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.

1. 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 **(M)**

2. Baculoviral vectors

Cho, H., Lee, H-J., Heo, Y-K., Cho, Y., Gwon, Y-D., Kim, M-G., Park, K.H., Oh, Y-K. and Kim, Y.B. (2014) *Immunogenicity of a trivalent human papillomavirus L1 DNA-encapsidated, non-replicable baculovirus nanovaccine* PLoS One, **9**: e95961

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

Lee, H-J., Cho, H., Kim, M-G., Heo, Y-K., Cho, Y., Gwon, Y-D., Park, K.H., Jin, H., Kim, J., Oh, Y-K. and Kim, Y.B. (2015) *Sublingual immunization of trivalent human papillomavirus DNA vaccine in baculovirus nanovector for protection against vaginal challenge* PLoS One, **10**: e0119408

3. Capsids and capsid protein

3-1. Capsid assembly

Day, P.M., Thompson, C.D., Pang, Y.Y., Lowy, D.R. and Schiller, J.T. (2015) *Involvement of nucleophosmin (NPM1/B23) in assembly of infectious HPV16 capsids* Papillomavirus Res. **1**, 74–89

3-2. DNA, separation from

Bzhalava, D., Johansson, H., Ekström, J., Faust, H., Möller, B., Eklund, C., Nordin, P., Stenquist, B., Paoli, J., Persson, B., Forslund, O. and Dillner, J. (2013) *Unbiased approach for virus detection in skin lesions* PLoS One, **8**: e65953

3-3. Dynein interacting domains

Florin, L., Becker, K.A., Lambert, C., Nowak, T., Sapp, C., Strand, D., Streeck, R.E. and Sapp, M. (2006) *Identification of a dynein interacting domain in the papillomavirus minor capsid protein L2* J. Virol., **80**, 6691-6696

3-4. L1 capsid protein

Bienkowska-Haba, M., Williams, C., Kim, S.M., Garcea, R.L. and Sapp, M. (2012) *Cyclophilins facilitate dissociation of the human papillomavirus type 16 capsid protein L1 from the L2/DNA complex following virus entry* J. Virol., **86**, 9875-9887

Ishii, Y., Kondo, K., Matsumoto, T., Tanaka, K., Shinkai-Ouchi, F., Hagiwara, K. and Kanda, T. (2007) *Thiol-reactive reagents inhibits intracellular trafficking of human papillomavirus type 16 pseudovirions by binding to cysteine residues of major capsid protein L1* Virol. J., **4:**110

Mistry, N., Wibom, C. and Evander, M. (2008) *Cutaneous and mucosal human papillomaviruses differ in net surface charge, potential impact on tropism* Virol. J., **5**:118

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

3-5. Maturation

Buck, C.B., Thompson, C.D., Pang, Y-Y-s., Lowy, D.R. and Schiller, J.T. (2005) *Maturation of papillomavirus capsids* J. Virol., **79**, 2839-2846 **(B)**

Cardone, G., Moyer, A.L., Cheng, N., Thompson, C.D., Dvoretzky, I., Lowy, D.R., Schiller, J.T., Steven, A.C., Buck, C.B. and Trus, B.L. (2014) *Maturation of the human papillomavirus 16 capsid* mBio, **5**: e01104-14

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

3-6. Neutralization-sensitive epitopes

Culp, T.D., Spatz, C.M., Reed, C.A. and Christensen, N.D. (2007) *Binding and neutralization efficiencies of monoclonal antibodies, Fab fragments and scFv specific for L1 epitopes on the capsid of infectious* HPV particles Virology, **361**, 435-446

3-7. 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

4. Cell entry/targeting

4-1. 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

4-2. Clathrin/caveolin

Spoden, G., Freitag, K., Husmann, M., Boller, K., Sapp, M., Lambert, C. and Florin, L. (2008) *Clathrin- and caveolin-independent entry of human papillomavirus type 16 - involvement of tetraspanin-enriched microdomains (TEMs)* PLoS One, **3**:e3313

4-3. Cyclophilin receptors

Bienkowska-Haba, M., Patel, H.D. and Sapp, M. (2009) *Target cell cyclophilins facilitate human papillomavirus type 16 infection* PLoS Pathog., **5**:e1000524 **(B)**

4-4. Cysteine proteases

Dabydeen, S.A. and Meneses, P.I. (2009) *The role of NH_4Cl and cysteine proteases in human papillomavirus type 16 infection* Virol. J., **6**:109

4-5. Dynamin inhibition

Abban, C.Y., Bradbury, N.A. and Meneses, P.I. (2008) *HPV16 and BPV1 infection can be blocked by the dynamin inhibitor dynasore* Am. J. Therapeut., **15**, 304-311 **(B)**

4-6. Dynein light chain requirement

Schneider, M.A., Spoden, G.A., Florin, L. and Lambert, C. (2011) *Identification of the dynein light chains required for human papillomavirus infection* Cell. Microbiol., **13**, 32–46

4-7. Focal adhesion kinase activation

Abban, C.Y. and Meneses, P.I. (2010) *Usage of heparan sulfate, integrins, and FAK in HPV16 infection* Virology **403**, 1–16

4-8. Gene delivery vectors

Cerqueira, C., Thompson, C.D., Day, P.M., Pang, Y-Y.S., Lowy, D.R. and Schiller, J.T. (2017) *Efficient production of papillomavirus gene delivery vectors in defined in vitro reactions* Mol. Ther. Meth. Clin. Dev., **5**, 165-179

4-9. Heparan sulphate receptors

Abban, C.Y. and Meneses, P.I. (2010) *Usage of heparan sulfate, integrins, and FAK in HPV16 infection* Virology **403**, 1–16

Day, P.M., Lowy, D.R. and Schiller, J.T. (2008) *Heparan sulfate-independent cell binding and infection with furin-precleaved papillomavirus capsids* J. Virol., **82**, 12565-12568

Donalisio, M., Rusnati, M., Civra, A., Bugatti, A., Allemand, D., Pirri, G., Giuliani, A., Landolfo, S. and Lembo, D. (2010) *Identification of a dendrimeric heparan sulfate-binding peptide that inhibits infectivity of genital types of human papillomaviruses* Anitmicrob. Agents Chemother., **54**, 4290-4299

Johnson, K.M., Kines, R.C., Roberts, J.N., Lowy, D.R., Schiller, J.T. and Day, P.M. (2009) *Role of heparan sulfate in attachment to and infection of the murine female genital tract by human papillomavirus* J. Virol., **83**, 2067-2074

Knappe, M., Bodevin, S., Selinka, H-C., Spillman, D., Streeck, R.E., Chen, X.S., Lindahl, U. and Sapp, M. (2007) *Surface-exposed amino acid residues of HPV16L1 protein mediating interaction with cell surface heparan sulfate* J. Biol. Chem., **282**, 27913-27922

Selinka, H-C., Florin, L., Patel, H.D., Freitag, K., Schmidtke, M., Makarov, V.A. and Sapp, M. (2007) *Inhibition of transfer to secondary receptors by heparin sulfate-binding drug or antibody induces noninfectious uptake of human papillomavirus* J. Virol., **81**, 10970-10980

4-10. Inhibition by thio-reactive agents

Ishii, Y., Kondo, K., Matsumoto, T., Tanaka, K., Shinkai-Ouchi, F., Hagiwara, K. and Kanda, T. (2007) *Thiol-reactive reagents inhibits intracellular trafficking of human papillomavirus type 16 pseudovirions by binding to cysteine residues of major capsid protein L1* Virol. J., **4:**110

4-11. Laminin-5 binding

Culp, T.D., Budgeon, L.R., Marinkovich, M.P., Meneguzzi, G. and Christensen, N.D. (2006) *Keratinocyte-secreted laminin 5 can function as a transient receptor for human papillomaviruses by binding virions and transferring them to adjacent cells* J. Virol., **80**, 8940-8950

4-12. L1/L2 protein interactions

Buck, C.B., Cheng, N., Thompson, C.D., Lowy, D.R., Steven, A.C., Schiller, J.T. and Trus, B.L. (2008) *Arrangement of L2 within the papillomavirus capsid* J. Virol., **82**, 5190-5197

Knappe, M., Bodevin, S., Selinka, H-C., Spillman, D., Streeck, R.E., Chen, X.S., Lindahl, U. and Sapp, M. (2007) *Surface-exposed amino acid residues of HPV16L1 protein mediating interaction with cell surface heparan sulfate* J. Biol. Chem., **282**, 27913-27922

4-13. Microtubules, L2 interaction with

Schneider, M.A., Spoden, G.A., Florin, L. and Lambert, C. (2011) *Identification of the dynein light chains required for human papillomavirus infection* Cell. Microbiol., **13**, 32–46

4-14. Phsophatidylinositol-3 kinase

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

4-15. PML expression

Day, P.M., Baker, C.C., Lowy, D.R. and Schiller, J.T. (2004) *Establishment of papillomavirus infection is enhanced by promyelocytic leukemia protein (PML) expression* Proc. Natl. Acad. Sci. USA, **101**, 14252-14257 **(B)**

4-16. γ-Secretase requirement

Huang, H-S., Buck, C.B. and Lambert, P.F. (2010) *Inhibition of gamma secretase blocks HPV infection* Virology **407**, 391–396

Karanam, B., Peng, S., Li, T., Buck, C., Day, P.M. and Roden, R.B.S. (2010) *Papillomavirus infection requires γ secretase* J. Virol., **84**, 10661–10670 **(CTR)**

4-17. Tetraspannin-enriched domains

Scheffer, K.D., Gawlitza, A., Spoden, G.A., Zhang, X.A., Lambert, C., Berditchevski, F. and Florina, L. (2013) *Tetraspanin CD151 mediates papillomavirus type 16 endocytosis* J. Virol., **87**, 3435–3446

Spoden, G., Freitag, K., Husmann, M., Boller, K., Sapp, M., Lambert, C. and Florin, L. (2008) *Clathrin- and caveolin-independent entry of human papillomavirus type 16 - involvement of tetraspanin-enriched microdomains (TEMs)* PLoS One, **3**:e3313

5. Epithelial cell, expression in

Israr, M., Biryukov, J., Ryndock, E.J., Alam, S. and Meyers, C. (2016) *Comparison of human papilloma-virus type16 replication in tonsil and foreskin epithelia* Virology, **499**, 82–90

6. Gene expression

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7. Genome

7-1. Amplification

Culp, T.D., Cladel, N.M., Balogh, K.K., Budgeon, L.R., Mejia, A.F. and Christensen, N.D. (2006) *Papillomavirus particles assembled in 293TT cells are infectious in vivo* J. Virol., **80**, 11381-11384 **(CTR)**

7-2. Encapsidation

Pyeon, D., Lambert, P.F. and Ahlquist, P. (2005) *Production of infectious human papillomavirus independently of viral replication and epithelial cell differentiation* Proc. Natl. Acad. Sci. USA, **102**, 9311-9316

7-3. Packaging

Cerqueira, C., Pang, Y-Y.S., Day, P.M., Thompson, C.D., Buck, C.B., Lowy, D.R. and Schiller, J.T. (2016) *A cell-free assembly system for generating infectious human papillomavirus 16 capsids implicates a size discrimination mechanism for preferential viral genome packaging* J. Virol., **90**, 1096-1107

8. Immunogenicity

Kwag, H-L., Kim, H.J., Chang, D.Y. and Kim, H-J. (2012) *The production and immunogenicity of human papillomavirus type 58 virus-like particles produced in Saccharomyces cerevisiae* J. Microbiol., **50**, 813-820

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

9. Infection

9-1. Anti-L1 antibodies

Hu, J., Budgeon, L.R., Cladel, N.M., Culp, T.A., Balogh, K.K. and Christensen, N.D. (2007) *Detection of L1, infectious virions and anti-L1 antibody in domestic rabbits infected with cottontail rabbit papillomavirus* J. Gen. Virol., **88**, 3286-3293 **(CTR)**

9-2. Antivirals

Huang, H-S., Pyeon, D., Pearce, S.M., Lank, S.M., Griffin, L.M., Ahlquist, P., Lambert, P.F. (2012) *Novel antivirals inhibit early steps in HPV infection* Antiviral Res., **93**, 280–287

Theisen, L.L., Erdelmeier, C.A.J., Spoden, G.A., Boukhallouk, F., Sausy, A., Florin, L. and Muller, C.P. (2014) *Tannins from Hamamelis virginiana bark extract:characterization and improvement of the antiviral efficacy against influenza A virus and human papillomavirus* PLoS One, **9**: e88062

9-3. Cell cycle progression requirement

Pyeon, D., Pearce, S.M., Lank, S.M., Ahlquist, P. and Lambert, P.F. (2009) *Establishment of human papillomavirus infection requires cell cycle progression* PLoS Pathog., **5**:e1000318

9-4. Dopachrome tautomerase

Aksoy, P. and Meneses, P.I. (2017) *The role of DCT in HPV16 infection of HaCaTs* PLoS One **12**: e0170158

9-5. L2 Cysteine residues

Gambhira, R., Jagu, S., Karanam, B., Day, P.M. and Roden, R. (2009) *Role of L2 cysteines in papillomavirus infection and neutralization* Virol. J., **6**: 176 **(B)**

9-6. Heparan sulphate

Cagno, V., Donalisio, M., Bugatti, A., Civra, A., Cavalli, R., Ranucci, E., Ferruti, P., Rusnati, M. and Lembo, D. (2015) *The agmatine-containing poly(amidoamine) polymer AGMA1 binds cell surface heparan sulfates and prevents attachment of mucosal human papillomaviruses* Antimicrob. Agents Chemother., **59**, 5250-5259

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9-7. Integrins

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9-8. Optical imaging

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9-9. Restriction factors

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9-10. γ-Secretase requirement

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9-11. Single particle tracking

Ewers, H. and Schelhaas, M. (2012) *Analysis of virus entry and cellular membrane dynamics by single particle tracking* Methods Enzymol., **506**, 63-80

9-12. Skin/vaginal/wart lesions

Bzhalava, D., Johansson, H., Ekström, J., Faust, H., Möller, B., Eklund, C., Nordin, P., Stenquist, B., Paoli, J., Persson, B., Forslund, O. and Dillner, J. (2013) *Unbiased approach for virus detection in skin lesions* PLoS One, **8**: e65953

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9-13. Syndecan-1

Huang, H-S. and Lambert, P.F. (2012) *Use of an in vivo animal model for assessing the role of integrin* $\alpha_6\beta_4$ *and Syndecan-1 in early steps in papillomavirus infection* Virology, **433**, 395–400

10. Infection inhibition

10-1. Carrageenen

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10-2. Cholesterol derivatives

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10-3. α-Defensins

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10-4. *E. coli* sulphated polysaccharides

Lembo, D., Donalisio, M., Rusnati, M., Bugatti, A., Cornaglia, M., Cappello, P., Giovarelli, M., Oreste, P. and Landolfo, S. (2008) *Sulfated K5 Escherichia coli polysaccharide derivatives as wide-range inhibitors of genital types of human papillomavirus* Antimicrob. Agents Chemother., **52,** 1374-1381

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