• 計畫中文名稱	PE092002 抗癌藥物的開發		
• 計畫英文名稱	--		
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• 英文關鍵字	Piperazinediones； PE092002； antitumor； anti-angiogenesis		
• 中文摘要	背景: 本研究團隊從 tyrosine kinases 設計研發出之 piperazinediones 系列 化合物(包括 TW01)具有強而廣效之抑癌(IC50 10-7~10-8 M)及抑制血管新生作用。其中 先導化合物 TW01 選擇性抑制與癌症相關之 18 種 serine/threonine kinases、抑制微管組合促使癌細胞凋亡、抗藥性癌細胞的抑制作用優於 taxol、延長 A549 人類非小細 胞肺癌及 HA22T 人類肝癌小鼠之餘命(ILS > 30)、對 118 個受器、10 種離子通道、7 種轉運體、15 種酵素及 CYP450 代謝酶之 IC50 爲抑癌 EC50 之 100-1000 倍。TW01 遭遇之 困難則爲物化性質不佳，水溶性低，配方及給藥劑型劑量無法改善，形成開發瓶頸。 Piperazinediones 系列化合物經過化學結構重新設計的嚐試後，得到新的化合物 PE092002，水溶性大幅改善(2 mg/mL)，對 PC-3 人類攝護腺癌細胞株之抑癌活性優於 TW01(IC50 12 nM vs 40~80 nM)，進一步活體腫瘤試驗顯示 PE092002 可延緩小鼠體內 A549 人類非小細胞肺癌之生長(6 隻小鼠腫瘤長到 1200 m3 所需之天數平均爲 22 天 (control)、38 天(PE092002/5 mg/kg/p.o.)及 48 天 (paclitexel/20 mg/kg/ip， NSC95-2323-B182-001& NSC96-2323-B182-001)。研究目的：Perazinediones 系列化 合物之藥效核心結構已界定，本階段規劃二年開發計畫，進行以 PE092002 爲 lead 之 藥效藥動最優化。研究內容：(1)研究可改善及降低 PE092002 毒性之給藥方式；(2) 研究可改善物化性質，俾降低 PE092002 劑量以提高藥效降低毒性之配方；(3)除肺癌 外，進行直腸癌、攝護腺癌抗癌及抗血管新生活性動物試驗；(4)合成 Groups A - H 具有不同特性取代基之 PE092002 衍生物做爲藥效藥動最適化 line-extension 備胎； (5)委外測試 PE092002 及 line-extension 衍生物對 tyrosine kinases 之抑制以確立 PE092002 作用機轉；(6)進行物化性質及結構-活性相關分析，並確立 piperazinediones 抑癌及抑制 tyrosine kinases 之核心結		

	構；(7)透過藥動學測試 及分析確立 2-3 個 PD/PK 最優化之 piperazinediones 做爲準藥物。預期成果：改進 配方，產生具有 PD/PK 優化、毒性降低之 PE092002 或其 line-extension 取代物，做 爲抗癌準新藥推向臨床試驗。
• 英文摘要	Background: A series of piperazinedione analogues developed in this laboratory exhibited broad spectrum of antitumor activities on 60 human cancer cell lines (IC50 10-7~10-8M) and anti-angiogenesis activities. The lead TW01 was characterized as protein kinase inhibitors by inhibiting 18 cancer-related serine/threonine kinases with activity on abl tyrosine kinase comparable to that of Gleevac (0.78 μM vs 0.34 μM). TW01 exhibited antitumor activities in mice bearing HA22T human hepatoma and A549 human non-small cell lung cancer (ILS >30). Unfortunately, poor physico-chemical property (water solubility 23 ug/mL) rendered TW01 difficult to be formulated as candidate for further preclinical development. Chemical modification of piperazinediones lead to PE092002. This compound demonstrated (1) improved water solubility to 2 mg/mL; (2) potent in vitro antitumor activity against PC-3 human prostate cancer cell line with activity higher than TW01 (IC50 12 nM vs 40-80 nM); (3) inhibition of tumor growth in mice bearing A549 non-small cell lung cancer (average days for tumor volume to reach 1200 m3 was 22 days (control), 38 days (PE092002, 5 mg/kg orally) and 48 days (paclitexel, 20 mg/kg/i.p., NSC95-2323-B182-001& NSC96-2323-B182-001). Purpose: With PE092002 as the new lead, we propose here a two year project to conduct PD/PK optimization of PE092002 via dosing regimen modification, formulation and chemical modification. Method: Tasks proposed to be conducted in this two year project are in following aspects: (1) dosing regimen design for animal studies in order to reduce the toxicity of PE092002 encountered in previous preliminary in vivo antitumor studies; (2) formulation design and pharmacokinetic determination for PD/PK optimization of PE092002; (3) determination of antitumor activities on tumors other than lung cancer for confirming the efficacy of PE092002 (colon or prostate etc); (4) seek for substitutes of PE092002 by chemical synthesis of at lease 50 line-extension products either as analogues, prodrugs or active metabolites; (5) confirmation of target protein specificity of on PE092002 and synthesized analogues by conducting protein kinase inhibition; (6) define the pharmacophore of these novel pipierzinediones via QSAR analysis, (7) efficacy evaluation of in vivo antitumor and anti-angiogenesis activities on the new leads; and (8) partnering with AngioRx Inc. for preclinical co-development. Aticipated results: Drug candidate(s) will be generated upon critical evaluation on the outcome after PD/PK optimization for further development toward clinical studies.