• 計畫中文名稱	利用經個別皮膚的生化參數與基因多型性因子標準化之皮膚滲透係數以建構滲透係數與結構特質之定量相關性(I)		
• 計畫英文名稱	Construction of Quantitative Structure Permeability Relationship (QSPR) with Skin Permeability Normalized to Biological Parameters/Genetic Polymorphism of Individual Skin (I)		
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• 研究人員	許明照		
• 中文關鍵字	滲透力; 滲透係數與結構關係式; 個體差異; 穿皮水分散失; 基因多型性		
• 英文關鍵字	permeability; QSPRs; variability; TEWL; polymorphism		
• 中文摘要	由於皮膚滲透力 (permeability) 是描述滲透質經由皮膚吸收之效能的重要 指標，所以在之前研究中經常利用結構與滲透力定量關係式 (QSRPs) 預測 滲透質經由皮膚吸收之滲透力。傳統上 QSRPs 是建立在皮膚滲透力與滲透 質之分子量、正辛醇與水分配係數（Ko/w）之間的關係。此關係式能夠合理 的定量描述透過皮膚吸收之滲透力，對一些較不親水性的藥物的預測結果也蠻合宜的，然而個體皮膚間的差異通常都會被忽略。在之前的實驗中經 常會使用一系列不同結構性的滲透質在不同的皮膚樣品進行測試，並取其 平均值當做各個滲透質的皮膚滲透力，再依照不同理論模式迴歸評估不同 滲透質結構特性對皮膚滲透力的定量關係，以作爲預估理論值之應用，但 在運算過程並沒有考慮個體間皮膚的差異，所造成皮膚滲透力數值的偏差 性，而此偏差性可能會是評估皮膚滲透力時最大的變異來源，因此在運用 會受皮膚差異所影響的皮膚滲透力時應對個體皮膚的差異進行標準化後再 迴歸運算，如此才能提高藉由此結構與皮膚滲透力關係式預測滲透係數的 準確度。在本三年的研究計畫中，第一年將藉由個體皮膚間角質脂質的各 組成含量以及 filaggrin 天然保濕因子 (NMF)，訂出水分經皮散失值 (TEWL)，作爲定量個體皮膚特質的滲透差異性。第二年，皮膚的滲透力將 利用模式藥物透過裸鼠皮得到，QSPR 回歸準確性的改善，將在簡單或是較 複雜的擴散模式下，以原始的滲透數據以及經過 TEWL 校正後的數據進行 迴歸比對。第三年將比較個體皮膚間 filaggrin 以及 ceramide 的基因多型性 (mRNA) 與酵素活性表現，包括 β-GlcCer』ase 和 SMase。最後，影響皮膚穿 透力的皮膚結構特質，將可藉由酵素的基因多型性以及水分經皮散失之間 關聯性來表現。因此，藉由校正皮膚穿透力以改善 QSPR		

	回歸準確性，以 及預測不同個體間皮膚穿透力將是未來可預期的方向。
• 英文摘要	Skin permeability is used as a key parameter for describing the percutaneous transport of solutes, and as such, it is essential for designing and evaluating the efficacy of drug delivery system through the skin. Historically, quantitative structure-permeability relationships (QSPRs) were aimed to construct a relationship between the percutaneous absorption of solutes through the skin and their physico-chemical and/or structural properties. Most of these attempts were based on empirical correlations between skin permeability and solute parameters including molecular weight, MW, and octanol water partition coefficient, Ko/w. Though empirical in nature, these equations describe percutaneous solute transport reasonably well and have been used to predict skin permeability of small hydrophobic drugs. However, the variability of individual skin was not considered in these studies when measurements of skin permeability or flux were taken. An average of skin permeability or flux for each individual solute was traditionally generated from several different skin samples and those for a series of solutes were also measured on skin samples with different permeation characteristics. Eventually, skin permeability or flux for a series of solutes used in the regression to obtain the best fit for theoretical prediction, either by (T)QSPR or Scaled Particle Theory, should involve the variability element coming from the variation of individual skin. With no doubt, the major variation in the measurement of skin permeability or flux could be attributed to variability in the characteristics of individual skin. Therefore, variability in skin characteristics from which permeability or flux was measured will be partitioned into the regression variability in the theoretical analysis of QSPR equation if normalization of skin permeability or flux with respective to individual skin characteristics was not done. This could lead to decrease the accuracy of prediction and have no ability to optimize percutaneous delivery for each individual. In this three-year proposal, quantitative skin variability represented by transepidermal water loss (TEWL) as a result of difference in the amount and the composition of SC lipids and natural moisture factors derived from filaggrin for each individual skin sample will be estimated in the first year period. Skin permeability data for selected model compounds using nude mouse skin as the barrier will be collected and improvement in the fitting regression of QSPRs based on either simple diffusion models or heterogeneous diffusion models with original permeability data and those normalized with respective to TEWL at the same level will be examined in the second year period. Genetic characteristics of enzymes responsible for formation of ceramide, main constituent in SC lipid, including β-GlcCer』ase and SMase and the mRNA expression of profilaggrin that is the precursor of filaggrin will be compared for each individual skin sample in third year period. In the final, the correlation between genetic polymorphism in responsible enzymes and TEWL will be constructed to express structural effect on skin permeability. Improvement in the fitting regression of QSPRs with normalized skin permeability is expected and prediction of skin permeability for each individual is anticipated.