• 計畫中文名稱	TW01001 及 TW01002 抗癌藥物的臨床前開發		
• 計畫英文名稱	Preclinical Development of TW01001 and TW01002 as Antitumor Agents		
• 系統編號	PD9808-0018	• 研究性質	應用研究
• 計畫編號	NSC98-2323-B038-002	• 研究方式	學術補助
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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	王惠珀		
• 中文關鍵字	piperazinedione；tyrosine kinase；抗癌活性；抑制血管新生活性		
• 英文關鍵字	Piperazinediones； tyrosine kinase inhibitors； 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(NSC95-2323-B182-001& NSC96-2323-B182-001, provisional patent application 2009)。該系列化合物經過 4D-QSAR 構效分析及最優化的嚐試後，得到 8 個最有發展潛力之先導化合物(TW01, TW01001, TW01002, TW01003, HPW044×111, PE092002, HPW082×328 and HPW096×013)。這 8 個先導 化合物依其抑癌效果(MDA-MB-231 Breast CA and PC-3 human prostate CA)、抑制血管新 生作用、水溶性、藥動學參數、口服吸收性及首渡代謝效應評估(NSC97-2323-B182-001)， 並與 Gleevec(第一個 US FDA 核准之 tyrosine kinase inhibitor)的公開資料比較,認爲 TW01002 (BA 79%)及 TW01001(BA 47%)是最值得進入臨床前開發之先導化合物。研究目的： Perazinediones 系列化合物之藥效核心結構已界定，本階段規劃一年進行以 TW01002 (1st) 或 TW01001(2nd)爲 lead 之臨床前開發計畫。研究方法：包括(1)升量合成 50 克 TW01001 及 TW01002；(2)研究可改善物化性質、讓藥效藥動最優化之劑型設計；(3) NOAEL 急毒及亞急 毒性研究測試安全性及選擇性毒性，俾建立可改善及降低毒性之劑量或給藥方式；(4)委外 測試 tyrosine kinases 之抑制活性以確立作用機轉;(5)除肺癌外，委外測試動物直腸癌、 攝護腺癌及抑制血管新生試驗；(6)尋求 CDE 關鍵途徑(critical path)之協助以加速研發 時程縮短審議時間；(7)與產學合作廠商安新藥物研發公司規畫早期臨床試驗。預期成果： 產生藥效/藥動最優化、低毒性高安全性之抗癌準新藥，推向臨床試驗。		

• 英文摘要	Background: Studies conducted on a series of piperazinedione compounds ended with 8 leads with promising antitumor and anti-angiogenesis activities (NSC95-2323-B182-001& NSC96-2323-B182-001, provisional patent application 2009). PD/PK assessment on 6 potential leads (TW01, TW01001, TW01002, TW01003, HPW044×111, PE092002, HPW082×328 and HPW096×013) was conducted in an ad hoc meeting with experts from USA experienced with clinical trials. The assessment was in the aspects of cytotoxicity, anti-angiogenesis effect, water solubility, oral absorption and metabolism, and in comparison with Gleevec, the first tyrosine kinase inhibitor approved by US FDA. The assessment ended with the conclusion that TW01002 and TW01001 are the 1st and the 2nd promising compounds for exploring preclinical development. Method: With TW01001 and TW01002 as new leads, the goal of this proposal will be achieved in the following aspects: (1) to scale up synthesis of 50 g of TW01002 (1st choice) and TW01001 (2nd choice) for extensive biological evaluation; (2) to conduct formulation design and pharmacokinetic determination for PD/PK optimization; (3) to conduct NOAEL acute and subacute toxicity studies with single and repeated dose regimen of dose finding for clinical studies; (4) to conduct protein kinase inhibition profiling and general pharmacology for better understanding of the mode of action underlying antitumor and anti-angiogenesis effect; (5) to conduct in vivo antitumor studies and expand to different human tumor types; (6) to conduct receptor-based QSAR modeling for better understanding the interaction between TW01001/TW01002 and the target enzyme; (7) to seek for the support of CDE via critical path for preclinical evaluation and (8) to partner with AngioRx Inc. for planning clinical development. Aticipated results: Drug candidate(s) will be generated for further development toward clinical studies upon critical evaluation of the outcome after PD/PK optimization.