



## FINOVI contract ([www.finovi.eu](http://www.finovi.eu))

**E Pecheur/ F Ruggiero project** : Role of the hepatic microenvironment in the infection of hepatocytes by the hepatitis C virus : an integrated microscopy approach.

The hepatitis C virus (HCV) is a strict human pathogen, and hepatocytes are its main targets for productive infection. At the approach to the liver, HCV diffuses through the hepatic microenvironment (ME) where it comes in contact or interacts with several molecules of the extracellular matrix (ECM). The involvement in HCV entry of glycosaminoglycans and proteoglycans of the hepatic ME was suggested but remains unclear. Hepatocyte invasion involves a set of factors or receptors most likely acting in combination to accomplish virus cell entry. However these receptors are ubiquitously expressed at the surface of several cell types.

In this context, we aim at studying the role of components of the hepatic ME and ECM in the early steps of HCV entry into hepatocytes, in order to understand HCV hepatotropism.

The project is centered around two axes :

1. To follow the dynamics of HCV entry into primary human hepatocytes and hepatoma cells by fluorescence (time-lapse) confocal microscopy and by (cryo)- transmission electron microscopy (TEM);
2. To study the involvement of components of the hepatic ME and ECM in HCV entry, by combining cell biology and biochemical approaches, in collaboration with a group at the IBCP with a strong expertise in TEM and ECM biology (F. Ruggiero).

**C Combet project** : COU®TESY.

Viral hepatitis are major public health causes. The Hepatitis B Virus (HBV) chronically infect 300 millions persons and the Hepatitis C Virus (HCV) 170 millions worldwide. If a preventive vaccine exists against HBV, it is not the case for HCV. In both cases infected patients are treated by mean of drugs. For HBV, DNA polymerase inhibitors in combination with interferon alpha are used. For HCV, interferon alpha in combination with ribavirin is the treatment currently used but promising HCV specific drugs are under development and clinical trials. The lack of HBV specific drugs is linked to the lack of experimentally solved HBV protein structures. For both viruses, the anti-viral drugs select resistant variants among the quasi-species (HBV YMDD motif, HCV NS3 protease R155K, *etc.*), preventing the cure of the virus and allowing rebound of viral load. Some resistant mutants confer multi-drugs resistance, but some drugs are less potent in selecting resistant variants. Combined or switched multi-drugs therapies provide better results in combating the virus, but can lead to some tolerance problem for the patient. According to this context, the implementation of bioinformatics tools that can help clinicians in choosing best treatment strategy or that can improve the drugs design is necessary. Thus, in the present project, bioinformaticians and physicians will focus on development of tools for better treatment strategy in order to counteract resistance phenomena and to improve patients' health.