• 計畫中文名稱	開發及測試本土合成之小分子抑制劑對人類多形性膠質母細胞瘤治療之可行性		
• 計畫英文名稱	Development and Exploration of the Feasibility of Using Locally Synthesized Small Molecule Inhibitors to Treat Human Glioblastoma Multiforme		
• 系統編號	PD9712-0182	• 研究性質	應用研究
• 計畫編號	NSC97-2323-B038-004	• 研究方式	學術補助
• 主管機關	行政院國家科學委員會	• 研究期間	9710 ~ 9809
• 執行機構	臺北醫學大學傷害防治學研究所		
• 年度	97 年	• 研究經費	1000 千元
• 研究領域	生物技術, 基礎醫學類, 藥學		
• 研究人員	洪國盛		
• 中文關鍵字	多形性膠質母細胞瘤；新藥開發；小分子抑制劑		
• 英文關鍵字	glioblastoma multiforme；new drug development；small-moleculeinhibitors		
• 中文摘要	多形性膠質母細胞瘤(Glioblastoma multiforme, GBM)是常見的惡性腦瘤之一。多形性膠質母細胞瘤因具高度侵略性與破壞神經細胞之能力，至今不論以放射線治療、手術取出腫瘤或者是輔以化療藥物治療，仍無法明顯改善病人的存活率。近年來，標靶藥物治療逐漸成爲癌症治療之主流，但在醫學界至今並無多形性膠質母細胞瘤的標靶藥物可供使用。組蛋白去乙醯基酵素(Histone deacetylases)抑制劑是標靶藥物中的一類，在許多癌症治療上具有不錯的效果，如 Suberoylanilide hydroxamic acid (SAHA) 可用於治療難治的 T 細胞淋巴瘤。在此計畫中，我們將以已申請專利的"indoline"類化合物結合組蛋白去乙醯基酵素抑制劑上的 short-chain fatty acids (butyric acid 及 Valproic acid) 、 N-hydroxy-3-phenyl-2-propenamides 或 N-(2-aminophenyl)-4-(aminomethyl)benzamides 以合成新的小分子治癌藥物。我們將新合成之小分子藥物用數種膠質母細胞瘤的細胞株進行篩選，找出最具潛力之藥物進行後續新藥開發實驗。從我們初步結果發現小分子藥物 MPT0E002 具有顯著抑制細胞生長之能力。未來將以 MPT0E002 作爲主要骨架合成更多新型小分子藥物(目標一)，再用數種膠質母細胞瘤細胞株篩選出具極佳效果之藥物(目標二)。當找到具最佳效果藥物後，將會建立膠質母細胞瘤之小鼠模式，進行藥效測試與藥物在動物體內的分布試驗(目標三)。最後，我們將探討 MPT0E002 與其相關化合物之作用機轉(目標四)。我們希望透過此計畫發展出能有效治療腦瘤的新化合物。		
• 英文摘要	Glioblastoma multiforme (GBM) is one of most common brain tumors in humans. GBM is aggressive, highly invasive, and neurologically destructive. Despite of the treatment such as radical therapy, neurosurgery, and/or combination with novel therapeutic agents, the survival has not significantly change. In recent years, targeting agent therapy has gradually become the mainstream infighting against cancers but it's not available for GBM in the medical world. Histone deacetylases (HDAC) inhibitors are a novel class of the agents. They have recently been used to treat multiple cancers with good effect. For example, suberoylanilide hydroxamic acid (SAHA) has been approved to treat refractory T-cell lymphoma. In this proposal, we intend to use our novel patented "indoline" compound to conjugated with short-chain fatty acids (butyric acid and Valproic acid), N-hydroxy-3-phenyl-2-propenamides, N-(2-aminophenyl)-4-(aminomethyl) benzamides of histone deacetylases inhibitors(HDACs) to generate novel small-molecule anticancer compounds. By screening GBM cell lines, we will look for compounds that have shown potential for future drug development. In our preliminary studies, we have identified a novel compound, MPT0E002, to have marked growth inhibitory activity, induce apoptosis and upregulate p21 protein level. We intend to use MPT0E002 as a basis to develop novel compounds (Specific aim 1) and test them in multiple GBM cell lines (Specific aim 2). Once we have identified the lead compounds, we will test the lead compounds using in vivo mice brain tumor model using GBM cell lines for its efficacy and to perform the animal organ distribution studies (Specific aim 3). Finally, we will investigate mechanism of MPT0E002 and related		

	compounds (Specific aim 4). Using this approach, we hope to develop novel compounds that are able to be used in future GBM therapy.