附件四、技術說明表

從依鈣抗生素衍伸之降依鈣抗生素

提案人： 朱忠瀚 教授

單　位： 國立臺灣大學　化學系/研究所

簡　歷： https://www.bioactivemolecules.org/john-chu

市場及需求：新型抗生素以對抗抗藥性細菌

技術摘要(含成果)：抗藥性細菌的流行預示著嚴重的醫療危機。鈣依賴性抗生素(CDA)於對抗此類細菌被寄予厚望，其原因是 CDA 的作用機制多與現有的抗生素不同。儘管如此，CDA 有著致命的弱點：它的「鈣依賴性」，沒有足夠的鈣它就沒有抑菌活性，此乃 CDA 發揮潛力的最大障礙。我們的研究工作以拉斯帕黴素(Laspartomycin C (LspC))的衍生化合物(**B1**)作為模型，可以減少甚至消除鈣依賴性。**B1** 是基於我們對 LspC 機制的理解而設計的，它不再依賴鈣，反而由苯硼酸(PBA)的所活化。**B1** 和 PBA 抑制細菌生長所需的劑量遠低於其造成細胞毒性的濃度。薄層色譜、質譜、核磁共振和互補分析均表明，**B1** 透過與細胞壁生物合成中間體五十五碳磷酸(undecaprenyl phosphate (C55P))的緊密結合來抑制細菌生長，此機制與 LspC 相同。**B1** 與 LspC 對於對抗多種革蘭氏陽性細菌一樣有效，包括抗甲氧西林金黃色葡萄球菌和耐萬古黴素腸球菌。

優勢：我們的新型抗生素 **B1** 透過與 C55P (細胞壁生物合成的必要中間體)緊密結合來抑制細菌生長，目前市面上沒有抗生素以這種方式發揮作用。CDA 需要足夠高的鈣濃度才能發揮作用，但人體內的碳濃度有時候不除以完全活化 CDA。由於 **B1** 並沒有「鈣依賴性」，因此它的潛在應用範圍比 CDA 具更廣泛。

競爭產品：目前市面上沒有以 C55P 為標的的抗生素。

專利現況：我們的分子設計是減低 CDA 的鈣依賴性的第一個成功例子，這項研究所產出的新抗生素(**B1**)不但維持了原抗生素的效力，且減少樂對鈣的依賴性。我們已經提交了美國專利臨時申請(Chu, C-H; Chiou, S-L. A reduced calcium-dependent antibiotic derived from a calcium dependent antibiotic. US provisional patent, application no. 63/605,584 (3 December 2023))。

以關鍵字搜尋相似的美國專利，顯示並無競爭對手（請見附檔）

聯絡方式(請不用填):
臺大產學合作總中心
Tel: 02-3366-9945, E-mail: ordiac@ntu.edu.tw

A Reduced Calcium-Dependent Antibiotic Derived from a Calcium-Dependent Antibiotic

PI： Professor CHUNG-HAN (JOHN) CHU
Department of Chemistry, National Taiwan University

Experience: https://www.bioactivemolecules.org/john-chu

Market Needs: Novel antibiotics to counter drug-resistant pathogenic bacteria

Our Technology: The prevalence of drug-resistant bacterial pathogens foreshadows a healthcare crisis. Calcium-dependent antibiotics (CDAs) are promising candidates to combat infectious diseases as many of them show modes of action orthogonal to widespread resistance mechanisms. The calcium dependence of CDAs is nonetheless one of the hurdles toward realizing their full potential. We showed, using a laspartomycin C (LspC) derived compound as a model (**B1**), that calcium dependence can be reduced or even eliminated. **B1** was designed based on a mechanistic understanding of LspC and no longer depends on calcium for its antibacterial activity; it is instead induced by the presence of phenylboronic acid (PBA). The required dose of **B1** and PBA for bacterial growth inhibition is much lower than their apparent cytotoxicity. In addition, thin-layer chromatography, mass spectrometry, nuclear magnetic resonance spectrometry, and complementation assays all showed that **B1** inhibits bacterial growth via the same mechanism as LspC, i.e., sequestering the cell wall biosynthetic intermediate undecaprenyl phosphate (C55P). **B1** is as potent and effective as LspC against several Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus.

Strength: Our new antibiotic **B1** inhibits bacterial growth by sequestering C55P, and no antibiotic currently on the market operates in this manner. CDAs need high enough calcium concentration to be active, and this requirement is not always met. Since **B1** shows no detectable calcium dependence, it may have broader applications than CDAs.

Competing Products: No antibiotics on the market targets C55P.

Intellectual Properties: Our design is the first example of successful CDA molecular engineering to yield a new antibiotic (**B1**) that maintained its potency but showed reduced-calcium-dependence. We have already filed a US provisional application (Chu, C-H; Chiou, S-L. A reduced calcium-dependent antibiotic derived from a calcium dependent antibiotic. US provisional patent, application no. 63/605,584 (3 December 2023)).

We conducted a preliminary prior search of US patents based on keywords. There are no apparent competition drugs and/or technologies.

Contact (do not need to fill out):
Center for Industry-Academia Collaboration, NTU
Tel: 02-3366-9945, E-mail: ordiac@ntu.edu.tw