出國報告(出國類別：開會)

國科會補助專題研究計畫項下出席國際學術會議心得報告

服務機關：臺北榮民總醫院病理檢驗部

姓名職稱：李麗花醫檢師

派赴國家：西班牙巴賽隆納

出國期間：113 年 4 月 27 日至 113 年 4 月 30 日

報告日期：113 年 5 月 16 日

摘要

2024 年的歐洲臨床微生物學和傳染病研討會（European Congress of Clinical Microbiology & Infectious Diseases, ECCMID）於 4 月 27 日至 30 日在西班牙巴塞羅那舉行，這是一個臨床微生物學和傳染病領域的重要國際會議，吸引來自全球的學術界和臨床專家參與。會議議程豐富多樣，涵蓋學術研究、臨床應用、產業發展和政策走向等諸多方面。新型抗生素 Cefiderocol 的應用是本次會議的一個重點。這種抗生素巧妙地利用了細菌對鐵的高需求，通過與鐵載體（siderophore）結合進入細菌體內。這種獨特的進入機制使得 Cefiderocol 在對抗傳統抗生素無效的多重耐藥性菌株方面展現了顯著效果，成功避開了細菌常見的抗藥性機制。我研究主題正是細菌的攝鐵系統，這次大會主題與我的研究方向高度契合。參加這次會議能讓我從中獲取靈感，為我未來研究指引方向。

關鍵字：歐洲臨床微生物學和傳染病研習； Stenotrophomonas maltophilia; Cefiderocol

目次

一、目的

1. 多歐洲臨床微生物學和傳染病研習（ECCMID）是一個匯集了來自全球各地專家的重要活動，旨在討論臨床微生物學和傳染病領域的最新研究進展和挑戰。2024 ECCMID 國際研討會是第 34 屆活動，吸引了來自學術界、臨床工作者和業界等多領域相關人員的參與，是歐洲最大的臨床微生物學和感染領域研究報告和討論大會。參加這次國際研討會的目的是參與 European Congress of Clinical Microbiology & Infectious Diseases (ECCMID)，並以海報形式發表自己的研究成果。除此之外，更重要的是在會上學習相關領域的新知識，了解新型抗生素的應用和臨床微生物學目前的最新趨勢和研究進展，為實驗室未來的研究提供可能的方向。其中，發表的海報題目為“FepA, FciA, and SbaA are the TonB-dependent transporters responsible for ferri-stenobactin uptake in Stenotrophomonas maltophilia KJ”

二、過程

1. 2024 年 4 月 27 日至 4 月 30 日，第 34 屆 ECCMID 國際研討會在西班牙巴賽隆納舉行。這是臨床微生物學和傳染病領域的重要國際盛會之一，吸引了來自世界各地的 16000 名與會者，涵蓋了所有相關學科(如下)。讓每位參與者都能獲得全面的教育和建立網絡的機會。
    1. Viral infection & disease [incl COVID-19]
    2. Bacterial infection& disease
    3. Bacterial susceptibility & resistance
    4. Diagnostic microbiology
    5. New antibacterial agents, PK/PD & Stewardship
    6. Fungal infection & disease
    7. Parasitic diseases & global health
    8. Healthcare-associated infections, infection prevention & control
    9. Experimental microbiology, microbial pathogenesis & biofilms
    10. Immunology, immune compromise& vaccinology
    11. Other
    12. Case reports and case series [n<10]

2. 本次研討會另安排九場Keynote Speech。均由國際知名學者、教授、醫師主講，包含Per Ljungman (Stockholm, Sweden), Jeanne Marrazzo (Bethesda, United States), Mihai Netea (Nijmegen, Netherlands), Kathryn Holt (London, United Kingdom), Nicola Segata (Trento, Italy), Sodiomon B. Sirima (Ouagadougou, Burkina Faso), Mervyn Singer (London, United Kingdom), Shiranee Sriskandan (London, United Kingdom), Margreet Vos (Rotterdam, Netherlands) 與會者獲益良多。抗藥性是一個重大問題，尤其是當細菌對抗生素產生抗藥性時，它對公共衛生帶來巨大挑戰。Prof. Kathryn Holt是一位專注於研究傳染病基因體學的計算生物學家。她指出，一旦細菌對抗生素產生抗藥性，治療感染就變得更加困難。這對人類健康和公共衛生造成直接影響，可能導致感染變得更加嚴重，甚至致命。例如，如果傷寒或肺炎克雷伯菌等病原體對抗生素產生抗藥性，將對醫療系統和公共衛生產生嚴重影響。因此，她的基因組監測技術能夠幫助我們及早發現細菌的抗藥性，進而制定更有效的公共衛生政策，控制抗生素的使用並預防感染，從而保護人類健康。
3. 此次會議，有多場 integrated symposia 與臨床微生物檢驗技術相關，包括 “Rapid genomic detection and characterization of pathogens using nanopore sequencing”、”Exploring molecular diagnostics for high burden infectious disease: assessing usability through performance testing”、及 “Removing barriers and improving pathways for more effective diagnostics. 參與會議後，對其他國家如何處理大量臨床檢體量的策略及效率的提升，有所了解。借助整合自動化機器及檢測平台，是未來的趨勢。
4. 在 4 月 30 日，有一場針對臨床血瓶培養應一次採檢或多次採檢的討論會。”Single vs. separate venipunctures to draw the same blood volume for diagnosing bacteraemia: pros and cons”. 在會議中，各有不同的演講者針對 一次採檢及多次採檢的優缺點，進行闡述，並說明自己的論點。收穫頗多。
5. 此次本人的海報展示排定於 4 月 30 日 12:00-16:00。於海報展示區，本人展示了自己的研究成果，同時也觀摩其他參展者的海報，這讓我對其他與會者的研究和創意有了更深入的了解。

三、與會心得

這次行程安排非常緊湊，但收穫頗豐。尤其是在臨床微生物學和傳染病領域，大家集中討論了抗生素抗藥性（AMR），這一直是全球的熱門話題。會議議程包括了新型抗生素的開發、抗生素濫用的控制措施以及抗藥性傳播機制等問題。值得一提的是，我們對新型抗生 Cefiderocol 在 Stenotrophomonas maltophilia 上的臨床應用格外感興趣。會議中，我的海報展示了鐵離子如何進入細菌細胞，以及細菌如何利用這些鐵離子。而 Cefiderocol 通過結合鐵載體，利用細菌對鐵的高需求，成功進入細菌體內，這使得 Cefiderocol 能夠高效穿透細菌外膜並發揮抗菌作用。這一新型抗生素的研究，正是我們實驗室目前的研究項目之一。參加這次會議，讓我對自己的研究方向和未來計劃有了更清晰的認識，也獲得了許多新的靈感和啟發，為未來的研究提供了有力的指引。

四、建議事項

建建議增加台灣學者參加國際研討會的資助名額。現在，大陸學者參加這樣的會議越來越多，他們通常以團隊形式參與，由教授帶領學生一起參加。這對於大陸在國際上的曝光度有所提升，同時也激勵了年輕學子，拓展了國際交流，對未來學術發展有著積極的影響。為了讓台灣學者也能參與其中，我們應該增加相對應的資助名額，以促進台灣學術界的國際交流和合作。

五、附錄

1. 大會議程手冊
2. 發表論文全文或摘要

FepA, FciA, and SbaA are the TonB-dependent transporters responsible for ferri-stenobactin uptake in *Stenotrophomonas maltophilia* KJ

Ting-Yu Yeh, Tsuey-Ching Yang, Li-Hua Li

Background

Stenotrophomonas maltophilia is ubiquitously distributed in the environment and is regarded as an opportunistic pathogen. Iron is an essential element for bacterial pathogens and plays significant roles in growth and developmental processes. In response to iron-depleted stress, *S. maltophilia* synthesizes the sole catecholate-type siderophore, stenobactin, for ferric iron acquisition. It has been reported that FepA, a TonB-dependent transporter (TBDT), is the sole outer membrane receptor for ferri-stenobactin uptake in *S. maltophilia* K279a strain. However, a *fepA* deletion mutant of

S. maltophilia KJ strain, a clinical isolate isolated in Taiwan, displayed comparable viability with wild-type KJ in iron-depleted conditions, suggesting that the involvement of additional TBDT for ferri-stenobactin uptake is not yet fully elucidated. In this study, we sought to uncover the additional TBDT for ferri-stenobactin uptake in KJ strain.

Materials

Transcriptome analysis of wild-type KJ with and without treatment of 2,2'dipyridyl, a ferrous iron chelator, was applied to reveal the putative TBDT candidates for ferri-stenobactin uptake. The involvement of these TBDTs in ferri-stenobactin uptake was assessed by in-frame deletion mutants construction and $FeCl_3$ utilization assay.

Results

Twelve TBDTs, whose expression were significantly upregulated in DIP-treated condition, were selected as candidates for the following study, including *hemA* (Smlt0795), *fciA* (Smlt1148), Smlt1233, *fepAsm* (Smlt1426), Smlt1762, *pacA* (Smlt2666), Smlt2714, *fecA* (Smlt2858), Smlt2937, Smlt3022, Smlt3898, and Smlt4135 (designated as SbaA based on the following study). The 12 single TBDT mutants exhibited comparable ability in $FeCl_3$ utilization in iron-depleted conditions, suggesting that the 12 TBDTs are not individually critical for ferri-stenobactin acquisition in *S. maltophilia*. However, KJΔFepAΔFciA (a *fepA* and *fciA* double mutant) and KJΔFepAΔSbaA (a *fepA* and *sbaA* double mutant) displayed compromised ability in $FeCl_3$ utilization in iron-depleted conditions. Furthermore, KJΔFepAΔFciAΔSbaA (a *fepA*, *fciA*, and *sbaA* triple mutant) almost lost the ability to utilize $FeCl_3$ as the sole iron source to support growth in iron-depleted conditions.

Conclusions

FepA, FciA, and SbaA are the TBDTs responsible for the ferri-stenobactin uptake in *S. maltophilia* KJ.

P3635

FepA, FciA, and SbaA are the TonB-dependent transporters responsible for ferri-stenobactin uptake in *Stenotrophomonas maltophilia* KJ

Ting Yu Yeh[1], Tsuey Ching Yang[1], Li Hua Li[2]
[1]National Yang Ming Chiao Tung University – Taipei City (Taiwan, Republic of China),
[2]Taipei Veterans General Hospital – Taipei City (Taiwan, Republic of China)

Introduction

Stenotrophomonas maltophilia is ubiquitously distributed in the environment and is regarded as an opportunistic pathogen. Iron is an essential element for bacterial pathogens and plays significant roles in growth and developmental processes. In response to iron-depleted stress, *S. maltophilia* synthesizes the sole catecholate-type siderophore, stenobactin, for ferric iron acquisition. It has been reported that FepA, a TonB-dependent transporter (TBDT), is the sole outer membrane receptor for ferri-stenobactin uptake in *S. maltophilia* K279a strain. However, a *fepA* deletion mutant of *S. maltophilia* KJ strain, a clinical isolate isolated in Taiwan, displayed comparable viability with wild-type KJ in iron-depleted conditions, suggesting that the involvement of additional TBDT for ferri-stenobactin uptake is not yet fully elucidated.

Flow chart

FepA is not the sole TBDT for ferri-stenobactin uptake in *S. maltophilia* KJ.

Transcriptome analysis
to reveal putative TBDT for ferri-stenobactin uptake

Double cross-over recombination
to construct specific gene deletion mutants

$FeCl_3$ utilization assay
to test the bacterial ability to utilize ferric iron under iron-depleted conditions

Transcriptome analysis

Table 1. Transcriptomic analysis of ferri-stenobactin acquisition-associated genes differentially expressed in *S. maltophilia* KJ with and without DIP treatment

Locus Smlt	TPM[a] Wild-type KJ	TPM[a] DIP-treated KJ	Fold change[b] None vs DIP-treated	Description
0795	4.38	1983.53	+452.54	HemA, hemin receptor
1144c	5.29	156.03	+29.51	TonB-dependent receptor
1148	42.58	919.30	+21.59	FciA, ferric citrate receptor
1426	33.63	3397.51	+101.02	FepA, enterobactin receptor
1762	2.01	194.32	+96.90	TonB-dependent receptor
2666	4.28	164.42	+38.41	PacA
2714	6.24	4544.96	+728.01	FecA-like
2858	3.29	127.36	+38.66	FecA, ferric citrate receptor
2937	1.73	539.48	+311.90	TonB-dependent receptor
3022	7.08	884.99	+125.07	Fiu, TonB-dependent receptor
3898	1.71	105.05	+61.52	TonB-dependent receptor
3999	4.51	1686.29	+373.66	TonB-dependent receptor
4135	22.95	2833.66	+123.45	TonB-dependent receptor

[a]TPM, transcript per kilobase million, represents gene expression levels.
[b]Positive fold changes represent the upregulation in response to DIP (2, 2'-dipyridyl) treatment.

$FeCl_3$ utilization assay

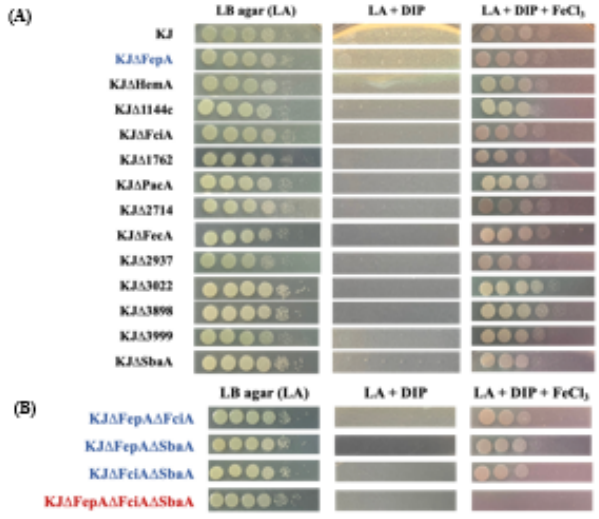
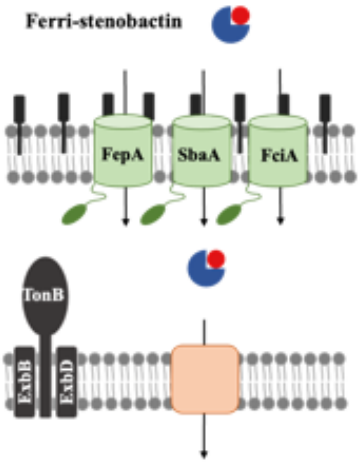


Figure 1. **The roles of *fepA*, *fciA*, and *sbaA* in ferric iron acquisition in an iron-depleted condition. (A) The ability of 12 TBDT mutants in $FeCl_3$ utilization in iron-depleted conditions. (B) The ability of multiple gene deletion mutants in $FeCl_3$ utilization in iron-depleted conditions.** The 2×10^6 CFU/μL logarithmic-phase bacterial cells tested were 10-fold serially diluted. A bacterial aliquot (5 μL) was spotted on LB agar plates as indicated. The concentrations of 2, 2'-dipridyl (DIP) and $FeCl_3$ used were 50 μg/mL and 35 μM, respectively. After a 24-h incubation at 37°C, bacterial growth was recorded.

Conclusion

FepA, FciA, and SbaA are the TBDTs responsible for the ferri-stenobactin uptake in *S. maltophilia* KJ.



3. 此次會議，本人投稿於Experimental microbiology, microbial pathogenesis &biofilms部分，進行poster發表。