Epigenomic profiling in innate immune memory reveals avenues for blocking and reversing immunological tolerance in humans

Boris Novakovic[1,7], Ehsan Habibi[1,7], Shuang-Yin Wang[1,7], Rob J.W. Arts[2], Robab Davar[1], Wout Megchelenbrink[1], Bowon Kim[1], Tatyana Kuznetsova[1], Matthijs Kox[3], Jelle Zwaag[3], Filomena Matarese[1], Simon van Heeringen[4], Eva M. Janssen-Megens[1], Nilofar Sharifi[1], Cheng Wang[1], Vivien Schoonenberg[1], Paul Flicek[5], Laura Clarke[5], Peter Pickkers[3], Simon Heath[6], Ivo Gut[6], Mihai G. Netea[2], Joost H. Martens[1], Colin Logie[1], Hendrik G. Stunnenberg[1]*

[1] *Radboud University, Faculty of Science, Department of Molecular Biology, 6525 GA Nijmegen, The Netherlands*
[2] *Department of Internal Medicine, Radboud University Medical Center, Radboud Center for Infectious Diseases (RCI), 6525 GA Nijmegen, The Netherlands*
[3] *Department of Intensive Care Medicine, Radboud University Medical Center, Radboud Center for Infectious Diseases (RCI), 6500 HB Nijmegen, The Netherlands*
[4] *Radboud University, Faculty of Science, Department of Molecular Developmental Biology, 6525 GA Nijmegen, The Netherlands*
[5] *European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, Cambridge CB10 1SD, UK.*
[6] *Centro Nacional de Análisis Genómico (CNAG), Parc Científic de Barcelona, Barcelona, Spain*

Abstract
Innate immune memory is the phenomenon whereby innate immune cells such as monocytes or macrophages undergo functional reprogramming after exposure to microbial components such as LPS. We apply an integrated epigenomic approach to characterize the molecular events involved in LPS-induced tolerance in a time dependent manner. Mechanistically, LPS treated monocytes fail to activate EGR2 and MITF, leading to low active histone marks at promoter and enhancers of genes in the lipid metabolism and phagocytic pathways. Transcriptional inactivity in response to a second LPS exposure in tolerized macrophages is accompanied with failure to deposit active histone marks at promoters of tolerized genes. A role of IRF and STAT TFs in control of tolerized gene induction was identified. The identification of early epigenetic and transcriptomic events induced by LPS exposure point to potential pathways that can be modulated to block or reverse the development of macrophage tolerance.