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Conmutaxol inhibits tumor metastasis through blocking NOD1/2 mediated NF-κB and MAPKs signaling

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Cancer metastasis is the major cause of more than 90% death with tumor related diseases. Therefore, successful clinical cancer treatment is optimal for combination of chemotherapy and immunotherapy. We previously designed and synthesized a conjugate of MDP and paclitaxel that not only retains its cytotoxicity against most tumor cell lines but also has immune enhancing capacity *in vitro*. Further experiments indicated this conjugate is powerless to prevent metastasis of Lewis lung carcinoma (LLC) in mice, which may be caused by its consistent ability to induce inflammatory cytokines, especially TNF-α(Li et al., Glycoconjugate Journal, 2008, 25: 415–25). *Conmutaxol*, a conjugate (MTC-220) of paclitaxel and muramyl dipeptide's analog, was further demonstrated in mice to prevent both tumor growth via releasing paclitaxel *in vivo* and tumor metastasis through suppressing myeloid derived suppressor cell accumulation in the spleen and bone marrow of tumor-bearing mice, and repressing inflammatory cytokines in tumor tissue (Ma et al., *J. Med. Chem. 2011, 54, 2767–77*). Recent studies revealed that *Conmutaxol* was highly absorbed by tumor tissue of mice and further increased the paclitaxel's concentration in murine tumor tissue that degraded from *Conmutaxol*. Mechanism investigation indicated that *Conmutaxol* inhibits NOD1 and NOD2 mediated NK-κB and MAPKs signaling in HEK-293 cells, THP-1 cells and human PBMCs-derived macrophages. Compare to paclitaxel, *Conmutaxol* significantly reduced the serum level of VEGF-D and MCP-1 in tumor bearing mice, which suggests that VEGF-D and MCP-1 may act as direct biomarkers of *Conmutaxel* treatment. Finally, *Conmutaxol* was prepared in large scale by a hybrid protocol of solid-phase synthesis of peptide and solution-phase conjugation of peptide and paclitaxel. *Conmutaxol*is formulated into a pair of bottles, whereas one contains lyophilized 50mg MTC-220 powder and another one fills with 10mL dissolving solvent by using solutol HS15 as a nonionic solubilizer. It is recommended for patient utilization with final 1mg/mL concentration in saline via intravenous injection. Injectable *Conmutaxol* is currently submitted to China Food and Drug Administration (CFDA) for phase I clinical trial approve.

Biography:

Gang LIU, Ph.D., Professor of Medicinal Chemistry, graduated from Beijing Medical University in 1994. He then moved to Beijing Institute of Pharmacology and Toxicology for his two years postdoctoral fellowship. He joined Dr. Kit Lam's lab in University of California at Davis from 1998 to 2000 as postdoctoral fellow and senior scientist. From 2000, he received a full professor position and Chair of department of synthetic medicinal chemistry in Institute of Materia Medica (IMM), Peking Union Medical College (PUMC) until 2011. Since 2011, he took a position of full professor and dept Chair in School of Pharmaceutical Sciences, Tsinghua University. Prof. Gang LIU's lab is currently interested in drug discovery and development with phenotype screening technology and novel target identification for cancer treatment and chronic infectious diseases, including HBV, HIV, and mycobacterium tuberculosis.