The Committee noted that a considerable amount of variola virus DNA sequence information was now available. It recommended that further sequence data from the terminal regions of the virus genome should be obtained.

11.4 The Committee noted that effective methods to detect variola virus infections are now available in the two certified laboratories that retain the virus and in a handful of other laboratories. Further work is needed to validate these procedures with clinical material derived from experimentally infected animals. It was acknowledged that if a variola virus outbreak should occur the diagnostic laboratories that are currently prepared could easily be overwhelmed. The Committee therefore stressed the importance of sharing primary detection protocols, diagnostic reagents and training materials with other approved diagnostic/detection facilities.

11.5 The Committee took note of the advances in developing new drugs for smallpox treatment and recommended that collaborative research should be encouraged to develop at least two different formulations of two drugs that had different modes of action.

11.6 The Committee acknowledged that the currently available vaccine preparations had a demonstrable and highly successful track record in protecting populations from smallpox. However, anticipated demands for vaccines that had fewer adverse side reactions indicated that a vaccine development programme to produce an improved, safer, yet as effective preparation is justified. It was felt that such a programme had a high priority given the possibility of a deliberate release of variola virus.

11.7 These considerations emphasized the importance of having access to a validated animal model of human smallpox with which tests to achieve licensure of smallpox drugs and vaccines could be done. This, in turn, underlines the importance of retaining variola virus stocks to assess candidate drugs and vaccines for both efficacy and regulatory purposes. The Committee therefore recommended that research to further refine the recently developed smallpox animal model should be promoted and that data allowing bridging to non-variola animal models should be obtained.

11.8 Finally, the Committee recommended that further research using live variola virus beyond 2002 should continue to be carefully monitored and reviewed under the auspices of the WHO and that steps should be taken to ensure that all approved research remains outcome focused and time-limited.

Annex 1: Agenda

3 December 2001

9:00-9:15	Welcome, purpose of the meeting Dr David L. Heymann Executive Director, Communicable Diseases
9:15-9:40	Review of variola virus strains in collection, results of viability studies
	Presentation by Dr Lev Sandakhchiev: "Inventory of variola strains in the Russian collection" (20 min)
9:40-10:00	PCR and extend PCR-RFLP analysis of orthopoxvirus DNA
	Presentation by Dr Inger Damon: "Update in nucleic acid based diagnostics development" (20 min)
10:00-10:30	COFFEE BREAK
10:30-11:15	PCR and extend PCR-RFLP analysis of orthopoxvirus DNA (cont.)
	Presentation by Dr Sergei Shchelkunov: "Current status of PCR and extend PCR-RFLP analysis of orthopoxvirus genome DNA" (15 min)
11:15-12:00	Sequence analysis of variola virus DNA
	Presentation by Dr Inger Damon: "Sequence analysis of variola virus DNA" (20 min)
12:00-13:30	L U N C H
13:30-14:30	Progress in development of serological assays
	Presentation by Dr David Ulaeto: "Antibodies and gene probes for the detection and diagnosis of variola virus" (20 min)
	Presentation by Dr Inger Damon: "Development of an IgM capture assay" (20 min)
14:30-15:30	Review of animal developments
	Presentation by Dr Peter Jahrling: "Exposure of cynomolgus monkeys to variola virus" (30 min)

15:30-16:00 COFFEE BREAK

16:00-17:30 Review of antiviral candidate drugs

Presentation by Dr Lev Sandakhchiev: "Search for antivirals active against human pathogenic orthopoxviruses" (20 min)

Presentation by Dr John Huggins: "Joint DoD-DHHS program for development of antiviral therapeutics for treatment of smallpox resulting from terrorist or biological warfare release of variola" (20 min)

4 December 2001

9:00-10:00 General presentations

Presentation by Dr Lev Sandakhchiev: "Development of recombinant vaccines against orthopoxvirus, hepatitis B and HIV under Russian national programs" (20 min)

Presentation by Dr Inger Damon: "Host factors in variola pathogenesis: do cheminoke receptors play a role?" (20 min)

10:00-10:30 COFFEE BREAK

10:30-12:00 General discussion on research progress

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

13:30-15:00 General discussion and preparation of draft recommendations

15:00-15:30 COFFEE BREAK

15:00-17:00 Consensus on recommendations

Annex 2: List of participants

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