**Title of the PhD project: Investigation of a new class of entry inhibitors of hepatitis B and delta viruses in hepatocytes**


**Laboratory** (lab. name, director name and when applicable, research team name):
1. EA 4446 B2MC, Université Claude Bernard Lyon 1, Faculté de Pharmacie-ISPB, Directeur Marc LE BORGNE.
2. Hépatocarcinogenèse et infection virale, CRCL, Inserm U1052 Université Claude Bernard Lyon 1, Directeur Alain Puisieux.

**Doctoral school:** Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205.

**Description:**
- **Scientific background and rationale:**
  2 billion people infected worldwide 240 million suffering from chronic hepatitis B virus (HBV) infection and ranking 10th leading cause of death worldwide (500 000 to 1.2 million deaths per year). Current treatment are virostatic but do not lead to a cure. The liver-specific receptor for infection of hepatocytes has recently been identified as the human liver bile acid transporter Na+/taurocholate cotransporting polypeptide (NTCP). The virus binds to NTCP via the myristoylated preS1 (myr-preS1) peptide domain of its large surface protein. This is an initiating step of HBV infection, and potentially a target for antiviral strategies. We decide to explore whether physiological bile acid transport process interferes with the viral receptor NTCP using a panel of chemically modified bile acids derivatives. The physiological bile acid transport function of NTCP interferes with productive HBV infection. Therefore, HBV infection via NTCP may be lockable by NTCP substrates derived from native bile acids.

  - **Aim:**
    To stop hepatocyte infections and viral propagation by blocking the viral « door » NTCP receptor via a physiological mean: using natural steroids (known metabolite with no or limited toxicity).

- **Description of the project methodology:**
  HBV infection assay and bile acid transport competition assay will be performed with several in vitro hepatocyte models such as primary human hepatocytes, HepaRG cell line and HuH7 NTCP hepatocytes, in the presence of various bile acids derivatives, and known competitors. We will test a number of bile acids derivatives, to inhibit HBV infection in vitro in PHH as well as in NTCP-expressing HuH7 cells and HepaRG. Preliminary results showed that HBV infection was inhibited to different extent ranging from 0 to 70% in a concentration-dependent manner by derivatives of cholic acid. The best candidate appeared efficient in all cell lines used, even if other molecules may have a substantial effect. Derivatives from the best candidate will be synthetized playing around the structure of the molecule. We will have access to animal models such as “humanized” mice and possibly macaques infected by HBV.

**Skills required** (HBV, HDV, Hepatocytes, NTCP, Steroids, Synthesis, SAR, Steroid metabolism): Knowledge on bioorganic chemistry, spectral tools, purification tools, rationale design, in silico calculations. A good knowledge of biochemistry, some of cell culture and virology would be a plus.

**Contact:** Marc Le Borgne (marc.le-borgne@univ-lyon1.fr); Luc Rocheblave (luc.rocheblave@univ-lyon1.fr); Isabelle Chemin (isabelle.chemin@inserm.fr).

Application should include: CV, application letter, Names and addresses of two references. The application file should be sent before May 18, 2018 to: (marc.le-borgne@univ-lyon1.fr; luc.rocheblave@univ-lyon1.fr; isabelle.chemin@inserm.fr).

The open competitive recruitment process is in two steps: 1. Internal laboratory procedure. 2. Interdisciplinary jury of EDISS.