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## Basic Principles & Clinical Implications

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### **SJ23B, A JATROPHANE DITERPENE, INDUCES HIV RECEPTORS DOWNREGULATION AND HIV TRANSCRIPTION THROUGH ACTIVATION OF RAS-MEK PATHWAY AND CLASSICAL PKCS**

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LM Bedoya<sup>1</sup>, N Márquez<sup>2</sup>, N Martínez<sup>3</sup>, S Gutiérrez-Eisman<sup>3</sup>, A Álvarez<sup>1</sup>, MA Calzado<sup>2</sup>, JM Rojas<sup>3</sup>, G Appendino<sup>4</sup>, E Muñoz<sup>2</sup> and J Alcami<sup>1</sup>

<sup>1</sup>Unidad de Inmunopatología del SIDA, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain;

<sup>2</sup>Departamento de Biología Celular, Fisiología e Inmunología, Facultad de Medicina, Universidad de Córdoba, Córdoba, Spain;

<sup>3</sup>Unidad de Biología Celular, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain; <sup>4</sup>Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università del Piemonte Orientale, Novara, Italy

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**BACKGROUND:** Despite the benefits of antiretroviral therapy eradication of HIV infection is extremely difficult because it does not eliminate viral reservoirs. Moreover, side effects, toxicities and emergence of viral resistances can limit their utility. Thus, discovery of new antiretroviral drugs is strongly needed. We describe here the effect of SJ23B on HIV reactivation and viral receptor expression.

**METHODS:** Antiviral assays were performed with recombinant virus carrying Renilla reporter genes (X4-tropic-NL4.3-Renilla or R5-tropic-JR-Renilla) or with wild-type HIV (NL4.3). Culture pretreatment with chemical inhibitors were performed to evaluate SJ23B implications in biochemical pathways. Transcriptional activity was evaluated in resting PBMCs transfected with luciferase plasmids under the control of the HIV-1LTR or consensus sequences for Sp1 or NFκB. Protein expression and induction of Ras, ERK, JNK and cRel/ NFκB family of transcription factors were analysed by western blotting and/or gel-shift assays. Expression of PKCs–GFP were analysed by confocal microscopy. Morphologically transformed foci were scored in NIH-3T3 fibroblasts and cell cycle analysis and apoptosis induction were evaluated in preactivated or resting PBMCs by annexin expression and long-term cell viability.

**RESULTS:** SJ23B induced internalization of HIV-1 receptors CD4, CXCR4 and CCR5 preventing R5 and X4 viral infection in human primary T-cells at the nanomolar range. Moreover, SJ23B was a potent

antagonist of HIV-1 latency in resting PBMCs, being at least 10-fold more potent than prostratin. Studies with isoform- specific PKC, MEK and JNK inhibitors suggest a clear involvement of classical PKCs and Ras-MEKERK pathway. We further demonstrated that SJ23B induces phosphorylation of ERK, JNK and I $\kappa$ B $\alpha$  as well degradation of I $\kappa$ B $\alpha$ . As an HIV transcription activator, SJ23B acts through interaction with NF $\kappa$ B and Sp1 sites in primary cells. SJ23B did not elicit transforming foci activity and induced a translocation pattern of PKCs different from that induced by PMA. Furthermore, SJ23B did not induce annexin expression and long-term viability assays in PBMCs showed no toxicity.

**CONCLUSIONS:** SJ23B is a potent anti-HIV agent, sharing some mechanisms of action with prostratin, but structurally different from phorbol-esters. This compound induces two responses: HIV reactivation through transactivation of HIV-LTR and downregulation of HIV receptors, preventing de novo infection of susceptible CD4+ T-cells.

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