• 計畫中文名稱	磺胺類抗癌化合物之臨床前研究		
• 計畫英文名稱	The Preclinical Studies on the Sulfonamide-Cotaining Anti-Cancer Agents		
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• 執行機構	臺北醫學大學藥學系(所)		
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• 研究領域	藥學, 生物技術		
• 研究人員	劉景平		
• 中文關鍵字	磺胺類化合物；血管裂解劑；抗血管新生；組織蛋白去乙醯酵素抑制劑；		
• 英文關鍵字	Sulfonamides； Anticancer； Vascular Disrupting Agents； Histone Deacetylase Inhibitors		
• 中文摘要	I. 合成磺胺類小分子化合物爲有效抗癌之血管裂解劑(Vascular Disrupting Agents)和抗血管新生化合物. 根據亞培藥廠正在人體臨床 II 期試驗之 ABT-751 結構，我們設計並合成之全新骨架"7-aryl(het)indoline(indole)-1-sulfonamides" 和"7-aryl(het)-6-azaindole-1-sulfonamides" 兩類結構化合物，其中先導化合物 MPT0B098 和 0B220 展現出抑制各種癌細胞生長的能力，其平均 IC50 分別爲 95 nM 和 12 nM，比 ABT-751 更具活性(mean IC50 = 211 nM)。先導 MPT0B098 明顯展現血管裂解及抗血管新生之活性，與 ABT-751 和 CA4P (combretastatin A-4P, ZYBRESTAT®, Phase II/III, as Vascular Disrupting Agents)比較起來，MPT0B098 更具造成血管裂解之能力。爲了進一步完成相關新藥開發臨床前的各種研究，我們設定以下之五項執行目標：(一)合成純度> 97%的先導化合物 MPT0B098 和 0B220 各 5 公克(specific aim 1)；(二) 合成 2-3 公克之標準化合物 ABT-751 (諮議委員建議須在動物實驗放入比較) (specific aim 2)；(三) 確定先導化合物的抗癌機轉並完成其造成血管裂解及抗血管新生的分子藥理研究(specific aim 3)；(四) 確立先導在肺癌(H460)、口腔癌(KB、KB-vin10)動物模式的抗癌活性，並與 ABT-751 做比較(specific aim 4)；(五) 探討相關化合物之結構與活性之間關係，並設立後備化合物(specific aim 5)。II. 合成磺胺類小分子化合物爲有效的組織蛋白去乙醯酵素抑制劑 (Histone Deacetylase inhibitor, HDACi) 分析及歸納目前正在臨床試驗的 HDACi 結構化合物後，我們設計並製備出新穎的磺胺類引朵及引朵琳骨架化合物，在我們初步實驗結果發現，MPT0E014 和 MPT0E028 在抑制各種血癌細胞生長活性比 SAHA (Vorinostat, Merck, FDA approved for treatment of refractory cutaneous T-cell lymphoma)來得強，是 nM range 的化合物，同時對正常的骨髓細胞具低的毒性。爲了進一步完成		

	本類先導化合物相關新藥開發臨床前的各種研究，我們設定以下之五項執行目標：(一)合成先導化合物 MPT0E014 和 0E028 各 5 公克(純度> 97%) (specific aim 1)；(二) 合成標準參考化合物 SAHA 和 MS-275 各 2g (specific aim 2)；(三) 與各種已知 HDACi 比較其抑制組織蛋白去乙醯酵素活性和比較其抑制各種癌細胞生長活性(specific aim 3)；(四) 確立先導化合物 MPT0E014 和 028 之抗癌分子藥理研究，包含 Histone deacetylase biomarker (H3、tubulin、p53 acetylation 和 p21 upregulation)，並評估 AKT 和 ERKs 的 phosphorylation，以及 Bcl-2 和 IAPs 的表現 (specific aim 4)；(五) 確立先導 MPT0E014 和 028 在前列腺癌(PC-3)和血癌動物模式之抗癌活性(specific aim 5)。
• 英文摘要	I. Syntheses of Sulfonamide-containing Small Molecule Compounds as Vascular-Disrupting agents and Anti-Angiogenesis agents On the basis of ABT-751 structure developed by Abbot (phase II clinical trial), two series of compounds, “7-aryl(het)indoline(indole)-1-sulfonamides” and “7-aryl(het)-6-azaindole-1-sulfonamides” were designed and prepared as anticancer/vascular disrupting agents(VDAs) and antiangiogenesis agents. The lead MPT0B098 and 0B220 demonstrated antiproliferative activity with mean IC50 values of 95 and 12 nM against a variety of human cancer cell lines from different organs, stronger than ABT-751 (mean IC50 = 211 nM). The lead MPT0B098 also displayed significant antivascular and antiangiogenesis activities. In the comparison of MPT0B098, ABT-751, and combretastatin A-4P (ZYBRESTAT®), which undergoing human clinical trial phase II/III as vascular disrupting agents, MPT0B098 exhibited comparable or slightly stronger antivascular activity. In order to achieve our goals towards the preclinical/clinical studies, the following five specific aims will be executed: 1. The syntheses of MPT0B098 and 220 with amount of 5g each (purity > 97%) (specific aim 1); 2. The preparation of ABT-751 with 2g amount (specific aim 2); 3. Investigate the mode of action and mechanisms with the corresponding anticancer, anti-angiogenesis, antivascular activities (specific aim 3); 4. Elucidate the efficacy using in vivo xenograft animal models (lung H460, cervical KB, MDR-positive KB-vin10) (specific aim 4); 5. Backup compounds evaluations and investigate their structure-activity relationships (specific aim 5). II. Syntheses of Sulfonamide-containing Small Molecule Compounds as Histone Deacetylase Inhibitor (HDACi) Analysis of structures of the current undergoing human clinical trial HDAC inhibitors, we designed and prepared a series of indolyl(indolinyl) hydroxamates derivatives. The lead MPT0E014 and MPT0E028 showed significant growth inhibition of human leukemia cell lines, including K562, HL60, NB4, kasumi1, and U937. They exhibited activity stronger than SAHA (Vorinostat, Zolinza®, Merck, FDA approved for treatment of refractory cutaneous T-cell lymphoma in 2006), and suppressing cancer cell growth with low toxicity to normal bone marrow. In order to achieve our goals towards the preclinical/clinical studies, the following five specific aims will be executed: 1. The syntheses of MPT0E014 and 028 with amount of 5g each (purity > 97%) (specific aim 1); 2. The preparation of known HDAC inhibitors, SAHA and MS-275 with each 2g amount (specific aim 2); 3. In vitro HDAC assay and antiproliferative activity as compared to known HDAC inhibitors (specific aim 3); 4. Characterizing the mode of action at both epigenetic and cellular levels. Histone inhibition biomarkers include H3, tubulin, and p53 acetylation, and p21 upregulation. Examine its effects on cellular biomarkers including the phosphorylation of AKT and ERKs as well as the expression of Bcl-2

	members and IAPs (specific aim 4); 5. Elucidate the MPT0E014 and 028 efficacy using in vivo xenograft model (prostate PC-3) and in vivo leukemia model (specific aim 5).