• 計畫中文名稱	利用運鐵蛋白導向之微脂粒奈米載體系統對白血病細胞進行 siRNA 之傳遞		
• 計畫英文名稱	siRNA Delivery to Leukemia via Transferrin-Targeted Liposomes		
• 系統編號	PC9609-3899	• 研究性質	基礎研究
• 計畫編號	NSC96-2628-B038-014-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	1365 千元
• 研究領域	藥學		
• 研究人員	邱士娟		
• 中文關鍵字	--		
• 英文關鍵字	--		
• 中文摘要	Antisense 藥物進到人體細胞內，可藉由阻礙特定基因表現的轉錄或轉譯程序而藉 由抑製造成疾病的相關蛋白質合成達到療效，其中相關載體的研究發展爲此類療法可否 有效成功地應用於癌症治療之速限步驟。與病毒性載體相比較之下，非病毒性載體具有 安全及提供較大設計彈性空間之優點，然而，目前其臨床上的發展因無法達到足夠效率及 缺乏組織專一性而有所受限，爲了克服這個瓶頸，目前的 antisense 療法(包括 ODN 及 siRNAs) 應選用對癌細胞具專一性的載體。 siRNA 是一類新的用於治療白血病的療法。運鐵蛋白(transferrin)導向(targeted)之載 體，可藉由運鐵蛋白受體被細胞吞噬而選擇性的進入表面有該受體的細胞，曾被廣泛地 運用在癌細胞有選擇性之藥物及基因遞送。因此我們認爲若將 siRNA 包覆於有細胞選擇 性(如表面具有運鐵蛋白)之微脂粒載體中，可以因微脂粒及導向系統之特性而顯著改善其 藥物動力學性質及提高臨床治療效果。微脂粒包覆可以提高 siRNA 在血液中之安定性及 停留在全身循環的時間，並減低腎清除率。運鐵蛋白導向系統則可藉由提高進入標的細 胞因而減少分佈至一般細胞之比例，更進一步地達到提高治療效果的目的。 過去曾有報導指出鐵缺乏可以提高細胞表面運鐵蛋白受體的表達。因此對於白血病 及癌症之治療，併用鐵鉗合物(Desferrioxamine, DFO)與運鐵蛋白可能可以達到藥物協同 作用。我們假設此運鐵蛋白導向奈米載體系統之進入細胞比率可藉由提高細胞表面的運鐵蛋白受體而顯著增加。 此爲一 3 年計畫，計劃預計完成之目標包含: 第一年 1. 設計並評估一創新的運鐵蛋白導向之奈米載體系統，此系統將用來包覆 siRNA 並 藉由微脂粒之特性來提高 siRNA 進入細胞的效率。於此部份之實驗，將會評估此 載體之物化性質、進入細胞的比率、以及使用劑量與抑制細胞內特定蛋白質生成 之能力的關係。 2. 評估 Bcl-2 siRNA	

	微脂粒劑型於細胞中抑制 Bcl-2 蛋白質生成之效果，並與 Bcl-2 ODN 微脂粒劑型作比較。 第二年 3. 評估 Bcl-2 siRNA 微脂粒劑型與化療藥物併用時是否可以達到藥效加成之作用 (synergistic effect) 。 4. 評估利用 DFO 提高細胞表面運鐵蛋白受體表現是否可增加包覆 siRNA 之運鐵蛋 白導向奈米載體系統進入細胞的比率。 第三年 5. 評估 Bcl-2 siRNA 微脂粒劑型於動物體內藥物動力學及藥效學之結果，並與未被 微脂粒包覆之 siRNA 作比較。
• 英文摘要	The numerous formulations developed to target specific receptors and the exciting preliminary results in cell culture reflect a high level of enthusiasm in the gene delivery community for this tumor targeting strategy. Development of gene transfer vectors is a rate-limiting step in the clinical application of antisense therapy for the treatment of cancer. Nonviral vectors are potentially safer and provide greater design flexibility than viral vectors. Their utility in antisense therapy is, however, hindered by insufficient efficiency and lack of tissue selectivity. Tumor-selective transgene delivery is required for antisense therapy such as antisense deoxyribonucleotides (ODNs) and small interference RNAs (siRNAs or RNAi – RNA interference) siRNA as an antisense agent is an exciting new class of agents for the treatment of leukemias. Transferrin (Tf)-targeted formulations have been evaluated for tumor cell selective delivery of therapeutic agents including plasmid DNA via the transferrin receptors (TfR). We hypothesize that the pharmacokinetic properties and therapeutic efficacy of siRNAs can be greatly enhanced by delivery via Tf-targeted PEG liposomes. Liposomal entrapment is anticipated to result in increased in vivo stability, greatly extended systemic circulation time and reduced normal tissue distribution and renal clearance for siRNAs. Selective targeting of leukemia cells via the TfR should provide additional enhancement in the efficacy and therapeutic index of this agent. It has been reported that iron deficiency can upregulate expression of transferrin receptor (TfR) at both the mRNA and protein levels. Thus, a possible synergistic effect of iron chelating agent (desferrioxamine (DFO)) and transferrin (Tf) could be very useful in Tf-targeted siRNA delivery in leukemia and other cancer treatment. We hypothesize that the cellular uptake of Tf-targeted formulations can be increased by up-regulate the TfR in cells. In the current study, a Tf-targeted siRNA-containing liposomal formulation will be developed and evaluated in human leukemia K562 cells. K562 cells will also be pretreated with DFO to investigate whether the enhancing effect is TfR-related. This is a 3-year project and the Specific Aims of this project are: Year 1 Aim 1.1. To design and evaluate in vitro properties of novel formulations of Tf-targeted siRNA liposomal nanoparticles (liposomes) Aim 1.2. To compare the downregulation properties of novel formulations of Tf-targeted siRNA liposomes and Tf-targeted ODN liposomes Year 2 Aim 2.1. To evaluate the synergistic effect of Tf-targeted Bcl-2 siRNA liposomes and chemotherapeutic agents in TfR-overexpressing cell lines Aim 2.2. To evaluate the effect of up-regulation of TfR in the cellular uptake of Tf-targeted liposomes in TfR-overexpressing cell lines Year 3 Aim 3. To evaluate the pharmacokinetic properties and the therapeutic efficacy of liposomal siRNAs in vivo. An optimized TfR-targeted synthetic vector will be used to deliver antisense agents into the tumor. The treatment, combined with chemotherapeutic agents such as daunorubicin or doxorubicin, should inhibit tumor growth and prolong the survival of mice bearing TfR(+) tumor models.