THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

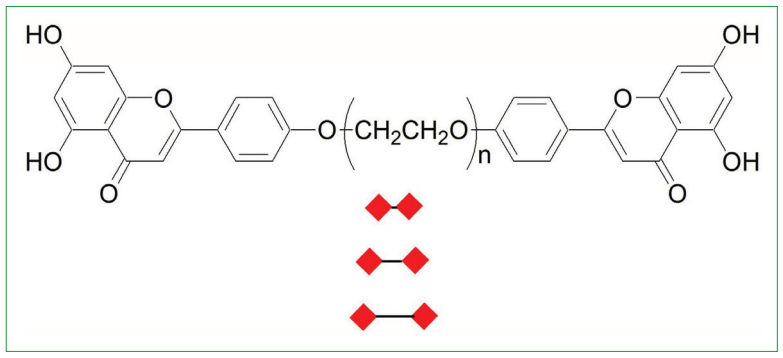
一種新型的腫瘤多藥耐藥逆轉劑黃酮類二聚物

Novel Flavonoid Dimers for Reversing Cancer Drug Resistance

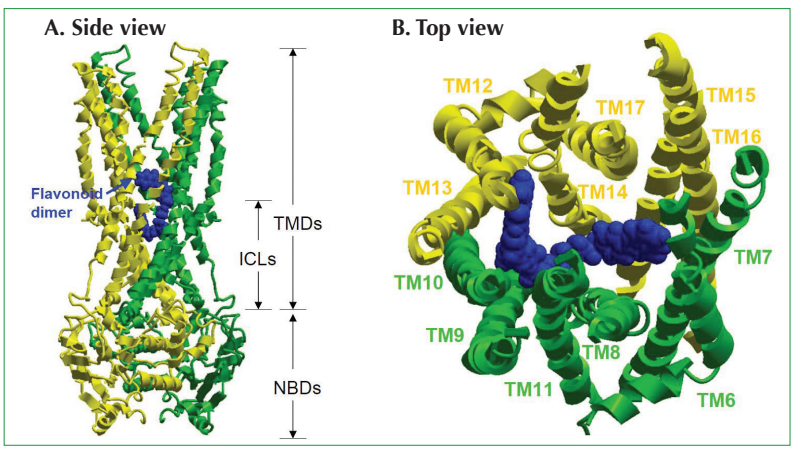
設計、合成及表徵高效黃酮類二聚物對由P-gp蛋白及乳腺癌耐藥蛋白(BCRP)介導的癌症多藥耐藥性的逆轉作用

Design, synthesis and characterization of highly potent flavonoid dimers in reversing P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP)-mediated cancer drug resistance

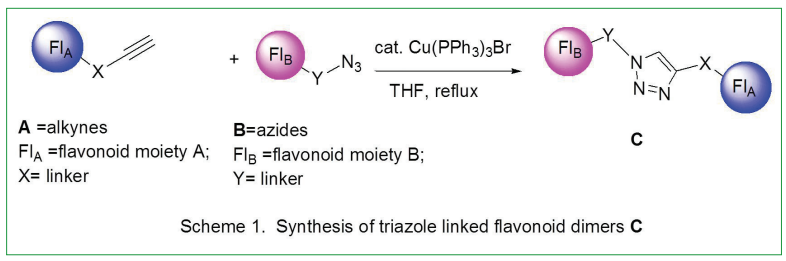
多藥耐藥性(MDR)是腫瘤化療的主要問題。我們已經設計并合成了可以逆轉MDR的一系列化學小分子。腫瘤細胞上的跨膜蛋白P-糖蛋白(P-gp)和乳腺癌耐藥蛋白(BCRP)能將細胞裏面的藥物排除從而減低化療的效果。我們已經設計、合成與表徵一類新型的天然黃酮二聚物。得益於其結構特點，這類藥物可以靶向識別P-gp和BCRP的二聚結構并特異性結合，從而抑制P-gp和BCRP的活性，達到有效逆轉腫瘤多藥耐藥性的目的(抑制BCRP的IC_{50}<1nM)。而且這類藥物的毒性非常低，治療指數高達$1X10^5$。



由不同長度橋接的芹黃素二聚物
Apigenin dimers of different linker lengths



分子模擬數據顯示黃酮二聚物結合在轉運蛋白的跨膜區并由此中斷藥物外排
Molecular modeling of P-gp binding to flavonoid dimers



Scheme 1. Synthesis of triazole linked flavonoid dimers **C**

合成由苯三唑橋接的黃酮二聚物C
Synthesis of triazole linked flavonoid dimers C

Multidrug resistance (MDR) in cancer is a major problem in chemotherapy. We have designed small molecules to reverse it. Membrane proteins P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) pump drugs out of cancer cells and reduce chemotherapy efficacy. We have designed, synthesized and characterized novel diet-derived flavonoid dimers which can target P-gp and BCRP's dimeric structure. Due to the unique design of dimeric in structure which can specifically bind to the pseudodimeric P-gp and BCRP, these flavonoid dimers can inhibit P-gp and BCRP, and reverse cancer drug resistance with very high potency (inhibiting BCRP at < 1 nM) and low toxicity (therapeutic index of $1x10^5$).

Principal Investigator

Dr Larry M. C. Chow, Prof. Tak-hang Chan

Department of Applied Biology and Chemical Technology

Contact Details

Institute for Entrepreneurship

Tel: (852) 3400 2929 Fax: (852) 2333 2410 Email: pdadmin@polyu.edu.hk

特色與優點

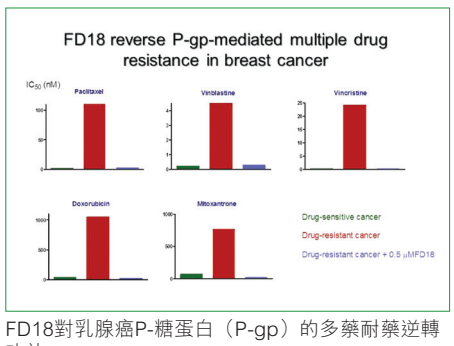
- 可以逆轉腫瘤的多藥耐藥性
- 對乳腺癌耐藥蛋白 (BCRP) 有很高的抑制活性 (EC_{50}＜1nM)
- 對正常的顯微組織細胞的毒性很低 (IC_{50}＞100 μM)
- 治療指數高達$1X10^5$
- 高通量合成黃酮類二聚物化合物庫有助於未來的快速活性篩選

應　用

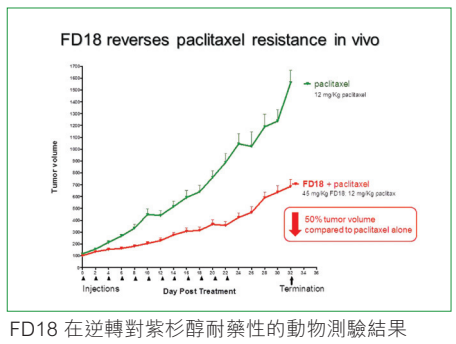
- 阻止耐藥腫瘤細胞將抗癌藥物排出
- 逆轉腫瘤的多藥耐藥性

獎　項

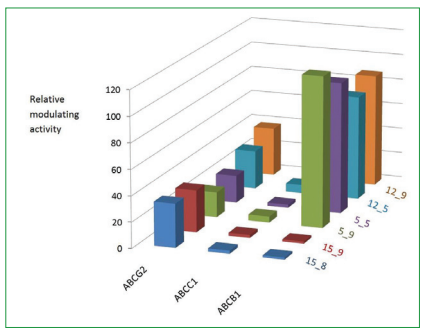
- 第41屆瑞士日內瓦國際發明展 - 金獎 (2013年4月)
- 羅馬尼亞代表團特別獎 (2013年4月)
- 第六屆中國國際發明展 - 銀獎 (2008年)



FD18對乳腺癌P-糖蛋白（P-gp）的多藥耐藥逆轉功效
FD18 reverse P-gp-mediated multiple drug resistance in breast cancer



FD18 在逆轉對紫杉醇耐藥性的動物測驗結果
FD18 reverses paclitaxel resistance in vivo



對乳腺癌耐藥蛋白（BCRP）和P-糖蛋白（P-gp）的專一性（單專一性 和雙專一性）
Specificity toward BCRP or P-gp (mono-specific & mono-specific)

Special Features and Advantages

- Reverse cancer resistance to multiple drugs
- High potency in inhibiting breast cancer resistance protein with effective concentration 50 (EC_{50}) lower than 1 nM
- Low toxicity towards normal fibroblast (IC_{50} > 100 μM)
- High therapeutic index of over 1×10^5
- High throughput synthesis of flavonoid dimer library for future activity screening

Applications

- Prevent drug efflux by drug-resistant cancer cells
- Reverse multidrug resistance in tumor

Awards

- Gold Medal – 41st International Exhibition of Inventions of Geneva, Switzerland (April 2013)
- Special Award from the Romanian Delegation (April 2013)
- Silver Award – 6th China International Invention Exhibition Awards (2008)

Access More info via mobile

Note: Subject to data charges by mobile operators

3_ABCT_01_0213