

P-37

## IH-901, AN INTESTINAL BACTERIAL METABOLITE DERIVED FROM THE PROTOPANAXADIOL GINSENSIDE, HAS ANTI-TUMOR PROMOTING EFFECTS IN MOUSE SKIN.

Ji-Yoon Lee<sup>1</sup>, Kyung-Soo Chun<sup>1</sup>, Jong-Hwan Sung<sup>2</sup>, and Young-Joon Surh<sup>1</sup>

<sup>1</sup>College of Pharmacy, Seoul National University, Seoul 151-742;

<sup>2</sup>Ilhwa Co. Ltd., Guri-shi, Korea.

Ginseng saponins (ginsenosides) have been regarded as principal components responsible for the majority of pharmacological activities exerted by ginseng. IH-901, an intestinal bacterial metabolite derived from the protopanaxadiol saponin of *Panax ginseng* C.A. Meyer, has been reported to have anti-tumor effects including inhibition of angiogenesis, invasion and metastasis, as well as induction of tumor cell apoptosis. In the present work, we have evaluated the anti-tumor promoting effects of IH-901 using a two-stage mouse skin carcinogenesis model. Topical application of 0.5 or 2.5  $\mu$ mole of IH-901 onto dorsal skins of 7,12-dimethylbenz[a]anthracene (DMBA)-treated female ICR mice 30 minutes before each topical dose of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) suppressed the incidence (by 13 and 27%, respectively) and multiplicity (by 47 and 63%, respectively) of papillomas at 19 weeks. In addition, ear edema and expression of epidermal ornithine decarboxylase induced by TPA in mice were inhibited by IH-901 pretreatment. Recent studies have demonstrated that the eukaryotic transcription factor NF- $\kappa$ B is involved in intracellular signaling pathways associated with inflammation and carcinogenesis. In an attempt to elucidate the molecular mechanisms underlying anti-tumor promoting activities of IH-901, we have determined its effect on activation of NF- $\kappa$ B in mouse skin using the electrophoretic mobility shift assay (EMSA). Pretreatment of dorsal skins of mice with IH-901 inhibited TPA-induced epidermal NF- $\kappa$ B DNA binding in a dose-dependent manner. The compound also attenuated TPA-induced degradation of I $\kappa$ B- $\alpha$  and subsequent translocation of p65 subunit to nucleus. IH-901 pretreatment led to inhibition of TPA-induced expression of cyclooxygenase-2 and prostaglandin E<sub>2</sub> production in mouse skin, which appeared to be mediated

through NF- $\kappa$ B inactivation. TPA-induced activation of extracellular-regulated protein kinase (ERK), one of the mitogen-activated protein kinases, was inhibited by IH-901 pretreatment in mouse skin. In addition, the compound inhibited activation of Akt, an upstream signaling enzyme that is known to phosphorylate I $\kappa$ B kinase (IKK) and to activate NF- $\kappa$ B.