Novel antiviral compound K21 effective against HSV-1

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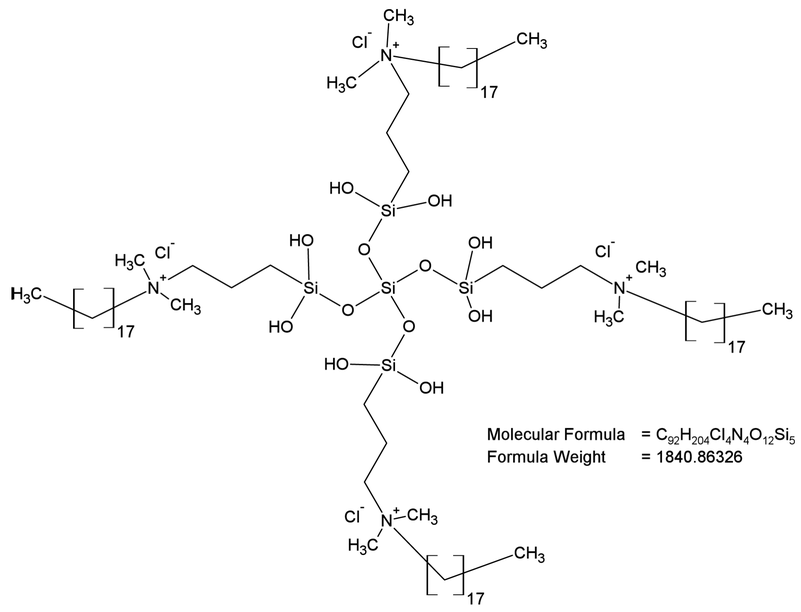
Background

The quaternary ammonium silane (K21) was created through sol-gel chemistry, using an ethoxylated version of an organosilane quaternary ammonium compound and TetraEthyl Ortho Silicate (TEOS) as precursors. Hydrolysis and condensation of K21 with TEOS produces a 3-dimensional antimicrobial macromolecule with multiple arms of membrane rupturing potential (1). K21 was originally developed to be used in dental healthcare (i.e. in tooth cavities and for coating of implants). Antimicrobial assessment of K18 (the methacrylate version of the QAM) and K21 showed inhibited growth of several types of microorganisms including *E. coli*, *Staphylococcus aureus*, *Porphyromonas gingivalis* (2, 3) and *Chlamydia trachomatis* (Unpublished). As some of the Human herpesviruses including HSV-1, HHV-6A, HHV-6B, HHV-7, HCMV and EBV reside in the human oral cavities and are shed in the saliva to induce infection; we tested *in vitro* the effect of K21 on HSV-1 infection.



Molecular structure of K21 molecule

Results

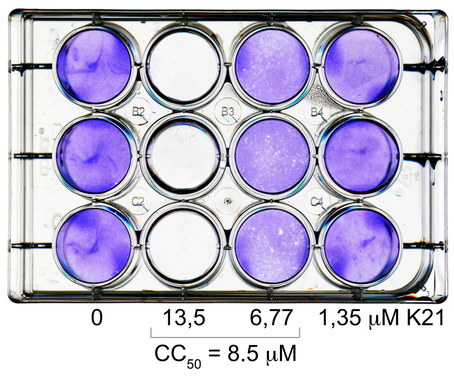


Figure 1: CC_{50} value for K21 is 8.5µM.

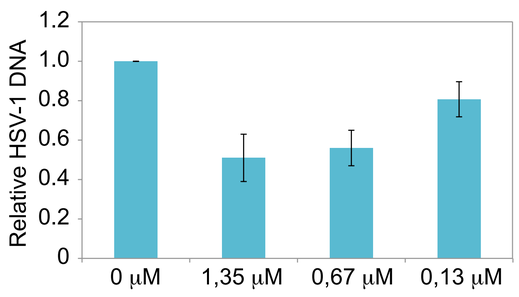


Figure 2: K21 at 1.35µM concentration can inhibit HSV-1* infection by 50% (EC_{50}).

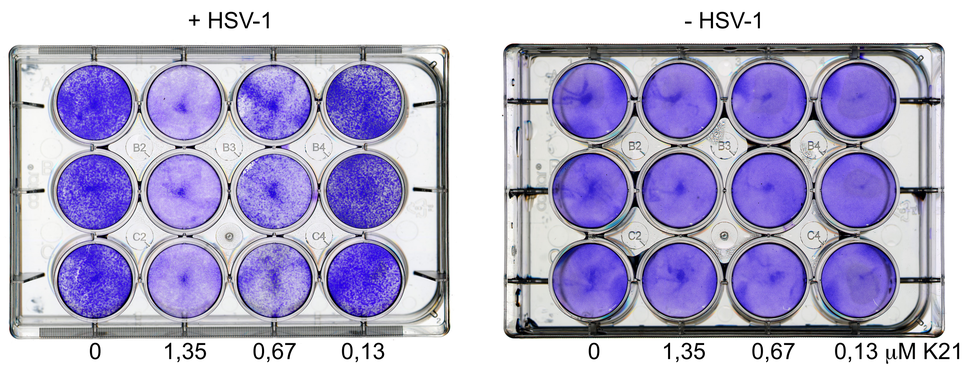


Figure 4: K21 induces cell death after 72hrs of HSV-1 infection in Vero cells as revealed by Plaque assay.

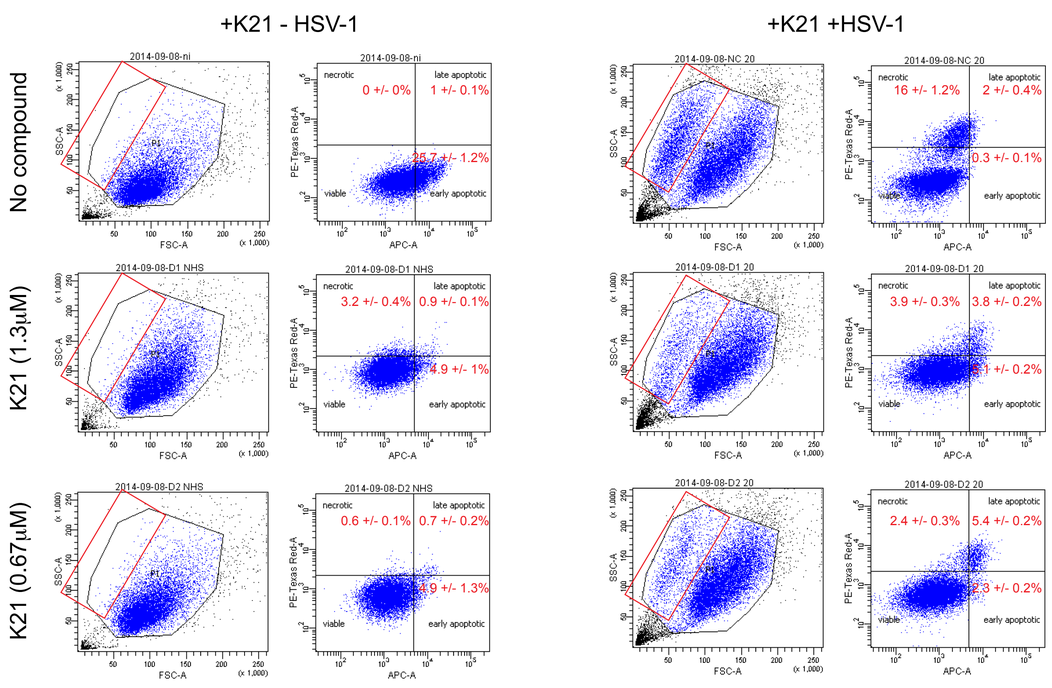


Figure 3: K21 decreases the HSV-1 induced cytopathic effect in Vero cells. Red boxes mark the non-viable cell population as studied by flow cytometry.

* HSV-1 strain F (ATCC VR-733)

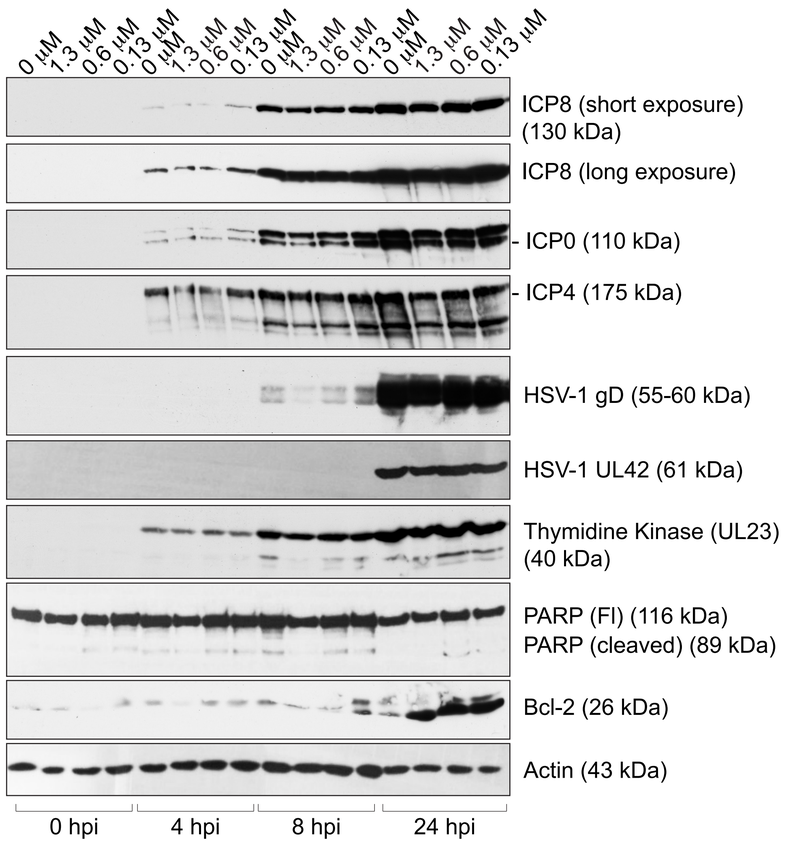


Figure 5: K21 downregulates ICP0, ICP4 and ICP8 expression leading to decreased viral replication in Vero cells. However, UL42 (DNA polymerase subunit) as well as viral infectivity associated Thymidine kinase gene expression are not altered in presence of K21. Only HSV-1 infected cells induce Bcl-2 expression after 8 hrs of viral infection, which might be responsible for decreased cell death in HSV-1 infected cells.

Conclusions

1. K21 possesses anti-HSV-1 activity.
2. K21 downregulates HSV-1 induced cell death possibly by inducing Bcl-2 expression.
3. K21-mediated downregulation of HSV-1 does not lead to viral latency.
3. K21 induces HSV-1 infection-mediated host cell death possibly by inducing senescence after 48-72 hrs of viral infection.
4. K21 downregulates viral replication by an unknown mechanism without affecting viral DNA polymerase activity.

References:

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2. Gong S-q, Niu L-n, Kemp LK, Yiu CKY, Rhou H, Qi Y-p, Blizzard JD, Nikonov S, Brackett MG, Messer RLW, Wu CD, Mao J, Brister LB, Rueggeberg FA, Arola DD, Pashley DH, Tay FR. Quaternary ammonium silane-functionalized, methacrylate resin composition with antimicrobial properties and self-repair potential. Acta Biomaterialia 2012b;8:3270-3282.
3. Meghil MM, Rueggeberg FA, El-Awady A, Miles B, Tay FR, Pashley DH, Cutler CW. Novel antimicrobial coating of surgical sutures and dental floss with activity against gram-negative and gram-positive bacterial pathogens. J Periodontol (in review, Sept. 2014).