• 計畫中文名稱	降血糖化合物 nstpbp168 及其衍生物之探討(II)		
• 計畫英文名稱	Discovery of Natural Anti-Diabetics: Hypoglycemic Compound Nstpbp168 and Its Derivatives (II)		
• 系統編號	PD9709-0052	• 研究性質	技術發展
• 計畫編號	NSC97-2323-B038-003	• 研究方式	學術補助
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• 執行機構	臺北醫學大學生藥學研究所		
• 年度	97 年	• 研究經費	3900 千元
• 研究領域	生物技術		
• 研究人員	徐鳳麟		
• 中文關鍵字	降血糖藥物；化合物 nstpbp168；化合物 nstpbp169；先導化合物；生技製藥國家型計畫		
• 英文關鍵字	Hypoglycemic drug； Nstpbp168； Nstpbp169； Lead compound； NSTP		
• 中文摘要	糖尿病目前雖有胰島素注射劑及口服降血糖藥物，但在臨床上之使用仍未達理想。然而，我國傳統醫學由於長期的實務亦累積了豐富的治療經驗，在民間有許多中藥或藥用植物被傳承使用，而且傳統用於抗糖尿病之植物，可能爲提供新口服降血糖藥物開發之有用資源或輔助治療劑。世界衛生組織亦建議對傳統治療糖尿病之方法應更深入之研究。過去幾年之研究中，本研究室於曾由中草藥陸續發現許多成分具有降血糖作用。因爲這些天然活性化合物，與目前臨床治療糖尿病之市售有機合成藥物，化學結構之骨架不同，其呈現之藥理作用機制亦相異，故其極具新穎性或特異性。最近，在生技製藥國家型計畫之支持下，發現 nstpbp168 等化合物，對於第一型糖尿病動物試驗呈現良好之降血糖生物活性，而且可藉由有機化學全合成之方式量產，極具有被發展爲藥物先導化合物之潛力。經計畫辦公室及財團法人生物技術開發中心之專利檢索、技術趨勢及市場評估，目前擬列入第三期生技製藥國家型計畫之重點發展項目。於第三期，本計畫將以糖尿病藥物開發爲目標，進行天然先導化合物之研究： 1. 標的化合物 nstpbp168 之合成、微生物及化學性結構修飾-- 探討其化學結構及藥效關係，進行有效成分最適當化學結構之評估，以期製備最理想的化合物作爲降血糖新藥開發之先導化合物（lead compound）。 2. 評估其他具降血糖作用天然化合物之開發與其於醫療上之應用價值。3. 委外臨床前試驗-- 評估將來進入臨床試驗之可行性。加強由 lead compound 推及至臨床前試驗階段，以期可創生技成功案例。其整體之研發成果將有助於國內製藥業技術層次之提高以及降血糖新藥開發相關經濟效益之提升。依照第一年度之初步研究結果發現： nstpbp168 及 nstpbp169 爲有效之 AMPK 活化物，於 C2C12 myotube，刺激增進 228 % AMPK phosphorylation 。 而 nstpbp169 以約兩倍之作用，促進 insulin-stimulated [3H]deoxyglucose 傳送入 C2C12 myotube。 因此，nstpbp 168 衍生物可活化 AMPK，導引 insulin 對糖類及脂肪酸之代謝之管控，而可望當作抗糖尿藥物。於未來，將繼續探討 nstpbp 168 對 AMPK 作		

	用及 於 C2C12 myotube，[3H]deoxyglucose uptake 之 SAR 關係。另外，藉由 2-bromo-1,3-xylene nstpbp 168 之合成，目前已達最後 aldehyde reduction 階段，本年度將探討 nstpbp 168 放大製程之最適當化。
• 英文摘要	The treatments for diabetes depend on either insulin injection or drugs attenuating the level of glucose in the blood. However, these approaches have drawbacks. Alternatively, traditional Chinese herbs might be good resources for the production of drugs to treat diabetes. Therefore, the WHO suggested a thorough investigation on diabetic mechanism. In the past few years, our laboratory discovers several ingredients from herbs that could decrease the level of glucose in the blood. The chemical structures of these natural ingredients are distinct from that of the synthetic ones. Recently, the compound nstbp168 was demonstrated to lower the level of glucose in the blood for the type I diabetics. It could be produced through organic chemical synthesis and has the potential to be the precursor of drugs. Evaluated by the Development Center for Biotechnology, nstpbp168 was one of the targets for further investigation. In third phase of this project, we will concentrate our efforts on the development of drugs for diabetics specifically the lead compound: 1. the relationship between the modification of the chemical structure of nstpbp168 and its efficacy. 2. the assessment and application of the development of natural compounds which lowers the level of glucose in blood. 3. the evaluation of preclinical trials by the third party. We are hoping the lead compounds could be included in the preclinical trials. The overall endeavors will stimulate the improvement of drug producers, in turn, enhance the economic benefits. Our preliminary data revealed that nstpbp168 analogue, nstpbp169 appeared to be a potent AMPK activator, which stimulated a 228% increment of AMPK phosphorylation in C2C12 myotube. In agreement, nstpbp169 enhanced insulin-stimulated [3H]deoxyglucose transport into C2C12 myotube by more than 2 folds. Taken together, these preliminary results suggest that nstpbp 168 derivatives may activate AMPK, which in turn regulate insulin regulation of carbohydrate and fatty acid metabolism, and can be considered as a potential anti-diabetic and antiobesity agent. In the future, we will continue to investigate the structure/activity relationship of nstpbp 168-stimulated AMPK activation and [3H]deoxyglucose uptake into C2C12 myotube. The synthesis of nstpbp 168 starts with 2-bromo-1,3-xylene has been conducted. Current progress has reached the final stage in which reduction of aldehyde will furnish the synthesis of nstpbp 168. Optimize sythesis for nstpbp 168 to scale up will be a target in this year.