

# **TB Vaccines** A Second Global Forum

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Tom H. M. Ottenhoff is professor in Immunology and Immunogenetics of Bacterial Infectious Diseases at Leiden University Medical Center. He obtained his MD in 1982 and his PhD in 1986, worked for a few years in Ethiopia and in the US, and currently leads a team of researchers in Leiden, the Netherlands. He is involved in several larger international research networks in tuberculosis and leprosy, sponsored amongst others by EU, BMGF.

### **Summary of major research interests**

Tuberculosis and leprosy are major infectious diseases that are caused by related mycobacterial pathogens, *M. tuberculosis* and *M. leprae*. Protective immunity to mycobacterial pathogens is highly dependent on antigen specific T-cells. Dr. Ottenhoff has longstanding expertise in T-cell mediated immunity in mycobacterial infectious diseases in man. He has made several contributions to the field, including:

- (1) The identification of novel antigens of *M. tuberculosis* and *M. leprae* that are recognized by human T cells. These include highly species-specific antigens, infection-phase variation related (“latency” and “reactivation”) antigens, and recently described HLA-E restricted *Mtb* antigens. These results have helped developing new diagnostic assays for TB; and the design of new TB subunit vaccines capable of inducing long lasting T<sub>helper</sub>-1 based immunity to *Mtb* in man.
- (2) The first description of a number of functionally different T cell subsets in man, namely: T<sub>helper</sub>-1 (T<sub>h</sub>1) cells, T<sub>regulatory/suppressor</sub> cells (T<sub>regs</sub>), and cytotoxic CD4<sup>+</sup> T-cells. This work also elucidated the role of these newly discovered subsets in protection (T<sub>h</sub>1), and in leprosy and TB disease (T<sub>regs</sub>).
- (3) The unravelling of essential cytokine networks in anti-mycobacterial immunity, including the identification of deleterious IL-12β1 and IFNγR1 mutations as causes of newly identified human immunodeficiencies.
- (4) The genetic control of immunity and susceptibility to leprosy and tuberculosis. In case-control studies, both HLA- and innate immunity genes (TLR8, TNF, IL10, IFNγ, etc.) were found to be associated with disease or protection. More recently, molecular dissection of genes involved in innate immunity towards *Mtb* and other intracellular pathogens has been achieved using genome broad RNAi and chemical genetic approaches; these have led to the identification of a new network of innate immunity genes under the control of Akt1.
- (5) The identification of polarized human macrophage subsets and their role in innate and adaptive immunity to mycobacteria. This work focused on dissecting the balance between pro-inflammatory and anti-inflammatory (alternatively activated) human macrophages, which have different roles in bacterial uptake and handling, and have opposing roles in T<sub>h</sub>1 activation vs. down regulation, as well as in T<sub>reg</sub> induction. These cells are present in human tissues, including leprosy lesions.

These discoveries have contributed to a general understanding of what constitutes cell-mediated immunity in man, particularly in relation to intracellular bacterial infectious diseases.