# Abstract of Presentation

**Note: This paper should be typed in "Times New Roman" of 12pt.**

Presentation Title(Should be no more than 20 words):

Interferon signaling in chronic viral hepatitis

Abstract :

A better understanding of interferon (IFN) signal transduction in hepatitis C virus (HCV) infected liver cells is imperative both for the understanding of the natural course of HCV infections, specifically the molecular mechansims responsible for the high persistence rate of HCV after infections, and for further improvements of the current HCV therapy with pegylated IFNα (pegIFNα) and ribavirin.

Over the last 10 years, our laboratory has systematically investigated IFN signaling in chronic hepatitis C (CHC). In 1999, we published the original discovery that IFNα induced signal transduction through the Jak-STAT pathway is inhibited by expression of HCV proteins in cells (Heim et al., J Virol, 1999). This finding was confirmed in HCV transgenic mice (Blindenbacher et al., Gastroenterology, 2003) and liver biopsies of patients with CHC (Duong et al., Gastroenterology, 2004). In the following years, we investigated the molecular mechanisms responsible for this inhibition, and found that HCV upregulates an important cellular phosphatase, PP2A, through induction of endoplasmatic reticulum stress response pathways (Christen et al., J Virol, 2007; Christen et al., Hepatology, 2007). PP2A inhibits protein arginine methyltransferase 1 (PRMT1) with consequences for both IFNα signaling and the activity of the viral helicase (Duong et al., Gastroenterology, 2004; Duong et al., J Virol, 2005). Most importantly, the negative effects of PP2A upregulation by HCV could be corrected by treating cells with the methyl-group donor S-adenosyl-methionine (AdoMet, SAMe) (Duong et al., Hepatology, 2006). As a result of this translational research, we performed a clinic pilot study where previous non-responders to pegIFNα/ribavirin are retreated with a combination of pegIFNα, ribavirin, AdoMet and Betaine (http://clinicaltrials.gov study nr. NCT00310336). AdoMet and Betaine significantly improved early response to pegIFNα/ribavirin.

More recently, we have investigated IFNα signaling in paired liver biopsies of 16 patients with CHC before and 4 hours after the first injection with pegIFNα. We discovered that non-responders to therapy had a pre-activated endogenous IFN system already before therapy, and injection of pegIFNα did not further activate Jak-STAT

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signaling nor did it further induce IFN target genes in liver cells (Sarasin-Filipowicz et al., PNAS, 2008). In this group of patients pegIFNα therapies have little chance for cure, because pegIFNα injections have no effect in liver cells.

In our most recent publication, we investigated the role of microRNA for host-HCV interaction in the liver of patients with CHC (Sarasin-Filipowicz et al., Nature Medicine, 2009). Several miRNAs, including liver-specific miR-122, have been implicated in the control of HCV RNA replication and its response to interferon (IFN) in human hepatoma cells. Our analysis of liver biopsies from patients with chronic hepatitis C (CHC) undergoing IFN therapy revealed no correlation of miR-122 expression with viral load and markedly decreased pre-treatment miR-122 levels in patients who had no virological response during later IFN therapy; other investigated miRNAs showed only limited changes. These data have implications for the prospect of targeting miRNAs for CHC therapy.