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New compound derived from seaweed with antiretroviral activity, with prospects of HIV microbicidal activity

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During the human immunodeficiency virus type 1 (HIV-1) replicative cycle, viral RNA undergoes reverse transcription, by means of the viral enzyme reverse transcriptase (RT), and the cDNA is further integrated in the host genome. The enzyme RT is a major target for antiretroviral therapy, and several RT inhibitors are in clinical use. Now the perspective of microbicides agents has been important approach to the protection and prevention of the HIV pandemic.

We performed kinetic studies and investigated whether D1 could synergize with other antiretrovirals. Initially, we found by PCR methods that D1 (0.8 or 10 μM) blocked the synthesis and integration of HIV-1 provirus and completely ablated HIV-1 replication in PBMCs. Next, we observed that D1 Ki value was 1,2 uM (AZT Ki = 0.1 μM), which is in agreement with D1 EC50 previously found (1.8 μM), indicating that RT is the main target of D1. Studies of kinetic mode of action with respect to dTTP/template-primer detected that D1 is a noncompetitive inhibitor of RT. Thus, D1 might act at the pocket of the palm region of RT, similarly to other non-nucleoside RT inhibitors (NNRTIs). Following, we addressed whether D1 could present additive or synergistic effects with other HIV-1 inhibitors. Thus, HIV-1-infected PBMCs were treated with D1 at EC50 dose plus sub-optimal concentrations of classical antiretrovirals. D1 presented an additive effect with AZT (HIV-1 inhibition: D1 = 50%; AZT 5 nM = 40%, D1 plus AZT = 90%), and a synergistic effect with atazanavir (HIV-1 inhibition: D1 = 50%; atazanavir 5 μM = 20%; D1 plus atazanavir = 100%). D1 plus nevirapine resulted in no additive effects. Here we describe the microbicide effect and observe that D1 has shown a strong protective effect against HIV-1 in human tissues demonstrating a possible potential microbicide. We are conducting various studies and obtained combinatorial chemical molecules that have shown strong effects antiretroviral toxicity and with a greatly diminished. Studies in animal experimentation also shows that these substances showed no toxicities hepatic, renal or nervous system.

D1 presented a potent antiretroviral activity against a panel of ten HIV-1 isolates carrying common NNRTI-associated resistance mutations. We propose that D1 could be considered as a potential candidate for HIV-1 therapy or prevention, possibly acting as a microbicide. Currently, we are carrying out pre-clinical studies on animal models and tissue explants.

Biography

Claudio Cirne-Santos completed his PhD in 2008 and is currently a postdoc at Fluminense Federal University in Rio de Janeiro. Has Masters and PhD students under his supervision in line antiretroviral research. Has 20 articles published in journals in the field and develops projects in the Oswaldo Cruz Foundation - FIOCRUZ

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