Induction of Differentiation in Acute Promyelocytic Leukemia Cells (HL-60) by the Verticillin Derivative Sch 52900

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The HL-60 cell line, derived from a patient with acute promyelocytic leukemia, is a widely used model system to study the cellular and molecular events involved in differentiation of leukemic cells. In a screening for inducers of differentiation of HL-60 cells, cultures of *Gliocladium* strain 4–93 were found to produce Sch 52900, a previously isolated diketopiperazine (Chu *et al,*. J. Antibiotics 48, 1440–1445). Sch 52900 induced the differentation of 50–69% of HL-60 cells at concentrations of 6.8–13.6 nM as measured by nitro-blue tetrazolium chloride (NBT) reduction which was followed by apoptosis as shown by DNA fragmentation. Our results demonstrate that growth arrest and the induction of differentiation by Sch 52900 is due to the induction of the cell cycle inhibitor $p21^{WAF}$ and an inhibition of the extracellular signal-regulated kinase (ERK) signaling pathway which leads to the activation of the transcription factor AP-1.