Rapid Induction of Human Cancer Cell Death by Synergistic Treatment of Tetra-O-Methyl Nordihydroguaiaretic Acid (M4N, Terameprocol) with 7-Hydroxystaurosporine (UCN-01)

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Technology description

Value Proposition:
Tetra-O-methyl nordihydroguaiaretic acid (M4N, EM1421, Terameprocol), a novel transcription inhibitor, is an effective anticancer agent with excellent safety profile (Smolewski, P. Idrugs 11, 204-214, 2008). In the current study, we report an enhancement of anticancer activities of M4N in combination with 7-hydroxystaurosporine (UCN-01), a mitochondrial uncoupler/kinase inhibitor. An M4N/UCN-01 drug combination treatment rapidly induced cell death in cancer cell lines LNCaP, DU145 and PC3 (Prostate), CAK140 and Panc215 (Pancreas), MCF-7, MDA-MB-231 and MDA-MB-468 (Breast), LN229 (Glioblastoma), HT29 (Colon), HepG2 and Hep3B (Hepatoma), and OC24 (Ovary). The drug combination was either synergistic or additive in induction of TUNEL-positive apoptosis in all the cell lines examined in the study. In the xenograft model study using OC24 human ovarian tumor-bearing nude mice, most significantly, we have shown that contiguous treatment of M4N/UCN-01 for a short period was able to decrease the peritoneal malignant ascites and reduce the amount of solid tumors significantly in 42% of the treated mice with a survival time beyond 50 days in apparent "disease-free" condition while 100% of not treated mice lived only 23 to 30 days from the tumor burdens.
• The M4N/UCN-01drug combination allows killing a variety of the human cancer cells including those extremely aggressive ones in a short period of time in an effective drug dose lower than required if used separately.
• Many cytotoxic drugs have been examined for the majority of the advanced ovarian cancer patients. Response rates were all under 20% and patients rarely survived more than a year (Kindler, H.L. Current Treatment Options in Oncology (2008) 9: 171-179). Present invention has the potential to become a good anticancer therapeutic regimen for all types of cancer patients including those with metastatic, malignant ascites.

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