vascularity in OSCC tissues. We found that miR-320 expression was regulated by hypoxia in growth factor deficient conditions by the hypoxia-inducible factor 1-alpha. Neuropilin 1 (NRP1), an important regulator of angiogenesis, was found to be a target of miR-320. The 3'-untranslated region of NRP1 mRNA contains multiple miR-320 binding sites and its expression was regulated by miR-320. By administering either miR-320 precursor or antagonist, we found that miR-320 suppressed the migration, adhesion and tube formation of vascular endothelial cells. Knockdown of NRP1 abolished antagomiR-320-induced cell migration. Furthermore, lentivirus carrying the miR-320 precursor suppressed the tumorigenicity of OSCC cells and tumor angiogenesis *in vivo*. Taken together, our data suggest that miR-320 regulates the function of vascular endothelial cells by targeting NRP1 and has the potential to be developed as an anti-angiogenic or anti-cancer drug.

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TAXOL®, TUBULIN AND TUMORS

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Microtubules, a major component of the eukaryotic cytoskeleton, comprise an effective, validated target for cancer chemotherapeutic drugs, essentially all of which are of natural product origin. One class of drugs, known as microtubule stabilizing agents, bind to microtubule polymers and stabilize them against depolymerization. The prototype of this class of drugs is Taxol®, but other natural products such as the epothilones, discodermolide, laulimalide and peloruside also stabilize microtubules. Although all of these molecules bind to β-tubulin, the binding sites are not identical. These small molecules suppress the normal dynamic behavior of microtubules that is required for normal cell division, thereby leading to inhibition of cell division, which is the basis of their antitumor activity. This presentation will highlight the fascinating history of the development of Taxol®, from the bark of the tree to the bedside. Microtubules, a family of complex proteins, are composed of α- and β- tubulin dimers. There are eight α-tubulin isotypes and seven β-tubulin isotypes, products of distinct genes that display extensive molecular heterogeneity at their C-terminal ends. There is evidence that differences in expressed tubulin isotypes are related to the development of Taxol® resistance. Our laboratory has developed proteomic methods, including high-resolution isoelectrofocusing, and mass spectrometry that allow us to determine the isotype content of tubulin in cells and tissues. Although electron crystallography and photoaffinity labeling experiments revealed that the binding site for Taxol® was in a hydrophobic pocket in β-tubulin, little was known about the effects of this drug on the conformation of the entire microtubule system. Research from our laboratory, utilizing hydrogen-deuterium exchange (HDX) in concert with various mass spectrometry (MS) techniques, has provided new information on the structure of microtubules upon Taxol® binding.

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THE GENOTYPE/PHENOTYPE STUDY FOR THE ROLE OF CAVEOLIN-1 IN GASTROINTESTINAL TRACT CANCERS

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High expression of caveolin-1 (Cav-1), which plays a regulatory role in signaling pathways and tumorigenesis, is positively correlated with higher cell invasion capacity and poor prognosis but the contribution of Cav-1 genetic variants during carcinogenesis is still largely unknown. In this report, we summarized the results of our investigation of the contribution of Cav-1 variant to the risk of gastrointestinal cancers from the multi-angles at DNA, RNA and protein levels. Take hepatocellular carcinoma (HCC) for instance, we have collected 298 HCC patients and 298 cancer-free controls frequency-matched by age and gender in this case-control study in Taiwan and the associations of six single nucleotide polymorphisms (SNPs) on the CAV-1 gene at C521A (rs1997623), G14713A (rs3807987), G21985A (12672038), T28608A (rs3757733), T29107A (rs7804372) and G32124A (rs3807992) with HCC risk in the representative Taiwanese population were evaluated. In addition, thirty HCC tissue samples with variant genotypes were tested to estimate the CAV-1 mRNA expression by real-time quantitative reverse transcription. Last, the HCC tissue samples of variant genotypes were examined by Western blotting to estimate their CAV-1 protein expression patterns. The results showed that there were significant differences between the HCC and control groups in the distributions of the Cav-1 G14713A genotypes (p=0.0124) and people carrying AG and AA genotypes have higher risk for HCC compared with those of GG genotype (OR=1.51 and 1.94, respectively). The patients with Cav-1 G14713A, AG or AA genotype had higher levels of mRNA (p=0.0001) and protein (p=0.0019) than those with GG genotype. Our multi-approach findings at DNA, RNA and protein levels suggested that Cav-1 may play a critical role in the hepatocellular carcinoma, gastric cancer and colorectal cancer in Taiwan and serve as a potential target for

the gastrointestinal tract cancer therapy mentioned in this report.

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EVALUATION OF THE CONTRIBUTION OF METHYLENETETRAHYDROFOLATE REDUCTASE GENOTYPES TO TAIWAN BREAST CANCER

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To evaluate the effects of the genotypic polymorphisms in methylenetetrahydrofolate reductase (MTHFR) and its interaction with early onset on breast cancer risk in Taiwan. Two well-known polymorphic variants of MTHFR, C677T (rs1801133) and A1298C (rs1801131), were analyzed and discussed about their joint effects with individual age- and estrogen-related factors on breast cancer risk. In total, 1,232 breast cancer patients and 1,232 healthy controls were genotyped by PCR-RFLP. The MTHFR C677T genotype, but not the A1298C, was differently distributed between the cancer and control groups. The T allele of MTHFR C677T was significantly more frequently found in controls than in cancer patients. In addition, those females carrying MTHFR C677T CT or TT genotypes conferred a higher odds ratio of 1.21 (95% confidence interval (CI)=1.03-1.42, p=1.85x10^{-5}) for breast cancer, especially before the age of 45.4 (odds ratio=1.51 and 95% CI=1.20-1.90). Our results indicate that the MTHFR C677T T allele was associated with increased risk of breast cancer in Taiwan, especially in who were younger than or equal to 45.4 years of age and earlier menarche age (<12.2 years).

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COPPER(II) COMPLEXES OF 5-(PYRIDIN-2-YL)-NORHYDRASTININE: CRYSTAL STRUCTURE, CYTOTOXICITY AND INTERACTION WITH DNA

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In addition to the Ru(II) complexes, Cu(II) complexes are regarded as the best alternatives to replace cisplatin as anticancer agents (1-3). In this work, three new copper(II) complexes of (1), [Cu(MPDQ)(H_2O)(SO_4)] (Figure 1) (2) and [Cu_2(MPDQ)$_2$(C_2O_4)(ClO_4)$_2$] (3) were synthesized and characterized. They exhibit enhanced cytotoxicity against the tested human tumor cell lines BEL-7404, SK-OV-3, HepG-2, A549, A375, MGC-803 and NCI-H460 with IC_{50} values of 1.41~34.54 μM in comparison to ligand MPDQ and corresponding copper(II) salts. Complex 1 can induce BEL-7404's apoptotic death by S cell cycle arrest (Figure 2), while complex 1 induced apoptosis, which was involved in an intrinsic pathway by up-regulating P53, down-regulating Bcl-2 and mitochondrial membrane potential, leading to sequential activation of caspase-9, caspase-3. ICP-MS testing implied that copper(II) complexes could enter cells and DNA was one important target. DNA binding studies revealed that the intercalation might be the most possible binding mode of new Cu(II) complexes with ct-DNA.

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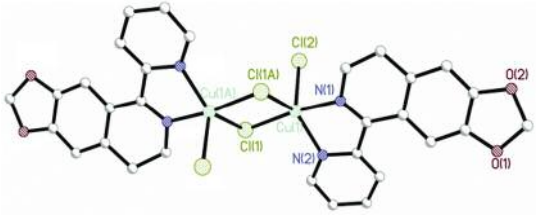

Figure 1. *ORTEP drawing of complex 1.*

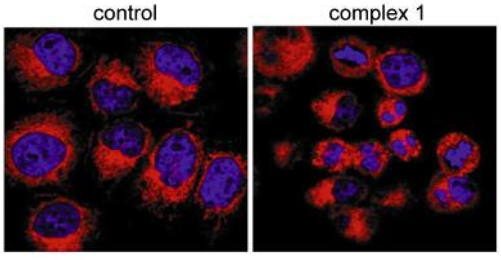

Figure 2. *DAPI/DiD assay of BEL-7404 cells treated by complex 1 (at IC_{50} concentration) measured by confocal microscopy.*