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# Keynote Forum

## Day 1

Peter Timms, J Infect Dis Ther 2018, Volume 6
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*Peter Timms*

*University of the Sunshine Coast, Australia*

## Development of a chlamydial vaccine for koalas: Protection against infection as well as disease

Wild koala populations continue to experience serious declines as a result of several threatening factors including: loss of habitat; motor vehicle trauma; dog attacks and; chlamydial disease. Chlamydial infections are associated with diseases ranging from ocular disease leading to blindness, as well as urinary and genital tract disease, leading to female infertility. Modeling shows that targeting chlamydial disease would have a major impact on stabilizing population decline. Our previous studies have demonstrated that koalas can be safely immunized with a vaccine containing a mixture of chlamydial major outer membrane protein (MOMP) antigens combined with a single or three-dose subcutaneous regime. In our most recent, large scale, field trial of the vaccine, we vaccinated 30 koalas that were outwardly clinically healthy but either chlamydia PCR negative or chlamydia PCR positive, and followed them for 1-2 years to assess the protective effect of the vaccine (compared to a control group of unvaccinated koalas). We observed strong, specific and long-lasting immune responses in the vaccinated koalas; high titer antibody responses (as measured by ELISA and also in vitro neutralization) as well as chlamydia-specific cytokine responses (interferon-gamma and IL-17 in particular). For animals which were chlamydia PCR positive at the time of vaccination, we observed a significant reduction in their infection PCR load (at both the ocular and urogenital tract sites). We also observed protection from progression to clinical disease in the vaccinated animals. We have also conducted a small trial to vaccinate animals which already have clinical signs of ocular disease. Instead of the normal practice of administering antibiotics (chloramphenicol, daily for 28 days, which severely disrupts the animal's gut microbiome) we vaccinated four animals with a single dose, 3-MOMP vaccine. For all vaccinated animals, their chlamydia PCR load decreased, often to zero, and in two animals at least, we observed a decrease in their clinical disease score. These results are promising for the future development of an effective chlamydial vaccine for use in captive as well as wild koalas.

**Recent publications**

1. Timms P (2017) Novel strategies for developing vaccines bring encouraging progress. Pathogens and Disease 29:75.
2. Desclozeaux M, Robbins A, Jelocnik M, Khan S, Hanger J, Gerdts V, Potter A, Polkinghorne A and Timms P (2017) Immunization of a wild koala population with a recombinant Chlamydia pecorum Major Outer Membrane Protein (MOMP) or Polymorphic Membrane Protein (PMP) based vaccine: New insights on immune response, protection and clearance. PLoS One 12(6):e0178786.
3. Desclozeaux M, Jelocnik M, Timms P, Whitting K, Saifzadeh S, Bommana S, Potter A, Gerdts V and Polkinghorne A (2017) Safety and immunogenicity of a prototype anti-chlamydia pecorum recombinant protein vaccine in lambs and pregnant ewes. Vaccine 35: 3461–3465.
4. Marsh J, Ong V, Lott W, Tyndall J, Timms P and Huston W (2017) Chlamydia trachomatis HtrA: the lynch pin of the chlamydial surface and a promising therapeutic agent. Future Microbiology 12:817–829.
5. Lau A, Kong F, Fairley C, Donovan B, Chen M, Bradshaw C, Boyd M, Amin J, Timms P, Tabrizi S, Regan D, McNulty A and Hocking J (2017) Treatment efficacy of azithromycin 1g single dose versus doxycycline 100mg twice daily for 7 days for the treatment of rectal chlamydia among men who have sex with men - a double blind randomised controlled trial protocol. BMC Infectious Diseases 17:35.

## Biography

Peter Timms is Professor of Microbiology at the University of Sunshine Coast in Queensland, Australia. He is a nationally and internationally renowned microbiologist with specific expertise in the area of Chlamydia. His laboratory is acknowledged as the leading Australian laboratory and one of the leading groups internationally working on all aspects of chlamydial infections. His research group of 12 staff and students is developing vaccines and new diagnostics for chlamydial diseases in humans and animals as well as an improved understanding of chlamydial genomics, cell biology and pathogenicity. The group is widely acknowledged for its major contributions to chlamydial infections in koalas and other wildlife, including the development of a vaccine for koalas. He has published over 250 papers, reviews and book chapters in peer-reviewed international scientific journals.

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**Notes:**

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## Tuberculosis risk is spread within the hallmarks of the disease

**Statement of the Problem**: Heritable susceptibility to tuberculosis (TB) is complex and polygenic in nature. Only five to ten percent of humans that come in contact with the bacterium *Mycobacterium tuberculosis* (Mt) will manifest the disease, provided no acquired- or congenital immunodeficiency were present. We still lack a viable explanation for the observed epidemiologic fact.

**Method**: Activation of macrophages via proinflammatory cytokines IFN-v and interleukin (IL)-17 can kill intracellular bacteria such as Mt. Instead, macrophages stimulated by the Toll-like receptor (TLR)-10 agonists show an anti-inflammatory effect. The TLR-10 acts by inhibiting the TLR-2 signaling from the cell membrane. The TLR-2 is the Mt-binding protein by which activated macrophages can internalize (and kill) Mt. Inactivation of the TLR-2 protein might convey a risk for developing the disease. This was supported by our finding that TLR2 gene polymorphisms, which either inactivate the TLR2 gene product or have a dominant-negative role in TLR-2-signaling, associated with elevated risk for tuberculosis in the Croatian Caucasian population.

**Findings**: The genome-wide study found that three single nucleotide polymorphisms (SNPs) within the HLA class II loci were significantly associated with TB; suggesting that adaptive immunity is of paramount importance for defense against TB. In our studied population, SNP in the TLR10 gene was associated with risk for TB, analyzed by the dominant model of inheritance. However, this was contrasted by the fact that SNPs in the IL17A&F genes were not.

**Conclusion & Significance**: Studying genetic risk by association analyses or genome-wide screening led us to propose that clinical manifestation of TB is a state above certain risk-threshold. Threshold is reached by accumulation of seemingly minor susceptibilities divided between the hallmarks of the disease (Fig 1). The model suggests that every human population has its own mosaic of genetic risks for TB.

**Recent publications**

1. Bretscher P A et al. (2017) Immune class regulation and its medical significance part II of a report of a workshop on foundational concepts of immune regulation. Scand J Immunol 85:242-250.
2. Sveinbjornsson G. et al. (2016) HLA class II sequence variants influence tuberculosis risk in populations of European ancestry. Nature genetics 48:318-322.
3. Vrbanec J et al. (2016) Genetic risk of tuberculosis is spread within the hallmarks of the disease. Immunother Open Acc 2:117.
4. Bulat-Kardum L. et al. (2015) Genetic polymorphisms in the toll-like receptor 10, interleukin (IL)17A and IL17F genes differently affect the risk for tuberculosis in Croatian population. Scand J Immunol 82:63-9.
5. Etokebe G E et al. (2010) Toll-like receptor 2 (P631H) mutant impairs membrane internalization and is a dominant negative allele. Scand J Immunol. 71:369-381 (2010).

## Biography

Zlatko Dembic is a Professor of Immunology, Cell-Biology and Microbiology at University of Oslo. He has been working in science at various institutions in Academia (Medical Faculty, Zagreb, Croatia; Max-Planck Institute for Immunogenetics, Tubingen, Germany; Basel Institute for Immunology, Switzerland; Institute of Immunology, Oslo, Norway) and industry (Roche, Switzerland). He has his expertise in molecular biology shown by over 100 publications to date and a monograph about cytokines in immunology. He is co-inventor of the US patent (Roche) covering the production and use of etanercept (Enbrel), which is a successful (anti-TNF) biological used to treat several autoimmune diseases including rheumatoid arthritis. He was the president of the Norwegian Society for Immunology and Editor-in-chief of the *Scand J Immunol* (at present, Associate Editor). He is a Visiting Professor of Medicine at medical school in his hometown Rijeka (Croatia).

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