Selective Apoptotic Induction in Cancer Cells

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Technology description

In cancer, the signaling cascade for programmed cell death, apoptosis, is often mutated leading to resistance from natural pro-death signals. PAC-1 and related compounds are small molecules capable of specifically killing cancer cells by inducing apoptosis. It does so by targeting an inactive apoptotic precursor, procaspase-3, that is up regulated in many cancer types. In vitro and in vivo studies have shown PAC-1 to be efficacious in reducing tumor cells at doses that show no toxicity in normal counterparts. This treatment could be used as a standalone cancer therapy or in combination with other chemotherapy drugs.

Numerous in vitro studies have demonstrated the mechanism of action and efficacy. PAC-1 was tested against several cancer cell lines (including leukemia, lymphoma, melanoma, neuroblastoma, breast cancer, lung cancer, adrenal cancer, and renal cancer) that have varying concentrations of procaspase-3. Toxicity of PAC-1 was positively correlated with procaspase-3 concentration with PAC-1 showing the greatest potency against the lung cancer cell line NCI-H226 (IC50 of 0.35 M). PAC-1 has also been shown efficacious against human resected colon tumors. PAC-1 induced cell death was observed in cancer cells with IC50 values from 0.003-1.41 M versus 5.02-9.98 M in adjacent noncancerous tissue.

In vivo studies have shown PAC-1 to be efficacious in both mice and dogs. Xenograft studies of human renal and lung cancer in mouse models have demonstrated PAC-1 to reduce tumor volume relative to controls when administered via subcutaneous injection or oral gavage. No gross toxicity was observed in any of the mouse studies at low doses. S-PAC-1 is a modification of PAC-1 which displays similar in vitro results and is tolerated at much higher doses than PAC-1 (no toxicity in mice following an intravenous injection of 350 mg/kg S-PAC-1 versus motor impairments following an intravenous injection 30 mg/kg of PAC-1). Recently S-PAC-1 has been tested in dogs and no toxicity was observed after a 60 mg/kg intravenous injection. S-PAC-1 was administered as treatment for six dogs with lymphoma. S-PAC-1 was successful in reducing tumors by 27% in one dog after just four treatments, while three other dogs showed stable response.

Institution

University of Illinois, Urbana-Champaign

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com