

• 系統編號	RG9611-0360		
• 計畫中文名稱	以幹細胞趨癌特性及分子基因造影技術來研究肺癌之分子轉移機制		
• 計畫英文名稱	--		
• 主管機關	行政院衛生署	• 計畫編號	DOH96-TD-G-111-013
• 執行機構	台北醫學大學生物醫學材料研究所		
• 本期期間	9601 ~ 9612		
• 報告頁數	33 頁	• 使用語言	中文
• 研究人員	鄧文炳；吳成文；楊泮池；李江琪 Deng, Win-Ping；Wu, Cheng-Wen；Yang, Pan-Chyr；Jiangqi-Li		
• 中文關鍵字	蛋白質疫苗；SDF-1/CXCR4；癌症轉移；非侵入性造影		
• 英文關鍵字	--		
• 中文摘要	近年來於醫學研究上，雖然已有大幅的進步，但肺癌仍是許多已開發國家的主要死因，其中包括台灣。理想的癌症治療應該是能全身性的移除不同部位的腫瘤，並能專一性的分辨惡性和良性的細胞。於我們先前的研究中已證實了幹細胞的活體趨癌特性，所以本計畫的第一個目標是了解參與調控趨癌特性的分子，先於體外建立癌細胞刺激幹細胞移動的實驗模式，並發現專一性針對 CXCR4 的中和抗體(12G5)的確可以降低幹細胞受癌細胞刺激所產生的移動。第二個目標則是以幹細胞趨癌特性為基礎設計了一個”木馬屠城計”（Trojan horse）的治療策略，應用幹細胞的趨癌特性和蛋白質疫苗的組成而達到抑制和預防腫瘤生長的作用，我們先建立了基因轉殖的人類間葉幹細胞，以及針對此基因的蛋白質疫苗，首先我們將基因轉殖的幹細胞引進腫瘤中並隨其共同發展，七天後注射疫苗而抑制或破壞腫瘤的生長。研究結果清楚的顯示，在皮下以及肺部腫瘤的模式中，我們利用分子造影監測到合併幹細胞和蛋白質疫苗的治療可以明顯的抑制腫瘤的生長，我們認為腫瘤抑制的效果和由疫苗所引起的專一性免疫反應有很高的相關性，並且我們也證實了合併療法會透過造成細胞產生程式性死亡而達到抑制腫瘤的效果。最後的部分則是了解和肺癌產生骨骼轉移的現象和相關調控機制。利用非侵入性分子造影監測肺癌細胞於活體內轉移的情形，成功的建立了肺癌骨骼轉移的動物模式，並利用體外共同培養的模式模擬肺癌產生骨骼轉移時的環境，再分析肺癌細胞中和癌症轉移相關的基因表現，其中包括了 SDF-1/CXCR4、CTGF、IL-11 和 PTHrP 都有明顯的上升。目前為止，我們發現 SDF-1/CXCR4 在幹細胞趨癌的移動中扮演重要的角色，而基因轉殖的人類間葉幹細胞可以作為一個萬用的追蹤腫瘤工具並媒介蛋白質疫苗抑制腫瘤的效果，所以這種應用幹細胞以及蛋白質疫苗的新策略具有作為移除多種癌症療法的潛能。此外我們也建立肺癌骨骼轉移的動物模式，並且初步篩選出和肺癌骨骼轉移相關的代表基因，而目前已有文獻指出肺癌轉移的機制和骨質疏鬆症之間存有相關性，所以我們開發了一個去除早老化老鼠的卵巢導致的骨質疏鬆症動物模式，目前此骨質疏鬆症動物模式的研究成果已投遞至 Nature medicine 期刊中，希望進一步的應用於癌症轉移研究和治療中。		

- 英文摘要

Despite of recent advances in medical research, lung cancer is still the leading cause for cancer death in many developed countries including Taiwan. Ideally, cancer treatments should eradicate systemic tumor at multiple sites including primary and metastatic, and also have the specificity to discriminate between neoplastic and nonneoplastic cells. In our previous studies, we have demonstrated that mesenchymal stem cells (MSCs) were able to target tumors lesions in vivo. Therefore, our first goal is to investigate which molecules that regulated the tumor targeting of stem cells. We established a model to observe the migration of stem cells induced by cancer cells in vitro. Our results indicated that antibody neutralization of CXCR4 on stem cell can diminish the its migration induced by cancer cell. The second goal is to devise a novel “Trojan horse” therapeutic strategy which consists of stem cell and protein vaccine to inhibit and prevent tumor growth. A protein vaccine was developed to recognize specifically the modified MSCs. These modified MSCs were then introduced to infiltrate the tumor followed by the inoculation of vaccine to destroy and or inhibit tumor growth, thereby constituting our “Trojan Horse” strategy. Our data clearly indicated that either in subcutaneous or in pulmonary tumor model, tumor development was greatly inhibited by the combined treatment of MSCs and protein vaccine. We investigated that the efficiency of tumor suppression was highly related with the specific immune response induced by the protein vaccine, and we also demonstrated that combined treatment inhibited tumor growth through inducing programmed cell death. The third part of this project is to utilize optical imaging (non-invasive) technique to monitor lung tumor formation and metastases of human lung cancer cells in a mouse model. We successfully established a non-invasive molecular imaging system for long-term monitoring of the migration and development of luciferase-transduced human lung cancer cells. Next, we identified bone-metastatic potential of human lung cancer cells with in vivo imaging and in vitro co-culture system. The bioluminescence imaging data demonstrated the bone-metastatic potential of human lung cancer cells in mouse. Similarly, in vitro co-culture system showed that after 28 days of co-culturing with bone marrow cells, bone metastases related genes such as CXCR4, PTHrP, CTGF and IL11 in the human lung cancer cells were found up-regulated. These data strongly implicated that cancer cells promote metastases via these genes. In summary, we have demonstrated that SDF-1/CXCR4 axis was important to the tumor-targeting of stem cells, and we have also shown that engineered MSCs could be used as an universal tumor-homing device and mediate the anti-tumor effect of fusion protein vaccine. Therefore, this novel strategy using MSCs and protein vaccine could be a potential therapeutic intervention for eradicating multiple cancers. In addition, we have established the animal model of bone metastases of lung cancer, and we have identified the marker genes related to the bone metastases of lung cancer. Recent studies indicated that osteoporosis related to bone metastases of lung cancer. Thus, senescence-accelerated mouse were performed ovariectomy to establish the animal model of osteoporosis. The results of senile ovariectomy-induced osteoporosis in senescence-accelerated mouse have been submitted to Nature Medicine. Then, the animal model of osteoporosis showed a great applicability in future studies of bone metastases in lung cancer.