• 計畫中文名稱	君臣佐使設計抗癌新藥		
• 計畫英文名稱	ADME-Driven Design of Novel Antitumor Agents		
• 系統編號	PC9708-0343	• 研究性質	應用研究
• 計畫編號	NSC95-2320-B038-049-MY3	• 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	9608 ~ 9707
• 執行機構	臺北醫學大學藥學系(所)		
• 年度	96 年	• 研究經費	970 千元
• 研究領域	藥學		
• 研究人員	王惠珀,李珮端		
• 中文關鍵字	--		
• 英文關鍵字	--		
• 中文摘要	由於藥物的動力學表現常常成爲新藥發明進入開發階段之瓶頸，藥物動力 學與藥效學最適化研究(PD/PK optimization)已成爲成功開發藥物的必要方法，越 早進行動力學與藥效學最適化研究，成功機率越大。本研究室一系列 azatyrosine 化合物對於轉型 ras 基因過度表現的 NIH 3T3 老鼠纖維腫瘤細胞具有選擇性的 細胞毒性， 對於 SW620 人類直腸癌細胞, T24 人類膀胱癌細胞, 以及 PC3 人 類攝護腺癌細胞都表現出令人很感興趣的抗癌活性，其中尤以 HPW071×001 具 有抗癌及抗血管增生而具有發展潛力。因此提出此三年計劃，擬開創一個藥物設 計方法，以 HPW071×001 爲題，利用身體的吸收分佈代謝排泄機轉(ADME)， 設計身體較能接受因此較無毒性之虞的藥物分子(body-friendy molecules)，做爲 爲分子設計/藥效/藥動最適化之新藥研發平台(platform)，並期望以此利用身體機 制求取藥效藥動最適化的方法，驗證與中藥君臣佐使之理論相契合。預計產出具 有開發潛力之抗血管增生、抗癌或免疫調節的新藥。		
• 英文摘要	The theme of this study is to use the mechanism of absorption, distribution, metabolism and excretion (ADME) to design body-friendly new molecular entities of azatyrosine analogues as antitumor and anti-angiogenesis agents. The series of azatyrosine analogues developed in this laboratory exhibited selective cytotoxicity on overexpressed ras-tansformed NIH 3T3 cancer cells, SW620 human colon, T24 human bladder and PC3 human prostate cancer cell lines. The antitumor activity on SCID mice bearing SW620 colon tumor were also confirmed on some analogues (HPW98-1, HPW98-2 and HPW071x001). Further studies indicated that the metabolites of these analogues might be responsible for their activity. The active metabolites need to be further investigated and identified for therapeutic use. The purpose of this study is thus (1) to		

	seek for active metabolites of azatyrosines, especially HPW071×001, as potential antitumor and anti-angiogenesis agents; (2) to increase the intracellular availability of azatyrosine analogues via transporter approach; (3) to seek for the feasibility of using folic acid or its antimetabolites as moieties for guiding azatyrosines ot enter cells via folate transporter located in cell membrane; (4) to seek for possible cellular oligopeptide transporter for transport di- or tripeptide memetic azatyrosine analogues into the cee. Studies proposed in this three-year proposal includes (a) the identification of active metabolite of HPW071×001 as true antitumor agent; (b) the synthesis of dipeptide mimetic azatyrosine analogues as antitumor agents; (b) the synthesis of NMEs hybridized from azatyrosine and folate antimetabolites, methotrexate, pemetrexate (alimta) or pyrimidines; (c) the synthesis of mutual prodrugs of azatyrosine analogues with folate antimetabolites; (d) biological evaluation on the antitumor and anti-angiogenesis effects; (e) biological evaluation on nutrophil for possible immunomodulating activities (IMiDs); (f) formulation for optimizing pharmacokinetic profile of lead compounds. The anticipated results will be (a) to prove the concept that body ADME is not only feasible for PD/PK optimization of existing drugs but also a fruitful mechanism for designing patentable new molecular entity; (b) to demonstrate that the body-friendly molecular entity design will lead to a high successful rate; (c) to generate azatyrosine analogues for further development as novel antitumor, anti-angiogenesis or immunomodulating agents and (d) to provide young researchers with a new direction on drug discovery.