• 計畫中文名稱	物理性促進作用對於 ALA 的經皮吸收效果評估以及在光動力治療上的應用		
• 計畫英文名稱	Enhancement of Topical 5-Aminolevulinic Acid Delivery by Physical Enhancers and Its Application in Photodynamic Therapy		
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• 中文關鍵字	光動力療法; 餌雅鉻雷射; 微晶磨皮; 皮膚癌; 細胞既定死亡		
• 英文關鍵字	5-aminolevulinic acid (ALA); photodynamic therapy (PTD); Er:YAG laser and microdermabrasion; skin tumors; apoptosi		
• 中文摘要	皮膚癌是最常見的癌症。基底細胞癌和鱗狀細胞癌是非黑色素細胞癌最多的兩種而且是可以治癒的。傳統的治療包括了外科手術、放射線治療、化學治療、電燒灼等，這些治療方式容易產生一些無法預期的副作用，如疼痛、疤痕等。近年來，光動力療法已成爲一種新穎且更容易被接受的治療方式。局部塗抹 ALA 加上光線照射引發光敏感的光動力療法是目前治療皮膚癌越來越被接受的一種治療。ALA 是一種親水性的分子，其分子量爲 167.7，其角質層與水的分配係數是 0.1。依據皮膚穿透原理，ALA 很不容易穿過爲受損的皮膚。以往經常以濃度爲百分之二十的 ALA 軟膏塗抹作爲臨床使用已增加其穿透，但是其容易引起皮膚刺激。目前使用的方法在局部的生物可利用性並不足夠達到完全治療的效果。餌雅鉻雷射和微晶磨皮是兩種可用來剝離角質層的新方法。餌雅鉻雷射可剝離角質且較少熱傷害。微晶磨皮比起其他的表淺剝皮方法的優點則是較少流血、較少副作用、無須局部麻醉。這兩種方法已被證實能促進親水性藥物的經皮吸收。除此之外，電泳導入和電穿洞也是屬物理性刺激劑可增進藥物的穿透。因爲 ALA 是一種親水性藥物且不容易穿過角質層，我們假設如果利用餌雅鉻雷射、微晶磨皮能準確剝離角質層的特點，先把角質層去除應該可以增加 ALA 的經皮吸收，達到更好的光動力療法抑制腫瘤生長的作用。細胞既定死亡是一種受到高度調控的反應，一連串的分子會被活化，而造成細胞的死亡，細胞死亡的特徵包括細胞型態的變化、染色質的濃縮以及去氧核醣核酸斷裂所所行程的細胞變化，很多基因的表現已被證實與調控細胞既定死亡有關，如半胱氨酸-天冬安酸蛋白酵素以及 BCL-2 家族。光動力療法對皮膚癌作用的轉仍不清楚，不過有一些利用細胞培養和動物實驗所作的研究顯示與細胞既定死亡有關。第一年的研究我們要以豬的皮膚作爲體外穿透的模式，在餌雅鉻雷射和微晶磨皮兩種方法中選出最適當的狀態來促進 ALA 的穿透，比較這兩種方法對豬皮膚所造成的組織變化，而且在使用這兩種方式來增進 ALA 穿透下如		

	果再上電泳導入和電穿洞的作用是否可達到加成的效果。一旦能選擇出最適當的促進方法和狀態，進一步推展到皮膚癌的動物模式。第二年的計劃主要比較不同的物理性刺激劑對 ALA 光動力療法的抗腫瘤效果，研究治療過的皮膚癌在細胞既定死亡的標的物質的表現。
• 英文摘要	Skin cancer is the most common of all cancers. Most of basal cell carcinomas and squamous cell carcinomas which are the most common non-melanoma skin cancers can be cured. Conventional methods used to treat these cancers via surgery, radiotherapy, chemotherapy, and electrodissection, produce undesirable effects, such as pain and scarring. Recently, photodynamic therapy (PTD) represents a new and better tolerated approach. Topical application of 5-aminolevulinic acid (ALA) is an increasingly popular method of photosensitization for the PDT of skin tumors. ALA is a hydrophilic molecule with a molecular weight of 167.7 and a stratum corneum (SC)/water partition coefficient of 0.1. Based on the skin permeability theory, ALA poorly permeates across intact skin. The commonly used dose of 20% for ALA in a clinical status is so high that it may cause irritation of the skin. The local bioavailability of the drug is normally insufficient for a complete therapeutic effect. Erbium:yttrium-aluminum-garnet (Er:YAG) laser and microdermabrasion are both new tools which can be used for ablation of the SC. The Er:YAG laser ablates the SC with minimal residual thermal damage. Microdermabrasion has the advantages of less bleeding, fewer complications, and no need for local anesthesia in comparison with other superficial peeling techniques. These two methods have been shown to enhance transdermal delivery of hydrophilic drugs. Iontophoresis and electroporation are the other types of physical enhancer to promote drug delivery. Since ALA is a hydrophic molecule with a poor penetration to stratum corneum. We hypothesize that using Er-YAG laser or microdermabrasion to precisely remove the SC will enhance transdermal ALA delivery to obtain a better anti-tumor action with PTD. Apoptosis, or programmed cell death, is a highly regulated process that involves activation of a serious of molecular events, leading to cell death that is characterized by cellular morphological change, chromatin condensation, and apoptotic bodies which are associated with DNA cleavage into ladders. Several genes』 expressions have been demonstrated to be critical in the regulation of apoptosis such as caspase cascades and Bcl-2 family proteins. The action mechanism of PTD remains unclear, several studies using cultured cells and experimental animals had suggested the involvement of apoptosis in tumor cell death after PTD. The objective of the first year study is (1) optimize and enhance the in vitro skin permeation of ALA by two resurfacing techniques: erbium (Er):YAG laser and microdermabrasion. (2) Light microscopic changes in the pig skin with these techniques will be compared. (3) The electrically assisted methods, iontophoresis and electroporation, will be used to facilitate ALA permeation across laser- or microdermabrasion-treated skin. After the most efficient condition to improve ALA permaeation is achieved by the 1st year project, it will be applied to the animal model for the 2nd year project. The aims of the 2nd year project are: (1) Compare the anti-tumor effects of different physical enhancing methods using animal model (2) Analyze the differential expression of apoptotic markers of ALA-PDT treated skin tumors.