ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Erasmus MC
Project Title:	Immunology of persistent viral infections (Hepatitis B, Hepatitis C and HIV)
Abstract:	The hepatitis B virus (HBV) and hepatitis C virus (HCV) are examples of human viral pathogens that are difficult to control by the immune system. As a result, about 80% of individuals infected with HCV become chronically infected. In the majority of cases, HBV infection results in self-limiting, acute hepatitis, which confers protective immunity and causes no further disease. The long-term consequences of chronic HBV/HCV infections can be severe, since patients are at increased risk for developing liver fibrosis, cirrhosis and/or hepatocellular carcinoma. Moreover, In HIV-infected individuals, co-infection with HBV and especially with HCV is common because of shared modes of transmission. It is known that HIV accelerates progression of liver disease and results in increased morbidity and mortality associated with viral hepatitis. Our research is aimed at understanding why the immune response to HBV/HCV is insufficient to clear the virus in infected patients, and what the immunological consequences are of co-infection with HIV. This knowledge is important and will be used to improve therapeutic strategies for chronic HBV/HCV patients. Our studies combine clinical and fundamental research. Our research covers 3 main topics: 1. The innate and adaptive immune response to HBV, HCV and HIV/HCV co-infections in patients: NK and virus-specific T cells 2. Study on the mechanism of action of current and novel therapies for HBV, HCV and HIV in patients. 3. Mouse infection models: intrahepatic immunology and viral hepatitis You will be working on various aspects of the immune response in chronic HBV or HCV by conducting *in vitro* as well as *in vivo* research in various available model systems. Techniques used are, among others, cell culture, cell purification by cell sorting, multi-color flow cytometry, various immunoassays, functional NK and T cell assays (cytotoxicity, cytokine secretion), DNA/RNA isolation, Q-PCR, proteomics and transcriptomics.

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Requirements of candidate:	You recently obtained your MSc degree and have an IELTS Grade of 7.0 (minimal 6.0 per component) or TOEFL: 100 (minimal 20 per component). You have a background in molecular and cellular biology and knowledge of basic immunology. You are experienced with molecular, biological and immunological laboratory techniques and are highly motivated to perform basic translational research. Experience with animal handling is desired for the topic using mouse infection models.
Supervisor information:	Dr. A. Boonstra p.a.boonstra@erasmusmc.nl www.gastrolab.nl Selected publications: 1. Spaan M, Kreefft K, Brouwer WP, de Knegt RJ, Ten Kate FJW, Vanwolleghem T, Janssen HLA, Boonstra A. CD4+CXCR5+ T cells in HCV infection are less capable of producing IL-21 but have a good ability to perform B cell help. **J Hepatol.** 2014. Accepted. 2. Hou J, van Oord G, Groothuismink ZMA, Claassen MAA, Kreefft K, Zaaraoui-Boutahar F, van IJcken WFJ, Osterhaus ADME, Janssen HLA, Andeweg AC, de Knegt RJ, Boonstra A. Gene expression profiling to predict and assess the consequences of therapy-induced virus eradication in chronic HCV. **J Virol.** 2014. pii: JVI.00775-14. 3. Hou J, Groothuismink ZMA, Koning L, Roomer R, van IJcken WFJ, Kreefft K, Liu BS, Jansen HLA, de Knegt RJ, Boonstra A. Analysis of the transcriptome and immune function of monocytes during IFNα-based therapy in chronic HCV revealed induction of TLR7 responsiveness. **Antivir Res.** 2014. 109: 116-124. 4. Boltjes A, Movita D, Woltman AM, Boonstra A. The role of Kupffer cells in viral hepatitis. **J Hepatol.** 2014. 61: 660-671. 5. Boltjes A, Groothuismink ZMA, Janssen HLA, Woltman AM, Boonstra A. Monocytes from chronic HBV patients react *in vitro* to HBsAg and TLR by producing cytokines irrespective of stage of disease. **PLoS ONE.** 2014 May 13;9(5):e97006. 6. Hakim MS, Spaan M, Janssen HLA, Boonstra A. Inhibitory receptor molecules in chronic hepatitis B and C Infections: novel targets for immunotherapy? **Med Rev Virol.** 2014 24(2): 125-138. 7. De Groen RA, Liu BS, Boonstra A. Understanding IFN-lambda in rheumatoid arthritis. **Arthritis Res Ther.** 2014. 16(1): 102. 8. De Groen RA, Mcphee F, Friborg J, Janssen HLA, Boonstra A.

Endogenous IFNλ in viral hepatitis patients. **J Interferon & Cytokine Res.** 2014. 34: 552-556.

9. Claassen MAA, Janssen HLA, de Knegt RJ, Boonstra A. Controversy on the role of FoxP3+ regulatory T cells in fibrogenesis in chronic hepatitis C virus infections. **J Hepatol.** 2014. 60: 231-232.
10. Nikolic T, Movita D, Lambers M, Ribeiro de Almeida C, Biesta P, Kreefft K, de Bruijn JW, Bergen I, Galjart N, Hendriks R, Boonstra A. The DNA-binding factor CTCF critically controls gene expression in macrophages. **Cell Mol Immunol.** 2014. 11: 58-70
11. Claassen MAA, Janssen HLA, Boonstra A. Role of T cell immunity in hepatitis C virus infections. **Curr Opin Virol.** 2013. 3: 461-467.
12. Tjwa ETTL, Zoutendijk R, van Oord GW, Verhey J, Janssen HLA, Woltman AM, Boonstra A. Intrahepatic NK cell activation, but not function, is associated with HBV-DNA and HBsAg in patients with chronic hepatitis B. **Liver Int.** 2013. Available online.
13. Spaan M, Groothuismink ZMA, Koning L, Robert R, Janssen HLA, de Knegt RJ, Boonstra A. Erythropoietin administration suppresses human monocyte function *in vitro* and during therapy-induced anemia in HCV patients. **Antiviral Res.** 2013. 98: 469-475.
14. Hotho DM, Kreefft K, Groothuismink ZMA, Janssen HLA, de Knegt RJ, Boonstra A. Natural killer cell activity and function in chronic HCV-infected patients during peginterferon and ribavirin: early effects of active substance use. **Antiviral Res.** 2013. 97 (3): 347-355.
15. Sonneveld MJ, Arends P, Boonstra A, Hansen BE, Janssen HL. Serum levels of interferon gamma-inducible protein-10 and response to peginterferon therapy in HBeAg-positive Chronic Hepatitis B. **J Hepatol.** 2013. 58 (5): 898-903.
16. Boltjes A, Op den Brouw ML, Biesta PJ, Binda RS, van der Molen RG, Boonstra A, Janssen HLA, Woltman AM. Assessment of the effect of ribavirin on myeloid and plasmacytoid dendritic cells during interferon-based therapy of chronic HBV patients. **Mol Immunol.** 2013. 53 (1-2): 72-78.
17. Boonstra A, Asselin-Paturel C, Gilliet M, Crain C, Trinchieri G, Liu Y-J, O'Garra A. Flexibility of mouse classical and plasmacytoid-derived dendritic cells in directing T helper type 1 and 2 cell development: dependency on antigen dose and differential Toll-like receptor ligation. J Exp Med. 2003. 197:

	101-109. 18. Asselin-Paturel C, Boonstra A, Dalod M, Durand I, Yessaad N, Dezutter-Dambuyant C, Vicari A, O'Garra A, Biron C, Brière F, Trinchieri G. The major type I interferon producing cells in the mouse are immature antigen-presenting cells exhibiting plasmacytoid morphology. Nature Immunol. 2001. 2: 1144-1150.