Functional expression of antiretroviral drug transporters and metabolic enzymes in HIV-1 myeloid cellular reservoirs - Potential contribution to HIV persistence

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CanCURE *Theme 1* & *Theme 2* pilot project

Antiretroviral drug (ARV) permeability into viral reservoirs and sanctuary sites is highly regulated by the drug physicochemical properties and a dynamic interplay between drug uptake, metabolism and efflux. Dr. Bendayan & colleagues hypothesize that drug transporters, in particular, efflux pumps (i.e., P-glycoprotein, product of the *MDR1* gene) and metabolic enzymes restrict the permeability and intracellular concentrations of ARVs in peripheral monocytes and monocyte-derived macrophages (MDM). Reduced ARV penetration due to efflux transporters could result in sub-therapeutic intracellular drug concentrations and contribute to both HIV-1 persistence and emergence of drug-resistant variants at these sites.

The objectives of their project are: 1) to investigate the functional expression of drug transporters, in particular efflux pumps, and their role in the permeability and distribution of ARVs in peripheral blood monocytes and MDMs of HIV-infected subjects receiving ART as well as uninfected controls (in collaboration with Dr. Ancuta and Dr. Routy); 2) to quantify ARV concentrations in these cellular sites and compare to ARV plasma concentrations (in collaboration with Dr. Fletcher); 3) to determine whether expression of drug transporters and intracellular ART concentration influence on HIV replication in MDMs generated from monocytes of ART-treated subjects (in collaboration with Dr. Ancuta) and 4) to assess the expression of drug transporters in primary cultures of macrophages infected *in vitro* with HIV-1 and investigate the effect of ARVs on HIV-1 replication (in collaboration with Dr. Tremblay). They expect to reveal resistance of myeloid cells to certain ARVs due to the expression of specific drug transporter efflux pumps such as P-glycoprotein.