**PROJECT 1**

**DoS**: **Prof.ssa Antonella CASTAGNA**

Title: **Investigation of pathogenetic and clinical assessment towards an HIV cure**

Curriculum: **Experimental and Clinical Medicine**

Residency Program: **Scuola di Specializzazione in Malattie Infettive e Tropicali, UniSR**

Link to OSR/UniSR personal page: **http://www.unisr.it/k-teacher/castagna-antonella/; https://www.hsr.it/ricerca/struttura/divisione-di-immunologia-trapianti-e-malattie-infettive/antonella-castagna/**

**Project description** (*Number of characters*, *including spaces*: 2.000 - 3.000):

Several different approaches exist for exploring potential cures for HIV, including genetic, 'kick and kill,' immune-based and early treatment strategies: unfortunately, none of the HIV remission trial has resulted in a successful outcome in terms of viral eradication.

The main barrier to a sterilizing cure is the latent reservoir, a population of HIV-infected cells that persist for the lifetime of the individual despite ART and the HIV-specific immune response (1).

Residual levels of viral replication may continuously replenish the latent reservoir during ART; the high CD4+ T cell density in anatomical sanctuaries, combined with lower sensitivity to ART inhibition, may favor cell-to-cell HIV transmission (2). So, validating assays to measure persistent HIV infection and to detect latently infected cells becomes necessary to assess the effectiveness of various therapies.

There are limited studies evaluating potential markers that could identify patients who would do well off therapy; this consideration reinforce the relevance to determine cellular and viral mechanisms that maintain HIV persistence during prolonged ART and host mechanisms that control HIV replication in the absence of therapy (3).

An analytical treatment interruption (ATI) trial was conducted at San Raffaele Hospital (APACHE study) on chronic HIV-1 infected individuals and all the patients experienced a rapid and consistent viral rebound; currently, this study allows the candidate to explore many virological and immunological aspects to better understand key elements towards an HIV cure:

- The HIV-1 DNA dynamics assessed by digital droplet at ATI, at viral rebound and at achievement of undetectable viral load after ART resumption;

- The impact of ATI on re-assortment of HIV-1 drug resistance mutations in peripheral reservoir;

- The modulation of B cell effector molecules, in order to investigate changes in neutralizing antibodies and chemokine CXCL13;

- The characterization of gut microbiota composition to assess phyla associated with viremia reactivation and host immune dysfunction;

- The evolution of anti-HIV antibody response by luciferase immunoprecipitation system, an assay that previous reports have suggested as a measure of HIV-1 reservoir;

Another aim of this project is to compare chronic and acute HIV-1 population who underwent to treatment interruption, leveraging the collaboration with Thai Red Cross AIDS Research Centre in Bangkok, Thailand, that has conducted several ATI trials both with and without interventional strategy on acute HIV-1 infected subjects and is actually enrolling individuals in ongoing studies.

In conclusion, ATI studies have generally resulted in a rapid viral rebound in almost all the HIV patients. Therefore, it's essential to evaluate differences between acute and chronic HIV population that could play a role in HIV remission and investigate biomarkers capable to predict post-treatment controllers and establish clinical endpoints in a cure strategy.

### Skills to be acquired by the student:

The PhD candidate will learn how to analyze and interpret results of the investigation, drawing conclusions from the data. The PhD candidate will acquire expertise in writing research reports/ paper and will be encouraged to improve oral communication skills and independent thinking.

### **References** (max. 3)

1. Ho YC, Shan L, Hosmane NN, et al. Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. Cell 2013.

2. Sigal A, Kim JT, Balazs AB, et al Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy. Nature 2011.

3. 1. Li JZ, Smith DM, Mellors JW. The need for treatment interruption studies and biomarker identification in the search for an HIV cure. AIDS 2015.