Journal of Controlled Release 277 (2018) 183

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

# Implants attenuating vaginal T lymphocyte activation and inflammation

In Africa, it is estimated that women are twice as likely to become infected with HIV during unprotected vaginal intercourse compared with men, and female sex workers are 13.5 times more likely to become HIV infected compared with other women [1]. A major biological factor that is strongly associated with increased HIV risk is the presence of inflammation prior to HIV exposure. Elevation of inflammatory mediators are responsible for the recruitment of T cells and other HIV-target immune cells in the vaginal environment, and it can facilitate HIV infection at the vaginal mucosa. Inflammation may occur due to abrasions during vaginal intercourse, the presence of other existing infections, such as bacterial vaginosis and gonorrhea, or the use of vaginal products such contraceptive spermicidal gels [2,3].

Activated CD4+ T lymphocytes are more susceptible to HIV infection in comparison to non-activated cells, and, once infected, produce up to 1,000 times more virus [4]. Despite the fact that condoms are effective for the prevention of HIV infection, the low availability of condoms and low frequency of condom use in developing countries due to socio-cultural factors hinder their protection against HIV infections. Thus, efforts have been made to seek effective and affordable strategies to protect women against HIV-1 infection, especially for those who live in developing countries. Professor Emmanuel Ho and his research group developed an implant system that can provide sustained release of hydroxychloroquine (HCQ) as a new strategy for inducing a T lymphocyte immune quiescent state (i.e., maintaining a low basal expression level of pro-inflammatory mediators and reducing the frequency of activated T cells) locally at the female genital tract (FGT) [5]. HCQ is an immunomodulatory drug widely utilized for the treatment of malaria and rheumatoid arthritis, and has also demonstrated direct anti-HIV activity by inhibiting gp120 glycosylation resulting in non-infectious HIV virions [6].

The FGT is a preferred administration route for a wide range of therapeutic agents, such as those for contraception, treatment of local vaginal infections, and for avoiding the first-pass effect to enhance the bioavailability of drugs. Medical devices that can provide sustained delivery within the FGT have significant advantages over other conventional dosage forms, e.g., gels, creams, and tablets. The ability of medical devices to provide long-term controlled delivery of bioactive agents at the FGT is expected to bring improved patient compliance, and thus improved efficacy of the drugs.

Current strategies for HIV prevention focus either on physically limiting interaction of virus with host cells by using condoms or neutralization of virus upon exposure through microbicides, pre/post-exposure prophylactics, or vaccines. The Ho research team has developed, for the first time, a therapeutic strategy to limit the availability of susceptible HIV target cells within the FGT as a new strategy for reducing HIV infection [5]. The non-invasive implant developed by the Ho team has no significant impact on the structural integrity of vaginal tissue. It was able to deliver HCQ within the FGT of a rabbit model and attenuate nonoxynol-9 (N9)-induced vaginal mucosal inflammation and T-cell activation. Topical delivery of HCQ is capable of attenuating the protein expression of the T cell activation marker RLA-DR (rabbit equivalent of human HLA-DR) and mRNA expression of CCR5 and CD69 on vaginal mucosal T lymphocytes when challenged with N9. The additional ability of HCQ to attenuate the expression of N9-induced inflammatory markers (IL-1β, IL-8, TNF-α, MIP-3α) within the FGT and cervicovaginal lavage demonstrates the potential of HCQ as a promising drug candidate to maintain a low baseline level of immune activation. This pioneering proof-of-concept study demonstrates for the first time that it is possible to pharmacologically induce a T cell immune quiescent state using HCQ, a cost-effective drug, as a new strategy for preventing HIV infection.

## References

[1] S. Baral, C. Beyrer, K. Muessig, T. Poteat, A.L. Wirtz, M.R. Decker, S.G. Sherman, D. Kerrigan, Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis, Lancet Infect. Dis. 12 (2012) 538–549.

[2] R.N. Fichorova, L.D. Tucker, D.J. Anderson, The molecular basis of nonoxynol-9-induced vaginal inflammation and its possible relevance to human immunodeficiency virus type 1 transmission, J. Infect. Dis. 184 (2001) 418–428.

[3] J.E. Cummins Jr., G.F. Doncel, Biomarkers of cervicovaginal inflammation for the assessment of microbicide safety, Sex. Transm. Dis. 36 (2009) S84–S91.

[4] X. Pan, H.M. Baldauf, O.T. Keppler, O.T. Fackler, Restrictions to HIV-1 replication in resting CD4+ T lymphocytes, Cell Res. 23 (2013) 876–885.

[5] Y. Chen, Y.L. Traore, S. Yang, J. Lajoie, K.R. Fowke, D.W. Rickey, E.A. Ho, Implant delivering hydroxychloroquine attenuates vaginal T lymphocyte activation and inflammation, J. Control. Release 277 (2018) 102–113.

[6] A. Savarino, L. Gennero, H.C. Chen, D. Serrano, F. Malavasi, J.R. Boelaert, K. Sperber, Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity, AIDS 15 (2001) 2221–2229.

Kinam Park
*Purdue University*
*Biomedical Engineering and Pharmaceutics*
*West Lafayette, IN 47907, USA*
*E-mail address:* kpark@purdue.edu

https://doi.org/10.1016/j.jconrel.2018.04.008