

Fishing for NEW ANTIBIOTICS

By Emily Law
文：羅翠欣

Exciting news in the battle to maintain the efficacy of antibiotics has been announced by CityU scientists investigating natural antibacterial agents in fish blood.

The team has identified a super antimicrobial peptide that can kill over 30 common bacteria. The peptide might be used to develop new drugs that can be combined with other antibiotics for better medical effect.

The research team, which named the super antimicrobial peptide “BING” (Blocker of the INtermembrane Stress Response in Gram Negative Bacteria), was inspired by the initial hypothesis that fish must possess a very strong immune system.



“That’s why we started to study the peptides contained in the blood of fish,” said Dr Lam Yun-wah, who has been working on this project along with fellow associate professors Dr Doris Au Wai-ting and Dr Sun Hongyan in the Department of Chemistry.

“Antimicrobial peptides are an important part of a living organism’s defense against bacteria,” Dr Lam explained.

Antibiotics were regarded as a “magic bullet” when they first appeared in the last century. Their potential to significantly reduce the number of deaths from bacterial infection was a major breakthrough in medical science. However, due to misuse over the years, antibiotics are losing their punch. In addition, the last new antibiotic was launched 30 years ago, mainly because of exceptionally high development costs, low returns, and no solution yet for the misuse of antibiotics. So now we are hearing more about resistance to antibiotics and an increasing number of super bugs rather than the introduction of new drugs. In fact, the United Nations has declared that antimicrobial resistance is one of the greatest threats to human health today.

In response to the crisis, the CityU research team is working together on ways to mitigate this threat. The three researchers came together out of mutual interest in the topic and a strong desire to contribute to the mitigation of the antibiotics crisis and develop new drugs. Dr Lam is a biochemist, Dr Au focuses her research on marine organisms, while Dr Sun specialises in protein biochemistry.

Specifically Dr Lam and Dr Au investigate natural antibacterial agents among Hong Kong’s rich marine resources, Dr Lam said. Although fish have a very strong immune system, relevant research is relatively sparse. “Fish must have a very strong immune system judging by the amount of bacteria that they have to fight against in the oceans,” Dr Lam said.

Medaka, a small fish about 2 centimetres in length, is the focus of the study. Although each medaka has only 0.001ml of blood, antimicrobial

peptides are present. However, critical information concerning the number and types of peptides in medaka has not yet been classified, which is where the CityU team comes in.

Using a technique called mass spectrometry, Dr Lam and his team first of all identified 6,399 types of peptide molecules in the blood of medaka and then conducted bioinformatics analysis to profile the physical and chemical features common to antimicrobial peptides. These processes enabled the team to predict which of the identified peptides were likely to possess the strongest antibacterial properties. As a result, they have set up the world’s largest collection of peptides in fish blood, with information on 430 previously unknown medaka peptides.

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The next step was to see how well the new peptides could combat other bacteria. The team tested 53 of the 430 newly identified medaka peptides using two common bacteria, *Staphylococcus aureus* and *Edwardsiella tarda*. The results showed that eight of those 53 were particularly effective at neutralising these two common bacteria.

After further tests, the team identified one super antimicrobial peptide, BING, which can kill over 30 common bacteria, including *Mycobacterium tuberculosis* and most other pathogenic bacteria.

The research team also managed to boost BING’s stability and ability of killing germs by 10 times by modifying BING’s chemical structure.

“Now we are studying how the eight peptides successfully kill off the *Staphylococcus aureus* and *Edwardsiella tarda* bacteria, and use our insights to develop new drugs,” Dr Lam said. “BING may reduce the effect of antimicrobial resistance, making existing antibiotics resume their functions against bacteria.”

Dr Lam said the research team would continue to study BING with the aim of developing new antibiotics. They would also study the other 380 or so peptides in medaka’s blood, hoping to identify more super antimicrobial proteins that can help solve the “threat of antibiotics resistance”. ◆

海中尋寶：研發新抗生素

城大科學家為應對抗生素抗藥性危機，致力研究魚血中的天然抗菌物質，最近有重大突破。

研究團隊在魚血中發現一種超級抗菌蛋白，能消滅30多種常見細菌。這項發現可結合現有藥物，製成更有效的新型抗生素。

團隊認為魚類擁有極強的免疫系統，便着手研究魚血的抗菌秘密。他們發現新的抗菌蛋白，將其命名為「冰」（英語縮寫為BING，全寫為Blocker of the INtermembrane Stress Response in Gram Negative Bacteria〔革蘭氏陰性菌內膜間擠壓反應的抑制劑〕）。

化學系副教授林潤華博士說：「我們相信魚擁有極強的免疫力，於是便開展魚血蛋白的研究。」共同參與研究的還有系內另外兩位副教授：歐慧婷博士和孫紅燕博士。

林博士解釋：「抗菌蛋白是生物用作對抗細菌的重要元素。」

抗生素於上世紀面世，為醫學的重大突破，曾以其能夠消滅或防止細菌生長，大大減少因細菌感染致死的個案而一度被稱為「神奇藥物」。然而多年來因濫用抗生素引致的抗藥性問題，令其藥效減退。上一次新抗生素面世已是30年前的事，除了因研藥成本高、回報低，也因為抗生素濫用的情況仍未受控。

抗藥性問題愈見嚴重，超級惡菌也愈來愈多，聯合國更指抗生素抗藥性是「現代醫學最大威脅」。有感於危機愈見嚴重，城大研究人員合作設法予以應對，林博士是生物化學家，而歐博士專研海洋生物，孫博士則為蛋白生物化學專家。三人均對這項課題甚感

興趣，並且希望能為解決抗生素抗藥性危機和研製新藥出一分力。

林博士指出，他和歐博士均認為香港擁有豐富的海洋資源，希望從中找出天然的抗菌藥。魚類天生擁有極強的免疫系統，但相關的研究和文獻卻不多。

林博士說：「魚類要抵抗海水中的大量細菌，因此必須擁有極強的免疫系統。」

團隊以鯖鱒魚為研究對象。這種魚體型細小，長度約兩厘米，全身血液只有千分之一

毫升，當中含有抗菌蛋白。不過，科學界尚未發現鯖鱒魚的抗菌蛋白種類和數量的關鍵資訊，因此城大團隊以此為研究重心。

林博士及其團隊首先利用質譜技術，發現鯖鱒魚血液內有6,399種蛋白分子，接着將這些蛋白逐一與其他動物體內已知的抗菌蛋白進行生物資訊分析，找出在物理和化學方面的共同特點，由此推斷哪些蛋白含有最強大的抗菌特性。他們確認了鯖鱒魚未為人知的430種抗菌蛋白，建立了現時世上最大的魚血抗菌蛋白資料庫。





團隊接下來要測試這些蛋白的抗菌能力。他們利用金黃葡萄球菌和愛德華氏菌這兩種常見細菌，對最新確認的430種鱈魚抗菌蛋白中的53種進行測試，發現有8種能有效對抗上述兩種細菌。

經過多番測試後，研究團隊終於發現超級抗菌蛋白「冰」，能殺死30多種常見細菌，包括肺癆菌及大部分致病細菌。團隊進一步

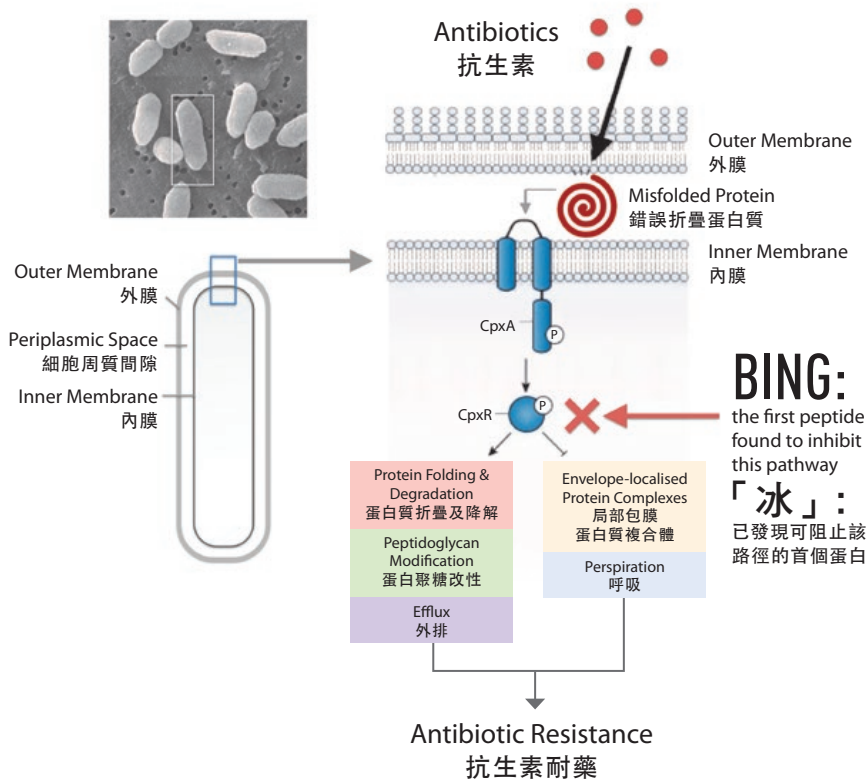
改變其化學結構，將其穩定性和殺菌能力提高達10倍。

林博士說：「我們現正仔細研究這8種抗菌蛋白消滅金黃葡萄球菌和愛德華氏菌的原理，希望有助日後研製新的藥物。『冰』也許能夠減低細菌的抗藥性，令現有的抗生素對細菌重新發揮作用。」

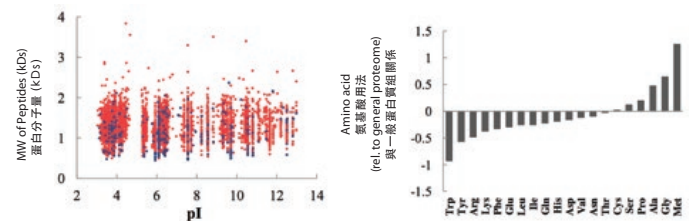
林博士指出，研究團隊會繼續研究「冰」，希望研發出新的抗生素。他們亦會繼續測試鱈魚血中其餘約380種抗菌蛋白，期望能找出更多超級抗菌蛋白，解除抗生素抗藥性的威脅。◆

「抗藥性問題愈見嚴重，超級惡菌也愈來愈多，聯合國更指抗生素抗藥性是『現代醫學最大威脅』。」

Why is BING Special? 「冰」有何特別之處？



Overview of the characteristics of the 6399 fish peptides identified
已確認的6399種魚蛋白的特性概覽



BING kills a diversity of bacterial species including drug resistant strains
「冰」能消滅多種細菌種類，包括耐藥菌株

