

ORAL PRESENTATION

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# Epigenetic drug Gar1041 in combination with antiretroviral therapy transiently reduces the proviral DNA reservoir in SIVmac251-infected macaques

MG Lewis<sup>1</sup>, S Norelli<sup>2</sup>, N Chomont<sup>3</sup>, S De Fonseca<sup>3</sup>, M Sgarbanti<sup>2</sup>, M Collins<sup>1</sup>, B Chirullo<sup>2</sup>, J Yalley-Ogunro<sup>1</sup>, J Greenhouse<sup>1</sup>, AT Palamara<sup>4</sup>, E Garaci<sup>2</sup>, A Savarino<sup>2\*</sup>

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## Background

It was recently hypothesized that the lentiviral reservoir in central memory ( $T_{CM}$ ) and transitional memory ( $T_{TM}$ ) CD4+ cells could be restricted by new therapies targeting pathways downstream of homeostatic proliferation or pathways associated with "stem cell-ness", such as those developed for the treatment of leukemias. Gar1041 is one such epigenetic drug adopted in the experimental treatment of certain types of leukemia.

## Methods

SIVmac251-infected primates with viral loads stably suppressed by ART (tenofovir/emtricitabine/raltegravir) were administered for two months: Gar1041 twice daily (a starting dose of 1.5g in the first week followed by 2g in the remaining period). ART was continued during Gar1041 treatment. Proviral DNA was quantitated using a Taqman real-time PCR.

## Results

The proviral DNA content of PBMCs, which had shown no significant changes during 54 days of treatment with ART alone ( $p > 0.05$ ), fell below the level of detection (2 copies/ $10^6$  cells) in all study subjects within one month of Gar1041 treatment ( $p < 0.05$ ; Bonferroni's test following significant [ $p = 0.0003$ ] repeated measures ANOVA). No significant changes were noticed in a control group treated with ART alone ( $p = 0.49$ ). The decrease in proviral

DNA was associated with a significant ( $p = 0.0156$ ) decrease in the proportions of the  $T_{CM}$  CD4+ cell subpopulation in peripheral blood. However, both proviral DNA and the proportions of  $T_{CM}$  CD4+ rebound after two months of therapy.

## Conclusions

The present study furnishes proof of concept that pharmacological strategies may impact on the proviral DNA reservoir. However, the renewal of the phenotype  $T_{CM}$  compartment, associated with the reconstitution of proviral DNA in peripheral blood from an as yet unidentified reservoir, will require integration with other experimental approaches.

## Author details

<sup>1</sup>BIOQUAL, Rockville, MD 20850, USA. <sup>2</sup>Istituto Superiore di Sanità, Rome, 00161 Italy. <sup>3</sup>VGTI-Florida, 11350 SW Village Parkway, 3rd Floor, Port St. Lucie, FL 34987, USA. <sup>4</sup>"Cenci Bolognetti" Foundation, University of Rome "La Sapienza", Rome, 00161 Italy.

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\* Correspondence: andrea.savarino@iss.it

<sup>2</sup>Istituto Superiore di Sanità, Rome, 00161 Italy

Full list of author information is available at the end of the article