

- Kliger, Y., Gallo, S.A., Peisajovich, S.G., Munoz-Barrosa, L., Avkin, S., Blumenthal, R. & Shai, Y. (2001) *J. Biol. Chem.* 276:1391-7
- McFarland, W., Gwanzura, L., Bassett, M. T., Machekano, R., Latif, A. S., Ley, C., Parsonnet, J., Burke, R. L. & Katzenstein, D., 1999. Prevalence and incidence of herpes simplex virus type 2 infection among male Zimbabwean factory workers. *J. Infect. Dis.* 180, 1459-1465.
- Moore, J. P. (2005) *N. Engl. J. Med.* 352, 298-300.
- Pope, M., Betjes, M. G., Romani, N., Hirmand, H., Cameron, P. U., Hoffman, L., Gezelter, S., Schuler, G. & Steinman, R. M. (1994) *Cell* 78, 389-98.
- Royce, R. A., Sena, A., Cates, W., Jr. & Cohen, M. S., 1997. Sexual transmission of HIV. *N. Engl. J. Med.* 336, 1072-1078.
- Rustomjee, R., Abdool Karim, Q., Abdool Karim, S. S., Laga, M. & Stein, Z. (1999) *AIDS* 13:1511-5.
- Saphire, A. C., Bobardt, M. D., Zhang, Z., David, G. & Gallay, P. A. (2001) *J Virol* 75, 9187-200.
- Turpin, J. A. (2002) *Expert Opin. Investig. Drugs* 11:1077-1097.
- Turville, S. G., Santos, J. J., Frank, I., Cameron, P. U., Wilkinson, J., Miranda-Saksena, M., Dable, J., Stössel, H., Romani, N., Piatak, M., Lifson, J. D., Pope, M. & Cunningham, A. L. (2004) *Blood* 103:2170-2179.
- Wei, X., Decker, J. M., Liu, H., Zhang, Z., Arani, R. B., Kilby, J. M., Saag, M. S., Wu, X., Shaw, G. M. & Kappes, J. C. (2002) *Antimicrob. Agents Chemother.* 46, 1896-1905.
- de Witte, L., Nabatov, A., Pion, M., Fluitsma, D., de Jong, M. A., de Grujij, T., Piguët, V., van Kooyk, Y. & Geijtenbeek, T. B. (2007) *Nat. Med.* 13, 367-371.
- de Witte, L., Bobardt, M., Chatterji, U., Degeest, G., David, G., Geijtenbeek, T. B. & Gallay, P. (2007) *Proc. Natl. Acad. Sci. USA.* 104:19464-19469

Chapter 7.3

Concluding remarks Section 7

Dendritic cells: to target or not to target? That is the question...

At present the role of different subsets of DCs at the site of HIV-1 entry *in vivo* is not fully elucidated. DC-SIGN⁺ DCs are thought to mediate HIV-1 transmission, whereas LCs protect against transmission. Therefore, care is required with candidate microbicides that target DC subsets. The distinct outcomes of these DC subsets upon HIV-1 encounter are attributed to the HIV-1 receptors, Langerin, DC-SIGN and syndecan-3. The *trans*-receptors syndecan-3 and DC-SIGN are attractive microbicide targets. Importantly, the carbohydrate specificities of DC-SIGN and the protective receptor Langerin partly overlap. This indicates that interference of the interaction between HIV-1 and DC-SIGN needs to be done at the site of the receptor and with specific compounds, to preserve the function of Langerin. Candidates are a blocking antibody against DC-SIGN or Lewis X containing structures, which specifically block DC-SIGN but not Langerin (Chapter 5.2). Recombinant DC-SIGN and high mannose containing ligands have been proposed to block interaction of DC-SIGN with HIV-1 (Table 7.1.2). However, these compounds interfere with Langerin function, and thus need to be revisited. Importantly, activation of LCs and DCs enhances HIV-1 transmission (**Section 6**). Thus, care should be directed to evaluate the effect of DC-specific compounds for activation.

To avoid activation of the different DC subsets, it might be worthwhile to directly target the virus, such as with the compound C5A. C5A is a promising microbicide candidate, inhibiting HIV-1 transmission at different levels: epithelial transcytosis, DC-mediated transmission and direct infection of target cells, including LC infection. To take this candidate into microbicide trials, the next steps will be to manipulate the molecule to higher biological activities and carefully test the compound for inflammation, activation and efficiency to inhibit HIV-1 transmission in an *in vivo* model.