Research Assessment Exercise 2020
Impact Case Study

University: The University of Hong Kong
Unit of Assessment (UoA): 9 - Chemistry

Title of case study: (#2)
The impact of novel antibacterial agents on human health and wellbeing

(1) Summary of the impact

Antimicrobial resistance poses huge threat to human health globally. HKU Chemistry researchers addressed this problem by developing innovative technologies to synthesise antibacterial peptides leading to new antibiotics, establishing therapeutic metal compounds targeting antibiotic resistance, and demonstrating the antibacterial action mechanisms of nano-silver and colloidal bismuth subcitrate (CBS). Three new antibiotics are currently licensed and undergoing pre-clinical studies. Our work on CBS provided scientific foundation for bismuth anti-ulcer drugs and that on nano-silver was used in health and environmental risk assessments informing regulation by European Commission's Scientific Committee on Emerging and Newly Identified Health Risks as it implements legislation on nanomaterials.

(2) Underpinning research

Researchers in HKU Chemistry, namely Che (joined HKU in 1983, currently Chair Professor), Sun (joined HKU in 1998, currently Chair Professor), and Li (joined HKU in 2009, currently Professor) have made outstanding advances in antimicrobial research developing new compounds, new synthesis techniques, and improved understanding of bacterial toxicity mechanisms.

The chemoselective STL(Serine/Threonine-Ligation)-mediated peptide cyclization invented by Prof. Li (2013) is able to overcome the challenge of synthesizing antimicrobial cyclic peptides that arise from entropy-disfavoured cyclization.[3.1] STL induces the N-terminal S/T residue of one peptide to react with the C-terminal peptidyl salicylaldehyde ester of another peptide fragment, to produce an N,O-benzylidene acetal intermediate. Subsequent acidolysis of the acetal creates a natural peptide bond. STL has also been applied intra-molecularly to mediate peptide cyclization in a head-to-tail fashion, between an N-terminal S/T and the C-terminal salicylaldehyde ester of an unprotected linear precursor. It has been successfully applied by Li's team to synthesize various proteins and cyclic peptide antibiotics including daptomycin[3.1] and teixobactin,[3.2] attracting pharmaceutical licensing. Li received Hong Kong Croucher Senior Research Fellowship (2017), WuXi PharmaTech Award (2013), the CAPA Distinguished Faculty Award (2016), a silver medal at Invention Geneva (2018), and the Rao Makineni Lectureship from the American Peptide Society (2019) for the innovative STL technology. In addition, the STL technology was featured by Faculty 1000 Prime and selected as the Cutting Edge of Chemistry by Thompson Reuters.[5.4]

Prof. Sun's research team has made innovative achievements on Colloidal Bismuth Subcitrate (CBS) for treating *Helicobacter pylori*-associated gastrointestinal ulcers. His team has determined the structure of CBS (De-Nol®, Lizhidele®) under physiologically relevant conditions and deciphered unique assembly using bismuth citrate dinuclear unit to a three-dimensional polymer to form a "protective coating" on the ulcer craters (2003). [3.3] Sun's team explored the "resistance-proof" ability of CBS for the treatment of superbug infections (2018). They discovered that CBS could "tame" New Delhi Metallo-β-lactamase-1 (NDM-1), the resistant determinant of the lethal *Carbapenem-resistant Enterobacteriaceae* (CRE) superbug. The therapy comprising CBS and Carbapenem

significantly lowered antibiotic resistance when compared to Carbapenem monotherapy[3.4] (2018). Sun's research has received the WuXi AppTec Award (2016) and the UC Berkeley Muetterties Lectureship (2017).

Prof. Che's group has made original discoveries about the physiochemical and biological properties of silver nanoparticles (nano-silver), which are powerful antibacterial agents widely used as biocidal materials. His group demonstrated for the first time that nano-silver at nanomolar particle concentrations trigger rapid inactivation of the bacteria via a membrane de-energization mechanism (2006) [3.5] and establish a model of oxidation-triggered release of chemisorbed Ag^+.[5.10] Furthermore, collaborative work with clinical surgeon demonstrated that topical dressing using in-house synthesized nano-silver can promote wound healing by modulating local and systemic inflammatory response following burn injury by cytokine modulation, and also has greater anti-inflammatory properties than standard silver sulfadiazine dressing. [3.6] Our work highlighted the environmental and health impacts of emerging nanomaterials in general and silver nanomaterials in particular.[5.10] Che's research on metal therapeutics received the Centenary Prize of Royal Society of Chemistry (2013) and the Davison Lectureship at MIT (2014).

(3) References to the research

3.1 H. Y. Lam, Y. F. Zhang, H. Liu, J. C. Xu, C. T. Wong, C. Xu, **X. C. Li**, "Total synthesis of daptomycin by cyclization via a chemoselective serine ligation". *J. Am. Chem. Soc.*, 2013, 135, 6272-6279. DOI: 10.1021/ja4012468 (Times Cited :57)

3.2 K. Jin, I. H. Sam, K. H. L. Po, D. Lin, E. H. G. Zadeh, S. Chen, Y. Yuan, **X. C. Li**, "Total synthesis of teixobactin". *Nature Commun.*, 2016, 7, 12394. DOI: 10.1038/ncomms12394 (Times cited: 47)

3.3 W. Li, L. Jin, N. Zhu, X. Hou, F. Deng, **H. Sun**, Structure of colloidal bismuth subcitrate (CBS) in dilute HCl: unique assembly of bismuth citrate dinuclear units ($[Bi(cit)_2Bi]^{2-}$). *J. Am. Chem. Soc.*, 2003, 12408-12409. DOI: 10.1021/ja037019x (Times cited: 55)

3.4 R. Wang, T. P. Lai, P. Gao, H. Zhang, P. K. Ho, P. C. Y. Woo, G. Ma, R. Y. T. Kao, H. Li, **H. Sun**, "Bismuth antimicrobial drugs serve as broad-spectrum metallo-β-lactamase inhibitors". *Nature Commun.*, 2018, 9, 439. DOI: 10.1038/s41467-018-02828-6 (Times cited: 20)

3.5 C. N. Lok, C. M. Ho, R. Chen, Q. Y. He, W. Y. Yu, H. Sun, P. K. Tam, J. F. Chiu, **C. M. Che**, "Proteomic analysis of the mode of antibacterial action of silver nanoparticles". *J. Proteome Res.*, 2006, 5, 916–924. DOI: 10.1021/pr0504079 (Times cited: 874, ISI record)

3.6 J. Tian, **K.K.Y. Wong**, C.M. Ho, C.N. Lok, W.Y. Yu, **C.M. Che**, J.F. Chiu, P.K. Tam, "Topical delivery of silver nanoparticles promotes wound healing". *ChemMedChem*, 2007, 2, 129-136. DOI: 10.1002/cmdc.200600171 (Times cited: 431, ISI record)

(4) Details of the impact

The impact of Che's research on the widely used nano-silver is evidenced by 10 research articles having citations of a total of 2,900 (two having citations >800 [3.5, 5.10] and one >400 [3.6]) in journals of diverse disciplines including nanotechnology, biomaterials, toxicology and environmental science. [5.10] Nano-silver is widely used for its antibacterial properties. The European Union considers that nano-particles should fall under the remit of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) managed by European Chemicals Agency. Che's work provides the key sources for the oxidation chemistry of nano-silver and the mode of its antibacterial action referred to in reports produced for this exercise [5.8] and others. For example, in the final opinion report (2014) "Nano-silver: safety, health, and environmental effects, and role in antimicrobial resistance" formulated by the Scientific Committee on Emerging and Newly Identified Health Risks, European Commission (SCENIHR, EC),[5.8] Che's findings on the antibacterial properties of nano-silver[3.5, 5.10] were repeatedly cited to support the Committee's opinion that "nano-silver acts as a source of

bioavailable silver, and it cannot be excluded that nano-silver represents a new source of environmental exposure to silver that delivers silver to organisms in a way that is not effective for other forms of silver", and "additional effects caused by widespread and long-term use of silver nanoparticles cannot be ruled out".[5.8] Thus, Che's research has informed public agencies of the complexity of nano-silver properties in regulatory considerations on the environmental and health impacts of nanomaterials. [5.8, 5.10]

In addition to informing governments, the antimicrobial materials developed by Li, Sun and Che have attracted considerable attention from industry, and several compounds are licensed and are currently undergoing preclinical studies:

Daptomycin is an antimicrobial peptide for the treatment of life-threatening infections. The main daptomycin developer – Cubist Pharmaceuticals – has been striving to develop more potent analogues but success has been limited. Li used his STL technology [3.1-3.2] to synthesize a daptomycin-based analogue (HY2371) as a next-generation antibiotic with efficacy against both daptomycin-susceptible and -resistant bacteria.[5.3–5.5] The patent for HY2371 has been licensed to Mudanjiang Youbo Pharmaceutical Co. Ltd for HKD 1m (2017), together with milestone payments and royalties (license agreement in attachment).[5.2] The licensee will develop HY2371, spending no less than HKD25 million on completing pre-clinical studies, which will start in 2020. They will make an IND application filing with the China Food and Drug Administration (CFDA) by 2021 and start the clinical trials in 2020. Using the same STL technique, Li also developed a small molecule (ALS-2) which targets bacterial virulence for the treatment of Methicillin-resistant Staphylococcus aureus (MRSA) infection. This was licensed to Acticule in 2019 for preclinical studies.

Sun's team has resolved the polymeric structures of CBS,[3.3] revealing unique assembly of the drug in the stomach, which has laid the crucial scientific foundation for Livzon Pharmaceutical Group to promote its bismuth antibacterial drugs, Lizhudele®.[5.6] In 2017, Livzon provided HKD 4.01m for evaluating the preclinical properties of bismuth compounds. CRE is a dangerous superbug on the World Health Organization's priority list for new antibiotics. Prof. Sun discovered that combined use of CBS and Carbapenem (both are FDA-approved drugs and demonstrate good safety) is an effective and economical approach to combat against CRE infection.[3.3-3.4, 5.7]

Che's research on nano-silver provides the scientific basis for the design of new antibacterial silver materials such as that by Anson Nanobiotechnology Co. Ltd. specializing in nano-silver medical products. [5.9] Che, in collaboration with, Dr. K. K. Y. Wong, a clinical surgeon in HKU, demonstrated that wound dressing employing Anson's or Che's in-house nano-silver preparation promoted wound healing through cytokine modulations and showed greater anti-inflammatory properties than standard silver sulfadiazine dressing.[3.6] These findings provide a new direction for achieving scar-less wound healing in clinical practice and were recognized in research studies of pharmaceutical companies on developing silver-based biomaterials for surgical wound management [5.10] as exemplified by the letter of Anson Nanobiotechnology.[5.9] Che's work has extended to potential product development: silver thiourea complexes have been granted a patent for anti-inflammatory applications. The patent is licensed to Sichuan Knowledge Express Institute for Innovative Technologies (KEIIT). KEIIT has further collaborated with Che and an agreement to establish "Aglaia-KEIIT Laboratory for Drug Discovery and Development" at HKU with an HKD30 million endowment fund was signed (2018).

Both Li's invention of STL Technology and Sun's discovery of antibacterial bismuth have been reported widely by mass media as game-changing technology in the field.[5.3–5.7] Therefore, HKU's work in this area has impacted the general public, industry, and governments both locally and globally.

(5) Sources to corroborate the impact - in attached files

5.1 Grants
5.2 Patents and License
5.3 News and Press Release

Representative News on Prof. Li's research impact of antibiotics synthesis (Full list in 5.3)

5.4 Cutting Edge of Chemistry from Thompson Reuters (2013).
https://www.hku.hk/press/news_detail_17235.html

5.5 Hong Kong Chemists Synthesize Promising Antibiotic Teixobactin (2015)
http://www.asianscientist.com/2016/09/pharma/hku-teixobactin-synthesis-antibiotics/

5.6 Endorsement letter and product leaflet from a Pharmaceutical company on the uses of Prof. Hongzhe Sun's research on bismuth antibacterial compounds.
(孙红哲教授的研究为丽珠得乐(柠檬酸铋钾)临床的使用奠定了很好的科学基础)
(Sun's research laid the scientific foundation of clinical application of bismuth subcitrate developed by Livzon Pharmaceutical Group (Zhuhai) (http://www.gyx66.com/English))

5.7 Representative news on Prof. Sun's research impact of bismuth compounds (Full list in 5.3)
Medical chemists discover peptic ulcer treatment metallodrug effective in "taming" superbugs (2018)
https://www.sciencedaily.com/releases/2018/04/180420122844.htm

5.8 Representative opinion reports citing Prof. Che's works on nano-silver (Full list in 5.3)
Opinion on Nano-silver: safety, health and environmental effects and role in antimicrobial resistance.
Scientific Committee on Emerging and Newly Identified Health Risks, European Commission (2014)
https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_039.pdf

5.9 Endorsement letter from a Nanobiotechnology R&D and Sales company on the uses of Prof. Che's research on nano-silver health care products
(安信纳米生物科技（珠海）有限公司根據香港大学支志明教授及其团队的研究成果及指导帮助已成为国际纳米银医疗产品产业化及医学临床应用的领先企业)
(Anson Nanobiotechnology (Zhuhai) Co. Ltd. (http://www.ansonnano.cn) relies on the research and guidance of Prof. Chi-Ming Che and his team in the University of Hong Kong to become a leading company in the international nano-silver medical product industrialization and medical applications)

5.10 Prof. Che's works on nano-silver and citing papers from non-academic disciplines
(Excel Table)