

Research Assessment Exercise 2020

Impact Case Study

University: The University of Hong Kong (HKU)

Unit of Assessment (UoA): 6 - Chinese Medicine

Title of case study: Modernization of Chinese medicine production

(1) Summary of the impact

Chinese medicine (CM) contains abundant amount of therapeutic wisdom that has been tested over millennia. Collaboration between Hong Kong University researchers and Purapharm International (H.K.) Ltd applied state-of-the-art technologies to delineate its mechanisms, modify factory production methods and established a biological quality control standard. We applied a patented protocol to enhance the efficacy of a traditional anti-flu formula by increasing the amount of our patented molecule. We invented a new CM product for chronic diseases undergoing a multi-centre clinical trial, leading to establishment of a spin-off research laboratory by Purapharm. Our approaches set a paradigm in the modernization process in scientific utilisation of CM.

(2) Underpinning research

Key Hong Kong University (HKU) Researchers:

Professor Godfrey Chan (Director of Molecular Chinese Medicine (MCM) Laboratory, 2014-present)

Late Professor Allan Lau (Director of MCM Laboratory, 2006-2014)

Dr. James Li (Scientific Officer 2006-present)

Dr Cindy Yang (Research Officer 2006-2019)

Mr Stanley Chik (Senior Technical Officer 2006-present)

In the Chinese community, CM is popular for treating chronic diseases. For example, Prof. Godfrey Chan and his colleagues showed that more than 42% of pediatric cancer patients took herbal medicine when they received conventional chemotherapy (3.1). This demonstrated that people in Hong Kong believed CM together with western medicine could help to fight against certain types of diseases. Although we believed in that, we need a scientific explanation on the drug mechanisms and the interaction with other drugs. In light of this, Prof. Allan Lau established the MCM Laboratory to understand the use of CM. Our success in delineating the molecular mechanisms of infectious diseases and chronic immune disorders lead us to understand the drug mechanisms and to identify the potential drug targets. Subsequently, we established the collaboration with different industries for the new development of CM on these diseases. Our scientific models on studying CM with industries attracted government bodies and benefactors to support our translational research (3.2-3.6).

Our first CM collaboration with Purapharm was to develop health supplement “Immuzac” which contained polysaccharides from Lingzhi (*Ganoderma lucidum*) and Yunzhi (*Coriolus Versicolor*) for strengthening the immune functions against viral and contagious pathogenic infection. It has been distributed freely to medical professionals at Tung Wah Group of Hospitals during the influenza pandemic. We also examined the effect of Yunzhi and patented the extraction protocol for future production (3.4). This project demonstrated that our research skills in establishing the production protocol and identifying the novel treatment targets could help an industry partner to develop their product in a scientific way, i.e. with laboratory experiment results. Consequently we started a program to study the anti-inflammatory activity of Black Cohosh (*Cimicifuga racemosa*). The use of single herb for treatment is not common in CM, and incompatible with CM theory. Using a novel bio-guided screening platform, we identified the active molecules from a single herb for the treatment of rheumatoid arthritis. Our findings indicated Sheng Ma has anti-inflammatory effects via the suppression of proinflammatory cytokines production (3.5). By using this method, we identified specific species of *Cimicifuga* in China containing high concentration of this patented molecule for

the production of product that sold in Canada in 2017 (3.5, D).

As seasonal influenza affects the society annually, and emergence of resistant strains of influenza virus is highly possible, a new treatment is needed which can both effectively resolve the symptoms and eliminate the viruses. HKU researchers investigated the anti-influenza effect of a CM formula Yin Qiao San, which is one of the most profitable CM products in Purapharm. Therefore, after we established the chemical composition of this formula, we identified a molecule that can suppress the influenza virus replication (3.6). This molecule could stop the budding of the new virion from the infected cell. As the mechanism of action of this molecule is different from the current anti-influenza drug, it can be used singly or in combination with the existing drugs, and delay the development of drug-resistant virus. We also demonstrated Yin Qiao San could affect the immune system during the influenza infection. Its effects were confirmed by *in vitro* and *in vivo* animal models (3.6). At last, we modified the anti-influenza formula to contain high concentration of active molecule so that can both boost the immune system and suppress the virus production (3.6).

(3) References to the research

- 3.1 Chan WK, Cheung CC, Law HK, Lau YL, Chan GC. Ganoderma lucidum polysaccharides can induce human monocytic leukemia cells into dendritic cells with immuno-stimulatory function. *J Hematol Oncol*. 2008 Jul 21;1:9. DOI: [10.1186/1756-8722-1-9](https://doi.org/10.1186/1756-8722-1-9)
- 3.2 Lee DC, Yang CL, Chik SC, Li JC, Rong JH, Chan GC, Lau AS. Bioactivity-guided identification and cell signaling technology to delineate the immunomodulatory effects of Panax ginseng on human promonocytic U937 cells. *J Transl Med*. 2009 May 14;7:34. DOI: [10.1186/1479-5876-7-34](https://doi.org/10.1186/1479-5876-7-34)
- 3.3 An J, Lee DC, Law AH, Yang CL, Poon LL, Lau AS, Jones SJ. A novel small-molecule inhibitor of the avian influenza H5N1 virus determined through computational screening against the neuraminidase. *J Med Chem*. 2009 Apr 14;52(9):2667-72. DOI: [10.1021/jm800455g](https://doi.org/10.1021/jm800455g)
- 3.4 Coriolus Versicolor Extracts, Methods of Preparation and Uses Thereof. Authors from HKU and Type: PI: Allan SY Lau. Co-Is: Stanley CC Chik, Anna HY Law and Cindy LH Yang. *Japan patent* No. 5959523. Date: 2-8- 2016
- 3.5 Yang CL, Chik SC, Li JC, Cheung BK, Lau AS. Identification of the bioactive constituent and its mechanisms of action in mediating the anti-inflammatory effects of black cohosh and related Cimicifuga species on human primary blood macrophages. *J Med Chem*. 2009 Oct 12;52(21):6707-15. DOI: [10.1021/jm9006164](https://doi.org/10.1021/jm9006164)
- 3.6 Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit against influenza A virus through reduction of viral M1 protein. *J Ethnopharmacol*. 2017 Jul 14;209:236-247. DOI: [10.1016/j.jep.2017.07.015](https://doi.org/10.1016/j.jep.2017.07.015)

Key grants to MCM laboratory

Research contracts from industries

- University Research of Immuzac[®]'s main ingredient PuB (Yunzhi) on its effect on Human Blood Macrophage, 2006 PI: Allan Lau
- Innovation and Technology Fund – “Chemical and Biological Characterization of Medicinal Herbs” R&D Cash Rebate Scheme (CRP/043/14) Apr 1, 2014 – Mar 31, 2017, Applicant: Purapharm
- Innovation and Technology Fund – “Antiviral Decoction - Yinqiaosan: its mechanism of action and clinical efficacy”, #ITS/088/12FX, approved in 2013, PI: Allan Lau, Sponsor: Purapharm, Innovation and Technology Fund

Donations for the R&D activities in MCM Lab

- Chung Kue Shuen Research Fund for Molecular Chinese Medicine Laboratory, 2011, PI: Prof. Allan Lau and Dr. James Li, HK\$ 2 million

- Ho Yuk Ching (Ching Ping) Research Fund for Molecular Chinese Medicine, 2013, Laboratory, PI: Prof. Allan Lau and Dr. James Li, HK\$ 2 million

Research grants from RGC/GRF

- HIV dysregulation of the toll-like receptor system, HKU 7594/06M, 2006-2008 PI: Allan Lau
- HIV suppression of the interferon-gamma signaling pathway, HKU 768507M, 2007-2011 PI: Allan Lau
- Mycobacteria Evasion of Immunity: a Potential Role for IL-10, HKU 768509M, 2009-2012 PI: Allan Lau
- A role for oncogenes in the regulation of immune response to Mycobacterial infection, HKU 769810M 2010-2014 PI: James Li

Research grants from RFCID/HMRF

PI: Allan Lau

- Immunotherapy of mycobacterial infections: a cell and molecular model, #01030512, 2005-2007
- Interferon dysregulation and virus-induced cell death in avian influenza H5N1 virus infections, #05050112, 2006-2008,
- HIV as a cofactor of mycobacterial infections, #06060612, 2007-2009,
- Factors affecting mycobacteria evasion of immunity, #09080512, 2009-2011
- Cellular response to influenza virus infection, #09080832, 2009-2011

PI: James Li

- Enhancement of innate immunity to the pathogen infection: anti-mycobacterial effect of IL-17, #09080542, 2009-2011
- Cellular Oncogene Dysregulation of Chemokine and Cytokine Expression in Influenza Virus Infection, #11100802, 2011-13
- A role for proto-oncogene c-Myc in antibiotics-sensitive and -resistant bacteria-induced immune responses: a potential building block for new treatment development, #11100762, 2011-13
- The role for c-Myc in anti-mycobacterial responses: from bacterial killing to T cell activation, #13121172, 2014-2016

(4) Details of the impact

Impacts include: commercial, health and welfare

Main beneficiaries include: industry, patients and the public

Our instrumental commercial impact, based on our collaboration with Purapharm is based a shared goal in CM research “innovation and pioneering research in the modernization of traditional medicine”. Our laboratory provided expertise to Purapharm in determining their R&D activities, including training technical staff, providing them the model for quality control, and giving advice for them to develop their R&D facilities and clinical studies. HKU and Purapharm agreed the intellectual properties arouse from the collaboration work was co-owned, and Purapharm had the exclusive right to use these patents. This has tightened our relationship, and equipped Purapharm in developing new CM products and acquire funding from HKSAR Government (CRP/043/14, ITS/088/12FX) for their R&D works and [A]. Currently, Prof. Paul Vanhoutte (HKU), is the Chairman of the Scientific Advisory Committee of Purapharm. Our collaboration has enriched the Purapharm’s R&D capability, provided them solid scientific evidence of their products, and consolidated their role in Chinese medicine industries, including listed on [Hong Kong Stock Exchange in 2015](#) [A]. One of our staff joined the R&D company spin-off from Purapharm to continue the CM research in September 2019 [A].

Rheumatoid Arthritis (RA) is a chronic inflammatory disorder that causes permanent disability and mortality. The current medication including nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs and expensive biologics. However, the long-term effectiveness of

these drugs has been far from satisfactory. Our findings indicated Sheng Ma had anti-inflammatory effect and control the arthritis progression (3.5). The patents related were approved in 2015 [B]. Following the patent, Purapharm initiated a clinical trial on methotrexate unresponsive RA patients [A]. This first single herb trial on RA started in 2019 at Toronto and Sydney.

Standardization of production protocol was also important for CM development. Using Sheng Ma study as an example, we improved the manufacturing protocol for Purapharm to produce granules with high concentration of active compounds [C]. At 2017, the final version of granules was produced and examined by different *in vitro* and *in vivo* assays to confirm the anti-arthritis activities. The Sheng Ma product was registered in Canada for sale [D]. The development of functional quality control procedure helps the industry to prepare a more consistent product. In addition to the quality control, we also performed acute toxicity test, pharmacokinetic study and drug interaction studies which are required for the clinical trial application and products registration.

In addition to RA, seasonal influenza is another major disease burden in Hong Kong for decades. As the major treatment for seasonal influenza is mainly on symptomatic relief, many Chinese in Hong Kong prefer to have CM. Yin Quao San is one of the most popular anti-flu formulas in Hong Kong and in the sales of Purapharm. We delineated the drug mechanisms and identify a molecule that can suppress the influenza virus replication. As the drug action is different from the current anti-influenza treatment, the potential to develop a single drug candidate is high (3.5). We patented the production protocol to produced new granules with enhanced anti-viral efficacy with Purapharm (HK) Ltd globally. Consequently, they adopted the new protocol to Nong's[®] Flu Formula [A, E] in 2015.

In recent years, our academics were interviewed by different media to promote the modernization of Chinese medicine. In 2015, Prof. Godfrey Chan were interviewed by TVB to introduce the use of CM for influenza, and this program was sponsored by Purapharm. The sales of the Nong's Flu formula have kept increasing since then [A]. Prof. Chan was also interviewed by CNN on his lifelong experience in Chinese medicine and Western medicine, including research and clinical use on cancer patients [F]. Dr. James Li also contributed articles to local magazine to introduce the modernization of Chinese medicine research. As invited by the HKU Clinical Trials Centre, Dr. Li wrote an article on drug discovery and Chinese medicine research in their book for general public [G]. Subsequently, Purapharm invited Dr. Li and his team in MCM laboratory to develop the clinical trial program with other experts invited by Purapharm for “Shing Ma” product [A].

(5) Sources to corroborate the impact

[A] Supporting letter from Purapharm International (H.K.) Ltd (not for open access)

[B] Novel compound and uses thereof for treating inflammation and modulating immune responses, PI: Allan SY Lau. Co-I: Cindy LH Yang, James CB Li, and Stanley C Chik. Owner: *HKU Versitech Limited and Bagi Research Limited*

[C] Efficient isolation of Cim-A and Methods of Use, PI: Cindy LH Yang. Co-I: Allan SY Lau. Owner: *HKU Versitech Limited and Bagi Research Limited*.

[D] Product License from Health Canada for Sheng ma. Date 16-06-2017

[E] Materials and Methods For Prevention and Treatment of Viral Infections., PI: Allan SY Lau. Co-I: Cindy LH Yang. Owner: *HKU Versitech Limited and Bagi Research Limited*.

[F] Interview with Prof. Godfrey Chan: Meera Senthilingam, Chinese medicine: The next step in cancer recovery? June 20. 2019, *CNN*.

[G] Publication of Dr. James Li: James Li. 眾裡尋它. 醫與研, P.32-33, March 2018, ISBN: 9789881242969