



Professor Matti K. Viljanen

## Host Defence in Lyme Borreliosis

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Lyme borreliosis is a tick-transmitted disease caused by the spirochete *Borrelia burgdorferi*. During the early infection the spirochete spreads in the skin leading within a few days to a typical ring-like erythema migrans lesion. In some individuals, the infection is limited to the skin and subsides even without treatment. However, in some cases the spirochete invades into the blood and disseminates into various organs, where it may survive and persist for months or even years. The main

aim of this project is to understand the mechanisms how borrelia manages to evade the first line immune response and spreads into a multi-organ infection. We further aim to elucidate the mechanisms of persistent and treatment resistant Lyme borreliosis, since these disease manifestations can lead to complicated and expensive investigations, delayed diagnosis and longstanding disability of the patients.

The histological picture of erythema migrans lesion is mainly lymphocytic with very few neutrophils, which is in striking contrast with other bacterial infections of the skin. Our hypothesis is that borrelia interferes with the function of dendritic cells and thus prevents the recruitment of neutrophils to the site of infection. Using large-scale gene expression studies we want to find out whether borrelia somehow manipulates neutrophils and dendritic cells to its benefit. The phagocytosis of borrelia takes place through "tube-phagocytosis". We want to elucidate the cellular mechanisms of this interesting phenomenon by studying the receptors and signalling pathways involved in the process.

One of the most debated questions in Lyme borreliosis research is pathogenesis of antibiotic treatment resistant disease manifestations. Two main hypotheses presented to explain this phenomenon are persistent infection and infection-induced autoimmunity. We have succeeded in establishing a much-needed animal model for this disease entity (Yrjänäinen *et al.*, submitted). Our results show that the presence of vegetative spirochetes is no prerequisite for the persisting symptoms. However, using this model we have found out that when the mice receive immunosuppressive treatment with anti-TNF- $\alpha$  after a latent period of several weeks, borreliae are activated from a dormant state and the animals develop spirochetemia (Yrjänäinen *et al.*, manuscript in preparation). Thus, our results support the persistent infection hypothesis. Our mouse model makes possible to investigate where the microbe is hiding during latency, how it is adapted to latency, how the microbe can be evicted from its hiding places, and how the immune response of the host behaves during latency. In this investigation, we use, among other methods, both mouse and borrelia gene arrays and modern imaging methods (e.g. live-cell confocal microscopy, molecular PET etc.). These studies should provide novel information concerning the pathogenesis and possible therapeutic approaches of antibiotic treatment resistant Lyme arthritis and Lyme borreliosis in general. The results may have an impact also on the understanding of other persistent infections like tuberculosis, chlamydia infections and certain viral diseases.

### Recent publications:

Suhonen, J., Komi, J., Soukka, J., Lassila, O. and Viljanen, M.K. (2003) Interaction between *Borrelia burgdorferi* and immature human dendritic cells. *Scand. J. Immunol.* 58: 67-75.

Suhonen, J., Hartiala, K., Tuominen-Gustafsson, H. and Viljanen, M.K. (2002) Sublethal concentrations of complement can effectively opsonize *Borrelia burgdorferi*. *Scand. J. Immunol.* 56: 554-560.

Suhonen, J., Hartiala, K., Tuominen-Gustafsson, H. and Viljanen, M.K. (2000) *Borrelia burgdorferi* -induced oxidative burst, calcium mobilization, and phagocytosis of human neutrophils are complement dependent. *J. Infect. Dis.* 181: 195-202.

Suhonen, J., Hartiala, K. and Viljanen, M.K. (1998) Tube phagocytosis, a novel way for neutrophils to phagocytize *Borrelia burgdorferi*. *Infect. Immun.* 66: 3433-3435.

Oksi, J., Savolainen, J., Pene, J., Bousquet, J., Laippala, P. and Viljanen, M.K. (1996) Decreased interleukin-4 and increased gamma interferon production by peripheral blood mononuclear cells of patients with Lyme borreliosis. *Infect. Immun.* 64: 3620-3623.



From left to right: Marju Niskala, Heta Yrjänäinen, Jarmo Oksi, Markus Penttinen, Matti Viljanen, Jukka Hytönen, Helena Tuominen-Gustafsson, Taina Kirjonen, Outi Leppäranta