

# HONG KONG PHARMACEUTICAL *JOURNAL*

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## News & Short Communications

Retrospective Assessment on Acceptance Level of Pharmacist-initiated Clinical Interventions in a Pharmacist-led Renal Medication Management Therapy Clinic (MTMC)

Refresher on Vaccines: Six Facts You Need to Know (2 CE Units)

CRISPR / Cas-Based Gene Editing Opens a New Era for Genome Engineering and New Drug Discovery

Chemical Components and Biological Activities of *Angelicae sinensis* (Danggui) and Its Closely Related Species

2017 – The Pearl Anniversary of SHPHK

Pharmacist Continuing Education – Fruitful September with Two CE Seminars

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The Practising Pharmacists Association of Hong Kong  
The Society of Hospital Pharmacists of Hong Kong*

## Seize the opportunity - Primary Healthcare Development



**Chief** Executive Ms. Carrie Lam has just released her maiden policy address. There are several important healthcare policies proposed by the Government.

### *Primary Healthcare Development*

The Government has highlighted the active promotion of primary healthcare as a measure for sustainable development of Hong Kong's healthcare system. The strategies include setting up a steering committee on primary healthcare development to comprehensively review the existing planning of primary healthcare services, and provide healthcare services via district-based medical-social collaboration in the community. The ultimate goal of primary health care is better health for all. WHO has identified five key elements to achieving that goal:

- reducing exclusion and social disparities in health (universal coverage reforms);
- organizing health services around people's needs and expectations (service delivery reforms);
- integrating health into all sectors (public policy reforms);
- pursuing collaborative models of policy dialogue (leadership reforms); and
- increasing stakeholder participation.

The primary health care centres should have a team of doctors, nurses, counsellors, physiotherapists and other healthcare professionals to help the patients. As pharmacists we can offer our expertise by counselling patients on drugs, conducting medication review for patients, and help them to administer the drugs properly. Pharmacists can also conduct Medication Therapy Review (MTR). The medication therapy review is a systemic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them. The Primary Care Centre can employ a pharmacist as the drug expert or refer patients to a nearby community pharmacy.

### *Care for the Elderly*

The government will provide additional resources to enhance community and home care services to achieve zero waiting time. Further increase the number of vouchers under the Second Phase of the Pilot Scheme on Community Care Service Voucher for the Elderly to a total of 6000 in 2018-19. Elderly residents in old aged homes are polypharmacy and are more likely to suffer from adverse effects of medicines which can lead to otherwise preventable hospital admissions. Community pharmacists can help the medication management in the old age homes by packing the drugs in dose packs for the elderly patients and also conduct medication review and medication reconciliation to reduce polypharmacy, adverse drug reactions and improving drug adherence. With the aging population, pharmacists can provide "home medicine reviews" which involves a pharmacist, referred by a GP, to visit a patient in their home and review their medications. This service has already been applied in many countries including Canada, US, Australia and Taiwan. We need a better body of evidence demonstrating costs and benefits, best practices, interventions that work best in specific situations, and the impact of these interventions on health outcomes. We need proof of programs, and proof

of progress to convince the government that the services are beneficial and they should pay for it for better health outcomes.

Talking about collecting evidence on impact of pharmacists interventions, the article on page 86, "Retrospective Assessment on Acceptance Level of Pharmacist-initiated Clinical Interventions in a Pharmacist-led Renal Medication Management Therapy Clinic (MTMC), AU, Alvin HC, SO, Simon WY and LAI, Kandy WK, described about the Medication therapy management program aimed at improving health outcome of chronic kidney disease patients. Records of 396 pharmaceutical care plans from renal medication therapy management clinic cases were analysed dated from 2011-14. Clinical pharmacist recommended an average of 3.5 pharmacist interventions per case and the total number of pharmacist interventions was 1403. The top three categories of common drug related problems were identified in chronic kidney disease-mineral and bone disorder related, hypertension and electrolyte related conditions. The acceptance level of all pharmacist interventions was 84.6% as accepted. In conclusion, pharmacist interventions recommended by the clinical pharmacist in this renal medication therapy management clinic can effectively deliver to physicians and optimise the physician pharmacotherapy decisions.

Immunization is one of the best means to prevent disease. Currently, 10 vaccines are listed as routine vaccines for all immunization programs by the World Health Organization. LEUNG, Tsz-Hin Stanley; NGAI, Cheuk-Yan Vivian; WONG, Kai-Chung Vincent; MAK, Wai-Ming Raymond; CHUI, Chun-Ming William wrote the article on page 93, "Refresher on Vaccines: Six Facts You Need to Know" which aim to serve as a refresher on vaccine knowledge for practicing pharmacists.

It is eye opening to read the article on page 98 written by TSAI, Jui-Ling & CHEUNG, Hon Yeung on CRISPR/ Cas-Based Gene Editing, and to learn that it is being successfully applied in many fields such as edition of defective genes in human embryos and creation of specific DNA fragment for correction of numerous genetic diseases as well as providing a platform for new drug discovery. The Supplementary Information on the CRISPR Timeline on page 103 summarized the discovery and research work done leading to the genome editing.

CHEUNG Hong-Yeung wrote about the chemical components and biological activities of *Angelica sinensis* (Danggui) which is an important traditional Chinese medicine for female ailments. Recent analytical studies reveal that phthalides, aromatic acids and their esters, polysaccharides are the main chemical components determining its bioactivities. (Page 105)

This year is the Pearl Anniversary of the Society of Hospital Pharmacists of Hong Kong and a series of activities is launched as reported in page 110. Mr. Simon So, Chairman of the Organizing Committee invites you all to participate in the upcoming Hong Kong Pharmacy Conference on 10-11 March 2018. Many exciting programs are planned for the 30th Pearl Anniversary of the Hong Kong Pharmacy Conference which you don't want to miss!

*Cheng Mary Catherine*  
Managing Editor  
15<sup>th</sup> October 2017

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The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- OTC & Health
- Medication Safety
- Society Activities
- Drugs & Therapeutics
- Pharmaceutical Techniques & Technology
- Herbal Medicines & Nutraceuticals
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

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Prepared by Bryan Kan, Tommy Lee, Hercules Tse

## Rise in Drug Resistant Gonorrhea

Date: July 7, 2017

The World Health Organization has reported a surge in antibiotic resistance in gonorrhea. This common sexually transmitted infection has become harder, and sometimes even impossible, to treat.

The WHO Global Gonococcal Antimicrobial Surveillance Programme monitors the trends in drug-resistance gonorrhea. Data in recent years showed a widespread resistance to ciprofloxacin, an increasing resistance to azithromycin and the emergence of resistance to extended-spectrum cephalosporins, including cefixime and ceftriaxone. As a result, an update has been made by WHO on treatment recommendations for gonorrhea in 2016 – the antibacterial regimen should include both ceftriaxone and azithromycin.

There is also a lack of incentive for pharmaceutical companies to develop new antibiotics for gonorrhea due to its short treatment

course. Currently there are only 3 candidate drugs in clinical development, including solithromycin with its phase III clinical trial completed. Zoliflodacin and gepotidacin have both completed their phase II trials.

Gonorrhea can be prevented by promoting safe sex and educating the public to recognized signs of gonorrhea. However, there is currently no affordable and rapid diagnostic test for gonorrhea. Many people infected with gonorrhea who are asymptomatic are left untreated. Patients with symptoms such as having a urethral discharge are often assumed to have gonorrhea and received antibiotics, even though they may be suffering from another kind of infection. These inappropriate uses of antibiotics contribute to the development of antibiotic resistance in gonorrhea.

Source: [www.who.int](http://www.who.int)

## WHO: Rise in HIV Drug Resistance Threat

Date: July 20, 2017

The World Health Organization (WHO) has warned countries about the increasing trend of resistance to HIV drugs. Such an alarming trend may possibly pose a negative influence on the progress of treatment and prevention of HIV infection.

The WHO HIV Drug Resistance Report 2017 reveals that over 10% people with antiviral therapy in 6 countries surveyed in Africa, Asia and Latin America has a strain of HIV which was resistant to the most widely used HIV medications. HIV drug resistance often develops when people do not adhere to the prescribed treatment plan. When individuals with resistance to HIV drug start failing

therapy, this may possibly transmit drug-resistant viruses to others.

The arising HIV drug resistance trends could lead to more infections and deaths. According to a mathematical model, an additional 135 000 deaths and 105 000 new infections could occur in the following 5 years if no further action is taken place. Tackling HIV drug resistance will require the concerted efforts of a broad parties. WHO has developed new tools to help countries monitor HIV drug resistance, improve the quality of treatment programmes and transition to new HIV treatments, if needed.

Source: [www.who.int](http://www.who.int)

## Dual Antithrombotic Therapy with Dabigatran Showing Lower Risks of Bleeding after PCI in Atrial Fibrillation

Date: August 27, 2017

In patients with atrial fibrillation (AF) who undergoing percutaneous coronary intervention (PCI), it can be challenging to strike a good balance between the prevention of stroke and the risk of bleeding. According to most of the guidelines, triple antithrombotic therapy (anticoagulant with dual antiplatelet therapy) is the standard approach for this group of patients. However, such approach is associated with high risk of bleeding and new strategies should be investigated.

A multi-centred and randomized RE-DUAL PCI trial aimed to compare the use of dual antithrombotic therapy (dabigatran and P2Y<sub>12</sub> inhibitor) and triple antithrombotic therapy (warfarin, P2Y<sub>12</sub> inhibitor and aspirin). The major or clinically relevant non-major

bleeding event and the noninferiority of both strategies with respect to thromboembolic events are the primary and secondary end points respectively.

The risk of non-major bleeding in those receiving dual therapy (dabigatran and P2Y<sub>12</sub> inhibitor) was lower than that in those receiving triple therapy (warfarin, P2Y<sub>12</sub> inhibitor and aspirin) (hazard ratio (HR) 0.52; 95% CI 0.42 - 0.63). Dual therapy (dabigatran and P2Y<sub>12</sub> inhibitor) was non-inferior to triple therapy (warfarin, P2Y<sub>12</sub> inhibitor and aspirin) with respect to the risk of thromboembolic events (HR, 1.04; 95% CI, 0.84 - 1.29).

Source: [www.nejm.org](http://www.nejm.org)

## FDA Approved New Antibiotic

Date: August 29, 2017

The U.S. Food and Drug Administration (FDA) has approved a new antibiotic, Vabomere, for adults with complicated urinary tract infections (cUTI), including pyelonephritis, caused by a susceptible organism. Vabomere is a drug composed of meropenem, an antibacterial, and vaborbactam, a beta-lactamase inhibitor. Vaborbactam protects meropenem from being degraded by certain beta-lactamases, such as *Klebsiella pneumoniae* carbapenemase.

Vabomere was found to be superior to piperacillin/tazobactam in a randomized, double-blinded clinical trial of 545 adult subjects with cUTI. 98.4% of subjects treated with Vabomere had shown clinical improvement with a negative urine culture test compared with only 94.3% for the piperacillin/tazobactam group. After 7 days, 76.5% of the subjects on Vabomere had their symptoms resolved

and had a negative urine culture test, compared with only 73.2% for the piperacillin/tazobactam group. Despite of its demonstrated efficacy, the FDA reminded that Vabomere should only be used when a susceptible organism has been proven or strongly suspected to be the cause of the infection to prevent the promotion of antibiotic resistance.

Common adverse reactions in patients taking Vabomere include headache, infusion site reactions and diarrhea. Serious risks such as allergic reactions or seizure have also been associated with Vabomere. Patients with a history of serious allergic reactions to beta-lactams should avoid using Vabomere.

Source: [www.fda.gov](http://www.fda.gov)

## EMA: Removal of Modified-release Paracetamol From The Market

Date: September 01, 2017

EMA has recommended removal of modified- or prolonged-release paracetamol product from the market together with suspension of marketing.

Paracetamol is a common medicine for pain and fever relief. Overdose of paracetamol leads to liver damage which can be prevented with acetylcysteine. Treatment strategy of paracetamol is highly dependent on the type of overdose and time elapsed since ingestion. However, paracetamol with prolonged release and inclusion of tramadol complicate the management. Therefore, EMA has conducted relevant review, with conclusion that risk of longer-acting paracetamol outweighs the benefit.

There are 7 registered pharmaceutical products containing paracetamol in modified- or prolonged-release dose form in Hong Kong. They include Clariflu Sustained Release Tab (HK-47205), Panadol Joint Extended Release Caplet 665mg (HK-59436), Panadol Long Lasting Tab 665mg (HK-51314), Panadol Extend Tab 665mg (HK-51316), Panadol Extend Tab 665mg (Ireland) (HK-52683), Xykaa Extend Prolonged Release Tablet 650mg (HK-61400) and Ensid-ER Extended Release Tablet 650mg (HK-62272). 10 adverse drug reaction cases related to liver injury with paracetamol overdose have been received by the Department of Health.

Source: [www.ema.europa.eu](http://www.ema.europa.eu)

## Rivaroxaban-Aspirin Combination More Effective in Stable Cardiovascular Disease Than Individual Monotherapies

Date: September 03, 2017

Cardiovascular disease (CVD) is the most common cause of death, illness, disability and reduced quality of life in industrialised countries. 5 to 10% of CVD patients have recurrent events each year even with effective secondary preventive strategy like aspirin and statin. Rivaroxaban is a selective direct factor Xa inhibitor and is one of the drugs being investigated.

A multi-centred, double-blinded, double-dummy and randomized COMPASS trial was initiated to investigate the effectiveness of rivaroxaban in secondary prevention of stable atherosclerotic disease as monotherapy or combination with aspirin. Patients were assigned in a 1:1:1 ratio to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100

mg once daily). Adverse cardiovascular events and bleeding are the primary efficacy and safety outcomes respectively.

The risk of major adverse cardiovascular events was significantly lower with rivaroxaban-aspirin combination than with aspirin alone (hazard ratio (HR) 0.76; 95% CI 0.66-0.86), but the risk of major bleeding was significantly higher (HR 1.70; 95% CI 1.40-2.05). Rivaroxaban alone did not result in a significantly lower risk of major adverse cardiovascular events than aspirin alone (HR 0.90; 95% CI 0.79-1.03) and resulted in a significantly higher risk of major bleeding (HR 1.51; 95% CI 1.25-1.84).

Source: [www.nejm.org](http://www.nejm.org)

## The Chief Executive's 2017 Policy Address

Date: October 11, 2017

In the Chief Executives 2017 Policy Address, some important highlights affecting healthcare and care for elderly are:

(i) Set up a steering committee on primary healthcare development to comprehensively review the existing planning of primary healthcare services, and provide healthcare services via district based medical-social collaboration in the community.

(ii) Set up a dedicated unit to oversee Chinese medicine development, co-ordinate and implement relevant strategies and measures.

(iii) Provide additional resources to enhance community and homecare services to achieve zero waiting time.

Source: [www.policyaddress.gov.hk](http://www.policyaddress.gov.hk)

# Retrospective Assessment on Acceptance Level of Pharmacist-initiated Clinical Interventions in a Pharmacist-led Renal Medication Management Therapy Clinic (MTMC)

AU, Alvin HC\*; SO, Simon WY; LAI, Kandy WK

Department of Pharmacy, Alice Ho Miu Ling Nethersole Hospital

(\*Corresponding author)

## ABSTRACT

Chronic kidney disease is associated with a decreased rate of survival and an increased rate of hospitalisation. The complications included electrolyte and fluid abnormalities, anaemia, hyperparathyroidism complications, metabolic bone condition, metabolic acidosis, hypertension, hyperlipidaemia. Medication therapy management program aimed at improving health outcome of chronic kidney disease patient with enhanced management of coexisting disease state, delay progression of chronic kidney disease related complications, increase patient survival rate, reduce healthcare cost. Clinical pharmacist provided interventions to optimise the identified drug related problems. The aim of this study was to identify the prevalence and pattern of the drug related problems in the medication therapy management clinic and to identify the acceptance level of pharmacist-initiated clinical interventions and the relationship between acceptance level and level of pharmacist interventions. Pharmacist interventions and identified drug related problems were categorised into five conditions with fifteen categories of drug related problems. Acceptance rate of the clinical interventions by renal physicians was measured. Records of 396 pharmaceutical care plans from renal medication therapy management clinic cases were analysed dated from 2011-14. Clinical pharmacist recommended an average of 3.5 pharmacist interventions per case and the total number of pharmacist interventions was 1403. The top three categories of common drug related problems were identified in chronic kidney disease-mineral and bone disorder related, hypertension and electrolyte related conditions. The acceptance level of all pharmacist interventions was 84.6% as accepted. In conclusion, pharmacist interventions recommended by the clinical pharmacist in this renal medication therapy management clinic can effectively deliver to physicians and optimise the physician pharmacotherapy decisions.

**Keywords:** *Chronic kidney disease, Medication therapy management, drug related problems, pharmacist interventions*

## INTRODUCTION

**Chronic** kidney disease (CKD) and end stage renal disease (ESRD) are associated with a decreased rate of survival and an increased rate of hospitalisation. The complications of

CKD included electrolyte and fluid abnormalities, anaemia, hyperparathyroidism complications, metabolic bone condition, metabolic acidosis, hypertension, hyperlipidaemia, etc. Patients with CKD or ESRD are at risk of cardiovascular diseases. All of these complications contributed to reduced life expectancy of patients with CKD and ESRD.<sup>(1)</sup>

Multiple issues experience by CKD patients were reported by reviews and studies. Non-compliance, polypharmacy, lack of understanding about purpose of medications, the feeling of lack of improvement, would be the issues experienced by CKD patients. Several studies had reported that poor quality and gaps in the care of CKD patients with respect to the treatment of co-existing disease state, medications therapy for renal replacement.<sup>(2)</sup>

In Hong Kong, the long waiting time to the specialist service in public hospital including renal specialist adversely affected the quality care and increased gaps in the care of complications experienced by CKD patients.<sup>(3)</sup>

This service gap poses a chance of multidisciplinary healthcare teams collaboration in aiming to delay disease progression and manage conditions and complication with CKD and ESRD patients. Researches and studies supported the involvement of clinical pharmacist in the management of the pharmacotherapy of CKD and ESRD patients to provide positive health outcome.<sup>(4, 5)</sup>

The implementation of medication therapy management clinic (MTMC) in renal day care centre in Alice Ho Miu Ling Nethersole Hospital started in 2010.<sup>(3)</sup> The MTMC is a patient-focused program aimed at improving collaboration among physicians, pharmacists, nurses and other health professionals in order to improve health outcome of ESRD patient with enhanced management of coexisting disease state, delay progression of CKD related complications, increase patient survival rate, reduce healthcare cost. Optimising health outcomes of patients was the key component of MTM program, including reducing drug-related problems (DRPs), patient education in CKD management, etc.<sup>(1)</sup>

The renal MTMC provided medication therapy review service to identify both DRPs and non-pharmacotherapy problems. An individualised care plan will be provided to the

physician after the medication therapy review. A routine follow-up session with the renal physician for the patient with the pharmaceutical care plan provided would be the next step of care. The renal physician would manage the case with the consideration with the pharmaceutical care plan provided by the pharmacist in the MTMC. However, the acceptance rate of pharmacist intervention by the physician was unknown for this MTMC. The extent of improvement of health outcome provided by the MTMC has not been revealed since the implementation year of 2010.

Studies and reviews have shown that pharmacist interventions in the ambulatory care setting resulted in improvement of patient outcome. However, the acceptance rate by physician varied as reported by studies that had an impact on possible improvement on patient outcome.<sup>(2, 6)</sup> In general, the implementation of pharmacist intervention usually reached an acceptance rate that ranged from 30%-100%.<sup>(1, 4, 7, 8)</sup>

A background research was performed from database MEDLINE, EMBASE in order to identify the model of renal MTM programme similar to our model. There was a study by Castro *et al.*<sup>(9)</sup> discussed about a MTM service model provided to ESRD patients that require haemodialysis (HD). Other studies described pharmacotherapy review of CKD patients by the clinical pharmacist at different hospital setting and improvement of patient education by the clinical pharmacist. Studies described a MTM service model on ESRD patients requires peritoneal dialysis has not been observed with the background literature research. This poses an opportunity to investigate the DRPs that experienced by the ESRD patients require peritoneal dialysis in the renal MTMC.

The provision of MTMC in renal centre in Alice Ho Miu Ling Nethersole Hospital has reached its fifth year since 2010, an in-depth evaluation of the MTMC has been proposed to identify the acceptance rate of pharmacist interventions by the physicians, the extent of improvement of patient outcome after the intervention and prevalence of different types of DRP.

## AIMS

This study aimed to identify the prevalence and pattern of the drug related problems (DRPs) in the MTMC and to identify the acceptance level of pharmacist-initiated clinical interventions (PIs) and the relationship between acceptance level and level of PIs.

## METHOD

### Study Population

The study population of this retrospective review study included the patients recruited in the renal MTMC in Alice Ho Miu Ling Nethersole Hospital dated from 1 January 2011 to 31 December 2014. The studied patients were those diagnosed with G5 CKD (GFR less than 15 ml/min.1.73m<sup>2</sup>) receiving peritoneal dialysis.

## Structure and Workflow of the Renal Medication Therapy Management Clinic (MTMC)

A clinical pharmacist provided medication therapy management to G5 CKD patients using peritoneal dialysis including continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD), and nocturnal intermittent peritoneal dialysis (NIPD). In the MTMC setting, pharmacist would directly interview and consult patient to identify any drug related problems with access of patient medications, medical history and lab results.

In this study, patients were categorised into two groups, 1. First time consultation of the renal MTMC and 2. Follow up consultation of the renal MTMC.

For patients attending the consultation with the renal physician for the first time, the patients would attend to pharmacist-led renal MTMC after completing the appointment of consultation with the renal physician. **(Figure 1)** The pharmacist would provide comprehensive medications counselling, self-care education, and life-style recommendation to the patients.

For patients attending follow-up consultation with renal physician, patients would first attend to the pharmacist-led renal MTMC before the follow-up physician consultation. Any drug related problems identified by the pharmacist will be addressed to the physician by submitting the pharmaceutical care plans with identified DRPs and pharmacist-initiated clinical interventions for the renal physician's consideration. **(Figure 2)**



Figure 1. Workflow of patients (first time) attending Renal MTMC

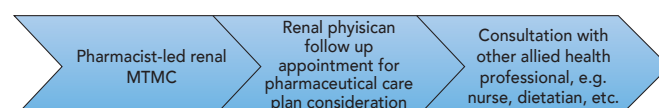


Figure 2. Workflow of patients (follow up) attending Renal MTMC

## Drug-related Problems (DRPs)

The drug-related problems (DRPs) were classified into the corresponding category according to the defined conditions and natures of DRPs.<sup>(4, 10)</sup> The DRPs documented in the pharmaceutical care plan were classified into five main category of conditions **(Table 1)** in this study including electrolytes related, chronic kidney disease-mineral and bone disorder (CDK-MBD), anaemia, hypertension, glycaemic control related. The natures of DRPs **(Table 2)** were further categorised within the five category of conditions, including allergy, therapeutic duplication, drug therapy omission, dose standardisation, non-compliance, contraindication, inappropriate drug, dose, route, frequency or duration, self-care education or counselling related, drug-drug interaction, drug-food interaction, drug-clinical status interaction, polypharmacy, discrepancy in regimen acknowledged during medication reconciliation (MR), unnecessary when required (PRN) medications and therapy goal unattained.<sup>(10, 11)</sup>

Table 1. DRPs - Category of conditions
DRPs - Category of Conditions
Electrolytes related
Chronic kidney disease - Mineral and bone disorder (CKD-MBD)
Anaemia
Hypertension (HTN)
Glycaemic control related

Table 2. Natures of DRPs within each five category of conditions
Natures of DRPs
Allergy
Therapeutic duplication
Drug therapy omission
Dose standardisation
Non-compliance
Contraindication
Inappropriate drug, dose, route, frequency or duration
Self-care education and counselling related
Drug-drug interaction
Drug-food interaction
Drug-clinical status interaction
Polypharmacy
Discrepancy in regimen acknowledged during medication reconciliation (MR)
Unnecessary when required (PRN) medications
Therapy goal unattained

### Pharmacist Initiated Clinical Interventions (PIs)

The pharmacist interventions were classified into the corresponding categories within of the defined conditions and natures of DRPs. The clinical interventions that matched with the corresponding DRPs were assessed with the classification of pharmacist intervention listed below on level of 1, 2 or 3.

Pharmacist interventions were suggested by the clinical pharmacist as part of the pharmaceutical care plan at the renal MTMC in order to solve the identified DRPs. The type of pharmacist interventions that matched with the corresponding DRPs were categorised into three levels, level 1, 2 and 3 as shown in **Table 3**.<sup>(4, 12)</sup>

Table 3. Level of pharmacist interventions	
Level of pharmacist intervention	Recommendations of pharmacist intervention
Level 1	Clinical monitoring Patient self-care management and monitoring Compliance Life-style and dietary modification Counselling on rational use of PRN medications
Level 2	Direction of adjustment trend on medication therapy regimen of: <ul style="list-style-type: none"> <li>▪ Dose</li> <li>▪ Frequency</li> <li>▪ Duration</li> <li>▪ PRN medications usage</li> </ul>
Level 3	Direction of specified adjustment on medication therapy regimen: <ul style="list-style-type: none"> <li>▪ Dosage/Frequency/Duration</li> <li>▪ Alternation of therapy or medications</li> <li>▪ Addition or deletion of medications</li> </ul>

### Acceptance Level of Pharmacist Interventions

The acceptance level of the pharmacist intervention were categorised into three different level of level A, B and C. (**Table 4**).<sup>(2)</sup> Acceptance level A consisted of pharmacist interventions accepted by physicians without alternation. Acceptance level B was consisted of pharmacist interventions accepted by physicians with alternation. Acceptance level C was consisted of pharmacist interventions was declined by physicians.

Table 4. Level of acceptance	
Level of acceptance	Description of the rate of acceptance
Level A	The pharmacist intervention was fully accepted
Level B	The pharmacist intervention was accepted with alternation of recommended management
Level C	The pharmacist intervention was declined

The pharmacist interventions suggested by the pharmacist in the pharmaceutical care plan were matched with the acceptance level assessed from the consultation notes written by renal physicians.

### Assessment of the Acceptance Level

The acceptance levels were assessed based on the pharmacist interventions recommended by the pharmacist and the plan of management from the consultation notes written by the renal physicians. If the management plan was matched with the PIs suggested by the clinical pharmacist correspondingly, the PIs were considered to attain level A of acceptance. If the management plan was matched with the corresponding PIs with altered interventions by the renal physicians, the PIs were considered to attain level B of acceptance. However, if the management plan did not include any plan to address to the corresponding pharmacist intervention, plan in opposite to the PIs or mentioned that the PIs would not be followed, the PIs were considered to attain level C of acceptance as a declined of the pharmacist interventions.

### Analysis Strategy

All data was recorded into a database created using Microsoft Access 2013 (Microsoft Corp., Redmond, WA). Descriptive statistics were generated for all types of DRPs, pharmacist interventions. Patients' characteristic were also reported in the demographics of age and sex. Patients would attend multiple follow up session within the data collection period of 3 years. Distribution of different levels of pharmacist intervention, e.g. level A, B or C, were analysed with the corresponding types of DRPs. Statistics were generated on overall acceptance rate and overall the PIs and DRPs using Microsoft Excel 2013. Furthermore, the acceptance rate were analysed with the distribution of the different level of the PIs.

## RESULTS

### The Demographic of Patients

Over a period of 4 years, a total of 473 patients received the service provided by the Renal MTMC. The average age



of patients is 62.3. The distribution of patient in different age groups were recorded as age group 31-40 (n=2), age group 41-50 (n=40), age group 51-60 (n=165), age group 61-70 (n=171), age group 71-80 (n=89), age group 81-90 (n=6).

The number of patients attended the MTMC receive comprehensive medications and self-management of CKD counselling were 89 patients including 56 male (n=56) and 33 female (n=33).

The distribution of patients attended the MTMC for pharmacotherapy management and resolving DRPs were 384 patients including 234 male (n=234) and 150 female (n=150).

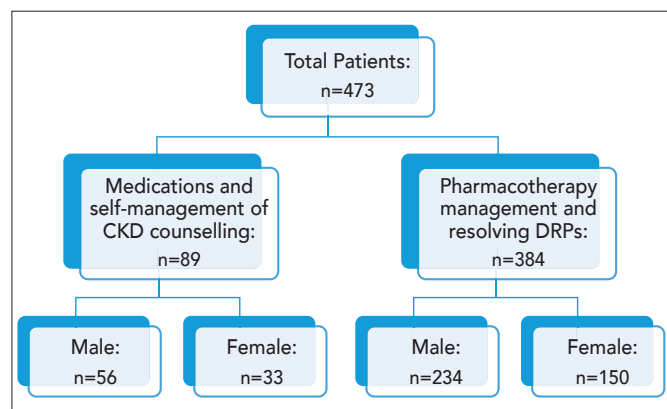


Figure 3. Demographic of patients

### Pharmacist Interventions

A total of 473 pharmacist consultations recorded in the period of 2011-2014. There were 77 cases of pharmacist counselling session for patient first start with medications for CKD and 396 cases of pharmacist consultations for pharmacotherapy management with the renal MTMC.

A total of 1403 pharmacist interventions (PIs) recorded in the 396 pharmacist consultations in the renal MTMC. The mean number was 3.5 PIs per pharmacist consultation.

There were 271 DRPs identified as electrolyte related, 521 DRPs as CKD-MBD, 191 DRPs as anaemia, 333 DRPs as hypertension and 87 DRPs as glycaemic control related.

For the distribution of different levels of PIs, there were 781 PIs identified as level 1 (55.7%), 477 PIs identified as level 2 (34.0%) and 145 PIs identified as level 3 (10.3%).

### The Characteristics of Pharmacist Interventions (PIs)

Each DRP identified would be regarded as one pharmacist intervention initiated by pharmacist. The majority of the PIs were identified as related to drug and disease interaction (356 DRPs). It was followed with PIs related to 3 other aspects that resulted in similar occurrence, including DRPs of non-compliance, therapeutic goal unattained and self-care education and counselling related. The rest of PIs were related to drug therapy omission, dose standardisation, inappropriate choice of drug/dose/route/frequency/duration, drug-drug interaction, drug food interaction and discrepancy found during MR. Lastly, there were 2 PIs which were related to the unnecessary use of as required (PRN) medications.

### Overall Acceptance Level of the Pharmacists Interventions (PIs)

There were 1012 PIs attained acceptance level A (72.1%), 175 PIs attained acceptance level B (12.5%) and 216 PIs attained acceptance level C (15.4%). The total acceptance rate of PIs accepted by physicians with or without adjustment of PIs (Level A and Level B) were 84.6%. The rate of PIs declined by physicians was 15.4%.

### DISCUSSION

The commonest DRP identified was CKD-MBD related DRPs. It was followed by DRPs related with hypertension, electrolyte, anaemia and glycaemia control correspondingly.

Table 5. Distribution of type of DRPs with different categories of conditions						
Distribution of DRPs within each conditions						
Conditions of DRPs	Electrolyte related	CKD-MBD	Anaemia	Hyperten-sion	Glycaemic control related	Total DRPs (per natures of DRPs)
Allergy	0	0	0	0	0	0
Therapeutic duplication	0	0	0	0	0	0
Drug Therapy Omission	4	9	9	1	0	23
Dose Standardisation	10	10	12	47	4	83
Non-compliance	21	151	9	18	4	203
Contraindication	0	0	0	0	0	0
Inappropriate drug, dose, route, frequency or duration	10	40	10	8	1	69
Self-care education and counselling related	76	98	11	25	15	225
Drug-drug interaction	0	8	13	0	0	21
Drug-food interaction	16	22	5	0	2	45
Drug-clinical status interaction	72	92	90	80	22	356
Polypharmacy	12	2	5	96	2	117
Discrepancy in regimen acknowledged during medication reconciliation	4	23	8	11	11	57
Unnecessary PRN medications	0	1	0	0	1	2
Therapeutic goal unattained	46	65	19	47	25	202
Total DRPs (per conditions)	271	521	191	333	87	

Table 6. Distribution of PIs in different condition with acceptance level									
Distribution of Pharmacist intervention in different conditions with level of PIs-Acceptance level									
Electrolyte related PIs									
Level 1-A	Level 1-B	Level 1-C	Level 2-A	Level 2-B	Level 2-C	Level 3-A	Level 3-B	Level 3-C	Total PIs
143	16	16	41	9	9	26	6	5	271(19.3%)
Level 1: 175; Level 2: 59; Level 3: 37									
CKD-MBD PIs									
Level 1-A	Level 1-B	Level 1-C	Level 2-A	Level 2-B	Level 2-C	Level 3-A	Level 3-B	Level 3-C	
288	27	19	97	17	16	44	4	9	521(37.1%)
Level 1: 334; Level 2: 130; Level 3: 37									
Anaemia PIs									
Level 1-A	Level 1-B	Level 1-C	Level 2-A	Level 2-B	Level 2-C	Level 3-A	Level 3-B	Level 3-C	
51	6	20	52	4	22	26	3	7	191(13.6%)
Level 1: 77 Level 2: 78; Level 3: 36									
Hypertension PIs									
Level 1-A	Level 1-B	Level 1-C	Level 2-A	Level 2-B	Level 2-C	Level 3-A	Level 3-B	Level 3-C	
84	35	28	100	31	47	3	2	3	333(23.7%)
Level 1: 147; Level 2: 178; Level 3: 8									
Glycaemic control related PIs									
Level 1-A	Level 1-B	Level 1-C	Level 2-A	Level 2-B	Level 2-C	Level 3-A	Level 3-B	Level 3-C	
33	8	7	20	5	7	4	2	1	87(6.3%)
Level 1: 48; Level 2: 32; Level 3: 7									

Table 7. Overall distribution of PIs with acceptance level			
Total of PIs with relationship of level of PI-acceptance level			
Number of PIs	Level 1-A 599 (42.7%)	Level 1-B 92 (6.6%)	Level 1-C 90 (6.4%)
Number of PIs	Level 2-A 310 (22.1%)	Level 2-B 66 (4.7%)	Level 2-C 101 (7.2%)
Number of PIs	Level 3-A 103 (7.3%)	Level 3-B 17 (1.2%)	Level 3-C 25 (1.8%)
Total	PIs-Level A 1012 (72.1%)	PIs-Level B 175 (12.5%)	PIs-Level C 216 (15.4%)

### The Level of Pharmacist Interventions and Acceptance Rate

The pharmacist interventions were graded into three different levels. Level 1 interventions consist of general intervention of polypharmacy, regular monitoring requirement, medication therapy adherence and counselling related. This is predictable that level 1 PIs constituted the highest prevalence of interventions among three levels of interventions as this category included majority of type of interventions besides dosage recommendations. The medication regimen of ESRD patients usually consisted of 10-11 medications excluding the peritoneal dialysis fluid and when required (PRN) medications. This indicated that polypharmacy in ESRD patients was severe. The level 1 PIs recommended physicians to review and streamline the medication regimen within a specific disease state, e.g. hypertension related, glycaemic control related, etc. The antihypertensive medication regimen was the area that pharmacist intervened physicians to streamline the therapy as majority of our ESRD patients were frequently prescribed average 4-5 antihypertensive medications. The complicated regimen for different ESRD-related complications had negative impact on adherence of regimen.<sup>(13, 14)</sup> As a result, the overall adherence of ESRD medications therapy were not achieved.

Self-care education, counselling, lifestyle and dietary modification related DRPs are one of the major groups of level 1 PIs. Self-care education was an important aspect in the management in CKD and ESRD patients.<sup>(15)</sup> Studies suggested that the self-care management could delay the progression of CKD and prevent complication of CKD.<sup>(16)</sup> ESRD patients were required to adopt many difficult lifelong self-care management including lifestyle and dietary modifications in order to prevent worsening of CKD. This is because ESRD patients are the solely responsible of their own everyday self-care management in order to delay CKD progression. Study showed that ESRD patients with higher awareness on the importance of self-care management may improve disease outcome by successfully performed daily self-care management behaviours that prevent the worsening of the disease condition.<sup>(16)</sup> However, ESRD patients possessed with low awareness on the importance of self-care management is more likely to forget the daily self-care management activities. Thus, they are more likely to lose control of their condition of disease and positive view of psychological well-being of their disease state.<sup>(17)</sup>

One of the roles of clinical pharmacist working in the MTMC is detecting self-care management issues. Recommendations were provided to physicians and patients aiming at optimising CKD self-care management, level of awareness of CKD and communication with ESRD patients. This could promote the patient-clinical pharmacist relationship that could reduce the barrier of assessing patients for DRPs to the clinical pharmacist to identify DRPs from patients and increase the willingness of ESRD patients to express any difficulties in engaging self-care activities.

Level 2 PIs constituted about 30% of the overall pharmacist interventions. The level 2 interventions were mainly consisted of interventions on drug-clinical status interaction, drug-drug interactions, therapeutic goal unattained, discrepancy identified

during medications reconciliation, etc. These DRPs would lead to interventions from clinical pharmacist recommended dosage adjustment of medications. Level 2 PIs provided more specific recommendations on dosage adjustment when compared to level 1 PIs. The medication therapy of ESRD patients for renal replacement including long-term dialysis can be highly complex and varied that included frequent monitoring, regular optimisation of pharmacotherapy, compliance improvement and risk reduction of co-morbidities. The nature of frequent adjustment on dosage, polypharmacy, poor medication compliance would eventually lead to additional level 2 PIs. Study reviewed the involvement of clinical pharmacist in medication management of CKD patients showed that more CKD patients achieved improved rate of electrolyte target in range, better glycaemic and blood pressure control, better medications knowledge and decreased rate of hospitalisation.<sup>(4)</sup> Another study compared CKD patients with standard patient care with additional care from clinical pharmacist showed that more CKD patients on angiotensin-converting enzyme inhibitors, sodium bicarbonate and iron supplement.<sup>(18)</sup> Clinical pharmacist provided medication management and resolving DRPs by level 2 pharmacist interventions that optimised the choice and dosage of medications.

Level 3 PIs constituted about 10% of the overall pharmacist interventions. This level of interventions provided by clinical pharmacist consisted of specific direction on the dosage of medications, alteration of medication therapy and addition or deletion of medications. They were more specific than the level 2 PIs as level 3 PIs provided exact directions. Level 3 PIs mainly resolved DRPs about drug-disease interactions, drug-drug interactions and therapeutic goal unattained which is similar to level 2 PIs. However, recommendations were more specific on level 3 PIs than that of level 2 PIs on dosage and addition or discontinuation of pharmacotherapy. The clinical status of electrolytes, haemoglobin, phosphorus-calcium, intact parathyroid hormone (iPTH) level, and other monitoring parameter changed frequently in CKD patients. The interventions of exact dosage recommendation and alteration of medications in the pharmacotherapy were recommended in relation to biomarkers target level and clinical presentation of patients. An intervention of discontinuation of potassium supplement as the serum potassium level of the ESRD patient has raised above the upper reference limit of 5mmol/L. Another example of pharmacist intervention would be the recommendation of the initiation of erythropoietin-stimulating agent (ESA) when the anaemic condition of ESRD patients did not improve after optimising all the underlying causes, e.g. iron deficiency, etc. The level 3 pharmacist interventions were infrequently recommended by clinical pharmacists as fewer DRPs required exact dosage recommendations, optimisation of electrolyte level, iron level and other therapeutic targets were performed before that avoid severely deviated from the normal range.<sup>(18)</sup>

## Acceptance Level of Pharmacist Interventions

The overall of acceptance rate of all pharmacist intervention was about 84%. This rate of acceptance of pharmacist interventions was considered high and was comparable to other studies providing medication therapy management services and other services involving pharmacist interventions.<sup>(2, 4)</sup> Studies reviewed clinical activities in CKD patients including MTM services, therapeutic optimisation of DRPs at ward level and pharmacist-led clinic on managing specific CKD-related complications, e.g. anaemia, hyperphosphatemia showed that the physician acceptance rate to the pharmacist intervention in these studies ranged from 76% to 100%.<sup>(4, 18)</sup> There were 2 studies with 100% acceptance rate showed bias in the methodology as their PIs were considered as accepted by default. Thus, the acceptance rate of these two studies may not be relevant to be compared to our study and the physician acceptance rate recorded usually range from 76% to 93%, as reported in other similar literatures.<sup>(4)</sup>

There were about 15% of the PIs that were not accepted by physicians. Majority of the declined PIs were level 1 and 2 interventions. The PIs in our pharmaceutical care plan were comprehensively addressed all DRPs detected by clinical pharmacist. However, physicians at each consultation with CKD patients aimed at resolving the most important issue within the limited consultation time. This poised further opportunities for pharmacists to manage DRPs in order to reduce the level 1 and 2 PIs to the physicians that further reduced burden to physicians and enhanced the physician-pharmacist collaboration.<sup>(22)</sup>

## CONCLUSION

The pattern of DRPs in ESRD patients were identified that provided important information possible on the future development of the renal clinical pharmacy service to address areas with high amount of DRPs. The acceptance rate of pharmacist interventions in this renal MTMC was high and comparable to other studies with pharmacist interventions or medication therapy management services internationally. The pharmacist interventions recommended by the clinical pharmacist in this renal MTMC can effectively deliver to physicians and optimise the physician pharmacotherapy decisions.

### Author's background

**Mr. AU, Alvin HC** is currently a pharmacist at Department of Pharmacy, Alice Ho Miu Ling Nethersole Hospital. His email address is: [ahc024@ha.org.hk](mailto:ahc024@ha.org.hk)

**Dr. SO, Simon WY** is currently a senior pharmacist at Department of Pharmacy, Alice Ho Miu Ling Nethersole Hospital. His email address is: [sowys@ha.org.hk](mailto:sowys@ha.org.hk)

**Ms. LAI, Kandy WK** is currently the Department Manager at Department of Pharmacy, Alice Ho Miu Ling Nethersole Hospital. Her email address is: [laiwk@ha.org.hk](mailto:laiwk@ha.org.hk)

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## Refresher on Vaccines: Six Facts You Need to Know

LEUNG, Tsz-Hin Stanley; NGAI, Cheuk-Yan Vivian; WONG, Kai-Chung Vincent; MAK, Wai-Ming Raymond; CHUI, Chun-Ming William\*

Department of Pharmacy, FI Pharmacy, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong SAR, China (\* Corresponding author)

### ABSTRACT

Since the first vaccine was developed and proven effective in 1796, vaccinations have prevented many deadly diseases globally. Pharmacists from different sectors including hospital and community often come across vaccination enquiries from other healthcare professionals or general public. This article has included 6 “Questions and Answers” covering the basic vaccine classification, safety of vaccine and justification of vaccination or revaccination in special populations. It aims to serve as a refresher on vaccine knowledge and hopefully could give practicing pharmacists some insights while dealing with vaccine related issues.

**Keywords:** vaccine, vaccine classification, safety, preterm, pregnancy, Hepatitis B vaccine booster

### INTRODUCTION

Since the first vaccine was discovered and proven effective in 1796 for smallpox,<sup>(1)</sup> it has successfully reduced the infection rate of many deadly diseases including measles and tetanus. It is estimated that each year, 2 to 3 million deaths can be averted by immunization.<sup>(2)</sup>

Currently, 10 vaccines are listed as routine vaccines for all immunization programs by World Health Organization (WHO),<sup>(3)</sup> and most are included in the government childhood vaccination program in Hong Kong (Table 1).<sup>(4)</sup> As a pharmacist, queries regarding vaccines often arise from patients or other healthcare

professionals. With discussions on six common questions, this article serves as a refresher for pharmacists and hopefully could answer some of the frequently encountered questions regarding vaccinations in pharmacy practice.

### What is the basic classification of vaccines?

Vaccines can be generally divided into two basic types: live attenuated vaccines and inactivated vaccines.<sup>(5)</sup>

Live attenuated vaccines are weakened forms of normal disease-causing viruses or bacteria. During vaccination, a relatively small amount of the weakened virus or bacteria is administered, and they start replicating and create enough organisms to stimulate the immune response. In the process of replication, they usually do not cause diseases as the original pathogens, but produce milder symptoms or responses resembling the original diseases only. As live attenuated vaccines stimulate our immune system in a similar manner to their natural infections, they often produce lifelong immunity in most recipients with 1 or 2 doses. Caution should be taken when they are used in immunocompromised patients as bacteria/virus in these vaccines can still replicate in human body, uncontrolled growth may result in serious and fatal reaction. Theoretically, these live attenuated vaccines may convert back to the original pathogenic form. However, it is known to happen only with live oral polio vaccine. Examples of live attenuated vaccines include: adenovirus, bacille Calmette-Guérin (BCG) vaccine, live attenuated influenza vaccine, Measles, Mumps & Rubella (MMR), rotavirus, smallpox, varicella, and yellow fever.<sup>(5,6)</sup>

Inactivated vaccine is produced by killing the bacteria or viruses (e.g. by chemical or heat) after culturing them. The products can be whole cell or fractional in that only specific components from pathogen are isolated (Table 2).

Vaccines recommended by WHO	Vaccines covered by the Hong Kong Childhood Immunization Program
Bacille Calmette-Guérin (BCG)	Bacille Calmette-Guérin (BCG)
Hepatitis B	Hepatitis B
Polio	DTaP-IPV (Diphtheria, Tetanus, acellular Pertussis and Inactivated Poliovirus Vaccine) dTap-IPV (Diphtheria, Tetanus, acellular Pertussis (reduced dose) & Inactivated Poliovirus Vaccine)
Pneumococcal (conjugate)	Pneumococcal 13-valent conjugate vaccine
Measles Rubella	MMRV (Measles, Mumps, Rubella and Varicella vaccine)
Rotavirus	/
Haemophilus influenza type B	/
Human Papillomavirus (HPV) (for females)	/

Inactivated vaccines			
Type	Example		
Whole	Viruses	Hepatitis A vaccine	
	Bacteria	Pertussis vaccine	
Fractional	Protein-based	Toxoid	Tetanus toxoid vaccine
		Subunit	Hepatitis B vaccine
	Polysaccharide-based	Pure	Pneumococcal polysaccharide vaccine
		Conjugate	Pneumococcal conjugate vaccine

1. Toxoid vaccine is employed when the toxin is the main cause of disease. The toxin is inactivated and administered in the body so that the immune system can learn how to cope with the natural toxin. It is safe as it cannot cause the original disease or reverse to the original virulent form.<sup>(6,7)</sup>
2. Subunit vaccines contain only the antigen that best stimulate immune system. As only the essential antigen but not the whole or most parts of the pathogen is extracted, it is less likely to cause adverse reactions.<sup>(6)</sup>
3. Polysaccharide vaccines contain long chains of sugar molecules, which constitute the surface capsule of certain bacteria. These polysaccharides typically stimulate B cells without assistance of T-helper cells, resulting in a T-cell independent immune response. It makes them not consistently immunogenic in children less than 2 years old probably due to immaturity of their immune system.<sup>(5)</sup>
4. Conjugated vaccine is developed by linking a polysaccharide antigen to a protein carrier so that it stimulates both B cells and T cells, resulting in a T-cell dependent immune response which produces more rapid and enhanced immune response on re-exposure to an antigen. This makes conjugated vaccine immunogenic in elderly and children less than 2 years old.

As inactivated vaccine cannot replicate in human body, the entire dose of antigen needs to be administered. Unlike live vaccine, inactivated vaccine does not cause infection in immunocompromised patients. However, most inactivated vaccine generates a weaker immune response and hence requiring additional doses to secure immunity. In general, the first dose only primes the immune system and the protective immunity will develop after the second or third doses of vaccination. As the antibody titres developed from inactivated vaccines diminishes with time, some may also require periodic supplemental doses to boost up the antibody titers.<sup>(5,6)</sup>

It should be noted that administration of commonly used live and inactivated vaccines on the same day does not cause reduced antibody responses or more adverse reactions. However, if two live parenteral vaccines are not administered on the same day, an interval of at least 4 weeks should be given in most cases so as to reduce interference from the first vaccine to the second one. For combinations of two inactivated vaccines, or live and inactivated vaccines, they may be administered at any time before or after each other in most cases.<sup>(8)</sup>

### **Is there any true relationship between autism and vaccination in children?**

Since the 1980s, there has been an increasing number of cases of autism, which coincided with the significant increase in the number of recommended childhood vaccines. Some professionals have suggested that certain vaccines (e.g. measles, mumps, and rubella [MMR]) and thimerosal (a preservative in some vaccines) are the culprits of this phenomenon.<sup>(9)</sup>

The Centers for Disease Control and Prevention has suggested that there is no linkage between vaccines and autism.<sup>(10)</sup> In 2013, a study has also evaluated the association between autism and level of immunologic stimulation received from vaccines during the first 2 years of life (measured

by exposure to total antibody-stimulating proteins and polysaccharides from vaccines).<sup>(11)</sup> It showed that the total antigen amount received from vaccines was the same between children with or without autism. As for MMR with autism, no scientific linkage has been found. Many epidemiologic studies and systematic reviews have still found insufficient evidence to support such relationship.<sup>(9)</sup>

Thimerosal (sodium ethylmercury thiosalicylate) has been used as a preservative in multi-dose vaccine vials.<sup>(12)</sup> One of the reasons why it is thought to cause autism is that mercury is known to be a neurotoxin, which may cause adverse neurological effects. However, the toxic effect of mercury is actually complex and depends on different factors including the mercury form.<sup>(12)</sup> Ethylmercury is generated when thimerosal is broken down in the body, but this form is rapidly eliminated from the body compared with methylmercury (the other mercury form, which could bio-accumulate in fish and shellfish). For example, the half-life of ethylmercury is less than 1 week while that of methylmercury is around 1.5 months and the former is actively excreted via the gut while the latter accumulates in the body.<sup>(13)</sup> Hence, the mercury form in vaccine (ethylmercury) is less likely to cause any harm. Moreover, studies have found that the features of mercury poisoning have little in common with those of autism; and multiple systematic reviews or epidemiologic studies have found insufficient evidence to support an association between autism and thimerosal-containing vaccines.<sup>(12)</sup> In addition, no association has been found between other vaccine ingredients and autism.<sup>(10)</sup>

To conclude, there is no clear association between vaccines, vaccine ingredients and autism. At the same time, benefits of vaccines are clear as patients can be protected from severe and fatal infections.

### **Should preterm babies receive vaccinations?**

Studies have shown that neonates with very low birth weight (less than 1500 g) or of very early gestational age (less than 29 weeks of gestation) may have decreased immune response, but most preterm infants produce sufficient vaccine-induced immunity for disease prevention.<sup>(14)</sup> Hence, most clinically stable preterm babies (born at less than 37 gestational weeks) or infants with low birth weight (born at less than 2500 g) should receive childhood vaccination as scheduled according to chronological age, without any dose reduction or division.<sup>(14,15)</sup> Preterm and low birth weight infants appear to tolerate most childhood vaccinations.<sup>(14)</sup> However, increase in apnea, bradycardia with oxygen desaturation has been reported in very low birth weight infants (body weight less than 1500 g) receiving certain vaccines.<sup>(14)</sup> While such cardiorespiratory effects have not been associated with detrimental effects in the clinical course of immunized neonates, it is advised to monitor patients at risk closely, including very low birth weight infants, those at younger age or those presented with apnea within 24 hours prior to immunization.<sup>(14)</sup>

Neonates staying in the hospital may receive scheduled vaccinations as inpatients. An exception is oral rotavirus vaccine,<sup>(14)</sup> which is not included in the government vaccination program but is available in private settings. It should not be administered until the patient is discharged from the hospital.<sup>(14)</sup> Such deferral is for the prevention of nosocomial disease

spread, as the vaccine is in the form of live virus.<sup>(14)</sup> Another vaccine of concern is hepatitis B vaccine. For neonates born to mothers with negative Hepatitis B surface antigen (HbsAg) status, the initial dose can be given at birth if the birth weight is at least 2kg; the dose should be delayed until 1 month after birth or at discharge if the birth weight is less than 2 kg.<sup>(14)</sup> If maternal HbsAg status is positive or unknown, the neonate should receive the initial dose within the first 12 hours of life regardless of birth weight.<sup>(14)</sup> However, for neonates weighing less than 2 kg at birth, the initial vaccine dose should not be counted towards the 3 doses of vaccine series to complete the immunization series due to potentially decreased immunogenicity.<sup>(14)</sup> Three more doses of vaccinations should be given subsequently.<sup>(14)</sup> While such practice is advocated by the American Academy of Pediatrics, local practice may vary among different hospitals.

### Can pregnant women receive vaccinations?

Vaccination is an effective means to protect the pregnant women from certain infections and can confer protection to the infant after birth.<sup>(16)</sup> Although it is preferable to get all the necessary vaccinations prior to pregnancy, some vaccinations should still be received during pregnancy if indicated.<sup>(16)</sup>

Based on the theoretical risk of infection to the fetus, live vaccines should not be given during pregnancy.<sup>(16)</sup> If a woman inadvertently received live vaccine during pregnancy or within 28 days before conception, she should be counseled for the possible adverse effects to the infant.<sup>(17)</sup> In circumstances in which the pregnant woman is under substantial risk of infection associated with mortality or serious morbidity, live vaccines could be given after careful consideration of risk and benefit.<sup>(16)</sup> For example, a pregnant woman at high risk of yellow fever exposure may be given yellow fever vaccine although it is a live vaccine.<sup>(16)</sup>

Other types of vaccines including inactivated and immune globulin are generally safe to be given during pregnancy.<sup>(16)</sup> There is no evidence of them causing harm to the fetus.<sup>(16)</sup> Inactivated vaccines such as inactivated influenza vaccine and hepatitis A, hepatitis B vaccines should be given to pregnant women if indicated.<sup>(16)</sup>

Despite the fact that Human Papillomavirus (HPV) vaccine is not a live vaccine, it is not recommended to be used in pregnancy due to lack of safety data. If a woman has already started the vaccination series and a shot is due during pregnancy, it should be postponed until after delivery.<sup>(16)</sup>

### What if the patient got an allergic reaction to the vaccine?

According to the World Allergy Organization (WAO), allergic reactions to vaccine is classified into immediate or delayed based on the timing of symptoms appearance.<sup>(18)</sup>

Immediate reactions happen within an hour of vaccination, and are often mediated by immunoglobulin E (IgE). There may be cutaneous (e.g. itching, flushing, angioedema), respiratory (e.g. wheezing, increased nasal discharge) or cardiovascular (e.g. syncope, hypotension) symptoms. The most severe systemic manifestation, anaphylaxis, is rare, with rates reported from 0.65 to 1.31 per million vaccine doses.<sup>(18)</sup>

Delayed reaction happens several hours or even days after vaccination. These reactions are usually due to mechanisms other than IgE. Most common reactions include fever and local reactions such as swelling and redness at injection site. Other less common reactions include vasovagal reactions (fainting) and encephalopathy.<sup>(18)</sup>

The approach to patients allergic to vaccinations depends on the nature of the reaction. Common delayed reactions (e.g. fever, local reactions) are usually self-limiting and do not preclude patients from receiving further vaccinations. They could be relieved by medications such as paracetamol or non-steroidal anti-inflammatory drugs. However, prophylaxis or empirical treatment with antipyretics is not routinely recommended as these medications may reduce the immune response to vaccination. Some less common delayed reaction (e.g. encephalopathy) could have serious sequelae, hence may preclude the patient from receiving further specific vaccines.<sup>(18)</sup>

Patient who experienced vasovagal reactions to a vaccine may receive further vaccinations, but subsequent vaccinations should be given while the patient is in a supine position. For patients having an IgE mediated allergy to a vaccine, it is important to differentiate whether the reaction was due to the vaccine itself or other constituents in the vaccine. If the patient is having true allergy to the vaccine itself and has not completed the vaccination series, a decision on whether further doses should be given has to be made. Some individuals could have an adequate immune response without completing the whole vaccination series. The antibody level could be tested and if sufficient protective antibodies could be detected, further doses of the vaccination series may not be necessary. However, one has to be aware that such antibody level may not persist for as long as that induced by a complete vaccination series. It is recommended that if it is decided that further dose(s) of the vaccine is needed, a series of skin tests should be conducted prior to vaccination. If the skin test is positive, the vaccine should be given in graded doses and should be done in an environment ready for treatment of anaphylaxis. If the skin test is negative, the vaccine can be given in the usual manner but the patient should be observed for at least 30 minutes.<sup>(18)</sup> However, such skin test may not be available in institutions in Hong Kong.

### Should booster doses of hepatitis B vaccine be given to patients with reduced antibody level?

Whether a booster vaccine is to be given as a result of low antibody level depends on the timing of serology testing.

In line with WHO recommendations, hepatitis B vaccination is included in the government vaccination program as a 3-dose-regimen, the first dose given at birth, second dose given at 1 month and third dose given at 6 month of life.<sup>(4)</sup> The complete vaccine series has a response rate of 95%.<sup>(19)</sup> While post-vaccination serology test is not considered necessary in the majority of patients, it could be considered in special situations (**Table 3**).<sup>(17,20)</sup> When post-vaccination serology testing is indicated, it should be conducted 1 to 2 months after completing the vaccination series (except infants born to HBV carrier mothers, who should be tested at 9 to 12 months of age). An inadequate response to the vaccine is defined as

Table 3. People in which post-vaccination serology test is recommended <sup>(17,20)</sup>	
Category	Examples
Patients at significant occupational risk	Healthcare workers
Patients at risk of recurrent hepatitis B exposure	Individuals with sexual partners who are HBV carriers Infants of HBV carrier mothers
Patients at risk of severe or complicated hepatitis B disease	Patients with immunocompromised state Patients with underlying liver disease unrelated to hepatitis B
Patients likely to have poor response to hepatitis B vaccination	Patients on hemodialysis Patients with bleeding disorders who received vaccination via the subcutaneous route

having an anti-HBs level lower than 10mIU/mL.<sup>(17)</sup> Such non-responders should receive a second 3-dose-vaccine series, and be retested after completion.<sup>(20)</sup> HBsAg should be tested for individuals failing to respond after the second vaccine series.<sup>(20)</sup> While such international recommendation exists, it may not be widely adapted in hospitals in Hong Kong.

For patients distantly vaccinated, serology test is no longer a reliable indicator of protection. Studies have shown that for patients who have been vaccinated years before, despite low or undetectable antibody levels, they were still protected against asymptomatic and symptomatic HBV manifestations after exposure.<sup>(19)</sup> In such patients, booster doses are probably not necessary as there is good anamnestic response with HBV vaccine.<sup>(21)</sup>

## CONCLUSION

Vaccination is undoubtedly a great means for attainment of global health, saving millions of lives every year. The advancements in vaccination have never stopped; many new vaccines are in the pipeline, with the hope to prevent fatal diseases such as Ebola and Human immunodeficiency virus (HIV). As experts in pharmacotherapy, pharmacists should continue to equip and update themselves. By providing appropriate advice to fellow healthcare professionals and the public, vaccinations could be better utilized for the benefits of our patients.

### Author's background

**LEUNG, Tsz-Hin Stanley** was graduated from the school of Pharmacy of The Chinese University of Hong Kong. He is currently a resident pharmacist working in Queen Mary Hospital. His corresponding e-mail address is lth468@ha.org.hk  
**NGAI, Cheuk-Yan Vivian** was graduated from the Department of Pharmacology and Pharmacy, The University of Hong Kong. She is currently a resident pharmacist working in Queen Mary Hospital. Her corresponding e-mail address is ncy675@ha.org.hk  
**WONG, Kai-Chung Vincent** is the Board Certified Geriatric, Pharmacotherapy and Oncology Specialists of USA. He is a registered pharmacist of Australia and Hong Kong and currently working in Queen Mary Hospital. His current address: wkc293@ha.org.hk  
**MAK, Wai-Ming Raymond** graduated from the School of Pharmacy of the University of Bradford, United Kingdom. He is the Board Certified Pharmacotherapy Specialist of USA and currently working as a clinical pharmacist in Queen Mary Hospital. His corresponding e-mail address is makwmr@ha.org.hk  
**CHUI, Chun-Ming William** is the Honorary Associate Professor of the University of Hong Kong, Clinical Stream Coordinator (Pharmacy) of Hong Kong West Cluster and the Department Manager of Pharmacy of QMH, Hospital Authority.

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# Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website ([www.pcccchk.com](http://www.pcccchk.com)) to fill in their answers there.)

1. Which of the following is a live attenuated vaccine?

- A. Measles, Mumps & Rubella (MMR) vaccine
- B. Hepatitis A vaccine
- C. Pertussis vaccine
- D. Pneumococcal conjugate vaccine

2. Which of the followings is a CORRECT statement about vaccination and autism?

- A. Although there are substantial evidence supporting the association of Measles, Mumps & Rubella (MMR) vaccination and autism, all patients should receive vaccination as the benefit outweighs the risk.
- B. The fact that mercury poisoning and autism share similar clinical features is supportive of the association between vaccination and autism, as some vaccines contain thimerosal (sodium ethylmercury thiosalicylate) as preservative.
- C. Patients with family histories of autism must not receive MMR vaccine.
- D. None of the above

3. Which of the following vaccines are covered by the Hong Kong Childhood Immunization Program?

- (i) Haemophilus influenzae type B vaccine
- (ii) Hepatitis B vaccine
- (iii) Bacille Calmette-Guérin (BCG) vaccine

- A. (i) and (ii)
- B. (ii) and (iii)
- C. (i) and (iii)
- D. (i), (ii) and (iii)

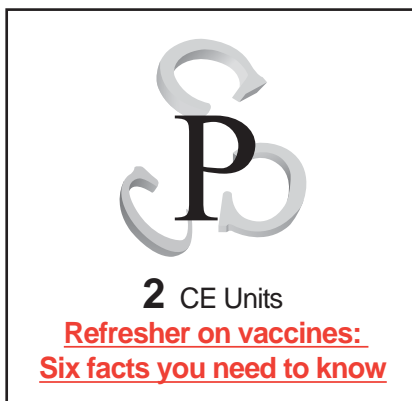
4. Which of the following statement(s) regarding thimerosal (sodium ethylmercury thiosalicylate) in vaccine is/are CORRECT?

- A. It is used to boost the immunogenic effect of the vaccine in children.
- B. It is broken down to ethylmercury in our body but it is actively excreted by our gut and its half-life is less than 1 week.
- C. Many studies have found that thimerosal in vaccine is a significant risk factor for autism.
- D. All of the above

5. Which of the following statements are INCORRECT regarding vaccination in pregnancy?

- (i) A pregnant woman who will be at risk of yellow fever exposure should not receive yellow fever vaccine since it is a live vaccine.
- (ii) A pregnant woman who has accidentally received live vaccine should consider abortion.
- (iii) Inactivated vaccines (e.g. influenza vaccine) may be given during pregnancy.

- A. (i) and (ii)
- B. (ii) and (iii)
- C. (i) and (iii)
- D. (i), (ii) and (iii)



6. Which of the following statements are CORRECT regarding vaccination in preterm neonates?

- (i) Preterm babies (gestational age less than 37 weeks) may receive childhood vaccinations but the dose should be adjusted based on body weight.
- (ii) Oral rotavirus vaccine should not be given to neonates before they are discharged from the hospital.
- (iii) Neonates of very low birth weight (less than 1500g) may have decreased immune response to vaccination.

- A. (ii) only
- B. (i) and (ii)
- C. (ii) and (iii)
- D. (i), (ii) and (iii)

7. Which of the following is a CORRECT approach to patients who had an IgE mediated allergy to a vaccine?

- A. The antibody level should be tested to see whether sufficient protective antibodies are detected.
- B. If the skin test for the vaccine is positive, the patient must not receive the vaccination again.
- C. The patient may receive the vaccination again with antihistamine and corticosteroid prophylaxis without conducting a skin test.
- D. If the skin test for the vaccine is negative, the patient may be given the vaccination again without additional monitoring.

8. Which of the following(s) are FALSE regarding the timing of vaccine administration?

- (i) When two or more vaccines are given on the same day, the risk of adverse reaction must be higher.
- (ii) Two inactivated vaccines should be given at least 4 weeks apart from each other.
- (iii) To ensure adequate antibody responses, vaccinations for different diseases should not be given on the same day.

- A. (i) and (ii)
- B. (i) and (iii)
- C. (ii) and (iii)
- D. (i), (ii) and (iii)

9. Which of the following statements are TRUE regarding vaccination and allergy?

- A. Anaphylaxis to vaccinations are rare, with reported rates of 0.65-1.31%.
- B. Delayed reactions to vaccinations may happen hours or even days after vaccination.
- C. Empirical antipyretics should be given to reduce the risk of delayed reactions such as fever.
- D. Vasovagal reactions may be dangerous and hence should be considered a contraindication for further vaccinations.

10. Which of the following statement(s) regarding Hepatitis B vaccine is/are TRUE?

- (i) Hepatitis B vaccination is commonly associated with autism.
- (ii) Hepatitis B vaccine should be given for 3 doses in total, with each separated by 2 months.
- (iii) Hepatitis B is available as an inactivated vaccine.

- A. (iii) only
- B. (i) and (ii)
- C. (i) and (iii)
- D. (ii) and (iii)

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 242(D&T)

Drug-induced Photosensitivity

1. C 2. B 3. D 4. A 5. D 6. A 7. B 8. B 9. B 10. C

# CRISPR / Cas-Based Gene Editing Opens a New Era for Genome Engineering and New Drug Discovery

**TSAI, Jui-Ling; CHEUNG, Hon-Yeung\***

*Research Group for Bioactive Products, Department of Biomedical Sciences, City University of Hong Kong, Hong Kong SAR, China*

*(\*Corresponding author. E-mail: cheung.honyeung@cityu.edu.hk Tel: +852 3442-7746; Fax: +852 3442-0522)*

### ABSTRACT

The CRISPR / Cas system (Clustered Regions of Interspersed Palindromic Repeats-Cas), is present in bacterial and archaeal genomes as an adaptive immune system for defense against viral attack. It was first discovered by Francisco Mojica in 1993. This system consists of a DNA-nuclease Cas protein and two noncoding RNAs, crRNA and tracrRNA; all of them fused with a single guide RNA (sgRNA) that are housed in on a target DNA sequence to allow precisely targeted mutations, transcriptome gene editing. It is a sophisticated adaptive immune system very different from T and B lymphocytes found in higher vertebrate animals. This newly discovered system has emerged as a masterpiece of technology for precise editing of the genome in all sorts of cells. It is more robust to be customized and optimized because selection of DNA cleavage site is guided by a short sequence of RNA (gRNA). Even though Off-target effects are a drawback for its applications, the CRISPR/Cas9 system is being widely and successfully applied in many fields, namely, edition of defective genes in human embryos and creation of specific DNA fragment for correction of numerous genetic diseases as well as providing a platform for new drug discovery. We believe in the very near future this technology will open up lots of new avenues for industries and therapeutic.

**Keywords:** CRISPR, Cas9, sgRNA, adaptive immune system, gene editing, new drug discovery, off-target effects

### INTRODUCTION

The development of recombinant DNA technology in the late 1970s marked the beginning of a new era for biology.<sup>(1)</sup> For the first time, molecular biologists gained the ability to manipulate DNA molecules, making it possible to study genes and harness them to produce novel medicine. Despite the significant understanding of genetics and technology, the challenge of precise alteration genomes at the level of a single gene persists. Even though genetic engineering has been applied to a diverse range of fields, including drug development, gene therapy, molecular evolution and synthetic biology, development of efficient and reliable ways to make precise, targeted changes

to the genome of living cell remains a long-standing goal for many biomedical researchers.<sup>(1-2)</sup>

### WHAT IS CRISPR-BASED GENE EDITING?

To overcome these challenges, a series of programmable nuclease-based genome editing technologies have been developed in recent years with aims to targeting and efficiently modifying a variety of eukaryotic genome, in particular, the mammalian genome. Of the current genome editing techniques, the most popular one is a class of RNA-guided endonucleases known as Cas9 isolated from the microbial adaptive immune system CRISPR. It is a DNA loci that contain multiple, short, direct repetitions of base sequences which are inherited as a result of previous infections. After expression, RNA-guided gene editing platform makes a small strand of RNA that interacts with invasive DNA. Cas gene coding for proteins involved in CRISPR function CAN make use of a bacterial protein 9 and a systematic guide RNA to introduce a double stranded break at a specific location within the genome.<sup>(1-4)</sup>

### HOW CRISPR-CAS9 SYSTEM IS USED IN DISEASE STUDY?

Much attention has been focused on the potential of CRISPR–Cas to cure Mendelian diseases, as it also holds promise to transform the development of therapies to treat complex heritable and somatic disorders.<sup>(5)</sup> CRISPR / Cas9 is an abbreviation name of a “clustered regularly interspaced short palindromic repeat / CRISPR associated protein 9”, which is mainly derived from the immune system of bacteria or ancient bacteria that contains snippets of DNA from viruses that attack the bacterium.<sup>(4,6)</sup> At present, we understand that these snippets are used by the bacterium to detect and destroy DNA from further attacks by other similar viruses. These sequences play a key role in a bacterial defense system. The CRISPR–Cas system, which targets DNA or RNA as a way of protecting against viruses and other mobile genetic elements, is found on both chromosomal and plasmid DNA, and the spacers are often derived from genetic sequences of viruses and plasmids. It is assumed that these viral genetic sequences were incorporated into the genomes of the host bacteria previously and now these

viral genetic elements can be utilized to degrade the same or similar viral genes, providing the host cells with adaptive immunity. The functions of CRISPR and CRISPR-associated (Cas) genes are critical in adaptive immunity in selected bacteria and archaea, empowering the organisms to respond to and eradicate invading genetic material. Three types of CRISPR mechanisms have been identified, of which type II is studied the most.<sup>(6)</sup>

In nature, the CRISPR/Cas system makes up the prokaryotic adaptive immune system by defending against infection by plasmids and phages through silencing of exogenous DNA invading material. Researchers can exploit this mechanism by introducing plasmids with Cas genes and specifically designed CRISPRs for an organism. This unique system fosters another genetic modification of the genome of most of the prokaryotic or eukaryotic organisms at a precise site. Here, we discuss the mechanism, applications, and future potential of CRISPR associated endonuclease Cas 9 system.<sup>(7)</sup>

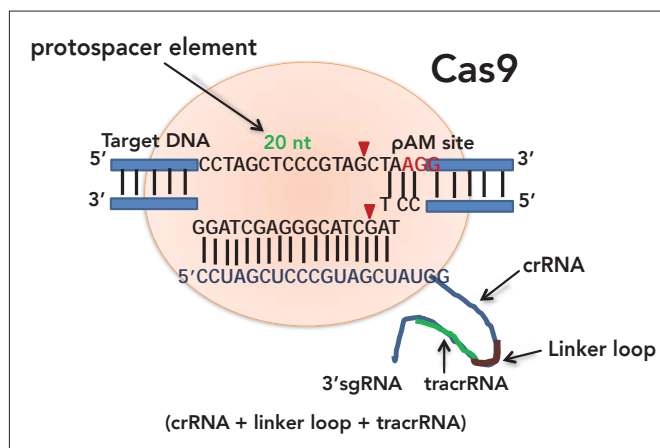
### HOW CRISPR-CAS9 SYSTEM IS USED FOR TARGET DISCOVERY AND FUNCTIONAL SCREENING OF BIOMOLECULES?

A simple version of the CRISPR/Cas system, CRISPR/Cas9, has been modified to edit genomes. By delivering the Cas9 nuclease complexing to a synthetic guiding RNA (gRNA) in a cell, the cell's genome can be cut at a desired location, allowing existing genes to be removed and/or addition of new one gene.<sup>(6)</sup> The Cas9-gRNA complex corresponding to the CAS III crRNA complex offers the unique ability of the Cas III protein and it is favored by scientists. It is well suited for use as a component of gene knockout technology.<sup>(8-9)</sup>

The Cas9/sgRNA complex binds double-stranded DNA sequences that contain a sequence match to the first 17-20 nucleotides of the sgRNA if the target sequence is followed by a protospacer adjacent motif (pAM) (**Figure 1**). Once bound, two independent nuclease domains in Cas9 will each cleave one of the DNA strands 3 bases upstream of the pAM, leaving a blunt end DNA double stranded break (DSB). DSBs can be repaired mainly through either the nonhomologous end joining (NHEJ) pathway or homology-directed repair (HDR). NHEJ typically leads to short insertion/deletion (indels) near the cutting site, whereas HDR can be used to introduce specific sequences into the cutting site if exogenous template DNA is provided. This discovery paved the way for use of Cas9 as a genome-engineering tool in other species.<sup>(1, 6, 8, 10, 11)</sup>

### REPAIR MECHANISM OF DOUBLE-STRANDED DNA BREAKS VIA HOMOLOGOUS RECOMBINATION AND NON-HOMOLOGOUS END-JOINING

In Brief, CRISPR / Cas9 technology utilizes the Cas9 protein to cut specific genomic loci, to achieve gene knockout. However, just cutting DNA and inhibiting DNA expression? For cells, double-stranded DNA break (DSB) is a serious damage, the cells certainly will carry out the repairs mechanisms and want to be completely repaired that it need a suitable "reference template", such as a complementary strand of double-stranded



**Figure 1. The CRISPR-Cas9 system.** The Cas9 nuclease from *S. pyogenes* (orange) is targeted to genomic DNA. Individual tracrRNA (green) and crRNA with protospacer element are fused through a linker loop sequence (brown) to generate a single sgRNA molecule. The sgRNA targets the Cas9 protein to genomic sites containing sequences complementary to the 5' end of the sgRNA. The target DNA sequence needs to be followed by a proto-spacer adjacent motif (pAM), typically NGG. Cas9 is a DNA endonuclease with two active domains (red triangles) cleaving each of the two DNA strands three nucleotides upstream of the PAM. The five nucleotides upstream of the PAM are defined as the seed region for target recognition.

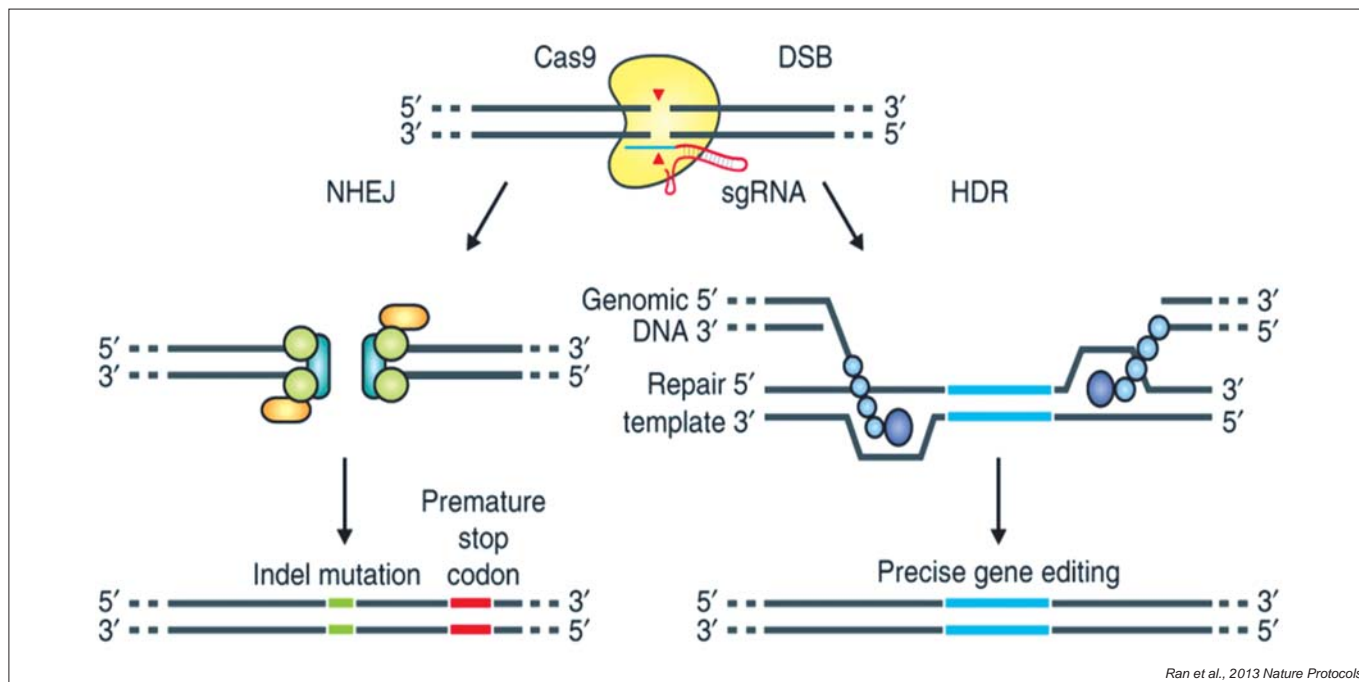
DNA.<sup>(12-13)</sup> In the evolution of we believe that DNA exists as in a double helix way. When DNA double-stranded breaks simultaneously, it will lose the continuity of DNA messages, which becomes a thorny problem. We have been aware of cells can be repaired via two pathways (**Figure 2**).<sup>(9, 14)</sup> The traditional approach is called the homologous recombination, which mainly uses the DNA as a template for another homologous chromosome, and then completes the repair of the damaged DNA.<sup>(15)</sup>

However, this paper focuses on the other systems is called non-homologous end-joining systems (NHEJ).<sup>(12)</sup> Compared with the former, it is obvious to have an insight into that the repair of this system is perfunctory. Because it binds to the breakage of the double-stranded DNA fragments by special proteins, and then "sticks" these DNAs which is not rigorous in matching any DNA sequences.

Even the NHEJ system sounds very rough in endogenous repair. In fact, it is expedient on crisis management. Under cell division, it is hard to correctly distribute the duplicate chromosomes in matching if DNA double-stranded breaks. Due to the NHEJ system hastily repaired and result in losing from one to several nucleotides nearby nick, causing the formation of "deletion" mutation.<sup>(9, 16)</sup> If the junction point is in gene, it will cause the codon "frameshift", making the nonfunctional proteins. Therefore, the principle of CRISPR / Cas9 via Cas9 protein attack the target genes to induce double-stranded DNA which produce the missing nucleotides results of repair mechanisms in a cell achieve genes deletion.<sup>(9, 13)</sup>

### NOVEL APPLICATIONS OF CRISPR/ CAS9 FOR GENE EDITING

Although use of CRISPR/Cas9 is still mainly confined to the basic research area in the drug discovery process, its potential with respect to the identification and validation of new



**Figure 2.** DSBs induced by Cas9 (yellow) can be repaired in one of two ways. In the error-prone NHEJ pathway, the ends of a DSB are processed by endogenous DNA repair machinery and rejoined, which can result in random indel mutations at the site of junction. Indel mutations occurring within the coding region of a gene can result in frameshifts and the creation of a premature stop codon, resulting in gene knockout. Alternatively, a repair template in the form of a plasmid or ssODN can be supplied to leverage the HDR pathway, which allows high fidelity and precise editing. Single-stranded nicks to the DNA can also induce HDR.

therapeutic targets, the investigation of mechanism of action and in the creation of screens to identify genes that regulate various cell biological processes are major objectives. Using this system, DNA sequences within the endogenous genome and their functional outputs are now easily edited or modulated in virtually any organism of choice. Cas9-mediated genetic perturbation is simple and scalable, empowering researchers to elucidate the functional organization of the genome at the systems level and establish causal linkages between genetic variations and biological phenotypes. Its application in genome-wide studies will enable large-scale screening for drug targets and other phenotypes and will facilitate the generation of engineered animal models that will benefit pharmacological studies and the understanding of human diseases (Figure 3).

Applying CRISPR-Cas editing to animals will lead to better models of human disease, more predictive safety testing, and improved stratification and treatment regimens for patients. Rapid gene editing and regulation also promise to enable innovative therapies for non-genetic diseases through the generation of customized autologous cellular treatments, including cancer-seeking T cells and reprogrammed iPSCs. While CRISPR-Cas systems will undoubtedly improve further, and new complementary or orthogonal methods will be developed to deliver reagents and edit somatic tissues directly in humans, we believe that gene editing is ready to have an immediate impact in real-world drug discovery and development. CRISPR-Cas-aided discovery, validation and safety testing allow acceleration and improvement of known protocols and pipelines, without the need to solve delivery or redefine administrative procedures. CRISPR-Cas will be key to the next generation of transformational therapies and treatment paradigms.<sup>(7)</sup> CRISPR-CAS9 applications in plants and fungi also promise to change the pace and course of agricultural research.

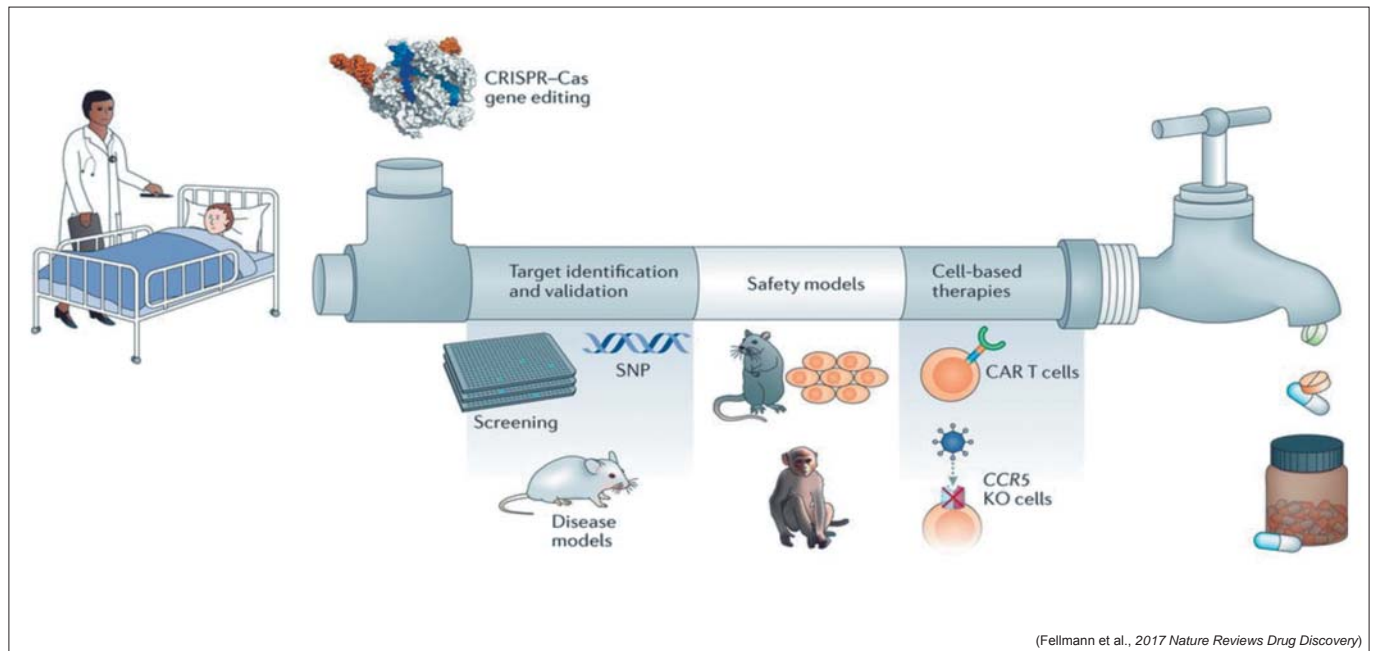
## THE PRACTICAL SETUP FOR CARRYING OUT A STUDY WITH THIS SYSTEM

CRISPR technology has not yet been adequately tested in humans, but there is no reason to suspect that it will not work just as well in people as in other animals. A Chinese team of researchers recently announced that they attempted to edit the genes in human embryos with the genetic disease beta-thalassemia. The results were mixed, and were not reliable enough to be a safe and effective treatment. The results suggest that the application of CRISPR to human disease needs to be further developed before we will begin seeing treatments based on this technology.

There are research teams currently working on just that. The low-hanging fruit for application in humans are diseases in which the cells are easily accessible. One company, Editas, is working on two possible applications. The first is a treatment for a rare retinal disease, Leber congenital amaurosis. This would involve treating the retina, which is easily accessible. The second application is the treatment of blood cancers by removing immune cells from the patient, then using CRISPR to target those immune cells against the cancer, and inject them back into the patient. There is no theoretical reason why any cell population in the body cannot be targeted, but there may be significant practical limitations.<sup>(17)</sup>

## THE ADVANTAGE AND DISADVANTAGE OF THE CRISPR/CAS9 IN APPLICATION

CRISPR / Cas9 technology is quite favored and popular recently, the main reason is because it makes use of nucleic acid as a tool to identify the target gene, which makes the experimental cost can be greatly reduced. And CRISPR / Cas9 technology has a higher tolerance on the target gene sequence and is not limited by the combination of certain DNA sequences.



**Figure 3. Unmet medical needs for numerous diseases and the rapid progress of CRISPR–Cas gene editing can feed into a drug discovery and development pipeline, which leads to improved therapies.** The CRISPR–Cas system allows for improved target identification and validation as well as faster generation of safety models. CRISPR–Cas can also be used to develop cell-based therapies, such as chimeric antigen receptor (CAR) T cells for immunotherapy and C-C motif chemokine receptor 5 (CCR5)-knockout (KO) cells for HIV treatment. CRISPR–Cas-assisted drug discovery will yield innovative therapies and treatment paradigms for patients. SNP, single-nucleotide polymorphism.

Since embryonic stem cells are not needed, emerging gene knockout techniques, including CRISPR / Cas9 technology, can be widely used in a variety of living organisms, unlike gene knockout only in mice only.<sup>(9,18)</sup> For this article, we summarize the advantage of the CRISPR-Cas9 is shown as below:

- (1) Using CRISPR-Cas9 system, it is a free-limit in species, such as animals, plants, bacteria and other organisms to find the target sequence.
- (2) To construct the plasmid is easy and quick to complete it successfully within a few days.
- (3) Design the target site is easy to find one time of the pAM sequence (NGG) within 128 nucleotides at least, and both sense strand and antisense strand of DNA sequences can also be designed.
- (4) Cas9 is a high-efficiency enzyme to recognize the pAM sequence to target the sequence.
- (5) It can be introduced two or more sgRNAs simultaneously to target multiple genes sites to reach the purpose of genes deletion in CRISPR-Cas9 system.
- (6) It can directly effect on the DNA sequence to make gene silencing easier, and CREISPR-Cas9 system instead of the RNA (RNAi) or Morpholino gene interference gradually.

The emerging technology of CRISPR/CAS9 system seems to be very perfect, but these methods are not without “Achilles’ heel”, their biggest problem lies in the editing process is not sufficiently transparent. As we known, the gene-knockout mice are treated by gene replacement with DNA fragments as a non-activated gene. We can use polymerase chain reaction (PCR) to confirm whether the specific DNA exists in mouse or not. However, it is hard to be validated by PCR if using CRISPR / Cas9 technique. Because the site of genes adjunction is deleted which part is removed certain one nucleotide and results in frame shift, reading previous stop codon, resulting in a change of all amino acids.<sup>(9)</sup> Actually, “off target” refers to the possibility of attacking other genes by Cas9,<sup>(19)</sup> in addition, the target gene which is easily demonstrated in the

study of gene knockout mice, but for CRISPR-CAS9 system is difficult to find it.<sup>(20)</sup>

### CORNCERNS OF DELIVERY AND OFF-TARGET EFFECT

The CRISPR-Cas9 has revolutionized the field of molecular biology, medical genetics and medicine. The technology is robust, facile and simple to achieve genome targeting in cells and organisms. The appropriate alternative of delivery system is critical if genome editing systems are to be effectively performed in the targeted cells or organisms. To date, the in vivo delivery of the Cas9 system remains challenging, we look back at the delivery approaches that have been used for the delivery of the Cas9 system and outline the recent development of nonviral vectors that might be potential carriers for the genome editing platform in the future. The efforts in optimizing cationic nanocarriers with structural modification are described and promising nonviral vectors under clinical investigations are highlighted.<sup>(23)</sup> On the other hand, to propagate these nucleases for therapeutic application, the on-target specificity is of paramount importance. Although the binding and cleavage of off-target sites by Cas9 is issue of concern, however the specificity of CRISPR technology is greatly improved in current research employing the use of engineer nucleases, improved gRNA selection, novel Cas9 orthologs and the advancement in methods to detect and screen off-target sites and its effects.<sup>(21-22)</sup>

### CONCLUSIONS

The CRISPR-CAS9 system may well have opened Pandora’s box, but it is also definitely the cornucopia of genome editing. We can do what we want in the genome: settle a mutation, correct a mutation, insert a fluorescent tag to a protein, add an exogenous gene, delete an endogenous function, suppress a cis-regulatory region, add a reporter.

Although the CRISPR / Cas9 technology was proposed in 2010, it has become the mainstream of academic research within the last few years. Besides its easy operation, cheaper cost and specific, it set off a revolution for life science.<sup>(7)</sup> The discovery of biological concepts can often provide a framework for the development of novel molecular tools, which can help increase understanding and manipulation life. CRISPR-Cas systems are now a useful tool kit for engineering eukaryotic cells, especially human cells. The CRISPR approach is an additional tool for biologists' use, and which can become a means for medical application.

The CRISPR/Cas9 system greatly simplifies genome editing and has great promise in many applications areas such as stem cell engineering, gene therapy, drug development, tissue and animals disease models, agriculture, plant disease resistance etc.

In drug development, CRISPR can provide a more effective method to probe the function of specific genes, that drug discovery and validation can be accelerated. In gene therapy CRISPR offers precise editing or knockout of specific segments of a genome, enabling genetic research of defective genes and their behavior. Future research on basic mechanistic details of the different CRISPR/Cas systems is expected to reveal a more complete picture of the extensive applicability of these immune complexes. The foremost problems that must be overcome are addressing CRISPR specificity (off-target effects) and developing effective and a safe delivery system.<sup>(7)</sup> There are a growing number of researchers from many disciplines collaborating to bring ambitious CRISPR-based insight, technology and therapeutics into the clinic. CRISPR-Cas9 has triggered a revolution in which laboratories around the world are using the technology for innovative applications in biology as well as future directions.<sup>(23)</sup> Eventually the benefits of biological technologies come to be recognized, while the worst fears never manifest. This does not mean we do not need to think carefully about new technologies, and to regulate them properly.

#### Author's background

**Dr. TSAI Jui-Ling**, obtained her PhD in life science from National Taiwan University. She worked as a Post-Doctoral Fellow in Professor Newman Sze's laboratory at Nanyang Technological University in Singapore before joining Dr. Cheung's laboratory. Her main interest is in cancer research and drug discovery. **Dr. CHEUNG Hon-Yeung**, who is an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong, is a Manufacturing Pharmacist and Biotechnologist. He has more than 400 publications and received many awards for both of his research and academic works.

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## Supplementary Information – CRISPR Timeline

The discovery of the CRISPR-Cas microbial adaptive immune system and its ongoing development into a genome editing tool represents the work of many scientists from around the world. This timeline presents a concise history of the seminal contributions and the scientists who pushed this field forward, from the initial discovery to the first demonstrations of CRISPR-mediated genome editing. For a narrative perspective of the history of CRISPR research, read “The Heroes of CRISPR,” by Eric S. Lander, in the January 14, 2016 edition of *Cell*.

### Discovery of CRISPR and its function

1993 - 2005 - - Francisco Mojica, University of Alicante, Spain

Francisco Mojica was the first researcher to characterize what is now called a CRISPR locus, reported in 1993. He worked on them throughout the 1990s, and in 2000, he recognized that what had been reported as disparate repeat sequences actually shared a common set of features, now known to be hallmarks of CRISPR sequences (he coined the term CRISPR through correspondence with Ruud Jansen, who first used the term in print in 2002). In 2005 he reported that these sequences matched snippets from the genomes of bacteriophage.<sup>(1)</sup> This finding led him to hypothesize, correctly, that CRISPR is an adaptive immune system. Another group, working independently, published similar findings around this same time.<sup>(2)</sup>

### Discovery of Cas9 and PAM

May, 2005 — Alexander Bolotin, French National Institute for Agricultural Research (INRA)

Bolotin was studying the bacteria *Streptococcus thermophilus*, which had just been sequenced, revealing an unusual CRISPR locus.<sup>(3)</sup> Although the CRISPR array was similar to previously reported systems, it lacked some of the known cas genes and instead contained novel cas genes, including one encoding a large protein they predicted to have nuclease activity, which is now known as Cas9. Furthermore, they noted that the spacers, which have homology to viral genes, all share a common sequence at one end. This sequence, the protospacer adjacent motif (PAM), is required for target recognition.

### Hypothetical scheme of adaptive immunity

March, 2006 — Eugene Koonin, US National Center for Biotechnology Information, NIH

Koonin was studying clusters of orthologous groups of proteins by computational analysis and proposed a hypothetical scheme for CRISPR cascades as bacterial immune system based on inserts homologous to phage DNA in the natural spacer array, abandoning previous hypothesis that the Cas proteins might comprise a novel DNA repair system.<sup>(4)</sup>

### Experimental demonstration of adaptive immunity

March, 2007 — Philippe Horvath, Danisco France SAS

*S. thermophilus* is widely used in the dairy industry to make yogurt and cheese, and scientists at Danisco wanted to

explore how it responds to phage attack, a common problem in industrial yogurt making. Horvath and colleagues showed experimentally that CRISPR systems are indeed an adaptive immune system: they integrate new phage DNA into the CRISPR array, which allows them to fight off the next wave of attacking phage.<sup>(5)</sup> Furthermore, they showed that Cas9 is likely the only protein required for interference, the process by which the CRISPR system inactivates invading phage, details of which were not yet known.

### Spacer sequences are transcribed into guide RNAs

August, 2008 — John van der Oost, University of Wageningen, Netherlands

Scientists soon began to fill in some of the details on exactly how CRISPR-Cas systems “interfere” with invading phage. The first piece of critical information came from John van der Oost and colleagues who showed that in *Escherichia coli*, spacer sequences, which are derived from phage, are transcribed into small RNAs, termed CRISPR RNAs (crRNAs), that guide Cas proteins to the target DNA.<sup>(6)</sup>

### CRISPR acts on DNA targets

December, 2008 — Luciano Marraffini and Erik Sontheimer, Northwestern University, Illinois

The next key piece in understanding the mechanism of interference came from Marraffini and Sontheimer, who elegantly demonstrated that the target molecule is DNA, not RNA.<sup>(7)</sup> This was somewhat surprising, as many people had considered CRISPR to be a parallel to eukaryotic RNAi silencing mechanisms, which target RNA. Marraffini and Sontheimer explicitly noted in their paper that this system could be a powerful tool if it could be transferred to non-bacterial systems. (It should be noted, however, that a different type of CRISPR system can target RNA.<sup>(8)</sup>)

### Cas9 cleaves target DNA

December, 2010 — Sylvain Moineau, University of Laval, Quebec City, Canada

Moineau and colleagues demonstrated that CRISPR-Cas9 creates double-stranded breaks in target DNA at precise positions, 3 nucleotides upstream of the PAM.<sup>(9)</sup> They also confirmed that Cas9 is the only protein required for cleavage in the CRISPR-Cas9 system. This is a distinguishing feature of Type II CRISPR systems, in which interference is mediated by a single large protein (here Cas9) in conjunction with crRNAs.

### Discovery of tracrRNA for Cas9 system

March, 2011 — Emmanuelle Charpentier, Umea University, Sweden and University of Vienna, Austria

The final piece to the puzzle in the mechanism of natural CRISPR-Cas9-guided interference came from the group of Emmanuelle Charpentier. They performed small RNA sequencing on *Streptococcus pyogenes*, which has a Cas9-

containing CRISPR-Cas system. They discovered that in addition to the crRNA, a second small RNA exists, which they called trans-activating CRISPR RNA (tracrRNA).<sup>(10)</sup> They showed that tracrRNA forms a duplex with crRNA, and that it is this duplex that guides Cas9 to its targets.

### CRISPR systems can function heterologously in other species

July, 2011 — Virginijus Siksnys, Vilnius University, Lithuania

Siksnys and colleagues cloned the entire CRISPR-Cas locus from *S. thermophilus* (a Type II system) and expressed it in *E. coli* (which does not contain a Type II system), where they demonstrated that it was capable of providing plasmid resistance.<sup>(11)</sup> This suggested that CRISPR systems are self-contained units and verified that all of the required components of the Type II system were known.

### Biochemical characterization of Cas9-mediated cleavage

September, 2012 — Virginijus Siksnys, Vilnius University, Lithuania

Taking advantage of their heterologous system, Siksnys and his team purified Cas9 in complex with crRNA from the *E. coli* strain engineered to carry the *S. thermophilus* CRISPR locus and undertook a series of biochemical experiments to mechanistically characterize Cas9's mode of action.<sup>(9)</sup> They verified the cleavage site and the requirement for the PAM, and using point mutations, they showed that the RuvC domain cleaves the non-complementary strand while the HNH domain cleaves the complementary site. They also noted that the crRNA could be trimmed down to a 20-nt stretch sufficient for efficient cleavage. Most impressively, they showed that they could reprogram Cas9 to a target a site of their choosing by changing the sequence of the crRNA.

June, 2012 — Charpentier and Jennifer Doudna, University of California, Berkeley

Similar findings as those in Gasiunas *et al.* were reported at almost the same time by Emmanuelle Charpentier in collaboration with Jennifer Doudna at the University of California, Berkeley.<sup>(12)</sup> Charpentier and Doudna also reported that the crRNA and the tracrRNA could be fused together to create a single, synthetic guide, further simplifying the system. (Although published in June 2012, this paper was submitted after Gasiunas *et al.*)

### CRISPR-Cas9 harnessed for genome editing

January, 2013 — Feng Zhang, Broad Institute of MIT and Harvard, McGovern Institute for Brain Research at MIT, Massachusetts

Zhang, who had previously worked on other genome editing systems such as TALENs, was first to successfully adapt CRISPR-Cas9 for genome editing in eukaryotic cells.<sup>(13)</sup> Zhang and his team engineered two different Cas9 orthologs (from *S. thermophilus* and *S. pyogenes*) and demonstrated targeted genome cleavage in human and mouse cells. They also showed that the system (i) could be programmed to target multiple genomic loci, and (ii) could drive homology-directed repair. Researchers from George Church's lab at Harvard University reported similar findings in the same issue of *Science*.<sup>(14)</sup>

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## Chemical Components and Biological Activities of *Angelicae sinensis* (Danggui) and Its Closely Related Species

CHEUNG, Hon-Yeung

Department of Biomedical Sciences, City University of Hong Kong, Kowloon Tong, Hong Kong SAR, China  
(Tel: +852 3442 7746, Fax: +852 3442 0522, E-mail address: cheung.honyeung@cityu.edu.hk)

### ABSTRACT

Danggui (DG), also known as Chinese Angelica Root, is considered one of the most important remedies in traditional Chinese medicine for female ailments. It is the dried root of *Angelicae sinensis*. It can promote blood circulation. Recent analytical studies reveal that phthalides, aromatic acids and their esters, polysaccharides are the main chemical components determining its bioactivities. Pharmacological studies indicate that DG inhibits platelet aggregation, dilates coronary arteries, lowers blood lipid levels, promotes the formation of hemoglobin and red blood cells, bi-directionally regulates uterine smooth muscles, and has anti-thrombotic, anti-arrhythmic, anti-inflammatory and analgesic effects. Efficacy of this herbal substance, however, could be affected by which parts of the herb used and also by the processing method.

**Keywords:** *Angelica sinensis* (Oliv.) Diels, Danggui, phthalides, aromatic organic acids, female disorders, blood-tonifying medicinal, menstrual discomfort, postmenopausal symptoms, male fertility

### GENERAL INFORMATION OF THE HERB

**Botanical name:** *Angelica sinensis* (Oliv.) Diels.

**Family:** Apiaceae (or Umbelliferae)

**Common names/other names:** Chinese Angelica Root, Dang Guei, Ganggui, Guei Tou, Guei Shen, Guei Wei, Cyuan Guei, Tang-Kuei (Japanese), Toki (Japanese), Tanggwi (Korean), Angelica root, Angelique, englewurzel, garden angelica, heiligenwurzel, root of the Holy Ghost, wild angelica, Eumenol

**Chinese Name:** 當歸

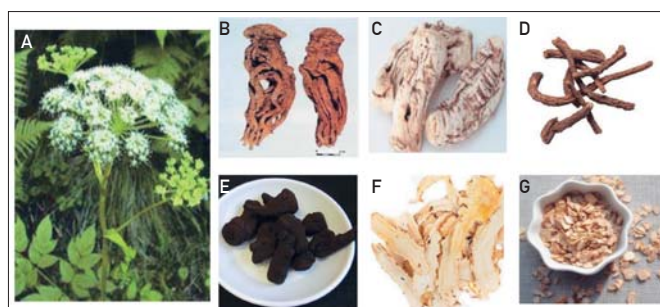
**Part Usually Used:** roots, leaf and seeds

**Common Uses:** Tonifying and replenishing medicinal (Blood-tonifying medicinal)

### INTRODUCTION

**Danggui** (DG) is a medicinal substance listed in the latest version of the Chinese Pharmacopoeia.<sup>(1)</sup> The name danggui means “proper order”. It is one of the major herbs in the Traditional Chinese, Korean and Japanese medicines. It was first mentioned as a medium-grade medicinal in The Compendium of Materia Medica (Shen Nong Ben Cao Jing, 200-300 A.D., Han Dynasty) and has been used in China for a variety of female health disorders for thousands of years. It is the dried or sliced root of *Angelica sinensis* (Oliv.)

Diels,<sup>(2)</sup> which is a Chinese species of the parsley family (**Figure 1A**). The herb is regarded as highly as ginseng.<sup>(3)</sup> It is one of the more frequently prescribed herbs and appears in many prescriptions.<sup>(4,5)</sup> In the late 1800s, an extract of DG, known as Eumenol, became popular in Europe as a “female tonic”, and this is how most people still understand in the West.<sup>(6)</sup>



**Figure 1. Morphological features of a plant and the root of *Angelicae sinensis* (Oliv.) Diels.** (A) whole vegetative plant of *Angelicae sinensis* (Oliv.) Diels; (B) crude *Angelicae Sinensis Radix*; (C) Angelica heads; (D) Angelica tails; (E) charred Angelica; (F) thin oblique slices of DG; (G) horizontal slices of DG root.



#### Contraindications

May alter hemostasis based on its potential interference with platelet aggregation. Contraindicated during the first 3 months of pregnancy and during acute respiratory infections, and in women with excessively active bleeding, e.g. peptic ulcer, intracranial bleeding.<sup>(33)</sup>

#### Undesirable Effect

May feel dizziness or a faint feeling. Avoid prolonged exposure to sunlight or ultra-violet radiation; may develop photosensitive because it contains furcoumarins.<sup>(34)</sup> Don't give it to pregnant and breast-feeding woman or patients with diarrhea as it is somewhat laxative.

#### Interaction with Conventional Drugs

Don't use angelica whenever taking coumadin or warfarin; it potentiates their blood thinning effect.<sup>(35)</sup> Use with caution in individual taking anticoagulant medications, including warfarin, aspirin, aspirin-containing products, NSAIDs, oral contraceptives or antiplatelet agents, e.g. Ticlopidine, Clopidogrel, Dipyriamole. Discontinue use at least two weeks prior to dental or surgical procedure.<sup>(33)</sup>

*Angelica sinensis* (Oliv.) Diels, also called the Chinese angelica, is a perennial herbal plant. The herb is native to China and Japan. When grown under proper cultivation, the plant is sturdy perennial reaching a height of up to 2 meter and bears bright green leaves and clusters of white flowers. Leaves with 3 leaflets, each divided again 3-5 times. Upper leafstalks have inflated sheaths. The umbels of greenish-white flowers, which are large and semiround, bloom from May to August. The plants are found in rich, damp mountain ravines and meadows, on river banks, and in coastal areas. In China, it is a widely cultivated species primarily for its medicinal uses.

There are about 80 species of plants in the Angelical genus all around the world. Among them, only 26 species, 5 varieties and 1 form can be found in China.<sup>(7)</sup> The medicinal part is used in raw form or processed with alcohol. Chinese angelica is closely related to the European *Angelica archangelica*, which is a common garden herb and the flavoring in Benedictine and Chartreuse liqueurs.<sup>(8)</sup>

*Angelicae Sinensis Radix* is generally harvested in late autumn after 2 years of plantation. The stems, leaf sheaths, rootlets and soil are removed, slightly dried and tied up in small bundles, then placed on a shelf and smoke-dried to obtain the medicinal herb.<sup>(9)</sup>

## DESCRIPTION AND IDENTIFICATION

### Morphological and Macroscopic Features<sup>(9)</sup>

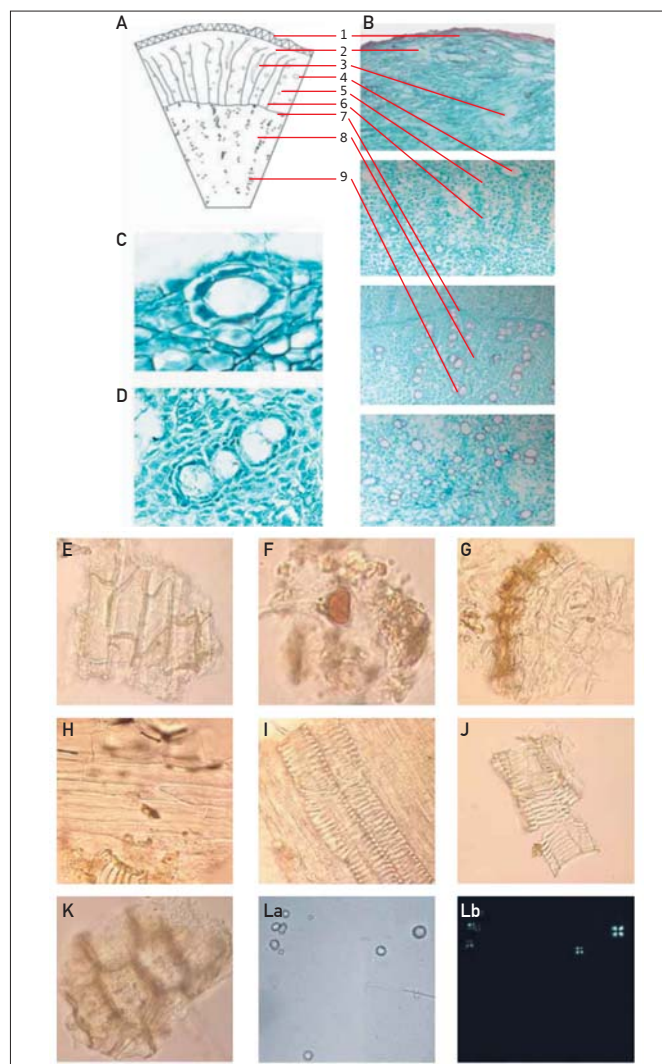
The shape of a DG is slightly cylindrical, externally yellowish-brown to dark-brown with some longitudinal wrinkles and transversely elongated lenticels (**Figure 1B**). The root stocks, the main root, the branch root and the entire root of DG are known as "guitou" (Angelica head, **Figure 1C**), "guishen" (Angelica body, **Figure 1C**), "guiwei" (Angelica tails, **Figure 1D**) and "quanguai" (entire Angelica, **Figure 1B**), respectively. Root stocks normally are 1.5-4 cm in diameter, annulated, apex obtuse, showing purple or yellowish-green remains of stems and leaf sheaths. Thick and short main roots frequently bear with numerous branch roots in the lower part; while upper portion of branch root thick and lower portion thin, mostly twisted, with a few rootlets scars.

Texture of the radix, in general, is flexible, fracture yellowish-white or pale yellowish-brown. It has thick bark, showing numerous brown spotted secretory cavities. Wood paler in colour than the bark, exhibiting with radial lines. Cambium ring yellowish-brown. Core of root stocks frequently displaying piths and cavities. The herb has strong aromatic odour. It is tasted pungent and slightly bitter.

### Microscopic description<sup>(9)</sup>

The transverse section of DG shows 5-16 layers of cells at the cork region. Cortex consists of 4-10 layers of cells with a few scattered oil cavities. The size of phloem clefts, which are broaden, and filling with many oil cavities at suborbicular, is 16-460 μm in diameter. These clefts are relatively large on the outer side and gradually becoming small inward. They are normally surrounded by 5-22 secretory cells and phloem rays. The cambium is present in a ring and the xylem is cleft and consists of 3-10 rays of cells. Vessels of the herb are scattered singly or in groups of 2-5. They are arranged radially (**Figure 2A**).

The powder of a blended Donggui is yellowish-brown. Surface view of cork subpolygonal, yellowish in colour, varying



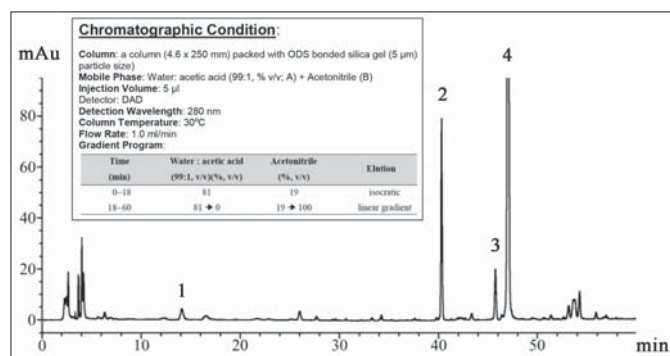
**Figure 2. Microscopic features of *Angelicae Sinensis Radix*. (A-D) transverse section; (E-L) features of powder under a microscope. A: Sketch; B: Transverse section illustration; C: Single oil cavity; D: Oil cavities in a group; E: Cork cells; F: Secretion from oil cavity; G: Oil cavity; H: Phloem parenchymatous cells; I: Reticulate vessels in a bundle; J: Single scalariform vessel; K: Starch grains in parenchymatous cells; L: Starch grains scattered. a: features under a light microscope; b: under a polarizing microscope. 1 = cork, 2 = cortex, 3 = clefts, 4 = oil cavity, 5 = phloem, 6 = phloem rays, 7 = cambium, 8 = xylem rays, 9 = xylem.<sup>(9)</sup>**

in size. Sometimes fragments of oil cavities containing yellowish oil droplets or oil mass secretions visible, 16-460 μm in diameter. Annular, scalariform and reticulate vessels frequent. Phloem parenchymatous cells fusiform, walls are fairly thick, with surface view showing very fine oblique crisscross striations, sometimes thin transverse septa visible. Most of starch gains composed of subspheroidal simple granules; showing a black, cross-shape under a polarizing microscope (**Figure 2E-L**).

### Chemical Identification

Aside from macroscopic and microscopic methods, authentication of this herb most often relies on chemical markers as it directly reflect the medicinal values of a herb. Ferulic acid and Z-ligustilide are usually used as marker to evaluate the quality of Danggui and its derived products.<sup>(10-14)</sup> According to a method described in the HKCMMS, a typical chromatogram of extract of *Angelicae Sinensis Radix* with a mixture of methanol and formic acid (95:5, v/v) should give a fingerprint similar to **Figure 3**; i.e. the sample should give four characteristic peaks with acceptable relative retention times

falling within the acceptable range of the corresponding peaks in the chromatogram. However, many components in Danggui are unstable. How to accurately reflect the true chemical contents of chemical components in Danggui is remained a problem.



**Figure 3.** A reference fingerprint chromatogram of extract of *Angelicae Sinensis Radix*. Peak 1: Ferulic acid (RRT=0.32); Peak 2: Unknown compound (RRT=0.86); Peak 3: Unknown compound (RRT=0.97) and Peak 4: Z-ligustilide (RRT=1).<sup>(9)</sup>

## BIOACTIVE COMPOUNDS

The chemical constituents of Danggui are generally belongs to essential oils, phthalide dimers, organic acids and their esters, vitamins, and polysaccharide.<sup>(2,15,16)</sup> Beside ferulic acid and Z-ligustilide, which have been adopted as the marker compound for the authentication and quality assurance of Donggui,<sup>(9)</sup> Chinese and Japanese angelica are composed of many similar low-molecular weight compounds such as phthalides, essential oils, flavonoids and coumarins, which are responsible for their medicinal actions.<sup>(17)</sup>

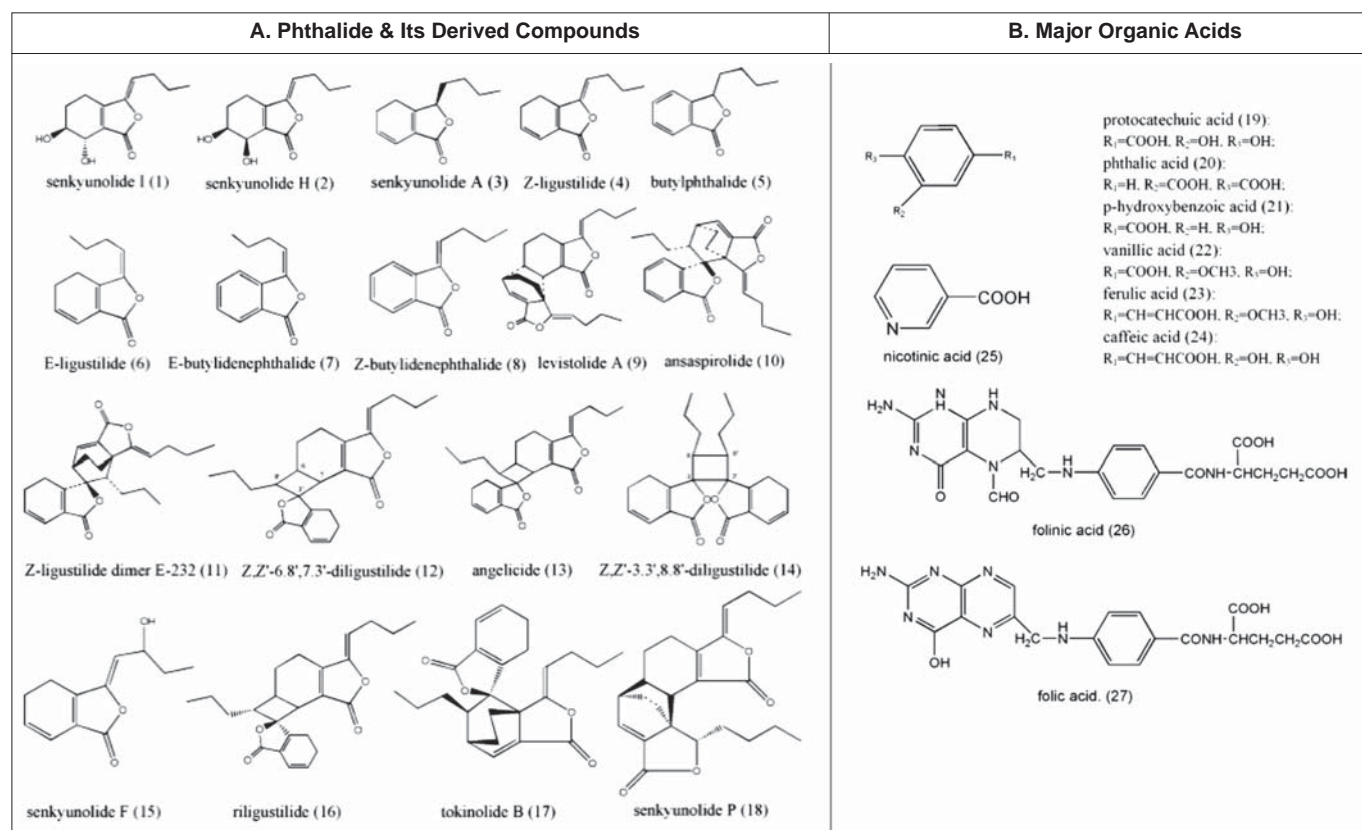
Chemical structure of some major phthalides in Danggui are shown in **Figure 4A**, containing monomeric phthalides (compound 1-7 of **Figure 4A**) and phthalide dimers (compound 8-14 of **Figure 4A**). The essential oils of oriental angelica are neutral and acidic oils, such as angelicone, *n*-butylidene phthalide, cadinene, carvacrol, *n*-dodecanal, isosafrole, folinic acid, linoleic acid, palmitic acids, safrole, sesquiterpene, and *n*-tetradecanol (**Figure 4B**). Water soluble extract of the herb includes butanedioic acid, nicotinic acid, adenine, stigmasterol-D-glucoside, vanillic acid and fluorescent gelsemine.<sup>(15)</sup>

## Comparison of Components in Different Part of Angelica Sinensis Radix

According to a recent conducted by Wei et al, they reported that the chemical compositions of different parts of Danggui are found to be significantly different among different region of the root.<sup>(17,18)</sup> By applying subwindow factor analysis (SFA), orthogonal projection approach-alternating least square (OPA-ALS) and evolving window orthogonal projection (EWOP), it was concluded from the statistical studies that principal components are difference and sameness among Danggui samples.

## Processing Affects the Quality of Angelicae Sinensis Radix

Traditionally, DG is dried in sunlight or shade during post-harvest handling. But the relatively lower efficiency and longer duration of these classical drying methods limit their applications in modern herbal industry. Moreover, motheaten is a common cause of its deterioration during long and slow drying process of DG. Recently, many advanced dehydration methods, such as hot air drying, vacuum drying, microwave drying and far infrared ray drying have been developed for herbal materials with an aim to obtain high quality herb. These



**Figure 4.** Chemical structures of some reported small organic molecules found in Danggui.<sup>(16)</sup>

alternative drying methods, however, may also change the content of major bioactive components in a herb.<sup>(19)</sup> When ten major bioactive components including two phenolic acids, two hydroxyl phthalide, four alky phthalide and two phthalide dimers were quantitatively determined by both high performance liquid chromatography photodiode array detector (HPLC-DAD) and by ultra-high performance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS/MS), it was concluded that DG slices dried in hot air kept the similar chemical composition to that of fresh DG, while DG whole roots dried in vacuum retained highest contents of the major components. Coniferyl ferulate and ligustilide degraded significantly in DG slide dried by microwave, far infrared ray and their combination.<sup>(19)</sup> Thus, the influence of such chemical changes induced by different drying methods on the bioactives of DG should be vindicated in order to obtain the best quality of DG for particular uses.<sup>(17,19)</sup>

## BIOLOGICAL ACTIVITIES

The biological effects of *Angelica* species relates to their high coumarin content. However, unlike scientific studies of other herbal medicines, much of the research done on *Angelica* species come from Asian plant extracts, rather than isolated constituents, leading to draw some precise interpretations of the studies. Nevertheless, some reported pharmacological effects revealed that DG has phytoestrogen activity, analgesic activity, cardiovascular effects, smooth muscle relaxing effects, antiallergy and immunomodulating activity, and antibacterial activity.<sup>(20)</sup>

### Phytoestrogenic Effects

Phytoestrogens exhibits an alternative effect by competing with estrogen for binding sites on cells. When estrogen levels are low, phytoestrogens exert some estrogenic activity; when estrogen levels are high, phytoestrogens reduce overall estrogenic activity by occupying estrogen receptor sites. DG is believed to have a balancing or adaptogenic effect on the female hormonal system, although the adaptogenic effect of DG, according to some opinions, is not potent enough to be regarded as a phytoestrogen in the body.<sup>(21)</sup> Their study concluded that DG capsules did not help women with menopausal symptoms. It was explained that a large part of its actions with regard to premenstrual syndrome might be related to its antispasmodic actions, particularly on smooth muscles.<sup>(22,23)</sup>

### Smooth Muscle Relaxing Functions

It has been reported that the essential oil of the *Angelica* could relax and protect the smooth muscles of the intestine and uterus, whereas the water extract produce an initial contraction followed by prolonged relaxation.<sup>(24,25)</sup> This observation confirms its traditional use in the treatment of intestinal spasm and uterine cramps. Its action on other smooth muscles could also explain its hypotensive action and historical use in asthma.

### Improving Blood Circulation of Cardiovascular System

Although not used historically for these purposes, *angelica* does possess significant blood pressure-lowering action.<sup>(26,27)</sup> This effect is largely due to its ability to dilate blood vessels. Dihydropyranocoumarins and dihydrofuranocoumarins from umbelliferous plants such as the *Angelica* have been shown to possess significant ability to dilate coronary vessels and relieve

vasospasms.<sup>(26)</sup> The mechanism of action appears to be largely a result of calcium channel antagonism. Agents that interact with calcium channels (calcium channel blockers) are quickly coming into prominence in the treatment of a wide variety of conditions, including hypertension and angina. *Angelica* and other umbelliferous plants may offer similar effects. Other cardiovascular effects noted for *angelica* include antiarrhythmic actions; inhibition of platelet aggregation; lowering of blood pressure; and increase in blood flow to the heart, brain, and extremities.<sup>(2,3)</sup>

### Analgesic Effects

Both Chinese and Japanese *angelica* have demonstrated pain-relieving and mild transquillizing effects in experimental studies in animals.<sup>(22,27)</sup> *Angelica*'s pain-relieving action was 1.7 times that of aspirin in one study.<sup>(28)</sup> Its analgesic activity, combined with its smooth muscle-relaxing activity, supports its historical use in such conditions as uterine cramps, trauma, headaches, and arthritis.

### Antiallergic and Immunodulatory Functions

Coumarin compounds have demonstrated immune-enhancing activity in both healthy and cancer patients.<sup>(29,30)</sup> Coumarins have been shown to stimulate white blood cells and increase their ability to destroy foreign particles and cancer cells.<sup>(29)</sup> Such activity is thought to offer significant protection against the growth and spread of tumor cells. On coumarin administration, specific white blood cells known as macrophages are said to be "activated" and thus capable of entering the tumor, where they can destroy tumor cells.<sup>(29,30)</sup> Coumarin compounds of *angelica* and the polysaccharides of the water extract of Japanese *angelica* have immune-modulating activity; they enhance the activity of white blood cells, increase interferon production, increase antitumor activity, and stimulate nonspecific host defense mechanisms.<sup>(31)</sup> These effects on the immune system by coumarins, polysaccharides, and extracts of *Angelica* species would seem to support their historical antitumor effects and their use as support agents in contemporary cancer therapy. DG has been found to help modulate the immune system by regulatory cytokines.<sup>(32)</sup>

### Antibacterial Effects

Extracts of Chinese *angelica* have been shown to possess antibacterial activity against both Gram-negative and -positive bacteria, whereas extracts of Japanese *angelica* exhibited no antibacterial action.<sup>(22)</sup> The inconsistency could be due to different essential oil concentrations of the extracts used in the studies. The oil of *Angelica archangelica* exhibits significant antifungal properties but virtually no antibacterial activity.<sup>(2)</sup> Because other herbs have much greater antimicrobial activity, *Angelica* species should be considered a less than optimum agent if this effect is desired.

## CLINICAL APPLICATIONS<sup>(1)</sup>

*Angelica* species have been used throughout the world in the treatment of a wide variety of health problems. At this time it appears that Chinese and Japanese *angelica* appear most useful in the treatment of disorders of menstruation, menopause, atopic conditions, smooth muscle spasm, and possibly as an immunostimulatory adjunct in cancer therapy, while *Angelica archangelica* and *A. atropurpurea* are most

indicated as expectorants, antispasmodics, and carminatives in the treatment of respiratory ailments, gas, and abdominal spasm.

## DOSAGE<sup>(1)</sup>

Take three times per day if 1 to 2 gm of powdered root or angelica tea are taken. For tincture (1:5) is taken, 4 ml or 1 teaspoon is enough and if fluid extract is prescribed, 1 ml, i.e. ¼ teaspoon is enough.

## ADVERSE ISSUES

Angelica is generally considered to be of low toxicity. However, it does contain many substances that can react with sunlight to cause a rash or severe sunburn. This possible side effect should be kept in mind when using any umbelliferous plant. This side effect can be used therapeutically in the treatment of vitiligo and psoriasis.

### Author's background

**Dr. CHEUNG Hon-Yeung**, who is an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong, is a manufacturing pharmacist and biotechnologist. He has more than forty years of work experience in industry, academic and consultancy jobs. He has been an expert witness in court and a member of the Biotechnology Committee for Hong Kong and Shenzhen Government. Dr. Cheung has published more than four hundred papers and articles in many prestigious international journals. His email address: cheung.honyeung@cityu.edu.hk

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# 2017 – The Pearl Anniversary of SHPHK

Reported by Vienna Leung

2017 has been a remarkable year for the Society of Hospital Pharmacists of Hong Kong (SHPHK) as it is the 30<sup>th</sup> anniversary of the Society! Over the past 30 years, the Society has been making steadfast progress. We are especially pleased to have more and more passionate young pharmacists to join us, and work with us to promote, improve and assist the advancement of hospital pharmacy practice in Hong Kong.

To share with readers on some of the treasured moments over the past months, the Society would like to highlight the 30<sup>th</sup> anniversary activities that we have specially organised this year, and present to you the latest refreshed look of our Drug Education Resources Centre (DERC) website.

### SHPHK 30<sup>th</sup> Anniversary Activities

SHPHK is committed to helping our members to keep up to date with their clinical and professional knowledge. In 2017, workshops and seminars on various clinical topics, including Parenteral Nutrition, Hepatitis, Diabetes and Cancers, were delivered by the Society. It was very encouraging that positive feedback was received from the audience. The Society would continue to organise such educational events regularly in the coming year to help equipping our members with the latest practice trends in various clinical areas.



The Paediatric Parenteral Nutrition Course held on 9<sup>th</sup> September 2017 at the Hospital Authority Head Office Building.

Learning aside, the Society also worked to strengthen the bonds between members, promote a sense of belonging for members in SHPHK, and to build a teamwork culture in pharmacy profession through a series of leisure activities this year, including :

*Treasure Hunt*, an orienteering competition, was one of the highlight events of the year. There were five teams in total competing. In order to win, each team had to follow the instructions given by the organising committee, and complete different tasks at various checkpoints in their shortest possible time. After much showcase of twists and turns, the Society would like to congratulate *Running PHARM* in becoming the champion team, and express its gratitude to the sporty

participation of other teams, namely *PharmaWomen*, *Pharm Rangers*, *Cephaloscoring* and *Apple Hunter*.



The Treasure Hunt Competition was a great success. All participants were awarded a complimentary gift of appreciation after the competition.

The Society values the contributions made by the frontline hospital pharmacists to the patient care. The coming 'Our Future Pharmacist Pearls' Election organised by SHPHK will offer an opportunity to recognise our outstanding hospital pharmacists with your active nominations. The Future Pharmacist Pearl Awards will be presented to the winners at the *SHPHK 30<sup>th</sup> Anniversary Gala Dinner* held on 18<sup>th</sup> November 2017 (Saturday). Please stay tuned.

Other 30<sup>th</sup> anniversary activities of the Society included *Hiking trip to Lamma Island*, *Movie Night – Beauty and the Beast*, *Photo Competition*....

### The Launch of DERC website

DERC was founded in 2002. It operates under the Society through a group of dedicated pharmacists aiming to promote the safe and effective use of medications by the public. The DERC website started its revamp since 2016, and the new website was successfully launched on 1<sup>st</sup> July 2017 at a press conference held on 29<sup>th</sup> June 2017 at the SHPHK Clubhouse.



A Press conference was held on 29<sup>th</sup> June 2017 to celebrate the launch of the new DERC website.

The new DERC website has the following features:

- 新醫藥透視 – Visitors would find the latest information on development of drugs in treating various diseases, including Cancers, Diabetes, Respiratory diseases etc. in this column
- 文章薈集 – A collection of articles written by the pharmacists of DERC are posted in this column, with comprehensive reviews on different treatment options and preventive measures for common diseases.

- 藥物視頻 – This column offers a selection of video channels to educate patients to administer their medications correctly to avoid incidents of adverse reactions.
- 最新消息- In this column, the latest local and international medical news, and articles from reputed medical journals translated by the pharmacists of DERC could be found.

The website is updated daily and the Society would like to invite you to help promoting this amazing website to your colleagues, patients, friends and family!

For more information on the DERC website, please visit [www.derc.org.hk](http://www.derc.org.hk). You are more than welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities.



The new DERC website offers comprehensive information about treatment options of different diseases and the latest news on drug development.

## Pharmacist Continuing Education – Fruitful September with Two CE Seminars

Reported by **Livia Ngai**  
Pharmacist, The Pharmaceutical Society of Hong Kong

The Pharmaceutical Society of Hong Kong values at advancing the pharmacy profession from different aspects, and the continuing education of pharmacists is certainly an important one. In September, PSHK organized two seminars themed as “Updates and Safety Monitoring Pearls on Cancer Immunotherapy” and “New Insights in Pathophysiology of GERD and the Management of PPI Non-Response: What Should We Do?” respectively. The following are the highlights of the events.

### IMMUNOTHERAPY SEMINAR

On the 14<sup>th</sup> of September, around 50 pharmacists attended the seminar presented by our honorary speakers, Dr. Angus Leung and Dr. Betty Chan. Dr. Leung is currently the Consultant in Clinical Oncology for the Radiotherapy & Oncology Centre of the Hong Kong Baptist Hospital, while Dr. Chan is a Board-Certified Oncology Pharmacist specialist practicing in the Norris Cancer Hospital at the University of Southern California. In fact, Dr. Chan visits Hong Kong every year to provide training on clinical oncology to our local pharmacists.

Dr. Leung started the presentation on local experience in cancer immunotherapy. He outlined the various approaches of various approaches in cancer immunotherapies. The role of PD-1 Immune Checkpoint Inhibitors was highlighted and different PD-1/ PD-L1 inhibitors were compared. The clinical responses were also explained with real patient cases.



Dr. Chan followed to talk about the safety profile of immunotherapy in cancer patients. Different types of immunotherapy including the inhibitors of CTLA-4, PD-1 and PD-L1 were introduced. Comparisons of their adverse events and the management were explained.

### GERD SEMINAR

Another seminar was held on the 26<sup>th</sup> September, for which we are so honored to have the world-renowned expert in Gastroenterology Professor - Peter J. Kahrilas to be the speaker. He is a professor in the Feinberg School of Medicine, with his research focusing on esophageal and oropharyngeal physiology and pathophysiology. He also authored international management guidelines for the American Gastroenterological Association.

During the lecture, Professor Kahrilas explained the unmet needs of GERD management, highlighting the ‘acid pocket’ which acts as a reservoir for postprandial reflux. Targeting treatment of alginate to neutralize the acid pocket was introduced.



We hope our pharmacists enjoyed the two lectures. To facilitate the continuing education of pharmacists in Hong Kong, PSHK will keep on organizing seminars with different topics. Stay tuned with our upcoming events, join us as member or like us on Facebook @pshongkong!



11 October 2017

Dear Fellow Pharmacists,

## INVITATION TO PARTICIPATE Hong Kong Pharmacy Conference 10-11 March 2018

It is my great honor and privilege to invite you to the Hong Kong Pharmacy Conference 2018 to be held on 10-11 March 2018 at the Hong Kong Convention & Exhibition Centre. On the same occasion, I am delighted to share the joyous news on the celebration of the 30th Pearl Anniversary of Hong Kong Pharmacy Conference in 2018. In celebrating the monumental event, we strive to engrave the core message to every member of the pharmacy profession by means of the conference theme. There is no dispute that embedding pharmacists into the model of collaborative practice can improve patients' continuity of care and health outcomes. To meet this goal, we advocate collaboration among pharmacists and other health-care professionals to explore on new frontiers for innovation and excellence as a sequel to last year's conference theme. This has brought forth the prospective while united theme for the Pharmacy Conference: **"30<sup>th</sup> Pearl Anniversary: PharmaCollaboration for New Frontiers"**.

The pharmacy profession has been rapidly growing since the emergence of new clinical services, technological advancement, and expansion of pharmacy academia in the past decade in Hong Kong. Alongside the growth of the pharmacy profession, collaboration helps shed light on new frontiers of pharmacy practice. Collaboration is an integral part of professional practice of any kind. The jargonized term of 'PharmaCollaboration' meant to emphasize the importance of strengthening all interfaces between various sectors of the profession via practice collaboration, which in turn optimizes the pharmacists' patient care services at all levels within the healthcare system.

In the ever-changing world, new frontiers of healthcare are rapidly evolving with the striking blend of innovation and integrated practice. In essence, it is the coordination of various interconnected care services where practice collaboration comes into play. Pharmacy practitioners need to embrace and promote shared responsibility with each other and other healthcare professionals in the patient care process. In this connection, the interlocking relationships among various levels of practice help gear up for successful collaboration and affirm the pharmacists' roles in the full extent in the healthcare system. In addition, the success of collaboration in practice depends on the sharing of information between all members of a health care team. The launch of the Electronic Health Record Sharing System (EHRSS) in 2016 has laid a solid foundation for a practice transition to more collaborative behaviors, which is expected to enhance the patients' continuity of care, promote public-private partnership and improve the quality of healthcare services. By exploiting these evolving advantages in the new frontiers, achieving a congruency of values will be close at hand while eventually better collaborating to improve health outcomes.

30 years of our conference journey has never been effortless, the Organizing Committee aims to widen the programme spectrum in 2018 in the context of practice collaboration across the diversity in the profession. Day 1 of the programme will lead off with the prospects of pharmacists in healthcare provision and strategic plan of pharmaceutical services in the Hospital Authority of Hong Kong, followed by a series of theme speeches on international perspectives of pharmacy development. Day 2 of the programme will not be abated but bring in three concurrent sessions covering topics from 9 major influential streams of evolving new frontiers of pharmacy practice in the healthcare system. Thereafter, the most exciting moment is reserved for a stimulating plenary session on the challenges and opportunities in manpower planning and professional development in pharmacy that undoubtedly will ignite new ways of thinking from all participants.

Information on the programme and registration will be available at: [www.pharmacyconference.org](http://www.pharmacyconference.org). I sincerely hope you will find the Hong Kong Pharmacy Conference 2018 enlightening and inspiring. Come share new perspectives about the new frontiers of pharmacy profession. "PharmaCollaboration for New Frontiers" will bring us to the new destination! I look forward to greeting you at the conference.

Sincerely yours,

Simon So  
Chairman, Organizing Committee  
Hong Kong Pharmacy Conference 2018



HONG KONG  
PHARMACY  
CONFERENCE

香港藥劑學術年會

2018 10-11 MARCH  
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學術年會三十載

# 藥劑協作拓新域

30<sup>th</sup> Pearl Anniversary:  
Pharma-Collaboration for New Frontiers



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SHPHK

# SUCRATE<sup>®</sup> gel

(Sucralfate 1g/5ml)

**Actively treat GERD & Gastritis with lesser early relapse  
Heal damaged G.I. lesions & promote complete recovery**

## Indication

Gastro-esophageal reflux disease (GERD), gastritis and peptic ulcers of various origin

## Composition

Per 5ml sachet containing 1 gram of sucralfate gel

## Product mechanism and features

Not offered by any Proton Pump Inhibitors, H2-blockers or other acid suppressing agents, Sucrate Gel uniquely forms a cyto-protective layer on the inflamed and damaged mucosae of the G.I. tract. This layer prevents stomach acid, pepsin and bile salts from further eroding the ulcerated tissues. Also, Sucrate Gel stimulates the production of endogenous tissue growth factors (epidermal growth factor, fibroblast growth factor, transforming growth factor alpha, platelet derived growth factor), which promote cell regeneration and angiogenesis.

Active ulcer healing is achieved through better reconstruction of mucosal architecture and thus prevents early relapse.

- Patented gel form with double surface area of bio-adhesion to ulcerated G.I. tissues
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- Easily swallowed with good tolerance

## Dosage

One sachet 2-4 times a day, according to physician's judgement.

## Manufacturer & origin

Product of Lisapharma S.p.A., Italy.  
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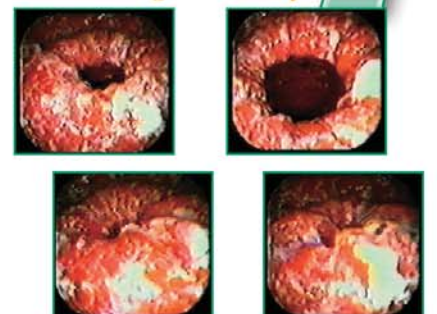
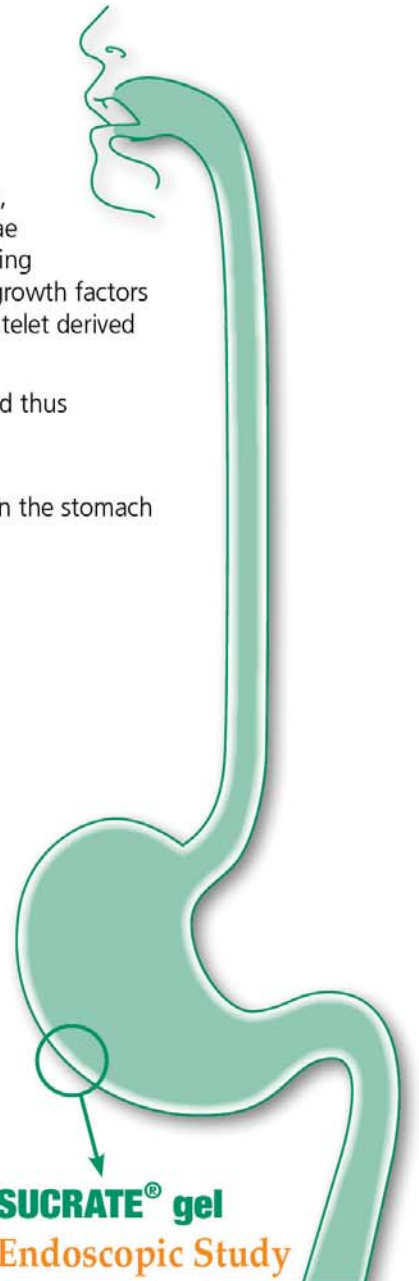
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Cosentino F. et al., Società Italiana di Endoscopia Digestiva, VII Simp. Naz, Napoli, 1992

## NEW INDICATION

### KEYTRUDA (pembrolizumab) Powder for Injection 50mg & 100mg (MSD)

By Weng Jingwen, Irene (Bachelor of Pharmacy, CUHK 2017)  
(Edited by Lucilla Leung)

#### Indications:

##### Melanoma

KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

##### Non-Small Cell Lung Cancer

KEYTRUDA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD L1 expression [Tumor Proportion Score (TPS)  $\geq 50\%$ ] as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS  $\geq 1\%$ ) as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA.

#### Dosage and Administration:

##### Patient Selection

Select patients for treatment of metastatic NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression.

##### Recommended Dosage for Melanoma

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

##### Recommended Dosage for NSCLC

KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose of KEYTRUDA is:

- 200mg for NSCLC that has not been previously treated with chemotherapy.
- 2mg/kg for NSCLC that has been previously treated with chemotherapy.

##### Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Grade 3 or 4 endocrinopathies
- Grade 2 nephritis
- Grade 3 severe skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
- Grade 3 or 4 nephritis
- Grade 4 severe skin reactions or confirmed SJS or TEN
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week

- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs

#### Preparation and Administration

##### Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

##### Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

#### Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

#### Administration

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

#### Precautions:

##### Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis.

Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation

(2.9%). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.

#### Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis.

Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.

#### Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.

#### Immune-Mediated Endocrinopathies

##### Hypophysitis

KEYTRUDA can cause hypophysitis. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis.

Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

##### Thyroid Disorders

KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism.

Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and Grade 3 (0.1%)

hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving KEYTRUDA, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

##### Type 1 Diabetes mellitus

KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia.

#### Immune-Mediated Nephritis and Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis.

Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients.

##### Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

##### Other Immune-Mediated Adverse Reactions

KEYTRUDA can cause other clinically important immune-mediated adverse reactions.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. The following was reported in other clinical trials with KEYTRUDA or in post-marketing use: myocarditis.

### Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUD.

### Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA.

### Side Effects:

Most common adverse reactions (reported in ≥20% of patients) were fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation, and nausea. Additional adverse reactions reported in ≥20% of patients with cancers other than melanoma and NSCLC were pyrexia, cough, and musculoskeletal pain.

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated pneumonitis.
- Immune-mediated colitis.
- Immune-mediated hepatitis.
- Immune-mediated endocrinopathies.
- Immune-mediated nephritis and renal dysfunction.
- Severe skin reactions.
- Other immune-mediated adverse reactions.
- Infusion-related reactions.

**Forensic Classification:** P1S1S3

## ZERBAXA® (MSD)

By Weng Jingwen, Irene (Bachelor of Pharmacy, CUHK 2017)  
(Edited by Lucilla Leung)

### Active Ingredient:

Zerbaxa powder for concentrate for solution for infusion contains two antibiotics: ceftolozane and tazobactam.

### Presentation:

Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam.

After reconstitution with 10 mL diluent, the total volume of the solution in the vial is 11.4 mL, which contains 88 mg/mL of ceftolozane and 44 mg/mL of tazobactam.

### Pharmacological Properties:

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins, resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death.

Tazobactam is a beta-lactam structurally related to penicillins. It is an inhibitor of many Molecular Class A beta-lactamases, including CTX-M, SHV, and TEM enzymes.

### Indications:

Zerbaxa is indicated for the treatment of the following infections in adults:

- Complicated intra-abdominal infections;
- Acute pyelonephritis;
- Complicated urinary tract infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### Dosage and Administration:

The recommended intravenous dose regimen for patients with creatinine clearance > 50 mL/min is shown by infection type in **Table 1**.

### Special populations

#### Elderly (≥ 65 years of age)

No dose adjustment is necessary for the elderly based on age alone.

#### Renal impairment

In patients with mild renal impairment (estimated creatinine clearance [CrCL] > 50 mL/min), no dose adjustment is necessary.

In patients with moderate or severe renal impairment, and in patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in **Table 2**.

**Table 2. Intravenous dose of ceftolozane/tazobactam in patients with creatinine clearance ≤ 50 mL/min**

Estimated CrCL (mL/min)*	Recommended dose regimen for Zerbaxa (ceftolozane/tazobactam)**
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 mg tazobactam intravenously every 8 hours
End stage renal disease on haemodialysis	A single loading dose of 500 mg ceftolozane / 250 mg tazobactam followed after 8 hours by a 100 mg ceftolozane / 50 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of haemodialysis)

\*CrCL estimated using Cockcroft-Gault formula

\*\*All doses of Zerbaxa are administered intravenously over 1 hour and are recommended for all indications. The duration of treatment should follow the recommendations in Table 1.

#### Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

#### Paediatric population

The safety and efficacy of ceftolozane/tazobactam in children and adolescents below 18 years of age have not yet been established. No data are available.

#### Method of administration

Zerbaxa is for intravenous infusion. The infusion time is 1 hour for 1 g / 0.5 g of Zerbaxa.

#### Precautions to be taken before handling or administering the product

Each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

#### Preparation of doses

The powder for concentrate for solution for infusion is reconstituted with 10 mL of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection per vial; following reconstitution the vial should be shaken gently to dissolve the powder. The final volume is approximately 11.4 mL. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam).

**Table 1. Intravenous dose of Zerbaxa by type of infection in patients with creatinine clearance > 50 mL/min**

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated intra-abdominal infection*	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	4-14 days
Complicated urinary tract infection Acute pyelonephritis	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	7 days

\*To be used in combination with metronidazole when anaerobic pathogens are suspected.

**CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.**

For preparation of the 1 g ceftolozane / 0.5 g tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

The preparations that follow relate to dose adjustments for renally impaired patients:

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

Zerbaxa solution for infusion is clear and colourless to slightly yellow.

Variations in colour within this range do not affect the potency of the product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### Contraindications:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- Hypersensitivity to any cephalosporin antibacterial agent;
- Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems).

#### Precautions:

##### Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible. If a severe allergic reaction occurs during treatment with ceftolozane/tazobactam, the medicinal product should be discontinued and appropriate measures taken.

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterial agents may also be hypersensitive to ceftolozane/tazobactam.

Ceftolozane/tazobactam is contraindicated in patients with a history of hypersensitivity to ceftolozane, tazobactam, or cephalosporins.

Ceftolozane/tazobactam is also contraindicated in patients with severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).

Ceftolozane/tazobactam should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or other beta-lactam antibacterial agents.

##### Effect on renal function

A decline in renal function has been seen in patients receiving ceftolozane/tazobactam.

##### Impaired renal function

The ceftolozane/tazobactam dose should be adjusted based on renal function.

In clinical trials the efficacy of ceftolozane/tazobactam was lower in patients with moderate renal impairment compared with those with normal or mildly impaired renal function at baseline. Patients with renal impairment at baseline should be monitored frequently for any changes in renal function during treatment and the dose of ceftolozane/tazobactam should be adjusted as necessary.

##### Limitations of the clinical data

Patients who were immunocompromised and patients with severe neutropenia were excluded from clinical trials.

In a trial in patients with complicated intra-abdominal infections, the most common diagnosis was appendiceal perforation or peri-appendiceal abscess (420/970 [43.3%] patients), of which 137/420 (32.6%) had diffuse peritonitis at baseline. Approximately 82% of all patients in the trial had APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of < 10 and 2.3% had bacteraemia at baseline. In the clinically evaluable (CE) patients, the clinical cure rates for ceftolozane/tazobactam were 95.9% in 293 patients aged less than 65 years and 87.8% in 82 patients aged 65 years or more.

Clinical efficacy data in patients with complicated lower urinary tract infection are limited. In a randomised active-controlled trial 18.2% (126/693) of microbiologically evaluable (ME) patients had complicated lower urinary tract infection (cLUTI), including 60/126 patients who were treated with ceftolozane/tazobactam. One of these 60 patients had bacteraemia at baseline.

##### *Clostridium difficile*-associated diarrhoea

Antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftolozane/tazobactam. These types of infection may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftolozane/tazobactam. In such circumstances, the discontinuation of therapy with ceftolozane/tazobactam and the use of supportive measures together with the administration of specific treatment for *Clostridium difficile* should be considered.

##### Non-susceptible micro-organisms

The use of ceftolozane/tazobactam may promote the overgrowth of non-susceptible micro-organisms. If super infection occurs during or following treatment, appropriate measures should be taken.

Ceftolozane/tazobactam is not active against bacteria that produce beta-lactamase enzymes which are not inhibited by tazobactam.

**Table 3. Adverse reactions identified during clinical trials with ceftolozane/tazobactam (N=1,015)**

System organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Infections and infestations		Candidiasis including oropharyngeal and vulvovaginal, <i>Clostridium difficile</i> colitis, fungal urinary tract infection
Blood and the lymphatic system disorders	Thrombocytosis	Anaemia
Metabolism and nutrition disorders	Hypokalaemia	Hyperglycaemia, hypomagnesaemia, hypophosphataemia
Psychiatric disorders	Insomnia, anxiety	
Nervous system disorders	Headache, dizziness	Ischemic stroke
Cardiac disorders		Atrial fibrillation, tachycardia, angina pectoris
Vascular disorders	Hypotension	Phlebitis, venous thrombosis
Respiratory, thoracic, and mediastinal disorders		Dyspnoea
Gastrointestinal disorders	Nausea, diarrhoea, constipation, vomiting, abdominal pain	Gastritis, abdominal distension, dyspepsia, flatulence, ileus paralytic
Skin and subcutaneous tissue disorders	Rash	Urticaria
Renal and urinary disorders		Renal impairment, renal failure
General disorders and administration site conditions	Pyrexia, infusion site reactions	
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased	Coombs test positive, increased serum gamma-glutamyl transpeptidase (GGT), increased serum alkaline phosphatase

### Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia

The development of a positive direct antiglobulin test (DAGT) may occur during treatment with ceftolozane/tazobactam. The incidence of DAGT seroconversion in patients receiving ceftolozane/tazobactam was 0.2% in the clinical trials. In clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment.

### Sodium content

Ceftolozane/tazobactam contains 10.0 mmol (230 mg) of sodium per vial. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 11.5 mmol (265 mg) of sodium. This should be taken into consideration while treating patients on controlled-sodium diet.

### Drug Interactions:

No significant medicinal product interactions are anticipated between ceftolozane/tazobactam and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs) based on *in vitro* and *in vivo* studies.

*In vitro* studies demonstrated that ceftolozane, tazobactam and the M1 metabolite of tazobactam did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma concentrations.

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, *in vitro* at therapeutic plasma concentrations. *In vitro* data indicate that ceftolozane did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MRP, BSEP, OAT1, OAT3, MATE1, or MATE2-K *in vitro* at therapeutic plasma concentrations. *In vitro* data indicate that neither tazobactam nor the tazobactam metabolite M1 inhibit P-gp, BCRP, OATP1B1,

OATP1B3, OCT1, OCT2, or BSEP transporters at therapeutic plasma concentrations.

Tazobactam is a substrate for OAT1 and OAT3. *In vitro*, tazobactam inhibited human OAT1 and OAT3 transporters with IC50 values of 118 and 147 mcg/mL, respectively. Co-administration of ceftolozane/tazobactam with OAT1 and OAT3 substrate furosemide in a clinical study did not significantly increase furosemide plasma exposures (geometric mean ratios of 0.83 and 0.87 for Cmax and AUC, respectively). However, active substances that inhibit OAT1 or OAT3 (e.g., probenecid) may increase tazobactam plasma concentrations.

### Side Effects:

#### Summary of the safety profile

Zerbaxa was evaluated in Phase 3 comparator-controlled clinical trials of complicated intra-abdominal infections and complicated urinary tract infections (including pyelonephritis), which included a total of 1,015 patients, treated with Zerbaxa (1 g / 0.5 g intravenously every 8 hours, adjusted to match renal function where appropriate) for up to 14 days.

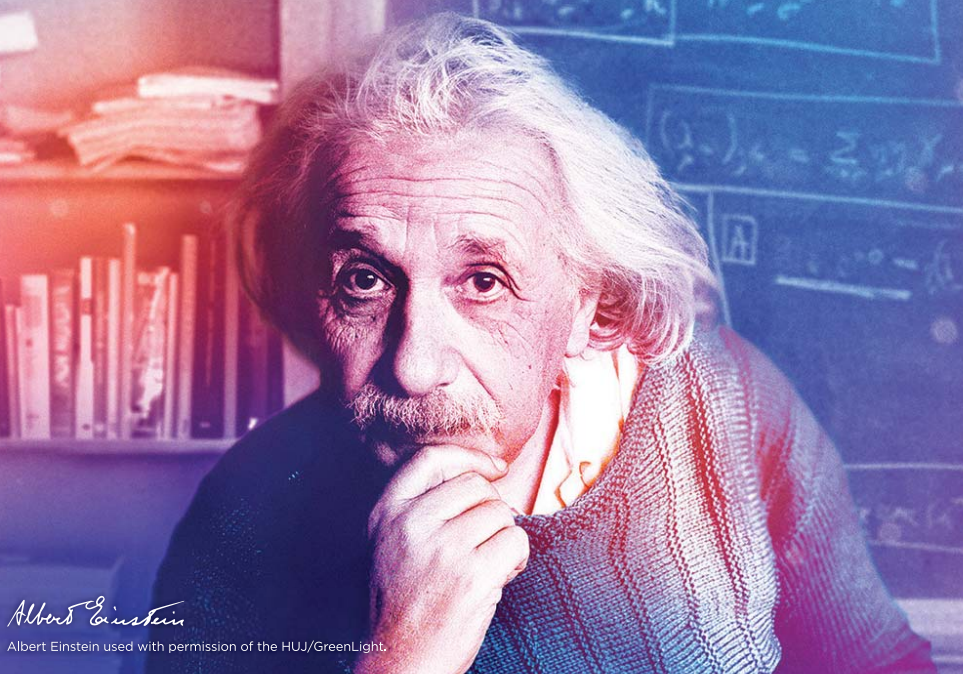
The most common adverse reactions (≥ 3% in pooled Phase 3 trials) occurring in patients receiving Zerbaxa were nausea, headache, constipation, diarrhoea, and pyrexia and were generally mild or moderate in severity.

#### Tabulated list of adverse reactions

The following adverse reactions have been identified during clinical trials with Zerbaxa. Adverse reactions are classified according to MedDRA System Organ Class and frequency. Frequency categories are derived according to the following conventions: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) (see **Table 3**).

### Forensic Classification:

Antibiotic



Albert Einstein

Albert Einstein used with permission of the HUJ/GreenLight.

# BE THE ONE

WHO CAN CHANGE WHAT'S POSSIBLE

For your HCV F0 to F4 compensated cirrhosis GT1 patients<sup>6</sup>:

### CURE

- Overall **97%** cure in HCV GT1 patients<sup>6,b,c</sup>
  - Overall cure rates of 94-99% across phase 3 studies<sup>1,3-6</sup>

### LOW DISCONTINUE RATE

- 99%** completed regimens of up to 12 weeks<sup>7</sup>
  - ≤1% of patients discontinued treatment with HARVONI due to adverse events<sup>1</sup>

### ONE pill, once a day<sup>1,d</sup>

- Single-Tablet Regimen for the majority of HCV GT1 patients<sup>1,d</sup>

- IFN free  RBV free<sup>4</sup>  PI free

#### HARVONI<sup>®</sup> Abbreviated Prescribing Information

**Presentation:** Orange colored, diamond-shaped, film-coated tablet containing 90 mg ledipasvir and 400 mg sofosbuvir.

**Indications:** Treatment of chronic hepatitis C genotype 1 infection in adults.

**Dosage:** Adults: One tablet taken orally once daily with or without food. **Pediatric Use:** Safety and effectiveness have not been established. **Geriatric Use:** No dosage adjustment is warranted in geriatric patients. **Renal Impairment:** No dosage adjustment is required for patients with mild or moderate renal impairment. Safety and efficacy have not been established in patients with severe renal impairment or end stage renal disease requiring hemodialysis. No dosage recommendation can be given for these patients. **Hepatic Impairment:** No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment. Safety and efficacy have not been established in patients with decompensated cirrhosis. **Pregnancy:** HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

**Warnings and Precautions:** **Serious symptomatic bradycardia when co-administered with amiodarone:** Co-administration of amiodarone is not recommended. Counseling patients about the risk of serious symptomatic bradycardia and cardiac monitoring are recommended for patients taking amiodarone, patients starting amiodarone therapy and patients discontinuing amiodarone just prior to starting HARVONI. **Risk of reduced therapeutic effect due to P-gp inducers:** use with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended. **Related products not recommended:** use with other products containing sofosbuvir is not recommended.

**Adverse reactions:** The most common adverse reactions were fatigue and headache in subjects treated with HARVONI during clinical trials. Serious symptomatic bradycardia has been reported in patients taking amiodarone from postmarketing experience.

**Drug interactions:** Any interactions that have been identified with ledipasvir and sofosbuvir individually may occur with HARVONI. **P-gp inducers** (e.g., rifampin or St. John's wort); **Acid reducing agents** including antacids (e.g., aluminum and magnesium hydroxide), H<sub>2</sub>-receptor antagonists (e.g., famotidine) and proton-pump inhibitors (e.g., omeprazole); **Antiarrhythmics** (amiodarone, digoxin); **Anticoagulants** (carbamazepine, phenytoin, phenobarbital, oxcarbazepine); **Antimicrobials** (rifabutin, rifampin, rifapentine); **HIV antiretrovirals** (combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate (TDF), regimens containing TDF and a HIV protease inhibitor/ritonavir (e.g., atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir), combination of elvitegravir, cobicistat, emtricitabine and TDF, and tipranavir/ritonavir); **HCV products** (simeprevir); **Herbal supplements** (St. John's wort); **HMG-CoA reductase inhibitors** (rosuvastatin).

**Before prescribing, please consult full prescribing information which is available upon request.**

HARVONI is a registered trademark of Gilead Sciences, Inc., or its related companies.

HK PI version: HK-MAY15-US-MAR15

#### References

- HARVONI HK PI version: HK-MAY15-US-MAR15.
- EASL Clinical Practice Guidelines, April 2014. Available at: [http://www.easl.eu/\\_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2014](http://www.easl.eu/_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2014).
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- Data based on studies IDN 1, 2 & 3 (Ref. 3, 4 & 5), available upon request.



Gilead Sciences Hong Kong Limited

Room 2603, 26th Floor, Hyman Place, 500 Hennessy Road, Causeway Bay, Hong Kong  
Tel: (852) 3129 2000 Fax: (852) 2856 2611

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Serving Size (每份重量)	1.45g (52mg)
Per Serving / 每份含	
Energy / 能量	86cal (千卡)
Protein / 蛋白質	0.1g (克)
Total fat / 總脂肪	0.1g (克)
- Saturated fat / 飽和脂肪	0.1g (克)
- Trans fat / 反式脂肪	0.1g (克)
Total carbohydrates / 總碳水化合物	0.1g (克)
- Dietary fibre / 膳食纖維	0g (克)
- Sugar / 糖	0g (克)
Sodium / 鈉	1mg (毫克)



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👍 《英國國家藥方集》記載<sup>2</sup>

👍 國家衛生和計劃生育委員會 (簡稱衛計委)<sup>5</sup> 及 中國優生科學協會權威推薦<sup>6</sup>

👍 經臨床驗證<sup>3-4</sup>

👍 有助胎兒良好神經管道及腦部發展

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1. Czeizel, Andrew E., et al. "Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects." *Nutrients* 5.11 (2013): 4760-4775.

2. British National Formulary. *Royal Pharmaceutical Society of Great Britain*, since 2001.

3. 1999年與國家計生委携手開展「出生缺陷干預工程」。通過懷孕前、出生前的干預措施，預防出生缺陷的發生和嚴重缺陷兒出生為主要目的。

4. 2004 - 2007年，口服「福施福」對預防出生缺陷的療效觀察。

5. 2000年納入為「國家計生委員會科技可推廣產品」。亦為同類保健品中唯一推廣產品。

6. 1999年成為「中國優生科學協會」推廣產品。