intraperitoneally injected once daily for seven days, PT4 strongly inhibited the growth of intraperitoneally implanted sarcoma 180 cells, the inhibition ratio being 85.1 % at 100 ㎎/㎏. PT4 also strongly induced the peritoneal exudate cells (PEC) and exerted stimulatory activity in that it significantly increased the mean FSC values of splenic CD8+ T cells. PT4 also showed mild *in vitro* inhibitory activity on sarcoma 180 at the concentration of 50 ㎍/㎖ or higher. These results strongly suggest that PT4 might exert its antitumor activity through immunostimulation as well as inhibitory activity on the tumor cells.

[PB4-6] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Flow Cytometrical Analysis on Antitumor and Immunological Activities of Protein - polysaccharide Fractions from Fruit body of Grifola frondosa

Lee IS°, Lee JS and Chung K-S*

Laboratory of Microbiology and Immunology, College of Pharmacy, Chung-Nam National University, Daejon, 305-764, Korea

Turkey-tail mushroom, *Grifola frondosa*, has recently studied as antitumor immunotherapeutic agent in Japan and USA. However, most of these studies used antitumor test methods based on survival length or tumor weight of the tumor-bearing animal and no investigation was carried out on the turkey-tail mushroom cultivated in Korea. In this study, two protein-polysaccharide fractions, KGF-1 and KGF-2, were prepared from the dried carpophores of *G. frondosa* cultivated in a Korean farm and then their antitumor and immunological activities were flow cytometerically determined in ICR mice bearing sarcoma 180 cells. Of these, KGF-1 exerted stronger activity than KGF-2 in that it increased the spleen weight, size of the splenocytes and the number of peritoneal leukocytes whereas it markedly decreased the number of sarcoma 180 cells. The percent tumor inhibition of KGF-1 (100 ㎎/㎏) was 88.2 %. KGF-1 also upregulated the expression of IL-2 receptor on $CD4^+$ T cells as well as $CD8^+$ T cells. Furthermore, it showed *in vitro* direct cytotoxicity against sarcoma 180 cells. These results strongly suggest that KGF-1 is a noble antitumor agent with a potent immunostimulating activity.

[PB4-7] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

A humanized anti-4-1BB monoclonal antibody suppresses antigen-induced humoral immune response in non-human primates

Hong HJ,* Lee JW,† Park SS,* Kang YJ,* Chang SY,† Kim KM,† Kim JO,† Murthy KK,‡ Payne JS,‡ Yoon SK,§ Park MJ,§ Kim IC,§ Kim JG,¶ and Kang CY2†

*KRIBB, Taejon 305-600; College of †Pharmacy and ¶Medicine, Seoul National University, Seoul; ‡ Southwest Foundation for Biomedical Research, San Antonio, TX; and §Biotech Biotech Research Institute, LG Chemical Ltd., Taejon 305-380

The interaction of 4-1BB and its ligand plays an important role in the regulation of T cell-mediated immune response. In this study, we examined the effect of a humanized anti-4-1BB monoclonal antibody (H4B4) on ovalbumine (OVA)-induced immune responses in baboons. Previously, we generated and characterized a mouse mAb, 4B4 against human 4-1BB molecule. Based on this Ab, we constructed a humanized version of 4B4 mAb and the resultant Ab, H4B4 showed full recovery of the binding activity of the original Ab 4B4: 1.5-fold increase in affinity for 4-1BB. In addition, H4B4 mediated ADCC of activated human PB T cells and CEM cells in a dose-dependent manner. Weekly administration of H4B4 at doses of 1 or 4 mg/kg could suppress IgG production against OVA. This was not due to the overall immune suppression since the numbers of B and T cells and the total IgG production were not altered during the treatment with H4B4. These findings suggest that the treatment of H4B4 may be a valid therapeutic approach to control unwanted

immune responses in the cases of various autoimmune diseases.

[PC1-1] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Apoptotic potential of Apicidin and its derivatives

Kwon SH[o], Lee HY*, Hong SY[§], Han JW, Lee HW

Lab. of Biochemistry, College of Pharmacy, Sungkyunkwan University. College of Medicine, Konyang University *. College of Life Science and Natural Resources, Sungkyunkwan University §

We previously reported that apicidin, a histone deacetylase (HDAC) inhibitor, arrests human cancer cell growth through selective induction of $p21^{WAF1/Cip1}$. In this study, the ability of apicidin and its derivative to induce apoptosis was evaluated. HL60 cell growth was completely arrested at G_2/M phase by treatment with apicidin and its derivative, which was correlated with marked induction of $p21^{WAF1/Cip}$ protein. These effects were paralleled by increase in cell death, nuclear morphological change, DNA ladder and apoptotic body formation. Furthermore, this apoptotic cell death was accompanied by conversion of the proenzyme form of caspase-3 to the catalytically active effector protease and subsequent cleavage of poly(ADP-ribose)polymerase and DFF45 (DNA fragmentation factor), one of the caspase-3 target. Taken together, these results suggest that apicidin and its derivative-induced apoptosis might be, in part, due to the activation of caspase-3

[PC1-2] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Effects of histone deacetylase inhibitor, apicidin, on the p21WAF1/Cip1 gene promoter

Ahn SH[o], Wang SY, Kwon SH, Han JW, Hong SY[§], Lee HW

Lab. of Biochemistry, College of Pharmacy, Sungkyunkwan University. College of Life Science and Natural Resources, Sungkyunkwan University §

We previously reported that apicidin, a histone deacetylase inhibitor, showed a broad spectrum of antiproliferative activity against various cancer cell lines through selective induction of $p21^{WAF1/Cip1}$, which plays important roles in the cell cycle. In this study, we examined the effects of apicidin on $p21^{WAF1/Cip1}$ gene promoter in a p53-mutated HeLa cells. $p21^{WAF1/Cip1}$ mRNA was markedly induced by treatment with 0.01μM apicidn, and dramatic $p21^{WAF1/Cip1}$ protein induction was detected. Using human wild-type $p21^{WAF1/Cip1}$ promoter, we found that apicidin strongly activates the $p21^{WAF1/Cip1}$ promoter in a dose and time dependent manner. Futhermore, the Sp1-luc plasmid containing SV40 promoter-derived three consensus Sp1 binding sites was markedly activated by apicidin. Theses results suggest that apicidin arrests the growth of HeLa by activating the $p21^{WAF1/Cip1}$ promoter through specific Sp1 sites in a p53-independent fashion.

[PC1-3] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Chemopreventive potential of the synthetic allylthiopyridazine derivatives on hepatocellular carcinoma cells

Chung MY, Kwon SK and Moon A

College of Pharmacy, Duksung Women's University, Seoul 132-714, Korea