ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Dept. of Gastroenterology and Hepatology Erasmus Medical Center (Research school: Erasmus Postgraduate School Molecular Medicine)
Project Title:	Understanding the regulation of the kinome in hepatitis virus infection and associated liver cancer
Abstract:	Hepatitis B and C virus (HBV, HCV) infections currently affect over 500 million people worldwide with high risk of developing hepatocellular carcinoma. Interferon-based standard medication represents milestone of the antiviral therapy. However, only part of the patients responds to the treatment with issues of potential severe side-effects. The future improvement in clinic would depend much on the understanding of virus-host interaction and the mechanism of virus induced carcinogenesis. A protein kinase is an enzyme that modifies proteins by chemically adding phosphate groups (phosphorylation). It can regulate almost every property of a protein and is involved in almost all fundamental cellular processes, including viral infection. Up to date, over 500 different kinases have been identified in human. We hypothesize that HBV/HCV can modulate particular kinase activity to result in persistent infection, attenuate antiviral interferon response and trigger oncogenic events. To systematic study the kinome, we will use RNAi library-based loss-of-function approach and PepChip-based genome-wide kinase array profiling (invented by Prof. M. Peppelenbosch, the head of the lab), in HBV and HCV cell culture models. Important findings will be further validated in mice models and patient materials. Therefore, the following research questions are proposed: 1. Identify two categories of kinases: - Regulated by HBV/HCV infection - Related to carcinogenesis 2. Bioinformatic analysis of identified kinases into key pathways 3. Validate the functions of discovered important kinases in mice models and patient materials.

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Requirements of candidate:	Master degree: Yes Background: Molecular Biology/Cell biology/Virology/Medicine IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*
Supervisor information:	**Prof.dr. M.P. Peppelenbosch** Dept. Of Gastroenterology and Hepatology Erasmus MC University Medical Center Rotterdam T: +31 10 7032792 E: m.peppelenbosch@erasmusmc.nl http://www.erasmusmc.nl/gastrolab/ Selected recent publications (from >200 peer-reviewed publications): ▪ Parikh K, Zhou L, Somasundaram R, Fuhler GM, Deuring JJ, Blokzijl T, Regeling A, Kuipers EJ, Weersma RK, Nuij VJ, Alves M, Vogelaar L, Visser L, de Haar C, Krishnadath KK, van der Woude CJ, Dijkstra G, Faber KN, **Peppelenbosch MP.** Suppression of p21Rac signaling and increased innate immunity mediate remission in Crohn's disease. ***Sci Transl Med.*** 2014 Apr 23;6(233):233ra53. (IF: 14.4) ▪ **Peppelenbosch MP**, Spaander MC, Bruno MJ. Glutathione peroxidase 7 prevents cancer in the oesophagus. ***Gut***. 2014 Apr;63(4):537-8. (IF: 13) ▪ Konstantinov SR, Kuipers EJ, **Peppelenbosch MP.** Functional genomic analyses of the gut microbiota for CRC screening. ***Nat Rev Gastroenterol Hepatol.*** 2013 Dec;10(12):741-5. (IF: 10.8) ▪ **The Esophageal Adenocarcinoma Genetics Consortium;** Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. ***Nat Genet*****.** 2012 Sep 9;44(10):1131-1136.(IF: 35.5) ▪ Qiuwei Pan, Anneke J. van Vuuren, Luc J.W. van der Laan, **Maikel P. Peppelenbosch** and Harry L.A. Janssen. Antiviral or proviral action of mycophenolic acid in hepatitis B infection? ***Hepatology***. 2012, (IF: 11.7) ▪ van Veelen W, Korsse SE, van de Laar L, **Peppelenbosch MP**. The long and winding road to rational treatment of cancer

	associated with LKB1/AMPK/TSC/mTORC1 signaling. ***Oncogene***. 2011 30(20):2289-303.(IF: 8.5) ▪ Parikh K, **Peppelenbosch MP**. Kinome profiling of clinical cancer specimens. ***Cancer Res***. 2010 70(7):2575-8. (IF: 9.3) ▪ van den Brink GR, Bleuming SA, Hardwick JC, Schepman BL, Offerhaus GJ, Keller JJ, Nielsen C, Gaffield W, van Deventer SJ, Roberts DJ, **Peppelenbosch MP**. Indian Hedgehog is an antagonist of Wnt signaling in colonic epithelial cell differentiation. ***Nature Genet***. 2004. 36:277-82. (IF: 30) ▪ **Peppelenbosch MP**, Spek CA. Type I diabetes: A role for tissue factor in islet transplantation? ***Lancet*** 2002. 360:1999-2000 (IF: 39) ▪ **Peppelenbosch MP**, Qiu RG, de Vries-Smits AMM, Tertoolen LGJ, de Laat SW, McCormick F, Hall A, Symons MH, Bos JL Rac mediates growth factor- induced arachidonic acid release. ***Cell***. 1996. 81: 849-856.(IF: 32.4) Co-supervision: **Dr. Q. Pan** Dept. Of Gastroenterology and Hepatology Erasmus MC University Medical Center Rotterdam T: +31 10 7037502 E: q.pan@erasmusmc.nl http://www.erasmusmc.nl/gastrolab/ Selected recent publications: ▪ Wang Y, Zhou X, Debing Y, Chen K, Van Der Laan LJ, Neyts J, Janssen HL, Metselaar HJ, Peppelenbosch MP, **Pan Q**. Calcineurin inhibitors stimulate and mycophenolic acid inhibits replication of hepatitis E virus. ***Gastroenterology***. 2014 Jun;146(7):1775-83. (IF: 13.9) ▪ Zhou X, Wang Y, Metselaar HJ, Janssen HL, Peppelenbosch MP, **Pan Q**. Rapamycin and everolimus facilitate hepatitis E virus replication: Revealing a basal defense mechanism of PI3K-PKB-mTOR pathway. ***J Hepatol.*** 2014 May 22. (IF: 10.4) ▪ Chen K, Man K, Metselaar HJ, Janssen HL, Peppelenbosch MP, **Pan Q**. Rationale of personalized immunosuppressive medication for hepatocellular carcinoma patients after liver transplantation. ***Liver Transpl.*** 2014 Mar;20(3):261-9. (IF: 3.8) ▪ Hernanda PY, Pedroza-Gonzalez A, van der Laan LJ, Bröker ME,

	Hoogduijn MJ, Ijzermans JN, Bruno MJ, Janssen HL, Peppelenbosch MP, **Pan Q**. Tumor promotion through the mesenchymal stem cell compartment in human hepatocellular carcinoma. ***Carcinogenesis***. 2013 Oct;34(10):2330-40. (IF: 5.3) ▪ **Pan Q**, Nicholson AM, Barr H, Harrison LA, Wilson GD, Burkert J, Jeffery R, Alison MR, Looijenga L, Lin WR, McDonald SA, Wright NA, Harrison R, Peppelenbosch MP, Jankowski JA. Identification of lineage-uncommitted, long-lived, label-retaining cells in healthy human esophagus and stomach, and in metaplastic esophagus. ***Gastroenterology***. 2013 Apr;144(4):761-70. (IF: 13.9) ▪ **Qiuwei Pan**, Petra E. de Ruiter, Herold J. Metselaar, Jaap Kwekkeboom, Hugo W. Tilanus, Harry L.A. Janssen and Luc J.W. van der Laan. Mycophenolic acid augments interferon-stimulated gene expression and inhibits hepatitis C virus infection in vitro and in vivo. ***Hepatology***. 2012 Jun;55(6):1673-83. (IF: 11.7) ▪ **Qiuwei Pan,** Vedashree Ramakrishnaiah, Scot Henry, Suomi Fouraschen, Petra de Ruiter, Jaap Kwekkeboom, Hugo W. Tilanus, Harry L.A. Janssen and Luc J.W. van der Laan. Hepatic cell-to-cell transmission of small silencing RNA extends the therapeutic reach of RNAi again hepatitis C infection. ***Gut*****.** 2012, Sep;61(9):1330-9. (IF: 13) ▪ **Qiuwei Pan**, Hugo W. Tilanus, Herold J. Metselaar, Harry L.A. Janssen and Luc J.W. van der Laan. Virus-drug interactions-molecular insight into immunosuppression and HCV. ***Nature Reviews Gastroenterology & Hepatology***. 2012 Apr 17;9(6):355-62. (IF: 10.8)