OptiPrep™ Mini-Review MV05

Purification and analysis of papillomaviruses

- OptiPrep™ is a sterile 60% (w/v) solution of iodixanol in water, density = 1.32 g/ml
- This Mini-Review principally provides (in Section 2) a bibliography of all those papers reporting the use of OptiPrep™ in the purification and analysis of papilloma virus and virus-like particles. Section 1 briefly summarizes the advantages of using OptiPrep™; the gradient strategy used for papillomavirus and the technical data that is available.

1. Technical background to the use of OptiPrep™

1a. Background

In all comparative studies between CsCl and iodixanol, the recovery of virus infectivity is much higher and the particle:infectivity ratio much lower when viruses are purified in iodixanol. Although sucrose is generally less deleterious to viral infectivity than CsCl, it can nevertheless also have serious effects on certain important aspects of viral function; in particular the loss of surface glycoproteins from enveloped viruses, particularly retroviruses, has been noted [1]. This may be related to its viscosity, which, in solutions of the same density, is much higher than that of iodixanol. Most iodixanol gradients can also be made isoosmotic over the entire density range.

Like CsCl, sucrose must be dialyzed before infectivity can be measured. In contrast both infectivity measurements using cultured cells and many add-on techniques can be performed without dialysis of iodixanol. Combined with the availability of OptiPrep™ as a sterile solution, this makes the use of OptiPrep™ for virus purification and assembly analysis much more convenient than the use of either CsCl or sucrose. The only analytical technique for which removal of the iodixanol is essential is electron microscopy. Consequently iodixanol is being increasingly used for the purification of papillomavirus particles from lysed cultured cells.

1b. Gradient strategy

Buck et al [2] observed that papillomavirus vector stocks could be purified by an iodixanol gradient centrifugation procedure that was substantially more effective than the standard CsCl gradient purification. The methodology developed [2] has been used more or less unchanged in all subsequent studies and has been found to be effective for human, bovine and cotton-tail rabbit viruses. A continuous gradient is usually generated from equal volumes of 27%, 33% and 39% (w/v) iodixanol allowed to diffuse for 3-4 h at room temperature, after which the clarified sample is laid on top. Although the continuous gradient might be prepared from 27% and 39% iodixanol using a two-chamber gradient maker, use of the latter is technically more difficult with these small volume gradients. The separation of the L1 protein from both DNA-containing and empty virus-like particles after 234,000 *g* for 3.5 h at 16°C is considered to be part buoyant density and part sedimentation velocity [2], so top-loading of the sample cannot be replaced by other frequently-used strategies such as bottom-loading of the sample or the use of self-generated gradients.

1c. References (to Sections 1a and 1b)

1. Palker, T.J. (1990) *Mapping of epitopes on human T-cell leukemia virus type 1 envelope glycoprotein* In: Human Retrovirology: HTLV (ed. Blattner, W.A.) Raven Press, NY, pp 435-445
2. Buck, C.B., Pastrana, D.V., Lowy, D.R. and Schiller, J.T. (2004) *Efficient intracellular assembly of papillomaviral vectors* J. Virol., **78**, 751-757

- The gradient protocol for the purification of isolation of papillomavirus particles (Application Sheet V10) may be accessed from the OptiPrep™ Applications flash-drive or from the following website: www.axis-shield-density-gradient-media.com, click on "Methodology" then "Viruses" to open up the Virus Index. Other OptiPrep™ Application Sheets on the preparation and harvesting of gradients may also be accessed from the top of the Index.

2. Bibliography

- This bibliography provides a comprehensive reference list of all the papers reporting the use of OptiPrep™ for papillomavirus purification, published before the end of January 2017.
- The references are divided alphabetically into **"Research topic" sections** and **subsections.**
- All references are listed alphabetically according to **First Author.**
- The vast majority of published papers describe studies on human papillomavirus (not flagged); those studies on bovine **(B)**, canine **(C)**, cotton-tailed rabbit **(CTR)**, equine **(E)**, Macaques **(MQ)** and mouse **(M)** are indicated as shown. In many cases these flagged papers will also include work on the human virus.

B-cell anergy reversal

Chackerian, B., Durfee, M.R. and Schiller, J.T. (2008) *Virus-like display of a neo-self antigen reverses B cell anergy in a B cell receptor transgenic mouse model* J. Immunol., **180**, 5816-5825 **(B)**

Baculoviral vectors

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Lee, H-J., Hur, Y-K., Cho, Y-D., Kim, M-G., Lee, H-T., Oh, Y-K. and Kim, Y.B. (2012) *Immunogenicity of bivalent human papillomavirus DNA vaccine using human endogenous retrovirus envelope-coated baculoviral vectors in mice and pigs* PLoS One, **7**: e50296

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Capsids and capsid protein

Capsid assembly

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DNA, separation from

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L1 capsid protein

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Ryndock, E.J., Conway, M.J., Alam, S., Gul, S., Murad, S., Christensen, N.D. and Meyers, C. (2014) *Roles for human papillomavirus type 16 L1 cysteine residues 161, 229, and 379 in genome encapsidation and capsid stability* PLoS One, **9**: e99488

Maturation

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Conway, M.J., Cruz, L., Alam, S., Christensen, N.D. and Meyers, C. (2011) *Differentiation-dependent interpentameric disulfide bond stabilizes native human papillomavirus type 16* PLoS One, **6**: e22427

Neutralization-sensitive epitopes

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Tumour cell binding

Kines, R.C., Cerio, R.J., Roberts, J.N., Thompson, C.D., de Los Pinos, E., Lowy, D.R. and Schiller, J.T. (2016) *Human papillomavirus capsids preferentially bind and infect tumor cells* Int. J. Cancer, **138**, 901–911

Cell entry/targeting

Autophagy inhibition

Surviladze, Z., Sterk, R.T., DeHaro, S.A. and Ozbun, M.A. (2013) *Cellular entry of human papillomavirus type 16 involves activation of the phosphatidylinositol 3-kinase/Akt/mTOR pathway and inhibition of autophagy* J. Virol., **87**, 2508–2517

Clathrin/caveolin

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Cyclophilin receptors

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Cysteine proteases

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Dynamin inhibition

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Focal adhesion kinase activation

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Heparan sulphate receptors

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Gene expression
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Infection

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Cell cycle progression requirement

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