

Attention with virus contaminated cell lines

O.-W. Merten

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Although (or probably because) quality control efforts are continuously increasing in animal cell technology, sometimes surprising news on contaminated cell lines are arriving. Recently a Japanese group (Li et al. in *J. Virol.*, doi:10.1128/JVI.00807-07, published online ahead of print on 8 August 2007) working on the development of the production of hepatitis E virus-like particles by infecting High Five insect cells (BTI-TN-5B1-4 (Tn5)) with recombinant baculovirus has observed the appearance of unknown viral particles with diameter of 35 nm containing RNA. The study established that these unknown viral particles were nodaviral particles and that they belong to the genus *Alphanodavirus*. The infection of the Tn5 cells with recombinant baculovirus induced the production of infectious nodaviral particles in parallel to the production of the recombinant protein.

The preoccupying fact is that this nodavirus was latently present in the 'High Five' cells and that other freshly purchased ampoules equally contained cells with latent nodavirus infection.

In principle, the presence of latent virus *per se* might not be a problem, however, in the case of nodaviruses their presence can be an issue because

1st there is a serious risk of contamination by this virus when virus-like particles for vaccine

purposes or recombinant proteins for therapeutic purposes are produced using the mentioned cell system, and

2nd nodaviruses (known as viruses infecting insects and fishes) are unique in being able to infect suckling mice and suckling hamsters (Garzon et al. *Arch. Virol.* 113 (1990) 165, Scherer & Hurlbut. *Am. J. Epidemiol.* 86 (1967) 271, Scherer et al. *Am. J. Trop. Med. Hyg.* 17 (1968) 120) with resulting paralysis and death, although no alphanodavirus infections of humans have been reported.

Today nobody knows if the original stock of these cells was contaminated thus we do not know if all established subcultures and all derived subclones of the 'High Five' cells also contain latent nodavirus or not. Therefore, the authors (Li et al.) of the paper further indicated that *all cell lines derived from the insect Tn5 cell line should be examined for the presence of such nodaviruses*, and that, because of the *ability of nodaviruses to establish latent and inapparent infections, all insect cell lines should be screened routinely* for the presence of virus.

What does this mean to the producer of biologicals using 'High Five' cells as cell substrate? In the case (the worst case scenario has to be assumed here), that the original stock of the 'High Five' cells was already contaminated and that these cells are used for the production of recombinant proteins for human use or virus like particles for vaccination

O.-W.Merten (✉)

Généthon, Department of Bioprocess Development, 1, Rue de l'Internationale, BP 60, Evry Cedex 2, F-91002, France
e-mail: omerten@genethon.fr

purposes, either the downstream processing protocol has to be able to eliminate any nodavirus present or potentially present, or, as a total elimination cannot unequivocally be proven, a supplementary virus inactivation step should be added to the purification protocol. Else, 'High Five' should not be further considered for production of biological substances for human use.

How is the situation for other insect cell lines?

- Schneider's cell line 1 (*Drosophila melanogaster* cells): a similar infection by a nodavirus has been reported previously for a sub clone of this cell line (Friesen et al. *J. Virol.* 35 (1980) 741).
- Sf9 cells: With respect to Sf9 cells, Li et al. (*J. Virol.* doi:[10.1128/JVI.00807-07](https://doi.org/10.1128/JVI.00807-07)) did not find any indication for the presence of a latent nodavirus infection.
- No information is available for other insect cell lines.

And for mammalian cell lines?

With respect to mammalian cells, many virus contaminations have been observed during the past and more details can be found in Merten (*Cytotechnology* 39 (2002) 91).

As a conclusion, I would like to ask any 'cell culturist' to follow the recommendations of Li et al. (*J. Virol.* doi:[10.1128/JVI.00807-07](https://doi.org/10.1128/JVI.00807-07)) and to be cautious because almost any animal cell is a potential virus producer. Although routine virus testing is a must and a valuable means for reducing the risk of using virus contaminated cell lines, it does not provide absolute safety because of the possibility of new emerging viruses and the permanently existing risk of contaminations by adventitious agents and viruses. Thus the users of animal cells as well as the producers of biotech products by using animal cells have to be attentive to this possible threat and they have to assure the absence of adventitious agents/viruses by any means.