



WHO Recommendations

concerning the distribution, handling and synthesis of variola virus DNA

Based upon recommendations made to WHO by the WHO *Ad Hoc* Committee on Orthopoxvirus Infections (1990 and 1994) and the WHO Advisory Committee on Variola Virus Research (2003, 2004 and 2007)

Revised 13 January 2016 (by the WHO Advisory Committee on Variola Virus Research at its seventeenth meeting)

Preamble

The only known stocks of variola virus are held at the two global repositories: the US Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America, and the State Research Center of Virology and Biotechnology (Vector), Koltsovo, Novosibirsk Region, Russian Federation, both of which are World Health Organization (WHO) Collaborating Centres¹. Any research using live variola virus has to be performed in the maximum containment laboratories of these institutions and requires prior permission from WHO.

Genetic engineering of variola virus and attempts to produce live variola virus from DNA are strictly prohibited.

The purpose of these recommendations is to prevent the reconstruction of variola virus or the construction of a virus which will cause a disease with the same attributes as smallpox, either through the reactivation of variola virus DNA or the incorporation of variola virus DNA sequences into other orthopoxviruses. There are several ways to achieve this goal; one is to limit the amount of variola virus DNA held by any one laboratory to an amount far less than a complete genome; another is to institute operations and practices that preclude any possibility of variola virus DNA coming in contact with another replication-competent orthopoxvirus. As the capacity to synthesize genes has improved to the point where genes and whole genomes can be created from sequence information, it is important to remember that DNA encoding variola virus proteins should also be handled with these restrictions in mind.

In its naked form, variola virus DNA is not infectious. Scientists wishing to perform research on individual variola virus genes may obtain parts of the variola virus genome from one of the two WHO Collaborating Centres for Smallpox. Alternatively, researchers may wish to synthesize or purchase such DNA directly. WHO or the WHO Collaborating Centres will advise scientists on the procedure to follow in order to obtain permission to receive or synthesize variola virus DNA. Scientists should be aware that the amount of DNA they request or hold must not exceed 20% of the total variola virus genome (see also below).

The scientific community must be fully aware that the distribution, synthesis and handling of variola virus DNA is governed by a series of recommendations made initially by the WHO *Ad Hoc* Committee on Orthopoxvirus Infections and updated by the WHO Advisory Committee on Variola Virus Research. These recommendations have been endorsed by the World Health Assembly. WHO's recommendations are intended to be incorporated into individual Member States' biosafety guidelines or legislation. Scientists must also comply with the requirements of local guidelines or legislation if they wish to obtain, handle or synthesize variola virus DNA. The present document gives an overview of these recommendations, which are reproduced in their original wording as found in the various WHO meeting reports (<http://www.who.int/csr/disease/smallpox/research/en/index.html>).

¹ WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA (Vector) and WHO Collaborating Centre for Smallpox and Other Poxvirus Infections (CDC).

Distribution of variola virus DNA

The two WHO Collaborating Centres, acting as repositories for variola virus, may distribute variola virus DNA fragments to appropriate research laboratories that request them provided that:

- a) The request has been submitted to the international repository through the WHO Secretariat (1, 2).
- b) The receiving laboratory agrees that the DNA will not be distributed to any third party unless authorization by WHO has been obtained. This must be controlled through a Material Transfer Agreement between the distributing and receiving laboratories (with copy to WHO) (1, 2, 3).
- c) The receiving laboratory must submit an annual report on the status of the variola virus DNA to WHO, and if appropriate, the WHO Collaborating Center (2).

No laboratory, other than the designated smallpox WHO global repositories, shall be permitted to hold variola virus DNA representing more than 20% of the variola virus genome at any one time (2).

Fragments of variola virus DNA for diagnostic kits, not exceeding 500 base pairs in length, may be freely distributed for use as positive controls or standards in diagnostic kits, providing collectively they do not exceed 20% of the total genome size held by any entity (4, 5).

Handling of variola virus DNA

Studies on variola virus DNA are permitted on conditions that:

- a) The DNA will not be used for insertion into other poxviruses (2).
- b) All work with variola virus DNA can be done only following approval of a written risk assessment by the appropriate local safety committee (2).
- c) No other orthopoxviruses are handled in the laboratory rooms where variola virus DNA is present (2).
- d) All by-products containing variola virus DNA must be disposed of at the conclusion of the work by autoclaving at 120°C for 30 minutes (6).

Synthesis of variola virus DNA

- a) Attempts to synthesize full-length variola virus genomes or infectious variola viruses from smaller DNA fragments are strictly forbidden (7).
- b) Synthesis of variola virus DNA to express a variola virus protein, or synthesis of codon-modified DNAs for the same purpose requires prior permission from WHO via the Chair of the ACVVR Scientific Sub-Committee. Similarly, mutagenesis of orthopoxvirus DNA with the aim of producing a variola virus protein requires prior permission from WHO through the same channel. Those undertaking synthesis of variola virus DNA are under the same obligations and constraints outlined above in the section on Distribution of variola virus DNA.

c) Under no circumstances can any single laboratory other than the designated WHO Collaborating Centres hosting the variola virus repositories hold DNA comprising more than 20% of the total genome (4, 7).

d) The only exception to c) is the production of DNA microarrays, on which small oligonucleotides (less than 80 base pairs) are covalently bound to a matrix and which, in aggregate, may span the entire variola virus genome, does not require permission from WHO (4, 5).

e) For diagnostic kit purposes, variola virus DNA fragments up to 500 nucleotides may be synthesized without notification to WHO.

These policies also extend to the manufacturers of synthetic DNA who must also be held responsible for upholding these recommendations and national policies.

Reporting obligations

Variola virus DNA is distributed to scientists on the understanding that an annual report on the status of variola virus DNA clones will be made to the international repository (see above: distribution of variola virus DNA, paragraph c). This reporting obligation also applies to scientists who have obtained permission from WHO to synthesize variola virus DNA larger than 500 base pairs or generate variola virus-like DNA by site-directed mutagenesis of other orthopoxvirus DNA.

Definition of variola virus DNA

Variola virus DNA is defined as any DNA sequence of any length:

- unique to variola virus, and/or
- which encodes one or more variola virus polypeptides.

A variola virus polypeptide is defined as any polypeptide of any length that contains amino acid sequences that are unique to variola virus.

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